CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217242Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 142047

MEETING MINUTES

Arcutis Biotherapeutics, Inc.
Attention: Chester G. Elias, III
Executive Director of Regulatory Affairs
3027 Townsgate Road, Suite 300
Westlake Village, CA 91361

Dear Mr. Elias:

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

We also refer to your July 15, 2022, correspondence, requesting a meeting to discuss your plans to submit a New Drug Application for the treatment of seborrheic dermatitis.

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 FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, at 240-402-4454.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH, FACP, FACC
Deputy Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office Of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 14, 2022, 1:30-2:00 pm EST
Meeting Location:	Teleconference
Application Number:	IND 142047
Product Name:	Roflumilast
Indication:	For the treatment of seborrheic dermatitis.
Sponsor Name:	Arcutis Biotherapeutics, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Kimberle Searcy, MPH
Meeting Recorder:	Shari Targum, MD

FDA ATTENDEES

Julie G. Beitz, MD, Office Director, Office of Immunology and Inflammation
Shari L. Targum, MD, MPH, FACP, FACC, Deputy 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 (DB III)
Marilena Flouri, PhD, Biometrics Reviewer, DB III
Kimberle Searcy, MPH, Regulatory Project Manager, Division of Regulatory Operations for Dermatology and Dentistry

SPONSOR ATTENDEES

David Berk, MD	Vice President, Clinical Development
Bruce Binkowitz, PhD	Vice President, Biometrics
Patrick Burnett, MD, PhD	Chief Medical Officer
Freda Cooner, PhD	Executive Director, Biometrics
David Chu, MD, PhD	Executive Director, Clinical Development
Chester G Elias III	Executive Director, Regulatory Affairs
David Krupa, MS	Director, Biometrics
Charlotte Merritt	Vice President, Regulatory Affairs
Scott Snyder, PharmD	Vice President, Patient Safety and Pharmacovigilance

1.0 BACKGROUND

Purpose of Meeting:

The purpose of the meeting is to discuss Arcutis' plans to submit a New Drug Application(NDA) to support the registration of roflumilast foam 0.3% for the treatment of seborrheic dermatitis.

CORONAVIRUS – 19 (COVID 19) CLINICAL TRIAL GUIDANCE
During the COVID-19 public health emergency, ensuring the safety of study participants is paramount. Sponsors should consider each circumstance, focus on the potential impact on the safety of study participants, and modify study conduct accordingly. It is critical that study 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. Category/Discipline A

2.2. Regulatory

Question 1:
As the Agency agreed in the Pre-IND written responses dated 15 August 2019, the nonclinical program for roflumilast cream is supportive of the roflumilast foam program. As such, for nonclinical reports that have previously been submitted to IND 135681 for roflumilast cream, Arcutis plans to cross-refer from the NDA for roflumilast foam to the IND for roflumilast cream rather than resubmit these reports.

Additionally, for CSRs that have been previously submitted to IND 142047 for roflumilast foam, Arcutis plans to cross-refer from the NDA to the IND rather than resubmit these reports.

Does the Agency agree to the proposal to cross-refer to nonclinical and clinical study reports previously submitted to both the roflumilast cream and foam INDs?

FDA Response to Question 1:
Yes, we agree. Submit a table that lists the nonclinical studies and provides links to the nonclinical study reports submitted to both the roflumilast cream and foam INDs. Also, indicate what nonclinical informational needs are being provided by the Right of Reference letter for DALIRESP (roflumilast) tablets.

Similarly, for the clinical study reports (CSRs) that you plan to submit with your roflumilast foam NDA, you may cross-refer to the CSRs for roflumilast foam or roflumilast cream which you have previously submitted to their respective INDs or NDA. Provide a Tabular listing and electronic links to the clinical study reports.

Question 2:
Arcutis has submitted (and the Agency has approved) an NDA for roflumilast cream (NDA 215985) for the treatment of plaque psoriasis. As indicated in this package, Arcutis is preparing for the submission of an NDA for roflumilast foam for the treatment of seborrheic dermatitis in late 2022/early 2023 (NDA 217242). Consistent with the plan for 2 NDAs for the roflumilast cream and foam formulations, Arcutis plans to maintain 2 USPIs, given the different indications/disease states targeted, although the plan is for roflumilast cream and roflumilast foam to have the same proprietary name (Zoryve™). Arcutis will ensure that relevant sections of the roflumilast foam USPI are consistent with labeling approved for roflumilast cream.

Does the Agency agree with our plan to maintain separate package inserts for topical roflumilast cream and foam?

FDA Response to Question 2:
Yes.

Question 3:

(b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

Question 4:

As noted in our Type C meeting package for Biometrics, the ISS analyses for NDA 217242 will integrate the data from ARQ-154-203 and ARQ-154-304. The rationale for this integration is that the Phase 2a study (ARQ-154-203) treated subjects with seborrheic dermatitis who had baseline IGA, BSA involvement, and topical roflumilast dose (exposure) consistent with those used in the pivotal study (ARQ-154-304) and intended in the proposed indication; therefore, integration will provide the broadest and most directly interpretable assessment of safety. Both ARQ-154-203 and ARQ-154-304 are vehicle-controlled studies that randomized subjects 2:1 to receive roflumilast foam 0.3% or vehicle.
The integrated safety analyses will provide summaries derived from subjects who received at least one dose of IP in ARQ-154-203 (N=226) or ARQ-154-304 (N=457) for a total of 683 subjects.

Arcutis intends to analyze and present the integrated data from ARQ-154-203 and ARQ-154-304 as the primary safety dataset in the NDA within Module 2.7.4, as it contains the largest and most robust safety population; thus, Arcutis will use these analyses to support product safety labeling. Does the Agency agree with this proposal?

FDA Response to Question 4:

Your approach to integrate data from ARQ-154-203 and ARQ-154-304 as the primary safety dataset for the Integrated Analysis of Safety appears reasonable.

Additional Biostatistics Comments:

We have the following comments regarding the submitted Protocol Amendment 2 and the final SAP for Trial ARQ-154-304:

- For the primary estimand, you proposed (b) (4) For intercurrent events of treatment discontinuation due to adverse events or lack of efficacy, we recommend a composite strategy policy where subjects will be defined as non-responders, as we consider this to be the appropriate approach for handling such events. Your proposal (b) (4)

Meeting Discussion:
There was general discussion about the primary estimand (b) (4) . The Agency reiterated the comment of using the composite strategy estimand for handling subjects who discontinued treatment due to adverse events or the lack of efficacy as non-responders. The sponsor agreed with the Agency's recommendation. For the Multiple Imputation, the Agency noted that the sponsor may use observed data for all subjects enrolled in the trial, including visits prior to treatment discontinuation due to AE or lack of efficacy.

For easier interpretation of the study findings, the Agency also recommended that the same approach using the composite strategy estimand should be used for the subgroup analysis, as well as for the Integrated Summary of Efficacy (ISE), which includes an additional phase 2 trial.

In addition, the Agency recommended that the sponsor submit an amended Statistical Analysis Plan (SAP), to reflect use of the composite strategy estimand as the primary estimand recognizing that the study already is completed. The Agency pointed out that such modification in defining the estimand being considered after completion of the trial is different to modifications related to endpoint(s), patient population, or multiplicity adjustment which would have major impact on decision making for this study.

2.2 Clinical

Question 1:
Based on Agency feedback in the Pre-NDA meeting for roflumilast cream, Arcutis plans to submit subject narratives and case report forms (CRFs) for all pregnancies, hypersensitivity reactions, deaths, serious adverse events (SAEs), and AEs resulting in permanent discontinuation of IP for the Phase 2 and 3 studies of roflumilast foam 0.3% in seborrheic dermatitis. CRFs will also be provided for subjects with a severe AE and those who permanently discontinued IP for a reason other than an AE.

The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials will be included.

Study-specific CRFs will be placed in a CRF folder under the applicable study with a file tag of "case-report-forms" in that study's stf.xml file. CRFs that are not submitted will be available upon request.

Does the Agency agree with the proposed approach for submission of narratives and CRFs?

FDA Response to Question 1:

Your plan to submit subject narratives and CRFs outlined above appears acceptable. Additionally, submit electronic links for all deaths, SAEs, severe AEs, and subject discontinuations regardless of reason.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our July 21, 2022 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]

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

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

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. 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.

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[2] and Pregnancy and Lactation Labeling Final Rule[3] 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.

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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.

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[4] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[5]. 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.

4.0 AGENDA

- **Question 4**

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

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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/

SHARI L TARGUM
10/13/2022 04:09:24 PM

IND 142047

MEETING MINUTES

Arcutis Biotherapeutics, Inc.
Attention: Chester G. Elias, III
Executive Director of Regulatory Affairs
2945 Townsgate Road, Suite 110
Westlake Village, CA 91361

Dear Mr. Elias:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for roflumilast foam, 0.3%.

We also refer to the meeting between representatives of your firm and the FDA on December 16, 2020. The purpose of the meeting was to discuss the development program for roflumilast foam and to ensure that the proposed Phase 3 study and other relevant late stage plans are adequate.

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 Kimberle Searcy, Regulatory Project Manager, at 240-402-4454.

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 Agenda

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

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: December 16, 2020 1:30 – 2:30 pm EST
Meeting Location: Teleconference

Application Number: IND 142047
Product Name: roflumilast foam, 0.3%

Proposed Indication: For the treatment of seborrheic dermatitis

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

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Kimberle Searcy, MPH

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDD
David Kettl, MD, FAAP, Clinical Team Leader, DDD
Hamid Tabatabai, MD, Clinical Reviewer, DDD
Barbara Hill, PhD, Pharmacology Supervisor, Division of Pharmacology Toxicology for Immunology and Inflammation (DPT – II)
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Liping Pan, PhD, Senior Staff Fellow, DIIP
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics III (DB III)
Marilena Flouri, PhD, Biometrics Reviewer, DB III
Barbara Gould, MBAHCM, Chief, Project Management Staff, Division of Regulatory Operations for Dermatology and Dentistry (DRO-DDD)
Kimberle Searcy, MPH, Regulatory Project Manager, DRO-DDD

SPONSOR ATTENDEES

David Berk, MD, Vice President Clinical Development
Patrick Burnett, MD, PhD, Chief Medical Officer
Chester G. Elias III, Executive Director, Regulatory Affairs
Robert Higham, MPAS, PA-C, Executive Director, Clinical Development
Charlotte Merritt, Vice President, Regulatory Affairs

Lynn Navale Vice President, Biometrics
David Osborne, PhD, Chief Technical Officer
Scott Snyder, PharmD, Executive Director Product Safety and Pharmacovigilance
(b) (4) Consultant
Frank Watanabe, CEO and President

1.0 BACKGROUND

Purpose of meeting:
The purpose of this meeting is to discuss the proposed phase 3 studies and the late stage development program for roflumilast foam. The sponsor plans to begin the phase 3 development in the first half of 2021.

CORONAVIRUS – 19 (COVID 19) CLINICAL TRIAL GUIDANCE

During the COVID-19 public health emergency, ensuring the safety of study participants is paramount. Sponsors should consider each circumstance, focus on the potential impact on the safety of study participants, and modify study conduct accordingly. It is critical that study 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

No regulatory questions were submitted for this meeting.

2.2. Chemistry, Manufacturing & Controls (CMC)

Question 1:
Does the Agency agree the proposed drug product specifications are adequate to support Phase 3 studies?

FDA Response to Question 1:
Your proposed drug product specification appears reasonable to initiate the Phase 3 clinical trials. However, for the commercial drug product, the stability acceptance criteria for the assay should be revised from (b) (4) Additionally, all acceptance criteria of "Report" in the drug product specification should be replaced with numeric limits. The proposed numeric limits should be based on the results from testing of the pivotal clinical batches of drug product. You should also add testing and acceptance criteria for elemental impurities (USP <232>/USP <233>, ICH Q3D) to the

drug product specification. If the elemental impurities are controlled by the drug substance specification, you should submit a risk-based assessment to justify omission of testing of the drug product for elemental impurities.

The microbiological tests you have proposed in the drug product release specification are adequate. However, to ensure the product quality is maintained through its shelf-life, microbiological tests should be performed on every batch during the stability studies. [redacted] (b) (4)

Question 2:
Does the Agency agree with Arcutis' plan to use both the current [redacted] (b) (4) and the [redacted] (b) (4) roflumilast drug substance in the manufacture of the foam drug product to support the Phase 3 clinical study?

FDA Response to Question 2:
Based on the fact that the API is [redacted] (b) (4)

Question 3:
Does the Agency agree the AET and microbial control strategies listed above is adequate to support, upon NDA approval, the removal from the post-approval stability protocol?

FDA Response to Question 3:
We agree with your proposed plan to perform antimicrobial effectiveness testing only on one registration batch during shelf-life. However, the post-approval stability program should include the other microbiological tests. See FDA Response to Question 1.

2.3. Nonclinical

Question 1:
Does the Agency agree that [redacted] (b) (4)

FDA Response to Question 1:

We do not agree that an [redacted] (b) (4) Information from appropriately conducted clinical studies that evaluate effects of roflumilast foam on previously agreed upon itch measures with the Agency can be included in labeling. Refer to FDA Response to Question 5.

Meeting Discussion:

The Agency re-iterated that [redacted] (b) (4)

Question 2:

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

FDA Response to Question 2:

The precise causes of seborrheic dermatitis are multifactorial and not completely elucidated. [redacted] (b) (4) .

Post-Meeting Comment:

[redacted] (b) (4) claim, the Sponsor should provide [redacted] (b) (4)

We also recommend that you review the FDA guidance document: "Microbiology Data for Systemic Antibacterial Drugs-Development, Analysis, and Presentation-Guidance for Industry" (https://www.fda.gov/media/77442/download). Although, this guidance document is intended for the development of antibacterial drug products, this will provide general information on what clinical microbiology data are needed and at what phases of development to provide the data for us to review.

References:

(b) (4)

2.4. Clinical Pharmacology

Question 8:
Considering the similarities in formulation of ARQ-154 foam 0.3% compared to ARQ-151 cream 0.3% and that both have been well tolerated with comparable PK following once daily application by study subjects, does the Agency agree with the plan not to repeat these Phase 1 clinical dermal safety studies with ARQ-154 foam 0.3%?

FDA Response to Question 8:
Yes, we agree that the results of dermal safety studies (ARQ-151-108/-109/-110/-111) conducted with ARQ-151 Cream, 0.3% in healthy subjects in your psoriasis development program may be used to support dermal safety, and that distinct dermal safety studies in healthy subjects are not necessary with ARQ-154 foam, 0.3%.

Question 9:
Does the Agency agree with the proposed design of our MUSE Study?

FDA Response to Question 9:
We acknowledge that you plan to conduct a maximal use PK trial to characterize the systemic exposure of your product in at least 16 evaluable male and female subjects with seborrheic dermatitis including at least 4 adolescents aged 12 to <17 years. We note that eligible subjects will have BSA involvement of ≥(b) (4) in adolescent subjects or ≥5% in adult subjects with Moderate ('3') to Server ('4') seborrheic dermatitis based on Investigator Global Assessment (IGA), and at least 6 subjects will have an IGA of severe ('4') for study entry. (b) (4) and we recommend that you enroll subjects down to 9 years of age in your maximal use PK study. Submit your protocol before you initiate your study.

As PK assessment under maximal use conditions will inform systemic safety and labeling of your product, we recommend that you target at least 8 to 10 adolescent subjects with a sufficient number of subjects with a lower age and body weight, and the dermatological disease of interest at the upper range of severity as anticipated. The protocol for the maximal use PK trial should be submitted for our review. See Written Responses dated August 13, 2019 for information on how to design a maximal use PK study.

Meeting Discussion:
The sponsor proposed to assess PK under maximal use conditions in subjects down to 9 years of age and they proposed to target at least (b) (4) completers between the age of 9 years to 16 years. Based on the experience in their soriasis development program; the sponsor proposed a minimum body surface area (BSA) of at least (b) (4) in pediatric subjects and they also proposed to obtain trough level PK samples in lieu of serial PK sampling in pediatrics.

The Agency acknowledged the sponsor's plan to assess PK under maximal use conditions in subjects down to 9 years of age and recommended surveillance PK sampling in pediatric subjects should be proposed based on PK experience in adult subjects with seborrheic dermatitis. The Agency further stated that trough level PK sampling in pediatric subjects should be obtained at steady state. The Agency advised the sponsor to not draw any analogies between the psoriasis and the seborrheic dermatitis programs as disease characteristics are very different. Furthermore, the Agency recommended the sponsor to target at least 8 to 10 completers in the pediatric age range and also recommend the sponsor to include pediatric subjects with at least 5% BSA involvement, which is similar to adults. The sponsor stated that enrolling subjects with at least 5% BSA involvement, especially within the lowest age range may be challenging (b) (4) . The Agency stated that at the moment they are recommending to enroll adult and pediatric subjects with at least 5% BSA involvement; however, if the sponsor would like to propose something different, then they should propose that in the protocol along with adequate scientific justification for Agency review and comment.

2.5. Clinical

Introductory Clinical Comments:

You propose to conduct a single R(2:1), DB, VC, Phase 3 trial (ARQ-154-304) in (b) (4) subjects >= (b) (4) years of age with moderate to severe seborrheic dermatitis at baseline (IGA=3, 4; involving <= 20% of BSA ;and overall assessment scores of moderate (b) (4) for erythema(0-3 scale) and scaling(0-3 scale)). Subjects will apply study drug to treatment areas QD for 8 weeks (b) (4)

Safety assessments include TEAEs, application site assessments/change in pigmentation, safety labs, C-SSRS/PHQ-8 (b) (4) PHQ-A.

The Primary Efficacy Endpoint will be IGA success [IGA score (= 0/1)] at week 8. Secondary efficacy endpoints include "WI-NRS Success (>= 4-point improvement from baseline) at Weeks 8, 4, 2; IGA success at Weeks 4, 2; Scaling Success at Week 8 [Achievement of an overall assessment of Scaling score (b) (4) Erythema Success at Week 8 [achievement of an overall assessment of Erythema score (b) (4)

Question 1:
Considering the highly statistically significant results from our Phase 2 study (ARQ-154-203), does the Agency agree that we can proceed to conduct a single Phase 3 study for the purpose of registration of ARQ-154 foam 0.3% for seborrheic dermatitis?

FDA Response to Question 1:
We note that, in general, replication of study findings from two adequate and well-controlled trials is needed to establish a new efficacy claim. For establishing an efficacy claim based on a single confirmatory trial, in the presence of supportive evidence, we refer you to the guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* for the cases when a single confirmatory trial is appropriate. We note that a small p-value is only one component of robust statistical findings. As discussed in the guidance, other factors such as consistency across centers and subgroups, among other criteria, contribute to robust statistical findings. For the purpose of powering a single Phase 3 trial to support establishing efficacy, the trial should be powered, and efficacy analyses should be conducted, at two-sided significance level much less than your proposed (b) (4)

Meeting Discussion:
The Agency noted that the proposed significance level of alpha 0.01 for powering a single proposed Phase 3 trial is only one component of robust statistical findings for establishing an efficacy claim based on a single confirmatory trial as noted in the preliminary comments and more detailed in the guidance. The Agency also noted that the equivalent of two independent Phase 3 trials powered at alpha 0.05 is a single Phase 3 trial powered at alpha 0.00625.

There was general discussion regarding the breadth of the safety data for this application which may be impacted by whether a regulatory determination will have been made for your product for another indication/formulation. To date, roflumilast in any formulation has not been approved in any application.

Question 2:
Does the Agency agree with the proposed design for our Phase 3 study (Section 13.3.6) to be conducted in subjects (b) (4) years of age and older with moderate to severe seborrheic dermatitis?

FDA Response to Question 2:
The general design of your Phase 3 trial (ARQ-154-304) appears reasonable. We may have additional comments following the submission of the complete protocol to the IND.

We recommend that you lower the minimum age limit for enrollment to 9 years of age in your proposed Phase 3 trial (ARQ-154-304) and your ongoing LTS study (ARQ-154-214); as the generally accepted age of onset for normal puberty is considered to be 9 years of age. While uncommon in the 9 to 12-year age group, consistency across other indications with pubertal onset is desirable.

Question 3:
Does the Agency agree with the use of IGA score of 'clear' or 'almost clear' to determine treatment success using the 5-grade IGA scale (clear, almost clear, mild, moderate, severe) as the primary endpoint in the planned Phase 3 pivotal trial in subjects with moderate and severe disease (see Appendix 4)?

FDA Response to Question 3:

Investigator Global Assessment of Disease (IGA)

Score	Description
0	(b) (4) clear: No erythema, no scaling (hypo-hyperpigmentation can be present)
1	Almost clear: (b) (4) slight erythema and/or trace amounts of scaling
2	Mild: Pink to red color and/or slight scaling
3	Moderate: Distinct redness and/or clearly visible scaling
4	Severe: Severe erythema (intense, fiery red) and/or severe scaling (coarse, thick scales with flaking onto clothes or skin)

We agree with your primary efficacy endpoint of IGA success (IGA score (0/1) with 2-point improvement) at week 8.

We reiterate the comment conveyed to you at the pre-IND WRO meeting on August 13, 2019, to characterize IGA score of "Almost clear (1)" by the presence of (b) (4) slight erythema but no other signs of the disease. Your currently proposed IGA score of "almost clear (1)" retains the descriptor "trace amount of scaling".

Meeting Discussion:
There was discussion regarding the category descriptors for the IGA, and in particular whether "trace scaling" could be included in the almost clear category. This issue was previously commented upon in the preIND meeting. The Agency expressed concern that slight scaling not be included in category 1, due to challenges in investigator discrimination between "slight scaling" in category 2 and "trace scaling" in category 1. The sponsor would need to provide justification that the IGA scale is fit for purpose for the indication and that category descriptors are distinct for accuracy and precision of treatment effect results.

Question 4:
Does the Agency agree with the proposed statistical testing method, imputation method, and alpha level?

FDA Response to Question 4:
The proposed method of CMH test stratified by randomization factors for the analysis of the co-primary and binary secondary endpoints appears reasonable. For the alpha level, you are referred to FDA Response to Question 1.

We have the following comments for the estimand framework and the handling of missing data:

a. The Phase 3 protocol(s)/SAP(s) should prespecify the primary estimand of interest along with methods for handling intercurrent events (e.g., study discontinuation, rescue medication). In addition, you should provide a justification that this estimand and the statistical methods utilized to estimate it are appropriate. Refer to ICH E9 (R1) for defining and explaining your estimand, available at https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

b. The proposed specified the multiple imputation (MI) method as the method for handling the missing data for the analyses of the primary and secondary efficacy endpoints appears reasonable. We note that the details of the MI method (seed number, imputation method, number of iterations, etc.) should specified in the protocol and the statistical analysis plan (SAP) in order to assure appropriateness of the statistical analysis method and interpretation of the study findings. In addition to the primary method of handling the missing data, the Phase 3 protocol(s)/SAP(s) should pre-specify at least two sensitivity analyses that utilize alternative assumptions from those of the primary method to ensure that efficacy results are not driven by the method of handling missing data. We recommend that you conduct a tipping point analysis to explore the space of plausible missing data assumptions.

Question 5:
Does the Agency agree that a secondary endpoint assessing the proportion of subject achieving a four point improvement in WI-NRS to determine itch response in the population of subjects with a baseline WI-NRS score of $\geq$ 4 in the Phase 3 trial would support labeling of itch response in the proposed indication?

FDA Response to Question 5:
As a footnote under the table with the schedule of visits and assessment on pages 332-333 of the briefing package, you stated that ' (b) (4) . We note that WI-NRS assessments should be conducted uniformly throughout the trial (e.g., daily assessments for the entire trial, (b) (4) In addition, your Phase 3 protocol(s) should provide information on how the daily scores will be used to calculate the WI-NRS score at study visits (e.g., average of the daily scores 7 days prior to the Week 16 visit) and how daily missing data will be handled to obtain such scores.

A single item NRS, in principle, is acceptable to assess pruritus intensity. Your proposed responder definition (≥4-point reduction from baseline) appears reasonable.

Your study population should enroll sufficient number of subjects with WI-NRS>= 4 at baseline to allow meaningful evaluation of WI-NRS responders at Week 8.

Post-Meeting Comment:
The Agency notes that WI-NRS assessments should be performed daily throughout the trial to capture variability of pruritus. WI-NRS scores at study visits (i.e., Baseline, Week 2, Week 4 and Week 8) can be obtained as weekly averages of the daily scores 7 days prior to the study visits. The Agency reiterates their comment that the phase 3 protocol(s) should provide information on how daily missing data will be handled to obtain such weekly scores.

Question 6:
Does the Agency agree with the method proposed to control for multiple comparisons between primary and secondary endpoints as well as within secondary endpoints?

FDA Response to Question 6:
You stated that continuous secondary endpoints will be analyzed using Analysis of Covariance with treatment and stratification factors as independent variables, however, you have not listed any continuous secondary endpoints.

Assuming that testing within secondary endpoints requires statistical significance before proceeding to the testing of the next secondary endpoint, your statistical testing approach allows for control of the Type I error rate at your proposed alpha level. However, you are referred to the FDA Response to Question 1 for the alpha level in a single Phase 3 trial.

Question 7:
Considering the similarities in the formulation, PK profile, and benefit-risk profile of ARQ-154 foam 0.3% in seborrheic dermatitis compared with ARQ-151 cream 0.3% in psoriasis, does the Agency agree that the planned NDA safety database for ARQ-154 foam 0.3% is sufficient to allow conclusions to be drawn on the safety of ARQ-154 foam and support registration of the product for the treatment of seborrheic dermatitis?

FDA Response to Question 7:

Table 3 . ARQ-154 Foam 0.3% Primary Safety Database

Study	Total Planned Enrollment	Randomization Ratio (IP:Vehicle)	Total NEW Exposures to ARQ-154 Foam 0.3%	TOTAL Exposures: 8 weeks	TOTAL Exposures: 24 weeks	TOTAL Exposures: 32 weeks
ARQ-154-203	226	2 to 1	154	141	0	0
(b) (4)						
ARQ-154-214	400	NA	307	282	300	39
ARQ-154-304	360	2 to 1	240	221	0	0
ARQ-154-116	16	NA	16	0	0	0
Totals	(b) (4)					

(b) (4) See our comments above regarding the recommendation for two adequate and well controlled trials to support safety and efficacy.

(b) (4)

The adequacy of the safety database will be a focus of the NDA application review, noting that different formulations may have differing adverse event profiles due to vehicle effects.

We will provide further comments for the pooling strategy and statistical analysis for the Integrated Summary of Safety (ISS) once you finalize your Phase 3 program and submit the statistical analysis plan for ISS.

Meeting Discussion:
See the Meeting Discussion to Question 1 under section 2.5 Clinical.

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*.[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]

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.[4]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, 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 are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data

[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] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

Standards Resources web page[5] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 started on or 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 FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

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[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

Additional information can be found at FDA.gov.[6]

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[7] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[8]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

4.0 SPONSOR AGENDA

Items for Discussion:

- Non-clinical Question 1
- Clinical Pharmacology Question 9
- Clinical Questions 1, 3, and 7

[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[8] https://www.fda.gov/media/109533/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/

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