CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213871Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 123554

MEETING PRELIMINARY COMMENTS

Pfizer Inc.
Attention: Jennifer Weissert, PhD
Director, Pfizer Global Regulatory Affairs
300 Technology Square, 3rd Floor
Cambridge, MA 02139

Dear Dr. Weissert:

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

We also refer to your correspondence dated and received October 31, 2019, requesting a meeting to discuss proposed content and data format for NDA submission.

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 301 796-4224.

Sincerely,

{See appended electronic signature page}

Barbara Gould, MBAHCM
Chief, Project Management Staff
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: January 22, 2020 at 9:00 am.
Meeting Location: Bldg. 22 Conference Room 1313, White Oak Campus

Application Number: IND 123554
Product Name: abrocitinib tablets, 100 mg and 200 mg

Proposed Indication: (b) (4)

Sponsor Name: Pfizer Inc.

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 January 22, 2020 at 9:00 a.m. between Pfizer Inc. and the Division of Dermatology and Dental 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

The purpose of this meeting is to discuss proposed content and data format for the original NDA submission and overall rolling submission plan in preparation for filing in mid-2020 for abrocitinib for the treatment of moderate to severe AD.

Regulatory Correspondence History:

We have had the following meetings/teleconferences with you:

- 10/08/2019 Guidance Meeting
- 02/24/2019 Final Written Response
- 05/23/2018 Breakthrough Therapy – Initial Comprehensive
- 10/30/2017 End of Phase 2

We have sent the following correspondences:

- 01/09/2020 Proprietary Name Denied
- 12/30/2019 Pediatric Study Plan – Initial Agreement
- 09/10/2019 Advice
- 08/14/2019 Advice /Information Request
- 03/27/2019 Advice/Information Request
- 12/20/2018 Special Protocol – Agreement
- 10/26/2018 Advice
- 08/30/2018 Advice
- 07/02/2018 Advice
- 02/15/2018 Advice
- 02/07/2018 Grant – Breakthrough Therapy Designation Request
- 01/23/2018 Special Protocol – Request Denied
- 10/04/2017 Special Protocol – Agreement (Carcinogenicity)
- 08/18/2017 Special Protocol Assessment – Request Denied (Carcinogenicity)
- 04/11/2016 Advice
- 12/15/2014 Study May Proceed

2.0 DISCUSSION

2.1. Regulatory

Question 15:

Does the Agency agree with the proposed rolling submission strategy and dataset format?

FDA Response to Question 15:

We reiterate previous advice from February 24, 2019. Applications which have received Fast Track and Breakthrough designations are appropriate for rolling review but note that the *Expedited Program guidance* states “this does not necessarily mean that review will commence or proceed before the complete application is submitted. Actual commencement and scheduling of review depends on many factors, including staffing,

workload, competing priorities, timeline for completing the application, and the perceived efficiency of commencing review before receipt of the complete submission."

Question 16:
Does the Agency agree with the studies for which financial disclosure information will be provided in the initial NDA submission?

FDA Response to Question 16:
Financial disclosures should include all relevant studies for which data is relied on in the approval of your drug product.

Question 17:
Pfizer is planning to request Priority Review for abrocitinib for the treatment of moderate to severe AD. If the Agency grants Priority Review for this program, does the Agency intend to request an earlier safety update (eg, at 3 months post submission) in lieu of the traditional 4-Month Safety Update?

FDA Response to Question 17:
If you request and are granted a Priority Review, submission of the safety update at three months would be appropriate. See FDA Response to Question 7 regarding the extent of safety data requested for your application.

A determination regarding the necessity of an advisory committee meeting for your application will not be made until receipt of the completed application.

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 14:
Pfizer proposes to provide (b) (4) month drug product primary stability data for the 50-mg tablet (this dose is intended to address the needs of special PK populations) in the NDA. Does the Agency agree with this proposed drug product stability strategy in light of the need to have this dose available at launch?

FDA Response to Question 14:
No, we do not agree. We generally require that 12 months of long-term stability be provided at the time of submission of a NDA. However, because your application has been granted breakthrough therapy designation, we will be willing to accept 9 months of long-term stability for the 50-mg strength at the time submission of your application with the commitment that you will provide 3 additional months long-term stability data for the 50-mg strength for a total of 12 months within 90 days from the date of submission of your application.

2.3. Nonclinical

Question 1:
Does the Agency concur that the nonclinical immune system assessment is adequate?

FDA Response to Question 1:
It appears that the effects of abrocitinib on the immune system have been sufficiently assessed non-clinically. However, the adequacy of the assessment will be determined after review of all nonclinical study reports.

Question 2:
Does the Agency concur, pending full review of the data during NDA review, and provided the Phase 3 clinical data are supportive, that the nonclinical package including effects on bone is adequate for the initial registration in adult (b) (4) AD patients (b) (4)

FDA Response to Question 2:
It appears that the non-clinical package is sufficient to support filing the NDA for treatment in adult (b) (4) atopic dermatitis (AD) patients (b) (4) (b) (4) However, the adequacy of the nonclinical data will be determined after review of all nonclinical study reports. The report of the definitive toxicity study in juvenile rats should be submitted when it is available. Refer to the nonclinical comments concerning submission of carcinogenicity study data relayed in the Written Response Only document sent on February 24, 2019.

2.4. Clinical Pharmacology

Question 11:
Does the Agency agree with the proposed safety analyses contained within the Population Modeling Analysis Reports?

FDA Response to Question 11:
Your approach appears reasonable and this will be a review issue at the time of NDA submission.

Question 12:
Does the Agency concur with the proposed clinical studies to support the clinical pharmacology and biopharmaceutics review of the initial NDA?

FDA Response to Question 12:
Your completed, ongoing and planned clinical studies summarized in Table 9 of your meeting package appear reasonable to support the review of the initial NDA. We remind you of our comments in our communication dated 02/24/2019 regarding addressing drug interaction potential of the metabolites in your NDA submission.

Question 13:
Does the Agency agree with the proposed analysis of active moiety pharmacokinetics, taking into account abrocitinib and its two active metabolites in systemic circulation, for the assessment of the effects of intrinsic and extrinsic factors for dosing recommendations?

FDA Response to Question 13:
Your proposed analysis plan of active moiety pharmacokinetics appears reasonable in general and will be reviewed in detail at the time of NDA submission.

2.5. Clinical/Biostatistics

Question 3:
Does the Agency agree that the data intended to be filed with the NDA is supportive of a therapeutic indication (b) (4) (b) (4)

FDA Response to Question 3:

Study Identifier	Brief Description[a]/Population	Data to be provided with Initial Submission	Data to be provided with 3 or 4 Month Safety Update
B7451006	Monotherapy Study/ Adults	Final CSR and data integrated into Modules 2 and 5 summary documents	
B7451012	Monotherapy Study/ Adults and Adolescents	Final CSR and data integrated into Modules 2 and 5 summary documents	-
B7451013	Monotherapy Study/ Adults and Adolescents	Final CSR and data integrated into Modules 2 and 5 summary documents	-
B7451029	Background Topical Combination Study/ Adults	Final CSR[b] and data integrated into Modules 2 and 5 summary documents	Supplemental CSR
B7451014	Regimen/ Adults and Adolescents	Data Snapshot integrated into Modules 2 and 5 summary documents	-
B7451015	Long term Extension/ Adults and Adolescents	Data Snapshot integrated into Modules 2 and 5 summary documents	Data Snapshot integrated into Safety Update
B7451036	Background Topical/ Adolescents	-	Final CSR

The Agency agrees that the proposed data package should support the indication of treatment in subjects (b) (4) with moderate to severe atopic dermatitis and your proposal appears adequate for filing of the application. The indication of combination use with topical treatment will be a review issue under the NDA review.

Question 4:
If both the 100 mg and 200 mg QD doses have a positive benefit:risk profile, the Sponsor plans to propose inclusion of both doses in the label to allow use of the most optimal dose for the patient. Specific labeling instructions on how to use each of the two doses would be discussed with the Agency after evaluating the benefit:risk of each dose. Does the Agency agree with this approach?

FDA Response to Question 4:
Clarify if weight strata will be evaluated for weight-based response by dose. It is possible to include more than one dose in prescribing information. Your labeling will be based on the completed package submitted with the NDA for your intended indication. See Administrative Comment – Discussion of Content of a Completed Application.

Question 5:
Does the Agency agree with the Case Report Forms to be included in the NDA submission, ie, those for all Deaths, Subjects Discontinued due to an Adverse Event (All Causalities) and all Serious Adverse Events?

FDA Response to Question 5:
Yes.

Question 6:
Does the Agency agree with the proposed subgroup analyses for efficacy?

FDA Response to Question 6:
The proposed subgroup analyses appear acceptable. Note that these analyses are exploratory in nature, and the Agency may request additional subgroup analyses during the NDA review. The Agency may request further subgroup analysis based on the safety profile during NDA review.

Question 7:
Does the Agency agree with the composition and size of the safety database to support the initial NDA submission and proposed content of the 4-Month Safety Update?

FDA Response to Question 7:

	Abrocitinib		
	100 mg	**200 mg**	**Total**
Initial Submission			
Any Exposure (n)	807	2035	2842
Exposure in the short-term placebo-controlled portion of the studies	610	604	1214
Exposure >1 year (n)	259 (range: 257-260)	394 (range: 393-395)	653 (range: 650-655)
Adolescents with any exposure (n)	61	304	365
Adolescents, 12-<16 years	35	172	207
Adolescents, 16-<18 years	26	132	158
Adolescents with > 1-year exposure (n)	37	84	121
Adolescents, 12-<16 years	22	48	70
Adolescents, 16-<18 years	15	36	51
4 Month Safety Update			
Exposure >1 year (n)	406 (range: 394-419)	647 (range: 638-658)	1053 (range: 1032-1077)

At the time of the 4MSU, the CSR for B7451036 will be available to further characterize adolescent safety.

As previously stated in the Agency written response from 24-FEB-2019 and the Type B meeting minutes on 23-MAY-2018, your safety database should include 1500 subjects in your short-term exposure and 750 subjects with moderate to severe atopic dermatitis who have received the to-be-marketed dose for at least 1 year, and of the 750 subjects, a minimum of 30% should be between the ages of 12 and 17 years, 11-months old. Table 3 of your briefing package suggests that you will have 2035 subjects at the 200 mg dose but only 304 subjects between the ages of 12 and 18 years old. This amount to less than 12% of your safety population as adolescents. Provide a rationale as to why this would be sufficient for your safety database.

(b) (4)

(b) (4) This will be a review issue under the NDA.

Question 8:

Does the Agency agree with the proposed Table of Contents for the Integrated Summary of Safety and the Summary of Clinical Safety for the filing?

FDA Response to Question 8:

Your proposal appears acceptable.

Question 9:

Does the Agency agree with definitions and analyses for the safety topics of special interest for the filing?

FDA Response to Question 9:

Your proposed analyses for special safety topics appear acceptable.

Question 10:
Does the Agency agree with the subgroup definitions and analyses planned for safety subgroup analysis?

FDA Response to Question 10:
Your proposed subgroup analyses appear acceptable.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our November 20, 2019 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 FDA.gov.[1]

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

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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*.[2] 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.[3]

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

[2] 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.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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*.

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

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

MANUFACTURING FACILITIES

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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*.[8]

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

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/

BARBARA J GOULD
01/19/2020 05:54:34 PM

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 123554
Request Receipt Date	November 30, 2017
Product	PF-04965842 tablets, 100 mg and 200 mg
Proposed Indication	for the treatment of atopic dermatitis
Drug Class/Mechanism of Action	JAK 1 Inhibitor
Sponsor	Pfizer, Inc
ODE/Division	ODE III/DDDP
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	January 29, 2017

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes,*** *and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

PF-04965842 (JAK1) is indicated for the treatment of patients with moderate to severe atopic dermatitis (AD) (b) (4)

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?

☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- *The **janus kinase (JAK)** family includes JAK1, JAK2, JAK3 and Tyk2. Evidence suggests that inhibition of JAK-mediated pathways is effective in treatment of moderate to severe AD. Specifically the inhibition of JAK1 selective pathway appear to have treatment effects on AD without the adverse effects of the non-selective JAK inhibition seem in tofacitinib, baricitinib, and upadacitinib (ABT-494. PF-04965842 is a novel JAK1-selective inhibitor being developed for the treatment atopic dermatitis (AD). JAK1 inhibition by PF-04965842 is expected to block or attenuate the signaling of multiple pathogenic cytokines implicated in AD including interleukin (IL)-4, IL-13, IL-22, thymic stromal lymphopoietin (TSLP), and IL-31. These cytokines prevent apoptosis of inflammatory T cell infiltrates in the skin, promote type 2 helper T cells (TH2) cell differentiation and IgE class*

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

switching in B cells, induce epidermal hyperplasia, impair barrier function and anti-microbial protein production, and act on neurons to promote pruritus.

- ***Atopic dermatitis (AD)** is a inflammatory, pruritic, chronic skin disease. AD affects up to 20% of children and 3% of adults, worldwide. In 70%-85% of cases, the onset of AD being in the first 5 years of life. Most cases resolve by adulthood, while AD persists in approximately 10 to 30% of cases. Common clinical characteristics vary by patient age and chronicity of lesions and include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification. Multiple comorbidities are associated with AD, including other atopic diseases such as allergic rhinitis, food allergies, and asthma. The pathogenesis of AD involves a complex interaction of immune, genetic, metabolic, infectious, neuroendocrine, and environmental factors. Atopic dermatitis is often associated with a personal or family history of type I allergies (i.e., immediate hypersensitivity reactions), allergic rhinitis, and asthma, and with elevated serum immunoglobulin E (IgE) levels. Defects in epidermal barrier function and cutaneous inflammation are hallmarks of AD, and these effects can be further exacerbated by a lack of endogenous protease inhibitors in atopic skin, exogenous proteases from Staphylococcus aureus and house dust mites, reduced antimicrobial peptide expression, and the use of soaps and detergents that may raise local pH and increase activity of endogenous proteases. Increased allergen absorption and microbial colonization can result with clinical sequelae including allergen sensitization and skin infections.*

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The Phase 2b study B7451006 assessed once daily (QD) doses ranging from 10 to 200 mg PF-04965842 or placebo for up to 12 weeks in adults with AD. The primary endpoint of the study was the proportion of patients achieving:

1. *the Investigator's Global Assessment (IGA) of clear (0) or almost clear (1) and 2 points or greater improvement from baseline at Week 12.*

Secondary Endpoints include:

2. *The percent change from baseline in the eczema area and severity index (EASI) score at Week 12*
3. *The proportion of subjects achieving ≥3 or ≥4 points improvement in the pruritus numerical rating scale (NRS) from baseline.*

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

In general, the Division recommends the primary endpoint in atopic dermatitis trials as defined:

i. *Subjects achieving both Investigators Global Assessments Scale (IGA) of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥ 2 points at evaluation.*

ii. *In addition, subjects achieving EASI75 (≥ 75% improvement from baseline) at evaluation (this co-primary endpoint is optional as some sponsors have proposed).*

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

A key secondary endpoint in atopic dermatitis tials would be a patient reported Prutitus Numeric Rating Scale (Pruritus NRS). The NRS should be a single 11-point scale that measures prutitus in AD patients. A 4-point or

greater improvement in the Pruritus NRS from baseline at different intervals in treatment would demonstrate improvement in pruritus of AD.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

Briefly, mild to moderate AD is managed with regular use of emollients, avoidance of irritants, and low to moderate potency topical corticosteroids (TCS), topical calcineurin inhibitors (TCIs), and/or topical PDE-4 inhibitors. Moderate to severe AD treatment recommendations start with moderate to high potency TCS and/or TCI, moving on to phototherapy or systemics (e.g., cyclosporine) after topical treatment failure. Systemic treatments include corticosteroids, systemic immunosuppressants (cyclosporine, azathioprine, methotrexate, mycophenolate mofetil are sometimes used off-label) and more recently, dupilumab, a monoclonal antibody that inhibits IL-4 and IL-3.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

In the Division, recent requests for BTD include a Abbivie product, upadacitinib (JAK1) for the treatment of atopic moderate to severe atopic dermatitis. Another JAK inhitor developed by Eli Lilly and Company, designated baricitinib had a preliminary BTD meeting, but is now on partial clinical hold for serious adverse reactions of thromboembolism observed in the rheumatoid arthritis (RA) development program for baricitinib.

In addition to specific atopic dermatitis products, CR845 from Cara therapeutics is being developed specifically for the pruritis of uremic disease has requested and been granted BTD.

Dupilumab for the treatment of moderate to severe atopic dermatitis in adults who are not adequately controlled with or are intolerant to topical prescription therapy or when those therapy are not advisable was granted Breakthrough Therapy designation, one in 2014 for adults and again in 2016 for the treatment of adolescents.

10. Information related to the preliminary clinical evidence:

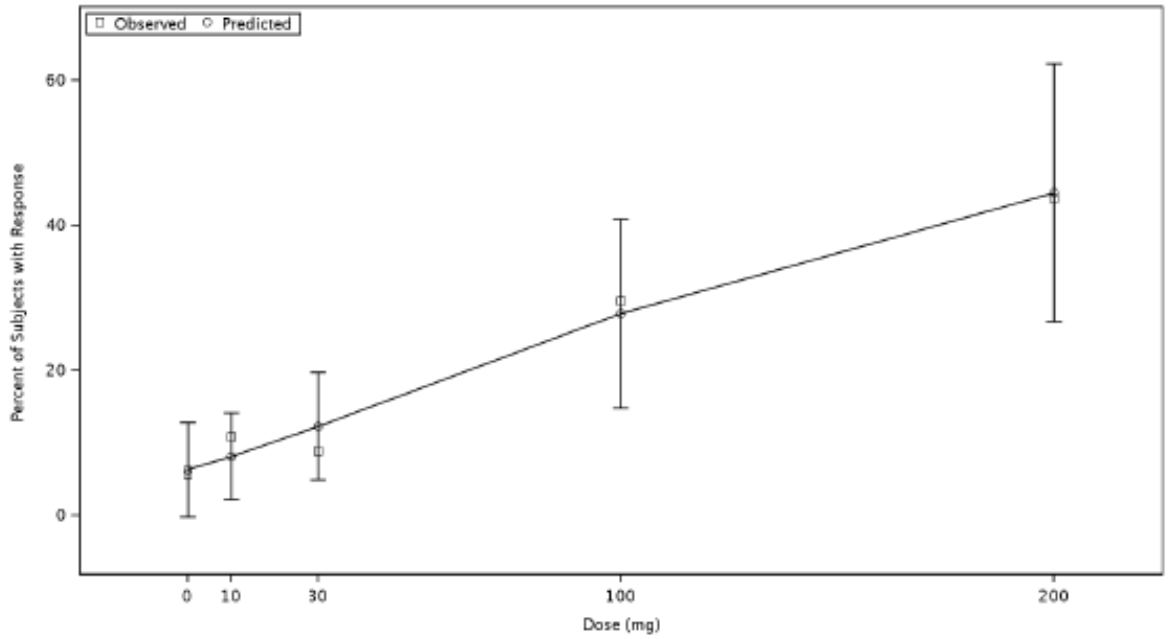
a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The sponsor submitted data from a single Phase 2b (B7451006), dose-ranging clinical study, as preliminary clinical evidence of treatment effects in moderate to severe atopic dermatitis in adults. This study assessed daily doses of 10, 30, 100, and 200 mg PF-04965842 or placebo for up to 12 weeks in adults (ages 18-75) with AD. The primary endpoint of study B7451006 was the proportion of subjects achieving an IGA score of clear (0) or almost clear (1) and a ≥2-point improvement from baseline at Week 12. In all 267 subjects werer randomized to the 5 arms of the study.

For IGA response at Week 12, the placebo-adjusted response was 38.2% for the 200 mg group, 21.5% for the 100 mg group, and for the 10 mg and 30 mg groups were not significantly different from placebo.

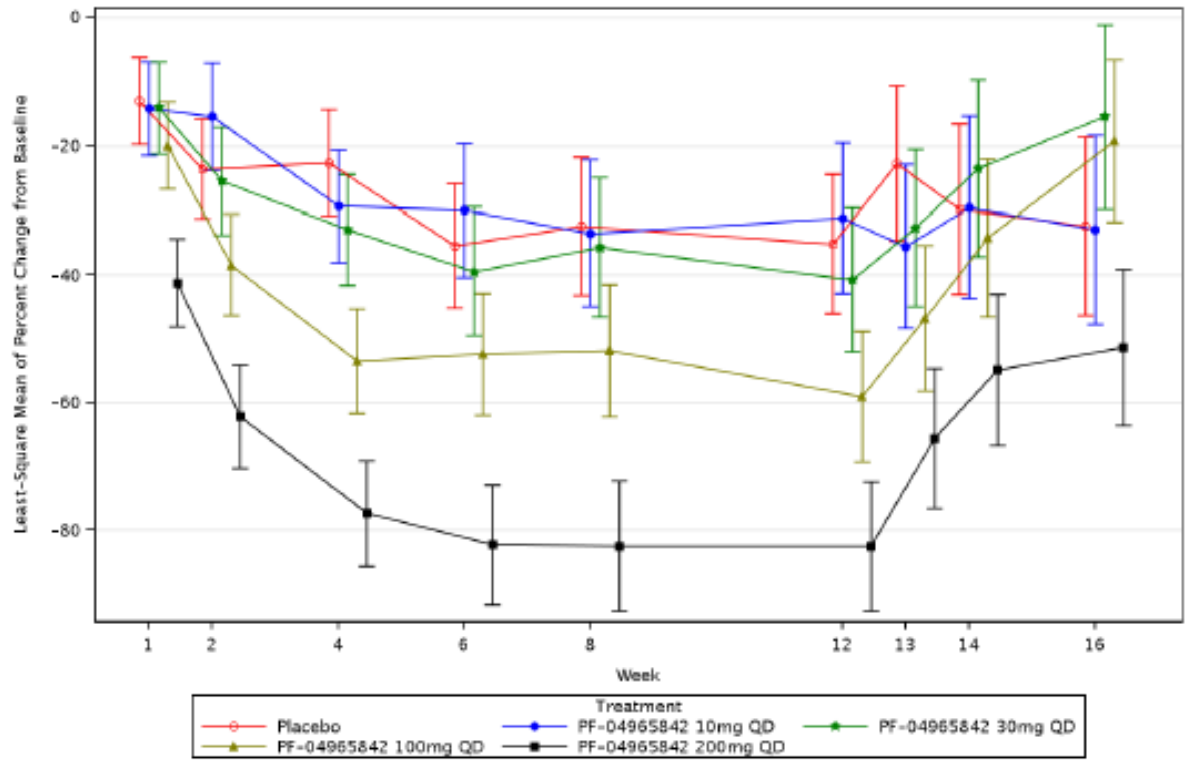
[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Figure 1: Emax Fitted Curve with 95% CI – Proportion of Subjects Achiving IGA Repsonse of Clear or Almost Clear and ≥ 2-point Improvement from the Baseline at Week 12 – (FAS, NRI, Placebo-Adjusted)



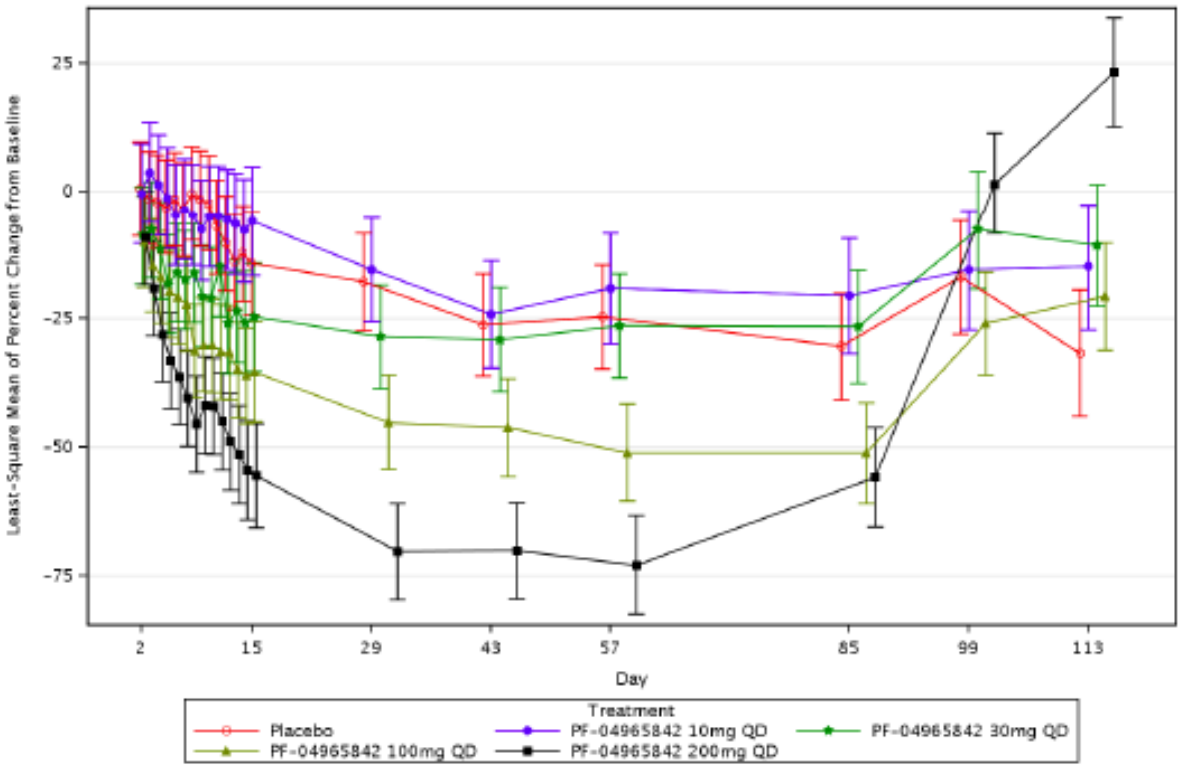
The percent change from baseline in the EASI score at Week 12 was more pronounced. The maximal percent change from baseline in the EASI total score in the PF-04965842 200 mg and 100 mg treatment groups was achieved at Week 4-6, and this response was maintained through the 12-week treatment period.

Figure 2: Plot of Least Square Mean of Percent Change from Baseline in EASI Score – MMRM (FAS, OC)



Other secondary endpoint evaluated included percentage of patients that exhibited an improvement in pruritus NRS of ≥ 4-points from baseline at Day 14 for PF-04965842 200 mg and 100 mg was 59.1% and 41.7% repectively; placebo was 10.4%.

Figure 3: Plot of Least-Square Mean of Percent Change from Baseline in the Puritus NRS at All Schduled Time Points – MMRM (FAS, OC)



For the safety evaluations in this study:

Table 1: Treatment Emergent Adverse Events (All Causality) Occuring in ≥ 4 Subjects in Any Treamtent Group and the Associated System Organ Class

System Organ Class Preferred Term n (%)	Placebo (N=56)	PF-049655842 QD dose			
		10 mg (N=49)	30 mg (N=51)	100 mg (N=56)	200 mg (N=55)
Gastrointestinal Disorders	**4 (7.1)**	**4 (8.2)**	**5 (9.8)**	**6 (10.7)**	**12 (21.8)**
Diarrhoea	1 (1.8)	3 (6.1)	1 (2.0)	1 (1.8)	5 (9.1)
Nausea	1 (1.8)	3 (6.1)	3 (5.9)	1 (1.8)	8 (14.5)
Nervous System Disorders	**4 (7.1)**	**2 (4.1)**	**8 (15.7)**	**7 (12.5)**	**7 (12.7)**
Headache	2 (3.6)	2 (4.1)	5 (9.8)	5 (8.9)	4 (7.3)
Infections and Infestations	**13 (23.2)**	**23 (46.9)**	**19 (37.3)**	**24 (42.9)**	**23 (41.8)**
Upper respiratory tract infection	5 (8.9)	3 (6.1)	5 (9.8)	3 (5.4)	5 (9.1)
Viral upper respiratory tract infection	5 (8.9)	5 (10.2)	6 (11.8)	10 (17.9)	7 (12.7)
Skin and Subcutaneous Tissue Disorders	**11 (19.6)**	**10 (20.4)**	**10 (19.6)**	**17 (30.4)**	**10 (18.2)**
Dermatitis atopic	7 (12.5)	8 (16.3)	9 (17.6)	7 (12.5)	7 (12.7)

Source: Clinical Study Report B7451006 Table 14.3.1.2.3
N = Number of subjects; QD = Once daily.

There were no death. SAEs were similar across the treatment groups. Two events (pneumonia and exzema) were considered related to treatment by the investigator. Mean changes in chemistry and lipid parameters did not show any clinically relevant treatment effects. Small increases in total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL) were observed in some higher dose

treatment groups; however, the LDL/HDL ratios did not change from baseline. There were decreases in mean platelet counts observed in the study with maximum at Week 4 that were resolving on treatment and returned to baseline by 4 weeks after end of treatment. No subject had an AE related to sequelae from reduced platelet count (ie, bruising or bleeding). One PF-04965842 treated subject, in the 200 mg group, had a platelet count that reached the discontinuation criterion of <75,000/mm^3. This subject, a 63 year-old female subject, with a history of alcohol abuse and smoking had baseline platelets of 261,000/mm3 and reached a maximum of 36,000/mm^3 on Day 28. AEs of leukopenia and neutropenia were also reported in this subject. AEs on platelet counts in subjects receiving PF-04965842 will be of particular safety concern and a focus of laboratory monitoring in future clinical trials.

b. Include any additional relevant information. Consider the following in your response:

The Division has received several JAK1 inhibitors under development for treatment of AD, requesting for Breakthrough Therapy Designation.

Difference in treatment effect (vs point estimates), when comparing PF-04965842, upadacitinib, to dupilumab monotherapy trials:

***Treatment Effect IGA:** ~38.2% PF-04965842, ~48% upadacitinib, ~28% dupilumab mono*

Keeping in mind caveats for cross study comparisons (small study, cross-study comparison, inclusion critera, patient populations, and disease assessments, etc.,). The evidence show that this product has some advantages over the currently approved systemic therapy, Dupilumab, in effiacay and route of administration (oral).

Safety in the JAK1 selective inhibitors are still not fully evaluated in large controlled trials.

It is this reviewer's opinion, there is sufficient preliminary clinical evidenceto grant Breakthrough Therapy Designation for product PF-04965842 in the treatment of moderate to severe atopic dermatitis in adults.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

The sponsor has provided preliminary evidence that upadacitinib for the systemic treatment of moderate to severe atopic dermatitis in adults meets the criteria for Breakthrough Therapy Designation in one or more clinically appropriate endpoint(s). The evidence from the Phase 2, dose-ranging study demonstrates that PF-04965842 provides some advantages over current systemic treatment options with acceptable safety margins.

This reviewer and the Division recommends granting PF-04965842 Breakthrough Therapy Designation.

☐DENY:

Provide brief summary of rationale for denial:

12. Division's next steps and sponsor's plan for future development:

The Division will continue to work closely with the Pfizer to develop PF-04965842 for the treatment of moderate to severe atopic dermatitis. The next steps will be to identify the proper dosing regimen for later phase trials and to develop a clinical plan for children and adolescents. The Division is currently reviewing the Phase 3 clinical trials for this product.

13. List references, if any:

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/17/17/M. Raggio

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

/s/

GARY T CHIANG
01/31/2018

DAVID L KETTL
01/31/2018

KENDALL A MARCUS
01/31/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 123554

MEETING MINUTES

Pfizer, Inc.
Attention: Jennifer Weissert, PhD
Senior Manager, Worldwide Safety and Regulatory
300 Technology Square, 3rd Floor
Cambridge, MA 02139

Dear Dr. Weissert:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-04965842 tablets, 100 mg and 200 mg.

We also refer to the End of Phase 2 meeting between representatives of your firm and the FDA on October 30, 2017. The purpose of the meeting was to discuss the development program for PF-04965842 tablets for the treatment of atopic dermatitis.

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 Barbara Gould, Chief, Project Management Staff at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minute
Pfizer Comment to FDA Preliminary Response
Pfizer Powerpoint Presentation

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 30, 2017 at 8:30 AM EDT
Meeting Location:	White Oak Campus and *Videoconference
Application Number:	IND 123554
Product Name:	PF-04965842 tablets, 100 mg and 200 mg
Proposed Indication:	For the treatment of atopic dermatitis
Sponsor Name:	Pfizer, Inc.
Meeting Chair:	Kendall Marcus, MD
Meeting Recorder:	Barbara Gould

FDA ATTENDEES
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
David Kettl, MD, Clinical Team Leader, DDDP
Gary Chiang, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jiaqin Yao, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biometrics III
Carin Kim, PhD, Biostatistics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DPC) III
Jihye Ahn, PharmD, MS, Clinical Pharmacology Reviewer, DCP III
Frederick Burnett, PhD, Product Quality Reviewer, Office of New Drug Product, Office of Product Quality (ONDP, OPQ)
Selena Daniels, PharmD, MS, Team Leader, Clinical Outcomes Assessment (COA)
Jing (Julie) Ju, PhD, Clinical Outcomes Assessment Reviewer
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

SPONSOR ATTENDEES
Christopher Banfield, PhD, Clinical Pharmacology
Christopher Voegeli, PharmD, Asset Team Lead
Douglas Ball, MS, Drug Safety Regulatory Strategy Lead
Jean Beebe, PhD, Development Team Lead
F. Owen Fields, PhD, Regulatory Therapy Area Lead
Gene Wallenstein, PhD, Patient Reported Outcomes

Jennifer Weissert, PhD, Regulatory Lead
Linda Chen, MPH, MPhil, Patient Reported Outcomes
Martin Dowty, PhD, Pharmacokinetics, Dynamics, and Metabolism
Michael Brown, PhD, Clinical Statistics
Michael Corbo, PhD, Chief Development Officer
Pankaj Gupta, PhD, Clinical Pharmacology
Pinaki Biswas, PhD, Clinical Statistics
Susan Johnson, MS, MD, Safety Risk Lead
Thomas Stock, DO, Clinical Development Therapeutic Area Lead
Tim Crook, MD, Clinical Therapeutic Area Lead
Zaher Radi, DVM, PhD Drug Safety Team Lead

1.0 BACKGROUND

Purpose

The purpose of this meeting is to discuss the development program for PF-04965842 for the treatment of AD.

Regulatory Correspondence History:

We have sent the following correspondence:

- 12/15/2014 Study May Proceed Letter
- 04/11/2016 Advice Letter
- 08/18/2017 Special Protocol Assessment – Request Denied (Carcinogenicity)
- 10/04/2017 Special Protocol – Agreement (Carcinogenicity)

2. DISCUSSION

2.1. Regulatory

Question 21:
Does the Agency agree that PF-04965842 for the treatment of moderate to severe AD could potentially be eligible for Breakthrough Therapy Designation based on the Phase 2b B7451006 clinical study results showing the rapid onset of pruritus relief +compared with placebo?

FDA Response to Question 21:
Yes, the Agency agrees that your drug product is potentially eligible for Breakthrough Therapy Designation. Submit your request and the Agency will review whether the BTD request submission addresses Section 506(a) of the FD&C Act, as added by section 902 of FDASIA, to support the case for BTD within 60 days of submission. The sponsor is referred to guidance for industry, *Expedited Programs for Serious Condition –Drugs and Biologics*. A Breakthrough Therapy Designation (BTD) may be granted "If a drug is intended, alone or

in combination with 1 or more drugs, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development."

2.2. Nonclinical

Question 1:
The Sponsor has completed nonclinical toxicity studies up to 9-months in duration and is planning to conduct additional nonclinical studies in accordance with ICH M3. The completed toxicity studies support clinical trials in adolescents and adults (≥12 years old) (b) (4) The planned carcinogenicity program is to be conducted as well, and these studies will be the subject of separate consultation with Agencies, as per regulatory guidance.

Does the Agency agree that the completed, ongoing, and planned nonclinical studies constitute a complete nonclinical safety program that (pending review of planned studies) should (subject to further consultation on the carcinogenicity program) support future registration in adults, adolescents, and children 6 months of age and above with atopic dermatitis?

FDA Response to Question 1:
Your completed, ongoing and planned nonclinical studies appear reasonable to support submission of an NDA for your drug product. However, the adequacy of the nonclinical data will be determined after review of the study reports.

Submit the full study report for the proposed juvenile animal toxicity study to the IND for review prior to initiation of clinical studies in pediatric subjects less than 12 years.

2.3. Clinical Pharmacology

Question 13:
Does the Agency agree that the completed and proposed clinical pharmacology development plan is adequate to characterize the clinical pharmacology of PF-04965842 to support future registration?

FDA Response to Question 13:
We note that in vitro studies indicated an induction potential of PF-04965842 on CYP2B6 and you should assess the need for additional in vivo assessment. We recommend you to adequately address the drug interaction potential in your NDA based on the criteria described in guidance for industry: *Drug interaction studies – study design, data analysis, implications for dosing, and labeling recommendations*. Any changes in formulation might need additional studies. The adequacy of clinical pharmacology data of your product will be a review issue.

2.4. Clinical/Biostatistics/Clinical Outcomes Assessment

Question 2:
Based on the totality of efficacy, safety, and pharmacokinetic (PK) data available from the completed clinical studies, does the Agency agree with the selected dose(s) and dose regimen(s) to be evaluated in the Phase 3 clinical development program?

FDA Response to Question 2:
Your dose-response data in Phase 2 study appears to be supportive of your proposed doses of 100 mg QD and 200 mg QD.

Clarify the inconsistency in your meeting package, as you stated the assessment of (b) (4) (b) (4) the 200 mg QD of PF-0498542. Confirm that the planned doses in your trials will be 100 mg QD and 200 mg QD.

Question 3:
Does the Agency agree with the study design for the proposed pivotal Phase 3 Studies B7451012 and B7451013?

Specifically, the Sponsor requests feedback on the following questions:

a. Does the Agency agree with the following inclusion criteria: requiring patients to have a clinical diagnosis of AD for at least 1 year based on the Hanifin & Rajka diagnostic criteria for AD, confirmed at time of screening; moderate to severe AD (defined as affected body surface area [BSA] ≥10%, IGA ≥3, and EASI ≥12); and have had an inadequate response to topical medications given for at least 4 weeks or for whom topical treatments are not appropriate within 12 months of study start, or who have required systemic therapies for control of their disease?

b. Does the Agency agree with the proposed co-primary endpoints to demonstrate the efficacy of PF-04965842 treatment in moderate to severe AD patients:

    i. Subjects achieving both IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 12.

    ii. Subjects achieving EASI75 (≥75% improvement from baseline) at Week 12.

c. Does the Agency agree with the patient reported Pruritus Numeric Rating Scale (Pruritus NRS) as a key secondary endpoint in studies B7451012 and B7451013?

    i. Does the Agency agree that the Pruritus NRS is a valid and accepted measure to assess pruritus in AD patients?

    ii. Does the Agency agree that a 4 point or greater improvement in Pruritus NRS from baseline at Weeks 2, 4 and 12 will demonstrate a clinically meaningful improvement in pruritus?

d. Does the Agency agree that the 12-week duration of treatment and 4-week follow-up periods in the proposed studies are sufficient to demonstrate the clinical profile of PF-04965842 in a monotherapy setting?

e. Does the Agency agree with the statistical analysis plans for B7451012 and B7451013 as described? Specifically, does the Agency agree with the use of the stepdown closed testing procedure for Type-I error control for testing the primary endpoint and the key secondary endpoints?

FDA Response to Question 3:

a. The recommended moderate to severe AD criteria at the time of screening are subjects with chronic AD with ≥ 10% body surface area (BSA), a score of ≥ 3 on the Investigator's Global Assessment (IGA), and a score on the Eczema Area Severity Index (EASI) of ≥ 16; average score for maximum (peak) itch intensity ≥ 4 on the Pruritus Numerical Rating Scale (NRS), and documented history of an inadequate response to (or medically inadvisable to use) topical treatment.

   The study designs proposed are generally acceptable based on the brief summary of the Phase 3 clinical trials, B7451012 and B7451013, in the briefing document. Full protocols should be submitted to the Agency for review and further recommendation.

b. Your proposed co-primary endpoints are acceptable for your Phase 3 clinical trials.

c. See FDA Response to Question 3a regarding the enrollment criterion concerning the maximum (peak) pruritus NRS.

   In general, the absolute change from baseline in the pruritus NRS score is acceptable as an endpoint.

   A single 11-point NRS, in principle, is acceptable to assess pruritus severity at its worst in patients with atopic dermatitis. The endpoint on the NRS should demonstrate a clinically meaningful change in pruritus for the target population, and a four-point or greater change on the NRS may be clinically meaningful.

   The sponsor should submit a copy of the proposed assessment with item stem and instructions, to ensure the scale design is appropriate. The proposed recall period of over the past 24 hours appears to be reasonable. However, more details are needed on scoring (i.e., how will the score be computed, e.g., daily score, weekly score, monthly score?)

   Note that studies B745112/3 indicates that patients will complete the pruritus NRS (b) (4) whereas in study B7451029 patients will complete the pruritus NRS (b) (4) Please clarify the rationale for having different frequency of assessments for the two trials.

Typically, the attribute of frequency (e.g., itch frequency) is rated on a verbal rating scale and not an NRS. Provide evidence to support that patients understand and interpret the use of an NRS to rate their pruritus frequency.

d. Yes.

e. For your two Phase 3 monotherapy trials, you plan to randomize subjects in a 2:2:1 ratio to PF-04965842 200 mg, 100 mg and placebo arms. You proposed that randomization will be stratified by IGA disease severity and age group (<18 vs. ≥18). We recommend that you further examine your Phase 2 data to investigate background factors that may impact the treatment effect, and consider such background factors, if any, as additional stratification factors in your Phase 3 trials as such factors may help interpret your clinical trial findings in determining whether a certain dose is appropriate for certain subpopulation(s).

Your proposed multiplicity control method for Type I error rate appears reasonable; however, we recommend that you consider a logical ordering of endpoints so that the endpoints within the same dose are tested before testing the endpoints for the other dose.

While your protocol outlines listed 3 key secondary endpoints along with several secondary endpoints including the percent change in EASI, BSA, PO SCOring Atopic Dermatitis (PO SCORAD) and SCORAD endpoints, your figure illustrating the sequence of testing on page 37 includes the co-primary, the three key secondary endpoints as well as the "PSAAD CF8" endpoints. Note that secondary endpoints (b) (4) should be clinically relevant, limited in number, and adjusted for multiplicity. Whether or not your "PSAAD CF8" endpoints are clinically relevant cannot be assessed without full detailed description about its clinical utility. It should be noted that your protocol outlines listed the co-primary endpoints as secondary endpoints (#4 and #5).

Question 4

Does the Agency agree with the study design for the proposed pivotal Phase 3 Study B7451014?

Specifically, the Sponsor requests feedback on the following questions:

a. Does the Agency agree with the definition of responders to be randomized to one of the two doses of PF-04965842 or placebo?

b. Does the Agency agree with the proposed primary efficacy endpoint for the study of "time to flare" with particular reference to the definition of flare?

c. Does the Agency agree with the proposed plan for a single course of flare rescue treatment?

d. Does the Agency agree [redacted]

e. Does the Agency agree that the proposed study design and duration is adequate for demonstrating the potential value of [redacted] dosing regimens [redacted] and informing final approved labeling?

f. Does the Agency agree with the statistical analysis plans for B7451014 as described? Specifically, does the Agency agree with the use of the step-down closed testing procedure for Type-I error control for testing the primary endpoint?

FDA Response to Question 4:

a. For randomization of the responders into the withdrawal period, you defined you are encouraged to consider subjects that are responders on both co-primary endpoints.

b. As with responders being based on both co-primary endpoints, the Agency recommends that flare/worsening be defined on the same primary efficacy endpoints (i.e., both the IGA as well as EASI). The Agency considers the definition of flare to be a complement of the IGA and EASI 75 success definition (i.e., IGA≥2 with at least 2-grade worsening. As for the criterion for flare based on the EASI 75 endpoint you should consider the change on EASI 75 which corresponds to a 2-grade improvement on the IGA and consider the magnitude of improvement as a criterion for flare on the EASI score.

Meeting Discussion:

The sponsor submitted a clarification for their proposed definition of loss of response based on the EASI score (see sponsor attachment). In response, the Agency reiterated the comment that loss of response should be defined as at least 2 grade worsening on the IGA. The sponsor is encouraged to examine data from their Phase 2 trial to define a threshold level for the EASI score for loss of response which corresponds to 2 grade worsening of the IGA.

c. Your plan to provide single rescue treatment of 200 mg QD of PF-0495842 for 12 weeks with or without topical therapy (per local standard of care) is acceptable. However, it is not clear whether your goal is to establish efficacy of your product with topical therapy, as the use of rescue therapy does not enable assessment of efficacy in this regard. For interpretation of study findings, we recommend that you document the use of rescue treatment (i.e., type of rescue therapies, length, frequency, amount of use, etc.).

d. [redacted] The utility [redacted] will be a review issue.

Meeting Discussion:

The Agency clarified that the proposed study design [redacted]

[redacted] The sponsor may make [redacted] and power their trial sufficiently for such comparison.

The sponsor provided another concept for such a trial (see attached sponsor document). The Agency replied that this concept might be acceptable in principle, but the detailed protocol would need to be submitted for review.

e. You only provided a protocol outline which makes it difficult to be able to provide any concurrence or detailed comments regarding your plan for [redacted] dosing regimens. In general, for assessing the duration of treatment effect, a comparison of responders based on the IGA success or EASI 75 should be made. Interpretation of study findings against placebo after establishing a treatment effect at the primary time point would not be meaningful. Taking into account that subjects randomized to placebo during the maintenance period are expected to "lose their response" at a certain time point during the maintenance period, all that would be needed to maintain a statistically significant difference is a small proportion to remain a success.

f. See FDA Response to Question 4b for the definition of flare and see Response to Question 4e concerning the comparison of maintenance response against the placebo. Note that all subjects will receive 200 mg in the run-in period, and in the case that only the PF-04965842 100 mg is approved, the results from this trial may have limited utility if there are thought to be underlying factors that might impact the maintenance of responses.

Question 5

Does the Agency agree with the overall design of the additional Phase 3 Study B7451029?

Specifically, the Sponsor requests feedback on the following questions:

a. Does the Agency agree that the proposed study design, a 3-arm randomized active comparator (dupilumab) and placebo-controlled double blind study, meets the aims and objectives of this study?

b. Does the Agency agree that the proposed primary efficacy endpoint for the study "proportion of patients achieving a 4 point or greater improvement in pruritus NRS score" from baseline at Week 4 is appropriate to demonstrate a clinically meaningful effect in the early onset of pruritus relief?

c. Does the Agency agree with the proposed key secondary endpoints for the study?

    i. Proportion of patients with both IGA of clear (0) or almost clear (1) (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 12 and/or

Proportion of patients with EASI75 (≥75% improvement from baseline) at Week 12

ii. Proportion of patients achieving a 4 point or greater improvement in pruritus NRS score from baseline at Week 2 and at Week 12

d. Does the Agency agree that the data from the primary and key secondary endpoints from the proposed comparator study would support the inclusion both PF-04965842 and dupilumab in the clinical trials experience section of the label?

e. Does the Agency agree with the blinding plan for this study?

f. Does the Agency agree with the statistical analysis plans for B7451029 as described? Specifically, does the Agency agree with the use of the step-down closed testing procedure for Type-I error control for testing the primary endpoint and the key secondary endpoints? The efficacy comparison of each active arm will be assessed separately with placebo, and no formal comparison will be performed between the 2 active arms. Safety will be assessed for contextualization only.

FDA Response to Question 5:

a. You may complete this active comparator trial as long as dupilumab is used as labeled; however, the utility of this data in labeling will be a review issue. In general, an active comparator trial is not required for marketing approval of your drug product for moderate-severe atopic dermatitis. You stated that there will be no head to head comparison of the active treatments, and that you plan to use "descriptive measures only". There is no utility in testing dupilumab vs placebo. For a comparative marketing claim against dupilumab, you will need to conduct formal testing of endpoints that are prespecified in the protocol. Furthermore, as the treatment duration is different for dupilumab (16 weeks), comparison should be made at both Weeks 12 and 16. While you may assess the pruritus endpoint, the co-primary endpoints should also be assessed. For a superiority claim, generally, results from 2 Phase 3 trials are needed. Note that in the case that only the PF-04965842 100 mg dose is approved, then the results from this trial may have limited utility.

   The Agency agrees that pruritus is a very important factor in the treatment of atopic dermatitis. However, pruritus is only one factor in the clinical spectrum of atopic dermatitis and may not represent meaningful improvement in the treatment of the disease itself. Whether your drug product demonstrates effective pruritus relief over an approved comparator remains to be determined.

b. See FDA Response to Question 5a.

c. Comparative claims not supported by formal statistical testing are generally not described in labeling.

Inclusion of any PRO data in the product label will be a review issue and will depend on the strengths and limitations of the PRO instrument; clinical trial design and conduct; adequacy of the data submitted; statistical significance; and clinical meaningfulness of the PRO results.

d. As you stated that there will be no head to head comparison of the active treatments, and that you plan to use "descriptive measures only", the utility of testing the dupilumab vs placebo is not clear. Furthermore, the goal of your proposed double dummy design is not clear.

e. Secondary endpoints intended for labeling should be clinically relevant, limited in number, and adjusted for multiplicity. While your proposal to sequentially test the endpoints is reasonable, whether or not your secondary endpoints are clinically relevant would require clinical judgement. For example, while EASI 75 endpoint is based on a prespecified threshold level which can be considered to be clinical meaningful, a mere percent change in the EASI score might not translate to a clinically meaningful difference. Since it is unclear as to the objective of your active comparator design, the Agency cannot comment on the appropriateness of your secondary endpoints in this trial.

Question 6:

Does the Agency agree with the overall design of the long term extension Phase 3 Study B7451015?

Specifically, the Sponsor requests feedback on the following questions:

a. Does the Agency agree that the proposed study design, a 2 arm randomized double blind study, is adequate considering the objectives of this study?

b. Does the Agency agree [redacted] (b) (4) based upon the safety criteria?

c. Does the Agency agree with the use of topical therapies in combination with active therapy?

d. Does the Agency agree that the proposed study design and duration is adequate for demonstrating the durability of effect and safety alone and in combination with standard of care using different doses (200 mg and 100 mg)?

FDA Response to Question 6:

a. You propose to conduct a long-term extension study (B7451015) for durability of response as well as the initial response in subjects transitioning from placebo or active comparator rolled over from parent Phase 3 studies. Subjects receiving active drug during the parent study will be randomized to the same dose level of active drug as in the parent study. Subjects randomized to placebo or active comparator will be

randomized to 100 mg or 200 mg. In general, your study appears to provide descriptive efficacy on long-term maintenance as well as long term safety data.

b. The method in which [redacted] (b) (4) occurs in your clinical trial needs to be clear in your protocol. [redacted] (b) (4)

c. See FDA Response Question 4d.

d. Your proposed duration of this study is acceptable.

Question 7:
Does the Agency agree that the projected safety database of AD subjects from the proposed Phase 3 program provides sufficient evidence to support future registration of the proposed indication?

FDA Response to Question 7:
Yes. It appears that you have described a sufficient safety database in your proposed Phase 3 clinical development plans for your drug product.

Question 8:
Does the Agency agree with the proposed safety assessments and safety monitoring plans in the proposed Phase 3 trials?

FDA Response to Question 8:
In general, the summary of your proposed clinical studies appears to have sufficient safety monitoring. However, your non-clinical monkey studies revealed specific safety signals that require safety monitoring in your Phase 3 clinical trials; specifically, tachycardia and hypotension in the immediate to intermediate post-dose administration period. The Agency recommends that you propose timely targeted cardiac and blood pressure monitoring in your Phase 3 clinical trials to assess these clinical parameters before and after dose administration.

Meeting Discussion:
The sponsor stated that the nonclinical safety data showed hypertension rather than hypotension. The Agency recommended cardiac monitoring post dose in all Phase 3 clinical trials. In addition, the Agency recommended cardiac monitoring in subjects under 45 kg in pediatric trials. The Agency requested that the sponsor submit summary data of blood pressure and heart rate collected in Phase 1 and 2 clinical trials. Phase 3 cardiac monitoring should be consistent with the level of safety concern.

The Agency noted that the sponsor still needed to address ICH-E14 issues including QT assessments.

Question 9:
Does the Agency agree that the Phase 3 program as designed, and contingent upon the results being supportive, could support the following posology statement:

(b) (4)

FDA Response to Question 9:

In general, indications are granted for the treatment of a disease or condition. (b) (4)
(b) (4)
The duration of treatment studied in clinical trials would be described in Section 14 Clinical Studies, and dosage regimens in Section 2 Dosage and Administration. Whether your trials will provide data that merit inclusion in labeling will be a review issue. We may have further comments upon review of the full protocols.

(b) (4)
However, your clinical program for PF04965842 may provide supportive data for maintenance and retreatment of atopic dermatitis.

See FDA Response to Question 4d regarding adjunctive therapy with topical agents.

Question 10:

Does the Agency agree with the inclusion of the (b) (4) claim in the proposed indication statement and within the clinical data section of the label?

FDA Response to Question 10:

See FDA Response to Question 5b. In addition to the establishing efficacy for this endpoint based on formal statistical testing, the improvement in the NRS may be represented in the Clinical data section 14 of the label.

Question 11:

Does the Agency agree (b) (4)
as part of the proposed indication?

FDA Response to Question 11:

The (b) (4) does not support an indication. (b) (4)

Question 12:
Does the Agency agree [redacted] (b) (4)

[redacted] (b) (4)

FDA Response to Question 12:
See FDA Response to Questions 4, 10 and 11.

Question 14:
The Sponsor is developing and validating an AD daily symptom diary as an eDiary to measure the change in severity of signs and symptoms of AD resulting from treatment. Eleven signs and symptoms of disease have been specified through qualitative research with AD patients. This eDiary is a PRO instrument developed in accordance with the specific guidance and methods provided in regulatory documents published by the FDA (2009) and EMA (2005) and also follows regulatory guidance on electronic data capture in clinical trials.

a. Does the Agency consider use of this patient-reported daily eDiary, currently being developed and validated in AD patients, to be an acceptable approach to measure outcomes and provide evidence for improvement in AD signs and symptoms?

b. Does the Agency find acceptable the Sponsors plan to include the AD symptom eDiary in the pivotal Phase 3 studies B7451012 and B7451013, implemented as a secondary endpoint (without multiplicity adjustment) in the US and an EU country to provide adequate evidence to support additional signs and symptoms claims, if data results are positive, to be included in the clinical data section of the label?

FDA Response to Question 14:
a. While the use of a daily eDiary appears to be a reasonable approach to collect data for the context of this drug development program, we have insufficient information to comment on the acceptability of the instrument. You will need to provide an exact copy of the tool and evidence to support its content validity and other measurement properties for review. Because you are using an electronic device, we recommend you implement reminder or alarm functions when feasible, as this tends to minimize missing data and allows collection of other important information (e.g., timestamps for data input), as well as a back-plan (e.g., paper, web-based) in the case there are any malfunctions with the devices. You may refer to the FDA Guidance for Industry on electronic source data.[1]

[1] Guidance for Industry: Electronic Source Data in Clinical Investigations (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf)

b. See FDA Response to Questions 14a and 15b.

Question 15:

Anxiety, depression, and psychosocial stress are discussed prominently in the scientific peer-reviewed literature in relation to AD and its negative impact on quality of life and psychosocial well-being.

Does the Agency agree [redacted] (b) (4)

Given these plans, the Sponsor requests feedback on the following questions:

a. Does the Agency consider HADS as a valid PRO instrument to detect states of anxiety and depression in AD patients?

b. Does the Agency consider SF-36 v.2 Acute a valid and accepted generic measure to assess [redacted] (b) (4) in AD patients?

FDA Response to Question 15:

a. Anxiety and depression are concepts secondary to the disease(s) under investigation and might be influenced by other factors beyond the treatment, and consequently may be insensitive to treatment effect. These concepts may be difficult to measure especially if the patients are not experiencing these symptoms at baseline. Additionally, it is unclear whether your product may positively or negatively impact these concepts, or both positively and negatively impact these concepts. Because of these challenges, we recommend that you measure these concepts for exploratory purposes. If you choose to elevate HADS as a higher endpoint in your clinical trials, we recommend that you submit information to support its content validity and psychometric performance in this context of use for FDA review.

b. You propose to use SF-36 v.2 [redacted] (b) (4) however, the SF-36v.2 is a generic measure of health status.

[redacted] (b) (4) we recommend that you use an instrument that measures the patient's general perception of the effect of both illness (e.g. atopic dermatitis) and treatment on physical, psychological, and social aspects of life.

You are proposing [redacted] (b) (4) Note that positive findings require formal hypothesis testing of appropriate endpoints that are agreed upon with the Agency, and appropriately adjusted for multiplicity. See FDA Response to Question 3e.

Question 16:
Does the Agency agree that inclusion of adolescents (≥12-<18 years old) in the Phase 3 studies is appropriate [redacted] (b) (4)

FDA Response to Question 16:
Your proposals to include a 20 adolescent PK sub-study in subject's ≥12 to <18 years old, in your initial Phase 3 (B7451012) clinical trial to confirm the dose-concentration relationship compared to adults is acceptable. Provided that the PK data is consistent in adolescent and adult subjects, you may enroll adolescents (≥12-<18 years old) in your Phase 3 atopic dermatitis clinical trials. [redacted] (b) (4)

Question 17:
The Dermatology Quality of Life Index (DLQI), Patient Oriented Eczema Measure (POEM), and HADS have versions validated for adolescents.

Does the Agency consider these adolescent versions as acceptable patient-reported measures to include in the Phase 3 program [redacted] (b) (4)

FDA Response to Question 17:
There is insufficient information to comment fully on the DLQI, POEM and HADS due to the limited information provided on their development in the target population and planned COA endpoint strategy.

To provide a more concrete recommendation, we recommend you submit the following for review:

- General analysis plans
- Evidence of content validity (e.g., qualitative research with patients and/or caregivers; expert clinicians) and other psychometric properties established for this specific context of use
- Exact copies of the instruments
- Scoring information
- Training/user manuals

Additionally, it will be important to understand how to interpret score changes in the proposed measures and what constitutes meaningful change in these instruments.

In regards to [redacted] (b) (4) Refer to FDA Response to Question 15b.

It is at your discretion to proceed with the use of these instruments. (b) (4) (b) (4)

Question 18:
Does the Agency agree (b) (4)

The Sponsor intends to request a deferral (b) (4) In addition, the Sponsor intends to request a waiver to assess PF-04965842 in children <6 months of age. Does the Agency agree with this proposal?

FDA Response to Question 18:
Your pediatric proposal and requested waivers will be reviewed by the Agency at the time of submission of your Initial Pediatric Study Plan (iPSP). 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.

Your proposed studies include patients (b) (4) An observer-reported outcome would be necessary to measure observable signs and behaviors present in this condition (e.g., scratching) (b) (4) The sponsor should propose an age cut-off for PRO assessment(s), as well as provide evidence to support the minimum age at which children can self-report reliably.

Considerations specific to pediatric populations should be taken into account when selecting an appropriate clinical outcome assessment, including: 1) selecting a well-defined and reliable instrument(s) that is developmentally appropriate for the entire age range included in your clinical trial population; and 2) using an instrument that is content and psychometrically valid for assessment in the patient population of interest. You may refer to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force paper for further clarification on pediatric clinical outcome assessment considerations (https://www.ispor.org/workpaper/PROchildrenadolescents/Matza_et_al_2013_ISPOR_Task_Force_PROs_in_Children.pdf).

Question 19:
Does the Agency agree (b) (4)

FDA Response to Question 19:
See FDA Response to Question 18 for your iPSP submission.

Question 20:

Does the Agency agree [redacted] (b) (4)

FDA Response to Question 20:
See FDA Response to Question 18.

Corrigendum:
Your proposal of defining flare as an IGA score of 2 or greater is reasonable, however for defining flare based on EASI score you are encouraged to examine the data from your Phase 2 trial and propose a threshold level on such scale that corresponds to at least one grade change on the IGA.

3.0 ADMINISTRATIVE 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* 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.

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.

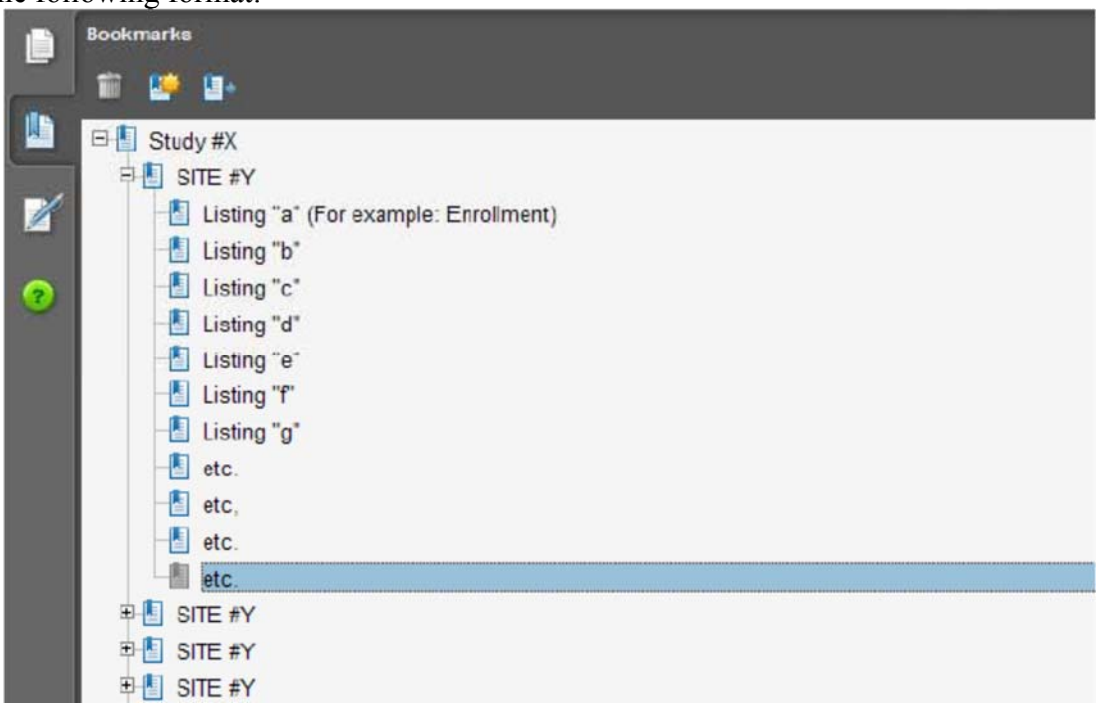
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere 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[2]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

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

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

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.

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

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

4.0 ATTACHMENTS AND HANDOUTS

The sponsor provided the appendix powerpoint presentation and points of clarification embedded in the FDA preliminary response document for the questions submitted in the September 06, 2017 meeting package.

8 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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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/

KENDALL A MARCUS
11/14/2017