# ARQ-154-304

A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-154 Foam 0.3% Administered QD in Subjects with Seborrheic Dermatitis (STRATUM)

| | |
|---|---|
| **Sponsor:** | Arcutis Biotherapeutics, Inc.<br>3027 Townsgate Road, Suite 300<br>Westlake Village, CA 91361 |
| **Sponsor Representative:** | [redacted] |
| **IND Number:** | 142047 |
| **Protocol Version:** | Amendment 2 |
| **Date:** | 05 May 2022 |

**GCP Statement**

This study is to be performed in full compliance with the protocol, International Conference on Harmonisation Good Clinical Practices (ICH GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

**Confidentiality Statement**

# SITE INVESTIGATOR SIGNATURE PAGE

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| **ISSUE DATE:** | 05 May 2022 |

I have read this protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the current International Conference on Harmonisation Good Clinical Practices (ICH GCPs) and applicable local and regional regulations.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Arcutis Biotherapeutics, Inc.. I will discuss the material with them to ensure that they are fully informed about ARQ-154 foam 0.3% and the study.

I agree that I or my designee will completely inform all subjects in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with cGCPs and regulatory authority requirements. I will be responsible for maintaining each subject's consent form in the study file and providing each subject with a signed copy of the consent form.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Investigational Site Name: _____

Print Investigator Name: _____

Investigator Signature: _____ Date: _____

# SUMMARY OF CHANGES

The following sections have been changed in Protocol Amendment 2 of the ARQ-154-304 protocol:

| Section | Summary of Changes |
|---|---|
| **Amendment 2** | |
| 4.5.2 Exclusion Criteria | Exclusion 6: Clarified that Baseline/Screening C-SSRS (for adolescents and adults 12 years old and older) indicative of suicidal ideation or behavior, whether lifetime or recent/recurrent is exclusionary. |
| 6.3.2 Secondary Endpoint | Updated the multiple testing strategy for the secondary endpoints to include use of the Fallback Method. |
| Appendix 1: Body and Scalp Diagram | Updated scalp diagram. |
| Editorial changes made throughout to improve accuracy or readability. | |

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| AMP | Adenosine Monophosphate |
| BSA | Body Surface Area |
| $C_{max}$ | Maximum Concentration |
| CDI | Children's Depression Inventory |
| CDLQI | Children's Dermatology Life Quality Index |
| COPD | Chronic Obstructive Pulmonary Disease |
| eCRF | Case Report Form |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLQI | Dermatology Life Quality Index |
| ERB | Ethics Review Board |
| FDA | U.S. Food and Drug Administration |
| FOCBP | Female of Childbearing Potential |
| GCP | Good Clinical Practices |
| IB | Investigational Brochure |
| $IC_{50}$ | Half Maximal Inhibitory Concentration |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ID | Identification |
| IGA | Investigator Global Assessment |
| IND | Investigational New Drug |
| IP | Investigational Product |
| IRB | Institutional Review Board |
| ITT | Intent to Treat |
| IWRS | Interactive Web Response System |
| Kg | Kilogram |
| LED | Light Emitting Device |
| μg | Microgram |
| MedDRA | Medical Dictionary for Regulatory Activities |

| Abbreviation | Definition |
|---|---|
| Mg | Milligram |
| Min | Minute |
| mL | Milliliter |
| NCI | National Cancer Institute |
| NIH | National Institutes of Health |
| Ng | Nanogram |
| NOAEL | No Observed Adverse Effect Level |
| NRS | Numeric Rating Score |
| P-450 | Cytochrome P450 |
| PDE-4 | Phosphodiesterase 4 |
| PHQ-8 | Patient Health Questionnaire |
| PHQ-A | Modified Patient Health Questionnaire for Adolescents |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| QD | Once Daily ("quaque die") |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| US | United States |
| WI-NRS | Worst Itch Numeric Rating Score |

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Arcutis Biotherapeutics, Inc. | | |
| **Protocol Number:** ARQ-154-304 | **Phase:** 3 | **IND:** 142047 |
| **Protocol Title:** A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-154 Foam 0.3% Administered QD in Subjects with Seborrheic Dermatitis | | |
| **Clinical Indication:** Seborrheic Dermatitis | | |
| **Investigational Product:** ARQ-154 foam investigational product (IP) will be supplied as ARQ-154 foam 0.3%. The active ingredient in ARQ-154 foam is roflumilast, a phosphodiesterase 4 (PDE-4) inhibitor. Matching vehicle foam will contain only excipients of ARQ-154 foam.<br>Subjects will be randomized 2:1 to receive ARQ-154 foam 0.3% or matching vehicle foam once daily (QD) applied to all areas of seborrheic dermatitis. Areas of application will be all areas affected including face, scalp, trunk, or intertriginous/genital regions, with a maximum BSA of 20%. Subjects should maintain treatment areas with IP for the duration of the study regardless of whether treatable areas of seborrheic dermatitis clear. New lesions that appear during the treatment period should also be treated. | | |
| **Study Design:** This is a phase 3, randomized, parallel group, double blind, vehicle-controlled study in which ARQ-154 foam 0.3% or vehicle foam is applied QD for 8 weeks to subjects 9 years of age and older with at least moderate seborrheic dermatitis affecting the scalp and/or rest of body. | | |
| **Primary Objective:** The purpose of this study is to assess the safety and efficacy of ARQ-154 foam 0.3% administered once daily (QD) vs vehicle foam for 8 weeks in subjects with seborrheic dermatitis. | | |
| **Study Sites:** Approximately 50 sites in North America | | |
| **Number of Subjects (planned):** 450 | | |
| **Study Population:** Subjects will be male and female children and adolescents (9-17 y/o) and adults (≥18 y/o). Subjects will have a minimum Investigator Global Assessment (IGA) = 'Moderate' (3) for study entry. Randomization will be stratified by study site and Baseline disease severity (IGA = 3 or IGA = 4). | | |

**Duration of Participation for Subjects:** Screening (up to 4 weeks) + Treatment phase (8 weeks) for a total of up to approximately 12 weeks.

**Main Criteria for Inclusion:**

1. Participants legally competent to sign and give informed consent or (for children/adolescents) assent with consent of a parent(s) or legal guardian, as required by local law.
2. Males and females ages 9 years and older (inclusive) at the time of consent.
3. Clinical diagnosis of seborrheic dermatitis of at least 3 months duration at Screening as determined by the Investigator. Stable disease for the past 4 weeks.
4. Seborrheic dermatitis up to 20% BSA involvement. Involvement may be of the scalp and/or face and/or trunk and/or intertriginous areas.
5. An Investigator Global Assessment (IGA) disease severity of at least Moderate ('3') at Baseline.
6. Overall Assessment of Erythema and Overall Assessment of Scaling scores of at least Moderate ('2') at Baseline.
7. Female subjects of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening (Visit 1) and negative urine pregnancy test at Baseline (Visit 2). In addition, sexually active FOCBP must agree to use at least one form of a highly effective or a barrier method of contraception throughout the trial according to Contraception Requirements for Female Subjects (see Figure 1).
8. Females of non-childbearing potential must either be premenarchal, post-menopausal with spontaneous amenorrhea for at least 12 months (post-menopausal status should be confirmed with FSH testing) or have undergone surgical sterilization according to Contraception Requirements for Female Subjects (Figure 1).
9. Subjects in good health as judged by the Investigator, based on medical history, physical examination, vital signs, serum chemistry labs, hematology values, and urinalysis.
10. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule according to the Investigator judgment.

**Main Criteria for Exclusion:**

1. Subjects who cannot discontinue treatment with therapies for the treatment of seborrheic dermatitis prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 1).
2. Planned excessive exposure to treated area(s) to either natural or artificial sunlight, tanning bed, or other LED.
3. Subjects who cannot discontinue to use of strong systemic P-450 cytochrome inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin for two weeks prior to the Baseline visit (Visit 2) and during the study.
4. Subjects with PHQ-8 (≥18 years old, inclusive) or modified PHQ-A (adolescents, 12 to 17 years old, inclusive) score ≥10 at Screening or Baseline visits.
5. Subjects (9-11 years old, inclusive) with a CDI-2 (parent report) raw score ≥17 for females and ≥18 for males at Screening or Baseline visits.
6. History of severe depression, suicidal ideation or behavior, Baseline/Screening C-SSRS (for adolescents and adults 12 years old and older) indicative of suicidal ideation or behavior, whether lifetime or recent/recurrent.
7. Previous treatment with ARQ-151 or ARQ-154.
8. Subjects who have received oral roflumilast (Daliresp®, Daxas®), or apremilast (Otezla®) within the past 4 weeks.
9. Known allergies or hypersensitivity to component(s) of the investigational product which includes roflumilast. [redacted]
10. Known or suspected:
    a. Severe renal insufficiency as evidenced by calculated creatinine clearance <30 mL/min
    b. Moderate to severe hepatic disorders (Child-Pugh B or C)
11. Liver function test results excursions that exceed:
    - AST or ALT > 2x ULN
    - Total bilirubin:
      – 1.5x ULN or
      – >ULN and ≤1.5x ULN and direct bilirubin is >35% of total bilirubin
    - ALP ≥ 2x ULN
12. Subjects with active pityriasis/tinea amiantacea.

13. Subjects with a history or a major surgery within 4 weeks prior to Baseline (Visit 2) or has a major surgery planned during the study.
14. Subjects with any serious medical condition or clinically significant laboratory abnormality that would prevent study participation or place the subject at significant risk, as determined by the Investigator.
15. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements.
16. Subjects/caregivers unable to apply product to the scalp due to physical limitations if the subject has current or history of seborrheic dermatitis involving the scalp.
17. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.
18. A clinically relevant history of abuse of alcohol or other drugs within 6 months prior to Screening.
19. Current or history of cancer within 5 years from Screening with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma, or carcinoma in situ of the cervix.
20. Subjects, parent(s)/legal guardian(s) of children/adolescent subjects who are unable to communicate, read, or understand the local language.
21. Subjects who are family members of the clinical study site, or clinical study staff, or Sponsor, or family members residing in the same household of enrolled subjects.
22. Any condition that in the Investigator's assessment would preclude the subject from participating in the study.

**Key Assessments:** Safety will be monitored through assessment of application site reaction, pigmentation, vital signs/weight, physical examinations, safety labs, and Adverse Events (AEs). Safety will also be monitored by C-SSRS, CDI-2 (children 9-11 y/o), and PHQ-8 (in adults) or modified PHQ-A (adolescents 12-17 y/o) assessments.

All AEs that occur after the first applications of IP through the end of the study should be collected. All SAEs should be collecting starting at Screening.

Efficacy assessments will be evaluated utilizing:

- IGA
- Overall Assessment of Erythema
- Overall Assessment of Scaling
- Worst Itch-Numeric Rating Scale (WI-NRS)
- Scalpdex, DLQI/CDLQI, and BSA.

Pharmacokinetic Assessment:

- Pharmacokinetic samples (trough) will be collected for all subjects at the Week 4 and Week 8 visits.

**Study Endpoints:**

The Primary Efficacy Endpoint will be:

- IGA success, defined as an IGA score of 'clear' or 'almost clear' plus a 2-point improvement at Week 8

The Secondary Efficacy Endpoints will include:

- In subjects with a Baseline WI-NRS pruritus score of ≥4, achievement of a ≥4-point improvement from Baseline in WI-NRS pruritus score at Week 8 ("WI-NRS Success at Week 8")
- WI-NRS Success at Week 4
- WI-NRS Success at Week 2
- IGA Success at Week 4
- Achievement of an Overall Assessment of Scaling (0-3 scale) score of 0 at Week 8
- Achievement of an Overall Assessment of Erythema (0-3 scale) score of 0 at Week 8
- Achievement of an IGA score of 'clear' at Week 8
- IGA Success at Week 2

Additional exploratory endpoints will be included in the Statistical Analysis Plan (SAP).

**Statistical Methods:** Approximately 450 subjects are planned for this study.

Approximately 300 subjects will receive ARQ-154 foam 0.3% QD; approximately 150 subjects will receive matching vehicle foam QD.

The randomization scheme will be 2:1 (ARQ-154 foam 0.3% QD: matching vehicle QD) stratified by study site and Baseline IGA (IGA=3 vs IGA=4).

This sample size provides >90% power to detect a 25% difference between treatment groups on IGA success at $\alpha$=0.01 using a 2-sided Cochran-Mantel-Haenszel test stratified by the randomization factors. The results from a recent phase 2a study (ARQ-154-203) of ARQ-154 compared to vehicle treatment were used to estimate the treatment difference. Specifically, in the phase 2a trial, 73.8% of subjects demonstrated IGA success in the ARQ-154 foam 0.3% group and 40.9% of subjects demonstrated IGA success in the vehicle group.

The number of subjects to be enrolled will also provide sufficient power for the secondary endpoints. Additionally, the larger study size is included in order to provide additional/sufficient numbers of subjects on ARQ-154 treatment for a safety database.

Descriptive statistics will be presented for the subject disposition, demographics, baseline characteristics, treatment compliance, efficacy endpoints, and safety data collected in the clinical trial. This includes the number and percentage of subjects for binary endpoints/categorical data, and mean, SD, median, minimum, and maximum for continuous data.

The primary endpoint of 'IGA success at Week 8' will be analyzed using a Cochran-Mantel-Haenszel test stratified by the randomization factors of the study center and IGA score at Baseline ('moderate' vs. 'severe'). The analysis will be performed on the Intention-to-Treat (ITT) population and missing data will be imputed using multiple imputations.

Continuous secondary endpoints will be analyzed using Analysis of Covariance with treatment and stratification factors as independent variables. The ITT population will be used, and missing data will be imputed using multiple imputation. Binary secondary endpoints will be analyzed similarly to the primary endpoint.

Secondary endpoints will only be tested statistically if the primary endpoint is considered statistically significant. To control for multiple comparisons among the secondary endpoints, the following multiplicity procedure will be used:

Upon demonstration of statistical significance of the primary endpoint, the alpha level of 0.01 will be split between testing of the WI-NRS success endpoints and other secondary efficacy endpoints. The testing over the WI-NRS success endpoints and the other secondary efficacy endpoints will be sequential, utilizing the Fallback Method for unused alpha.

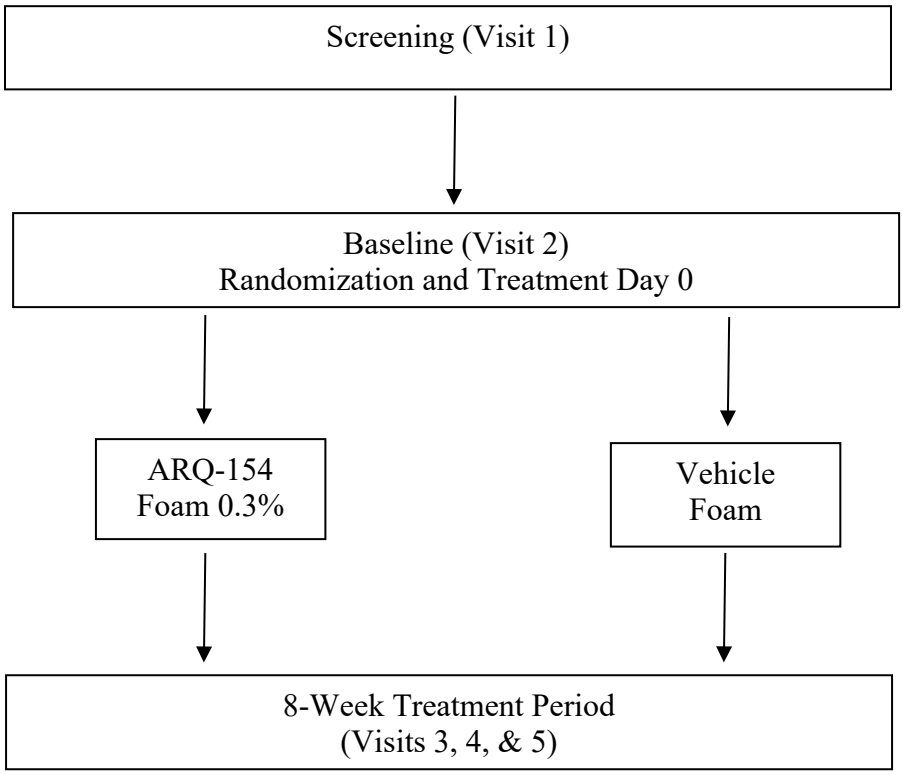
For the testing of WI-NRS success endpoints, an alpha level of 0.0033 will be used and will use a hierarchical method to first test WI-NRS success at Week 8, followed by WI-NRS at Week 4, followed by WI-NRS success at Week 2. Should all three of these endpoints be statistically significant at the 0.0033 level, then this unused alpha will be carried to the other secondary endpoint group, which would then be tested at the .0033+.0067=0.01 level.

An alpha level of 0.0067 (the remainder of the allotted 0.01) or the full 0.01 pending the results of the WI-NRS endpoint testing, will be used to hierarchically test IGA Success at Week 4, Scaling score of 0 at Week 8, Erythema score of 0 at Week 8, the percentage of subjects who attain IGA of 0 at Week 8, and IGA Success at Week 2.All subjects who are randomized and receive at least one confirmed dose of investigational product or vehicle foam will be included in the safety population.

Efficacy analyses will be conducted in the ITT population. Sensitivity analyses may be conducted in the subset of the ITT population for whom the primary endpoint assessment was not missed due to COVID-19 disruption.

Adverse events will be summarized by preferred term, system organ class, and treatment group for all AEs, serious AEs, related AEs, AEs leading to withdrawal from investigational product, and AEs leading to withdrawal from study.

## 1.2. Study Schema




A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-154 Foam 0.3% Administered in Subjects with Seborrheic Dermatitis

Approximately 450 children, adolescent and adult subjects with seborrheic dermatitis will be randomized 2:1 to receive either:

- ARQ-154 foam 0.3%, or
- Vehicle foam

## 1.3. Schedule of Visits and Assessments

| Study Procedure | Screen | Baseline Day 0 | Week 2 Day 14 | Week 4 Day 28 | Week 8[a] Day 56 |
|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** |
| **Visit Window** | **-4 weeks** | | **± 3 days** | **± 5 days** | **± 5 days** |
| Informed consent/assent | X | | | | |
| Medical/surgical history, demography | X | | | | |
| Physical examination[b] | X | X | | | X |
| Fitzpatrick Skin Type | X | | | | |
| I/E criteria | X | X | | | |
| Randomization | | X | | | |
| Hematology, Chemistry, and Urinalysis[c] | X | X | | X | X |
| Vital signs, weight, height[d] | X | X | X | X | X |
| IGA, Overall Assessment of Erythema, Overall Assessment of Scaling[e] | X | X | X | X | X |
| BSA[f] | X | X | X | X | X |
| DLQI/CDLQI[g], Scalpdex | X | X | X | X | X |
| Daily WI-NRS[h] at home (non-clinic) | | Day -7 through Day 56 | | | |
| Local Tolerability Assessment[i] | | X | | X | X |
| Pigmentation Assessment[j] | X | X | X | X | X |
| C-SSRS, CDI-2/PHQ-8/PHQ-A[k] | X | X | | X | X |
| Medical Photography[l] | | X | X | X | X |
| Serum pregnancy test[m] | X | | | | |
| Urine pregnancy test[n] | | X | | X | X |
| PK sampling[o] | | | | X | X |
| IP application and subject/family training[p] | | X | X | | |
| Dispense investigational product kit[q] | | X | X | X | |
| Dispense / review dosing diary | | X | X | X | X |
| Weigh investigational product[r] | | X | X | X | X |
| Compliance calculation[s] | | | X | X | X |
| Adverse event assessment[t] | | X | X | X | X |
| Prior & Concomitant medications | X | X | X | X | X |

### *Footnotes from table above:*

[a] Subjects that terminate early should return to the study site for the Week 8 assessments.

[b] Limited physical examination: skin (including assessment of Fitzpatrick Skin Type at Screening only), lungs, and heart only.

[c] To be collected at Screening, Baseline/Day 0, Week 4/Day28, and Week 8/Day 56. For subjects <18 years of age, if the Baseline/Day 0 visit occurs within 3 weeks of Screening, the Screening lab results may be utilized.

[d] Height will be collected at Baseline and Week 8. Weight will be collected at all study visits. Subject to void prior to weight.

[e] IGA will be a 5-point scale ranging from clear (0) to severe (4). **IGA should be completed prior to other physician assessments and by the same Evaluator at each study visit.** Overall Assessment of Erythema (0-3 scale) and Overall Assessment of Scaling (0-3 scale) will be completed.

[f] Total BSA affected by seborrheic dermatitis will be determined by the subject's hand method, where the subject's hand (including fingers) surface area is assumed to equal 1% of body surface area.

[g] The DLQI will be completed by subjects ≥17 years of age. The CDLQI will be completed for subjects 9 to 16 years old, inclusive.

[h] WI-NRS will be completed by subjects daily at home starting 7 days prior to the Baseline/Day 0 visit to Day 56 (Week 8) visit. Daily WI-NRS will be completed in the evening prior to IP application (except at Baseline and Week 2 when IP is applied at the clinic).

[i] Local tolerability assessments to be recorded prior to IP application for the Investigator assessment of skin irritation (Berger and Bowman skin irritation score) and 10-15 minutes post IP application for the subject's '0-3' burning/stinging assessment. **Note for investigator tolerability assessments: reactions at the site of IP application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's seborrheic dermatitis. At Week 4 and Week 8, subjects will provide a recall assessment of burning/stinging experienced post IP application on the day prior to the clinic visit.**

[j] An assessment for hypopigmentation and hyperpigmentation will be performed by the Investigator at all visits.

[k] Adolescents and adults will complete the C-SSRS (12 years of age and older). Adults will complete the PHQ-8. Adolescents (ages 12 to 17 inclusive) will complete the PHQ-A (PHQ-9 modified). Parents/caregivers will complete CDI-2 (parent report) for children 9-11 years of age, inclusive. The CDI-2 will be completed throughout the study for subjects 9-11 years old at the time of assent.

[l] Medical photography will be obtained for target lesions by all study sites. All efforts will be made to de-identify the subjects.

[m] A serum pregnancy test will be administered to all females of child-bearing potential at the Screening visit only. Follicle Stimulating Hormone (FSH) testing will be performed at Screening (if indicated) to confirm post-menopausal status.

[n] A urine pregnancy test will be performed at the Baseline, Weeks 4 and 8 to all females of child-bearing potential. A negative result is required for continued participation in the study, and results must be available at each visit prior to dispensing of investigational product.

[o] PK samples (trough) will be collected on Day 28 (Week 4) and Day 56 (Week 8). Ensure investigational product is not applied in the area where PK will be drawn.

[p] Subjects to apply assigned IP in the study site at every designated visit.

[q] Kits will be dispensed based on % BSA. See IP Handling Plan for details.

[r] Each IP canister in the Kit should we weighed and recorded at every visit. See IP Handling Plan for details.

[s] Compliance calculation is described in the IP Handling Plan.

[t] All AEs should be collected starting after the first application of the IP through the end of the study. All SAEs should be collected starting after the signing of the informed consent through 30 days after the last day of the IP application or the end of the study (whichever is later).

# 2. BACKGROUND AND RATIONALE

## 2.1. Introduction

Roflumilast is a phosphodiesterase 4 (PDE-4) inhibitor approved globally to reduce the risk of exacerbations in patients with severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis. Roflumilast and its active metabolite, roflumilast N-oxide, are high affinity selective inhibitors of PDE-4 (a major cyclic-3′,5′-adenosine monophosphate (cyclic AMP)-metabolizing enzyme), whose activity leads to accumulation of intracellular cyclic AMP. There are four different subtypes of PDE-4: PDE-4a, PDE-4b, PDE-4c, and PDE-4d, each with several isoforms (splicing variants). $IC_{50}$ values of both roflumilast and roflumilast N-oxide for the different PDE-4 isoforms and subtypes are mostly sub-nanomolar and single digit nanomolar (Hatzelmann 2010). The PDE-4 family of enzymes are the most prevalent phosphodiesterases in immune cells and inhibition of PDE-4 subtypes has been associated with anti-inflammatory effects in many biological systems.

Roflumilast was initially developed as a 500 µg tablet for oral therapy in patients with COPD, and as such has been thoroughly evaluated in nonclinical studies. The safety profile is well-established, and the results of those studies are relevant to the dermal roflumilast (ARQ-151 cream and ARQ-154 foam) development program. Oral roflumilast (500 µg tablet) was approved by Health Canada as DAXAS® in December 2010 and by the US FDA as DALIRESP® in February 2011 for the treatment of COPD. The study sponsor has conducted nonclinical studies in which roflumilast is applied dermally.

The dermal nonclinical program for ARQ-151 cream followed current International Conference on Harmonisation (ICH) guidelines and includes a 13-week dermal toxicity study in minipigs, a 13-week dermal toxicity study in mice, a 39-week dermal toxicity study in minipigs, a skin sensitization study in guinea pigs, a phototoxicity study, an eye irritation study and a 104-week carcinogenicity study in mice, the in life portion of which is complete.

Refer to the current ARQ-154 Investigator's Brochure (IB) for the most current PDE-4 dermal and oral/systemic nonclinical and clinical information.

Seborrheic dermatitis is a common, chronic inflammatory skin disease characterized by erythematous, scaly plaques, often with a yellowish, oily, moist, and/or greasy appearance, affecting areas of sebaceous gland abundance. Frequently involved sites include the scalp (including retroauricular areas), eyebrows, ears, nasolabial folds, eyelids, trunk, and intertriginous areas. There may be associated pruritus and/or pigmentary changes. Seborrheic dermatitis affects about 2% of the adult population (Borda 2015, Dessinioti 2013) and occurs in the adolescent population as well. Treatment of seborrheic dermatitis may vary by location on the body involved, eg, scalp or non-scalp and periocular or not. For the scalp, anti-dandruff shampoos are often used such as anti-fungals, zinc products, selenium sulfide, salicylic acid, or tar. Topical corticosteroid products may also be used. Scalp lesions of seborrheic dermatitis can present a particular treatment challenge and form thick crusts which may not respond to topical steroids or antifungals. On non-scalp regions such as the face, topical antifungals or low potency topical corticosteroids are typically used. However, importantly, topical antifungals may demonstrate limited efficacy and topical steroids may demonstrate tachyphylaxis and cause

important adverse events, particularly on the face, such as telangiectasias, acne, atrophy, rosacea, and ocular complications. Since seborrheic dermatitis is a chronic condition, treatment with topical steroids is particularly problematic due to the need for prolonged treatment duration, which may result in side effects. Other medications which have been used for seborrheic dermatitis include topical sulfur/sulfonamide products, topical calcineurin inhibitors, and oral retinoids.

Given the unmet need for new medical therapies for seborrheic dermatitis, and the precedent of topical anti-inflammatory agents as treatments for seborrheic dermatitis, the Sponsor pursued development of ARQ-154 foam for the treatment of seborrheic dermatitis. Relative to topical formulations such as a cream or gel, the foam formulation in the present study is well suited for the treatment of the scalp, where seborrheic dermatitis may predominate and be most difficult to treat. Foams have the ability to access skin lesions in hair-bearing areas and have commonly been used for treating scalp psoriasis (e.g., Olux® and Luxiq® foams) and seborrheic dermatitis (e.g., Extina® foam). Results of the phase 2a study of ARQ-154 foam 0.3% in adults with seborrheic dermatitis suggest that ARQ-154 may be a highly efficacious and well-tolerated novel topical treatment.

Arcutis is also developing a related cream formulation of roflumilast, ARQ-151 cream. A phase 3 program of ARQ-151 cream 0.3% for plaque psoriasis recently completed, and phase 2 results of ARQ-151 cream 0.15% and 0.05% for atopic dermatitis are available. The composition of ARQ-154 topical roflumilast foam includes minimal qualitative or quantitative changes relative to the composition of ARQ-151 topical roflumilast cream. Compared to ARQ-151, ARQ-154 foam also involves addition of a propellant that is eliminated at delivery. [redacted]

## 2.2. Conclusions on Toxicity Findings

[redacted]

[redacted]

## 2.3. Clinical Studies

### 2.3.1. Seborrheic Dermatitis Phase 2a

ARQ-154-203 (NCT 04091646) was a Phase 2a, parallel group, double blind, vehicle-controlled study that evaluated ARQ-154 foam 0.3% for the treatment of seborrheic dermatitis involving the scalp, face, and/or body. ARQ-154 foam 0.3% or matching vehicle was applied once daily (QD) for eight weeks to adult subjects with a minimum Investigator Global Assessment (IGA) of moderate (IGA of 3 on a 5-point scale from 0 to 4). A total of 226 subjects were randomized at a ratio of 2:1 to receive ARQ-154 foam 0.3% or matching vehicle foam. All randomized subjects were included in both the safety and intent-to-treat (ITT) populations.

The study demonstrated that ARQ-154 foam 0.3% was highly efficacious (including early timepoints), safe, and well-tolerated following once-daily topical application in subjects with moderate to severe seborrheic dermatitis. The study's primary endpoint was IGA Success, defined as achievement of an IGA score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at Week 8. This endpoint was met with IGA success in 73.8% of subjects in the ARQ-154 treatment group vs. 40.9% of vehicle-treated subjects ($p<0.0001$). IGA success was greater with ARQ-154 than vehicle starting at the first post-baseline visit at Week 2 (33.8% of ARQ-154 vs 14.5% of vehicle subjects, $p=0.0029$). Worst Itch-Numeric Rating Scale (WI-NRS) success at Week 8, defined as a ≥4-point improvement from Baseline was 64.6% for ARQ-154 vs. 33.3% for vehicle ($p=0.0006$), with statistical significance as early as Week 2 (52.8% for ARQ-154 vs 22.8% for vehicle, $p=0.0005$).

ARQ-154 foam 0.3% was safe and demonstrated excellent tolerability based on adverse event (AE) reporting and both investigator-rated and subject-rated local tolerability assessments. No serious adverse events (SAEs) were reported, and only a few subjects reported treatment-related adverse events (TEAEs) (1.9% with ARQ-154 and 4.2% with vehicle) or discontinued study drug due to AEs (1.3% with ARQ-154 and 2.8% with vehicle). Most (>90%) TEAEs were grade 1 or grade 2, i.e., mild or moderate. Systemic exposure to roflumilast and roflumilast N-oxide in subjects with seborrheic dermatitis treated with ARQ-154 foam 0.3% appeared comparable to that of subjects with psoriasis treated with ARQ-151 cream 0.3%, when adjusted for body surface area (BSA).

## 2.4. Rationale for Development

The development plan for ARQ-154 foam will leverage experience to date with ARQ-151 cream, which has been safe, well tolerated, and effective in multiple Phase 2 studies for the treatment of plaque psoriasis or atopic dermatitis. Given the unmet need for new medical therapies for seborrheic dermatitis and the results of a phase 2a study of ARQ-154 foam 0.3% in seborrheic

dermatitis, the Sponsor is pursuing development of ARQ-154 foam 0.3% for the treatment of seborrheic dermatitis in this phase 3 study. Relative to topical formulations such as a cream or gel, the foam formulation in the present study is expected to be well suited for the treatment of the scalp, where seborrheic dermatitis may predominate.

### 2.4.1. Dose Selection

ARQ-154 foam at 0.3% was selected for this study to match the dose of ARQ-154 foam from the phase 2a study ARQ-154-203. The 0.3% dose is also consistent with the dose of the related roflumilast cream formulation (ARQ-151 cream 0.3%) which is being evaluated in phase 3 for plaque psoriasis. The 0.3% dose for ARQ-151 cream was selected based on results of the phase 2b study plaque psoriasis study ARQ-151-201, in which the 0.3% concentration demonstrated greater efficacy that the 0.15% concentration. In that phase 2b study, there were no differences in the safety profiles of the two doses, supporting that it was not necessary to evaluate doses less than 0.3% in seborrheic dermatitis. The Sponsor expects similar doses to be safe and effective in seborrheic dermatitis, as supported by the phase 2a seborrheic dermatitis study ARQ-154-203. Additionally, many cases of seborrheic dermatitis may be challenging to treat or refractory to standard treatment (particularly in patients with neurologic conditions, as included here) and the Sponsor is targeting greater efficacy than commonly used topical antifungals and low potency steroids, further supporting the choice to evaluate the 0.3% dose.

Consistent with the close similarities between ARQ-151 and ARQ-154 formulations, study ARQ-154-203 demonstrated comparable pharmacokinetics with ARQ-154 foam as have been described with ARQ-151 cream. Additionally, pharmacokinetics in seborrheic dermatitis appeared comparable to those seen in plaque psoriasis and atopic dermatitis.

### 2.4.2. Risks and/or Benefits to Subjects

Based on efficacy data from subjects randomized to active treatment group of the phase 2a study ARQ-154-203, including at Week 2, it is expected that subjects in the present study ARQ-154-304 will experience improvement in their seborrheic dermatitis. Subjects randomized to the vehicle treatment group may also see some improvement as the formulation of ARQ-154 may have a moisturizing effect.

The safety monitoring practices employed in this protocol (i.e., physical examinations, vital signs/weight, local skin toleration assessments, hematology, serum chemistry, urinalysis, PHQ-8/PHQ-A/CDI-2, C-SSRS and AE questioning) are adequate to protect the subjects' safety and should detect expected AEs. The lack of nausea and vomiting seen in ARQ-151 cream and ARQ-154 foam studies to date may be related to the lack of 'peak to trough' $C_{max}$ variation, lower $C_{max}$ values than observed following oral administration, or bypassing of the gastrointestinal tract with topical administration.

Oral roflumilast has now been used for almost a decade in the treatment of COPD exacerbations and its safety record has been well-documented. The known adverse effects of oral treatment in the COPD population (nausea, diarrhea, weight loss, psychiatric AEs) are readily monitored as specific in this protocol. The current protocol is designed to detect these adverse events and others should they occur, and provides guidance for management, as necessary, to ensure patient safety. Furthermore, the safety profiles of ARQ-151 and ARQ-154 at doses ranging from

0.15% to 0.5% in the preceding studies in seborrheic dermatitis and psoriasis suggests that ARQ-154 foam 0.3% will be similarly safe and well tolerated in the present study.

# 3. STUDY OBJECTIVES AND ENDPOINTS

## 3.1. Study Objectives

### 3.1.1. Primary Objective

The primary objective of this study is to assess the safety and efficacy of ARQ-154 foam 0.3% administered once daily (QD) vs vehicle foam for 8 weeks in subjects with seborrheic dermatitis.

## 3.2. Study Endpoints

### 3.2.1. Primary Endpoint

The primary efficacy endpoint in this study is success in Investigator Global Assessment (IGA) of disease severity, defined as an IGA score of 'clear' or 'almost clear' plus a 2-point improvement at Week 8.

### 3.2.2. Secondary Endpoints

The Secondary Efficacy Endpoints will include:

- In subjects with a Baseline WI-NRS pruritus score of ≥4, achievement of a ≥4-point improvement from Baseline in WI-NRS pruritus score at Week 8 ("WI-NRS Success at Week 8")
- WI-NRS Success at Week 4
- WI-NRS Success at Week 2
- IGA Success at Week 4
- Achievement of an Overall Assessment of Scaling (0-3 scale) score of 0 at Week 8
- Achievement of an Overall Assessment of Erythema (0-3 scale) score of 0 at Week 8
- Achievement of an IGA score of 'clear' at Week 8
- IGA Success at Week 2

Additional exploratory endpoints will be included in the SAP.

# 4. INVESTIGATIONAL PLAN

## 4.1. Overall Study Design and Plan

This is a phase 3, parallel group, double blind, vehicle-controlled study in which ARQ-154 foam 0.3% or vehicle foam is applied QD x 8 weeks to subjects 9 years of age and older with at least moderate seborrheic dermatitis affecting the scalp and/or rest of body.

## 4.2. Number of Sites and Subjects

A total of up to approximately 450 subjects will be enrolled at approximately 50 study sites in North America. Additional countries or study sites may be added, as necessary. Subjects will be male and female children (9 - 11 y/o), adolescents (12 - 17 y/o) and adults (≥18 y/o). Subjects will have an IGA of disease severity of at least Moderate ('3') at Baseline. Subjects must have no more than 20% BSA of seborrheic dermatitis. All lesions on a subject will be treated including the scalp, face, trunk, and intertriginous areas.

## 4.3. Subject Participation

Subject participation involves a minimum of 5 clinic visits, including Screening, Baseline/Day 0, Week 2, Week 4, and Week 8. The interval between Screening and Baseline visits may take up to 4 weeks, the anticipated maximum duration of subject participation is 12 weeks.

## 4.4. Subject Identification Number Assignment

All subjects who sign an informed consent or assent (children/adolescents) form will be assigned a unique 5-digit subject identification (ID) number by the interactive web response system (IWRS). The first 2 digits correspond to the study site number (assigned by the Sponsor), the next 3 digits (starting with 800) correspond to the sequential order in which the subject is screened for the study (e.g., Subject ID <11800>: Site 11, subject number 800, as the first subject screened by that site). The subject ID will remain the same in the event the subject is rescreened.

The study site is responsible for maintaining a current log of subject ID number assigned to each subject. The subject ID number will be used to identify the subject throughout the study and is required to be entered on all clinical study documentation (e.g., case report forms, labeling of clinical materials and sample containers, investigational product accountability logs, etc.).

## 4.5. Selection of Study Population

### 4.5.1. Inclusion Criteria

Subjects must fulfill all the following inclusion criteria to be eligible for participation in the study:

1. Participants legally competent to sign and give informed consent or (for children/adolescents) assent with consent of a parent(s) or legal guardian, as required by local law.
2. Males and females ages 9 years and older (inclusive) at the time of consent.

3. Clinical diagnosis of seborrheic dermatitis of at least 3 months duration at Screening as determined by the Investigator. Stable disease for the past 4 weeks.
4. Seborrheic dermatitis up to 20% BSA involvement. Involvement may be of the scalp and/or face and/or trunk and/or intertriginous areas.
5. An Investigator Global Assessment (IGA) disease severity of at least Moderate ('3') at Baseline.
6. Overall Assessment of Erythema and Overall Assessment of Scaling scores of at least Moderate ('2') at Baseline.
7. Female subjects of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening (Visit 1) and negative urine pregnancy test at Baseline (Visit 2). In addition, sexually active FOCBP must agree to use at least one form of highly effective or a barrier method of contraception throughout the trial according to Contraception Requirements for Female Subjects (see Figure 1).
8. Females of non-childbearing potential must either be premenarchal, post-menopausal with spontaneous amenorrhea for at least 12 months (post-menopausal status should be confirmed with FSH testing) or have undergone surgical sterilization according to Contraception Requirements for Female Subjects (Figure 1).
9. Subjects in good health as judged by the Investigator, based on medical history, physical examination, vital signs, serum chemistry labs, hematology values, and urinalysis.
10. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule according to the Investigator judgment.

### 4.5.2. Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be excluded from participation in the study:

1. Subjects who cannot discontinue treatment with therapies for the treatment of seborrheic dermatitis prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 1).
2. Planned excessive exposure to treated area(s) to either natural or artificial sunlight, tanning bed, or other LED.
3. Subjects who cannot discontinue to use of strong systemic P-450 cytochrome inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin for two weeks prior to the Baseline visit (Visit 2) and during the study.
4. Subjects with PHQ-8 (≥18 years old, inclusive) or modified PHQ-A (adolescents, 12 to 17 years old, inclusive) score ≥10 at Screening or Baseline visits.
5. Subjects (9-11 years old, inclusive) with a CDI-2 (parent report) raw score ≥17 for females and ≥18 for males at Screening or Baseline visits.

6. History of severe depression, suicidal ideation or behavior, Baseline/Screening C-SSRS (for adolescents and adults 12 years old and older) indicative of suicidal ideation or behavior, whether lifetime or recent/recurrent.
7. Previous treatment with ARQ-151 or ARQ-154.
8. Subjects who have received oral roflumilast (Daliresp®, Daxas®), or apremilast (Otezla®) within the past 4 weeks.
9. Known allergies or hypersensitivity to component(s) of the investigational product which includes roflumilast, [redacted]
10. Known or suspected:
    a. Severe renal insufficiency as evidenced by calculated creatinine clearance <30 mL/min
    b. Moderate to severe hepatic disorders (Child-Pugh B or C)
11. Liver function test results that exceed:
    - AST or ALT > 2x ULN
    - Total bilirubin
      - 1.5x ULN or
      - >ULN and ≤1.5x ULN and direct bilirubin is >35% of total bilirubin
    - ALP ≥ 2x ULN
12. Subjects with active pityriasis/tinea amiantacea.
13. Subjects with a history or a major surgery within 4 weeks prior to Baseline (Visit 2) or has a major surgery planned during the study.
14. Subjects with any serious medical condition or clinically significant laboratory abnormality that would prevent study participation or place the subject at significant risk, as determined by the Investigator.
15. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements.
16. Subjects/caregivers unable to apply product to the scalp due to physical limitations if the subject has current or history of seborrheic dermatitis involving the scalp.
17. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.
18. A clinically relevant history of abuse of alcohol or other drugs within 6 months prior to Screening.

19. Current or history of cancer within 5 years from Screening with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma, or carcinoma in situ of the cervix.
20. Subjects, parent(s)/legal guardian(s) of children/adolescent subjects who are unable to communicate, read, or understand the local language.
21. Subjects who are family members of the clinical study site, or clinical study staff, or Sponsor, or family members residing in the same household of enrolled subjects.
22. Any condition that in the Investigator's assessment would preclude the subject from participating in the study.

## 4.6. Randomization

Randomization will take place at the Baseline (Day 0) visit after the Investigator confirms the subject to be fully eligible for participation as outlined in Section 4.5. Subjects will be randomly assigned to apply ARQ-154 foam 0.3% QD or vehicle foam QD. Assignment of ARQ-154 or vehicle will be made at a 2:1 ratio and stratified by study site and baseline disease severity (IGA = 3 or IGA = 4) according to a computer-generated randomization list. Kits containing canisters of IP will be assigned to each subject using the IWRS. A subject may receive more than one kit for the treatment period. The kits and canisters are blinded and each kit is numbered with a unique kit number.

## 4.7. Prohibitions and Concomitant Therapy

Prohibited medications and products are detailed in Table 1.

Generally, the addition of new medications, including nonprescription medications, during the study is discouraged. However, the short-term use of a medication may be authorized by the Investigator. The Investigator must make the decision to authorize the use of any such a medication only after consideration of the clinical situation, the potential for masking symptoms of a more significant underlying event, and whether the use of the medication will compromise the outcome or validity of the clinical investigation. If medication is required, the name, strength, frequency, duration of use, and reason for use will be recorded in source documents and transcribed to Case Report Forms. Medications which have been used chronically by subjects, in particular statins and anti-hypertensives, are allowed for use during the study, except as prohibited in 'Excluded Medications and Treatments' (Table 1).

**Table 1: Excluded Medications and Treatments**

| Excluded Medications and Treatments | Wash Out Period Prior to Baseline (Day 0) |
|---|---|
| Etanercept | 4 weeks |
| All other Biologics | 12 weeks or 5 half-lives, which is longer |
| Systemic treatment with antifungal agents, corticosteroids, immunosuppressive therapies, retinoids, roflumilast, or Otezla® | 4 weeks |
| Topical antifungals, corticosteroids, calcineurin inhibitors, sulfur-based treatments, medical devices, Eucrisa®, azelaic acid, or metronidazole | 2 weeks |
| Medicated shampoos (e.g., coal tar, keratolytics including salicylic acid, antifungals, zinc pyrithione, selenium sulfide, corticosteroids, medical devices) | 2 weeks |
| Topical medications used on the scalp for conditions besides seborrheic dermatitis, e.g., use of topical minoxidil for androgenetic alopecia | 2 weeks |
| Phototherapy, tanning beds, other light emitting devices | 4 weeks |
| Investigational drugs | 12 weeks (biologics) or 5 half-lives, whichever is longer;<br>5 half-lives (orals);<br>2 weeks (topical) |
| Strong systemic P-450 cytochrome inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin). | 2 weeks |
| Intravenous administration of antibiotics or antiviral agents | 1 week |

Note:

1. Eye drop and nasal corticosteroid preparations are allowed. Inhaled corticosteroid preparations are allowed if used for a stable condition and at a stable dose for > 28 days before Screening and are continued at the same dose throughout the study.
2. Non-medicated emollients, moisturizers and sunscreens will be allowed once daily as normally used by the subjects and applied at least 3 hours after application of investigational product to untreated areas only.
3. Only non-medicated shampoos are permitted. Medicated shampoos (e.g., coal tar, keratolytics including salicylic acid, antifungals, zinc pyrithione, selenium sulfide, corticosteroids, medical devices) are prohibited. Subjects should not use other hair products for at least an hour before or after application of investigational product.

## 4.8. Treatment

### 4.8.1. IP Supplies, Packaging, and Labeling

The active ingredient in ARQ-154 foam is roflumilast, a phosphodiesterase 4 (PDE-4) inhibitor. Matching vehicle foam will contain only excipients of ARQ-154 foam. ARQ-154 foam 0.3% or vehicle foam will be provided in a canister containing approximately 60 grams of foam. Two canisters of IP will be packaged in each kit. The number of kits dispensed to a subject will be based on the BSA involvement. The kits and canisters will be labeled with a unique number to maintain blinding.

The Sponsor will supply sufficient quantities of the IP (ARQ-154 foam 0.3%, and matching vehicle) to each site to allow for completion of this study.

Records will be made of the receipt and dispensing of the investigational product supplied. At the conclusion of the study, any unused investigational product will be returned to the Sponsor or designee, or destroyed, as per Sponsor instructions.

Refer to the most current version of the IP Handling Manual for details on the accountability, storage, and management of ARQ-154 and matching vehicle.

### 4.8.2. Treatment Administration

Initial treatment with the IP will occur on Day 0. At the randomization visit (Baseline), the study staff will demonstrate to the subject how to apply ARQ-154 foam 0.3% or vehicle foam using the first canister from the kit that is assigned to the subject at randomization. Study site staff will be trained to ensure a proper amount is dispensed from the foam can and applied to seborrheic dermatitis lesion(s) as a thin film and rubbed in thoroughly but gently, until the 'white' has disappeared. **For scalp lesions, special attention should be given to ensuring adequate investigational product is applied to scalp skin and not rubbed off on hair**. The subject will then practice dispensing a similar amount of investigational product and applying to seborrheic dermatitis lesion(s). The study staff will confirm that the subject's application technique is correct.

Subjects will be instructed to apply IP QD in the evening (except at Baseline and Week 2, in which case IP will be applied at the study site) to areas of seborrheic dermatitis lesions identified by the Investigator at Baseline using a Body and Scalp Diagram (see Appendix 1). IP will be applied at least 20 minutes before going to bed.

For Scalp Lesions: IP will be applied when the skin and hair on the scalp is dry. Subjects should dispense IP on their fingers, then part hair where there are lesions and rub IP into scalp skin. As the IP is applied, the subject should move any hair away to ensure that sufficient foam is applied directly to the affected skin on the scalp. Subjects should not use other hair products for at least an hour before or after application.

For Non-scalp Lesions: IP should be applied to affected areas as a thin layer and rubbed in thoroughly but gently until the foam has disappeared.

Subjects should not wash areas (or otherwise expose to water, e.g., swimming) where ARQ-154 foam or vehicle has been applied until at least 4 hours after IP application and preferably not until the following morning.

Subjects should continue to apply the IP to all treatment areas identified by the Investigator at Baseline using the Body and Scalp Diagram (see Appendix 1), even if that area has cleared during the treatment period. New lesions that develop during the study should be treated as well. Application will be to all areas affected including the face, scalp, trunk, and intertriginous areas. A Body and Scalp Diagram should be used to record existing and new areas of seborrheic dermatitis involvement that are subject to treatment.

Parents/caregivers should wash their hands with soap and water after applying IP to a child. Parents/caregivers who are pregnant or women of childbearing potential who are trying to become pregnant, or who are breastfeeding, or planning to breastfeed during the study should avoid accidental exposure by either avoiding applying IP or by wearing gloves during its application.

### 4.8.3. Treatment Compliance

Weight of the IP applied will be measured for reporting purposes. Each IP canister will be weighed individually prior to dispensing at the Baseline visit or subsequent visits. IP canisters must be returned by subjects at each study visit (both empty and full) and will be weighed individually. Record IP canister weight in the source notes and in the eCRF.

Subjects will complete a daily diary recording the date and time of each IP dose applied, any missed doses, and any relevant comments (e.g., potential AEs or reason for missed dose). Site personnel will review the diary at each visit and use the information to question the subject regarding compliance and AEs and then record appropriate information in source documents and complete eCRFs. If a subject misses a scheduled dose, they should be instructed to return to the protocol IP administration schedule (i.e., if subject forgets a dose they should wait until that evening and apply as usual).

A subject will be considered compliant with the dosing regimen if the subject applies at least 80% of the expected applications during the entire IP application period (Baseline to Week 8) and does not miss more than 3 consecutive doses.

Compliance will be assessed by review of the dosing diary. Re-training will be conducted at subsequent visits as needed, i.e., if the returned canister weighs substantially different than the expected weight, the diary shows less than 80% of expected use, or more than 3 consecutive doses are missed.

Compliance will be documented in the source and eCRF.

### 4.8.4. Blinding

This is a double-blinded study, therefore neither the subjects nor the Investigator, clinical personnel, or Sponsor will be aware of which treatment an individual subject receives.

### 4.8.5. Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the Investigator may obtain treatment assignment directly from the IWRS system for that subject. Refer to the current version of the ARQ-154-304 IWRS Plan for details on unblinding. Treatment assignment should, however, remain blinded unless the assignment knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the eCRF, along with the date on which the treatment assignment was obtained. The Investigator is requested to contact the Medical Monitor promptly in the event of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the Investigator, the subject will have the study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

### 4.8.6. Removal of Subjects from Investigational Product

A subject may discontinue from receiving the IP for any of the following reasons:

- Occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements for IP administration as per the Protocol.
- Occurrence of or considerable worsening of an AE (described in Section 5.7) that, in the opinion of the Investigator in consultation with the Medical Monitor and Sponsor, represents an unacceptable risk to the subject if he/she continues in the study. The Investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
- IP application must be discontinued immediately in the event of a female subject's pregnancy.
- Subject's decision to withdraw from receiving IP.
- Weight loss of >5% from Baseline, if not dieting or intentionally trying to lose weight, at the Investigator's discretion and after consultation with the Medical Monitor and Sponsor.
- C-SSRS indicative of suicidal ideation
- PHQ-8/PHQ-A score ≥15 if determined by Investigator in consultation with a mental health professional.
- CDI-2 raw score of ≥32 if determined by Investigator in consultation with a mental health professional.
- Requirement for use of prohibited concomitant medication (Table 1) after consultation with the Sponsor and Medical Monitor.
- Subjects repeated failure to comply with protocol requirements or study related procedures.

### 4.8.7. Removal of Subjects from the Study

A subject may be removed from study participation for any of the following reasons:

- Subject's decision to withdraw from the study.
- Subject's death.
- Subject is lost to follow-up. A subject will be considered lost to follow-up after three phone and three email attempts and documentation of a certified letter sent to the subject's address.
- Termination of the study by the Sponsor, FDA, or other regulatory authorities.

# 5. STUDY PROCEDURES

The Schedule of Visits and Assessments (Section 1.3) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the Investigator and/or the Sponsor for reasons related to subject safety.

## 5.1. Safety Assessments

This study assesses the safety and efficacy of ARQ-154 foam 0.3%. Safety will be determined by evaluating physical examinations, vital signs/weight, local tolerability assessments, pigmentation, clinical laboratory parameters, PHQ-8/PHQ-A/CDI-2, C-SSRS, and AEs as outlined in the Schedule of Visits and Assessments (Section 1.3). If deemed necessary, additional safety assessments will be performed at the discretion of the Investigator.

### 5.1.1. Screening

Before a subject's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the subject or written assent from subjects (ages 9-17yrs) and consent from their parent(s) or legal guardian(s) after adequate explanation of the study design, anticipated benefits, and the potential risks. Informed consent must be obtained before completion of any non-standard of care study-specific procedures. Procedures that are part of standard of care are not considered study-specific and, therefore, may be performed prior to obtaining consent and used to confirm eligibility provided they occur within the time allowance outlined in the Schedule of Visits and Assessments (Section 1.3). A subject is considered a participant of the trial once the ICF or written assent for subjects ages 9-17yrs is completely signed.

The following procedures/assessments will be performed at the Screening Visit (within 4 weeks after signing the ICF/assent):

- Review of medical and surgical history
- Review of childbearing potential (female subjects) and contraceptive use (Section 5.1.2)

- Collection of demographic data including age, sex, race, ethnicity
- Limited physical examination of skin (including assessment of Fitzpatrick Skin Type at Screening only), lungs, and heart
- Vitals signs including temperature, heart rate, blood pressure
- Collection of body weight (kg)
- Laboratory tests: hematology, chemistry, urinalysis, serum pregnancy (for female subjects of childbearing potential)
- Seborrheic dermatitis assessments: IGA, BSA, Overall Assessment of Erythema, Overall Assessment of Scaling, Pigmentation Assessment
- Completion of DLQI/CDLQI, Scalpdex, C-SSRS, CDI-2/PHQ-8/PHQ-A
- Collection of prior and concomitant medication

All screened subjects will receive a subject identification number (see Section 4.4) and be entered into the eCRF. Subjects that fail to meet the eligibility criteria will be designated as a screen failure and entered in the IWRS and eCRF as such. Subjects who are unable to enroll within the screening window will be rescreened.

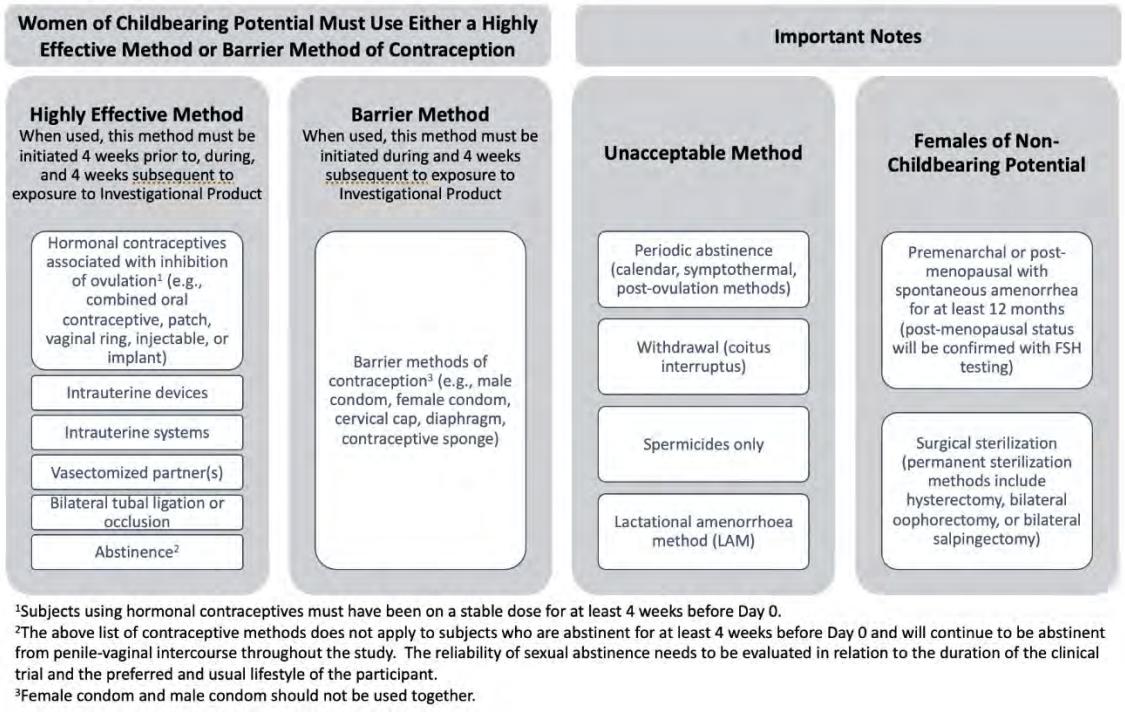
Subjects may be re-screened one time. The original assigned subject ID number will be used for re-screening.

Subjects who consent but do not proceed with enrollment will be considered a screen failed subject.

### 5.1.2. Contraception Requirements

Females of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at Baseline (Visit 2). In addition, sexually active FOCBP must agree to use at least one form of a highly effective or barrier method of contraception throughout the trial according to Contraception Requirements for Female Subjects (Figure 1).

**Figure 1: Contraception Requirements for Female Subjects**




[1]Subjects using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Day 0.
[2]The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 0 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.
[3]Female condom and male condom should not be used together.

### 5.1.3. Baseline

Each subject will undergo Baseline assessments outline in the Schedule of Visits and Assessments (Section 1.3). For subjects <18years, if the Baseline (Day 0) visit occurs within 3 weeks of Screening, the Screening lab results may be utilized.

Randomization and IP kit assignment will take place, via IWRS, after the subject has been found to be fully eligible for participation. A subject will be considered enrolled into the study upon randomization.

### 5.1.4. Physical Examination

Physical examinations will be performed according to the Schedule of Visits and Assessments (Section 1.3). The physical exam will be limited to skin (including assessment of Fitzpatrick skin type at Screening only), lungs, and heart only.

Fitzpatrick skin phototype assessment will be rated as follows:

I. Always burns easily; never tans (sensitive)
II. Always burns easily; tans minimally (sensitive)
III. Burns moderately; tans gradually (light brown) (normal)
IV. Burns minimally; always tans well (moderate brown) (normal)
V. Rarely burns; tans profusely (dark brown) (insensitive)
VI. Never burns; deeply pigmented (insensitive)

### 5.1.5. Vital Signs, Height and Weight

Vital signs will be performed according to the Schedule of Visits and Assessments (Section 1.3).

Blood pressure, heart rate, and temperature will be measured while the subject is sitting/resting for at least 5 minutes.

Height will be collected at Baseline and Week 8.

Subjects should void prior to weight being taken and remove any objects of significant weight (i.e., jackets, outerwear, shoes, cell phones, wallet, key chains, etc.). A 5% unintentional weight loss from Baseline should be reported to the medical monitor.

### 5.1.6. Laboratory Tests

All tests listed in Table 2 will be performed according to the Schedule of Visits and Assessments (Section 1.3) unless otherwise noted. For subjects <18 years old, Screening safety lab results collected within 3 weeks of the Baseline visit may be utilized as the Baseline safety lab assessment. No food restrictions are required for the collection of specimens. In addition, laboratory safety tests may be performed at unscheduled time points, if deemed necessary by the Investigator. Laboratory samples will be sent to the central lab. Refer to the most current Central Laboratory Manual for collection, processing, shipping, and report receipt instructions.

**Table 2: Laboratory Tests**

| **Hematology** | **Serum Chemistry** |
|---|---|
| • Hemoglobin<br>• Hematocrit<br>• Total and differential leukocyte count<br>• Red blood cell count with indices and morphology<br>• Platelet count | • Blood Urea Nitrogen<br>• Bilirubin (total and direct)<br>• Alkaline phosphatase<br>• Aspartate aminotransferase<br>• Alanine aminotransferase<br>• Albumin<br>• Sodium<br>• Potassium<br>• Chloride<br>• Glucose<br>• Creatinine |
| **Urinalysis** | **Additional Tests** |
| • pH<br>• Specific gravity<br>• Protein*<br>• Glucose<br>• Ketones<br>• Bilirubin<br>• Blood*<br>• Nitrite*<br>• Urobilinogen<br>• Leukocyte esterase* | • Urine pregnancy test (for females of childbearing potential only)<br>• Serum pregnancy test (hCG) **<br>• FSH test (post-menopausal females only)<br>• Pharmacokinetic (PK) assessments |

*If urinalysis is positive for protein, blood, nitrite, and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.
**At Screening for FOCBP only

### 5.1.7. Patient Health Questionnaire Depression Scale (PHQ-8)

The PHQ-8 Assessment (see Appendix 2) will be completed by adult subjects according to the Schedule of Visits and Assessments (Section 1.3).

PHQ-8 score is the sum of the responses for the 8 questions.

Five severity categories of depression are defined as follows:

- None – Minimal depression (0 to 4)
- Mild depression (5 to 9)
- Moderate depression (10 to 14)
- Moderately severe depression (15 to 19)
- Severe depression (20 to 24)

A subject with a PHQ-8 score of 10-14 should be referred to a mental health professional for evaluation, regardless of the reason for their change in score.

A subject with with a PHQ-8 score of ≥15 should be immediately referred to a mental healthcare professional and Investigators in consultation with the mental health professional should consider interruption or discontinuation of the IP.

### 5.1.8. Patient Health Questionnaire Depression Scale (Modified PHQ-A)

The Modified PHQ-A Assessment (Appendix 3) will be completed by adolescent subjects (12-17 years old, inclusive) according to the Schedule of Visits and Assessments (Section 1.3).

Modified PHQ-A score is the sum of the responses for the 8 questions.

Five severity categories of depression are defined as follows:

- None - Minimal depression (0 to 4)
- Mild depression (5 to 9)
- Moderate depression (10 to 14)
- Moderately severe depression (15 to 19)
- Severe depression (20 to 24)

A subject with a modified PHQ-A score of 10-14 should be referred to a mental health professional for evaluation, regardless of the reason for their change in score.

A subject with a modified PHQ-A score ≥15 should be immediately referred to a mental health professional, and Investigators in consultation with the mental health professional should consider interruption or discontinuation of the IP.

### 5.1.9. Children's Depression Inventory 2 (Parent Report)

The CDI-2 Assessment will be performed according to the Schedule of Assessments (Section 1.3) for subjects 9-11 years old, inclusive. Subjects 9-11 years old at the time of assent will complete the CDI-2 throughout the study.

The CDI-2 quantifies depressive symptomatology using reports from children/adolescents, teachers, and parents or caregivers. It is recommended for use in initial evaluation and is appropriate when there is a need for an assessment and robust description of a child's depressive symptoms.

This study will use the CDI Parent Report Form. An example of the Parent Repot Form is presented in Appendix 4.

A subject with a CDI-2 raw total score of ≥21 for females and ≥22 for males should be referred to a mental health professional for evaluation.

A subject with a CDI-2 raw total score of ≥32 should be referred to a mental health professional, and Investigators in consultation with the mental health professional should consider interruption or discontinuation of the investigational product.

### 5.1.10. Columbia-Suicide Severity Rating Scale (C-SSRS)

C-SSRS Assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3) for subjects 12 years old and older.

The administration schedule of the C-SSRS will be:

- The Baseline-Screening version (Appendix 5) will be used at Screening to provide a pre-treatment assessment baseline.
- On all subsequent visits, the Since Last Visit version (Appendix 6) will be used.
- A score greater than 0 at the Screening or Baseline visit in suicidal ideation may indicate the need for mental health intervention. The Investigator should not enroll the subject in the study.
- Any score greater than 0 in the suicidal ideation score may indicate the need for mental health intervention. The Investigator should give consideration for the subject to discontinue from the IP and prompt referral to a mental health professional and/or possibly the emergency room. The Medical Monitor should be contacted.

The C-SSRS administrator will be trained via C-SSRS training video. A training certificate for the administrator(s) will be on file in the trial master file at the site.

The Investigator must review the completed C-SSRS. A qualified mental health care provider must be available, immediately if needed, to refer the subject for further evaluation.

### 5.1.11. Local Tolerability Assessment

The Investigator Local Tolerability Assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3).

Application site reactions will be graded at each timepoint. Irritation reactions are graded using the scale detailed in the following section (Berger 1982). **Reactions at the site of product application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's seborrheic dermatitis**.

For the Baseline visit, when IP is applied in the clinic, the Investigator assessments will be conducted by the Investigator prior to IP application.

Dermal Response

0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definite erythema, readily visible; minimal edema or minimal papular response
3 = erythema and papules
4 = definite erythema
5 = erythema, edema and papules
6 = vesicular eruption
7 = strong reaction spreading beyond application site

Other Effects

A = slight glazed appearance
B = marked glazing
C = glazing with peeling and cracking
D = glazing with fissures
E = film of dried serous exudates
F = small petechial erosions and/or scabs
G = no other effects

The Subject Local Tolerability Assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3).

This assessment will be administered by the site 10 to 15 minutes after IP application in the clinic at Baseline and recall assessments at Weeks 4 and 8.

| Grade | Sensation Following Investigational Product Application |
|---|---|
| 0 (none) | No sensation |
| 1 (mild) | Slight warm, tingling sensation; not really bothersome |
| 2 (moderate) | Definite warm, tingling sensation that is somewhat bothersome |
| 3 (severe) | Hot, tingling/stinging sensation that has caused definite discomfort |

### 5.1.12. Pigmentation Assessment

The Investigator will assess for pigmentation in areas affected previously and/or currently by seborrheic dermatitis according to the Schedule of Visits and Assessments (Section 1.3).

Hypopigmentation and hyperpigmentation will be scored individually using a 0 – 3 scale: '0' for none, '1' for mild, '2' for moderate, and '3' for severe.

### 5.1.13. Adverse Events

Adverse events (AEs) will be collected and assessed throughout the study according to the Schedule of Visits and Assessments (Section 1.3). The Investigator is responsible for ensuring that all adverse events observed by the clinical staff or reported by the subject that occur after the first application of investigational product through the end of the study are recorded in the subject's medical record and the eCRF.

The Investigator is responsible for ensuring that all serious adverse events observed by the clinical staff or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the application of the investigational product or the end of study (whichever is later) are recorded in the subject's medical record and are submitted per SAE reporting requirements (Section 5.7.2).

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI and treated and/or followed up for up to 30 days after end of treatment or until the symptoms or value(s) return to the subject's baseline value, or acceptable levels, as judged by the Investigator.

Refer to Section 5.7 for further details on Adverse Events.

## 5.2. Efficacy Evaluations

Investigators will be trained in the administration of rating scales. A training certificate is issued upon successful completion of the training and will be valid for 12 months, unless compliance issues are identified that warrant retraining.

### 5.2.1. Investigator Global Assessment (IGA)

Investigator's Global Assessments ('whole body' and 'intertriginous area') will be performed at according to the Schedule of Visits and Assessments (Section 1.3). The IGA should be completed prior to any other physician assessments.

The IGA is a static evaluation of qualitative overall seborrheic dermatitis severity. This global assessment scale is an ordinal scale with five severity grades (reported only in integers of 0 to 4). Each grade is defined by a distinct and clinically relevant morphologic description that minimizes inter-observer variability.

**Every effort must be made for the same Evaluator to complete the IGA for the subject at every study visit, particularly for Baseline and Week 8.**

**Investigator Global Assessment of Disease (IGA)**

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

### 5.2.2. Overall Assessment of Erythema

Overall Assessment of Erythema will be performed according to the Schedule of Visits and Assessments (Section 1.3).

Overall Assessment of Erythema is a static qualitative evaluation, involving an ordinal scale with 4 severity grades (reported only in integers of 0 to 3). Each grade is defined by a distinct and clinically relevant morphologic description that minimizes inter-observer variability.

**Every effort must be made for the same Evaluator to complete the Overall Assessment of Erythema for the subject at every study visit, particularly for Baseline and Week 8.**

**Overall Assessment of Erythema**

| Symptom | Score | Description |
|---|---|---|
| **Erythema** | **0** | **None:** No evidence of erythema |
| | **1** | **Mild:** Barely perceptible erythema which is faint or patchy |
| | **2** | **Moderate:** Distinct erythema, |
| | **3** | **Severe:** Intense (fiery red) erythema |

### 5.2.3. Overall Assessment of Scaling

Overall Assessment of Erythema will be performed according to the Schedule of Visits and Assessments (Section 1.3).

Overall Assessment of Scaling are static qualitative evaluations, involving an ordinal scale with 4 severity grades (reported only in integers of 0 to 3). Each grade is defined by a distinct and clinically relevant morphologic description that minimizes inter-observer variability.

**Every effort must be made for the same Evaluator to complete the Overall Assessment of Scaling for the subject at every study visit, particularly for Baseline and Week 8.**

**Overall Assessment of Scaling**

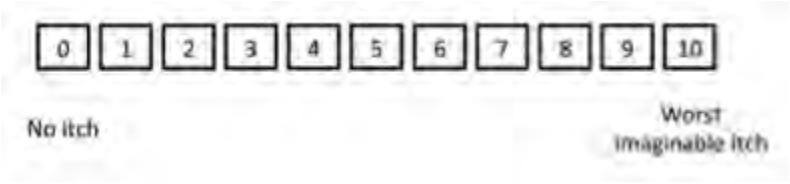
| Symptom | Score | Description |
|---|---|---|
| **Scaling** | **0** | **None:** No scaling evident on lesions |
| | **1** | **Mild:** Barely detectable, scattered, small flaking scales |
| | **2** | **Moderate:** Scales clearly visible and prominent |
| | **3** | **Severe:** Coarse, thick scales, with flaking into clothes or skin |

### 5.2.4. Worst Itch-Numerical Rating Scale (WI-NRS)

Given that itch is an important symptom of seborrheic dermatitis, a WI-NRS assessment is included in the present study. A responder analysis will be performed to evaluate 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 in other skin conditions, including other forms of eczema (Yosipovitch 2019) and psoriasis (Kimball 2016).

WI-NRS Assessment will be performed by subjects **daily** at home according to the Schedule of Visits and Assessments (Section 1.3) starting 7 days prior to the scheduled Baseline/Day 0 visit up to the Week 8/Day 56 visit. Subjects will be provided with a diary to record their daily WI-NRS assessments.

The WI-NRS has been developed as a simple, single item to assess the patient-reported severity of this symptom at its highest intensity during the previous 24-hour period. (Naegeli 2015). The WI-NRS will be determined by asking the subject's assessment of worst itch over the past 24 hours. The scale is from '0 to 10' ("no itch" to "worst imaginable itch").




### 5.2.5. Scalpdex

The Scalpdex (Appendix 7) will be performed by subjects according to the Schedule of Visits and Assessments (Section 1.3).

### 5.2.6. Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI)

The DLQI (ages 17+ years) and CDLQI (ages 9-16 years, inclusive) will be performed according to the Schedule of Visits and Assessments (Section 1.3). The DLQI/CDLQI is a simple, self-administered and user-friendly validated questionnaire. The DLQI/CDLQI is designed to measure the health-related quality of life of patients suffering from a skin disease. The DLQI/CDLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week.

The DLQI (Appendix 8) will be completed by subjects ages 17 years and older. The CDLQI (Appendix 9) will be completed by caregivers of subjects ages 9-16 years.

#### 5.2.7. Body Surface Area (BSA)

BSA assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3).

The BSA affected by seborrheic dermatitis will be determined by the subject's hand method, where the subject's hand (including fingers) surface area is assumed to equal 1% of body surface area.

## 5.3. Other Evaluations

#### 5.3.1. Pharmacokinetics Assessment

Pharmacokinetic (PK) samples will be collected according to the Schedule of Visits and Assessments (Section 1.3) for all subjects.

- PK will be evaluated through trough sampling at Week 4 and Week 8.

PK samples will be collected while the subject is having serum chemistries drawn, when applicable. Ensure the IP is not applied in the area where PK will be drawn.

#### 5.3.2. Dermal Imaging

Medical photography as supportive evidence of clinical outcome will be conducted by all sites using Canfield equipment. Photos will be obtained according to the Schedule of Visits and Assessments (Section 1.3). Photography should be focused on single lesions or specific body sections (e.g., arm). Body or half body photos should only be taken if necessary. For subjects with seborrheic dermatitis lesions on the face, scalp, and/or body, effort should be made to prioritize obtaining a photograph of the facial lesion(s). All efforts will be made to de-identify the subjects. Subjects who are unwilling to participate in the medical photography will be allowed to opt out of this procedure and documented on the informed consent. Refer to the current Photography Manual for instructions regarding photography.

## 5.4. Final Study Visit

The approximate final study visit will occur at Week 8 (Day 56). The procedures performed during this visit are described in the Schedule of Visits and Assessments (Section 1.3). A 5-day scheduling window is allowed for this visit. Adverse events will be recorded as reported by the participant or and followed to resolution (as necessary) as outlined in Section 5.7.

## 5.5. Early Termination Visit

If a subject is withdrawn from the study, an early termination visit will be scheduled. This visit should include the procedures and assessments that would be performed at the Week 8 visit (Day 56). Subjects who withdraw consent from study participation, will not be required to perform an early termination visit.

## 5.6. Unscheduled Visit

Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted in the judgement of the Investigator.

The following information will be collected for all subjects:

- Concomitant medications/procedures
- AEs

## 5.7. Adverse Events

### 5.7.1. Adverse Event Definition

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. When recording such events, provide descriptions that the pre-existing condition has changed (e.g., worsening hypertension for a subject with pre-existing hypertension). A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should NOT be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae, or that require therapy or adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

### 5.7.2. Serious Adverse Event

The definitions and reporting requirements of the Food and Drug Administration (FDA)/ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A will be adhered to. Mandatory reporting of all serious unexpected adverse drug reactions (SUSARs) to Health Canada [as per C.05.014 (1) of the FDR] will be adhered. If any AEs are serious, as defined by ICH Guidelines for Clinical Safety, required procedures will be followed.

As SAE is defined as any AE that, in the view of either the PI or Sponsor, meets at least 1 of the following serious criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity/disability
- Congenital anomaly/birth defect
- Other important medical events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities or respite care (e.g., caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency department visits
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- <24 hour admissions for observation or evaluation

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the individual subject
- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

Unexpected is defined as an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or study documentation.

### 5.7.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

SUSAR is defined as a serious adverse reaction, the nature or severity of which is not consistent with the known study treatment information. A serious event or reaction is not defined as a SUSAR when: 'it is serious but expected' or it does not fit the definition of an SAE, whether expected or not.

### 5.7.4. Safety Review with Subject

At each subsequent clinic visit after the Screening visit, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?' Additionally, the study staff will review subject diaries and, if it appears that a potential AE was recorded, study staff will query the subject and determine if an AE occurred.

### 5.7.5. Adverse Event Reporting

The Investigator is responsible for recording all adverse events, observed by the clinic staff, or reported by the subject that occur after the first application of investigational product through the end of the study are recorded in the subject's medical record and the eCRF. Serious adverse events observed by the clinic staff or reported by the subject after signing the informed consent form will be recorded.

All adverse events that meet the criteria for "serious" (i.e., SAEs) will be reported to the Sponsor via fax or e-mail to ArcutisPV@EVERSANA.com within 24 hours of becoming aware of the event, whether or not the serious events are deemed drug-related.

All serious event reporting will adhere to ICH E6: Guideline for Good Clinical Practice and ICH E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. The Institutional Review Board (IRB) will be notified of the Alert Reports as per FDA, ICH and the IRB's policies and procedures.

The Sponsor, or delegate, will be responsible for reporting SAEs to health authorities per local reporting requirements. The Investigator will be responsible for reporting events to their respective IRBs/ Ethics Review Board (ERB) in accordance with the IRB/ERB requirements.

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI and treated and/or followed for up to one month after end of treatment until the symptoms or value(s) return to the subject's baseline value, or acceptable levels, as judged by the Investigator. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s).

The Investigator will review each adverse event and assess its relationship to Investigational Product (unrelated, unlikely, possibly, probably, likely). Each sign or symptom reported will be graded on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5). The date and time of onset, time relationship to drug dosing, duration, and outcome) of each event will be noted.

The relationship of each AE to the Investigational Product will be assessed using the following definitions:

| | |
|---|---|
| **Unrelated** | • The AE must clearly be caused by the subject's clinical state, or the study procedure/conditions.<br>• Definitely not related to drug.<br>• Temporal sequence of an AE onset relative to administration of drug not reasonable.<br>• Another obvious cause of an AE. |
| **Unlikely** | • Time sequence is unreasonable.<br>• There is another more likely cause for an AE. |
| **Possibly** | • Corresponds to what is known about the drug.<br>• Time sequence is reasonable.<br>• Could have been due to another equally, likely cause. |
| **Probably** | • Is a known effect of the drug.<br>• Time sequence from taking drug is reasonable.<br>• Ceases on stopping the drug.<br>• Cannot be reasonably explained by the known characteristics of the subject's clinical state. |
| **Likely** | • Is a known effect of the drug (e.g., listed in Physicians' Desk Reference, Compendium of Pharmaceuticals and Specialties, IB).<br>• Time sequence from taking drug is reasonable.<br>• Event stops upon stopping drug, event returns upon restarting drug. |

The following CTCAE toxicity grading scale 5-point severity scale definitions for rating maximum severity will be used:

| | |
|---|---|
| **Grade 1** | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| **Grade 2** | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.* |
| **Grade 3** | Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.**<br>Note: An experience may be severe but may not be serious, e.g., severe headache). |
| **Grade 4** | Life-threatening consequences; urgent intervention indicated. |
| **Grade 5** | Death related to AE. |

Note: A semi-colon indicates 'or' within the description of the grade.

* Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

AEs will be coded using the most current MedDRA® version available at the start of the study.

## 5.8. Reporting Pregnancy

During study participation, all subjects should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, Investigational Product must be discontinued immediately, the subject should be referred to an obstetrician experienced in reproductive toxicity for evaluation and counseling, and the subject should be followed until conclusion of the pregnancy.

The Investigator is responsible for reporting all available pregnancy information on the pregnancy report to ArcutisPV@EVERSANA.com within 24 hours of becoming aware of the event, although pregnancy itself is not considered an AE. Follow-up information detailing the outcome of the pregnancy and the health of the newborn should be reported as it becomes available. In addition, any pregnancy resulting in a congenital abnormality or birth defect of the newborn, or neonatal death occurring within 30 days of the birth must be reported as a SAE, regardless of causality.

Partner pregnancies of a male subject do not need to be reported.

## 5.9. Treatment Stopping Rules

If a subject has non-cutaneous adverse events of concern, clinically significant laboratory values or any condition that the investigator determines could possibly be related to the investigational product, the Investigator should immediately contact the Medical Monitor to discuss if the subject should be discontinued from treatment with investigational product.

Treatment for any individual subject will be discontinued if the subject experiences:

- A SAE or a clinically significant non-serious AE which in the opinion of the Principal Investigator or Medical Monitor warrants discontinuation from the study for that subject's well-being
- A treatment-emergent severe (Grade 3) laboratory abnormality (confirmed by repeat sample; see Appendix 10 for more information).

A subject with a PHQ-8/PHQ-A score ≥15 should receive immediate referral to a mental health care professional, and Investigators in consultation with the mental health professional should consider interruption or discontinuation of the investigational product.

- Subjects with a PHQ-8 or modified PHQ-A score of 10-14 should be referred to a mental health professional for evaluation, regardless of the reason for their change in score.

A subject with a CDI-2 raw total score ≥32 should be referred to a mental health professional, and Investigators in consultation with the mental health professional should consider interruption or discontinuation of the investigational product.

- Subjects with a CDI-2 raw score ≥21 for females and ≥22 for males should be referred to a mental health professional for evaluation.

A subject that is experiencing suicidal ideation and behavior should be referred immediately to a qualified mental health care provider and consideration given to discontinuation from IP.

As noted above, IP must be discontinued immediately in the event of a female subject's pregnancy.

IP Treatment should be interrupted:

- If a subject develops an application site reaction with the clinical appearance of an 'irritation reaction', and with a severity of a Dermal Response Score of 5 (erythema, edema, and papules) or greater on the scale of Berger and Bowman, treatment should be interrupted for up to one week and may then be resumed if the reaction has, in the opinion of the Investigator, adequately resolved.

IP Treatment should be discontinued:

- If the reaction reoccurs. IP should be discontinued permanently, and the subject followed until the reaction resolves.

For cases of suspected allergic contact dermatitis, the medical monitor and sponsor should be notified and there should be discussion about performing patch testing to further evaluate. Patch testing is encouraged in such cases.

In the event of a medical emergency where unblinding is required to provide medical care to the subject, refer to the most current IWRS Plan and Breaking Treatment Codes (Section 4.8.5). Contact the Medical Monitor and the Sponsor promptly.

# 6. DATA ANALYSIS

Data will be handled and processed according to the Contract Research Organization's (CRO) Standard Operating Procedures, which are written based on the principles of GCP.

## 6.1. Statistical Methods

The methodology presented below is a summary of the more detailed analysis plan that will be presented in the Statistical Analysis Plan (SAP). The SAP will be finalized before the database is locked and unblinded. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

All statistical processing will be performed using SAS® (Version 9.4 or later) unless otherwise stated.

Descriptive statistics will be used to provide an overview of the efficacy, safety and pharmacokinetic results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentage will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation (SD), median, minimum, and maximum.

### 6.1.1. Determination of Sample Size

A sample size of approximately 450 subjects is planned for the study.

The randomization scheme will be 2:1 (ARQ-154 foam 0.3% QD: matching vehicle QD). Randomization will be stratified by site and baseline disease severity (IGA = 3 or IGA = 4). Approximately 300 subjects will receive ARQ-154 foam 0.3% QD; approximately 150 subjects will receive vehicle foam QD.

A sample size of 450 subjects will provide at least 90% power to detect a 25% difference between treatment groups on IGA success at $\alpha$=0.01 using a 2-sided Cochran-Mantel-Haenszel test stratified by the randomization factors. The results from a recent Phase 2a study (ARQ-154-203) of ARQ-154 compared to vehicle treatment were used to estimate treatment difference. Specifically, in the Phase 2a trial, 73.8% of subjects demonstrated IGA success in the ARQ-154 0.3% group and 40.9% of subjects demonstrated IGA success in the vehicle group.

The number of subjects to be enrolled will also provide sufficient power for the secondary endpoints. Additionally, the larger study size is included in order to provide additional/sufficient numbers of subjects on ARQ-154 treatment for a safety database.

### 6.1.2. Subjects to Analyze

The analysis populations are defined as follows:

- Safety population will include all subjects who are randomized and receive at least one confirmed dose of IP or vehicle foam. This population will be used for all safety analyses.
- Efficacy analyses will be conducted in the Intent-to-Treat (ITT) population. Sensitivity analyses may be conducted in the subset of the ITT population for whom the primary endpoint assessment was not missed due to COVID-19 disruption
- The Intention-to-Treat (ITT) population will include all randomized subjects. This population will be the primary analysis population for the analysis of efficacy endpoints.
- The pruritus population is a subset of the ITT population and include subjects with WI-NRS pruritus score ≥4 at Baseline. This population will be used for the analysis of achievement of a 4-point reduction in WI-NRS pruritus score as compared to Baseline.

### 6.1.3. Interim Analysis

No interim analyses are planned.

### 6.1.4. Background and Demographic Characteristics

Descriptive statistics will be presented for the subject disposition, demographics, Baseline characteristics, treatment compliance, efficacy endpoints and safety data collected in the clinical trial. This includes the number and percentage of subjects for binary endpoints/categorical data, and mean, SD, median, Minimum, and maximum for continuous data.

### 6.1.5. Study Disposition

Number of subjects randomized, receiving IP, completing study, and withdrawing prematurely (with reason for withdrawal) will be summarized by treatment group.

### 6.1.6. Protocol Deviations and Eligibility Deviations

The number of subjects with important protocol deviations and/or eligibility deviations will be summarized in categories by treatment group.

### 6.1.7. Investigational Product Application Compliance

The number of IP applications by each subject based on diary data will be summarized using descriptive statistics.

The amount of IP used by each subject based on can weight will be summarized by treatment using descriptive statistics.

IP dose compliance will be calculated based on number of applications divided by the expected number (amount) of IP applications for each subject. Compliance will be summarized descriptively by treatment group. Amount of IP (weight) used will also be summarized.

### 6.1.8. Pharmacokinetics Analysis

The PK population will include all subjects receiving the active drug with sufficient plasma concentrations of roflumilast to define a profile, as determined by the pharmacokineticist. This population will be used for analyses of PK parameters.

## 6.2. Safety Analysis

Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. The safety population will be used for these analyses.

### 6.2.1. Adverse Events

Adverse events (AEs) will be summarized by preferred term, system organ class, and treatment group for all AEs, serious AEs, related AEs, AEs leading to withdrawal from investigational product, and AEs leading to withdrawal from study.

### 6.2.2. Clinical Laboratory Results

Shifts in clinical laboratory parameters from Baseline to worst post-Baseline grade will be provided.

### 6.2.3. Vital Signs

The subject incidence rate of >5% weight loss or gain on study will be provide, as well as whether weight loss was explained or unexplained.

### 6.2.4. Local Tolerance Assessments

For both the Investigator's and Subject's assessment of the numeric application site reaction, scores will be summarized individually by using number and percentage of subjects by visit, as well as mean/median scores.

### 6.2.5. Medical History and Physical Examinations

Medical history for all subjects will be presented in a by-subject listing.

Clinically significant changes observed during physical examination will be captured as adverse events and included in AE tabulations.

## 6.3. Efficacy Evaluation

Efficacy analyses will be conducted in the Intent-to-Treat (ITT) population. Sensitivity analyses may be conducted in the subset of the ITT population for whom the primary endpoint assessment was not missed due to COVID-19 disruption.

### 6.3.1. Primary Endpoint

The primary endpoint of 'IGA success at Week 8' will be analyzed using a Cochran-Mantel-Haenszel test stratified by the randomization factors of the study center and IGA score at baseline ('moderate' v. 'severe'). The analysis will be performed on the Intention-to-Treat (ITT) population and missing data will be imputed using multiple imputation.

### 6.3.2. Secondary Endpoint

Continuous secondary endpoints will be analyzed using Analysis of Covariance with treatment and stratification factors as independent variables. The ITT population will be used and missing data will be imputed using multiple imputation. Binary secondary endpoints will be analyzed similarly to the primary endpoint.

Secondary endpoints will only be tested statistically if the primary endpoint is considered statistically significant. To control for multiple comparisons among the secondary endpoints, the following multiplicity procedure will be used.

Upon demonstration of statistical significance of the primary endpoint, the alpha level of 0.01 will be unequally split between testing of the WI-NRS success endpoints and the other secondary efficacy endpoints. The testing over the WI-NRS success endpoints and the other secondary efficacy endpoints will be sequential, utilizing the Fallback Method for unused alpha.

For the testing of WI-NRS success endpoints, an alpha level of 0.0033 will be used and will use a hierarchical method to first test WI-NRS success at Week 8, followed by WI-NRS at Week 4, followed by WI-NRS success at Week 2. Should all three of these endpoints be statistically significant at the 0.0033 level, then this unused alpha will be carried to the other secondary endpoint group, which would then be tested at the .0033+.0067=0.01 level.

An alpha level of 0.0067 (the remainder of the allotted 0.01) or the full 0.01, pending the results of the WI-NRS endpoint testing, will be used to hierarchically test IGA Success at Week 4,

Scaling score of 0 at Week 8, Erythema score of 0 at Week 8, the percentage of subjects who attain IGA of 0 at Week 8, and IGA Success at Week 2.

# 7. STUDY ADMINISTRATION

## 7.1. Ethics

### 7.1.1. Ethics Review Board

Before screening of subjects into the study, the current protocol, ICF, and any accompanying material to be provided to the subjects will be reviewed and approved by an appropriate IRB/ERB, as required by FDA (21 CFR § 56) or Health Canada and ICH GCP regulations. A letter documenting the IRB approval must be received by the Sponsor before the initiation of the study at a clinical site. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator, Sponsor, or designee will submit a progress report at least once yearly to the IRB. However, the frequency of these reports will depend on IRB requirements. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB per the IRB requirements, and in compliance with FDA and ICH GCP guidelines.

The Investigator, Sponsor, or designee shall promptly notify the IRB of any SAEs, SUSARs, or any other information that may affect the safe use of the IP during the study, per the IRB local requirements, and in compliance with FDA regulations and ICH GCP guidelines.

### 7.1.2. Ethical Conduct of the Study

This research will be conducted in accordance with the protocol, the principles of the Tri-Council Policy Statement, the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding E6 (R2), December 2016.

### 7.1.3. Subject Information and Consent/Assent

The Investigator is responsible for obtaining written informed consent or assent (for children/adolescents) from everyone participating in this study after adequate explanation (in non-technical terms) of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must use the most current IRB or ERB-approved consent/assent forms for documenting written informed consent and assent (for children/adolescents). Subjects will be assured that they may withdraw from the study at any time without jeopardizing their medical care. Each informed consent (or assent as applicable) will be read, appropriately signed, and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and by an impartial witness if required by the IRB/ERB local requirements.

Subjects will be given a copy of their ICF/assent.

## 7.2. Study Completion and Termination

### 7.2.1. Study Completion

The study is considered completed with the last visit of the last subject participating in the study. The final data from the investigational site will be sent to the Sponsor (or designee) after completion of the final subject visit at that site, in the time frame specified in the Clinical Trial Agreement.

### 7.2.2. Study Termination

The Sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed. The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further drug development.

## 7.3. Study Monitoring

Prior to the initiation of the clinical investigation, Sponsor representatives or designees may visit the clinical site where the investigation is to be conducted. Sponsor representatives or designees shall ensure that the Investigator understands the investigational status of the investigational product, all requirements of the investigation to be undertaken, and all of his/her responsibilities as an Investigator. Sponsor representatives or designees will also visit the clinical site at appropriate intervals as required to ensure compliance with the protocol and to verify the accuracy and completeness of data reported on the eCRFs. The Study Director or designees shall be available for consultation with the Investigator and serve as liaisons between the clinical site and the Sponsor.

The Sponsor or authorized designees may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) and investigational product dispensation logs for the subjects in this clinical investigation. The Investigator must permit access to such records. The Investigator must obtain, as part of informed consent, permission for an authorized representative of the Sponsor, or regulatory authorities, to review, in confidence, any records identifying subjects.

## 7.4. Data Quality Assurance

To ensure the collection of adequate, consistent, complete, and reliable data during this clinical investigation, Sponsor representatives or designees may conduct audits of participating sites at appropriate intervals throughout the study. The results of these periodic site audits may be subject to review by independent auditors at completion of the clinical investigation.

All clinical data will undergo a quality control check prior to clinical database lock. Edit checks are performed for appropriate databases as a validation routine to check for missing data, data inconsistencies, data ranges etc. Corrections are made prior to database lock.

## 7.5. Data Handling and Record Keeping

During the clinical study, the Investigator will maintain adequate source records, including medical records, records detailing the progress of the study for each subject, laboratory reports, signed informed consent forms, IP disposition records, correspondence with the IRB or IEC and Study Monitor/Sponsor, AE reports, and information regarding subject discontinuation and completion of the clinical investigation.

All required study data will be recorded on eCRFs. Any change of data will be recorded on the audit trail and a reason for the change will be entered.

The Principal Investigator must retain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

## 7.6. Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the Investigator or Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator and Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the Investigator and Sponsor. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s)/IEC(s) will be promptly notified.

No deviation from the protocol will be made except to protect the life or physical well-being of a subject in an emergency. Except in such emergencies, prior approval of the Sponsor, and the IRB/IEC, is required before deviations from the planned protocol. All protocol deviations that occur during the study will be documented and reported to Sponsor and to the IRB(s)/IEC(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

No waivers to inclusion/exclusion criteria will be granted; subjects need to meet all criteria, exactly as specified, to be enrolled. Additionally, prospective deviations from the protocol or investigational plan are not permitted except to protect the life or physical well-being of a subject in an emergency. Deviations that occur unintentionally or are the result of action by the subject

must be documented and reported to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

## 7.7. Confidentiality and Privacy

The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as date of birth) will be recorded on any form or biological sample submitted to the Sponsor.

The Investigator agrees that all information received from Arcutis Biotherapeutics Inc., including but not limited to the IB, this protocol, eCRF, the IP, and any other study information, remain the sole and exclusive property of Arcutis Biotherapeutics Inc. during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from Arcutis Biotherapeutics Inc. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

## 7.8. Conflict of Interest

All study Investigators will provide documentation of their financial interest or arrangements with Arcutis Biotherapeutics Inc., or proprietary interests in the investigational drug under study. This documentation must be provided prior to the Investigator's participation in the study. Any change to the Investigator's financial interest during the study and up to one year after study completion will be reported to the Sponsor. All Investigators with reported conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study.

## 7.9. Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

## 7.10. Publication Policy

The Sponsor is supportive of publishing clinical trial findings. Any form of publication that is derived from this study must be submitted to Arcutis Biotherapeutics Inc. for review and approval. The process of coordinating publication efforts is detailed in the Clinical Trial Agreement.

# 8. REFERENCES

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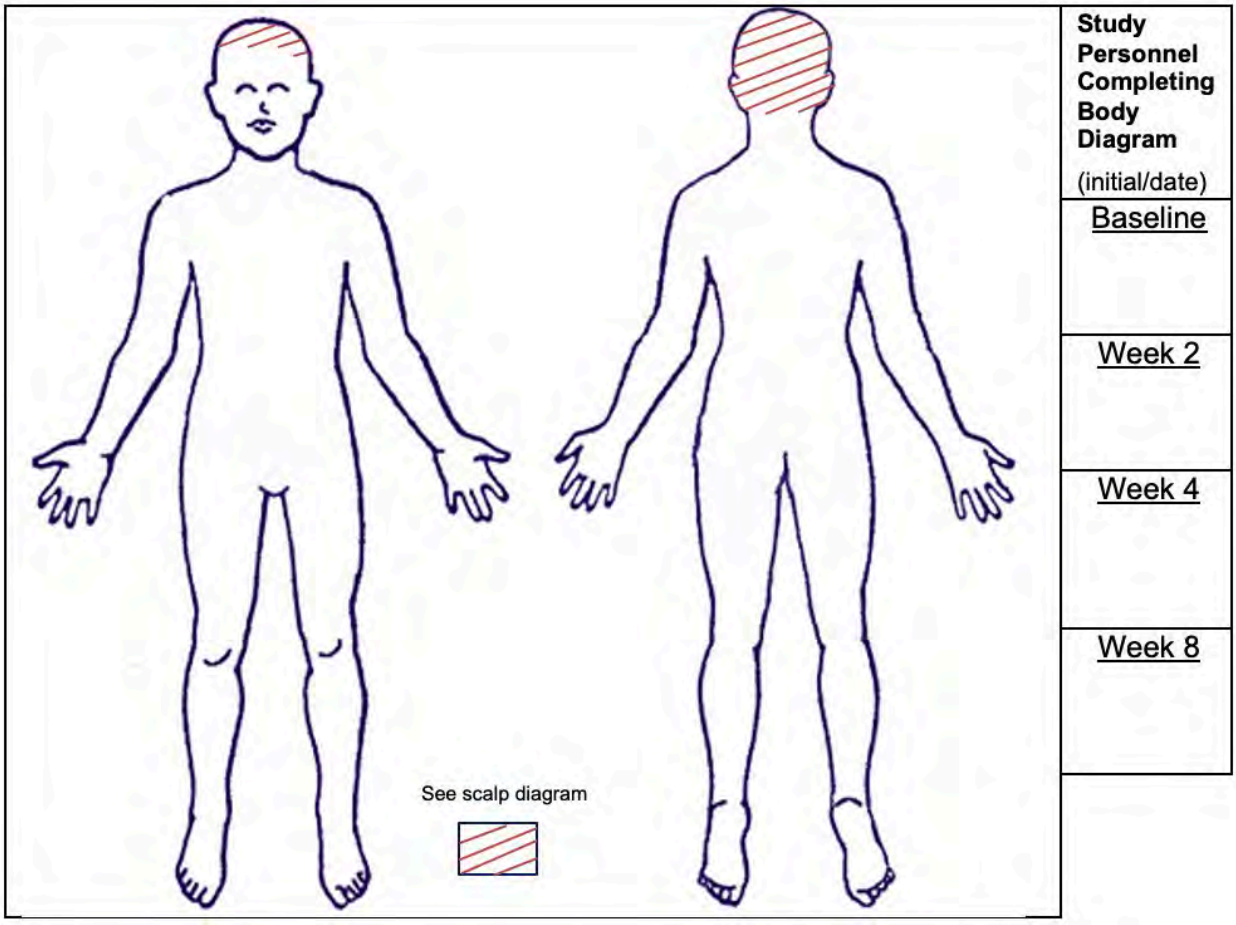
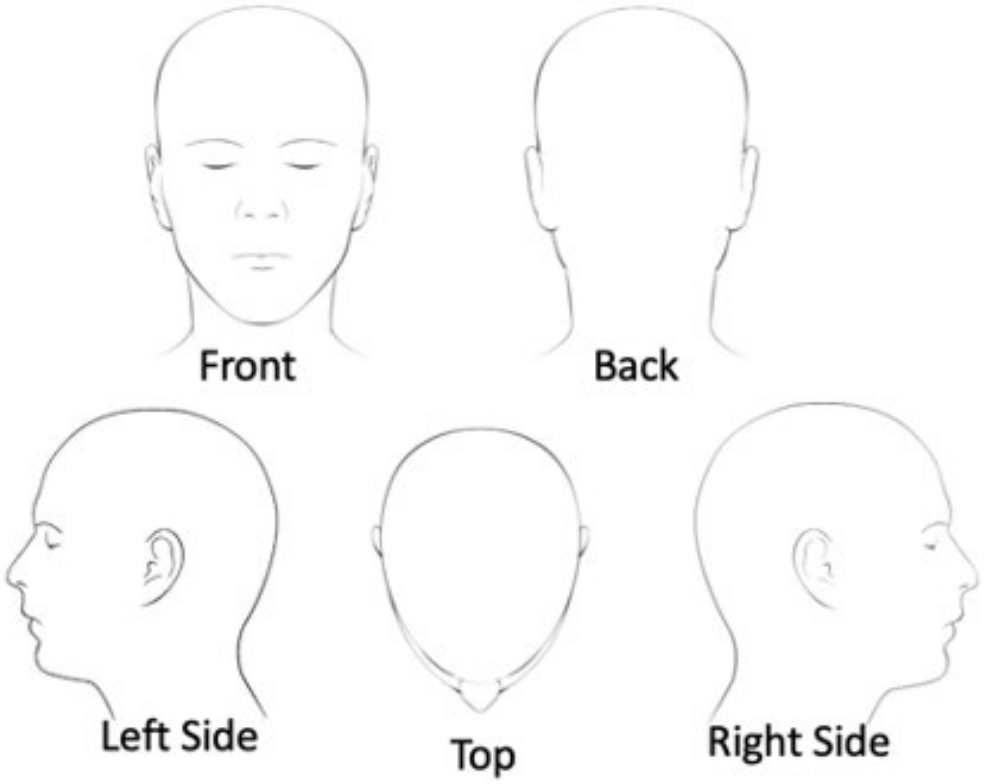
# 9. APPENDICES

## APPENDIX 1. BODY & SCALP DIAGRAM

**Site personnel to mark treatable areas identified by the Investigator.**

**Reminder:** Application will be all areas affected including scalp, face, trunk and/or intertriginous/genital regions. Subject should continue to apply even if area(s) clears and treat new lesions.





# APPENDIX 2. PATIENT HEALTH QUESTIONNAIRE DEPRESSION SCALE (PHQ-8)

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?
*(circle **one** number on each line)*

| How often during the past 2 weeks were you bothered by... | Not at all | Several days | More than half the days | Nearly every day |
|---|---|---|---|---|
| 1. Little interest or pleasure in doing things | 0 | 1 | 2 | 3 |
| 2. Feeling down, depressed, or hopeless | 0 | 1 | 2 | 3 |
| 3. Trouble falling or staying asleep, or sleeping too much | 0 | 1 | 2 | 3 |
| 4. Feeling tired or having little energy | 0 | 1 | 2 | 3 |
| 5. Poor appetite or overeating | 0 | 1 | 2 | 3 |
| 6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down | 0 | 1 | 2 | 3 |
| 7. Trouble concentrating on things, such as reading the newspaper or watching television | 0 | 1 | 2 | 3 |
| 8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual | 0 | 1 | 2 | 3 |

# APPENDIX 3. MODIFIED PATIENT HEALTH QUESTIONNAIRE DEPRESSION SCALE (PHQ-A)

| Instructions: How often have you been bothered by each of the following symptoms during the past two weeks? For each symptom put an "X" in the box beneath the answer that best describes how you have been feeling. | | | | |
|---|---|---|---|---|
| | (0) Not at all | (1) Several days | (2) More than half the days | (3) Nearly every day |
| 1. Feeling down, depressed, irritable, or hopeless? | | | | |
| 2. Little interest or pleasure in doing things? | | | | |
| 3. Trouble falling asleep, staying asleep, or sleeping too much? | | | | |
| 4. Poor appetite, weight loss, or overeating? | | | | |
| 5. Feeling tired, or having little energy? | | | | |
| 6. Feeling bad about yourself – or feeling that you are a failure, or that you have let yourself or your family down? | | | | |
| 7. Trouble concentrating on things like school work, reading, or watching TV? | | | | |
| 8. Moving or speaking so slowly that other people could have noticed?<br><br>Or the opposite – being so fidgety or restless that you were moving around a lot more than usual? | | | | |

# APPENDIX 4. CHILDREN'S DEPRESSION INVENTORY 2 (PARENT REPORT)

By Maria Kovacs, Ph.D.

**CDI 2 PARENT**

Child's Name/ID: _____ Child's Sex: Male Female

Parent's Name/ID: _____ Date of Birth: ____/____/____

Relationship to Child: _____ Today's Date: ____/____/____

Child's Age: _____ Child's Grade: _____

**Instructions:**

For each of the statements below, select one response that best describes your observations of your child in the **past two weeks**.

Indicate your response for each item by circling the number that best corresponds to your choice. You may change an item response by drawing an X through your original choice and selecting a new response.

Remember, for each statement, pick **one** answer that best describes your observations of your child in the PAST TWO WEEKS.

| My child... | Not at all | Some of the time | Often | Much or most of the time |
|---|---|---|---|---|
| 1. looks sad. | 0 | 1 | 2 | 3 |
| 2. has fun. | 0 | 1 | 2 | 3 |
| 3. does not like himself or herself. | 0 | 1 | 2 | 3 |
| 4. blames himself or herself for things. | 0 | 1 | 2 | 3 |
| 5. cries or looks tearful. | 0 | 1 | 2 | 3 |
| 6. is cranky or irritable. | 0 | 1 | 2 | 3 |
| 7. enjoys being with people. | 0 | 1 | 2 | 3 |
| 8. thinks that he or she is ugly. | 0 | 1 | 2 | 3 |
| 9. has to push himself or herself to do school work. | 0 | 1 | 2 | 3 |
| 10. has trouble sleeping at night. | 0 | 1 | 2 | 3 |
| 11. looks tired or fatigued. | 0 | 1 | 2 | 3 |
| 12. seems lonely. | 0 | 1 | 2 | 3 |
| 13. enjoys school. | 0 | 1 | 2 | 3 |
| 14. spends time with friends. | 0 | 1 | 2 | 3 |
| 15. is showing worse school performance than before. | 0 | 1 | 2 | 3 |
| 16. does what he or she is told. | 0 | 1 | 2 | 3 |
| 17. has disagreements and conflicts with others. | 0 | 1 | 2 | 3 |

# APPENDIX 5. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) BASELINE/SCREENING VERSION

## COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

***Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.***

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in* ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu*

| ***SUICIDAL IDEATION*** | | |
|---|---|---|
| *Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.* | **Lifetime: Time He/She Felt Most Suicidal** | **Past __ Months** |
| **1. Wish to be Dead**<br>Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.<br>***Have you wished you were dead or wished you could go to sleep and not wake up?***<br>If yes, describe: | **Yes** ☐ **No** ☐ | **Yes** ☐ **No** ☐ |
| **2. Non-Specific Active Suicidal Thoughts**<br>General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.<br>***Have you actually had any thoughts of killing yourself?***<br>If yes, describe: | **Yes** ☐ **No** ☐ | **Yes** ☐ **No** ☐ |
| **3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**<br>Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*<br>***Have you been thinking about how you might do this?***<br>If yes, describe: | **Yes** ☐ **No** ☐ | **Yes** ☐ **No** ☐ |
| **4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan**<br>Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*<br>***Have you had these thoughts and had some intention of acting on them?***<br>If yes, describe: | **Yes** ☐ **No** ☐ | **Yes** ☐ **No** ☐ |
| **5. Active Suicidal Ideation with Specific Plan and Intent**<br>Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.<br>***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***<br>If yes, describe: | **Yes** ☐ **No** ☐ | **Yes** ☐ **No** ☐ |
| ***INTENSITY OF IDEATION*** | | |
| *The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.*<br>Lifetime - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*)<br>Past X Months - ***Most Severe Ideation:*** _____ (*Type # (1-5)*) _____ (*Description of Ideation*) | Most Severe | Most Severe |
| **Frequency**<br>***How many times have you had these thoughts?***<br>(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day | ____ | ____ |
| **Duration**<br>***When you have the thoughts how long do they last?***<br>(1) Fleeting - few seconds or minutes<br>(2) Less than 1 hour/some of the time<br>(3) 1-4 hours/a lot of time<br>(4) 4-8 hours/most of day<br>(5) More than 8 hours/persistent or continuous | ____ | ____ |
| **Controllability**<br>***Could/can you stop thinking about killing yourself or wanting to die if you want to?***<br>(1) Easily able to control thoughts<br>(2) Can control thoughts with little difficulty<br>(3) Can control thoughts with some difficulty<br>(4) Can control thoughts with a lot of difficulty<br>(5) Unable to control thoughts<br>(0) Does not attempt to control thoughts | ____ | ____ |
| **Deterrents**<br>***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?***<br>(1) Deterrents definitely stopped you from attempting suicide<br>(2) Deterrents probably stopped you<br>(3) Uncertain that deterrents stopped you<br>(4) Deterrents most likely did not stop you<br>(5) Deterrents definitely did not stop you<br>(0) Does not apply | ____ | ____ |
| **Reasons for Ideation**<br>***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?***<br>(1) Completely to get attention, revenge or a reaction from others<br>(2) Mostly to get attention, revenge or a reaction from others<br>(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain<br>(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)<br>(0) Does not apply | ____ | ____ |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| ***SUICIDAL BEHAVIOR***<br>*(Check all that apply, so long as these are separate events; must ask about all types)* | **Lifetime** | **Past __ Years** |
|---|---|---|
| **Actual Attempt:**<br>A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>***Have you made a suicide attempt?***<br>***Have you done anything to harm yourself?***<br>***Have you done anything dangerous where you could have died?***<br>***What did you do?***<br>***Did you_____ as a way to end your life?***<br>***Did you want to die (even a little) when you_____?***<br>***Were you trying to end your life when you _____?***<br>***Or Did you think it was possible you could have died from_____?***<br>***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent)<br>If yes, describe: | Yes ☐ No ☐<br>Total # of Attempts<br>_____ | Yes ☐ No ☐<br>Total # of Attempts<br>_____ |
| **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **Interrupted Attempt:**<br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*.<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?***<br>If yes, describe: | Yes ☐ No ☐<br>Total # of interrupted<br>_____ | Yes ☐ No ☐<br>Total # of interrupted<br>_____ |
| **Aborted Attempt:**<br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?***<br>If yes, describe: | Yes ☐ No ☐<br>Total # of aborted<br>_____ | Yes ☐ No ☐<br>Total # of aborted<br>_____ |
| **Preparatory Acts or Behavior:**<br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br>***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?***<br>If yes, describe: | Yes ☐ No ☐ | Yes ☐ No ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | Yes ☐ No ☐ | Yes ☐ No ☐ |

| ***Answer for Actual Attempts Only*** | Most Recent Attempt Date: | Most Lethal Attempt Date: | Initial/First Attempt Date: |
|---|---|---|---|
| **Actual Lethality/Medical Damage:**<br>0. No physical damage or very minor physical damage (e.g., surface scratches).<br>1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death | *Enter Code*<br>_____ | *Enter Code*<br>_____ | *Enter Code*<br>_____ |
| **Potential Lethality: Only Answer if Actual Lethality=0**<br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care | *Enter Code*<br>_____ | *Enter Code*<br>_____ | *Enter Code*<br>_____ |


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# APPENDIX 6. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) SINCE LAST VISIT VERSION

## COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

***Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.***

*Disclaimer:*

*This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.*

*Definitions of behavioral suicidal events in this scale are based on those used in* ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

*For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu*

## *SUICIDAL IDEATION*

*Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.*

**Since Last Visit**

**1. Wish to be Dead**
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
***Have you wished you were dead or wished you could go to sleep and not wake up?***
If yes, describe:
Yes ☐ No ☐

**2. Non-Specific Active Suicidal Thoughts**
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
***Have you actually had any thoughts of killing yourself?***
If yes, describe:
Yes ☐ No ☐

**3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*
***Have you been thinking about how you might do this?***
If yes, describe:
Yes ☐ No ☐

**4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan**
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
***Have you had these thoughts and had some intention of acting on them?***
If yes, describe:
Yes ☐ No ☐

**5. Active Suicidal Ideation with Specific Plan and Intent**
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?***
If yes, describe:
Yes ☐ No ☐

## *INTENSITY OF IDEATION*

*The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).*

***Most Severe Ideation:*** ____ _____
***Type # (1-5)*** ***Description of Ideation***

Most Severe

**Frequency**
***How many times have you had these thoughts?***
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

**Duration**
***When you have the thoughts, how long do they last?***
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

**Controllability**
***Could/can you stop thinking about killing yourself or wanting to die if you want to?***
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

**Deterrents**
***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?***
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

**Reasons for Ideation**
***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?***
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____


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| ***SUICIDAL BEHAVIOR***<br>*(Check all that apply, so long as these are separate events; must ask about all types)* | **Since Last Visit** |
|---|---|
| **Actual Attempt:**<br>A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.<br>Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.<br>***Have you made a suicide attempt?***<br>***Have you done anything to harm yourself?***<br>***Have you done anything dangerous where you could have died?***<br>***What did you do?***<br>***Did you_____ as a way to end your life?***<br>***Did you want to die (even a little) when you_____?***<br>***Were you trying to end your life when you _____?***<br>***Or did you think it was possible you could have died from_____?***<br>***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent)<br>If yes, describe:<br><br>**Has subject engaged in Non-Suicidal Self-Injurious Behavior?** | **Yes No**<br>☐ ☐<br><br>Total # of Attempts<br>_____<br><br>**Yes No**<br>☐ ☐ |
| **Interrupted Attempt:**<br>When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*.<br>Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.<br>***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?***<br>If yes, describe: | **Yes No**<br>☐ ☐<br><br>Total # of interrupted<br>_____ |
| **Aborted Attempt:**<br>When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.<br>***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?***<br>If yes, describe: | **Yes No**<br>☐ ☐<br><br>Total # of aborted<br>_____ |
| **Preparatory Acts or Behavior:**<br>Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).<br>***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?***<br>If yes, describe: | **Yes No**<br>☐ ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | **Yes No**<br>☐ ☐ |
| **Suicide:** | **Yes No**<br>☐ ☐ |
| ***Answer for Actual Attempts Only*** | Most Lethal Attempt Date: |
| **Actual Lethality/Medical Damage:**<br>0. No physical damage or very minor physical damage (e.g., surface scratches).<br>1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).<br>2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).<br>3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).<br>4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).<br>5. Death | *Enter Code*<br>_____ |
| **Potential Lethality: Only Answer if Actual Lethality=0**<br>Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).<br>0 = Behavior not likely to result in injury<br>1 = Behavior likely to result in injury but not likely to cause death<br>2 = Behavior likely to result in death despite available medical care | *Enter Code*<br>_____ |


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# APPENDIX 7. SCALPDEX

## Scalpdex

These questions concern your feelings over the past 4 weeks about **your scalp condition.** Check the answer that comes closest to the way you have been feeling.

| HOW OFTEN DURING THE PAST 4 WEEKS DO THESE STATEMENTS DESCRIBE YOU? | NEVER | RARELY | SOMETIMES | OFTEN | ALL THE TIME |
|---|---|---|---|---|---|
| 1. My scalp hurts | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 2. My scalp condition makes me feel depressed | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 3. My scalp itches | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 4. I am ashamed of my scalp condition | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 5. I am embarrassed by my scalp condition | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 6. I am frustrated by my scalp condition | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 7. I am humiliated by my scalp condition | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 8. My scalp condition bleeds | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 9. I am annoyed by my scalp condition | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 10. I am bothered by the appearance of my scalp condition | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 11. My scalp condition makes me feel self-conscious. | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 12. I am bothered that my scalp condition is incurable. | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 13. My scalp condition affects how I wear my hair (hairstyle, hats) | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 14. I am bothered by people's questions about my scalp condition. | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 15. My scalp condition affects the color of clothes I wear. | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 16. I am bothered by the persistence/reoccurrence of my scalp condition. | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 17. I feel stressed about my scalp condition. | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 18. Caring for my scalp condition is inconvenient for me. | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 19. I feel that my knowledge for caring for my scalp is adequate | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 20. The cost of caring for my scalp condition bothers me. | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 21. My scalp condition makes my daily life difficult. | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 22. My scalp condition makes me feel different from others. | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |
| 23. My scalp condition makes it hard to go to the hairdresser/barber. | ☐1 | ☐2 | ☐3 | ☐4 | ☐5 |

# APPENDIX 8. DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Site No: Date: **DLQI** Score:
Name:
Address: Diagnosis:

**The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.**

| | | | |
|---|---|---|---|
| **1.** | Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been? | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ |
| **2.** | Over the last week, how **embarrassed** or **self conscious** have you been because of your skin? | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ |
| **3.** | Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**? | Very much<br>A lot<br>A little<br>Not at all<br>Not relevant | ❒<br>❒<br>❒<br>❒<br>❒ |
| **4.** | Over the last week, how much has your skin influenced the **clothes** you wear? | Very much<br>A lot<br>A little<br>Not at all<br>Not relevant | ❒<br>❒<br>❒<br>❒<br>❒ |
| **5.** | Over the last week, how much has your skin affected any **social** or **leisure** activities? | Very much<br>A lot<br>A little<br>Not at all<br>Not relevant | ❒<br>❒<br>❒<br>❒<br>❒ |
| **6.** | Over the last week, how much has your skin made it difficult for you to do any **sport**? | Very much<br>A lot<br>A little<br>Not at all<br>Not relevant | ❒<br>❒<br>❒<br>❒<br>❒ |
| **7.** | Over the last week, has your skin prevented you from **working** or **studying**? | Yes<br>No<br>Not relevant | ❒<br>❒<br>❒ |

| | | | |
|---|---|---|---|
| | If "No", over the last week how much has your skin been a problem at **work** or **studying**? | A lot<br>A little<br>Not at all | ❒<br>❒<br>❒ |
| **8.** | Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**? | Very much<br>A lot<br>A little<br>Not at all<br>Not relevant | ❒<br>❒<br>❒<br>❒<br>❒ |
| **9.** | Over the last week, how much has your skin caused any **sexual difficulties**? | Very much<br>A lot<br>A little<br>Not at all<br>Not relevant | ❒<br>❒<br>❒<br>❒<br>❒ |
| **10.** | Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time? | Very much<br>A lot<br>A little<br>Not at all<br>Not relevant | ❒<br>❒<br>❒<br>❒<br>❒ |

**Please check you have answered EVERY question. Thank you.**

# APPENDIX 9. CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX (CDLQI)

Subject Number: Diagnosis: CDLQI SCORE:
Age: Date:

**The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ✓ one box for each question.**

| | | | |
|---|---|---|---|
| **1.** | Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been? | | Very much ☐<br>Quite a lot ☐<br>Only a little ☐<br>Not at all ☐ |
| **2.** | Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin? | | Very much ☐<br>Quite a lot ☐<br>Only a little ☐<br>Not at all ☐ |
| **3.** | Over the last week, how much has your skin affected your **friendships**? | | Very much ☐<br>Quite a lot ☐<br>Only a little ☐<br>Not at all ☐ |
| **4.** | Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin? | | Very much ☐<br>Quite a lot ☐<br>Only a little ☐<br>Not at all ☐ |
| **5.** | Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**? | | Very much ☐<br>Quite a lot ☐<br>Only a little ☐<br>Not at all ☐ |
| **6.** | Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble? | | Very much ☐<br>Quite a lot ☐<br>Only a little ☐<br>Not at all ☐ |
| **7.** | Last week, was it **school time?**<br>**OR**<br>was it **holiday time?** | **If school time**: Over the last week, how much did your skin problem affect your **school work**?<br>**If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**? | Prevented school ☐<br>Very much ☐<br>Quite a lot ☐<br>Only a little ☐<br>Not at all ☐<br><br>Very much ☐<br>Quite a lot ☐<br>Only a little ☐<br>Not at all ☐ |

| | | | |
|---|---|---|---|
| **8.** | Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **9.** | Over the last week, how much has your **sleep** been affected by your skin problem? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |
| **10.** | Over the last week, how much of a problem has the **treatment** for your skin been? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |

**Please check that you have answered EVERY question. Thank you.**

# APPENDIX 10. NIAID DMID TOXICITY TABLE

**NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) Toxicity Table for Use in Trials Enrolling Healthy Adults (2014) Modified**

**ABBREVIATIONS USED IN THE FOLLOWING TABLES:**

| Abbreviation/Term | Definition/Explanation |
|---|---|
| ALT | alanine aminotransferase |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AV block | atrioventricular block |
| bpm | beats per minute |
| BUN | blood urea nitrogen |
| CK | creatine kinase |
| CPK | creatine phosphokinase |
| $FEV_1$ | forced expiratory volume in 1 second |
| g | Gram |
| HI | High |
| HPF | high power field |
| IU | international unit |
| IV | Intravenous |
| K/CUMM | $x10^3/mm^3$ |
| LLN | lower limit of normal |

| Abbreviation/Term | Definition/Explanation |
|---|---|
| LO | Low |
| mEq | Milliequivalent |
| mmHg | millimeter of mercury |
| Ms | Millisecond |
| N | Normal |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| QTc | QT-interval corrected for heart rate |
| QTcB | Bazett's corrected QT interval |
| QTcF | Fridericia's corrected QT interval |
| RBC | red blood cell |
| Rx | Therapy |
| S | Second |
| U | Unit |
| ULN | upper limit of normal |

**ESTIMATING SEVERITY GRADE**

For abnormalities NOT found elsewhere in the Toxicity Tables use the scale below to estimate grade of severity:

| | | |
|---|---|---|
| **GRADE 1** | **Mild**: | Transient or mild discomfort (<48 hours); no medical intervention/therapy required |
| **GRADE 2** | **Moderate**: | Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required |
| **GRADE 3** | **Severe**: | Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalizations possible. |

**LABORATORY RANGES**

Where discrepancies in the ULN and LLN of laboratory ranges occur between those included in this document and those of the laboratory that performs the assays, the values provided by the laboratory will be used for assignment of severity grade.

**CLINICAL ADVERSE EVENTS**

| **Cardiovascular** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** |
|---|---|---|---|
| Arrhythmia | | Asymptomatic, transient signs, no Rx required | Recurrent/persistent; symptomatic Rx required |
| Hemorrhage, blood loss | Estimated blood loss ≤100 mL | Estimated blood loss >100 mL, no transfusion required | Transfusion required |
| QTcF (Fridericia's correction)[1] or QTcB (Bazett's correction) | Asymptomatic, QTc interval 450-479 ms, *OR*<br>Increase in interval<30 ms above baseline | Asymptomatic, QTc interval 480-499 ms, *OR*<br>Increase in interval 30-59 ms above baseline | Asymptomatic, QTc interval ≥500 ms, *OR*<br>Increase in interval ≥60 ms above baseline |
| PR interval (prolonged) | PR interval 0.20-0.25 s | PR interval >0.25 s | Type II 2nd degree AV block *OR* Ventricular pause >3.0 s |
| **Respiratory** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** |
| Cough | Transient-no treatment | Persistent cough | Interferes with daily activities |
| Bronchospasm, acute | Transient wheeze; no treatment | Requires treatment; normalizes with bronchodilator and<br>$FEV_1$ < 80% predicted before bronchodilator | Minimal normalization with bronchodilator and$FEV_1$ <80% predicted after bronchodilator |
| Dyspnea | Does not interfere with usual and social activities | Interferes with usual and social activities, no treatment | Prevents daily and usual social activity or requires treatment |

[1] Inclusion dependent upon protocol requirements

| **Respiratory** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** |
|---|---|---|---|
| Nasal discharge (rhinitis infective per **CTCAE 4.0)** | - | Localized; local intervention indicated (e.g. topical antibiotic, antifungal, or antiviral) | - |
| Pharyngitis **(CTCAE 4.0)** | - | Localized; local intervention indicated (e.g. topical antibiotic, antifungal, or antiviral) | IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated |
| Pneumonitis (rales or rhonchi) **(CTCAE 4.0)** | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Symptomatic; medical intervention indicated; limiting instrumental ADL | Severe symptoms; limiting self-care ADL; oxygen indicated |
| Lung infection **(CTCAE 4.0)** | - | Moderate symptoms; oral intervention indicated (e.g. antibiotic, antifungal, antiviral) | IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated |
| **Gastrointestinal** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** |
| Nausea | No interference with activity | Some interference with activity | Prevents daily activities |
| Vomiting | No interference with activity or 1-2 episodes/24 hours | Some interference with activity or >2 episodes/24 hours | Prevents daily activity or requires IV hydration |
| Diarrhea | 2-3 loose or watery stools or <400 g/24 hours | 4-5 loose or watery stools or 400-800 g/24 hours | 6 or more loose or watery stools or >800 g/24 hours or requires IV hydration |

| Urinary Tract | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) |
|---|---|---|---|
| Urinary tract infection **(CTCAE 4.0)** | - | Localized; local intervention indicated (e.g. oral or topical antibiotic, antifungal, antiviral) | IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated |
| **Reactogenicity** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** |
| ***Local reactions*** | | | |
| Pain | Does not interfere with activity | Repeated use of non-narcotic pain reliever >24 hours or interferes with activity | Any use of narcotic pain reliever or prevents daily activity |
| Tenderness | Discomfort only to touch | Discomfort with movement | Significant discomfort at rest |
| Erythema/redness [2] | 2.5-5 cm | 5.1-10 cm | >10 cm |
| Induration/swelling [3] | 2.5-5 cm and does not interfere with activity | 5.1-10 cm or interferes with activity | >10 cm or prevents daily activity |
| ***Systemic reactions*** | | | |
| Allergic reaction | Pruritus without rash | Localized urticaria | Generalized urticaria; angioedema or anaphylaxis |
| Headache | No interference with activity | Repeated use of non-narcotic pain reliever >24 hours or some interference with activity | Significant; any use of narcotic pain reliever or prevents daily activity |
| Fatigue | No interference with activity | Some interference with activity | Significant; prevents daily activity |

[2] In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
[3] Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

| Reactogenicity | Mild (Grade 1) | Moderate (Grade 2) | Severe (Grade 3) |
|---|---|---|---|
| Myalgia | No interference with activity | Some interference with activity | Significant; prevents daily activity |
| **All Other Conditions** | **Mild (Grade 1)** | **Moderate (Grade 2)** | **Severe (Grade 3)** |
| Illness or clinical adverse event (as defined according to applicable regulations) | No interference with activity | Some interference with activity not requiring medical intervention | Prevents daily activity and requires medical intervention |

**LABORATORY AND VITAL SIGNS TOXICITY GRADING (Some laboratory values have been modified to be consistent with the normal ranges of the ACM laboratory used in the present study)**

| Blood, Serum, or Plasma Chemistries [a] | LO/HI/N [b] | Mild (Grade 1) [c] | Moderate (Grade 2) | Severe (Grade 3) |
|---|---|---|---|---|
| Sodium (mEq/L or mmol/L) | LO | 131-<LLN | 130 | <130 |
| | HI | >ULN-148 | 149-150 | >150 |
| Potassium (mEq/L or mmol/L) | LO | <LLN-3.2 | <3.2-3.1 | <3.1 |
| | HI | >ULN-5.6 | >5.6-5.7 | >5.7 |
| Glucose (mg/dL) | LO mmol/L | <LLN-3.0 | <3.0-2.2 | <2.2 |
| | HI mmol/L | >ULN-8.9 | >8.9-13.9 | >13.9 |
| Blood urea nitrogen | HI mmol/L | >8.9-17.8 | >17.8-35.5 | >35.5 |
| Creatinine | N | 115-151 (µmol/L) | 152-177 (µmol/L) | > 177 (µmol/L) |

| **Blood, Serum, or Plasma Chemistries** [a] | **LO/HI/N** [b] | **Mild (Grade 1)** [c] | **Moderate (Grade 2)** | **Severe (Grade 3)** |
|---|---|---|---|---|
| Calcium **(CTCAE 4.0)** | LO mmol/L | <LLN-2.0 | <2.0-1.75 | <1.75 |
| | HI mmol/L | >ULN-2.9 | >2.9-3.1 | >3.1 |
| Magnesium **(CTCAE 4.0)** | LO mmol/L | <LLN-0.5 | <0.5-0.4 | <0.4 |
| Phosphorous **(CTCAE 4.0)** | LO mmol/L | <LLN-0.8 | <0.8-0.6 | <0.6 |
| Creatine kinase (CPK or CK) **(CTCAE 4.0)** | HI | >ULN-2.5xULN | >2.5xULN-5xULN | >5xULN |
| Albumin | LO g/L | <30-28 | <28-25 | <25 |
| Total protein | LO g/L | <LLN-52 | <52-50 | <50 |
| Alkaline phosphatase (U/L) **(CTCAE 4.0)** | HI | >ULN-2.5xULN | >2.5xULN-5xULN | >5xULN |
| AST (U/L) **(CTCAE 4.0)** | HI | >ULN-3xULN | >3xULN-5xULN | >5xULN |
| ALT (U/L) **(CTCAE 4.0)** | HI | >ULN-3xULN | >3xULN-5xULN | >5xULN |
| Bilirubin, serum total (mmol/L) **(CTCAE 4.0)** | HI mmol/L | >ULN-1.5xULN | >1.5xULN-3xULN | >3xULN |
| Bilirubin, serum total (mg/dL) when ALT ≥105 (Hy's law) | HI | 1.3-1.5 | 1.6-2.0 | >2.0 |
| Bilirubin, serum direct (mmol/L) **(CTCAE 4.0)** | HI mmol/L | >ULN-1.5xULN | >1.5xULN-3xULN | >3xULN |
| Amylase (U/L) **(CTCAE 4.0)** | HI | >ULN-1.5xULN | >1.5xULN-2xULN | >2xULN |
| Lipase (U/L) **(CTCAE 4.0)** | HI | >ULN-1.5xULN | >1.5xULN-2xULN | >2xULN |

| **Blood, Serum, or Plasma Chemistries** [a] | **LO/HI/N** [b] | **Mild (Grade 1)** [c] | **Moderate (Grade 2)** | **Severe (Grade 3)** |
|---|---|---|---|---|
| Uric acid (mg/dL/mmol/L) **(CTCAE 4.0)** | HI | >ULN – 10 mg/dL (0.59 mmol/L) without physiologic consequences | - | >ULN – 10 mg/dL (0.59 mmol/L) with physiologic consequences |

[a] Depending upon the laboratory used, references ranges, eligibility ranges and grading may be split out by sex and/or age.
[b] Low, High, Not Graded (N).
[c] If initial boundary of grade 1 has gap from reference range or eligibility range, calculations based on the New England Journal of Medicine (NEJM) reference ranges.

| Hematology | LO/HI/N [a] | Mild (Grade 1) [b] | Moderate (Grade 2) | Severe (Grade 3) |
|---|---|---|---|---|
| Hemoglobin (women) (g/dL) | LO | 10.8-11.3 | 9.2-10.7 | <9.2 |
| Hemoglobin (men) (g/dL) | LO | 12.0-12.5 | 10.0-11.9 | <10.0 |
| White blood cell count (K/CUMM) | HI | 11.00-15.00 | 15.00-20.00 | >20.00 |
| | LO | 2.50-3.50 | 1.50-2.49 | <1.50 |
| Lymphocytes (K/CUMM) | LO | 0.76-0.90 | 0.50-0.75 | <0.5 |
| Neutrophils (K/CUMM) | LO | 1.50-1.95 | 1.00-1.49 | <1.00 |
| Eosinophils (K/CUMM) | HI | 0.58-0.74 | 0.75-1.50 | >1.50 |
| Platelets (K/CUMM) | LO | 120-130 | 100-120 | <100 |
| **Coagulation** | | | | |
| Prothrombin time (PT, seconds) | HI | > ULN-14.4 | 14.5-15.7 | >15.7 |
| Partial thromboplastin time (PTT or aPTT, seconds) | HI | >ULN-42.1 | 42.2-50.0 | >50.0 |
| Fibrinogen (mg/dL) **(CTCAE 4.0)** | HI | >ULN-500 | 501-600 | >600 |
| | LO | <LLN-0.75xLLN | <0.75xLLN-0.5xLLN | <0.5xLLN |
| **Urine** | | | | |
| Protein (dipstick) | HI | 1+ | 2+ | >2+ |
| Glucose (dipstick) | HI | 1+ | 2+ | >2+ |
| Blood (microscopic) - red blood cells per high power field (RBC/HPF) | HI | 5-10 for males<br>9-10 for females | 11-50 | >50 and/or gross blood |

[a] Low, High, Not Graded.
[b] If initial boundary of grade 1 has gap from reference range or eligibility range, calculations based on the New England Journal of Medicine (NEJM) reference ranges.

| Vital Signs | LO/HI/N [a] | Mild (Grade 1) [b] | Moderate (Grade 2) | Severe (Grade 3) |
|---|---|---|---|---|
| Fever (°C) [c] | HI | 38.0-38.4 | 38.5-38.9 | >38.9 |
| Fever (°F) | HI | 100.4-101.1 | 101.2-102.0 | >102.1 |
| Tachycardia - beats per minute | HI | 101-115 | 116-130 | >130 or ventricular dysrhythmias |
| Bradycardia - beats per minute | LO | 40-45 | 35-40 | <35 |
| Hypertension (systolic) - mm Hg [d] | HI | 141-150 | 151-160 | >160 |
| Hypertension (diastolic) - mm Hg | HI | 91-95 | 96-100 | >100 |
| Hypotension (systolic) - mm Hg | LO | 85-89 | 80-84 | <80 |
| Tachypnea - breaths per minute | HI | 23-25 | 26-30 | >30 |

[a] Low, High, Not Graded.
[b] If initial boundary of grade 1 has gap from reference range or eligibility range, calculations based on the New England Journal of Medicine (NEJM) reference ranges.
[c] Oral temperature; no recent hot or cold beverages or smoking. A protocol should select either °C or °F for inclusion.
[d] Assuming subject is awake, resting, and supine; for adverse events, 3 measurements on the same arm with concordant results

# APPENDIX 11. COVID-19 STUDY SITE GUIDANCE

## BACKGROUND

As the impact of coronavirus disease 2019 (COVID-19) continues to develop, Premier Research Inc. and Arcutis Biotherapeutics Inc. have collated the following guidelines in response for study sites participating in the ARQ-154-304. While it is ideal for subjects to perform all protocol-specific assessments at the study site, both Premier and Arcutis are focused on prioritizing subject safety and data integrity. Therefore, the following guidelines will identify challenges and mitigation strategies while operating clinical trials remotely.

## REMOTE DATA COLLECTION

In the event subjects are unable to complete protocol-specific assessments onsite, study sites may collect data from subjects remotely via telephone and/or by traditional mail or email. The method used for data collection must be clearly documented in the source. Whenever possible, sites should adhere to the protocol visit window for remote data collection. Screening and Baseline (Day 0) visits/assessments must be performed in the clinic and must NOT be completed remotely. If necessary, these visits can be delayed ensuring they are conducted in the clinic and not remotely.

Data collection by phone may be performed. Subjects are contacted via telephone and site staff will collect data verbally for all critical data points applicable. Subject responses should be recorded in the site source documents. Data collected remotely should be entered into the EDC system (iMedidata Rave).

Data collection by mail or email may also be performed for applicable assessments. Site staff will contact subjects via traditional mail or email to collect data using paper versions of study questionnaires. C-SSRS cannot be collected by mail/email as this requires subject interview by site staff.

Investigator assessments and subject questionnaires normally completed during on-site visits should be completed on the appropriate paper source documents and entered in the EDC. The following subject assessments/questionnaires are approved to be collected via telemedicine/remotely:

- C-SSRS
- PHQ-8/PHQ-A/CDI-2
- DLQI/CDLQI
- Scalpdex
- Subject Local Tolerability
- Adverse Events
- Concomitant medication

The following Investigator assessments cannot be completed via telemedicine/remotely:

- IGA
- BSA
- Investigator Local Tolerability
- Pigmentation Assessment
- Overall Assessment of Erythema
- Overall Assessment of Scaling
- Subject Weight

**GUIDELINES FOR REMOTE DATA COLLECTION**

1. Highest priorities: the subject safety and preserving integrity of data are critical.
2. Study visits and procedures must be followed per protocol whenever possible. Any specific changes in study conduct that deviate from the protocol should be communicated to the IRB and Sponsor (via reporting to your site assigned CRA). All protocol deviations which occurred as a result of COVID-19 disruptions (e.g., visits out of window, missed assessments, etc.) should be differentiated from other PDs. It is prudent to receive IRB guidance or approval if a deviation is known to occur in advance (i.e., extending IP application or changing assessment windows, etc.).
3. If, despite all efforts, a planned clinic visit is absolutely not possible due to a COVID-19 related issue (e.g., site has closed, subject prohibited from coming to clinic, etc.), sponsor's strong preference is a delayed clinic visit. If the subject can come to clinic within a reasonable amount of time considering the protocol allowed visit window. If a delayed clinic visit cannot be completed within 14 days of the protocol specified visit window, please contact the Medical Monitor for additional guidance.
4. It is critical to ensure subjects have enough IP in the event timely clinic visit(s) is/are not possible. It is also critical to ensure subjects are instructed to continue to apply IP per protocol for the duration of their participation in the study. Subjects should also be reminded to complete their daily diaries and IP compliance should be assessed via phone if clinic visits are not possible or are delayed.
5. It is critical for preserving data integrity to make every effort possible to have a subject return to clinic for the Week 8 visit. For visits conducted in the clinic, it is critical to ensure Rater consistency for all efficacy assessments (e.g., IGA, etc.). If absolutely necessary, it is preferred to have several missed visits and a delayed Week 8 visit versus having an Early Termination and no Week 8 visit. If it is not possible for a subject to return on-site within window for the Week 8 visit, sites should:
    a. Ensure the subject has signed the most current IRB approved ICF.
    b. Contact subjects to discuss continue administration of IP and continue to complete their dosing diaries per regular IP administration instructions.

c. Subjects are approved to continue applying IP post Week 8 as long as the following have been discussed with the subject:
   - Site should confirm the subject has adequate IP to continue dosing and if not ask the subject to return to the site to pick up additional IP or refer to the current IP Handling Plan for instructions on shipment of IP from site to subject.
   - Confirm the subject has no AEs that would warrant discontinuation of the IP.
   - Site should discuss any new or ongoing conmed(s) and determine if the use of any warrant having the subject stop IP application or not.
   - For any female subject of childbearing potential that site should discuss and confirm the subject has continued her methods of ensuring pregnancy does not occur. Any deviation from these methods should be discussed further and the site should determine if IP should be halted or contact the medical monitor or Arcutis if they have any questions. A pregnancy test can be performed at the next onsite visit (this is applicable to prior visits being missed due to COVID-19 as well).
   - Subjects are approved to continue dosing for up to 14 days past their Week 8 visit. After this, sites should reach out to the Medical Monitor and/or Arcutis directly for approval to have subjects continue dosing.
   - All the above discussions must be documented in the source.

d. If available, home health nurse visits could be considered for collection of Vital Signs and Clinical Labs.
e. In the event a subject is quarantined, has symptoms, or is confirmed positive for COVID-19, it is the Sponsor's opinion that IP can continue, assuming no other contraindications.