

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215985Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 135681

MEETING MINUTES

Arcutis, Inc.
Attention: Mridula Shukla
Director, Regulatory Affairs
3027 Townsgate Road, Suite 300
Westlake Village, CA 91361

Dear Ms. Shukla:

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

We also refer to the telecon between representatives of your firm and the FDA on May 3, 2021. The purpose of the meeting was to discuss the development program for roflumilast cream.

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 Craig Johnson, Regulatory Project Manager at 301-796-3921.

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



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: May 3, 2021; 1:30 – 2:30 PM EDT
Meeting Location: Teleconference

Application Number: IND 135681
Product Name: roflumilast cream

Proposed Indication: For the topical treatment of plaque psoriasis, in patients (b) (4) years of age and older

Sponsor Name: Arcutis Biotherapeutics, Inc.

Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetics Act

Meeting Chair: Dr. Kendall Marcus, MD
Meeting Recorder: Dr. Craig Johnson, PharmD

FDA ATTENDEES

Kendall Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
David Kettl, MD, FAAP, Clinical Team Leader, DDD
Hamid Tabatabai, MD, Clinical Reviewer, DDD
Mohamed Alish, PhD, Biometrics Team Leader, Division of Biometrics III
Marilena Flouri, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Luke Oh, PhD, Clinical Pharmacology Reviewer, DIIP
Hamid Shafiei, PhD, Quality Assessment Lead, DNDP II, NDPB V
Yan Xu, Primary Reviewer for manufacturing review in OPMA
CDR Renmeet Grewal, PharmD, MS, RAC, Director, Project Management Staff, Division of Regulatory Operations for Immunology and Inflammation (DRO – II)
LT Sascha Randolph, BSDH, PHDHP, Regulatory Health Project Manager, DRO – DD
Craig Johnson, PharmD, Regulatory Health Project Manager, DRO – DD

SPONSOR ATTENDEES

David Berk, MD Vice President, Clinical Development
Patrick Burnett, MD, PhD Chief Medical Officer
David Chu, MD, PhD Executive Director, Clinical Development
Robert Higham, MPAS, PA-C Executive Director, Clinical Development
Jennifer Mahilo Director, Regulatory Affairs CMC

Charlotte Merritt Vice President, Regulatory Affairs
Girish Aras, PhD Vice President, Biometrics
David Osborne, PhD Chief Technical Officer
Mridula Shukla Director, Regulatory Affairs
Scott Snyder, PharmD Executive Director, Product Safety and Pharmacovigilance
Archie Thurston, PhD Consultant, Drug Metabolism and Pharmacokinetics
Frank Watanabe President and Chief Executive Officer

1.0 BACKGROUND

Purpose of Meeting:

The purpose of the meeting is to discuss Arcutis' plans to submit an NDA, to support the registration of roflumilast cream 0.3% for the treatment of plaque psoriasis.

2.0 QUESTIONS AND RESPONSES

2.1. Regulatory

Regulatory Question 1:

As a non-NME product, it is understood that the NDA for roflumilast cream 0.3% would not be part of the PDUFA "Program" and thus all steps outlined as part of the 21st Century Review Process may not take place in the same timeframe.

Could FDA share the general timing of milestone communications that take place as part of a non-NME NDA review?

FDA Response to Regulatory Question 1:

The timeline of the NDA will be determined at the time of filing.

Meeting Discussion: No discussion occurred at the meeting.

Regulatory Question 2:

For nonclinical and clinical study reports that have been previously submitted to IND 135681 for topical roflumilast cream, Arcutis plans to cross link from the NDA to the IND rather than resubmit these reports.

Does the Agency agree to the proposal to cross link nonclinical and clinical study reports previously submitted to the IND?

FDA Response to Regulatory Question 2:

It is acceptable to cross link nonclinical study reports previously submitted to the IND in the NDA submission. Provide a table that lists the nonclinical studies and provides links to the nonclinical study reports in the IND submission.

Meeting Discussion: No discussion occurred at the meeting.

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2.2. Chemistry, Manufacturing and Controls (CMC)

CMC Question 1:

(b) (4)

As agreed with FDA at the EOP2 meeting held 23 October 2019, Arcutis has conducted a 4-week dermal repeat-dose toxicity study in minipigs of (b) (4). In qualifying (b) (4) as a non-compendial excipient, data from the dermal repeat-dose toxicity study in minipigs (b) (4) an in silico mutagenicity assessment completed by Arcutis, as well as the large amount of dermal safety data from Arcutis' Good Laboratory Practices (GLP)-compliant repeat-dose dermal safety studies that used roflumilast cream drug product and vehicle control test articles containing (b) (4). The study report and Standard for Exchange of Nonclinical Datasets (SEND) datasets from the 4-week dermal minipig study will be included in Module 4 of the NDA and will be cross-referenced from Module 3.

In Module 3, the supporting documents for (b) (4) will be provided in a separate 3.2.P Control of Excipients section specific for (b) (4). All other excipients are compendial. The CMC CTD location along with the list of document sections are provided below.

- 3.2.P.4 Control of Excipients (b) (4)
- 3.2.P.4.1 Specifications
 - 3.2.P.4.2 Analytical Procedures
 - 3.2.P.4.3 Validation of Analytical Procedures
 - 3.2.P.4.4 Justification of Specifications

Does the Agency agree with the proposed location and list of sections that will be provided in Module 3 of the NDA for the control of this excipient?

FDA Response to CMC Question 1:

The proposed location for the 4-week dermal minipig study, that used roflumilast cream drug product and vehicle control containing (b) (4) and corresponding SEND dataset in Module 4 of the NDA is acceptable. The adequacy of this study will be determined during the NDA review.

Meeting Discussion: No discussion occurred at the meeting.

CMC Question 2:

The roflumilast drug substance information is maintained in DMF (b) (4) by the DMF holder, (b) (4). In addition to the letter of authorization, Arcutis will include the following drug substance sections in the NDA:

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3.2.S.1 General Information

3.2.S.4.1 Specification

3.2.S.4.2 Analytical Procedures

3.2.S.4.3 Validation of Analytical Procedures

3.2.S.4.4 Batch Analyses (CoAs from Phase 3 and three primary registration batches)

Does the Agency agree with the drug substance sections to be included in the NDA?

FDA Response to CMC Question 2:

The scope of the drug substance information to be included in the NDA appears reasonable. Include a Letter of Authorization to cross-reference the DMF in the NDA.

Meeting Discussion: No discussion occurred at the meeting.

CMC Question 3

A draft roflumilast USP monograph was published for comment in PF 46(5). The comment period has closed. Based on the USP-NF publication schedule, PF 46(5) is targeted for publication in USP-NF 2022, issue 1. The release date for USP-NF 2022, issue 1 is 01 November 2021, becoming official on 01 May 2022. If the USP monograph for roflumilast is issued in USP-NF 2022, issue 1, the release date will be during the review of the roflumilast cream 0.3% NDA. It is probable that once released, (b) (4) will work towards adhering to the drug substance monograph by 01 May 2022 (b) (4)

FDA Response to CMC Question 3:

(b) (4)

Meeting Discussion: No discussion occurred at the meeting.

CMC Question 4

(b) (4)

The validation plan is provided in Section 14.5.

Does FDA agree with items 1 and 2 in the validation plan?

FDA Response to CMC Question 4:

FDA does not approve process validation protocols or reports during an application review (this does not refer to sterility assurance validation protocols and supporting information which shall be provided in 3.2.P.3.5 for sterile products). The actual protocols, acceptance criteria, study outcomes, and supportive development and qualification studies will be evaluated during an inspection of your manufacturing facilities. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

Meeting Discussion:

As long as you provide data to show that (b) (4) drug substance has the same stability profile and that the drug substance is fully solubilized and remains solubilized in the formulation, we do not have any concerns from product quality.

CMC Question 5:

Given the challenges with using typical analytical techniques for the determination of leachables (see Section 14.2.2), Arcutis is proposing to use a simulation solvent. Per USP <1664>, simulation studies may be used in circumstances where "it is not analytically feasible (due to challenging thresholds, for example) to successfully discover and identify all actual leachables in a drug product leachables study."

Does the Agency agree with this approach for the leachable studies?

FDA Response to CMC Question 5:

It is reasonable to use simulation studies according to USP <1664> for the determination of leachables. In your NDA, you should provide sufficient information to demonstrate that the drug product cannot be directly tested for leachables.

Meeting Discussion: No discussion occurred at the meeting.

2.3. Nonclinical

No Nonclinical Pharmacology questions were submitted for this meeting.

2.4. Clinical Pharmacology

Clinical/Biostatistics Question 1:

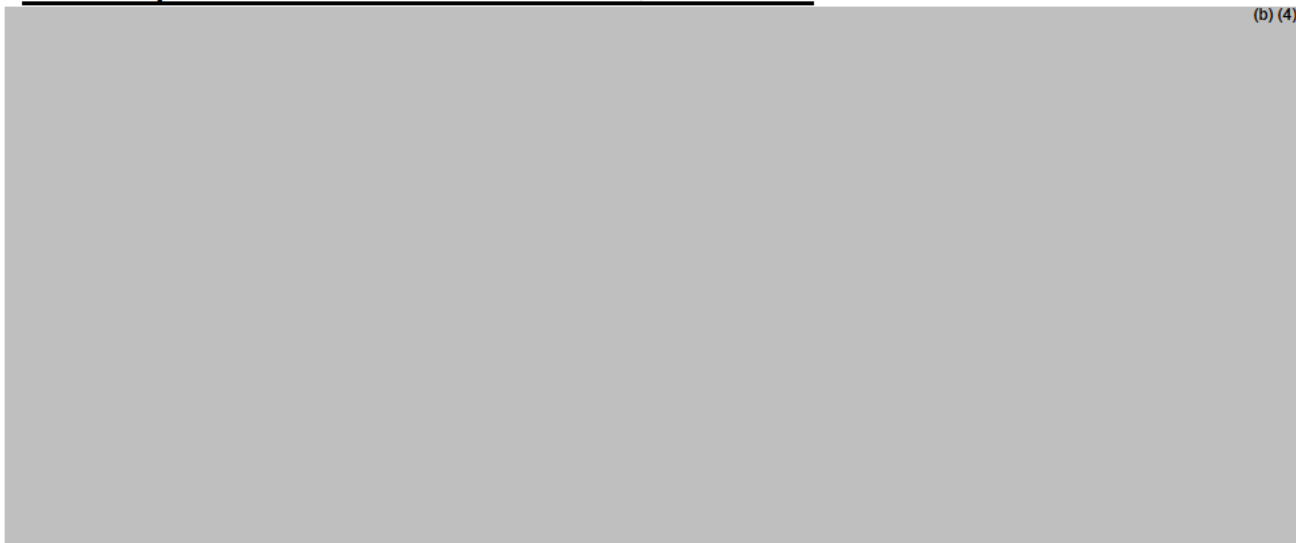
As summarized in Section 5.3, pediatric studies ARQ-151-215 and ARQ-151-216 are ongoing. The current estimate to complete enrollment of these studies is the end of 2021, with the data becoming available approximately 4 months later. The number of pediatric subjects who participated in roflumilast cream studies to be included in the NDA, including subjects from these studies and pediatric subjects enrolled in ARQ-151-301, ARQ-151-302, ARQ-151-306, and ARQ-151-107, is summarized in Section 13.4.2, along with a summary of currently available pediatric data. Data from ARQ-151-215 (for 4 subjects) and ARQ-151-216 (for 1 subject) to be included in the NDA are detailed in Appendix 2. Available pediatric data suggest consistent efficacy, safety, and PK profiles across age groups (Section 13.4). (b) (4)



- 1a. Does FDA agree with Arcutis' plan to submit an NDA for roflumilast cream 0.3% for the treatment of plaque psoriasis containing all study data previously agreed to with the Agency, but with less than the full study cohorts from ongoing studies ARQ-151-215 and ARQ-151-216? All available data from subjects participating in the ARQ-151-215 and ARQ-151-216 studies by a cutoff date of 26 March 2021 would be included in the NDA. Data from additional subjects will be included in the 120-Day Safety Update.

FDA Response to Clinical/Biostatistics Question 1a:

(b) (4)



Meeting Discussion

The sponsor plans to submit their initial NDA with data in subjects 12 years of age and older. The sponsor stated that ongoing enrollment issues present challenges and propose that the NDA be submitted prior to completion of studies 215 and 216. The Agency acknowledged enrollment issues for younger psoriasis subjects but stated that the recommended numbers of pediatric subjects be included. Ultimately this will be a business decision for the sponsor. If the application deviates from the agreed upon PSP, a rationale should be included in the application. The Agency noted that the issues would require review by the Pediatric Review Committee during the NDA review and a final determination regarding the pediatric populations will be completed at that time.

1b.

(b) (4)

FDA Response to Clinical/Biostatistics Question 1b:

See FDA response to Question 1a

1c.

(b) (4)

FDA Response to Clinical/Biostatistics Question 1c:

No, we do not agree

(b) (4)

1d. Does FDA agree with the sponsor's plans to request a Pediatric Study Deferral for ARQ-151-216 in subjects 2 to 5 years of age?

FDA Response to Clinical/Biostatistics Question 1d:

Yes. Based on your description of recruitment challenge, you may request a deferral of Study ARQ-151-216.

Clinical/Biostatistics Question 2:

Because ARQ-151-215 and ARQ-151-216 are ongoing, and data from only some of the planned subjects will be available at the time of the NDA, Arcutis proposes to summarize study-level data from these subjects in Modules 2.7.2, 2.7.3, and 2.7.4,

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supported by tables and listings, as described in Appendix 2. Due to the need to review data from these subjects separately, the data from ARQ-151-215 and ARQ-151-216 will not be formally integrated with the other studies for either the NDA or the 120-Day Safety Update. Disposition, demographic and disease characteristics, exposure, and safety data from the studies would be submitted in CDISC format at the time of the NDA and the 120-Day Safety Update submissions. Pharmacokinetic data will be submitted in tabular summaries. Full CSRs will be written and submitted to the NDA upon completion of the studies.

Does the Agency agree with plans to submit the data tables and listings described in Appendix 2 for studies ARQ-151-215 and ARQ-151-216 in the NDA in lieu of CSRs and to update these data tables and listings for the 120-Day Safety Update?

FDA response to Clinical/Biostatistics Question 2:

Yes. We agree with your plan. See *FDA response to Question 1a*.

Additional Clinical Pharmacology Comments:

1. It appears that the systemic exposure of Roflumilast and its active metabolite Roflumilast-N-Oxide are higher than the approved oral product. Hence you would need to address the drug interaction potential of your product.
2. You will also need to address PK of your product in subjects with renal and hepatic impairment in your NDA.
3. In your NDA, you would need to submit the bioanalytical as well as bioanalysis reports for review and you would also need to provide data to support the storage stability of your PK samples.

Meeting Discussion: No discussion occurred at the meeting.

2.5. Clinical/Biostatistics

Clinical/Biostatistics Question 3

Arcutis will submit integrated summaries of efficacy and safety (ISE and ISS) to support the clinical summaries of efficacy and safety (Modules 2.7.3 and 2.7.4).

Module 2.7.3 will include data from the 2 pivotal Phase 3 studies, ARQ-151-301 and ARQ-151-302 and will also present long-term efficacy data from the 2 long-term open-label studies, ARQ-151-202 and ARQ-151-306 (Section 13.1). The proposed ISE will integrate data from ARQ-151-301 and ARQ-151-302 and will present data from ARQ-151-202 and ARQ-151-306 separately. The rationale for integrating the data from the 2 pivotal studies is that they have consistent study design, efficacy assessments, duration, data collection, analytical derivations, methods of handling missing data, vehicle control, and investigator training on efficacy assessments, and therefore provide the most direct interpretation of integrated efficacy in the proposed indication. The SAP

for the ISE is provided in Appendix 3. The proposed ISE will provide integrated summaries of subject disposition, demographic characteristics, baseline characteristics, and primary efficacy endpoints, and secondary efficacy endpoints. Subgroup analyses of efficacy endpoints will also be presented as defined by age, sex, ethnicity, race, baseline BSA, and baseline IGA.

The objective for Module 2.7.4 is to provide integrated data on safety for subjects with plaque psoriasis treated with topical roflumilast of any formulation and dose. Therefore, the proposed Module 2.7.4 will include safety data from the studies outlined in Section 13.1.2. These studies encompass all safety data in subjects with psoriasis with any baseline psoriasis involvement (including subjects in the MUSE study) at any dose level, (b) (4) as well as dermal safety studies conducted in healthy subjects.

On an integrated level, the ISS will include integrated data and analyses from the following studies:

- ARQ-151-101 (Cohort 2 only)
- ARQ-151-201
- ARQ-151-202
- (b) (4)
- ARQ-151-301
- ARQ-151-302
- ARQ-151-306

The rationale for this integration is that these studies treated subjects with psoriasis, with baseline BSA involvement and topical roflumilast doses (exposure) generally consistent with those used in the pivotal studies and intended in the proposed indication; thus, these studies provide the broadest yet most directly interpretable assessment of safety.

The SAP for the ISS is provided in Appendix 4. The integrated safety analysis will provide data summarized in 3 analysis pools derived from all subjects who received at least 1 dose of investigational product (IP):

- Pooled safety data from the pivotal Phase 3 studies (ARQ-151-301 and ARQ-151-302) (N = 881)
- Pooled safety data from all vehicle-controlled studies (ARQ-151-101 [Cohort 2], ARQ-151-201, (b) (4) ARQ-151-301, and ARQ-151-302) (N = 1613)
- Pooled safety data from the long-term open-label studies (ARQ-151-202 and ARQ-151-306) (N = 594)

The record-level integrated datasets will include all 3 of these data pools.

The integrated safety analysis will include extent of exposure, subject disposition, demographic and baseline characteristics, adverse events, adverse events leading to withdrawal, deaths and other serious adverse events, local tolerance assessments, clinical laboratory evaluations, vital signs, electrocardiograms (ECGs), patient health questionnaire depression scales (Patient Health Questionnaire Depression Scale [PHQ-8] and Patient Health Questionnaire Depression Scale Modified for Adolescents [PHQ-A]), Columbia Suicide Severity Rating Scale (C-SSRS), and Children's Depression Inventory (CDI-2). Subgroup analyses of adverse events will be presented by age, sex, ethnicity, race, exposure duration, baseline BSA group, and baseline IGA.

Does the Agency agree with the plans for integrating the efficacy and safety data in the NDA?

FDA Response to Clinical/Biostatistics Question 3:

Integrated Summary of Efficacy (ISE):

Your proposal to pool efficacy data from the two identically-designed Phase 3 trials for the integrated summary of efficacy (ISE) is acceptable. The ISE should include discussions regarding the strength of evidence across all trials, including discussion of any difference in outcomes across trials. We recommend that subgroup analyses be conducted for the individual trials in addition to the subgroup analyses on the pooled data. We also note that the objective of the ISE is to support the analysis results obtained from the individual trials and not to establish a new efficacy claim based on pooled data. Therefore, analyses based on pooled efficacy data are considered exploratory.

Integrated Summary of Safety (ISS):

Your plan to include integrated safety data for subjects with plaque psoriasis treated with topical roflumilast of any formulation and dose in M 2.7.4 of your NDA (b) (4) appears acceptable.

(b) (4)

We expect that the safety data from the final clinical study reports (including the final CSR for trial ARQ-151-306) should be included at the time of your NDA submission. Submission of large safety datasets at the time of 120-day safety update will not be acceptable.

Meeting Discussion:

For study 306, data presentation is planned for 267 subjects and follow up safety data for 12 subjects and 6 new pediatric subjects will be submitted at the 120-day safety

update. The final CSR would be submitted with the pediatric supplement following the initial approval. The Agency found this proposal acceptable.

Additional Comments for the ISS:

- You propose three pools for the ISS, the pivotal Phase 3 pool, the vehicle-controlled pool and the long-term open-label pool. The Phase 3 pool will be integrating identically designed trials; therefore, the pooling methodology for this pool appears reasonable. The vehicle-controlled pool will be integrating results across 4 trials with roflumilast cream (ARQ-151-101 (Cohort 2), ARQ-151-201, ARQ-151-301, and ARQ-151-302) (b) (4). These trials have different randomization ratios, patient populations, treatment arms, treatment duration and investigational product formations. 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. Therefore, we recommend pooling vehicle-controlled trials with the 0.3% cream formulation of similar design, i.e., Trials ARQ-151-201, ARQ-151-301, and ARQ-151-302. We further note that 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. Crude pooling of AEs across studies to compare treatment arms may cause difficulty in interpreting safety signals, as a result of what is known as the Simpson's paradox. For discussion about the impact of improper pooling on interpretation of study findings which may leads to the Simpson's paradox in reporting adverse events we refer you the following articles:
 - o Crowe, B., Chuang-Stein, C., Lettis, S., & Brueckner, A. (2016). Reporting adverse drug reactions in product labels. *Therapeutic Innovation & Regulatory Science*, 50(4), 455-463.
 - o 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.
- The SAP specified providing summaries for AEs where the number and percent of subjects who reported at least 1 AE will be presented. Tables or graphs 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 measure (e.g., proportion and/or

incidence rate) is calculated within each study and then a combined summary measure is calculated based on planned weights for the individual studies. Refer to the articles above for more information. The SAP for the ISS should pre-specify the weights.

- We recommend that, in addition to the number and percent of subjects who reported at least 1 AE, the AE tables present the within-arm summary measure of incidence rate (expressed in number of subjects with events per 100 subject years) adjusted for exposure, also known as exposure-adjusted incidence rate (EAIR) and also adjusted for study size, along with 95% CI. We further recommend that you consider a between-arm summary measure (e.g., difference in exposure-adjusted incidence rates between treatment arms) for comparison between roflumilast cream 0.3% and vehicle. In particular, we recommend that the tables present the following in each treatment arm:
 - a) The number of subjects
 - b) The number of subjects with the adverse event
 - c) The study-size adjusted percent of subjects with the event
 - d) The number of exposure years
 - e) The point estimate of the study-size adjusted EAIR, along with the corresponding 95% confidence interval
 - f) The point estimate of the between-group summary measure (e.g., difference in study size-adjusted EAIR), along with the corresponding 95% confidence interval
- The SAP for the ISS should provide definitions for the time to last dose, the risk period, exposure time and exposure-adjusted incidence rate. In addition, the SAP should pre-specify an appropriate statistical method to construct the 95% CIs.

We recommend submitting the final SAP for ISS for Agency review.

Meeting Discussion

There was general discussion related to presentation of the safety data and exposure adjusted incidence rates in the application. The sponsor stated that the EAIR did not need to be included in the ISS as the numbers of observed events was low. The Agency noted that the pooling of data would need to be adjusted by study size to account for differences in study size and design, particularly to avoid Simpson's paradox. Different randomization ratios would impact the results of the proposed analyses and presentation of the data, and the Agency has not reviewed the statistical analysis plans

for these analyses. The Agency proposed that the sponsor rationale and full SAP should be submitted for review to allow further Agency comments.

Clinical/Biostatistics Question 4:

As described in Clinical/Biostatistics Question 3, Arcutis plans to generate pooled analyses for both efficacy and safety (an ISE and ISS). The text portions of the ISE and ISS will be placed in Module 2 in 2.7.3 and 2.7.4, respectively. Summary table and data listings of the pooled data, along with the respective SAPs, will be provided in Module 5.3.5.3. The Table of Contents for the ISE is provided in Appendix 5 and the Table of Contents for the ISS in is provided in Appendix 6.

- a. Does the Agency agree with the proposal for placement of the text and data portions of ISE and ISS in the NDA?
- b. Does the Agency have any comments on the planned content for the ISE and ISS?

FDA Response to Clinical/Biostatistics Question 4:

- a. Your plan to place the text of the ISE/ISS in Modules 2.7.3/2.7.4, and the summary table/data listings/SAPs for the pooled data in Module 5.3.5.3 appears acceptable.
- b. The content for the ISE appears reasonable. See also our comments for the ISE under *FDA Response to Question 3*.

Refer to *FDA Response to Question 3* regarding [REDACTED] (b) (4) inclusion of final CSR safety datasets from trial ARQ-151-306 in the ISS.

Refer to *FDA Response to Questions 1,2* regarding acceptability of submission of interim safety datasets from the maximum use Trials ARQ-151-215/-216 at the time of the NDA submission.

You plan to include the following safety data in the ISS (reported for 3 safety data pools: pivotal Phase 3 studies, all vehicle-controlled studies, and all long-term open-label studies) to include subgroups (by age, sex, race/ethnicity, duration of exposure, baseline BSA, baseline IGA) appears acceptable:

- Disposition, demographics, and exposure
- Summary of TEAEs (overall/subgroups, by SOC/PT/subgroups, by SOC/PT/severity/subgroups, by SOC/PT/causality/subgroups, by PT, by SOC/PT/causality/severity)
- Summary of TEAEs leading to discontinuation (by SOC/PT/subgroups, by PT/subgroups)
- Summary of SAEs (by SOC/PT/subgroups, by SOC/PT/severity/subgroups, by SOC/PT/causality/subgroups)

- Summary of SAEs leading to discontinuation (by SOC/PT/subgroups, PT/causality/subgroups)
- Listing of all SAEs and all deaths.
- Laboratory assessments (chemistry, hematology, urinalysis) to include summaries of results, shifts from baseline, and clinically significant results with subject listings
- Summaries of vital sign results, shift from baseline in weight/BMI, investigator interpretation of ECG results, PHQ-8/PHQ-A results and shift from baseline, Quantitative/Categorical summaries of investigator/subject local tolerability assessments, Summary of C-SSRS suicidal ideation and suicidal behavior, and CDI-2 results

Meeting Discussion: No discussion occurred at the meeting.

Clinical/Biostatistics Question 5:

In order to support the Agency's review of the NDA, and consistent with the agency "Guidance for Industry, Providing Regulatory Submissions in Electronic Format—Standardized Study Data", Arcutis intends to submit CDISC datasets, including SDTM and ADaM datasets, for all individual clinical studies included in the NDA. In addition, Arcutis will submit integrated ADaM datasets for the ISE and ISS.

Additional details on the datasets are provided in Section 15.

Does the Agency agree with the CDISC dataset submission plans?

FDA Response to Clinical/Biostatistics Question 5:

eData's Response: From technical standpoint the proposed CDISC dataset submission plans are acceptable.

The eSub team reviewed Section 15 of the briefing package. You indicated the following:

"The electronic submission will be prepared in accordance with the most current version of the ICH eCTD Specifications, as well as FDA Specifications for the following: eCTD Backbone Files Specification for Module 1, eCTD Backbone Files Specification for Modules 2 through 5, eCTD Backbone Files Specifications for Study Tagging Files, eCTD Table of Contents Headings and Hierarchy, and Study Data Specifications." Assuming you adhere to the specifications as written above, the eSub team does not have any issues. However, since you did not provide the exact location(s) to where the datasets will be placed in the submission, we cannot determine if you adhere to the FDA specifications.

Your proposal to submit datasets according to CDISC formatting is acceptable. The Multiple Imputation (MI) approach is the primary method for handling the missing data in your phase 3 trials, which involves generating multiple datasets. In addition to the

multiple imputed datasets, submit the SAS program used to implement MI and the SAS program for the analysis of these imputed datasets. Furthermore, submit the SAS program to implement the tipping point analysis in the NDA. We also recommend submitting the SAS programs for ISS analyses that employ pooling strategies stratified by study; see discussion under Response to Question 3. The SAS programs should be self-contained and executable with the datasets that will be submitted in the NDA.

For the analysis datasets, we have the following comments:

- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.
- The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated treatment assignment lists, the actual treatment allocations (along with the date of enrollment) and the ERT Cyber Security Incidence Report.

Additional Comments for the pivotal phase 3 trials:

- We remind you of our previous comment conveyed at the EOP 2 meeting and the advice letter dated January 20, 2020 that endpoints based on PASI may not be clinically meaningful for mild psoriasis, (b) (4)
- You provided results for the Intertriginous IGA (I-IGA) success in the pivotal Phase 3 trials; however, only about 20% of the subjects in each arm had I-IGA score of at least 2 at baseline. Whether such number is reasonable to allow meaningful assessment in the intertriginous area will be a review issue.
- We remind you of our previous comment conveyed in the advice letter dated January 20, 2020 that investigation of site-to-site variability should be conducted on the original sites, with reasonable number of subjects, as the merging of sites could mask site effects.
- The SAP submitted on November 2, 2020 (SDN 99) specified the estimand of the ratio of the odds of achieving IGA success after 8 weeks of using roflumilast cream 0.3%, relative to the odds of IGA success after 8 weeks of using vehicle cream. We recommend that you also assess the estimand of the difference in IGA success rates at Week 8 between roflumilast cream 0.3% and vehicle treatment arms for easier interpretation. The estimate in this case would be the strata-adjusted proportion difference (along with 95% CI) using the CMH method

adjusted for investigative site, baseline IGA and baseline intertriginous involvement.

- On page 25 of the SAP, you stated that binary endpoints will be analyzed using CMH test stratified by site, baseline IGA, and baseline intertriginous involvement similar to the primary analysis, with the exception that missing data will not be imputed. However, on page 16 you stated that data for secondary endpoints intended for hypothesis testing will be imputed. Address this discrepancy in the SAP and clarify how missing data will be handled for the analysis of key secondary endpoints intended for labelling. We remind you of our previous comment conveyed in the advice letter dated January 20, 2020 that the protocols/SAPs should specify a primary method for handling the missing data for both the primary and secondary endpoints intended for labelling, as findings from secondary endpoints are usually considered supportive of those of the primary endpoint.

Meeting Discussion:

There was discussion regarding discrepancies in the SAP for the handling of missing data for the primary and secondary endpoints. The Agency stated that consistent methods for imputing missing data, and that differences between imputation methods for primary and secondary endpoints may cause difficulty in interpreting study finding taking into account that secondary endpoints are usually supportive of the primary endpoint. The sponsor stated that the primary method for handling missing data will be the multiple imputation for the primary and secondary endpoints.

Clinical/Biostatistics Question 6:

Arcutis proposes, for Phase 2 and 3 studies, to submit subject narratives and case report forms (CRFs) for all deaths, serious adverse events (SAEs), and adverse events resulting in permanent discontinuation of IP.

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

FDA Response to Clinical/Biostatistics Question 6:

You should also provide CRF and narratives for all pregnancies and hypersensitivity reactions.

The following data should also be included:

1. The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.
2. Case report forms (CRFs) for all severe AEs, and for all subjects who discontinued from the studies for any reason.
3. A study's CRFs should be placed in a CRF folder under the applicable study with a file tag of "case-report-forms." Also provide the following:

- Electronic links for:
 - a) all serious AEs
 - b) all severe AEs
 - c) all patients discontinued regardless of reason
 - d) all deaths
 - CRFs should be referenced under the study in which it belongs and tagged as “case-report-forms” in that study’s stf.xml file. CRFs that are not submitted should be readily available upon request.
4. Adverse reaction tables (adverse reactions defined as those AEs with possible or probable causality) $\geq 1\%$.
 5. Adverse event tables $\geq 1\%$ regardless of causality.
 6. Line listings for all safety data.
 7. Group means for irritancy safety study results.
 8. Frequency tables for sensitivity safety study results. Define and justify the threshold for calling a score positive (or negative) for sensitization.

Meeting Discussion: No discussion occurred at the meeting.

2.6. Safety Question

Safety Question 1

Based on the safety profile demonstrated in clinical trials of roflumilast cream and the established safety profile of oral roflumilast based on more than 10 years of marketing experience in patients with COPD, Arcutis considers labeling to be sufficient to ensure the safe use of roflumilast cream 0.3% in the treatment of plaque psoriasis and does not plan to submit a Risk Evaluation and Mitigation Strategy (REMS).

Does the Agency agree with the plan not to submit a REMS for topical roflumilast cream 0.3%?

FDA Response to Safety Question 1:

Based on our current understanding of your development program, we do not anticipate that a REMS will be required, but the final determination of this issue will be made during review of the safety experience during the NDA review.

Meeting Discussion: No discussion occurred at the meeting.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 17, 2021 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

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.

¹ <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.² In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.³

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ 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.

² When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

- 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.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

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

SUBMISSION FORMAT REQUIREMENTS

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

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

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*

⁶ <http://www.fda.gov/ectd>

⁷ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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*.⁸

⁸ <https://www.fda.gov/media/85061/download>

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

/s/

KENDALL A MARCUS
06/04/2021 06:49:58 PM



IND 135681

MEETING MINUTES

Arcutis, Inc.
Attention: Charlotte B. Merritt
Vice President, Regulatory Affairs
2945 Townsgate Road
Suite 110
Westlake Village, CA 91361

Dear Ms. Merritt: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 cream.

We also refer to the meeting between representatives of your firm and the FDA on October 23, 2019. The purpose of the meeting was to discuss the development plan for roflumilast cream.

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 Strother D. Dixon, Senior Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor Response to Meeting Preliminary Comments

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: B
Meeting Category: End of Phase 2

Meeting Date and Time: October 23, 2019, 10:30 AM ET
Meeting Location: FDA, White Oak, Building 22

Application Number: IND 135681
Product Name: roflumilast cream

Proposed Indication: For the topical treatment of plaque psoriasis including treatment of psoriasis in the intertriginous areas, in patients 12 years of age and older

Sponsor Name: Arcutis, Inc.

Meeting Chair: Tatiana Oussova, MD, MPH
Meeting Recorder: Strother D. Dixon

FDA ATTENDEES

Tatiana Oussova, MD, MPH, Deputy Director for Safety, Division of Dermatology and Dental Products (DDDP)
David Kettl, MD, FAAP, Clinical Team Leader, DDDP
Hamid Tabatabai, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Carmen Booker, PhD, Pharmacology Reviewer, DDDP
Mohamed Alish, PhD, Biometrics Team Leader, Division of Biometrics III (DB III)
Marilena Flouri, PhD, Biometrics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DCP) 3
Luke Oh, PhD, Clinical Pharmacology Reviewer, DCP 3
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Charlotte Merritt, VP, Regulatory Affairs
Todd Watanabe, CEO and President
David Osborne, Chief Technical Officer
David Berk, VP Clinical Development
Lynn Navale, VP, Biometrics
Chester Elias, Exec Director, Regulatory Affairs

(b) (4)

1.0 BACKGROUND

Purpose:

To discuss the development plan for roflumilast cream for the topical treatment of plaque psoriasis including treatment of psoriasis in the intertriginous areas, in patients 12 years of age and older.

FDA sent Preliminary Comments to Arcutis, Inc. on October 11, 2019.

Regulatory Correspondence History:

We have had the following meetings with you:

- July 19, 2018 – Written Responses Only
- September 13, 2017 – Type B/Pre-IND

We have sent the following correspondences:

- July 31, 2019 – Advice
- April 11, 2019 – Advice
- November 2, 2018 – Advice
- May 2, 2018 – Special Protocol – Agreement
- February 21, 2018 – Study May Proceed

2. DISCUSSION

2.1. Chemistry, Manufacturing and Controls (CMC)

CMC Question 1:

Details on the available CMC information to support the proposed Phase 3 clinical studies are included in [Section 13.1](#). The test parameters, analytical methods, and acceptance criteria in the specifications have been set based on current process capabilities, data generated on batches from earlier phases and common industry practice.

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

FDA Response to CMC Question 1:

You should add testing and acceptance criteria for globule size to the drug product specification. You should also consider the recommendations by the FDA Biopharmaceutics and Microbiology Teams provided below:

Biopharm recommendation: We recommend that you develop an *in vitro* release test (IVRT) methodology and propose *in vitro* release acceptance criteria (range) for your drug product to be used systemically at release and during stability as a quality control parameter. Your proposed acceptance criteria should be based on generated data for

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pivotal clinical drug product-batches and primary registration batches. Submit all the generated data in electronic format (e.g. MS Excel) as described below:

Chamber ID: # (identify each cell assignment)

Sample volume removed: mL

Diffusion cell area: cm²

Time (min, hr, etc.)	Sq. rt. Time	Concentra tion in Cell (µg/mL)	Amount in Cell (µg)	Cumulativ e Amount in Cell (µg)	Cumulativ e Diffusion (µg/cm ²)
T1					
T2					
T3					
T4					
T5					
Tn					

- Also, along with the proposed *in vitro* release specification, include the IVRT method development and validation report. The IVRT method development report should contain (but is not limited to) justification for the selection of the following methodology components:
 - Diffusion apparatus
 - Receptor medium selection
 - Membrane selection
 - Sampling time points
 - Temperature
- The IVRT method validation report should contain (but is not limited to) the following validation components:
 - Linearity and Range
 - Accuracy/Precision and Reproducibility
 - Mass Balance
 - Sensitivity and Specificity
 - Selectivity
 - Robustness
 - Membrane Inertness
 - Receptor Solution Solubility/Stability
- The IVRT method's sensitivity, specificity, selectivity and robustness should to be performed with altered product lots that contain 50% and 150% of the label claim of active pharmaceutical ingredient (API) in the reference product, with the test evaluating a minimum of one run of 6 diffusion cells each per product concentration, including the reference.

Microbiology recommendation: The proposed acceptance criteria for microbiological quality comply with those specified by USP <1111> for non-sterile dosage forms for

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cutaneous use. However, we recommend including a test for the absence of *Burkholderia cepacia* complex (BCC) to the drug product specification in Phase 3 studies.

For the NDA submission, please consider non-sterile aqueous drug products may potentially be contaminated with organisms in the BCC. BCC strains have a well-documented ability to ferment a wide variety of substrates and are known to proliferate in the presence of many traditional preservative systems. Thus, despite the presence of otherwise adequate preservative systems, BCC strains can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC please see PDA J Pharm Sci Tech 2011; 65(5): 535-43.

In order to control for the presence of BCC in your product you should consider the following:

1. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
2. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing. USP <60> *Microbiological Examination of Nonsterile Products – Tests for Burkholderia cepacia Complex*, although not yet official, is recommended as a source for reference.

If BCC testing is not performed per USP <60>, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your NDA should describe the preconditioning step [time, temperature, and solution(s) used], the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to ensure that the proposed recovery methods are adequate to recover organisms potentially present in the environment.

For more information, we refer you to *Envir Microbiol* 2011; 13(1):1-12 and *J. Appl Microbiol* 1997; 83(3):322-6.

2.2. Nonclinical

CMC Question 2:

The formulation of ARQ-151 as a stable cream product

(b) (4)

known as cetostearyl alcohol (CAS 67762-27-0),
and ceteth-10 phosphate (CAS 50643-20-4).

cetearyl alcohol, also

(b) (4)

(b) (4)

Likewise, ceteth-10 phosphate administered topically, orally or by injection is expected to quickly convert into phosphate and ceteth-10, which is IID listed up to 2.5% in a topical cream.

(b) (4)

The dermal safety of (b) (4) has been assessed in GLP-compliant repeat dose dermal safety studies (13-week toxicity in mice and minipigs, 39-week in minipigs) conducted using ARQ-151 drug product and vehicle control test articles containing (b) (4). The reports for these studies have been submitted to the IND, and a summary can be found in [Section 13.2.3](#). Additionally, a 104-week dermal mouse carcinogenicity study is currently in progress, which contains both a vehicle control (with (b) (4)) and a naïve control group. Arcutis also intends to conduct a 4-week dermal repeat dose toxicity study of (b) (4) in minipigs. Data from this study and the mouse carcinogenicity study will be available for inclusion in the NDA.

Finally, we have conducted an *in-silico* mutagenicity assessment of (b) (4) according to ICH M7 criteria. (b) (4) (Ceteth-10 phosphate, Cetearyl alcohol, (b) (4)) were predicted clearly negative in rule-based DEREK and in statistical-based Model Applier. No alerts were identified, and relevant analogs were shown to support the predictions. Therefore, with negative mutagenicity predictions in two complimentary in silico systems, (b) (4) can be considered non-mutagenic (Class 5). We will submit the report from this assessment to the IND.

Does the Agency agree that the nonclinical data generated, including the 4-week toxicity data in minipigs to be included in the NDA, are sufficient to support the safety of (b) (4)

FDA Response to CMC Question 2:

The nonclinical data previously generated and to be provided appear reasonable to support the safety of (b) (4). The adequacy of all the available nonclinical data will be determined after review of the full study reports.

Nonclinical Question 1:

Oral roflumilast is approved globally for COPD, and its safety profile is well-established. An extensive systemic toxicity program that evaluated both roflumilast and its active N-oxide metabolite in multiple species via the oral route of administration was conducted to support registration. These studies are relevant to the ARQ-151 cream development program, and we intend to refer to them in our NDA (Arcutis has a Letter of Authorization from AstraZeneca for NDA 22-522 for DALIRESP.)

To support the development of ARQ-151 topical cream, GLP-compliant dermal toxicity and toxicokinetic studies are being conducted. To date, no new risks have been identified through the dermal toxicity program. In 13-week dermal toxicity studies in mice and minipigs and a 39-week dermal toxicity study in minipigs, no evidence of systemic toxicity was observed. Histopathological evaluation of skin in the mouse and minipig studies included minimal to mild epidermal hyperplasia and/or inflammation which was observed with low incidence and severity, and as such, was not considered adverse in either species. No dermal irritation and no microscopic skin findings were noted in either the 13-week or 39-week studies in minipigs. The NOAEL in each of the repeat dose studies was the 1% concentration of ARQ-151 (20 mg/kg), the highest dose administered and the maximum feasible concentration. A 104-week dermal carcinogenicity study of ARQ-151 in mice is ongoing, the results of which will be included in the NDA.

Refer to [Section 13.2](#) for a more detailed description of the nonclinical development program.

Does the Agency agree that the extent of the nonclinical development program is sufficient to support the eventual registration of ARQ-151 cream, 0.3%?

FDA Response to Nonclinical Question 1:

Your proposed nonclinical development plan appears reasonable to support your eventual NDA. The adequacy of the nonclinical studies will be a review issue under the IND and NDA.

Nonclinical Question 2:

As noted in Nonclinical Question 1, a 104-week dermal carcinogenicity study is ongoing. A final report from that study will be included in the NDA. Arcutis would like to propose

that the SEND data from this study could be submitted while the NDA is under review (within 45 days of NDA submission).

Does the Agency agree that the SEND data from the 104-week dermal carcinogenicity study could be submitted within the first 45 days after NDA submission?

FDA Response to Nonclinical Question 2:

We do not agree that submitting SEND data from the dermal carcinogenicity study within 45 days of the NDA submission is acceptable. The SEND data from the dermal carcinogenicity study should be included in the original NDA submission. In addition, to enable us to conduct the statistical review of the dermal carcinogenicity study, submit the SAS tumor data sets (tumor.xpt) for the dermal carcinogenicity study in the original NDA submission. Follow the standard format provided below 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.

2.3. Clinical Pharmacology

Clinical Question 11:

Arcutis will conduct a MUSE study using the 0.3% concentration of ARQ-151 cream. The study will target at least 10 evaluable adult subjects with $\geq 20\%$ BSA psoriasis involvement and at least 6 evaluable subjects 12 to 17 years of age with $\geq 10\%$ BSA psoriasis involvement; see [Section 13.3.5](#). This study will be conducted according to FDA's prior advice during the pre-IND meeting for IND 135681 (September 13, 2017) and in alignment with the recommendations in [Bashaw 2015](#). This study will establish the definitive PK profile for ARQ-151 cream 0.3% for inclusion in the product label.

Does the Agency agree with Arcutis' plans for the MUSE study?

FDA Response to Clinical Question 11:

Your proposed maximal use PK study outline appears reasonable. We may have additional comments when you provide full study protocol.

Clinical Question 12:

The distribution, metabolism, excretion (mass balance) and pharmacokinetic properties of ^{14}C -roflumilast were fully characterized following IV and PO administration as a part of the DALIRESP development package. Thus, Arcutis does not believe these ^{14}C ADME studies need to be repeated following topical administration. From our Phase 2a clinical study ARQ-151-101, following multiple topical administrations of ARQ-151, the presence of roflumilast and roflumilast N-oxide (the active metabolite) were detected in all treated subjects, while the presence of ADCP and ADCP N-oxide (putative metabolite of toxicological concern) were generally near or below the LLOQ (all values $< 1.0 \text{ ng/mL}$). In skin biopsy punches taken 24 hours following the last dose administered after 28 days of daily topical application, the presence of roflumilast was detected in all but one of the skin samples, while roflumilast N-oxide was only detected in a sample from one subject and was near the LLOQ (0.216 ng/g). The presence of ADCP or ADCP N-oxide was not detected in any subject samples. Following topical administration, the systemic exposure of roflumilast N-oxide circulates at about 5 to 6-fold higher than roflumilast exposure, which is consistent with the ratios observed following IV administration, and lower than the ratios observed following oral administration (ratios were about 10-fold higher). The differences in the systemic exposure ratios are likely due to the hepatic first pass effect that would only be observed following oral administration. Since our data appear to be in alignment with the previous data characterized, we do not believe the ^{14}C ADME studies need to be repeated for topical administration.

Does the Agency agree with Arcutis' plan not to conduct a clinical ADME study with ARQ-151 cream?

FDA Response to Clinical Question 12:

Your plan not to conduct an ADME study with ARQ-151 cream appears reasonable.

Clinical Question 13:

Extensive evaluations of potential drug interactions were conducted to support the DALIRESP approval and are well described in the labeling. Since the approval of oral roflumilast, there have been changes to ADME practices through updates in guidance documents (e.g., the draft guidance for industry *Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing and Labeling Recommendations*). However, considering the extent of existing data with oral roflumilast ([DALIRESP PI 2018](#)) and the unlikely impact of topical dosing on the drug interaction profile, Arcutis does not plan to conduct additional drug interaction characterizations with the topical product (e.g., expand the transporter characterization as specified in the draft guidance, hepatocyte induction analysis, time dependent inhibition analysis, etc.) or conduct additional clinical drug interaction studies.

Does the Agency agree with Arcutis' plan not to conduct additional drug interaction testing with ARQ-151 cream?

FDA Response to Clinical Question 13:

It is premature to agree with your plan not to assess drug-drug interactions with ARQ-151 cream without reviewing the results of your maximal use PK study. In your eventual NDA submission, we advise you to adequately address the potential for drug interactions.

Clinical Question 14:

The prescribing information for DALIRESP includes a contraindication for moderate to severe liver impairment (Child-Pugh B or C). This labeling also informs clinicians to consider the risk benefit of administering DALIRESP to patients who have mild liver impairment (Child-Pugh A). This labeling is based on the results of a study (CP-062 in the DALIRESP NDA) in which roflumilast 250 µg once daily for 14 days was studied in subjects with mild-to-moderate hepatic impairment classified as Child-Pugh A and B (8 subjects in each group). The AUCs of roflumilast and roflumilast N-oxide were increased by 51% and 24%, respectively, in Child-Pugh A subjects and by 92% and 41%, respectively, in Child-Pugh B subjects, as compared to age-, weight-, and gender-matched healthy subjects. The C_{max} of roflumilast and roflumilast N-oxide were increased by 3% and 26%, respectively in Child-Pugh A subjects and by 26% and 40%, respectively in Child-Pugh B subjects, as compared to healthy subjects. DALIRESP 500 µg has not been studied in hepatically impaired patients ([DALIRESP PI 2018](#)).

Oral roflumilast (DALIRESP) has a relatively narrow therapeutic margin, with GI AEs and weight loss being dose-limiting. On the contrary, based on data from the ARQ-151 Phase 2b study (ARQ-151-201), there is no imbalance between treatment groups for GI AEs or weight change with topical roflumilast.

Does the Agency agree, based on a wider therapeutic margin with ARQ-151 cream relative to DALIRESP and the fact that the roflumilast and N-oxide AUC values increased by less than 2-fold following oral roflumilast administration in

subjects with moderate hepatic impairment, that a contraindication in patients with moderate to severe hepatic impairment (as is reflected in the labeling for DALIRESP) is unnecessary? Is the Agency willing to consider data already generated with oral roflumilast in a hepatic impairment study in the development of labeling specific to topical roflumilast?

FDA Response to Clinical Question 14:

It is premature to agree to this proposal without reviewing the results of your maximal use PK study. You will need to provide adequate scientific rationale and/or clinical data to support your labeling proposal. We will consider your proposal at the time of your NDA submission.

Meeting Discussion:

The Agency acknowledged the sponsor's plan to conduct a maximal use study and also noted the anticipated higher systemic exposure of the topical product compared to the approved oral product. Based on the results of the maximal use study, the sponsor should assess the need for additional DDI and hepatic impairment studies.

The Agency further stated that the sponsor could include an oral dose arm administered in healthy subjects in their max use study and obtain relative bioavailability information. Another approach the sponsor could consider would be to use PK data of the oral product that they have right of reference. The Agency cautioned that the cross study comparison should be adequately justified.

2.4. Clinical/Biostatistics

Introductory Clinical Comments:

You propose to conduct 2 identical Phase 3, efficacy/safety studies (ARQ-151-301, -302) and a long term, open-label safety study (ARQ-151-306) in subjects ≥ 12 years of age. Trials -301/-302 are 8-week, randomized (2:1), parallel group, double blind, vehicle-controlled studies. Each trial will enroll 400 subjects with mild to moderate plaque psoriasis ($\text{IGA} \geq 2$, affected $2\% \leq \text{BSA} \leq 20\%$, $\text{PASI} \geq 2$). Each subject will apply ARQ-151 cream, 0.3% or vehicle cream to psoriasis lesions once daily for 8 weeks. All subjects will have PK samples collection and safety assessments to include TEAEs, application site reactions, vital signs (pulse, blood pressure, temperature), physical examinations (and height, weight), safety laboratory (hematology/clinical chemistry/urinalysis/pregnancy tests), C-SSRS, PHQ-8 (in adults) or a modified version of the PHQ-A (in adolescents). The Primary Efficacy Endpoint will be IGA success, defined as an IGA score of 'clear' (0) or 'almost clear' (1) **and** a 2-grade improvement from Baseline at week 8.

Study -306 is a 24-week, open label, long term safety study in approximately 250 subjects ≥ 12 years of age who complete the studies -301/-302. Subjects will continue to apply ARQ-151 cream, 0.3% QD to psoriasis lesions, but will stop drug application when lesions resolve and may resume application of drug to recurrent lesions or any

new psoriasis lesions. The primary (safety) endpoint will include assessments of TEAEs, application site reactions (Berger and Bowman method), clinical laboratory testing (hematology/clinical chemistry/urinalysis/ pregnancy tests), PHQ-8/Modified PHQ-A, and C-SSRS.

Clinical Question 1:

The pathogenesis of pediatric and adult psoriasis is believed to be similar. Psoriasis has been associated with elevation of the pro-inflammatory cytokines TNF- α , IL-17A, and IL-23, and increased activity of the Th17/IL-23 pathway ([Eichenfield 2018](#)). Similar potential triggers, e.g., trauma/mechanical, infections, and medications, have been described in pediatric and adult psoriasis. In adults, the prevalence of psoriasis is approximately 2 to 3%, varying by geographic region. Approximately 30% of cases ([Raychaudhuri 2000](#)) have onset prior to adulthood, although not all patients are diagnosed during childhood ([Relvas 2017](#)). In children, the prevalence of psoriasis increases linearly with older age, increasing 10-fold from 1 year to 18 years of age ([Augustin 2010](#), [Bronckers 2015](#)). Hence, most children with psoriasis are adolescents.

Roflumilast has a well-established safety profile. A 500 μ g oral tablet has been approved as DALIRESP in the US for COPD since 2011. According to the sponsor, the cumulative global post-marketing patient exposure of roflumilast from launch through 2018 is estimated at over one million patient years. AEs reported with roflumilast tablets have been consistent with those expected for systemic PDE-4 inhibitors. In a pooled analysis of safety data from 6-month and 1-year clinical trials (N=8630), the most common AEs were diarrhea, weight loss and nausea ([Michalski 2012](#)).

While oral roflumilast is currently marketed for COPD only, a full clinical development program was conducted in adults and adolescents down to 12 years of age with asthma. A 14-day PK study [AZ NDA 22-522 CP-065] in children 6 to 17 years old, conducted as part of the asthma development program, demonstrated that systemic exposure of roflumilast adjusted by dose and body weight in children and adolescents was below the systemic exposure observed in adults. In this study, a 9% and 19% lower mean value of total PDE-4 inhibition in the pediatric and adolescent population, respectively, was seen, compared with the adult population. The most frequently reported AEs in this study were headache and gastrointestinal disorders, including vomiting, diarrhea and nausea. No age- or dose-related effects regarding the type, causality, or intensity of AEs were observed.

ARQ-151 cream 0.15% and 0.05% is currently being administered to adolescent and adult subjects (age 12 and older) in ARQ-151-212, an ongoing Phase 2 study in subjects with atopic dermatitis.

Data from a recently-completed Phase 2b study of ARQ-151 cream 0.3% and 0.15% in adult subjects with chronic plaque psoriasis demonstrate a very different safety and tolerability profile compared to oral roflumilast. Rates of GI AEs were similar between ARQ-151 and vehicle and low across all groups. Comparable rates of psychiatric AEs

and of weight loss and weight gain were also observed across treatment groups. (Refer to [Section 13.3.2.2.](#)) While oral PDE-4 inhibitors (DALIRESP, OTEZLA) have been associated with, in particular, a moderate incidence of GI AEs, these AEs, and perhaps others, are reported at a greatly decreased frequency with topical PDE-4 inhibitors, including EUCRISA, and ARQ-151 cream to date in clinical trials. Arcutis believes that the lack of nausea, vomiting and diarrhea seen in ARQ-151 studies to date may be related to the lack of 'peak to trough' Cmax variation, lower Cmax values than observed following oral administration, and/or bypassing of the gastrointestinal tract with topical administration.

Arcutis is planning to conduct the Phase 3 psoriasis studies in subjects 12 years of age and older. The inclusion of adolescents in these studies is justified by the prevalence of psoriasis in adolescents, the known safety profile of oral roflumilast, the low incidence of AEs reported to date with topical roflumilast, and the likelihood that the PK profile of topically applied roflumilast in adolescents will mirror that seen in adults (given the similar PK profile of roflumilast in adolescent and adult asthma patients).

Does FDA agree with Arcutis' plan to include both adults and adolescents in the Phase 3 clinical studies with ARQ-151 cream?

FDA Response to Clinical Question 1:

Yes, we agree with your plans to Include adolescent subjects ≥ 12 years of age in Phase 3 trials.

Clinical Question 2:

There is substantial medical need for new topical approaches in the treatment of psoriasis. In particular, the management of psoriasis in intertriginous regions (occurring in approximately 20-30% of psoriasis patients ([Dopytalska 2018](#))) is especially difficult with currently approved products. Potent topical steroids should not be used to treat psoriasis in the thin-skinned intertriginous regions due to the risk of skin atrophy. Topical vitamin D derivatives and tazarotene are irritating, and thus not suitable for use in these areas. This leaves patients with milder forms of psoriasis, or those who are not candidates for systemic therapies, without a safe, well-tolerated and efficacious option to treat their psoriasis in intertriginous areas. Based on both safety and efficacy data from our Phase 2b study (ARQ-151-201), ARQ-151 cream 0.3% appears to be an optimal treatment for this unmet medical need.

ARQ-151-201 enrolled 331 adult subjects with plaque psoriasis, approximately 15% of whom had psoriasis affecting the intertriginous regions. In this subgroup with intertriginous involvement at baseline, investigators not only assessed the effect of treatment on the subjects' psoriasis overall using the Investigators Global Assessment (IGA) but conducted a second assessment of the intertriginous regions only using the Intertriginous-IGA (I-IGA). In the pre-specified subset of subjects with an I-IGA >2 at baseline, ARQ-151 cream 0.3% showed statistically greater I-IGA success than vehicle at Weeks 6, 8, and 12, based on achievement of an I-IGA score of 'clear' or 'almost

clear' plus a 2-grade improvement from baseline. Indeed, by week 12, over 90% of subjects treated with ARQ-151 cream 0.3% with an I-IGA ≥ 2 at baseline demonstrated I-IGA success and most responders had I-IGA scores of 'clear' (0) (see [Section 13.3.2](#)). There were no safety or tolerability differences in the subgroup compared to the overall Phase 2b population.

- As in the Phase 2b study, approximately 15% of the Phase 3 study population is anticipated to be subjects with psoriasis in the intertriginous regions (N = ~60/pivotal study). In these subjects, investigators will assess efficacy of ARQ-151 cream 0.3% using the I-IGA (see [Section 13.3.3](#)). The achievement of an I-IGA score of 'clear' or 'almost clear' plus a 2-grade improvement from baseline at week 8 for subjects with intertriginous lesions of at least mild (I-IGA ≥ 2) at baseline will be prespecified as a secondary endpoint. Although approximately 15% of the Phase 3 study population is anticipated to be subjects with psoriasis in the intertriginous region, this secondary endpoint is considered to be appropriately powered based on observed Phase 2b data.
- The apparent efficacy of ARQ-151 cream 0.3% in the treatment of psoriasis in intertriginous areas, without tolerability issues seen with other topical products, appears to be a key differentiating feature of our product. Considering the current limitations in treating psoriasis in intertriginous areas, and the critical need for better options, if the results of the ARQ-151 Phase 3 I-IGA assessments are positive, Arcutis believes it will be important to reflect this benefit in the Indications section of the label. While the sponsor fully understands that it is too early to discuss the specifics of labeling, we would appreciate FDA's comments on the concept: *ARQ-151 (roflumilast) cream, 0.3% is indicated for the topical treatment of plaque psoriasis, including treatment of psoriasis in the intertriginous areas, in patients age 12 and older.*

2a. Does the Agency agree

(b) (4)

FDA Response to Clinical Question 2a:

We do not consider

(b) (4)

(b) (4)

2b. Does the Agency agree that the Phase 2b results are encouraging in terms of the ability of ARQ-151 cream to treat psoriasis in these sensitive areas?

FDA Response to Clinical Question 2b:

You did not provide information regarding the subject disposition, demographics and baseline disease characteristics for the Phase 2b trial. In addition, you did not provide the number of subjects enrolled in each treatment arm and the number of subjects with missing data, along approach for handling missing data. Furthermore, you did not provide the number of subjects with I-IGA>2 at baseline. Therefore, it is difficult to comment on the reliability of the treatment effect estimates from the completed Phase 2 trial.

See also above discussion. Your development plan appears reasonably safe to proceed.

2c. Does the Agency agree with the assessment in the planned Phase 3 studies of psoriasis in intertriginous areas using the I-IGA, as was done in the Phase 2b (ARQ-151-201) study?

FDA Response to Clinical Question 2c:

No. Refer to response to Question 2a.

2d. Does the Agency agree that positive results in the subgroups of psoriasis subjects with intertriginous involvement in the two planned Phase 3 studies could support specific language in the Indications section of the label?

FDA Response to Clinical Question 2d:

The final language for labeling will be discussed during the NDA review. We anticipate that the likely indication for your program, if successful, will be for the “topical treatment of plaque psoriasis”. Qualitative statements for secondary endpoints may be appropriate for inclusion in Section 14 (Clinical Studies) of the label depending on the robustness of clinical data obtained in the trials and the content validity of the endpoint.

Since the endpoint based on intertriginous-IGA will only be assessed in a subset of subjects enrolled in the Phase 3 trials, a reasonable number of enrolled subjects will need to have sufficient baseline disease severity based on intertriginous-IGA (I-IGA>2) to allow meaningful assessment.

2e. Considering the size of the patient subgroups with intertriginous involvement anticipated to enroll in the Phase 3 studies, there is a possibility that statistical significance will not be achieved in one or both studies, even though results are considered clinically meaningful. Does the Agency agree that positive results on the I-IGA endpoint could be confirmed if non-significant, but clinically meaningful, treatment differences are observed in the subgroup of subjects with psoriasis in intertriginous areas in the individual phase 3 trials and this treatment

difference is statistically significant at the 5% significance level in the combined analysis of the two phase 3 trials?

FDA Response to Clinical Question 2e:

No. See above discussion. Refer to Response to Questions 2b-2d.

In general, replication of findings from two adequate and well-controlled Phase 3 trials is recommended for efficacy claims. It should be noted that new efficacy claims cannot be established based on pooling data from the individual confirmatory trials.

Clinical Question 3:

The safety profile from the Phase 2a and 2b psoriasis studies is supportive of the 0.3% dose to be evaluated in Phase 3 studies. Excellent local and systemic toleration was observed for both the 0.15% and 0.5% doses in the Phase 2a study and both the 0.15% and 0.3% doses in the Phase 2b study. In the Phase 2b study, both ARQ-151 cream 0.3% and ARQ-151 cream 0.15% were efficacious, with the 0.3% concentration showing consistently better efficacy across efficacy measures, including secondary endpoints based on I-IGA, PASI-75, PASI-90, WI-NRS, and Psoriasis Symptom Diary (PSD). At Week 8, ARQ-151 cream 0.3% demonstrated rates of IGA Success comparable to a potent steroid, based on historical comparisons. (See Section 13.3.2.) Thus, the 0.3% dose of ARQ-151 cream has been selected as the dose to be evaluated in the Phase 3 studies.

Based on the results of the Phase 2b study (ARQ-151-201), does the Agency agree with Arcutis' choice of ARQ-151 cream 0.3% as the dose to be evaluated in the planned vehicle-controlled Phase 3 studies in subjects with chronic plaque psoriasis?

FDA Response to Clinical Question 3:

Your proposed dose of Roflumilast cream, 0.3% appears reasonably safe for your planned Phase 3 trials. Whether the current concentration and dosage regimen is optimized for your Phase 3 trials cannot be determined given the submitted information.

As noted in Response to Question 2 b), it is difficult to comment on the reliability of the treatment effect estimates from your Phase 2 trial due to lack of information on the number of subjects enrolled in each treatment arm, the number of subjects with missing data, subject disposition, and baseline disease characteristics. Therefore, you may be taking the risk of not selecting the appropriate dose and/or underpowering your Phase 3 trials.

Clinical Question 4:

Itch is an important and especially bothersome symptom in patients with psoriasis, with some studies reporting itch severity in psoriasis similar to that seen in atopic dermatitis. In psoriasis patients, itch has been linked to depression, anxiety, stress, occupational impairment, stigmatization, and quality of life impairment, especially affecting mood,

sexual desire, concentration, sleep, and appetite (Reich 2014, Shahwan 2017). By causing scratching, itch may exacerbate psoriasis via koebnerization (Shahwan 2017). In Arcutis' Phase 2b study, ARQ-151-201, itch was measured based on the Worst Itch Numeric Rating Scale (WI-NRS), a well-established tool (Naegeli 2014). At baseline, mean WI-NRS score ranged from 5.6-6.1 across treatment groups (median WI-NRS scores ranged from 6-7). In addition to analyzing change from baseline in WI-NRS score among all subjects, Arcutis performed a responder analysis evaluating achievement of a 4-point reduction of WI-NRS, which has been described as optimal for demonstrating a level of clinically meaningful improvement in itch severity (Kimball 2016). When the success rate in achieving a 4-point reduction in WI-NRS was analyzed for subjects with a WI-NRS score of ≥ 6 at Baseline (almost 60% of all subjects), the percentages of subjects with success was significantly higher in the 0.3% dose group versus vehicle ($p \leq 0.034$) at all post-baseline visits and in the ARQ-151 0.15% dose group at Week 6 and 12 ($p \leq 0.012$) compared to vehicle. (See Section 13.3.2.1.)

Does FDA agree with Arcutis' plan to include achievement of a 4-point reduction in WI-NRS pruritus score at week 2 as compared to baseline in subjects with a WI-NRS pruritus score ≥ 6 at baseline as a secondary endpoint in the ARQ-151 cream 0.3% Phase 3 studies?

FDA Response to Clinical Question 4:

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

You propose to assess pruritus at Week 2 as a secondary endpoint using the Worst Itch Numerical Rating Scale (WI-NRS); however, the primary timepoint is Week 8. Secondary endpoints should support the primary endpoint, and therefore, need to be assessed at the primary timepoint (i.e., Week 8); assessments at earlier timepoints can be additional.

Secondary endpoints in Phase 3 trials intended for labeling should be limited in number, clinically meaningful, and analyzed with appropriate multiplicity control.

Meeting Discussion:

The Agency noted that taking in to account that assessments are two weeks apart and that the event is not well defined (such as death), it may be difficult to interpret time to event endpoints for pruritus. The Agency noted that the sponsor may assess WI-NRS success at the specific time points, starting with week 8 (i.e. the primary time point).

Clinical Question 5:

The primary endpoint (IGA Success, defined as an IGA score of 'clear' or 'almost clear' plus a 2-grade improvement from Baseline at week 8) chosen for the Phase 3 studies is widely used and accepted historically. In these studies, treatment comparison will be performed using Cochran-Mantel-Haenszel test stratified by study site, baseline disease

severity (IGA = 2 vs IGA $\geq$ 3) and presence of psoriasis of the intertriginous regions (I-IGA $\geq$ 2 at baseline (yes vs. no)). Missing data will be imputed using multiple imputation. Treatment comparison between active and vehicle for the primary endpoint will be performed at the 5% significance level (2-sided).

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

FDA Response to Clinical Question 5:

Your proposal to analyze the primary endpoint (IGA success) using Cochran-Mantel-Haenszel test appears reasonable. Furthermore, your proposal to perform treatment comparison between active and vehicle for the primary endpoint at the 5% significance level (2-sided) also appears reasonable.

You specified the multiple imputation method as the primary method for handling the missing data. It should be noted that full details regarding the multiple imputation method (e.g., the number of replications, the imputation model, and the randomization seed for the multiple imputation) should be included in the protocol. In addition to a primary method of handling missing data, you will need to propose at least two alternate imputation methods that use alternate assumptions as sensitivity analyses to ensure that the conclusions of the study are not driven by the methods of handling missing data.

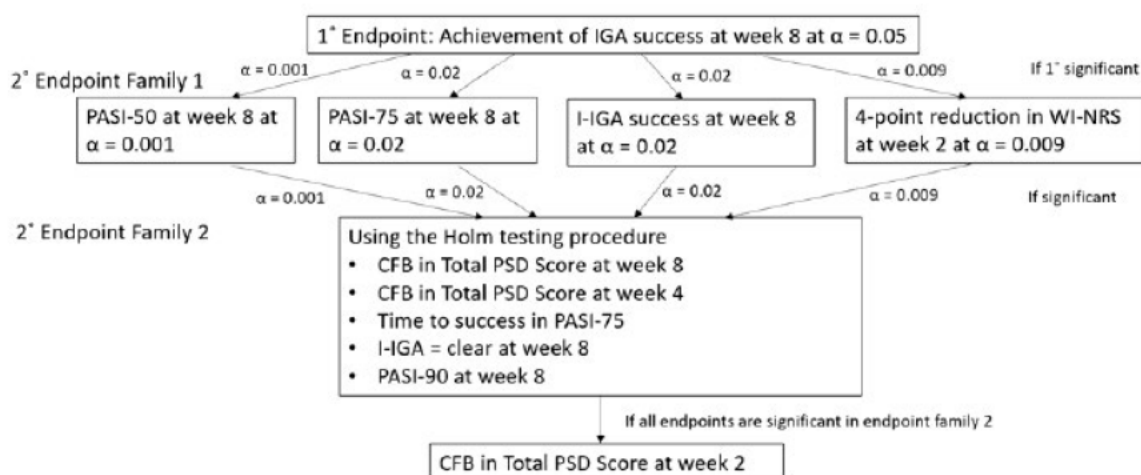
Clinical Question 6:

The secondary endpoints proposed for the Phase 3 studies are listed on the next page along with a rationale/comments regarding the importance to the program. To control for multiple comparisons, secondary endpoints will only be statistically tested if the primary endpoint is considered statistically significant at the 5% significance level. To control for multiple comparisons among the secondary endpoints, the first 4 secondary endpoints (Secondary Endpoint Family 1) will be tested independently using a Bonferroni split of the alpha (see [Figure 1](#)). The next 5 secondary endpoints (Secondary Endpoint Family 2) will be tested using the alpha available after testing Endpoint Family 1, and the Holm procedure will be used to control for multiple comparisons in this endpoint family. The final secondary endpoint will only be tested if all endpoints in Endpoint Family 2 are considered statistically significant.

Secondary Endpoint	Rationale/Comments
PASI-50 at Week 8	Clinically relevant differentiator of treatment success (Carlin 2004); easily understood by physicians; precedent for inclusion in labeling
PASI-75 at Week 8	Easily understood by physicians; precedent for inclusion in labeling
I-IGA success* at Week 8 among subjects with I-IGA ≥ 2 at Baseline	Psoriasis in the intertriginous regions is an unmet medical need. Based on the results of ARQ-151-201 (see Clinical Question 2), ARQ-151 cream 0.3% is expected to be highly effective and well-tolerated in psoriasis in intertriginous regions.
4-point reduction in WI-NRS at Week 2 among subjects with a baseline WI-NRS ≥ 6	Itch is an important component of psoriasis that is bothersome to many patients, can cause exacerbation of disease through scratching, and adversely affects quality of life (Shahwan 2017). Based on the results of ARQ-151-201 (see Clinical Question 5), ARQ-151 cream can provide meaningful relief of this important symptom within 2 weeks of initiating treatment.
Change from baseline in Total Psoriasis Symptom Diary (PSD) Score at Week 8	The PSD assesses patients' daily self-reports of psoriasis symptoms and their functional impact. Precedent for description in labeling.
Change from baseline in Total PSD Score at Week 4	Early positive results in Phase 2b study with ARQ-151 cream
Time to success based on PASI-75	This endpoint will be evaluated using a Kaplan-Meier analysis. The sponsor plans to use it to graph efficacy over time in the Clinical Studies section of the label. See time to success based on PASI-75 results from ARQ-151-201 in Section 13.3.2.1 .
I-IGA = 'clear' at Week 8 among subjects with I-IGA ≥ 2 at baseline	Early positive results in Phase 2b study with ARQ-151 cream
PASI-90 at Week 8	Clinically meaningful differences were observed in Phase 2b (ARQ-151-201) as early as week 6; easily understood by physicians; (b) (4)
Change from baseline in Total PSD Score at Week 2	Early positive results in Phase 2b study with ARQ-151 cream

* Defined as an I-IGA of 'clear' or 'almost clear' plus a 2-grade improvement from baseline

Figure 1. Statistical Testing Procedure



6a. Does the Agency agree that PASI-50 is a clinically relevant differentiator of treatment success (b) (4)

FDA Response to Clinical Question 6a:

For topical drug products for treatment of psoriasis, the recommend primary efficacy endpoint is IGA success (IGA=0, 1 and ≥ 2-point improvement from baseline). Efficacy endpoints based on PASI (PASI-75/PASI 50/time to PASI 75) may not represent clinically meaningful measures of efficacy endpoints for treatment of milder psoriasis (b) (4)

Meeting Discussion:

The Agency noted that the sponsor may evaluate different endpoints for different regulatory regions. The Agency reiterated the comment that endpoints based on PASI may not be clinically meaningful given the study population (mild psoriasis) and therefore recommended removal of these endpoints from the multiplicity adjustment plan for the Agency.

6b. (b) (4)

FDA Response to Clinical Question 6b:

No. See response to question 6a.

6c. 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 Clinical Question 6c:

You listed many secondary endpoints which include patient reported outcomes (PROs). We note that for confirmatory Phase 3 trials, the scales for the PROs need to be fit for purpose. For information on the use of a Patient Reported Outcome (PRO) for efficacy assessments in clinical studies, refer to guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

Your multiple testing approach should include secondary endpoints that are few in number, clinically meaningful and agreed-upon with the Agency (b) (4)

Clinical Question 7:

In the placebo-controlled clinical trials conducted to support the COPD development program, psychiatric-related AEs were greater in patients treated with roflumilast tablets (5.9%) compared to those treated with placebo (3.3%). The most common psychiatric-related AEs were insomnia, depression and anxiety. A small number of cases of suicide ideation and behavior, including completed suicide, and have been reported in patients taking oral roflumilast in clinical trials (4 on roflumilast vs. 1 on placebo) and also during post-marketing experience. These cases were reported in patients with and without a history of depression. The prescribing information for roflumilast tablets advises physicians to carefully weigh the risks and benefits of treatment in patients with a history of depression and/or suicidal thoughts or behavior. Physicians should also discuss the risks of psychiatric AEs with their patients and evaluate the risks and benefits of continuing treatment should they occur ([DALIRESP PI 2018](#)).

The PHQ-8 and the C-SSRS were included in the Phase 2b (ARQ-151-201) study to monitor for signs of depression and suicide ideation and behavior. A C-SSRS score indicative of suicidal ideation or a PHQ-8 score ≥ 15 were grounds for potential removal from the study.

In ARQ-151-201, the changes in depression scores using the PHQ-8 were generally comparable across all treatment groups. Among the subjects in ARQ-151-201 with at least one posttreatment C-SSRS assessment, one subject from the vehicle group reported suicidal ideation at week 12. (See [Section 13.3.2.2](#))

Arcutis plans to incorporate the C-SSRS, PHQ-8, and a slightly modified version of the PHQ-8 for use in adolescents into the Phase 3 trials. The PHQ-9 modified for use in adolescents is called the PHQ-A ([Johnson 2002](#)). This tool is partially duplicative of the C-SSRS in that it includes a question on suicide ideation and behavior. So that depression is assessed consistently in adults and adolescents in our Phase 3 trials, we plan to use a modified version of the PHQ-A in adolescents. The modifications entail the deletion of Question 9 and the related sub-questions on suicide ideation and behavior. The resulting questionnaire aligns with the PHQ-8 (to be used in adults) but uses the format, ordering, and slightly revised wording of the PHQ-A. See [Appendix 2](#).

Does the Agency agree with the use of the PHQ-8, the modified PHQ-A (for adolescents), and the C-SSRS to monitor depression and suicidal ideation and behavior in the planned Phase 3 studies?

FDA Response to Clinical Question 7:

Your plan to use C-SSRS and PHQ-8/modified PHQ-A at baseline visit to screen subjects with depression/suicidal ideation/behavior (SIB) for exclusion from trial, and at Weeks 4 and 8 visits for assessment of treatment-emergent depression/SIB appears reasonable.

Clinical Question 8:

Arcutis plans to conduct two identical Phase 3, randomized, parallel group, double blind, vehicle-controlled studies in which ARQ-151 cream 0.3% or vehicle cream will be applied QD for 8 weeks to subjects (N = 400/study) 12 years of age and older with chronic plaque psoriasis (IGA ≥ 2) involving between 2 and 20% BSA. In addition, a long-term open-label, single-arm, 24-week study of ARQ-151 cream 0.3% will be available to subjects (N = ~250) who complete one of the two 8-week Phase 3 studies and have disease involving between 2 and 25% BSA. (Additional long-term (1 year) data is being generated in the currently ongoing ARQ-151-202 study.) See [Section 13.3.3](#), [Section 13.3.4](#), [Appendix 3](#), and [Appendix 4](#).

Does the Agency agree with the general design of the planned Phase 3 studies?

FDA Response to Clinical Question 8:

The treatment period duration for the Phase 2 trial was 12 weeks with primary timepoint at Week 6, yet for the proposed Phase 3 trials you are proposing a primary timepoint at Week 8. Provide a rationale for choosing Week 8 as the primary timepoint for the Phase 3 trials. If the rationale relies on the results from the Phase 2 trial reaching a plateau, full results for Week 8 need to be submitted, including the number of subjects enrolled in each treatment, the baseline disease characteristics, the number of subjects with missing data, the method for handling the missing data etc.

The general designs of your Phase 3 Protocols ARQ-151-301/-302 and Long-term safety Study ARQ-151-306, appear reasonable; see endpoint discussion above. Additional comments may be provided upon review of your final Phase 3 study protocols following their submission to the IND. We have the following comments:

- Include adequate cardiovascular monitoring for all subjects in your Phase 3 trials (including ECG measurements similar to ECG measurements during studies - 201/-202).
- Inclusion criteria for PASI need not be included in your protocols. We do not agree with the inclusion criterion of a baseline PASI score of ≥ 2 (excluding the scalp, palms and soles) as it may not represent mild severity of disease, and changes in PASI are typically not included for topical products.

- We do not agree [REDACTED] (b) (4)
[REDACTED]
as this may not represent the patient population expected to use the product after approval.

Meeting Discussion:

The Agency agreed that no ECG monitoring is required for Phase 3 studies.

Clinical Question 9:

The primary safety database to support the eventual NDA for ARQ-151 cream 0.3% for chronic plaque psoriasis will include data from the replicate vehicle-controlled Phase 3 studies. The 8-week safety data from these studies will be supported by longer-term data from two open-label safety studies which are 6 months and 1 year in duration. Refer to [Section 13.3](#). The following are estimates of subject exposure to ARQ-151 cream $\geq$ 0.3% during the psoriasis development program.

Product	Total Exposures to Drug	2 wk - < 2 mo	2 - < 3 mo	6 mo - < 1 yr	1 yr	> 1 yr
ARQ-151 Cream $\geq$ 0.3%	1165	1100	700	430	245	60

(b) (4)

Does the Agency agree that the planned NDA safety database for ARQ-151 cream 0.3% (both number of subjects and intermittent duration of use in the long-term studies) is sufficient to allow conclusions to be drawn on the safety of ARQ-151 cream in the treatment of chronic plaque psoriasis?

FDA Response to Clinical Question 9:

Your expected subject exposure to ARQ-151 cream (of strength $\geq 0.3\%$) includes a total of 1165 subjects exposed, 430 subjects exposed for 6 months, and 245 subjects exposed for 1 year, does not appear to satisfy the recommendations for ICH E1A. Depending on the safety experience observed in your development program, a larger safety population may be needed.

Meeting Discussion:

The proposed safety database appears adequate unless unexpected additional safety concerns are identified in your development program.

Clinical Question 10:

In the oral toxicity program, treatment of rats with roflumilast or roflumilast N-oxide induced epididymal sperm granulomas and secondary testicular changes (seminiferous tubular dilation and degeneration/atrophy). In parallel, male fertility was reduced in rats, whereas no effects on male fertility were observed in repeat-dose toxicity studies in mice up to the highest doses tested. No treatment-related changes were observed in epididymides and testes of other animal species tested, i.e., mice, hamsters, dogs and monkeys, at even higher drug exposures. The safety margins for potential male reproductive effects in relation to an oral clinical dose of roflumilast 500 μg QD in humans are 628-, 1.7-, 22-, 47-, and 43-fold for roflumilast and 249-, 6-, 56-, 3.8-, and 26-fold for roflumilast N-oxide based on the drug exposure (plasma/serum AUC of unbound drug) in repeat-dose toxicity studies in mice, rats, hamsters, dogs, and monkeys, respectively.

Three studies in healthy volunteers were performed to investigate male reproductive function during roflumilast treatment. A summary of each follows.

AZ Study FHP033 was a double-blind, placebo-controlled, 3-period crossover study that investigated the effect of roflumilast on male endocrine function in 25 healthy male subjects. During the 15-day administration periods, subjects received roflumilast 250 μg or 500 μg QD, or placebo. The results did not indicate any clinically relevant influence of roflumilast on hormone levels. Median values of testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), inhibin B, progesterone, as well as aldosterone, adrenocorticotrophic hormone (ACTH), sodium and potassium did not show any changes evaluated as clinically relevant during the study. The incidence of AEs was comparable across treatment groups. AEs reported most frequently were headache, diarrhea, arthralgia, neck pain and asthenia. The intensity of AEs was predominantly mild or moderate. No SAEs were reported, and no changes of clinical relevance in laboratory values, vital signs or ECG were observed.

AZ Study FHP035 was a double-blind, placebo-controlled, parallel-group study of the effect of roflumilast on male reproductive parameters conducted in 351 healthy men. The subjects received roflumilast 500 μg QD or placebo for 12 weeks and no treatment during an additional 12-week follow-up period. Equivalent effects between the

roflumilast and the placebo group were found for changes in sperm concentration and progressive sperm motility. Forty-one percent and 45%, respectively, of patients in the roflumilast and placebo group showed a > 50% decrease from baseline sperm concentration or progressive motility during the treatment and follow-up periods. In addition, no differences between the treatment groups were seen for male reproductive hormones (testosterone, FSH, LH, inhibin B). In the roflumilast group, 71% of patients compared with 65% in the placebo group reported AEs. Headache, diarrhea, nausea and back pain were more frequently documented AEs in the roflumilast than in the placebo group. For two subjects receiving roflumilast (1.1%) appendicitis was documented as SAE. The investigator assessed both cases as unrelated to the study medication. No deaths were reported during the study. No differences were found between the roflumilast- and placebo group for clinical laboratory values, ECG assessments, and vital signs.

AZ Study CP-052 was a post-study observation of 96 subjects (out of whom 48 had received roflumilast and 48 had received placebo) who had reached the primary endpoint [decrease of sperm concentration or progressive motility by more than 50% of the average of the baseline values at any of the visits during the treatment or follow-up period] while taking roflumilast 500 µg or placebo in study FHP035 (see above). No treatment was administered during this study. The observation period was planned for up to 48 weeks, during which several semen samples were collected for analysis. No relevant differences were found between the groups previously treated with roflumilast or placebo for semen variables with respect to mean values, mean differences from baseline, or numbers of clinically relevant cases. Incidences of AEs were similar for the roflumilast and the placebo groups. No subject in the roflumilast treatment group experienced an SAE or discontinued the study due to an AE. One subject in the placebo group died from a traffic accident. No relevant differences were found between the treatment groups for variables of male reproductive hormones, clinical laboratory values, ECG, and vital signs.

The labeling for oral roflumilast (DALIRESP) states: *In a human spermatogenesis study, roflumilast 500 mcg had no effects on semen parameters or reproductive hormones during the 3-month treatment period and the following 3-month off-treatment period. In a fertility study, roflumilast decreased fertility rates in male rats at 1.8 mg/kg/day (approximately 29 times the MRHD on a mg/m2 basis). The male rats also showed increases in the incidence of tubular atrophy, degeneration in the testis and spermiogenic granuloma in the epididymides. No effect on rat fertility rate or male reproductive organ morphology was observed at 0.6 mg/kg/day (approximately 10 times the MRHD on a mg/m2 basis).*

Arcutis does not plan to conduct studies with ARQ-151 cream to evaluate male reproductive function.

Does the Agency agree that the results of the prior studies/evaluations relating to any potential effect of roflumilast on male reproductive function, reviewed by FDA

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

to support approval of DALIRESP, are applicable to the topical roflumilast (ARQ-151 cream) development program and that additional studies are not warranted?

FDA Response to Clinical Question 10:

From a pharmacology/toxicology perspective, additional nonclinical studies to evaluate male reproductive function are not warranted.

Clinical Question 15:

Although roflumilast absorbs light within the range of natural sunlight, DALIRESP has been marketed globally for approximately 10 years without demonstrating concerns for either phototoxicity or photoallergy. Moreover, topical roflumilast did not demonstrate phototoxic potential in the *in vitro* 3T3 Neutral Red Uptake Phototoxicity Test (See [Section 13.2.3.3](#)). Additionally, photosafety concerns have not been seen with other approved PDE-4 inhibitors. Accordingly, Arcutis requests a waiver from the requirements to conduct a clinical phototoxicity study and a photoallergy study.

Does the Agency agree that clinical phototoxicity and photoallergy testing with ARQ-151 cream is not warranted?

FDA Response to Clinical Question 15:

Phototoxicity and photoallergenicity trials can be waived if your drug product does not absorb light between 290 and 700 nm. The initial consideration for assessment of photoreactive potential is whether a compound absorbs photons at any wavelength between 290 and 700 nm. A compound that does not have a molar extinction coefficient (MEC) greater than 1000 L mol⁻¹ cm⁻¹ at any wavelength between 290 and 700 nm is not considered to be sufficiently photoreactive to result in direct phototoxicity. See the ICH guidance, *S10 Photosafety Evaluation of Pharmaceuticals*.

It appears that roflumilast has an MEC value greater than 1000 L mol⁻¹ cm⁻¹ at wavelengths between 290 and 700 nm; therefore, phototoxicity testing and photoallergy assessment using the to-be-marketed formulation is warranted. Refer to *S10 Photosafety Evaluation of Pharmaceuticals*.

Clinical Question 16:

Does the Agency have any other specific input on sufficiency of the ARQ-151 clinical development program to support registration for use of ARQ-151 cream 0.3% to treat chronic plaque psoriasis, including psoriasis of the intertriginous areas in patients age 12 and older?

FDA Response to Clinical Question 16:

Specific comments on the Phase 3 protocols can be provided upon submission of the complete protocols and accompanying statistical analysis plans.

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*

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>

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,⁵ as well as email access to the eData Team (cdeleredata@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 Standards Resources web page⁶ 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.⁷ 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

⁵ <https://www.fda.gov/media/88173/download>

⁶ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

⁷ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

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 Guide⁸ (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.⁹ When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.¹⁰

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length,

⁸ <https://www.fda.gov/media/88173/download>

⁹ <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹⁰ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

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

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 Resources¹¹ and the CDER/CBER Position on Use of SI Units for Lab Tests website.¹²

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

¹¹ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹² <https://www.fda.gov/media/109533/download>

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*.¹³

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

¹³ <https://www.fda.gov/media/85061/download>

and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

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

6.0 ATTACHMENTS AND HANDOUTS

In response to the Agency's Meeting Preliminary Comments provided on October 11, 2019, the sponsor provided a response and an agenda on October 21, 2019; and slides on October 22, 2019.

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