# Protocol ARQ-151-312

## A Phase 3, 4-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.15% Administered QD in Subjects with Atopic Dermatitis

| | |
|---|---|
| **Sponsor:** | Arcutis Biotherapeutics, Inc.<br>2945 Townsgate Road, Suite 110<br>Westlake Village, CA 91361 |
| **Sponsor Representative:** | [redacted] |
| **Medical Monitor:** | [redacted] |
| **IND Number:** | [redacted] |
| **Protocol Version:** | Original |
| **Date:** | 04 November 2020 |

**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

**ARQ-151-312**

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**SPONSOR:** Arcutis Biotherapeutics, Inc.
2945 Townsgate Road, Suite 110
Westlake Village, CA 91361

**ISSUE DATE:** 04 November 2020

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-151 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: _[redacted]_

Print Investigator Name: _[redacted]

Investigator Signature: _[redacted] Date: _[redacted]

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# ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| α | Alpha Level (significance level) |
| AE | Adverse Event |
| AMP | Adenosine Monophosphate |
| AD | Atopic Dermatitis |
| AUC | Area Under the Curve |
| BSA | Body Surface Area |
| CDI | Children's Depression Inventory |
| CDLQI | Children's Dermatology Life Quality Index |
| $C_{max}$ | Maximum Concentration |
| cm | Centimeter |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRF | Case Report Form |
| C-SSRS | Columbia-Suicide Severity Rating Scale |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DFI | Dermatitis Family Impact |
| DNA | Deoxyribonucleic Acid |
| DLQI | Dermatology Life Quality Index |
| EASI | Eczema Area and Severity Index |
| FDA | U.S. Food and Drug Administration |
| FOCBP | Female of Child Bearing Potential |
| FSH | Follicle-Stimulating Hormone |
| GCP | Good Clinical Practices |
| GLP | Good Laboratory Practices |
| hr | Hour |
| IB | Investigational Brochure |
| $IC_{50}$ | Half Maximal Inhibitory Concentration |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| ID | Identification |
| IGA | Investigator Global Assessment |

| Abbreviation | Definition |
|---|---|
| IL | Interleukin |
| 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 |
| mg | Milligram |
| min | Minute |
| mL | Milliliter |
| MTD | Maximum Tolerated Dose |
| NCI | National Cancer Institute |
| NIH | National Institutes of Health |
| NOAEL | No Observed Adverse Effect Level |
| ng | Nanogram |
| P-450 | Cytochrome P450 |
| PDE-4 | Phosphodiesterase 4 |
| PHQ-8 | Patient Health Questionnaire-8 |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| POEM | Patient-Oriented Eczema Measure |
| QD | Once Daily ("quaque die") |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SCORAD | Scoring Atopic Dermatitis |
| SD | Standard Deviation |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TCPS | Tri-Council Policy Statement |

| Abbreviation | Definition |
|---|---|
| TEAE | Treatment Emergent Adverse Event |
| $T_{max}$ | Time to Reach Maximum Concentration |
| TPA | Target Plaque Area |
| TPSS | Target Plaque Severity Score |
| US | United States |
| UVR | Ultraviolet Radiation |
| V79 | Chinese Hamster Cell Line |
| vIGA-AD | Validated Investigator Global Assessment - Atopic Dermatitis |
| WI-NRS | Worst Itch - Numeric Rating Score |

# 1. PROTOCOL SUMMARY

## 1.1. Synopsis

| | |
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| **Protocol Title:** | A Phase 3, 4-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.15% Administered QD in Subjects with Atopic Dermatitis |
| **Clinical Indication:** | Atopic Dermatitis |
| **Investigational Product:** | • ARQ-151 will be supplied as an emollient cream at 0.15% strength<br>• Matching vehicle cream will contain only excipients of ARQ-151 |
| **Study Design:** | This is a Phase 3, parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.15% or vehicle is applied QD for 4 weeks to subjects 6 years of age and older with mild to moderate atopic dermatitis.<br>At entry, subjects will have ≥3% BSA involvement (excluding the scalp, palms, soles) and mild or moderate atopic dermatitis (AD) based on vIGA-AD assessment.<br>Upon determination of eligibility, subjects will be randomized 2:1 to either ARQ-151 cream 0.15% cream or matching vehicle cream. The randomization will be stratified by vIGA-AD score at Baseline/Day 1 ('Mild' vs. 'Moderate') and by study site.<br>Subjects/caregivers will apply ARQ-151 cream 0.15% or vehicle cream QD for 28 days to all AD affected areas and any newly appearing AD lesions that arise during the study, <u>except on the scalp</u>. Subjects/caregivers should maintain treatment of these areas with study drug for the duration of the study regardless of whether treatable areas of AD clear prior to Week 4/Day29.<br>At the Week 4 visit, subjects may be eligible to enroll in a 12-month, open label extension study (ARQ-151-313) evaluating ARQ-151 cream 0.15% QD. |
| **Study Objective:** | To assess the safety and efficacy of ARQ-151 cream 0.15% vs vehicle administered QD x 4 weeks to individuals with atopic dermatitis. |
| **Study Sites:** | Approximately 40 sites in the US and Canada. |

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| **Study Population:** | Subjects will be male and female children and adolescents (6-17 years), and adults (≥18 years). Subjects will have mild to moderate atopic dermatitis involvement with a vIGA-AD score of '2' (Mild) or '3' (Moderate) for study entry. Up to 25% of the subjects will be ≥18 years old. Approximately 650 subjects are planned to be randomized in this study. |
| **Duration of Participation for Subjects:** | Screening (up to 30 days) + Treatment phase (4 weeks) for a total of about 8 weeks.<br>Upon completion of the treatment phase of the study (Week 4/Day 29) subjects may have the opportunity, subject to regulatory approval and enrollment has not been completed, to participate in an open-label extension study (ARQ-151-313) of up to 12 months. |
| **Inclusion Criteria:** | 1. For adult subjects: Participants legally competent to sign and give informed consent. For pediatric and adolescent subjects: Informed consent of parent(s) or legal guardian, and, if age appropriate, assent by the subjects, as required by local laws.<br>2. Males and females, ages 6 years and older at time of signing Informed Consent (Screening).<br>3. Diagnosed with mild to moderate atopic dermatitis according to the criteria of Hanifin and Rajka (1980) prior to or at the screening visit. Subjects must have at least 3 of the 4 basic features per Hanifin and Rajka (1. Pruritus; 2. Typical morphology and distribution [flexural lichenification in adults and facial and extensor eruptions in infants and children]; 3. Chronic or chronically relapsing dermatitis; or 4. Personal or family history of atopy), in addition to 3 or more minor criteria.<br>4. History of AD for at least 3 months in subjects 6-17 years of age or 6 months in subjects ≥18 years of age, as determined by the Investigator using information from the subject's medical chart, from the subject's physician, or through subject/parent/caregiver interview. Stable disease for the past 4 weeks with no significant flares in atopic dermatitis before screening.<br>5. EASI Score ≥5. EASI is evaluated for the entire body except the scalp, palms, and soles.<br>6. vIGA-AD score of 'Mild' ('2') of 'Moderate' ('3') at Baseline. The vIGA-AD is evaluated for the entire body except the scalp, palms, and soles.<br>7. Has AD involvement of ≥3% BSA (excluding the scalp, palms, soles). |

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| | 8. Females of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline/Day 1. 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. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a lifestyle choice and an acceptable backup method has been identified if the subject becomes sexually active.<br>9. Females of non-childbearing potential should either be pre-menarchal, or post-menopausal with spontaneous amenorrhea for at least 12 months (post-menopausal status should be confirmed with FSH testing) or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy).<br>10. In good health as judged by the Investigator, based on medical history, physical examination, vital signs, serum chemistry labs, hematology values, and urinalysis.<br>11. Subjects and parent(s)/legal guardian(s) are considered reliable and capable of adhering to the Protocol and visit schedule, according to the judgment of the Investigator. |
| **Exclusion Criteria:** | 1. Subjects with any serious medical condition or clinically significant laboratory, vital signs, or physical examination abnormality that would prevent study participation or place the subject at significant risk, as judged by the Investigator<br>2. Liver function tests excursions that exceed:<br>• AST or ALT > 2X ULN<br>• Total bilirubin:<br>– > 1.5 x ULN or<br>– > ULN and ≤ 1.5 x ULN AND direct bilirubin is > 35% of total bilirubin<br>• ALP ≥ 2x ULN<br>3. Subjects who cannot discontinue medications and treatments prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 2).<br>4. Has unstable AD or any consistent requirement for high potency topical steroids to manage AD signs or symptoms.<br>5. Subjects who have significant active systemic or localized infection (e.g., molluscum contagiosum), including known actively infected AD, or have had any infection that required |

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| | oral or intravenous administration of antibiotics, antifungal or antiviral agents within 14 days prior to Baseline/Day 1.<br>6. Subjects who are unwilling to refrain from prolonged sun exposure and from using a tanning bed or other artificial light emitting devices (LEDs) for 4 weeks prior to Baseline/Day 1 and during the study.<br>7. Subjects with skin conditions other than AD that would interfere with evaluations of the effect of the study medication on AD, as determined by the Investigator. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements, e.g., molluscum contagiosum.<br>8. Subjects with known genetic dermatological conditions that overlap with AD, such as Netherton syndrome.<br>9. Known allergies to excipients in ARQ-151 cream [redacted]<br>10. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin for 2 weeks prior to Baseline/Day 1 and during the study period.<br>11. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin, and carbamazepine for 2 weeks prior to Baseline/ Day 1 and during the study period.<br>12. Subjects who have received oral roflumilast (Daxas®, Daliresp®) within 4 weeks prior to Baseline/ Day 1.<br>13. Known or suspected:<br>• Severe renal insufficiency<br>– Severe renal insufficiency is defined as calculated creatinine clearance <30 mL/min.<br>• Moderate to severe hepatic disorders (Child-Pugh B or C)<br>14. 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/current. |

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| | 15. Subjects with a PHQ-8 (adults) or modified PHQ-A (adolescents, 12-17 years old inclusive) score ≥10 at Screening or Baseline/Day 1 visits.<br>16. Subjects (6 to 11 years old, inclusive) with a CDI-2 (parent report) raw score ≥17 for females and ≥18 for males at Screening or Baseline/Day 1 visits.<br>17. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.<br>18. Previous treatment with ARQ-151.<br>19. Subjects currently undergoing allergy testing (e.g., food allergy testing or skin prick testing), patch testing, food challenges, or allergy desensitization, or plan to do so during the study.<br>20. Subjects with any serious medical condition (e.g., hypo- or hyper-thyroidism) or clinically significant laboratory abnormality that would prevent study participation or place the subject at significant risk, as determined by the Investigator.<br>21. Subjects with a history of a major surgery within 4 weeks prior to Baseline/Day 1 or subjects who have a major surgery planned during the study.<br>22. Subjects with a history of chronic alcohol or drug abuse within 6 months prior to Screening.<br>23. Current or a history of cancer within 5 years with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix.<br>24. Parent(s)/legal guardian(s) who are unable to communicate, read, or understand the local language(s). Subjects who are unable to communicate, read or understand the local language, or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation.<br>25. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members of enrolled subjects living in the same house. |
| **Key Assessments:** | <u>Safety Assessments</u><br>• Safety will be monitored through local tolerability assessments, vital signs, physical examination, safety labs, Children's Depression Inventory 2 (CDI-2, parent report for children 6-11 years old, inclusive), modified PHQ-A (for adolescents 12-17 years old, inclusive), PHQ-8 (for adults), C-SSRS (for adolescents and adults 12 years old and older), and AEs. |

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| | • After obtaining consent, all AEs and TEAEs should be collected.<br>• The investigator or a properly trained and designated subinvestigator will perform local tolerability assessments at Baseline/Day 1, and Weeks 1, 2, and 4 (Days 8, 15, and 29). Subjects will have vital signs measured at each study visit. Height will be collected at Visit 1 (Screening) only.<br>• A limited physical exam (skin, lungs, and heart only) will be performed at Screening, Baseline/Day 1 and Week 4/Day 29. Blood and urine samples for routine safety laboratory tests (hematology, serum chemistry, and urinalysis) will be obtained at Screening, Baseline/Day 1 and Week 4/Day 29. For all female subjects of childbearing potential, a urine pregnancy test will be administered at all clinic visits except for Screening where a serum pregnancy test will be performed. A negative pregnancy result is required for continued participation in the study, and results (of the urine pregnancy test) must be available prior to dispensing of study drug at study visits.<br>**Efficacy Assessments**<br>• Efficacy assessments will include vIGA-AD (Appendix 7), EASI, WI-NRS, BSA, DLQI/CDLQI (Appendix 8 and Appendix 9), DFI (Appendix 10), SCORAD (Appendix 11), and POEM (Appendix 12).<br>**Pharmacokinetic Assessment**<br>• A single PK assessment (trough) will be performed in all subjects with a blood sample collected at Week 4/Day 29. |
| **Study Endpoints:** | 1. The Primary Efficacy Endpoint will be tested in all randomized subjects and defined as:<br>• The proportion of all randomized subjects who attain IGA Success, defined as a vIGA-AD score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at Week 4<br>2. Upon demonstration of statistical significance for the primary endpoint, a hierarchical testing scheme will be used to test the Secondary Efficacy Endpoints defined as:<br>• The proportion of randomized subjects with a vIGA-AD score of 'Moderate' at randomization who attain IGA Success at Week 4<br>• Among subjects with baseline WINRS ≥ 4, the proportion who attain a 4-point reduction on the WI-NRS at Week 4 |

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| | • The proportion of subjects who attain at least a 75% reduction in the Eczema Area and Severity Index (EASI-75) at Week 4<br>• Time to achievement of vIGA-AD success<br>• Time to achievement of EASI-75<br>3. Pharmacokinetic endpoints include concentrations of roflumilast and its N-oxide metabolite. |
| **Power and Sample Size:** | Approximately 650 subjects are planned to be randomized in this study. To test the key secondary endpoint of IGA success in subjects with a vIGA-AD score of 'Moderate' at randomization, approximately 488 of the subjects to be accrued will have vIGA-AD score of 'Moderate' at randomization. Randomization will be stratified by vIGA-AD score ('Mild' vs. 'Moderate') and by study site.<br>This sample size provides approximately 95% power to detect an overall 15% difference between treatment groups on vIGA-AD success at Week 4 at α-0.05 using a 2-sided stratified (vIGA-AD at randomization and study site) Cochran-Mantel-Haenszel test. The results from a recent phase 2 study (ARQ-151-212) of ARQ-151 cream 0.15% compared to vehicle treatment were used to estimate the treatment difference. Specifically, in the phase 2 trial, approximately 37% of subjects demonstrated vIGA-AD success at Week 4 in the ARQ-151 0.15% group compared to 22% in the vehicle group. This sample size also provides approximately 90% power to detect an overall 17% difference between treatment groups on IGA success at Week 4 among subjects with vIGA-AD score 'Moderate' at randomization. The same testing method, the stratified Cochran-Mantel-Haenszel test, will be used as for the primary endpoint. |

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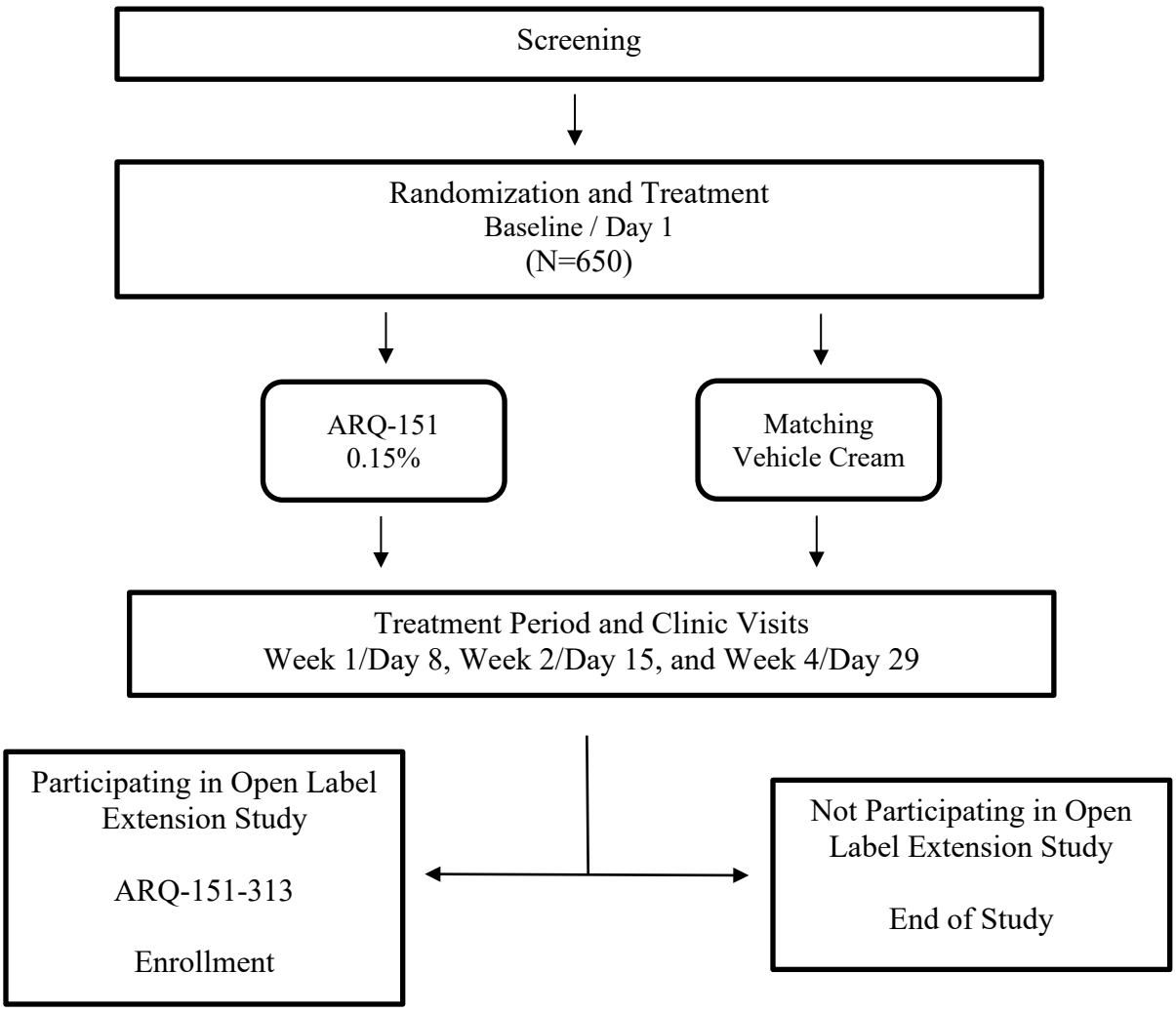
| **Statistical Analysis:** | The analysis populations are defined as follows:<br>• Safety population will include all subjects who are enrolled and received at least one confirmed dose of study medication.<br>• Intent-to-Treat (ITT) population will include all subjects who are randomized.<br>• vIGA-AD Moderate ITT population will be a subset of the ITT population with vIGA-AD score 'moderate' at randomization.<br>• WI-NRS population will be a subset of the ITT population with a baseline WI-NRS score ≥ 4.<br>• PK population will include all subjects receiving the active drug with quantifiable plasma concentrations of roflumilast.<br>To control for multiple comparisons, the key secondary endpoint will only be tested if the primary endpoint demonstrates statistical significance. In addition, the remaining secondary endpoints will be inferentially tested only if the primary and key secondary endpoint comparisons are statistically significant. To control for multiple comparisons among the remaining secondary endpoints, partitioning of alpha and the Holm's procedure will be used.<br>Descriptive statistics for continuous variables will include mean, median, standard deviation, min, max. Descriptive statistics for categorical variables will include frequencies and percents. For missing data, the primary imputation method and sensitivity methods will be detailed in the SAP. The primary endpoint and key secondary endpoints of vIGA-AD success will be analyzed with a Cochran-Mantel-Haenszel test stratified by the randomization factors (disease severity determined by vIGA-AD and by study site).<br>Categorical secondary efficacy analysis will be analyzed in the same manner as the primary endpoint.<br>Continuous secondary endpoints will be analyzed analysis of covariance with treatment, the randomization stratification factors, and baseline value as independent variables. Statistical comparisons between the treatment groups will be obtained using contrasts.<br>The incidence of adverse events will be summarized as well as changes in laboratory parameters and vital signs. |

## 1.2. Study Schema




**A Phase 3, 4-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.15% Administered QD in Subjects with Atopic Dematitis**

Approximately 650 subjects with atopic dermatitis will be randomized 2:1 to receive either:

- ARQ-151 cream 0.15% or Vehicle cream

Subjects will have ≥3% BSA involvement (excluding the scalp, palms, soles) with a vIGA-AD score of '2' (mild) or '3' (moderate) for study entry

Up to 25% of the subjects will be ≥ 18 years old

## 1.3. Schedule of Visits and Assessments

| Study Procedure | Screen | Baseline Day 1 | Wk 1 Day 8 | Wk 2 Day 15 | Wk 4 Day 29 / ET |
|---|---|---|---|---|---|
| **Visit** | **1** | **2** | **3** | **4** | **5** |
| **Visit Window** | **-30 days** | **N/A** | **+/- 3 days** | **+/- 3 days** | **+/- 3 days** |
| Informed consent/assent | X | | | | |
| Demographics | X | | | | |
| Medical and surgical history | X | | | | |
| Physical examination[a] | X | X | | | X |
| I/E criteria | X | X | | | |
| Hematology, Serum Chemistries, and Urine Analysis[b] | X | X | | | X |
| Vital signs, height, weight[c] | X | X | X | X | X |
| vIGA-AD, EASI, BSA, SCORAD[d] | X | X | X | X | X |
| WI-NRS pruritus[e] | X | X | X | X | X |
| POEM[f] | X | X | X | X | X |
| Local Tolerability Assessment[g] | | X | X | X | X |
| CDI-2, PHQ-8, PHQ-A, C-SSRS[h] | X | X | X | X | X |
| DLQI, CDLQI, DFI[i] | X | X | X | X | X |
| Medical Photography[j] | | X | X | | X |
| Serum pregnancy test (FOCBP only) | X | | | | |
| Urine pregnancy test[k] | | X | X | X | X |
| PK draws[l] | | | | | X |
| Drug/vehicle application in clinic[m] | | X | X | X | |
| Dispense/Re-dispense study medication kit[n] | | X | X[o] | X[o] | X[o] |
| Dispense/review diary | | X | X | X | X |
| Weigh study medication kit[p] | | X | X | X | X |
| Compliance determination[q] | | | X | X | X |
| Adverse event assessment[r] | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X |
| Study Exit [s] | | | | | X |

[a] Limited physical examination: skin (including assessment of Fitzpatrick skin type at Screening only), lungs, and heart only

[b] To be collected at Screening, Baseline/Day 1, and Week 4/Day 29. For subjects <18 years of age, if Baseline/Day 1 is within 3 weeks of Screening, the Screening results will be utilized.

[c] Height will be collected at Screening only. Weight should be obtained using a calibrated weight scale and the same scale should be used for a subject throughout the duration of the study. The subject should remove shoes and heavy clothing (sweaters or jackets), and empty pockets. The subject should stand with both feet in the center of the scale with their arms at their side and hold still. Record the weight to the nearest decimal fraction (for example, 25.1 kilograms). For subjects <18 years of age, measure the weight in triplicate and report the average weight in EDC. A 5% or greater weight loss (whether or not intentional or other explained) should be reported to the medical monitor.

[d] The vIGA-AD assessment will be a 5-point scale ranging from clear (0) to severe (4) and is evaluated for the entire body except the scalp, palms, and soles. EASI takes into account overall severity of erythema, infiltration/papulation, excoriation, and lichenification, in addition to extent of BSA affected. The 4 clinical signs will be graded on a 4-point scale (0 [absent] to 3 [severe]) for 4 body regions (head and neck, upper extremities, lower extremities, and trunk). Total EASI score will be calculated as a sum of scores of all 4 body regions. EASI total score will range from 0 (absent) to 72 (severe). Total BSA affected by AD will be determined for all body surfaces except the scalp, palms and soles. **The vIGA-AD assessment should be completed prior to other physician assessments**. SCORAD total score will range between 0 and 103.

[e] Subjects will self-assess their pruritus at home on a daily basis starting 7 days prior to the Baseline/Day 1 visit, and then every day thereafter. WI-NRS score will be determined by the subject assessing worst itch over the past 24 hours. The scale is from 0 (no itch) to 10 (worst itch) and this value will be recorded by the subject each day.

[f] POEM will be completed by all subjects either by self or by proxy completion (for children unable to read and/or understand the POEM questionnaire, the parent/guardian/caregiver will complete the questionnaire).

[g] Local tolerability assessments should be recorded prior to study drug application for the Investigator assessment of skin irritation (Berger and Bowman skin irritation score). **Note for investigator tolerability assessments: reactions at the site of product application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's atopic dermatitis.** The subject will assess burning/stinging (0-3 score) 10-15 minutes post drug application. **Note subject burning stinging assessment: at Day 29, subjects will provide a recall assessment of burning/stinging experienced post drug application on the previous day (Day 28).**

[h] 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 6-11 years of age, inclusive.

[i] The DLQI will be completed by subjects ≥17 years of age. The CDLQI will be completed for subjects 6 to 16 years old, inclusive. The Dermatitis Family Impact Questionnaire (DFI) will be completed by parents/caregivers for all subjects 6 to ≤17 years of age.

[j] Photography of AD lesion(s) selected by the Investigator will be performed at all investigational sites. All efforts will be made to de-identify the subjects. Canfield equipment will be used to capture photographs. Subjects who are unwilling to participate in the medical photography will be allowed to opt out of this procedure, as documented on the Informed Consent Form.

[k] A urine pregnancy test will be administered to all females of child-bearing potential. A negative result is required for continued participation in the study, and results must be available prior to dispensing of study drug at each visit.

[l] Single PK trough draw will be collected at Day 29. Ensure study medication was not applied in the area where PK will be drawn.

[m] Subjects to apply assigned IP during clinic visits, except for the Day 29 visit.

[n] Kits will be dispensed based on %BSA affected. See IP Handling Manual for details.

[o] On Day 8 and 15, dispensing of IP is optional. Site should review IP kit to ensure sufficient IP is available until the next visit and only dispense additional IP if needed. On Day 29, if the subject is unable to perform the Day 29 clinic visit due to COVID-19 restrictions (isolation, quarantine, etc.) then additional IP may need to be dispensed so IP can continue to be applied at home until the subject is able to return to the clinic to complete the Day 29 assessments (see IP Handling Manual for the process to dispense additional IP at or after Day 29).

[p] Every tube should be weighed and recorded when dispensed and returned.. See IP Handling Manual for details.

[q] Compliance determination is described in the IP Handling Manual

[r] All AEs should be collected starting after the first application of the investigational product 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 application of the investigational product or the end of the study (whichever is later). Any AEs (whether serious or non-serious) and clinically abnormal laboratory test values(s) will be evaluated by the PI and treated and/or followed up for up to 30 days after end of treatment or until symptoms or value(s) return to normal, or acceptable level, as judged by the PI

[s] Subjects who enroll into the open label extension study (ARQ-151-313) must complete the ARQ-151-312 visit requirements at Week 4.

# 2. INTRODUCTION

## 2.1. Background

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. 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-151 Investigator's Brochure (IB) for the most current PDE-4 dermal and oral/systemic nonclinical and clinical information.

Atopic dermatitis is a chronic inflammatory skin disorder affecting children and adults, with the majority presenting with disease of mild to moderate severity. The use of topical corticosteroids and/or topical calcineurin inhibitors, in combination with emollients has been the mainstay for treating atopic dermatitis. In 2016, Eucrisa® (crisaborole), a PDE-4 inhibitor was approved for the topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older.

Topical calcineurin inhibitors block the activation of T-lymphocytes and diminish inflammation, but are accompanied by a boxed warning for the development of lymphomas and other lymphoproliferative diseases. Topical corticosteroids can cause skin atrophy and hypothalamic-pituitary axis suppression, and their use is often accompanied by poor adherence due to corticophobia (fear of using corticosteroids in patients or doctors). Eucrisa provides precedence for the effectiveness of topical PDE-4 inhibitors in atopic dermatitis, but it is a twice-daily ointment, its efficacy may be modest, and its use may be accompanied by burning, stinging, and local skin reactions. As a result, there is a need for the development of new topical products for the treatment of atopic dermatitis (Nygaard 2017).

The therapeutic use of PDE-4 inhibitors in AD is based on the recognized intracellular role of PDE-4 in keratinocytes (Dastidar 2007, Hanifin 1996). Circulating leukocytes in AD patients have PDE-4 activity, which has been associated with higher production of proinflammatory mediators and lower production of the anti-inflammatory mediator IL-10, in part due to hydrolyzation of cyclic adenosine monophosphate (cAMP) (Grewe 1982, Furue 2014, Baumer 2007). This consequently diminishes levels of cAMP, which leads to increased transcription of numerous cytokines, accelerating a number of intracellular functions involved in acute and chronic inflammation (Grewe 1982). Thus, targeting PDE-4 has been shown to directly attenuate inflammation due to inhibition of the breakdown of cAMP, consequently reducing the levels of tumour necrosis factor-α, IL-12, IL-23, and other signaling effectors (Murrell 2015, Nazarian 2009).

## 2.2. Conclusions on Toxicity Findings

The safety profile of oral roflumilast is well-established. An extensive systemic toxicity program that evaluated both roflumilast and its active N-oxide metabolite in multiple species via the oral route of administration was conducted to support registration of the 500 µg tablet for COPD.

The previously-conducted systemic toxicity program included studies to evaluate reproductive toxicity, genotoxicity and carcinogenicity, and the results of those studies are included in the labeling for oral roflumilast.

To support the development of ARQ-151 topical cream a GLP-compliant dermal toxicity program is being conducted. To date, no new risks have been identified through the dermal toxicity program. In 13-week dermal toxicity studies in minipigs and mice, and a 39-week dermal toxicity study in minipigs, no evidence of systemic toxicity was observed. Histopathological evaluation of skin in the minipig study included very slight to slight erythema at all treatment levels, and minor degrees of irritation such as hyperplasia. The NOAEL in both studies was the 1% concentration of ARQ-151 (20 mg/kg), the highest dose administered and the maximum feasible concentration.

Across the dermal and systemic toxicology programs, the exposure to parent drug and N-oxide metabolite differs by route and species. While exposure to roflumilast and its active metabolite are likely to be higher following topical administration of ARQ-151 relative to oral administration, when the margins from the toxicity studies are considered as a whole, the NOAELs across routes and species provide assurance that the anticipated exposures with ARQ-151 cream will be safe.

## 2.3. Clinical Studies

### 2.3.1. Topical Roflumilast Cream

The formulation of topical roflumilast, ARQ-151 cream, has been evaluated in both plaque psoriasis (currently in Phase 3) and atopic dermatitis (through Phase 2).

#### 2.3.1.1. Psoriasis Phase 2a (ARQ-151-101)

ARQ-151-101 (NCT03392168) was a Phase 2a study of two active doses of ARQ-151, 0.5% and 0.15% vs vehicle in the topical treatment of adult patients with chronic plaque psoriasis of up to 5% BSA involvement.

An initial cohort (Cohort 1) of 8 adult psoriasis subjects (no vehicle subjects) was treated as follows with the results indicated:

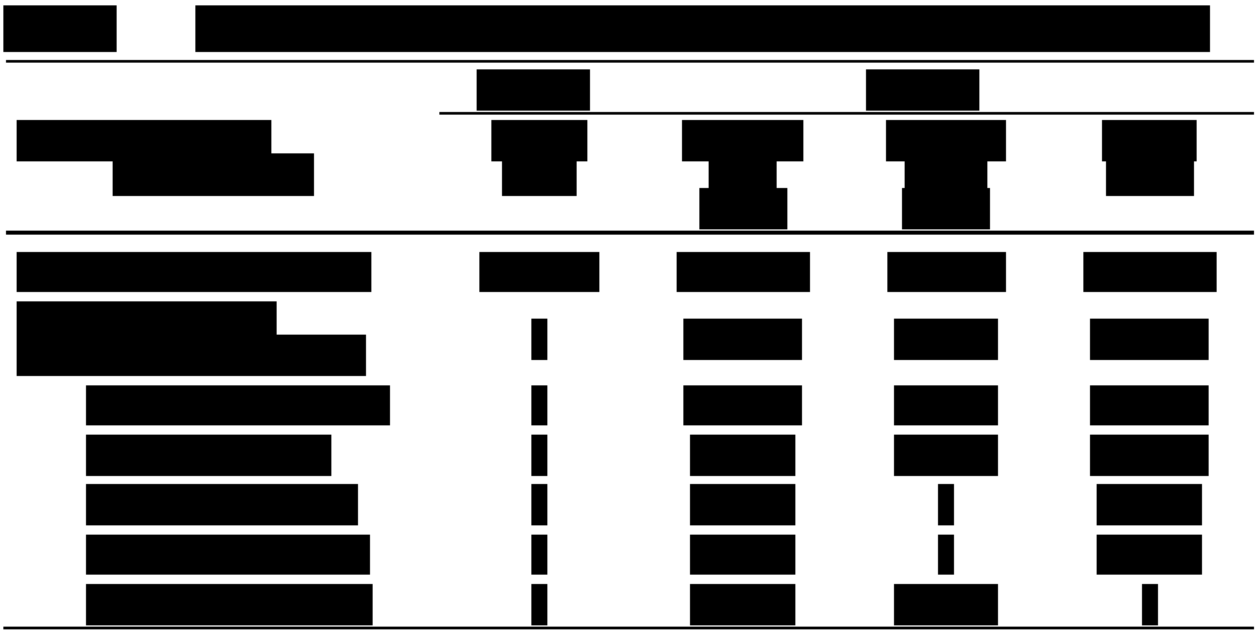
- Single dose application of ARQ-151 cream 0.5% to a 25 $cm^2$ area of psoriatic plaque on the trunk or extremities (not on the face, genital area, palms or soles)
- Local tolerability and systemic safety labs monitored
- PK assessments at baseline (pre-dose), 1, 2, 4, 6 and 24 hours
- Skin permeation of topically applied drug was ~0.4%
- Local tolerability and systemic safety labs were unremarkable

Six Cohort 1 subjects plus 83 additional psoriasis subjects were then enrolled into Cohort 2, an inter-individual, parallel group, randomized and blinded assessment of two concentrations of ARQ-151 drug product (0.15% and 0.5%) versus vehicle applied QD x 28 days, analyzing target psoriatic plaques for efficacy. Subjects were randomized 1:1:1 to receive 0.5% drug product, 0.15% drug product or vehicle to psoriatic plaques up to 5.0% of BSA. In each subject, up to 3 target plaques were identified for efficacy analysis.

PK assessments conducted on Day 1: 1, 2, 4 and 6 hours; Day 14: pre-dose (trough) and 1-hour post-dose; and Day 28: pre-dose (trough), 1, 2, 4, 6 and 24 hours.

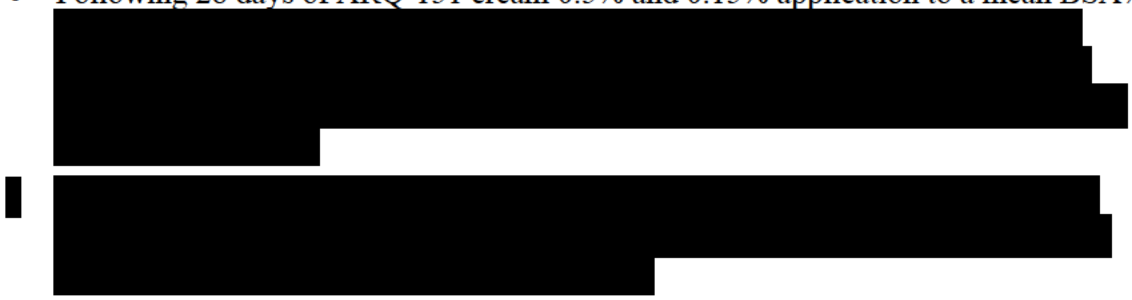
Safety results follow:

- [redacted]



Day 28 pharmacokinetic results of ARQ-151-101 are as follows:

- Following 28 days of ARQ-151 cream 0.5% and 0.15% application to a mean BSA%



#### 2.3.1.2. Psoriasis Phase 2b (ARQ-151-201)

ARQ-151-201 (NCT03638258) was a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.15%, ARQ-151 cream 0.3%, or vehicle cream was applied QD for 12 weeks to over 300 adult subjects with 2% to 20% BSA of chronic plaque psoriasis and baseline IGA of Mild or greater. In this study, both ARQ-151 cream 0.3% and ARQ-151 cream 0.15% were safe and well tolerated, demonstrating similar safety and tolerability profiles compared to each other and compared to vehicle. The safety data are summarized below:

- [redacted]

- [redacted]

Pharmacokinetic results of ARQ-151-201 are as follows:

- [redacted]

### 2.3.1.3. Atopic Dermatitis Phase 1 PK Study in Adults (ARQ-151-102)

ARQ-151-102 was an open label, Phase 1, pharmacokinetics and safety study of ARQ-151 Cream 0.15% and ARQ-151 Cream 0.05% administered QD in adult subjects with mild to moderate AD.

[redacted]

[redacted]

#### 2.3.1.4. Phase 1 Study in Adolescents and Pediatrics (ARQ-151-105)

ARQ-151-105 (NCT04156191) is an ongoing open-label, Phase 1, pharmacokinetics, maximal usage PK, safety, and efficacy study of ARQ-151 cream 0.15% administered QD in adolescent and pediatric subjects with mild to moderate atopic dermatitis.

The study is being conducted in three parts, the first two of which are completed. The first part consisted of three cohorts in which subjects aged 2 to 17 years old had 1.5-35% BSA involvement (excluding the scalp, palms, soles) and mild or moderate atopic dermatitis based on vIGA-AD.

The second part of the study consisted of three cohorts in which subjects were evaluated under maximal use conditions (MUSE) and had BSA involvement (excluding the scalp, palms, soles) of ≥35% in subjects 2 to 11 years old (inclusive) or ≥25% in subjects 12 to <17 years old with mild or moderate atopic dermatitis based on vIGA-AD. At least 60% of the enrolled subjects had moderate atopic dermatitis.

The third part of the study will consist of one cohort (Cohort 7) in which subjects 2 to 5 years of age (inclusive) will be administered a lower concentration of ARQ-151 cream (0.05%) and evaluated under maximal use conditions (MUSE). Subjects will have BSA involvement (excluding the scalp, palms, soles) of ≥35% with mild or moderate atopic dermatitis based on vIGA-AD. At least 60% of the enrolled subjects had moderate atopic dermatitis.

*Preliminary Study Results*

[redacted]

[redacted]

#### 2.3.1.5. Atopic Dermatitis Phase 2 Dose Ranging Study (ARQ-151-212)

ARQ-151-212 (NCT03916081) was a parallel group, double blind, vehicle-controlled, Phase 2 study that evaluated ARQ-151 cream 0.05% and 0.15% in the treatment of mild to moderate atopic dermatitis in 136 adolescent and adult subjects with 1.5 to 35% BSA of involvement.

Ninety-three female (68.4%) and 43 male (31.6%) subjects with mild to moderate AD participated in the study. Overall, the demographic and baseline disease characteristics were similar across all study groups. The mean age for all 136 study subjects was 41.6 years, including 8 adolescent subjects (between 12-17 years). The mean EASI score at Baseline for all study subjects was 9.04. The majority of subjects were in the moderate vIGA-AD category (77.9%). The mean BSA involvement was 9.5% for all study subjects.

[redacted]

Overall, ARQ-151 was found to be well-tolerated at both tested doses following once-daily topical application in subjects with mild to moderate AD. ARQ-151 showed a favorable overall safety profile at both tested doses.

### 2.3.2. Oral Roflumilast Tablet

Oral roflumilast (DALIRESP®) has been approved globally for the treatment of COPD and has been evaluated in nine Phase III/IV randomized double-blind clinical trials (Wedzicha 2016). Overall, the safety of oral roflumilast has been well established in its targeted population of mostly middle- and upper-aged individuals who currently smoke cigarettes or have smoked them

extensively in the past. Adverse events (AEs) reported with roflumilast tablets have been consistent with those expected for oral PDE-4 inhibitors. In a pooled analysis of safety data from 6-month and 1-year clinical trials (N=8630), the most common AEs were diarrhea, weight loss and nausea. Other AEs reported more frequently with roflumilast treatment than with placebo were back pain, influenza, insomnia and decreased appetite (Michalski 2012), (Wedzicha 2016).

In addition to the self-reported cases of weight loss in the 6-month and 1-year oral trials, clinically significant weight loss was also reported in two prospective studies that evaluated weight (Michalski 2012).

Psychiatric-related AEs were also greater in patients treated with roflumilast tablets (5.9%) compared to those treated with placebo (3.3%). The most common psychiatric-related AEs were insomnia, depression and anxiety. A small number of cases of completed suicide and suicide ideation have been reported in patients taking oral roflumilast in clinicals trials and also during post-marketing experience (Michalski 2012).

The only contraindication to oral roflumilast is use in patients with moderate to severe liver impairment (Child-Pugh B or C), where systemic levels of roflumilast may become elevated.

## 2.4. Rationale for Development

Atopic dermatitis is currently treated with topical calcineurin inhibitors and/or topical corticosteroids in combination with emollients. In 2016, Eucrisa® (crisaborole), a less potent PDE-4 inhibitor than roflumilast, was approved for the topical treatment of atopic dermatitis. Topical calcineurin inhibitors block the activation of T-lymphocytes and diminish inflammation, but are accompanied by a 'black box' warning for the development of lymphomas and other lymphoproliferative diseases. Topical corticosteroids can cause skin atrophy and hypothalamic-pituitary axis suppression, and their use is often accompanied by poor adherence due to corticophobia (fear of using corticosteroids in patients or doctors). Eucrisa provides precedence for the effectiveness of topical PDE-4 inhibitors in atopic dermatitis, but it is a twice-daily ointment, its efficacy is modest, and its use is often accompanied by burning, stinging, and local skin reactions. In our Phase 2 AD study (ARQ-151-212), we observed excellent local toleration of ARQ-151 cream formulations. Since roflumilast is a more potent PDE-4 inhibitor than crisaborole (Hatzelmann 2010), we believe that ARQ-151 has potential to provide greater efficacy with better local toleration than Eucrisa.

This study will evaluate the safety and efficacy of ARQ-151 cream in children, adolescent, and adult subjects with mild to moderate atopic dermatitis.

### 2.4.1. Dose Selection

In ARQ-151-212, results for the primary efficacy endpoint, mean absolute change from baseline in EASI score at Week 4, were numerically higher in the ARQ-151 cream 0.05% and ARQ-151 cream 0.15% (p= 0.097) groups than in the vehicle group. Furthermore, the result of the sensitivity analysis of the primary endpoint at Week 4 was statistically significant (ARQ 151 cream 0.15%, p= 0.027). Statistical significance was reached for numerous other clinically important efficacy endpoints including % change from baseline in EASI score, EASI-75

responders, and patients achieving vIGA-AD score of clear or almost clear. Both doses of topical roflumilast (0.15% and 0.05%) had a similar and favorable safety and tolerability profile, with generally more favorable efficacy observed at the ARQ-151 cream 0.15% dose. Results of this study support the use of ARQ-151 cream 0.15% in studies of adult and adolescent subjects with mild to moderate AD. PK data from ARQ 151 105 support the use of the same concentration (0.15%) in subjects 6 to 11 years old and the use of a lower concentration in subjects 2 to 5 years old.

### 2.4.2 Risks and/or Benefits to Subjects

A favorable local and systemic benefit-risk profile has been observed in prior studies of ARQ-151. Subjects 6 years of age and older, included in this study, randomized to active treatment group may see an improvement in their atopic dermatitis with ARQ-151 0.15% cream, based on the activity of doses tested in atopic dermatitis (0.05%-0.15%) and psoriasis (0.15%-0.5%), and approval of a less potent topical PDE-4 inhibitor (crisaborole) for atopic dermatitis. Subjects may also see some benefit as the cream formulation of ARQ-151 may have a moisturizing effect.

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, vomiting, diarrhea, weight loss, psychiatric AEs (see Section 2.3.2) may be readily monitored as specified in this protocol. The profile that is emerging from studies of topical roflumilast appears different from the safety and tolerability profile of oral roflumilast. While oral PDE-4 inhibitors (DALIRESP, OTEZLA) have been associated with, in particular, a moderate incidence of GI AEs, these AEs, and perhaps others, appear to be reported far less frequently with topical PDE-4 inhibitors, including EUCRISA®, and ARQ-151 cream to date in clinical trials. For ARQ-151 cream, this 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.

This study has been designed with adequate safety monitoring practices (i.e., physical examinations, vital signs/weight, local skin toleration assessments, hematology, serum chemistry, urinalysis, PHQ-A/PHQ-8, CDI-2, C-SSRS and AE reporting).

# 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-151 cream 0.15% vs vehicle administered QD x 4 weeks to individuals 6 years of age and older with atopic dermatitis.

## 3.2. Study Endpoints

### 3.2.1. Primary Endpoint

The primary endpoint of this study is:

- The proportion of all randomized subjects who attain IGA Success, defined as a vIGA-AD score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at Week 4

### 3.2.2. Secondary Endpoints

The secondary endpoints of this study are:

- The proportion of randomized subjects with a vIGA-AD score of 'Moderate' at randomization who attain IGA Success at Week 4
- Among subjects with baseline WINRS ≥ 4, the proportion who attain a 4-point reduction on the WI-NRS at Week 4
- The proportion of subjects who attain at least a 75% reduction in the Eczema Area and Severity Index (EASI-75) at Week 4
- Time to achievement of vIGA-AD success
- Time to achievement of EASI-75

### 3.2.3. Pharmacokinetic Endpoint

- Pharmacokinetic endpoints include concentrations of roflumilast and its N-oxide metabolite.

# 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-151 cream 0.15% or vehicle is applied QD x 4 weeks to subjects with mild to moderate atopic dermatitis.

- At entry, subjects will have ≥3% BSA involvement (excluding the scalp, palms, soles) and mild or moderate atopic dermatitis (AD) based on vIGA-AD assessment.
- Upon determination of eligibility, subjects will be randomized 2:1 to either ARQ-151 cream 0.15% or matching vehicle cream. The randomization will be stratified by vIGA-AD score at baseline ('Mild' vs. 'Moderate') and by study site.
- Subjects/caregivers will apply ARQ-151 cream 0.15% or vehicle cream QD for 28 days to all AD affected areas and any newly appearing AD lesions that arise during the study, except on the scalp. Subjects/caregivers should maintain treatment of these areas with study drug for the duration of the study regardless of whether treatable areas of AD clear prior to Week 4.
- At the Week 4 visit, subjects may be eligible to enroll in a 12-month, open label extension study (ARQ-151-313) in which they will receive ARQ-151 cream 0.15% QD.

## 4.2. Number of Sites and Subjects

A total of up to approximately 650 subjects will be randomized at approximately 40 study sites in the United States and Canada. During the conduct of the study, additional countries and/or sites may be added if necessary. Subjects will be male and female children and adolescents (6-17 years), and adults (≥18 years). Subjects will have mild to moderate atopic dermatitis involvement with a vIGA-AD score of '2' (mild) or '3' (moderate) for study entry. Up to 25% of the subjects will be ≥18 years old and up to 25% of subjects will have a vIGA-AD score of '2'.

## 4.3. Subject Participation

Subject participation involves a minimum of 5 clinic visits including Screening, Baseline, Week 1, Week 2, and Week 4. The interval between the Screening and Baseline visits could be up to 30 days, therefore the anticipated maximum duration of subject participation is approximately 8 weeks.

Upon completion of the treatment phase of the study (Week 4) subjects may have the opportunity, subject to regulatory approval and enrollment has not been completed, to participate in an open-label extension study (ARQ-151-313) of up to 12 months.

## 4.4. Numbering of Subjects

All subjects who sign an informed consent form will be assigned a unique 6-digit subject identification (ID) number by the IWRS system.

The subject identifier number is 6-digits (SXX-YYY) and will contain the study number-site number (where S = 2 and XX is this study site number such as 01, 02, etc.) and the subject number (YYY). It will be assigned in numerical order at the screening visit based on chronological order of screening dates.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened once, if deemed acceptable by the investigator. Rescreened subjects should be assigned a different subject number than the initial screening. All procedures planned at the screening visit, including signature of a new consent form, will be performed.

In the case of a screening laboratory value abnormality, the test can be repeated once within the original screening time window, if the investigator believes there is a reasonable possibility that the subject would be eligible if re-tested. This would not be considered a screen failure and a new subject number would not be assigned.

The clinical 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 of the following inclusion criteria to be eligible for participation in the study:

1. For adult subjects: Participants legally competent to sign and give informed consent. For pediatric and adolescent subjects: Informed consent of parent(s) or legal guardian, and, if age appropriate, assent by the subjects, as required by local laws.
2. Males and females, ages 6 years and older at time of signing Informed Consent (Screening).
3. Diagnosed with mild to moderate atopic dermatitis according to the criteria of Hanifin and Rajka (1980) prior to or at the screening visit. Subjects must have at least 3 of the 4 basic features per Hanifin and Rajka (1. Pruritus; 2. Typical morphology and distribution [flexural lichenification in adults and facial and extensor eruptions in infants and children]; 3. Chronic or chronically relapsing dermatitis; or 4. Personal or family history of atopy), in addition to 3 or more minor criteria.

4. History of AD for at least 3 months in subjects 6-17 years of age or 6 months in subjects ≥18 years of age, as determined by the Investigator using information from the subject's medical chart, from the subject's physician, or through subject/parent/caregiver interview. Stable disease for the past 4 weeks with no significant flares in atopic dermatitis before screening.
5. EASI Score ≥5. EASI is evaluated for the entire body except the scalp, palms, and soles.
6. vIGA-AD score of 'Mild' ('2') of 'Moderate' ('3') at Baseline/Day 1. The vIGA-AD is evaluated for the entire body except the scalp, palms, and soles.
7. Has AD involvement of ≥3% BSA (excluding the scalp, palms, soles).
8. Females of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at Baseline/Day 1. 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. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a lifestyle choice and an acceptable backup method has been identified if the subject becomes sexually active.
9. Females of non-childbearing potential should either be pre-menarchal, or post-menopausal with spontaneous amenorrhea for at least 12 months (post-menopausal status should be confirmed with FSH testing) or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy).
10. In good health as judged by the Investigator, based on medical history, physical examination, vital signs, serum chemistry labs, hematology values, and urinalysis.
11. Subjects and parent(s)/legal guardian(s) are considered reliable and capable of adhering to the Protocol and visit schedule, according to the judgment of the Investigator.

### 4.5.2. Exclusion Criteria

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

1. Subjects with any serious medical condition or clinically significant laboratory, vital signs, or physical examination abnormality that would prevent study participation or place the subject at significant risk, as judged by the Investigator
2. Liver function tests excursions that exceed:
   - AST or ALT > 2X ULN
   - Total bilirubin:
     - > 1.5 x ULN or
     - > ULN and ≤ 1.5 x ULN AND direct bilirubin is > 35% of total bilirubin
   - ALP ≥ 2x ULN

3. Subjects who cannot discontinue medications and treatments prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 2).
4. Has unstable AD or any consistent requirement for high potency topical steroids to manage AD signs or symptoms.
5. Subjects who have significant active systemic or localized infection (e.g., molluscum contagiosum), including known actively infected AD, or have had any infection that required oral or intravenous administration of antibiotics, antifungal or antiviral agents within 14 days prior to Baseline/Day 1.
6. Subjects who are unwilling to refrain from prolonged sun exposure and from using a tanning bed or other artificial light emitting devices (LEDs) for 4 weeks prior to Baseline/Day 1 and during the study.
7. Subjects with skin conditions other than AD that would interfere with evaluations of the effect of the study medication on AD, as determined by the Investigator. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements, e.g., molluscum contagiosum.
8. Subjects with known genetic dermatological conditions that overlap with AD, such as Netherton syndrome.
9. Known allergies to excipients in ARQ-151 cream [redacted]
10. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin for 2 weeks prior to the Baseline/Day 1 and during the study period.
11. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin, and carbamazepine for 2 weeks prior to the Baseline/Day 1 and during the study period.
12. Subjects who have received oral roflumilast (Daxas®, Daliresp®) within the past 4 weeks.
13. Known or suspected:
    - Severe renal insufficiency
      - Severe renal insufficiency is defined as calculated creatinine clearance <30 mL/min.
    - Moderate to severe hepatic disorders (Child-Pugh B or C)
14. 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/current

15. Subjects with a PHQ-8 (adults) or modified PHQ-A (adolescents, 12-17 years old inclusive) score ≥10 at Screening or Baseline visits
16. Subjects (6 to 11 years old, inclusive) with a CDI-2 (parent report) raw score ≥17 for females and ≥18 for males at Screening or Baseline/Day 1 visits
17. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.
18. Previous treatment with ARQ-151.
19. Subjects currently undergoing allergy testing (e.g., food allergy testing or skin prick testing), patch testing, food challenges, or allergy desensitization, or plan to do so during the study.
20. Subjects with any serious medical condition (e.g., hypo- or hyper-thyroidism) or clinically significant laboratory abnormality that would prevent study participation or place the subject at significant risk, as determined by the Investigator.
21. Subjects with a history of a major surgery within 4 weeks prior to Baseline/Day 1 or subjects who have a major surgery planned during the study.
22. Subjects with a history of chronic alcohol or drug abuse within 6 months prior to Screening.
23. Current or a history of cancer within 5 years with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix.
24. Parent(s)/legal guardian(s) who are unable to communicate, read, or understand the local language. Subjects who are unable to communicate, read or understand the local language(s), or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation.
25. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members of enrolled subjects living in the same house.

## 4.6. Randomization

Randomization will take place at the Baseline visit after the Investigator confirms that the subject meets all eligibility criteria listed in Section 4.5.

Subjects will be randomly assigned to apply ARQ-151 cream 0.15 % QD, or matching vehicle QD. Assignment of drug or vehicle will be made at a 2:1 ratio (drug:vehicle) and stratified by vIGA-AD score ('Mild' vs. 'Moderate'), and by study site according to a computer-generated randomization list. Kits containing tubes of study medication will be assigned to each subject using an internet-based response system (IWRS). A subject may receive more than one kit for the treatment period. The kits and tubes are blinded and each kit is numbered with a unique kit number.

## 4.7. Study Restrictions

### 4.7.1. Prohibitions and Concomitant Therapy

Prohibited medications and products are detailed in Table 2 (Excluded Medications and Treatments).

Generally, the addition of new medications, including nonprescription medications, during the course of 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. Other medications may be authorized by the Investigator for conditions other than AD. If medication is required, the name, strength, frequency, duration of use, and reason for use will be recorded in source documents and entered into the CRFs. 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 Table 2. No rescue medication for AD is allowed during this study up to Week 4.

**Table 2: Excluded Medications and Treatments**

| Excluded Medications and Treatments | Washout Period Prior to Day 1 |
|---|---|
| Approved biologics such as dupilumab | 6 months |
| Investigational biologics | 6 months |
| • Systemic treatments that could affect AD; e.g. corticosteroids, retinoids, calcineurin inhibitors, hydroxycarbamide (hydroxyurea), methotrexate, cyclosporine, azathioprine, hydroxychloroquine, mycophenolate mofetil, or other immunosuppressive therapies, or systemic treatment with nonsedating antihistamines in a nonstable regimen.<br>• Systemic treatments with nonsedating antihistamines (e.g., cetirizine, desloratadine, loratadine) in a stable regimen is allowed. | 4 weeks or 5 half-lives, whichever is longer |
| PUVA or NBUVB phototherapy | 4 weeks |
| Topical products containing urea | 1 week |
| Sedating antihistamines and other over the counter remedies containing sedating antihistamine, such as sleep aids (e.g., ZzzQuil™ LIQUICAPS®SLEEP-AID), and cough/cold remedies (e.g., Theraflu® night time, NyQuil™ Cold & Flu Night time) | 1 week |
| Topical corticosteroids, calcineurin inhibitors, or Eucrisa®. Topical antibacterial medications or products, including soaps, dilute bleach baths, or sodium hypochlorite-based products anywhere on the body. | 2 weeks |

**Table 2: Excluded Medications and Treatments (Continued)**

| Excluded Medications and Treatments | Washout Period Prior to Day 1 |
|---|---|
| Strong cytochrome P-450 CYP3A4 inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin | 2 weeks |
| Strong cytochrome P-450 CYP3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin, and carbamazepine | 2 weeks |
| Systemic antibiotics | 2 weeks |
| Tanning beds, other light emitting devices | 4 weeks |
| Oral roflumilast (Daxas®, Daliresp®) | 4 weeks |
| All other investigational drugs | 4 weeks or 5 half-lives, whichever is longer |

- Eye / ear 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.
- All subjects should apply medication each evening, except on clinic visit days when the study product will be applied at the clinical site. If the subject takes an evening shower/bath, the ARQ-151 cream or vehicle can be applied as soon as the skin is nearly dry, but no later than 20 minutes before going to bed. Subjects are not to wash areas where ARQ-151 cream or vehicle has been applied until at least 4 hours after study drug application. Non-medicated emollients or moisturizers will be allowed once daily in a stable regimen as normally used by the subjects. For subjects that apply a non-medicated emollient or moisturizer after an evening shower/bath, the study drug must be applied first to the treatment areas. The non-medicated emollient or moisturizer can then be applied but only to other untreated areas of the subject's skin.
- Sunscreens will be allowed daily, as needed by the subjects when applied at least 2 hours after application of randomized study drug.
- Concomitant other medications for chronic conditions (e.g., NSAIDs, statins, anti-hypertensives) are permitted unless specifically prohibited in the Protocol.
- Topical antibiotics, topical antihistamines, or any other topical agents are not allowed to be applied to treated areas.

## 4.8. Treatment

### 4.8.1. Drug Supplies, Packaging and Labeling

ARQ-151 cream or matching vehicle will be supplied in 45 gram tubes. The tubes will be packaged in kits, containing multiple tubes of investigational product. The number of kits dispensed to a subject will be based on the BSA involvement of atopic dermatitis. The kits and tubes will be labeled in a blinded manner. The kit(s) dispensed to a subject will be labeled with a unique number.

The Sponsor will supply sufficient quantities of the study drug and matching vehicle to each site to allow for completion of this study.

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

Refer to the most current version of the IP Handling Plan for details on accountability, storage, and management of ARQ-151.

### 4.8.2. Blinding

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

### 4.8.3. 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-151-312 IWRS User Manual 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 CRF, 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.

### 4.8.4. Treatment Administration

Initial treatment with the IP will occur on Day 1. ARQ-151 cream 0.15% is administered once daily as a topical product to cover the skin surface at an application rate of approximately 2 $mg/cm^2$.

At Baseline visit, the study staff will demonstrate to the subject/caregiver(s) how to apply ARQ-151 cream using the first tube from the kit that is assigned to the subject. Study site staff will be trained to ensure a unit dose (a pea size unit of ARQ-151 cream will cover approximately 1% BSA) is properly squeezed from the tube and applied to atopic dermatitis lesion(s) as a thin film and rubbed in using the index and middle finger, rubbing in thoroughly but gently, until the 'white' has disappeared. The subject/caregiver will then practice squeezing a similar amount onto their index and middle finger and apply a thin film to other areas to be treated. At Baseline/Day 1, the study staff will ensure that the subject/caregiver's application technique is correct and that a thin layer is applied as instructed (which represents an application rate of approximately 2 $mg/cm^2$).

Re-training will be conducted at subsequent visits as needed (i.e., if the returned tube(s) weighs substantially different than the expected weight).

Subjects/caregivers will be instructed to apply investigational product once daily to all treatment areas identified by the Investigator at Baseline using a Body Diagram (see Appendix 1).

Note:

- All subjects should apply medication each evening (except on clinic visit days when the investigational product will be applied at the clinic). If the subject takes an evening shower/bath, the ARQ-151 cream or vehicle can be applied as soon as the skin is nearly dry, but no later than 20 minutes before going to bed. Subjects are not to wash areas where ARQ-151 cream or vehicle has been applied until at least 4 hours after study drug application.
- Caregivers should wash their hands with soap and water after applying IP to a child.
- Parents/guardians/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 investigational product or by wearing gloves during its application.
- Subjects should maintain treatment of areas with study drug for the duration of the study regardless of whether treatable areas of AD clear prior to Week 4 visit.
- New lesions that develop during the study should be treated (except scalp). An unscheduled visit is not required for starting treatment of new lesions.

Each investigational product tube will be weighed prior to dispensing at the Baseline visit and at each subsequent visit. Investigational product tubes must be returned by subjects at each study visit, both empty and full, and will be weighed. If the subject's actual use is substantially different than the expected use for the subject's BSA (see IP Handling Plan), the subject/caregiver will be retrained on the study drug application technique.

### 4.8.5. Treatment Compliance

Investigational product tubes will be weighed at each clinic visit.

Subjects/caregivers will complete a daily diary recording the date and time of each dose applied, any missed doses, and a comment section should the subjects have a comment, e.g., record potential AEs. Site personnel will review the diaries and use the information to question the subject regarding compliance and AEs and then record appropriate information in source documents and complete Case Report Forms (CRFs). If a subject misses a dose, they should be instructed to return to the protocol investigational product 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 meets both of the following requirements:

- applies at least 80% of the expected applications during the study drug application period
- does not miss more than 3 consecutive doses

Compliance will be assessed by review of the dosing diary. Weight of investigational product applied (via dispensed and returned tube weights) will be measured for reporting purposes.

If the diary shows less than 80% of expected daily applications (but not more than 3 consecutive missed doses), the subject is using too little study drug and retraining must be conducted and documented.

Compliance will be documented in source and in eCRF.

### 4.8.6. Removal of Subjects from Study Treatment

Subject treatment with study drug in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that, in the opinion of the Investigator does not allow the subject to adhere to the requirements of the Protocol.
2. Adverse Events as described in Section 5.1.12 and Section 5.9. The Investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
3. Treatment must be discontinued immediately in the event of a female subject's pregnancy.
4. Subject's decision to discontinue treatment with study drug.
5. C-SSRS (Section 5.1.10) indicative of suicidal ideation
6. PHQ-8 (Section 5.1.7) or modified PHQ-A (Section 5.1.8) score ≥15 if determined by Investigator in consultation with mental health professional
7. CDI-2 (Section 5.1.9) raw total score of ≥32 if determined by Investigator in consultation with mental health professional
8. Requirement for use of prohibited concomitant medication after consultation with the Sponsor and Medical Monitor.
9. Subject's repeated failure to comply with protocol requirements or study related procedures.
10. The subject interrupts trial study drug application for more than 50% of scheduled doses.
11. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

### 4.8.7. Removal of Subjects from the Study

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

- Subject death.
- Subject's decision to withdraw from the study.
- 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.

## 5.1. Safety Assessments

This study assesses the safety and efficacy of ARQ-151 cream. Safety will be determined by evaluating physical examinations, local tolerability assessments, vital signs/weight, clinical laboratory parameters, either PHQ-8 (adults, ≥18 years old) or modified PHQ-A (adolescents, 12-17 years old) or Children's Depresssion Inventory 2 (CDI-2, parent report for children 6-11 years old, inclusive), C-SSRS (12 years and older) and AEs as outlined in the Schedule of Visits and Assessments (Section 1.3).

Additional evaluations/testing may be deemed necessary by the PI and/or the Sponsor for reasons related to subject safety.

### 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 adolescent subjects and consent from their parent(s) or legal guardian(s) for children and/or adolescents after adequate explanation of the study design, anticipated benefits, and the potential risks. A subject is considered a participant of the trial once the ICF or written assent for adolescent subjects is completely signed.

Subjects must provide informed consent/assent as per their age group at screening. During the study, if a subject changes age group, the subject must provide informed consent/assent relative to his/her current age group. Subjects will continue with the assessments specific to their age group at the time of consent/assent at Screening.

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

- Review of medical and surgical history
- Collection of demographic data including sex, age, race, ethnicity
- Vital signs including temperature, heart rate, and blood pressure
- Collection of body weight (kg), and height (cm)
- Atopic dermatitis assessments (e.g., vIGA-AD, BSA, EASI, SCORAD)
- Limited physical examination of skin (including assessment of Fitzpatrick skin type at Screening only), lungs, and heart
  - Fitzpatrick skin phototype 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)

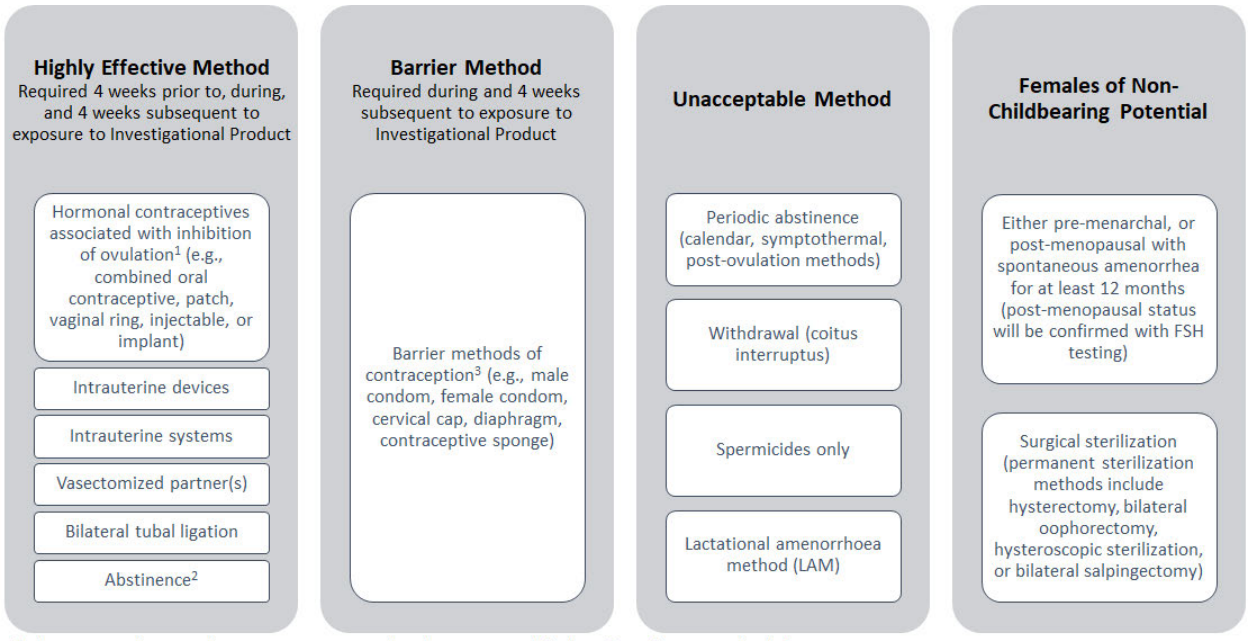
- Laboratory tests: hematology, chemistry, urinalysis, serum pregnancy test (for female subjects of child bearing potential)
- Completion of WI-NRS, CDI-2, DLQI, CDLQI, DFI, C-SSRS, POEM, and PHQ (-8 or -A)
- Collection of concomitant medications and adverse events

Subjects may be re-screened one time and the subject will assigned a new Subject ID.

### 5.1.2. Contraception Requirements

Females of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (Day 1). In addition, sexually active FOCBP must agree to use at least one form of an highly effective or barrier method of contraception throughout the trial according to Contraception Requirements (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 1.
[2]The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 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 (Day 1)

Randomization will take place at the Baseline visit after the subject has been found to be fully eligible for participation. A subject will be considered enrolled into the study upon the first IP application.

If the Baseline visit occurs within 21 days of Screening for subjects < 18 years old, the Screening results may be used.

### 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, lungs and heart only.

### 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 collected in seated position after 5 mins of rest. For weight measurement, subjects will be instructed to void prior to weight being taken and to remove any objects of significant weight (i.e. jackets, outerwear, shoes, cell phones, wallet, key chains, etc.). Weight should be obtained using a calibrated weight scale and the same scale, whenever possible, should be used for a subject throughout the duration of the study. The subject should stand with both feet in the center of the scale with their arms at their side and hold still. Record the weight to the nearest decimal fraction (for example, 55.5 pounds or 25.1 kilograms). For subjects <18 years of age, measure the weight in triplicate and report the average weight in EDC. An unexplained, clinically significant weight loss should be reported to the Medical Monitor.

Height will be measured at Screening only.

### 5.1.6. Laboratory Tests

All tests listed in Table 3 below will be performed according to the Schedule of Visits and Assessments (Section 1.3) unless otherwise noted. No food restrictions are required for the collection of specimens. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator.

**Table 3: 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**<br>(for females of child bearing potential only)<br>Serum pregnancy test (hCG)***<br>FSH test, (post menopausal) *** |

* 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 Baseline and Weeks 1, 2, and 4 for FOCBP only
*** At screening only

### 5.1.7. Patient Health Questionnaire depression scale (PHQ-8)

The PHQ-8 Assessment (Appendix 2) will be performed in 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 a PHQ-8 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 study drug.

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

The Modified PHQ-A Assessment (Appendix 3) will be performed in adolescent subjects (12-17 years old, inclusive).

Modified PHQ-A score is the sum of the responses for five severity categories of depression 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 study drug.

### 5.1.9. Children's Depression Inventory 2

The CDI-2 Assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3) for subjects 6 to 11 years old, inclusive.

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 report form is presented in Appendix 4.

A subject with a CDI-2 raw 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 study drug.

### 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.
- On all subsequent visits, the "Since Last Visit" version (Appendix 6) will be used (Baseline/Day 1, Week 1/Day 8, Week 2/Day 15 or Week 4/Day 29).
- 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 study drug and prompt referral to an identified mental health professional and/or an appropriate emergency room. The Medical Monitor should be contacted.

The C-SSRS administer will be trained via the C-SSRS training video. A training certificate for the administer(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 atopic dermatitis.**

The investigator assessments will be conducted by the investigator or a properly trained and designated subinvestigator prior to study drug application in the clinic.

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 edema
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).

The subject will assess burning/stinging (0-3 score):

| **Grade** | **Sensation Following Drug 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 |

This assessment will be administered by the site 10 to 15 minutes after study drug application in the clinic at Baseline and at every clinic visit.

- Note: for subject burning stinging assessment at Day 29, subjects will provide a recall assessment of burning/stinging experienced post drug application on the previous day (Day 28).

### 5.1.12. 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 5.7.5).

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 normal, or acceptable levels, as judged by the PI. Refer Section 5.7 for further details on Adverse Events.

## 5.2. Efficacy Evaluations

For efficacy evaluation subjects will have ≥3% BSA of AD involvement (excluding the scalp, palms, soles). Palms and soles may be treated with investigational product in this study, but will not be counted towards vIGA-AD, EASI, or BSA assessments. EASI is evaluated for the entire body except the scalp, palms, and soles..

### 5.2.1. Validated Investigator Global Assessment Scale for Atopic Dermatitis

**Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD) assessments should be completed prior to other physician assessments.**

vIGA-AD assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3). The vIGA-AD is a static evaluation of qualitative overall AD 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 (see Appendix 7). vIGA-AD is evaluated for the entire body except the scalp, palms, and soles.

**Note:** All atopic dermatitis lesions on a subject will be treated including the face, trunk, genitals/skin folds, or limbs (excluding the scalp). The palms and soles will be treated but will not be counted towards any measurements of efficacy (EASI, vIGA-AD, BSA).

**Every effort must be made for the same Evaluator to complete the IGA for the subject at every study visit.**

**IGA will be assessed at clinic visits prior to the subject applying Investigational Product at the site.**

### 5.2.2. Eczema Area and Severity Index (EASI)

EASI scores (Hanifin 2001) will be performed according to the Schedule of Visits and Assessments (Section 1.3)

Four anatomic sites—head, upper extremities, trunk, and lower extremities—are assessed for erythema, induration/infiltration (papules), excoriation, and lichenification as seen on the day of the examination. The severity of each sign is assessed using a 4-point scale (half steps **are** allowed; e.g. 0.5, 1.5 and 2.5):

- 0 = none
- 1 = mild
- 2 = moderate
- 3 = severe

The area affected by atopic dermatitis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of atopic dermatitis involvement as follows:

- 0 = no involvement
- 1 = 1-9%
- 2 = 10-29%
- 3 = 30-49%
- 4 = 50-69%
- 5 = 70-89%
- 6 = 90-100%

The EASI score is obtained by using the formula below for subjects ≥8 years old:

$$\text{EASI} = 0.1\,(E_h + I_h + Ex_h + L_h)\,A_h + 0.2\,(E_u + I_u + Ex_u + L_u)\,A_u + 0.3\,(E_t + I_t + Ex_t + L_t)\,A_t + 0.4\,(E_l + I_l + Ex_l + L_l)\,A_l$$

The EASI score is obtained by using the formula below for subjects <8 years old:

$$\text{EASI} = 0.2\,(E_h + I_h + Ex_h + L_h)\,A_h + 0.2\,(E_u + I_u + Ex_u + L_u)\,A_u + 0.3\,(E_t + I_t + Ex_t + L_t)\,A_t + 0.3\,(E_l + I_l + Ex_l + L_l)\,A_l$$

Where E, I, E*x*, L, and A denote erythema, induration, excoriation, lichenification and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively.

Note: Palms and soles may be treated with investigational product in this study, but will not be counted towards IGA, EASI, or BSA assessments. EASI is evaluated for the entire body except the scalp, palms, and soles.

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

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. (Newton 2019). The WI-NRS will be determined by the subject's recording of daily assessment of worst itch over the past 24 hours. The scale is from '0 to 10' ("no itch" to "worst itch imaginable" or "worst imaginable itch").

WI-NRS Assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3) starting 7 days prior to the Baseline/Day 1 clinic visit (during the 7 days prior to Baseline/Day 1 the subject will record the WI-NRS value every day).

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

The DLQI (ages 17+ years) and CDLQI (ages 6-16 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 adult 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. Subjects/caregivers will complete the CDLQI/DLQI. Refer to Appendix 8 for the DLQI and Appendix 9 for the CDLQI.

#### 5.2.5. Dermatitis Family Impact Questionnaire (DFI)

This questionnaire measures how much having a child with atopic dermatitis affects the quality of life of other (adult) members of the family. To be completed by parents/guardians/caregivers of subjects ≤17 years of age (Appendix 10).

### 5.3. Other Evaluations

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

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

The BSA affected for atopic 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 (excluding the scalp, palms, soles).

#### 5.3.2. SCORAD ("SCORing Atopic Dermatitis")

SCORAD is a clinical tool for assessing the severity (i.e. extent, intensity) of atopic dermatitis as objectively as possible. It gives approximate weights of 60% to intensity and 20% each to spread (extent) and subjective signs (insomnia, etc.).

See Appendix 11.

#### 5.3.3. Patient-Oriented Eczema Measure (POEM)

The Patient-Oriented Eczema Measure (POEM) is a tool used for monitoring atopic eczema severity. It focuses on the illness as experienced by the patient.

POEM is a 5-point scale measuring the frequency of each of seven AD symptoms (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) over the past week scored as occurring "no days" (0), "1 to 2 days" (1), "3 to 4 days" (2), "5 to 6 days" (3) or "every day" (4). Total score ranges from 0–28, with higher score indicating greater symptom impact.
See Appendix 12. The self/proxy report questionnaire will be used in this study (for children unable to read and/or understand the POEM questionnaire, the parent/guardian/caregiver will complete the questionnaire).

### 5.3.4. Pharmacokinetics Assessment

PK draws will be performed according to the Schedule of Visits and Assessments (Section 1.3) for all subjects at all sites:

- A single PK assessment (trough) will be performed in all subjects with a blood sample collected at Week 4/Day 29.

Ensure study medication is not applied in the area where PK will be drawn.

### 5.3.5. Medical Photography

Photography of AD lesion(s) selected by the Investigator will be performed by all sites at all investigational visits, except Week 2/Day 15. All efforts will be made to de-identify the subjects. Canfield equipment will be used to capture photographs.

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. 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 – End of Study

The approximate final study visit will occur at Week 4/Day 29. The procedures performed during this visit are as described in the Schedule of Visits and Assessments (Section 1.3). A 3-day scheduling window is allowed for this visit. Adverse events will be recorded as reported by the participant or and followed to resolution or stabilization (as necessary).

## 5.5. Early Termination Visit

If a subject is withdrawn or wishes to exit the study, a termination visit will be scheduled. This visit should include the procedures and assessments that would be performed at the Week 4/Day 29 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

The following information also will be collected:

- vIGA-AD and EASI
- BSA affected with AD

- Local tolerability assessment (by Investigator)

The rules for how to tally vIGA-AD, BSA or other proportions of categorical responses will be described in the Statistical Analysis Plan.

## 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 a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A treatment emergent adverse event (TEAE) is defined as an AE that started post application of study medication at the Baseline visit or was present at treatment initiation but worsened during treatment, through study completion.

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 (eg, 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 atopic dermatitis 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 Definition

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. Statements regarding 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.

An 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 room 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 document.

If a SAE occurs to a subject on this study, contact the Medical Monitor within one business day of knowledge of event.

### 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.

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 normal, 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). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

### 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 one month after treatment permanently discontinues. 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 within 24 hours of becoming aware of the event, whether or not the serious events are deemed drug-related. Reporting should be done by sending the completed SAE form to the following e-mail address (faxing can also be done as a second option in case e-mailing is not possible).

**Safety Contact Information:** [redacted]

**E-mail:** [redacted]

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 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 in accordance to the IRB requirements.

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 (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) 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 and submitting to the Medical Monitor 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. Any pregnancy complication must be reported as a SAE. 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. Any infant death that occurs after the 30 day reporting period that the investigator suspects is related to Investigational Product must also be reported as an SAE.

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 study drug, 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 serious adverse event (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 13 for more information).

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

- 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

Subjects 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 study drug

- Subjects with a CDI-2 raw score of ≥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 study drug.

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

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.

Treatment should be discontinued:

- If the application site reaction reoccurs, treatment 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 User Manual (Section 4.8.3). Contact the Medical Monitor and the Sponsor promptly.

# 6. DATA ANALYSIS

Data will be handled and processed according to the Contract Research Organization's 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) unless otherwise stated.

## 6.2. Determination of Sample Size

There are approximately 650 subjects planned for this study. In order to test the key secondary endpoint of IGA success in subjects with a vIGA-AD score of 'Moderate' at randomization, approximately 488 of the subjects to be accrued will have vIGA-AD score of 'Moderate' at randomization. Randomization will be stratified by vIGA-AD score ('Mild' vs. 'Moderate') and by study site.

This sample size provides approximately 95% power to detect an overall 15% difference between treatment groups on vIGA-AD success at Week 4 at α-0.05 using a 2-sided stratified (vIGA-AD at randomization and study site) Cochran-Mantel-Haenszel test. The results from a recent phase 2 study (ARQ-151-212) of ARQ-151 cream 0.15% compared to vehicle treatment were used to estimate the treatment difference. Specifically, in the phase 2 trial, approximately 37% of subjects demonstrated vIGA-AD success at Week 4 in the ARQ-151 0.15% group compared to 22% in the vehicle group. This sample size also provides approximately 90% power to detect an overall 17% difference between treatment groups on IGA success at Week 4 among subjects with vIGA-AD score 'moderate' at randomization. The same testing method, the stratified Cochran-Mantel-Haenszel test, will be used as for the primary endpoint.

To control for multiple comparisons, the key secondary endpoint will only be tested if the primary endpoint demonstrates statistical significance. In addition, the remaining secondary endpoints will be inferentially tested only if the primary and key secondary endpoint comparisons are statistically significant. To control for multiple comparisons among the remaining secondary endpoints, partitioning of alpha and the Holm's procedure will be used.

## 6.3. Subjects to Analyze

The analysis populations are defined as follows:

- Safety population will include all subjects who are enrolled and received at least one confirmed dose of study medication.
- Intent-to-Treat (ITT) population will include all subjects who are randomized.
- vIGA-AD Moderate ITT population will be a subset of the ITT population with vIGA-AD score 'moderate' at randomization.
- WI-NRS population will be a subset of the ITT population with WI-NRS score ≥ 4 at baseline.
- Pharmacokinetic (PK) population will include all subjects receiving the active drug with quantifiable plasma concentrations of roflumilast.

## 6.4. Background and Demographic Characteristics

Descriptive statistics will be used to summarize demographic characteristics (age, sex, ethnicity, and race) and background characteristics for the randomized subjects.

## 6.5. Study Medication Compliance

The number of study drug applications by each subject based on diary data will be summarized using summary statistics (mean, standard deviation [SD], median, minimum, and maximum), and categorically.

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

The amount of investigational product used by each subject based on tube weight will be summarized by treatment using descriptive statistics, and categorically.

Investigational product application compliance will be calculated based on number of applications divided by the expected number (amount) of investigational product applications for each subject. Compliance will be summarized descriptively by treatment group.

## 6.6. 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.

**Adverse Events:**

The subject incidence of treatment-emergent adverse events (TEAE) will be summarized overall, by severity, and by attribution.

**Clinical Laboratory Results:**

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

**Vital Signs:**

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

## 6.7. Efficacy Analysis

The Primary Efficacy Endpoint will be tested in all randomized subjects and defined as:

- The proportion of all randomized subjects who attain IGA Success, defined as a vIGA-AD score of ‘clear’ or ‘almost clear’ PLUS a 2-grade improvement from Baseline at Week 4

Upon demonstration of statistical significance for the primary endpoint, a hierarchical testing scheme will be used to test the key secondary endpoint defined as:

- The proportion of randomized subjects with a vIGA-AD score of ‘Moderate’ at randomization who attain IGA Success at Week 4

Missing IGA scores will be imputed using multiple imputation.

Upon successful demonstration of statistical significance for the secondary endpoint, the remaining endpoints will be grouped into secondary endpoint family 1, comprised of the 4-point reduction on the WI-NRS, and secondary endpoint family 2, comprised of the EASI-75 at Week 4, vIGA-AD of 'clear' or 'almost clear' at Week 4, time to achievement of vIGA-AD success, and time to achievement of EASI-75. An alpha level of 0.03 will be used to test the 4-point reduction in the WI-NRS at Week 4. An alpha level of 0.02 will be used to test the endpoints in secondary endpoint family 2. The Holm procedure will be used to control for multiple comparisons within secondary endpoint family 2. The endpoints listed below will be tested among all randomized subjects, unless otherwise noted.

**Secondary Endpoint Family 1** ($\alpha$=0.03)

- Among subjects with baseline WI-NRS ≥ 4, the proportion of subjects who attain a 4-point reduction in the WI-NRS at Week 4

**Secondary Endpoint Family 2** ($\alpha$ = 0.02, Holm's procedure)

- The proportion of subjects who attain at least a 75% reduction in the Eczema Area and Severity Index at Week 4 (EASI-75)
- Proportion of patients with vIGA-AD score of 'clear' or 'almost clear' at Week 4
- Time to achievement of vIGA-AD success
- Time to achievement of EASI-75

The ITT population will be used for the primary and secondary efficacy analyses, with the exception of the key secondary endpoint analysis which will be performed on the vIGA-AD Moderate ITT population.

## 6.8. Adverse Events

All TEAEs occurring during the study will be recorded and classified on the basis of MedDRA terminology for the safety population. TEAEs are defined as those AEs with an onset on or after the time of first study drug application. All reported TEAEs will be summarized by treatment group.

Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data.

**Adverse Events:**

The subject incidence of treatment-emergent adverse events (TEAE) will be summarized overall, by severity, and by attribution.

**Clinical Laboratory Results:**

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

**Vital Signs:**

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

## 6.9. Body Surface Area

Body surface area (BSA) affected by AD will be analyzed descriptively.

## 6.10. Local Tolerance Assessment

For Investigator's assessment, 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.

## 6.11. Medical History and Physical Examinations

Medical history for all subjects will be presented descriptively by parameter.

Physical examination for all subjects will be presented descriptively by parameter. Changes in physical examinations will be described in the text of the final report.

## 6.12. Clinical Laboratory Results and Vital Signs

All clinical laboratory results and vital signs measurements and their change from baseline (pre-dose), will be summarized descriptively by parameter, visit, and treatment group along with time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

A shift table will identify subjects who gain or lose >5% body weight over the course of the study.

## 6.13. Prior and Concomitant Medications

Prior and concomitant medication information for all randomized subjects will be presented in a by-subject listing. Summary tables will be presented by World Health Organization-Anatomical Therapeutic Chemical Classification System (WHO-ATC) therapeutic category and product.

## 6.14. Subject Reported Outcomes Analyses

WI- WI-NRS scale will be analyzed for change from Baseline (measured as a weekly average during the week before the Baseline/Day 1 visit) in itch severity of at least 4 at Week 4/Day 29 as a weekly average during the week before the Week 4/Day 29 visit.

#### 6.14.1. Dermatology Life Quality Indexes, Children's Dermatology Life Quality Index, SCORAD and POEM

Dermatology Life Quality Index (DLQI), Children's Dermatology Life Quality Index (CDLQI), the Dermatitis Family Impact (DFI), the Scoring Atopic Dermatitis (SCORAD), and the Patient-oriented Eczema Measure (POEM) will be analyzed by evaluation of the reduction in total score at Week 4. These efficacy endpoints will be analyzed descriptively.

### 6.15. Pharmacokinetic Analysis

Plasma drug concentrations will be summarized using descriptive statistics, reporting n, mean, standard deviation, median, minimum, and maximum. The PK population will be used for these analyses.

## 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, as required by FDA (21 CFR § 56) 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, the Sponsor, or designee shall promptly notify the IRB of any SAEs, SUSARs, or any other information that may affect the safe use of the study drug(s) 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 carried out in accordance with the protocol, the principles of the Tri-Council Policy Statement (TCPS), the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

#### 7.1.3. Subject Information and Consent/Assent

The investigator is responsible for obtaining written informed consent from each individual 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 IEC-approved consent form for

documenting written informed consent. 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 also by an impartial witness if required by IRB or IEC or local requirements.

Subjects will be given a signed 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 CRFs. 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

In order to ensure the collection of accurate, 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 using SAS version 9.4 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 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) 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, 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), 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 investigator brochure, this protocol, CRF/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. 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.

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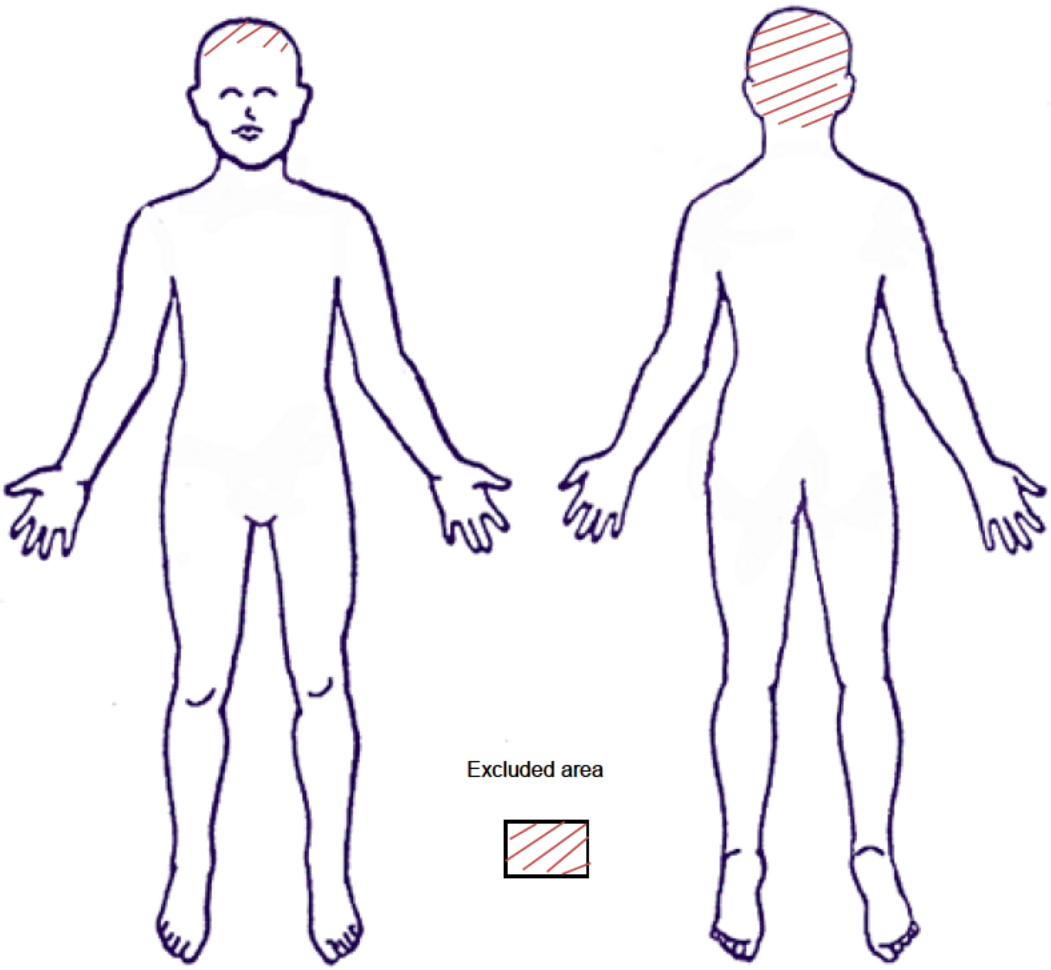
# 9. APPENDICES

## APPENDIX 1. BODY DIAGRAM

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

(**Reminder**: Application will be all areas affected (except for the scalp). Continue to apply even if area(s) clears and treat new lesions (except scalp).

| **Study Personnel Completing Body Diagram (initial/date)** |
|---|
| Baseline |




*Site to photocopy this page after updating at the Baseline and retain the original in source. Provide the copy to the subject to refer to for study application at home.*

# APPENDIX 2. PATIENT HEALTH QUESTIONAIRE-8 (PHQ-8)

SMRC
Self-Management
Resource Center

## Personal 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 |

### Scoring

If two consecutive numbers are circled, score the higher (more distress) number. If the numbers are not consecutive, do not score the item. Score is the sum of the 8 items. If more than 1 item missing, set the value of the scale to missing. A score of 10 or greater is considered major depression, 20 or more is severe major depression.

# APPENDIX 3. PATIENT HEALTH QUESTIONNAIRE DEPRESSION SCALE (MODIFIED 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 (Circle One)

Parent's Name/ID: _____ Date of Birth: ____/____/____ (Year / Month / Day)

Relationship to Child: _____ Today's Date: ____/____/____ (Year / Month / Day)

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 schoolwork. | 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>_____ |

# 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
____

| ***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: | Yes ☐ No ☐<br><br>Total # of Attempts<br>_____ |
| **Has subject engaged in Non-Suicidal Self-Injurious Behavior?** | 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><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>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 ☐ |
| **Suicidal Behavior:**<br>Suicidal behavior was present during the assessment period? | Yes ☐ No ☐ |
| **Suicide:** | Yes ☐ No ☐ |
| ***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>_____ |

 C-SSRS—Since Last Visit (Version 1/14/09) Page 2 of 2

# APPENDIX 7. VALIDATED INVESTIGATOR GLOBAL ASSESSMENT SCALE FOR ATOPIC DERMATITIS

**Validated Investigator Global Assessment scale for Atopic Dermatitis**

**vIGA-AD™**

***Instructions:***

*The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.*

| Score | Morphological Description |
|---|---|
| **0 – Clear** | No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present. |
| **1 – Almost clear** | Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting. |
| **2 – Mild** | Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting. |
| **3 – Moderate** | Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present. |
| **4 – Severe** | Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present. |

***Notes:***

*1. In indeterminate cases, please use extent to differentiate between scores.*

*For example:*

- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*

*2. Excoriations should not be considered when assessing disease severity.*

# APPENDIX 8. DERMATOLOGY LIFE QUALITY INDEX

**DLQI**

Site No: Date: 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 ❒ |
| **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 ❒ |
| **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 ❒ |

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

# APPENDIX 9. CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

Site No.:
Name: Diagnosis: CDLQI
Age: SCORE:
Address: 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 | ☐<br>☐<br>☐<br>☐ |
| **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 | ☐<br>☐<br>☐<br>☐ |
| **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 | ☐<br>☐<br>☐<br>☐ |
| **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 | ☐<br>☐<br>☐<br>☐ |
| **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 | ☐<br>☐<br>☐<br>☐ |
| **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 | ☐<br>☐<br>☐<br>☐ |
| **7**. | <u>Last week</u>, was it **school time?** → **If school time**: Over the last week, how much did your skin problem affect your **school work**? | Prevented school<br>Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐<br>☐ |
| | **OR** | | |
| | was it **holiday time?** → **If holiday time**: How much over the last week, has your skin problem interfered with your enjoyment of the **holiday**? | Very much<br>Quite a lot<br>Only a little<br>Not at all | ☐<br>☐<br>☐<br>☐ |

| | | | |
|---|---|---|---|
| **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>☐ |

# APPENDIX 10. DERMATITIS FAMILY IMPACT QUESTIONNAIRE (DFI)

**Child's Name:** **Mother/Father/Carer** **Date:** **Score**

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

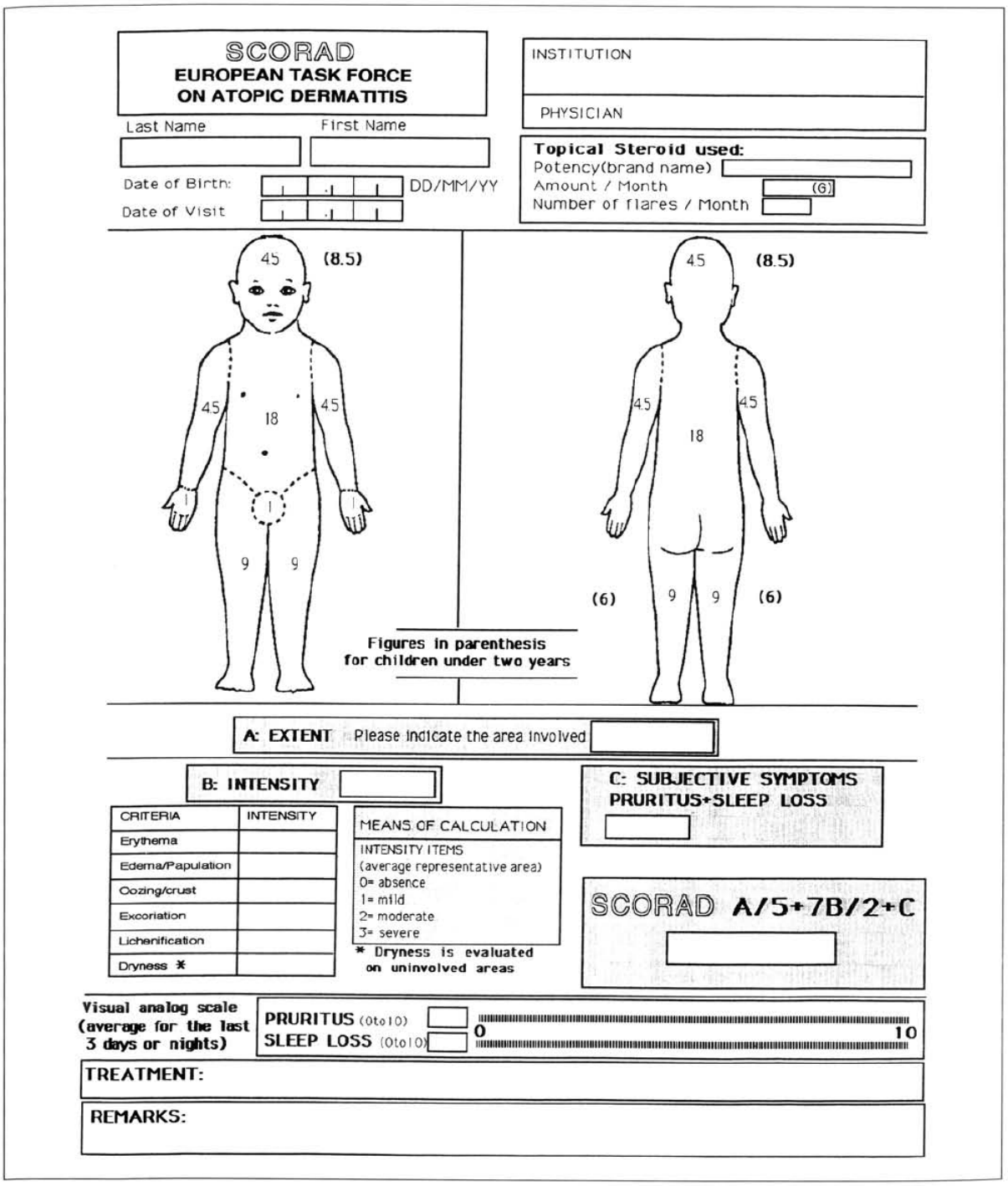
| | | | |
|---|---|---|---|
| 1. | Over the last week, how much effect has your child having eczema had on **housework**, e.g. washing, cleaning. | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ |
| 2. | Over the last week, how much effect has your child having eczema had on **food preparation** and **feeding**. | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ |
| 3. | Over the last week, how much effect has your child having eczema had on the **sleep of others in family**. | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ |
| 4. | Over the last week, how much effect has your child having eczema had on **family leisure activities**, eg swimming. | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ |
| 5. | Over the last week, how much effect has your child having eczema had on **time spent on shopping for the family.** | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ |
| 6. | Over the last week, how much effect has your child having eczema had on your **expenditure**, eg costs related to treatment, clothes, etc. | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ |
| 7. | Over the last week, how much effect has your child having eczema had on causing **tiredness** or **exhaustion** in your child's parents/carers. | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ |
| 8. | Over the last week, how much effect has your child having eczema had on causing **emotional distress** such as depression, frustration or guilt in your child's parents/carers. | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ |

| | | | |
|---|---|---|---|
| 9. | Over the last week, how much effect has your child having eczema had on **relationships** between the **main carer and partner** or between the **main carer and other children** in the family. | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ |
| 10. | Over the last week, how much effect has **helping with your child's treatment** had on the main carer's life. | Very much<br>A lot<br>A little<br>Not at all | ❒<br>❒<br>❒<br>❒ |

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

# APPENDIX 11. SCORAD

**SCORAD** https://www.ncbi.nlm.nih.gov/pubmed/8435513



# APPENDIX 12. PATIENT-ORIENTED ECZEMA MEASURE (POEM)

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion and/or proxy completion

Patient Details: _____

_____

_____

_____ Date: _____

Please circle one response for each of the seven questions below about your/your child's eczema. If your child is old enough to understand the questions then please fill in the questionnaire together. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your/your child's skin been itchy because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

2. Over the last week, on how many nights has your/your child's sleep been disturbed because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

3. Over the last week, on how many days has your/your child's skin been bleeding because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

4. Over the last week, on how many days has your/your child's skin been weeping or oozing clear fluid because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

5. Over the last week, on how many days has your/your child's skin been cracked because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

6. Over the last week, on how many days has your/your child's skin been flaking off because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

7. Over the last week, on how many days has your/your child's skin felt dry or rough because of the eczema?

No days | 1-2 days | 3-4 days | 5-6 days | Every day

Total POEM Score (Maximum 28): .....

# POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion and/or proxy completion

## How is the scoring done?

Each of the seven questions carries equal weight and is scored from 0 to 4 as follows:

| | |
|---|---|
| No days | = 0 |
| 1-2 days | = 1 |
| 3-4 days | = 2 |
| 5-6 days | = 3 |
| Every day | = 4 |

**Note:**

- If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 28
- If two or more questions are left unanswered the questionnaire is not scored
- If two or more response options are selected, the response option with the highest score should be recorded

## What does a poem score mean?

To help patients and clinicians to understand their POEM scores, the following bandings have been established (see references below):

| | |
|---|---|
| • 0 to 2 | = Clear or almost clear |
| • 3 to 7 | = Mild eczema |
| • 8 to 16 | = Moderate eczema |
| • 17 to 24 | = Severe eczema |
| • 25 to 28 | = Very severe eczema |

## Do I need permission to use the scale?

Whilst the POEM scale is protected by copyright, it is freely available for use and can be downloaded from: www.nottingham.ac.uk/dermatology
We do however ask that you register your use of the POEM by e-mailing cebd@nottingham.ac.uk with details of how you would like to use the scale, and which countries the scale will be used in.

**References**

Charman CR, Venn AJ, Williams HC. The Patient-Oriented Eczema Measure: Development and Initial Validation of a New Tool for Measuring Atopic Eczema Severity From the Patients' Perspective. Arch Dermatol. 2004;140:1513-1519

Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. Br J Dermatol. Dec 2013; 169(6): 1326–1332.

# APPENDIX 13. 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 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)a 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 |

a 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 b | 2.5-5 cm | 5.1-10 cm | >10 cm |
| Induration/swelling c | 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 |

b In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
c 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 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.