CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215830Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 131503

MEETING MINUTES

Pfizer, Inc.
Attention: Mark J. Evans, PhD
Pfizer Global Regulatory Affairs
500 Arcola Road
Collegeville, PA 19426

Dear Dr. Evans:

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

We also refer to the teleconference between representatives of your firm and the FDA on June 14, 2021. The purpose of the meeting was to discuss the development program for ritlecitinib.

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

If you have any questions, call Jennifer Harmon, Regulatory Project Manager at 240-402-4880.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's Meeting Agenda

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 14, 2021, 9:30 – 10:30 a.m. EDT

Meeting Location: Teleconference

Application Number: IND 131503
Product Name: ritlecitinib immediate release tablets, [redacted] (b) (4) 50mg

Proposed Indication: Treatment of adult and adolescent patients with alopecia areata (AA) [redacted] (b) (4)

Sponsor Name: Pfizer, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Kendall A. Marcus
Meeting Recorder: Jennifer Harmon

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
David Kettl, MD, FAAP, Clinical Team Leader, DDD
Hamid Tabatabai, MD, Clinical Reviewer, DDD
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics III
Marilena Flouri, PhD, Biometrics Reviewer, DB III
Hamid Shafiei, PhD, Quality Assessment Lead, DNDP II, NDPB V
Katherine Duncan, PhD, Product Quality Assessor, OPQ/ONDP/DNDAPI/Branch II
CDR Renmeet Grewal, PharmD, MS, RAC, Director, Project Management Staff, Division of Regulatory Operations for Immunology and Inflammation (DRO – II)
Jennifer Harmon, PharmD, Regulatory Health Project Manager, Division of Regulatory Operations for Dermatology and Dentistry (DRO – DD)

SPONSOR ATTENDEES

Susan Anway, Safety Risk Lead
Julia Claus, Global CMC Team Lead
Annette Diehl, Clinician
Heather Dowty, Nonclinical Drug Safety Team Lead
Mark Evans, Regulatory Lead
Rana Fayyad, Clinical Statistics Lead
Owen Fields, VP Regulatory Affairs

Amy Freyman, Lead Clinician
Dayo Jagun, Global Medical Epidemiology
Nabila Marshall, Portfolio Lead Regulatory Affairs
Yea Min Huh, Clinical Pharmacology Lead
Vivek Purohit, Clinical Pharmacology Lead
Annette Silvia, Safety Risk Lead
Jean-Baptiste Telliez, Research & Development
Dalia Wajsbrot, Clinical Statistics Lead
Martina Wallace, Global CMC Lead
Robert Wolk, Clinical Lead
Samuel Zwillich, Medicine Team Lead

1.0 BACKGROUND

The purpose of the meeting is to discuss the development program for ritlecitinib for the treatment of adult and adolescent patients with alopecia areata (AA) (b) (4)

FDA sent Preliminary Comments to Pfizer, Inc. on June 10, 2021.

Regulatory History:

We have had the following meetings/teleconferences with you:

- November 4, 2020 – Guidance Meeting
- April 8, 2020 – Guidance Meeting
- March 11, 2019 – MIDD Paired Meeting
- December 19, 2018 – MIDD Paired Meeting
- August 8, 2018 – End of Phase 2 Meeting
- August 6, 2018 – Guidance Meeting
- March 14, 2018 – Guidance Meeting
- September 10, 2014 – Pre-IND

We have sent the following correspondences:

- March 10, 2021 – Agreed Initial Pediatric Study Plan
- August 11, 2020 – Advice Letter
- August 14, 2019 – Advice Letter
- July 30, 2019 – Advice Letter
- April 17, 2019 – Special Protocol Agreement
- November 5, 2018 – Grant Breakthrough Therapy Designation Request
- August 23, 2018 – Advice Letter
- April 4, 2018 – Special Protocol Agreement
- December 15, 2016 – Study May Proceed

Coronavirus 19 (COVID-19) Clinical Trial Guidance:
During the COVID-19 pandemic, ensuring the safety of trial participants is paramount. Sponsors should consider each circumstance, focus on the potential impact on the safety of trial participants, and modify study conduct accordingly. It is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them, and that the Agency is appropriately informed of these changes. Refer to the *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*. We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

2.0 DISCUSSION

2.1. Regulatory

There were no regulatory questions submitted.

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 1: Stability Package
The Sponsor proposes to provide drug product (DP) registration stability data through 12 months at the time of the initial NDA submission and to submit 18-month DP stability data during the review period (within 90 days of the initial NDA submission). An initial shelf life in accordance with ICH Q1E guidelines will be proposed. Does the Agency agree the proposed strategy is acceptable and will not extend the regulatory review period?

FDA Response to Question 1:
Yes, we agree if this is designated as a priority application. Your strategy for submission of the stability data appears reasonable. However, the expiration dating period (shelf-life) for your drug product will be determined during the review of your NDA.

Alternatively, if your application is not granted a priority review, all stability data intended for use in the determination of drug product expiration dating period (shelf-life) should be submitted to the application within 30 days from original date of the submission of your NDA.

Meeting Comments:
The Sponsor asked for clarification of stability information required at the time of submission during a standard review. The Agency stated that applications should be complete at the time of submission, but that additional stability data submitted within the first 30 days for determination of the expiration dating period of the drug product will be reviewed.

2.3. Nonclinical

Question 2: Nonclinical Package

Does the Agency concur that the nonclinical package, as summarized in this briefing document, adequately supports the NDA submission review for the registration of ritlecitinib in adult and adolescent AA patients 12 years of age and above?

FDA Response to Question 2:

The pivotal nonclinical studies conducted with ritlecitinib include a 6-month oral rat toxicity study, two 9-month oral dog toxicity studies, a complete battery of safety pharmacology studies, a complete battery of genotoxicity studies, a complete battery of reproductive toxicity studies (i.e., oral fertility study in rats, oral embryofetal and development studies in rats and rabbits and oral pre- and post-natal development study in rats), an oral rat carcinogenicity study and an oral transgenic mouse carcinogenicity study. We agree that the nonclinical studies conducted with ritlecitinib support submission of an NDA for adult and adolescent AA patients 12 years and older. The adequacy of the conducted nonclinical studies will be determined during the NDA review.

In addition to the SEND datasets for the two carcinogenicity studies, we request that you submit the SAS tumor data sets (tumor.xpt) for each carcinogenicity study in your NDA submission. This will allow for conduct of the statistical review for the two carcinogenicity studies. Follow the attached standard format for preparing the data.

Table 1: FDA Biostatistics Data Format Sheet

Tumor Dataset For Statistical Analysis[1,2] (tumor.xpt)				
Variable	**Label**	**Type**	**Codes**	**Comments**
STUDYNUM	Study number	char		[3]
ANIMLNUM	Animal number	char		[1,3]
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3, 4,... in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		[3,4]
TUMORNAM	Tumor name	char		[3,4]

ORGANCOD	Organ/tissue code	char		[3,5]
ORGANNAM	Organ/tissue name	char		[3,5]
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	[4]
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	[4]
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

[1] Each animal in the study should have at least one record even if it does not have a tumor.
[2] Additional variables, as appropriate, can be added to the bottom of this dataset.
[3] ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.
[4] A missing value should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD when the organ is unusable or not examined.
[5] Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

2.4. Clinical Pharmacology

Question 3: Clinical Pharmacology and Biopharmaceutics Package
Does the Agency concur that the completed and ongoing clinical studies to be submitted as part of the NDA are adequate to support the clinical pharmacology and biopharmaceutics review of the NDA?

FDA Response to Question 3:
Your clinical pharmacology studies and MIDD plan appear reasonable at this time. However, the adequacy of your studies and MIDD analysis will be a review issue at the time of NDA submission. We note that your clinical studies were conducted with tablet formulation and that you have developed capsule formulation as a commercial product. The adequacy of bioequivalence of your final to-be-marketed capsule formulation to tablet formulation as well as effect of food on the systemic exposure of your to-be-market formulation will be reviewed at the time of NDA submission.

If the relative bioavailability between your to-be-marketed formulation and the formulation used in your phase 3 trials is outside the no effect boundary of 80% to 125%, you will need to provide a scientific justification to support the adequacy of your clinical trials or you may need to conduct new clinical studies using your to-be-marketed formulation.

We advise you address a potential drug interaction of your product with acid-reducing agent in the NDA. Refer to Guidance to Industry: Evaluation of gastric pH-

dependent drug interactions with acid-reducing agents: Study design, data analysis, and clinical implications (https://www.fda.gov/media/144026/download)

2.5. Clinical/Biostatistics

Question 4: Summary of Clinical Efficacy Content
Does the Agency agree with the presentation of data (Table of Contents) proposed for the SCE?

FDA Response to Question 4:
From a technical perspective (and not content related), the presentation of data (Table of Contents) proposed for the SCE provided in Appendix 2 is acceptable.

Question 5: Efficacy Data and Pooling Strategy
A) Does the Agency agree with the analyses for the specific AA clinical trial efficacy data and pooling strategy in the clinical efficacy iAP?

B) The subgroup analyses, including those for adolescent and AT/AU subgroups, will be presented for each individual dose and for the combined treatment groups for each given maintenance dose (ie, 30 mg or 50 mg) for the placebo-controlled phase (through Week 24), regardless of the effect of loading dose.

Does the agency agree that the consistency of efficacy responses across subgroups can be assessed based on these analyses?

Does the Agency agree that the analyses based on individual and combined treatment groups in adolescents and patients with AT/AU and the expected consistency of the results in subgroups and those in the whole sample can support the indication statement: "Ritlecitinib is indicated for the treatment of adolescent and adult patients with alopecia areat (b) (4) ?

FDA Response to Question 5:
You noted that because this program consists of a single pivotal trial, there will not be pooling of trials, but rather longitudinal data from patients who participated in one study and rolled over to another will be summarized in the All-Exposure Cohort. In addition, you plan to combine treatment groups for the Placebo-Controlled Cohort (independent of the effect of loading dose from the exposure response analysis), which consists of data during placebo-controlled period (first 24 weeks) of pivotal Trial B7981015. Such strategy appears reasonable; however, we note that the objective of the Integrated Summary of Efficacy (ISE) is to support the analysis results obtained from the individual trials and not to establish a new efficacy claims. Therefore, analyses described in the iAP for clinical efficacy are considered exploratory. Establishing an efficacy claim would be based on efficacy data from the Phase 2b/3 trial.

You plan to repeat and expand the subgroup analyses planned for Trial B7981015 using the combined treatment groups for the Placebo-controlled Cohort. You stated that the primary purpose of the subgroup analyses is to check for consistency of results across subgroups and that there is no intention to have any specific inferences within subgroups. You also stated that this descriptive analysis is planned to be utilized also to support the indication statement that ritlecitinib is indicated for the treatment of adolescents and adult patients with alopecia areata (b) (4) Combining treatment arms disregarding the loading can be meaningful if the loading dose does not impact efficacy and safety, and thus, it is data driven. Subgroup analysis after completion of clinical trials is exploratory.

Additional Comments for the Protocol Amendment and SAP for Trial B7981015 submitted on 4/29/2021:

a. According to the Protocol Amendment 5 and SAP Version 4 for Trial B7981015, you plan to test the primary endpoint (SALT ≤20) and consider control of the Type I error rate for the trial, over the 4 dosing regimen, at alpha=0.00125. For testing the secondary endpoints, including SALT ≤10 and testing for the onset of efficacy as measured by SALT ≤20 at the earliest time points, you plan testing at each dosing regimen and testing at the 5% level of significance, without adjustments for multiple comparisons. As you noted your proposed testing approach for each dosing regimen does not control the Type I error rate. Further, you noted that "for continuous secondary endpoints, a mixed-effect model with repeated measures (MMRM) will be used." We note that for secondary endpoints intended for labeling, testing needs to control the Type I error rate at the same level as that of the primary endpoints on the trial level (i.e., 0.00125), in addition to the requirement that the endpoints be clinically meaningful. As secondary endpoints are intended to support the efficacy findings of the primary endpoint(s), testing for secondary endpoints should be based on data for relevant time point instead of using repeated measure approach which consider data from earlier time points. Testing using repeated measure approach may lead to statistically significant findings which may not be clinically relevant.

b. In addition to the proposed supplementary analyses based on repeated measures (i.e., using GLMM), we recommend conducting sensitivity analyses to assess the impact of missing data on the primary analysis at Week 24, (e.g., multiple imputation, tipping point). Use of the GLMM to impute missing values is acceptable, however use of the GLMM for the analysis of the imputed dataset(s) will not address missing data alone as it uses data from other time points as well.

c. We reiterate our comment conveyed at the Type C meeting dated 11/4/2020 that it is not clear what is the objective of your proposed interim analysis, how its findings would be utilized and what will its impact be on the clinical trial findings and their interpretation. As such, we discourage such an interim analysis without laying down the clear objectives of the interim analysis and ensuring that the integrity of the trial is not compromised, the interpretation of study findings is still sound and the control of Type I error is preserved, if medication to trial design to be planned.

d. The primary analysis to establish efficacy excludes subjects with missing values due to COVID-19. Supportive analysis treats such missing data due to COVID-19 as non-responders. We recommend that you conduct additional sensitivity analysis for the missing data due to COVID-19, such as multiple imputations.

Meeting Comments:

There was general discussion regarding MMRM analyses and the clinical relevance of these analyses. The Sponsor stated that the numbers of subjects with missing data was small and an ANCOVA analysis would provide similar results. The Agency stated that the same methods for handling missing data should be used as for the primary analysis. The Agency stated that ANCOVA appears reasonable, but that endpoints need to be clinically meaningful and multiplicity needs to account for an alpha of < 0.00125 for inclusion into labeling. The Agency pointed out that if the endpoints are not clinically meaningful, there may not be a need for extensive statistical analysis. The Agency inquired about the continuous endpoint for which the Sponsor requested input about the analysis. The Sponsor noted that they plan to include change or percent change from baseline in SALT. The Agency replied that such endpoints are not clinically meaningful for labeling because they are driven by the magnitude of the baseline.

In addition, the Sponsor noted that they plan to analyze patient reported outcomes (PROs). The Agency noted that, while PROs are meaningful, there are criteria concerning assessing their validity and reliability prior to trial conduct and determining threshold level for such endpoints prior to conducting Phase 3 trials in addition to inclusion of these endpoints in the multiplicity adjustment. The Agency pointed out that the Phase 3 trial is already completed and therefore it is difficult at this stage to concur with the proposal to include PROs as secondary endpoints.

The Sponsor clarified that the GLMM approach would be used to predict missing values and the analysis would be done on the Week 24 data using the Miettinen and Nurminen method. The Agency responded that this approach is acceptable.

Question 6: Clinical Safety Database

Does the Agency agree with the composition and size of the safety database to support the initial NDA submission and content of the Safety Update?

FDA Response to Question 6:
Your proposed safety database for AA subjects (exposed to oral ritlecitinib 50 mg QD for >= 1 year) (b) (4) at the time of 3-month safety update is not acceptable. The number of subjects in your safety database appears inadequate at the time of filing and at the time of 3-month safety update for your NDA. At the time of NDA submission your safety database should include at least 1000 subjects who have received the proposed to-be-marketed dose for at least 1 year.

As you are aware, the safety experience of Janus kinase products continues to expand as more trial results are reported for various products in this class. Longer term treatment with ritlecitinib, particularly in patients with mild clinical disease or those with limited distribution, may not be justified given the known and potential risks of the Janus kinase class of products.

Meeting Comments:
The Sponsor presented their perspective on safety of their proposed product, stating that their product is selective for JAK 3 and safety data regarding related products may therefore not be applicable to ritlecitinib. The Sponsor stated that alopecia areata is thought to be a low-risk population as well as a low prevalence population and that additional real world evidence could be presented post-approval.

The Agency stated that the safety relationships between various JAK isoform risks based on in vitro activity is not conclusory at this time and may not be sufficient to draw clinical conclusions. The Agency therefore stipulated that a complete safety database would be necessary at the time of NDA submission and that Agency analyses would be based on clinical experience. The Agency continued to recommend 1000 subjects exposed for one year to allow an adequate risk/benefit determination and stated that the previous recommendations remain unchanged.

The Agency stated that they anticipate lifetime treatment because the treatment is not curative and long-term use may accumulate increasing safety concerns as the treated population continues to age and accumulates drug exposure.

The Sponsor stated that reopening trials to enroll additional subjects would be challenging at this stage of development.

Question 7: Clinical Safety Analysis Pooling
A) Does the FDA agree with the general pooling strategy approach as described in the Ritlecitinib iAP for Clinical Safety?

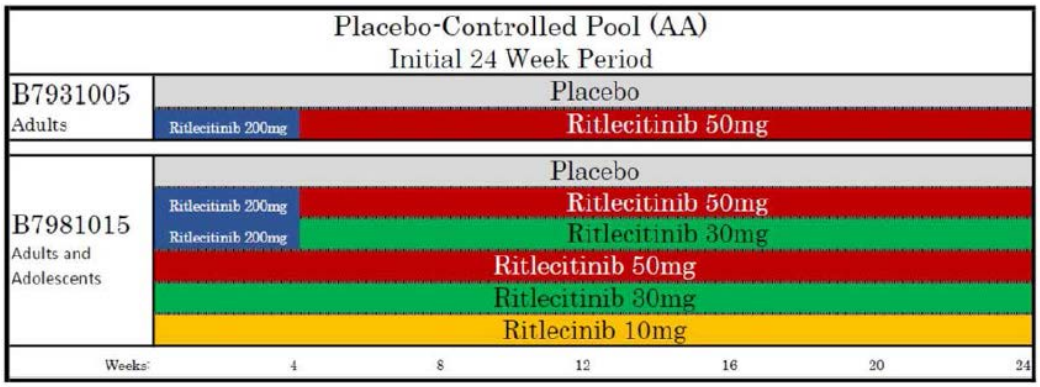
B) Does the FDA agree with the dosing/treatment groupings outlined within each pooled group described in the Ritlecitinib iAP for Clinical Safety?

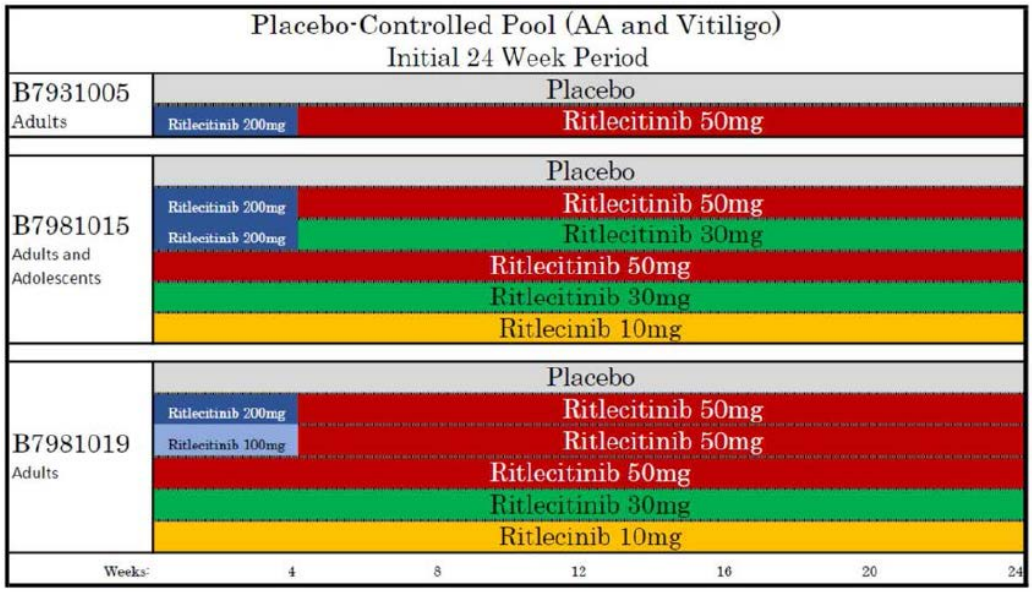
C) Does the FDA agree in general with the proposed table summaries of the data for each integrated safety pool?

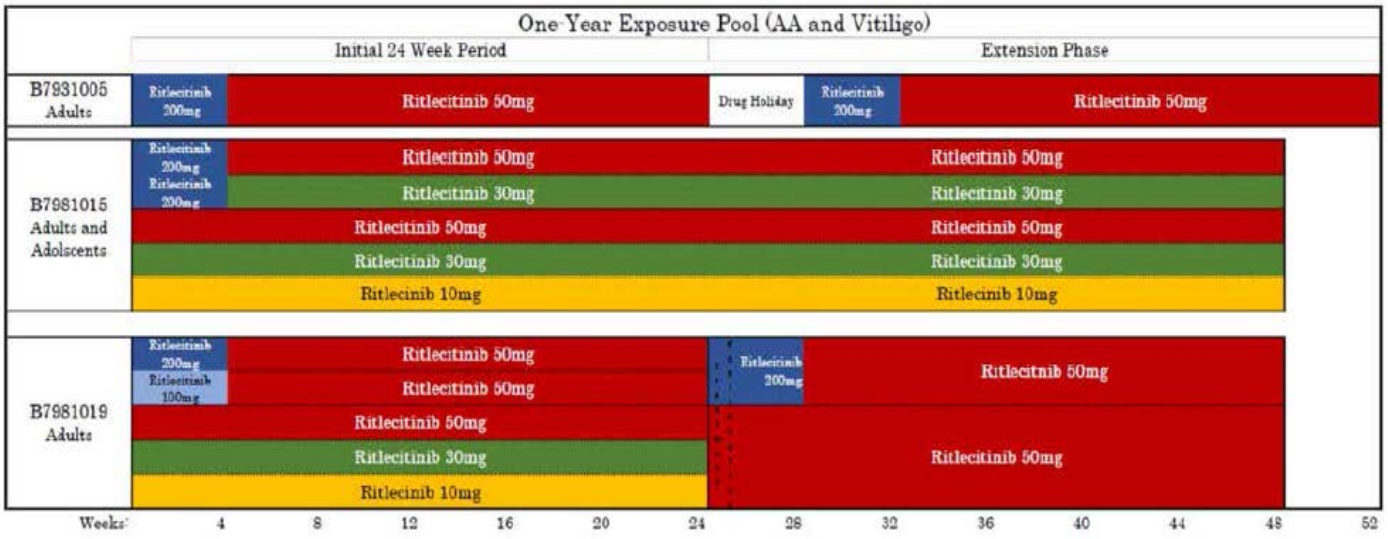
FDA Response to Question 7:

You plan to pool safety data for subjects treated with the same dose (ritlecitinib:10 mg, 30 mg, 50 mg [to-be-marketed dose], or placebo) during the PC period (weeks 0-24) for the AA pool and the AA+Vitiligo pool, during weeks 0-48 in the One-year Exposure pool (AA+Vitiligo), and for the All-Exposure pool (any ritlecitinib dose or placebo in AA+Vitiligo studies).

The pooled safety data will inform the comparison of dose-dependent AEs for your drug product. However, we reiterate the comment conveyed at the EOP2 meeting (August 2018):" The utility of safety information obtained from subjects treated at lower doses and with different dosing regimen may be limited when determining the safety of higher doses of your product and different dosing regimen."







We also have the following comments regarding the proposed safety pools:

a. You plan to compare each dose of 50 mg, 30 mg and 10 mg (regardless of loading dose) against placebo using the Placebo-Controlled AA Pool and the Placebo-Controlled AA + Vitiligo Pool. We note that integration of multiple trials should be considered when: (1) more than one study collects data on an important safety outcome; (2) there is an interest in gaining more precision in the evaluation of the outcome than the individual studies provide; and (3) the studies are sufficiently similar in key design characteristics that may substantially modify drug effects, such as dose(s) of the drug, duration, population, etc. You may need to make different choices of trials to integrate for different outcomes or different comparisons. We further note that for a specific comparison of interest, only trials that include both treatment arms should be included in the integrated analysis. Since 30 mg and 10 mg doses are not included in Trial B7931005, we recommend comparisons of 30 mg and 10 mg doses against placebo be conducted based on placebo-controlled pools that do not include Trial B7931005. In addition, we recommend that you also present results for 200/50 mg against placebo based on the placebo-controlled pools.

b. You plan to compare the 50 mg dose against the 30 mg dose using the One-Year Exposure Pool, which includes subjects randomized to active ritlecitinib treatment in Trials B7931005 (0-48 weeks), B7981015 (0-48 weeks) and randomized/assigned in Trial B7981019 (0-48 weeks). We note that such comparison can be conducted based on Trial B7981015 for long-term safety, since it is the only trial that includes treatment with the 30 mg dose for 48 weeks.

c. We note that safety analysis when pooling data across trials that have different randomization ratios, patient populations, length of follow-up, etc., simple pooling may cause difficulty in interpreting safety signals, as a result of what is known as the Simpson's paradox. In addition, you plan to pool doses with different loading doses creating imbalances in the randomization ratio. Appropriate statistical approaches for integrating safety data across these trials should be considered to account for differences in trial design, such as the randomization ratio.

d. You specified presenting tables with the number and the proportion (crude incidence proportion) of subjects with the event for all TEAEs. For serious AEs and AESIs, you also plan to present exposure-adjusted incidence rates (IR), and incidence rates differences (IRD). We recommend that you include the exposure-adjusted incidence rates for all reported Adverse Events in your safety data. We also note that tables of integrated analysis results, even when including only summary measures within treatment arms, should be based on analyses stratified by study. In these analyses, within each arm, the summary measures (e.g., proportions and incidence rates) are calculated within each study and then a combined summary measure is calculated based on planned weights for the individual study. We refer you to the following article for reasonable options for weights. Weights should be prospectively planned.

    - Chuang-Stein, C., & Beltangady, M. (2011). *Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies.* Pharmaceutical Statistics, 10(1), 3-7.

Meeting Comments:

The Sponsor inquired whether to only include Study B7981015 in the AA placebo-controlled pool and only Studies B7981019 and B7981015 in the AA and vitiligo placebo-controlled pool. The Agency reiterated that for different comparisons the Sponsor may consider different pools. The Agency provided an example for comparison between 200/50mg dose against placebo, where trials B7931005 and B7981015 may be pooled (additionally the AA and vitiligo placebo-controlled pool may be considered for such comparisons).

For the 50mg versus 30mg comparison, the Agency noted that both the one-year exposure pool and trial B7981015 may be considered, where trial B7981015 alone will provide a cleaner approach.

The Agency noted that safety results for trial B7981015 should be presented for each individual treatment arm without combination of arms similar to the comparison of 200/50mg against placebo (noted above).

Question 8: Summary of Clinical Safety Table of Contents

Does the Agency agree with the proposed presentation of data (Table of Contents) for the SCS?

FDA Response to Question 8:
From a technical perspective (and not content related), the proposed presentation of data (Table of Contents) for the SCS provided in Appendix 3 is acceptable.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

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

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

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended*

Pediatric Study Plans.[1] 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.[2]

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[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include

[1] 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.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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,* and the associated conformance guide, *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*.[7]

26 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[5] https://www.fda.gov/media/84223/download
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[7] 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/

KENDALL A MARCUS
08/10/2021 05:28:57 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 131503

MEETING MINUTES

Pfizer, Inc.
Attention: Mark J. Evans, PhD
Worldwide Safety and Regulatory
500 Arcola Road
Collegeville, PA 19426

Dear Dr. Evans:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PF-06651600 immediate release tablets, 50 mg.

We also refer to the meeting between representatives of your firm and the FDA on August 8, 2018. The purpose of the meeting was to discuss the clinical development plan to support the future registration of PF-06651600 for the treatment of patients 12 years old and older with (b) (4) severe AA (b) (4)

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 Minutes
Pfizer's Response to FDA Preliminary Comments – AA

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:	August 8, 2018 at 9:00 a.m.
Meeting Location:	White Oak, Bldg. 22, Conference Room 1415
Application Number:	IND 131503
Product Name:	PF-06651600 immediate release tablets, 50 mg
Proposed Indication:	For the treatment of patients 12 years old with (b) (4) severe alopecia areata (b) (4)
Sponsor:	Pfizer, Inc.
Meeting Chair:	Kendall A. Marcus, MD
Meeting Recorder:	Barbara Gould

FDA ATTENDEES
Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Snezana Trajkovic, MD, Clinical Team Leader, DDDP
Hamid Tabatabai, MD, Clinical Reviewer, DDDP
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics III
Matthew Guerra, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DCP) III
Luke Oh, PhD, Clinical Pharmacology Reviewer, DCP III
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Nan Zheng, QT-IRT Reviewer, DCP III
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

SPONSOR ATTENDEES
Anindita Banerjee, Clinical Statistics Lead
Christopher Banfield, Clinical Pharmacology Lead
Mike Brown, Clinical Statistics
Michael Corbo, SVP, Chief Development Officer
Heather Dowty, Nonclinical Drug Safety Team Lead
Mark Evans, Regulatory Lead

Owen Fields, VP, Global Regulatory Strategy
Susan Johnson, Safety Risk Lead
Elena Peeva, Asset Team Lead
Vivek Purohit, Clinical Pharmacology Lead
Rominder Singh, Regulatory
Rachel Sobel, Epidemiology Group Lead
Michael Vincent, SVP, Chief Scientific Officer
Jason Xenakis, Health Economics and Outcomes Research Lead
Samuel Zwillich, Medicine Team Lead

1.0 BACKGROUND

Meeting Purpose:
The purpose of this meeting is to discuss the clinical development plan to support the future registration of PF-06651600 for the treatment of patients 12 years old with (b) (4) severe AA (b) (4)

Regulatory Correspondence History:

We have had the following meetings/teleconferences with you:

- 03/14/2018 Type C Guidance Meeting

We have sent the following correspondences:

- 07/31/2018 Grant Breakthrough Therapy Designation Request
- 04/04/22018 Special Protocol Agreement (SPA-1 Carcinogenicity)
- 01/17/2017 Harmonized Annual Review Date Granted
- 12/15/2016 Study May Proceed Letter

2.0 DISCUSSION

2.1. Regulatory

No regulatory questions were provided by the Sponsor at this time.

2.2. Chemistry, Manufacturing, and Controls (CMC)

No CMC questions were provided by the Sponsor at this time.

2.3. Pharmacology/ Toxicology

Question 1:
Does the Agency agree that the completed, ongoing, and planned nonclinical studies with PF-06651600 constitute a complete nonclinical safety program that (pending review of planned studies) would support future registration for treatment of adult and adolescent (≥12 years old) patients with (b) (4) severe AA (b) (4)?

FDA Response to Question 1:
Yes, we agree.

2.4. Clinical Pharmacology

Question 3:
Does the Agency agree that the clinical pharmacology package addressing the influence of intrinsic and extrinsic factors adequately supports the clinical program and eventual registration package of PF-06651600 as an oral medication for the treatment of AA?

FDA Response to Question 3:
We note that your proposed clinical study plan includes the evaluation of the product in adolescent subjects aged from (b) (4) We recommend that you change the adolescent age group from 12 to < 17 years and that you enroll sufficient number of adolescent subjects to characterize pharmacokinetic profile of your product in adolescent subjects.

To help you design renal and hepatic impairment studies, we recommend you refer to guidance for industry: *Pharmacokinetics in patients with Impaired Renal Function* and *Pharmacokinetics in Patients with Impaired Hepatic Function*, respectively.

The adequacy of the available information will be considered during review of the NDA.

Meeting Discussion:
The sponsor proposed PK assessment in a subpopulation of individuals ages 12 to <17 years and the safety and efficacy in subjects ages 12 to <18. The Agency agreed with the sponsor's proposal (see appended document).

Question 4:
Does the Agency agree that, (b) (4) the proposed plan for (b) (4) in Study B7981015 is adequate to support registration and a separate thorough QT (TQT) study is not required?

FDA Response to Question 4:
No, we do not agree (b) (4) (b) (4) We therefore propose that you either resubmit justification for the dosing and include a description of the highest clinically relevant therapeutic exposure based on important intrinsic and extrinsic factors, or you should conduct a thorough QT study to satisfy E14. The TQT study can be designed using concentration-QTc analysis as the primary analysis.

If your product is likely to increase or decrease the heart rate significantly (e.g., >10 bpm) in the study, you will need to consider the use of alternative methods for assessing changes in the QT

interval, such as QTcI (individualized QT correction). To support alternative methods, it is important that drug-free baselines are available from a wide enough span of heart rates to cover on treatment changes in heart rate, within each individual. One way to achieve this could be to have the subjects undergo postural maneuvers (e.g. unsupported sitting and standing) on drugfree visits. In addition, it is also important to account for QT/RR hysteresis prior to deriving the individual QT/RR relationship to avoid bias when estimating the individual QT/RR relationship. For additional information, please see "Methodologies to characterize the QT/corrected QT interval in the presence of drug-induced heart rate changes or other autonomic effects" (Garnett, C. et al., Am Heart J 2012;163(3):912-30). In the absence of significant heart rate effects, we recommend the use of QTcF for the primary analysis.

The ECG monitoring plan in Study B7981015 Draft Protocol is not acceptable because small mean QTc effect cannot be ruled out with available data.

Meeting Discussion:
The sponsor's proposal to submit a TQT waiver request appears reasonable and the adequacy of supporting data will be a review issue. The ECG monitoring appears reasonable as stated in the sponsor's response to FDA comments (see appended).

2.5. Clinical/Biostatistics
Introductory Clinical Comments:

You are currently conducting a Phase 2a, randomized, double-blind, placebo controlled, multicenter trial (B7931005), to evaluate the efficacy and safety of PF-06651600 and PF-006700841 in adult subjects with moderate to severe alopecia areata (scalp hair loss ≥ 50%, no evidence of hair regrowth within prior 6 months, current episode of hair loss ≤7 years).

The trial consists of two treatment periods, a 4-week induction period and a 20-week maintenance period. One hundred thirty-two (132) subjects with moderate to severe alopecia areata are being treated as follows: PF-06651600, 200 mg QD x 4 weeks, then 50 mg QD x 20 weeks; or PF-006700841 at 60 mg QD x 4 weeks, then 30 mg QD x 20 weeks.

The primary efficacy endpoint is the mean change from baseline of Severity of Alopecia Tool (SALT) score at 24 weeks. Following a drug holiday (after losing 30% of hair regrown in treatment period, but no sooner than 4 weeks), subjects entered a 24-week re-treatment extension period.

Safety evaluations included TEAEs, physical examinations, vital signs, electrocardiograms, clinical laboratory (chemistry, hematology, liver function, lipid panel, urinalysis, urine pregnancy test, Cystatin-C based eGFR, and viral surveillance for EBV, CMV, HSV1, HSV2, VZV), and hearing tests.

You propose a Phase 2b/3, randomized, double-blind, placebo-controlled, multicenter trial (B9781015), with a treatment period (24 weeks) and an extension period (24 weeks), to evaluate efficacy and safety of PF-06651600 in 600 adult and adolescent subjects (≥ 12 years of age) with

alopecia areata (≥ 50% scalp hair loss, no hair regrowth in prior 6 months, current episode of hair loss ≤ 10 years). The treatment period includes the following arms:

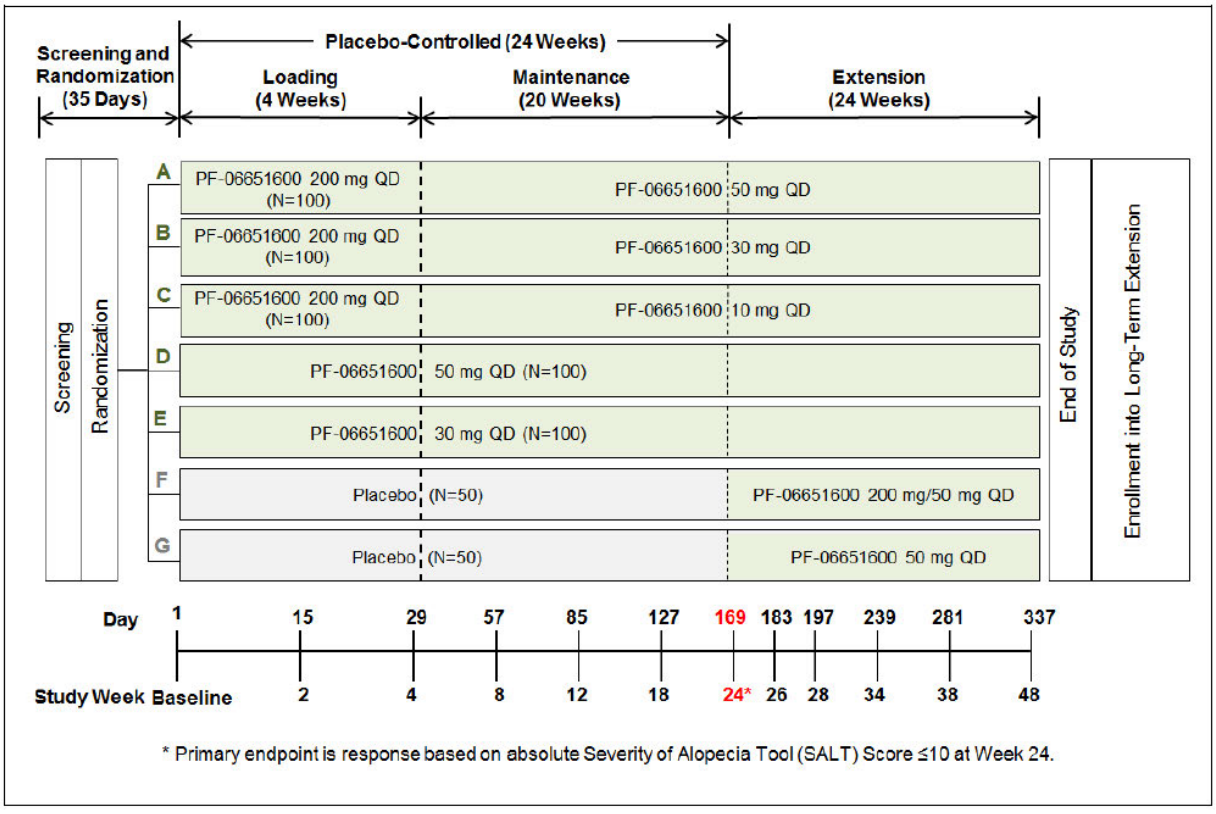
- an induction dose of 200 mg QD x 4 weeks, followed by a maintenance dose of 50 mg QD, 30 mg QD, or 10 mg QD x 20 weeks
- continuous dose of 50 mg QD or 30 mg QD x 24 weeks

In the extension period, each treatment arm will continue to receive the same dose they received at the end of treatment period. Placebo arm in the treatment period will be randomized to receive one of the following in the extension period:

- 200 mg QD x 4 weeks, followed by 50 mg QD x 20 weeks
- 50 mg QD x 24 weeks

Your proposed primary efficacy endpoint is absolute SALT score ≤ 10 at 24 weeks.
Safety evaluations will include TEAEs, physical examinations, vital signs, electrocardiograms, clinical laboratory (chemistry, hematology, liver function, lipid panel, urinalysis, and urine pregnancy test).

Figure 1. Study Design Schematic



In the proposed dose-ranging Phase 2b/3 trial (B7981015), you plan to investigate the efficacy and safety of 5 doses of PF-06651600 in adult and adolescent subjects with AA with 50% or greater scalp hair loss; however, it should be noted that your Phase 2a trial investigated a single dose (PF-06651600 200 mg QD/50 mg QD). You propose the Phase 2b/3 trial to be used as a single clinical study to support an initial NDA of your product for the treatment of (b) (4) severe alopecia areata. In addition, you plan to conduct a future Phase 3 study for the selected dose in the Phase 2b/3 study. It should be noted that one may consider results for the completed Phase 2a trial to provide supportive evidence for the proposed Phase 2b/3 trial; however, this is only for one dose (PF-06651600 200 mg QD/50 mg QD). Whether the proposed Phase 2b/3 is adequate to support the review of an initial NDA will depend on the selected dose (Refer to response to Question 15 regarding the adequacy of the safety data for doses other than 200 mg/50mg).

In addition, consider the criteria for establishing treatment effect based on a single trial, so that findings from such trial are driven by clinically meaningful primary endpoints with robust statistical findings that are consistent across subpopulations and centers, among other criteria. You are referred to the criteria for a single study submission listed in the guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. You stated that you consider a significance level of 0.01 as providing "clear and compelling" evidence of efficacy, such as demonstration of efficacy in one or more arms, yet you powered your Phase 2b/3 trial using a significance level of 0.05. We reiterate our comment conveyed during the guidance meeting on March 14, 2018 that for establishing efficacy based on a single trial, the study should be powered at much smaller significance level than the customarily 0.05. The significance level for testing should be pre-specified in the protocol.

Meeting Discussion:
The sponsor noted that they would use alpha = 0.01 to support application for a single study submission. The Agency noted that replication of study findings is generally required. While there is supportive data for the highest dose from the Phase 2a trial, (b) (4) *The sponsor inquired whether a dose that does not make it under a prespecified alpha= 0.001 but makes it at alpha = 0.05 can be considered for approval if another dose in the study makes it at alpha = 0.001. In response, the Agency noted that such dose failed under the prespecified significance level and information from this dose could be used as supportive data if such dose were to be investigated in future clinical trial(s).*

The sponsor inquired if the study does not make at the 0.001 level but makes it at the 0.05 level, then could that study be considered along with another trial using alpha = 0.05. The Agency noted the study technically failed on its predetermined significance level; however, information from such a study could be used as supportive evidence for planning future clinical trial(s). The significance level for the new study would depend on the level of evidence of the completed study that did not make at the 0.001 level.

The sponsor noted that they expect results for the two highest doses to be statistically significant and inquired about whether findings from these dose regimens can (b) (4) *serve as replication of a dose finding. In response, the Agency noted that selection of a dose* (b) (4) *will be driven by both efficacy and safety considerations when more than one dose achieves statistical significance. Furthermore, the Agency noted that if the sponsor expects results for the two highest doses to be similar, then the sponsor may consider an alternative study design of reducing the number of doses to be investigated and increase the number of subjects for the doses under investigation to get more reliable estimates of treatment effect.*

Question 2: Registration Package and Proposed Indication

Does the Agency agree that the proposed AA development program, if results are positive, clear and compelling, will be sufficient to support the review of an initial NDA filing of PF-06651600 for the treatment of patients ≥12 years old with (b) (4) severe AA and will support the following indication statement?

{Brand Name} is indicated for the treatment of patients ≥12 years old with (b) (4) severe alopecia areata (b) (4)

{Brand Name} is indicated for the treatment of patients >12 years old with (b) (4) severe alopecia areata (b) (4)

FDA Response to Question 2:

Whether your development program will be sufficient to support an initial NDA filing will be a review issue. Generally, two adequate and well-controlled clinical trials (of appropriate design and endpoints agreed upon with the Agency) are recommended to demonstrate the safety and efficacy of your product. For establishing an efficacy claim, replication of study findings is needed. Trials need to be powered so the study findings are meaningful and interpretable. See Introductory Comments.

Question 5: B7981015 SALT scoring

Does the Agency agree with use of the response based on absolute SALT score ≤10 at Week 24 as the primary efficacy endpoint?

FDA Response to Question 5:

Yes. We agree with the responder definition of absolute SALT score ≤ 10 at 24 weeks as the primary efficacy endpoint for your Phase 2b/3 trial.

For your Phase 2a trial, you pre-specified analysis based on SALT 90, which measures percent change from baseline to Week 24. Later you conducted ad-hoc analysis for the absolute SALT score ≤ 10 at Week 24. Please clarify the relationship between SALT 90 and absolute SALT score ≤ 10.

See Additional Comments for specific comments and recommendation on the SALT.

Question 6: B7981015 Primary Endpoint Scoring

Does the Agency agree with the Sponsor's proposal [redacted] (b) (4)

FDA Response to Question 6:

We do not agree. In your Phase 2b trial (B7981015), [redacted] (b) (4)

[redacted] (b) (4)

Question 7: B7981015 Additional Endpoints

In order to demonstrate the benefits of PF-06651600 to AA patients on patient reported outcomes concepts of symptoms and quality of life, the Sponsor will be utilizing the modified Alopecia Areata Symptom and Impact Scale (mAASIS), short form 36 (SF-36), and Hospital Anxiety and Depression Rating Scales (HADS) as secondary endpoints for PRO evidence. Does the Agency agree with this measurement strategy?

FDA Response to Question 7:

You listed many secondary endpoints in your Phase 2b/3 study. It should be noted that secondary endpoints in intended for labeling need to be limited in number, clinically meaningful and adjusted for multiplicity. Endpoints not included in the multiplicity strategy will be considered exploratory. In addition, endpoints that rely on patient-reported outcomes (PROs) need to be fit-for-purpose for the context of the drug development program (i.e., appropriate for its intended use; validly and reliably measures concepts that are both clinically relevant and important to patients; and data can be communicated in labeling in a way that is accurate, interpretable and not misleading). A clinically meaningful threshold level needs to be identified for treatment response prior to using such endpoint in confirmatory studies. Change by itself may not be clinically meaningful.

We have the following comments regarding the specific PRO instruments:

- mAASIS:
  - Refer to previous communications for comments on this instrument.

- HADS:
  - Anxiety and depression are concepts secondary to alopecia areata and might be influenced by other factors beyond the treatment, and consequently may be insensitive to treatment effect. Because of these challenges, it might be better to measure this concept for exploratory purposes. If you seek to measure these concepts, we recommend that you obtain patient input to determine what are the most important impacts of this condition (e.g., anxiety or depression) that are

expected to have a meaningful impact on how patients feel or function in daily life, and then select instruments that appropriately measure those impacts.

- If you intend to use this instrument to support labeling claims submit information to support the HADS content validity and psychometric performance in this context of use for FDA review.

- On the face, there might be some issues with translatability and cross-cultural relevance with the use of some of the idioms (e.g., "feeling like butterflies in the stomach," "I can laugh and see the funny side of things"). PRO instruments should be culturally adapted and adequately translated for all intended study populations for use in multinational trials. We refer you to the ISPOR principles for the translation and cultural adaptation process.[1]

- The HADS appears to be designed as a screener based on the scoring. Please clarify how you intend to use this scale.

- SF-36v2 (Acute):
  - The SF-36 is a measure of general health status, which makes it difficult to ascertain the effect of treatment on the disease or condition under treatment. At this time, we have insufficient information to comment on whether the SF-36v2 is fit-for-purpose in the target population. The sponsor should provide evidence to support that the SF-36v2 content is relevant to their target population.

- EQ-5D:
  - The EQ-5D-5L is a generic preference-based measure intended to provide a single health utility index value for use in economic analyses and lacks evidence of content validity for use in estimating clinical benefit for labeling claims. However, we acknowledge that the EQ-5D-5L may be necessary for other regulatory authorities and/or payers.

Question 8: B7981015 Enrollment Criteria

Does the Agency agree that the inclusion/exclusion criteria for study B7981015 are appropriate to support the intended indication?

In particular, does the Agency agree with the following inclusion criteria: (b) (4) (lesser grade); ≥50% hair loss of the scalp, including AT and AU, without evidence of hair regrowth within 6 months at the screening and baseline visits; current episode of hair loss ≥10 years?

[1] Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P. (2005). ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health, 8(2):94-104.

FDA Response to Question 8:
We agree with the AA-related inclusion criteria of scalp hair loss ≥ 50% (including AT and AU), without evidence of regrowth for ≥ 6 months, and duration of current episode of hair loss ≤ 10 years.

Provide your rationale for excluding subjects older than 75 years.

We do not agree (b) (4)

Question 9: Definition of AT/AU
Does the FDA agree with the Sponsor proposal for the clinical definition of AT and AU?

FDA Response to Question 9:
Definitions of AT and AU are not clear as described in your meeting document.

We consider subjects with complete (100%) scalp hair loss to have AT and we consider subjects with complete (100%) scalp, facial and body hair loss to have AU.

Subjects with lesser amounts of hair loss are considered to have AA.

Question 10: B7981015 Inclusion of Adolescents
Pfizer will submit an initial pediatric study plan (iPSP) within 60 days following this EOP2 meeting. Prior to Agency review of the iPSP, does the FDA agree with the inclusion of adolescents' ages 12 through 18 years in Study B7981015?

FDA Response to Question 10:
Yes, however, your pediatric plan should cover adolescent ages 12 through <17 years.

Question 11: B7981015 Dose Selection
Does the Agency agree with the selected dose(s) and dose regimen(s) to be evaluated in the Study B7981015 for PF-06651600?

FDA Response to Question 11:
Your proposed dose ranging strategy appears reasonable. We recommend that you further consider dosing strategies for the open label extension period. The dosing regimen that achieved the treatment response may not necessarily be the dosing regimen necessary to maintain the response. It is possible that a treatment response could be maintained with lower dose or less frequent dosing than was required to achieve the response. In addition to evaluating maintenance of response, we recommend you evaluate potential for relapse and rebound.

Question 12: B7981015 Endpoints and Statistical Analyses
Does the Agency agree with the proposed statistical analysis for the primary endpoint and the Type I error control scheme? Does the Agency agree that this plan would support review of Study B7981015 as the single pivotal study for the proposed indication, provided clear, robust, and compelling evidence of the efficacy of at least one dose / regimen of PF-06651600 versus

placebo were demonstrated? (b) (4)

FDA Response to Question 12:
See Introductory Comments under Section 2.5 Clinical/Biostatistics.

Additional biostatistics comments:

- You listed as secondary endpoints the proportion of subjects with eyelash/eyebrow assessment scores of at least a 2-grade improvement from baseline or a score of 3; however, you did not specify a minimum eyelash/eyebrow assessment score for enrollment in the study. The enrollment criteria should specify a minimum eyelash/eyebrow assessment score at baseline for enrollment and a good proportion of subjects who meet such baseline criterion should be enrolled to get a reasonable estimate of the treatment response.

Meeting Discussion:
The sponsor stated that the analysis will be based on only subjects with eyelash and eyebrow involvement at baseline. The sponsor stated that they expect an adequate proportion of subjects will have partial or complete loss of eyelashes and eyebrows at baseline and noted that 76% (108/142) and 85% (120/142) of subjects from the Phase 2a trial had eyelash and eyebrow loss, respectively at baseline. The Agency reiterated that establishing an efficacy claim for eyelash and eyebrow would be dependent on having a good proportion of subjects that have eyelash and eyebrow involvement at baseline. In addition, the Agency noted that secondary endpoints intended for labeling claims should be limited in number, clinically meaningful, and analyzed with appropriate multiplicity control.

- You specified analyzing the continuous secondary endpoints using a mixed-effect model with repeated measures (MMRM). It should be noted that use of repeated measures approach, such as MMRM, that incorporates information from each visit might not be clinically meaningful, yet the analysis may yield a statistically significant treatment effect due to the incorporation of all of the data.

- You specified using the non-responder imputation to handle the missing data for the primary and secondary endpoints. In addition to the primary method of handling missing data, you should propose at least two sensitivity analyses that use alternate assumptions, such as tipping point analysis and multiple imputation, to ensure that the method of handling missing data does not impact the results.

- If you desire to make claim concerning (b) (4) then your study should have a reasonable power along with formal inference for this subgroup along with control for the Type I error rate for the study; otherwise clinically relevant results of subgroup analysis may be reported depending on size of subgroup and differential treatment effect. The same apply for the adolescent population. However, it should be noted that for proper interpretation

of study findings, study enrollment should reflect the disease prevalence in the overall population.

Question 13: Demonstration of Efficacy in AA

Does the Agency agree that the proposed B7981015 study of subjects with AA, supported by the Phase 2a study (B7931005), has the potential to fulfill efficacy requirements for registration, provided that the B7981015 study primary endpoint provides clear and compelling evidence of efficacy of PF-06651600 versus placebo, with consistent support from secondary endpoints?

FDA Response to Question 13:

See FDA Response to Questions 2 and 15.

Question 14: B7981015 Safety Assessments

Does the Agency agree with the proposed clinical safety assessments and safety monitoring plans in Study B7981015?

FDA Response to Question 14:

The Agency expects adequate monitoring to be in place for all adverse events, including known and potential, associated with this drug product and the class of products, in any future clinical trials.

Your safety monitoring includes assessments of TEAEs, physical examinations, vital signs, clinical laboratory (chemistry, hematology, urinalysis, urine pregnancy test), and electrocardiograms. We recommend that you include screening and monitoring for hearing loss, Cystatin-C based renal function, and suicidality.

We agree with your plan to monitor additional TEAEs of special interest, including infections (serious, opportunistic, viral reactivation), malignancy, lymphoproliferative disorders, changes in hematologic parameters and lipid profiles, and dermatologic effects (including drug-related rash).

We recommend that you propose screening a safety monitoring plan for progressive multifocal leukoencephalopathy (PML) for your future clinical trials.

Meeting Discussion:

The Agency agreed to the sponsor proposal for auditory monitoring, routine creatinine assessment and for ECG monitoring. The sponsor indicated they will monitor for SIB using the C-SSRS; however, monitoring will not occur at every study visit. The Agency requested that the sponsor submit their proposal for monitoring in their study protocol.

The Agency agreed with the sponsor's proposal (see appended) for minimizing potential risk for PML.

Question 15: Safety Database

Does the Agency agree that the proposed overall clinical safety data set would be adequate to support NDA review and registration for an AA indication?

FDA Response to Question 15:
Because you have not yet selected the to-be-marketed dose and dosing regimen, we cannot estimate whether the size of the safety database will be sufficient to adequately characterize the safety of your product. The utility of safety information obtained from subjects treated at lower doses and with different dosing regimen may be limited when determining the safety of higher doses of your product and different dosing regimen.

Your safety database should have adequate numbers of subjects exposed to PF-06651600 for at least one year, because AA patients will require chronic therapy to maintain their treatment response; therefore, your database should have a minimum of 750 subjects exposed to PF-06651600 for at least one year. Whether you can rely on safety data obtained in other development programs will depend on the safety profile observed in the AA population.

Meeting Discussion:
The Agency clarified that 750 subjects would need to be exposed to the to-be-marketed dose or higher and that their proposal to include vitiligo subjects in the safety database is acceptable. The Agency also stated that it would be acceptable to submit final one year data with the 120-day safety update.

Question 16: Real World Evidence Collection
The Sponsor is planning to utilize RWE as one of the complementary approaches to supplement the Phase 2b/3 data with longer term safety data.

a. Given the lack of any approved or uniform standard of care therapies (and therefore no viable "active comparator" group) in this area of high unmet medical need, does the Agency agree that the RWE safety study(-ies) could utilize a descriptive active surveillance approach, ideally in one or more electronic medical records (EMR) – or insurance claims databases?

FDA Response to Question 16a:
See FDA Response to Question 2.

b. Are there any other areas (REMS effectiveness evaluation, drugs utilization patterns, etc) that the Agency feels the Applicant should consider now in post-approval RWE collection?

FDA Response to Question 16b:
See FDA Response to Question 2.

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 https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

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: http://www.fda.gov/ectd.

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 http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

OFFICE OF SCIENTIFIEC INVESTIATIONS (OSI) REQUESTS

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

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

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

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

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 ATTACHMENT(S)

19 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BARBARA J GOULD
10/26/2018

KENDALL A MARCUS
10/26/2018