Protocol ARQ-151-315

A Phase 3, 4-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.05% Administered QD in Subjects with Atopic Dermatitis

Sponsor:

Arcutis Biotherapeutics, Inc.
3027 Townsgate Road, Suite #300
Westlake Village, CA 91361

Sponsor Representative:

[redacted]

Medical Monitor:

[redacted]

IND Number:

[redacted]

Protocol Version: Amendment 2

Date: 10 April 2023

GCP Statement

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

SITE INVESTIGATOR SIGNATURE PAGE

ARQ-151-315

A Phase 3, 4-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.05% Administered QD in Subjects with Atopic Dermatitis

SPONSOR: Arcutis Biotherapeutics, Inc.
3027 Townsgate Road, Suite #300
Westlake Village, CA 91361

ISSUE DATE: 10 April 2023

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: _____

Print Investigator Name: _____

Investigator Signature: _____ Date: _____

SUMMARY OF CHANGES

The following sections have been changed in Amendment 1 of the ARQ-151-315 protocol:

Version/Date	Description
December 13, 2020	Original Protocol

Amendment 1
July 16, 2021
	• Added Summary of Changes section.
	• Updated Arcutis Biotherapeutics, Inc. address
	• Updated number of sites to approximately 65. Added statement "During the conduct of the study, additional countries and/or sites may be added if necessary."
	• Removed statement "enrollment has not completed" from "A the Week 4 visit, subjects may be eligible to enroll in a 12-month, open label extension study (ARQ-151-313), subject to regulatory approval, evaluating ARQ-151 cream 0.15% QD and 0.05% QD." All subjects will have the option to enroll into the ARQ-151-313 study.
	• Clarification added that if an unscheduled visit is required for reasons other than safety, the following assessments are not required:
	  • vIGA-AD and EASI
	  • BSA affected with AD
	  • Local tolerability assessment (by Investigator)
	• Removed safety labs and PK draw at Week 4/Day 29 to reduce patient burden and because no longer considered necessary based on review of emerging data from other studies including maximal usage study.
	• Updates to statistical sections
	  • Added estimand language in the primary analysis section
	  • Updated "key secondary endpoints" to "secondary endpoints" and updated the language to be consistent throughout the document
	  • Updated the multiple testing procedure to hierarchical testing for secondary endpoint family 2
	  • Removed WI-NRS from multiple testing procedure
	  • Added per protocol population
	  • Added the ARQ-151-212 Roflumilast cream 0.05% results to the sample size calculation.

Version/Date	Description

Amendment 1
July 16, 2021 (Continued)
	• Updates to endpoints sections
	  • Removed time to event endpoints
	  • Updated the wording to be consistent throughout the document
	  • Added new endpoints of vIGA-AD success at Week 1 and Week 2, vIGA-AD of 'clear' or 'almost clear' at Week 1 and Week 2
	• WI-NRS: added statement that caregiver/parents will be given instructions on how to complete this questionnaire.

Amendment 2 April 10, 2023	• Modified the hierarchical order of testing for the secondary endpoints so that vIGA-AD of 'clear' or 'almost clear' at Week 2 is tested before vIGA-AD success at Week 1. • Updated the method of handling the intercurrent events of discontinuation due to adverse event or lack of efficacy to identify these subjects as non-responders at any visit that occurred or would have occurred after the date of last dose of study treatment. • Removed stratification by pooled site from efficacy analyses. • Revised Per Protocol Population to add "have a vIGA-AD assessment within the Week 4 visit window," and deleted "In addition, subjects who miss the Week 4 vIGA-AD assessment specifically only due to novel coronavirus disease-19 (COVID-19) disruptions will be excluded from per protocol population." • Changes to the method for summarizing IP use by tube weight (removed "categorically"). • Revisions to Population summary in Section 8.2.1. • Revisions to the supplemental analysis of observed data for the PP population in Section 8.2.1. • Revisions to Section 8.3.4 to clarify laboratory results that will be summarized. • Added WI-NRS analysis population for analysis of WI-NRS. • Removed the vIGA-AD Moderate PP Population. • Updated number of sites to approximately 109 and participating countries. • Updated medical monitor information. • Deleted Urine from LABORATORY AND VITAL SIGNS TOXICITY GRADING since there is no urine sample collected in this study.

Version/Date	Description
	• Minor grammatical/editorial changes.

1. SYNOPSIS

<table>
<tr><td colspan="3">Name of Sponsor/Company: Arcutis Biotherapeutics, Inc.</td></tr>
<tr><td colspan="3">Name of Investigational Product: ARQ-151 will be supplied as an emollient cream at 0.05% strength or as a matching vehicle cream containing only excipients of ARQ-151</td></tr>
<tr><td colspan="3">Name of Active Ingredient: Roflumilast, a PDE-4 inhibitor</td></tr>
<tr><td>Protocol Number:
ARQ-151-315</td><td>Phase: 3</td><td>Country: US, Canada, and Poland</td></tr>
<tr><td colspan="3">Title of Study:
A Phase 3, 4-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.05% Administered QD in Subjects with Atopic Dermatitis</td></tr>
<tr><td colspan="3">Clinical Indication: Atopic Dermatitis</td></tr>
<tr><td colspan="3">Number of Sites: Approximately 109 in the US, Canada, and Poland. During the conduct of the study, additional countries and/or sites may be added if necessary.</td></tr>
<tr><td colspan="3">Study Population:
Subjects will be male and female children (2-5 years old, inclusive). Subjects will have mild to moderate atopic dermatitis involvement with a vIGA-AD score of ‘2’ (mild) or ‘3’ (moderate) for study entry. Approximately 650 subjects are planned to be randomized in this study.</td></tr>
<tr><td colspan="3">Objectives:
Primary:
To assess the safety and efficacy of ARQ-151 cream 0.05% vs vehicle administered QD x 4 weeks to subjects aged 2-5 years with atopic dermatitis.</td></tr>
<tr><td colspan="3">Summary of Study Design:
This is a Phase 3, parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.05% or vehicle is applied QD x 4 weeks to subjects aged 2-5 years 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 0.05% or matching vehicle cream. The randomization will be stratified by vIGA-AD score at baseline (‘Mild’ vs. ‘Moderate’), and by study site.
Caregivers will apply ARQ-151 cream 0.05% or vehicle cream QD to all AD affected areas and any newly appearing AD lesions that arise during the study, except on the scalp. 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/Day 29.
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 and 0.05% QD. All subjects will have the option to enroll into the ARQ-151-313 study.</td></tr>
</table>

Methodology:

This is a blinded study with a randomization scheme of 2 to 1 for the following treatment group:

- Approximately 433 subjects will receive ARQ-151 cream 0.05% QD
- Approximately 217 subjects will receive matching cream vehicle QD

The primary comparison will be performed at the 2.5% significance level and will include:

- ARQ-151 cream 0.05% vs. vehicle cream

Sample Size Justification:

Approximately 650 subjects are planned to be randomized in this study. To test the secondary endpoint of IGA success in subjects with a vIGA-AD score of 'Moderate' at randomization, approximately 490 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 study site.

This sample size provides more than 90% power to detect 15% difference between treatment groups on vIGA-AD success at Week 4 at α=0.025 using a 2-sided stratified Cochran-Mantel-Haenszel test. The results from a recent Phase 2 study (ARQ-151-212) of ARQ-151 cream 0.05% compared to vehicle treatment were used to estimate the treatment difference. The vIGA-AD success rate at Week 4 was 38% in the ARQ-151 cream 0.05% group compared to 22% in the vehicle. Similarly, 37% of subjects demonstrated vIGA-AD success at Week 4 in the ARQ-151 cream 0.15%. This sample size also provides more than 80% power to detect 15% 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.

Number of Patients (planned):

Approximately 650 subjects; randomized 2:1 to ARQ-151 cream 0.05%: vehicle

Duration of Treatment:

Screening (up to 30 days) + Treatment phase (4 weeks) for a total of about 8 weeks.

Upon completion of the treatment phase of the study (Week 4/Day 29) subjects may have the opportunity, to participate in an open-label extension study (ARQ-151-313) of up to 52 weeks (12 months).

Main Criteria for Inclusion:

1. Informed consent of parent(s) or legal guardian as required by local laws.
2. Males and females, ages 2 to 5 years old (inclusive) at time of signing the Informed Consent (Screening) and at Baseline/Day 1.
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 [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 6 weeks as determined by the Investigator through subject interview. Stable disease for the past 4 weeks with no significant flares in atopic dermatitis before screening.
5. EASI Score $\geq$5 at Baseline/Day 1. EASI is evaluated for the entire body except the scalp, palms, and soles.

6. vIGA-AD score of 'Mild' ('2') or '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 at Baseline/Day 1 (excluding the scalp, palms, soles).
8. In good health as judged by the Investigator, based on medical history, physical examination, vital signs, serum chemistry labs, and hematology values.
9. 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.

Main Criteria for Exclusion:

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. Subjects who cannot discontinue medications and treatments prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 1).
3. Has unstable AD or any consistent requirement for high potency topical steroids to manage AD signs or symptoms.
4. 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 and during the study.
5. Subjects who are unwilling to refrain from prolonged sun exposure for 4 weeks prior to Baseline/Day 1 and during the study.
6. 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.
7. Subjects with known genetic dermatological conditions that overlap with AD, such as Netherton syndrome.
8. Known allergies to excipients in ARQ-151 cream [redacted]
9. 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 visit and during the study period.
10. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, and rifampin and carbamazepine for 2 weeks prior to the baseline visit and during the study period.
11. Subjects who have received oral roflumilast (Daxas®, Daliresp®) within the past 4 weeks prior to Baseline/Day 1.
12. Known or suspected:
    a. Severe renal insufficiency
        – Severe renal insufficiency is defined as calculated creatinine clearance <30 mL/min

b. Moderate to severe hepatic disorders (Child-Pugh B or C)

13. Previous treatment with ARQ-151.
14. 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.
15. Subjects with any serious known medical condition or clinically significant laboratory abnormality that would prevent study participation or place the subject at significant risk, as determined by the Investigator.
16. 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.
17. Any history of cancer.
18. Parent(s)/legal guardian(s) who are unable to communicate, read, or understand the local language(s). Subjects who display any condition which in the Investigator's opinion, makes them unsuitable for clinical study participation.
19. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members of enrolled subjects (subjects enrolled in other studies of ARQ-151) living in the same house.

Investigational Product, Dosage and Mode of Administration:

ARQ-151 cream 0.05% or matching vehicle cream is to be applied topically QD to all atopic dermatitis (AD) affected areas and any newly appearing AD lesions that arise during the 4-week study, except on the scalp. 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.

Key Assessments:

- Safety will be monitored through local tolerability assessments, vital signs, physical examination, safety labs, and AEs. Parents/caregivers will be advised to promptly report any changes in behavior that could signal psychological distress or emotional distress.
  - After obtaining consent, all SAEs should be collected. After application of the first dose of Investigational Product, all AEs should be collected.
  - The investigator or a properly trained and designated sub-investigator 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) and Week 4/Day29.
  - A limited physical exam (skin, lungs, and heart only) will be performed at Screening, Baseline/Day 1 and Week 4/Day 29. Blood samples for routine safety laboratory tests (hematology, serum chemistry) will be obtained at Screening.
- Efficacy will be assessed using:
  - vIGA-AD
  - EASI
  - WI-NRS
  - BSA
  - CDLQI (for 4-5 years old)
  - IDQoL (for 2-3 years old)
  - DFI

- SCORAD
- POEM

Study Endpoints:

Primary Efficacy Endpoint:

IGA Success, defined as a vIGA-AD score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at Week 4.

Secondary Efficacy Endpoints:

- In subjects with vIGA-AD score of 'Moderate' at randomization, IGA Success at Week 4
- Achievement of at least 75% reduction in the Eczema Area and Severity Index (EASI-75) at Week 4
- vIGA-AD score of 'clear' or 'almost clear' at Week 4
- vIGA-AD Success at Week 2
- vIGA-AD of 'clear' or 'almost clear' at Week 2
- vIGA-AD success at Week 1
- vIGA-AD of 'clear' or 'almost clear' at Week 1

Criteria for Evaluation:

Safety:

The safety population will include all subjects who are randomized and received at least one confirmed dose of study medication.

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

The incidence of adverse events will be summarized as well as changes from baseline in vital signs.

Statistical Methods:

Subjects will be stratified by Baseline vIGA-AD score ('Mild' and 'Moderate') and by study site.

- The primary endpoint will be tested in all randomized subjects

The primary endpoint will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline vIGA-AD score. Statistical significance will be concluded at the 2.5% significance level (2-sided).

To control for familywise type I error at level of 0.025, the remaining secondary endpoints will be tested sequentially at an alpha level of 0.025 upon successful demonstration of statistical significance for the primary endpoint.

The analysis populations are defined as follows:

- Intent-to-Treat (ITT) population will include all subjects who are randomized.
- Per protocol (PP) population will include all subjects in the ITT population, who are at least 80% compliant with study medication application, have a vIGA-AD assessment within the Week 4 visit window, and show no major deviations from the study protocol that would affect the interpretation of efficacy.
- vIGA-AD Moderate ITT population will be a subset of the ITT population with vIGA-AD score 'Moderate' at randomization.

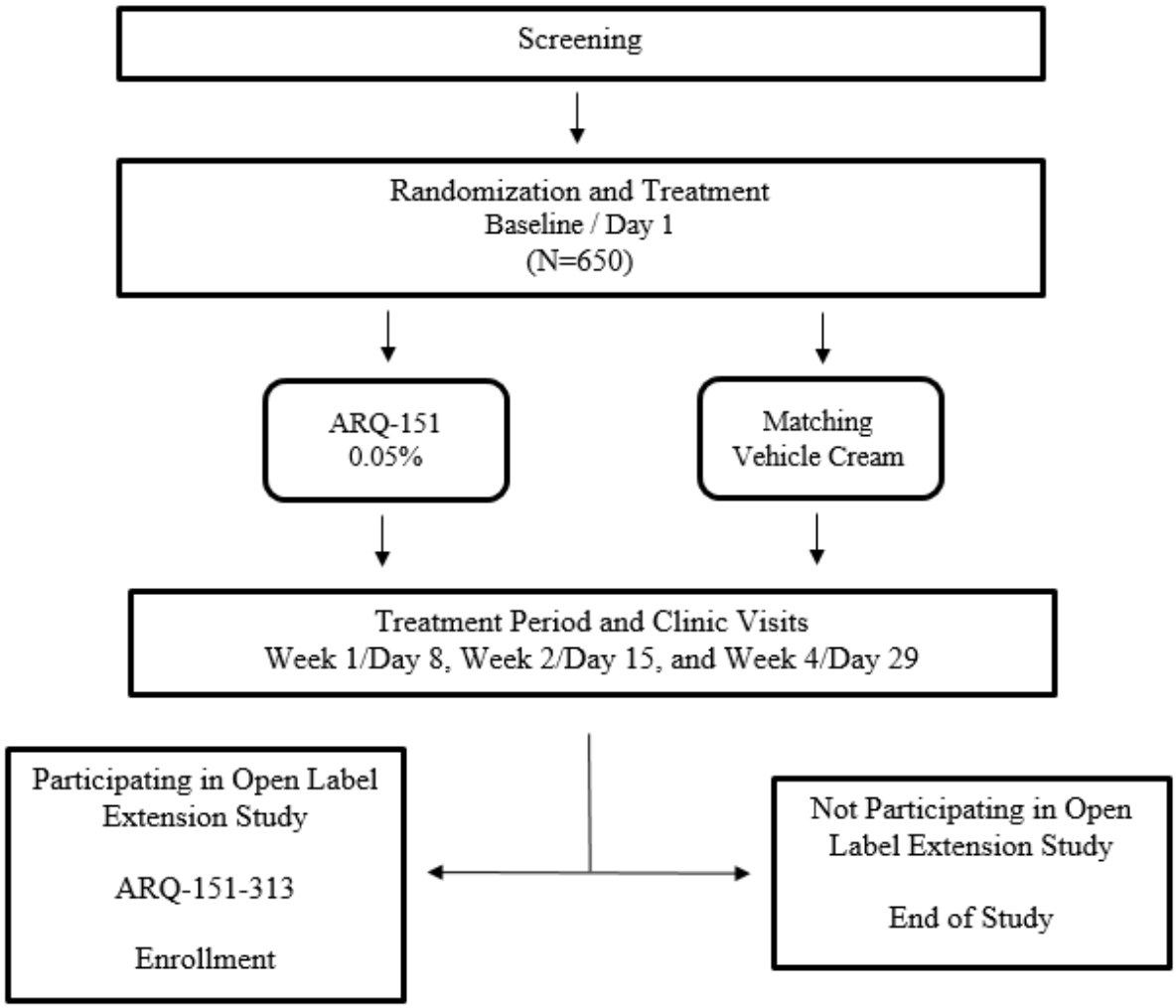
- The WI-NRS population will be a subset of the ITT population who:
  - Parent/caregiver completed at least 4 of 7 evaluable daily WI-NRS questionnaires during the last 7 days of the Screening period;
  - Have a mean baseline WI-NRS score ≥4.0, defined as the average of all non-missing scores reported during the last 7 days of the Screening period.
- Safety population will include all subjects who are enrolled and received at least one confirmed dose of study medication.

Descriptive statistics for continuous variables will include mean, median, standard deviation, Q1, Q3, min, max. Descriptive statistics for categorical variables will include frequencies and percentages. For missing data, the primary imputation method and sensitivity methods will be detailed in the SAP. The primary endpoint and secondary endpoint of vIGA-AD success will be analyzed with a Cochran-Mantel-Haenszel test stratified by disease severity determined by baseline vIGA-AD used to stratify randomization.

Categorical efficacy analysis will be analyzed in the same manner as the primary endpoint.

The incidence of adverse events will be summarized as well as changes in laboratory parameters and vital signs.

1.1. Study Schema



A Phase 3, 4-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.05% Administered QD in Subjects with Atopic Dermatitis

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

- ARQ-151 cream 0.05% 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

2. SCHEDULE OF VISITS AND ASSESSMENTS

Study Procedure	Screen	Baseline Day 1	Week 1 Day 8	Week 2 Day 15	Week 4 Day 29/ET
Visit	**1**	**2**	**3**	**4**	**5**
Visit Window	**-30 days**	**N/A**	**± 3 days**	**± 3 days**	**± 3 days**
Parents/Caregivers informed consent	X				
Demographics	X				
Medical and surgical history	X				
Physical examination[a]	X	X			X
I/E criteria	X	X			
Hematology and Serum Chemistries[b]	X				
Vital signs, weight, height[c]	X	X	X	X	X
vIGA-AD[d], EASI[d], BSA[d], 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 Assessments[g]		X	X	X	X
CDLQI[h], IDQoL[h], DFI[h]	X	X	X	X	X
Medical Photography[i]		X	X		X
Drug application and Parents/Caregivers training in clinic[j]		X	X	X	
Dispense/Redispense investigational product kit[k]		X	X	X	X[l]
Weigh investigational product tubes[l]		X	X	X	X
Dispense/review diary	X	X	X	X	X
Compliance determination[m]			X	X	X
Adverse event assessment[n]	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Study Exit[o]					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. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator.

c. Height will be collected at Screening and Week 4/Day 29. 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). Measure the weight in triplicate and report the average weight in EDC. A 5% weight loss (whether or not intentional or other explained) should be reported to the medical monitor in a timely manner and before the next clinic visit.

Footnotes from above table:

[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.] Parents/guardians/caregivers of children will report pruritus at home on a daily basis starting 7 days prior to the Baseline/Day 1 visit, and then every day thereafter using a diary. WI-NRS score will be determined by 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 each day. Caregiver/parents will be given instructions on how to complete this questionnaire.

[f.] POEM will be completed for all subjects by proxy completion.

[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) and 10-15 minutes post-drug application for the Subject's '0-3' burning/stinging assessment. Parents/guardians will complete assessment for subjects. Subject's burning stinging assessment at Week 4/Day 29 will be provided by a recall assessment of burning/stinging experienced post drug application on the previous day (Day 28). **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.** If a subject is entering ARQ-151-313 Open Label Extension study, then the Subject's '0-3' burning/stinging assessment will be performed as described in the ARQ-151-313 protocol for Baseline/Day 1.

[h.] The CDLQI will be completed by parents/caregivers for subjects ≥4 years of age. The IDQoL will be completed by parents/caregivers for subjects <4 years. The Dermatitis Family Impact Questionnaire (DFI) will be completed by parents/caregivers for all subjects.

[i.] 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.

[j.] Subjects to apply assigned IP during clinic visits, except for the Day 29/ET visit. If a subject is entering ARQ-151-313 Open Label Extension study, then subjects will apply IP as described in the ARQ-151-313 protocol for Baseline/Day 1.

[k.] It is expected that kits will be dispensed based on %BSA affected. See IP Handling Manual for details. 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 using Unscheduled Visits or home delivery of IP, 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 (contact sponsor representative for guidance).

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

[m.] Compliance determination is described in the IP Handling Manual and in Section 6.10.4 of this protocol.

[n.] 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 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 value(s) will be evaluated by the Principal Investigator (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 (if the subject is continuing into the ARQ-151-313 OLE study, then AEs from this study (ARQ-151-315) will only be followed until they exit from this study).

[o.] Subjects who enroll into the open label extension study (ARQ-151-313) must complete the ARQ-151-315 Week 4/Day 29 visit as this visit (Week 4/Day 29) is the Day 1 visit for ARQ-151-313.

TABLE OF CONTENTS

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
AMP	Adenosine Monophosphate
AD	Atopic Dermatitis
AUC	Area Under the Curve
BSA	Body Surface Area
CFB	Change from Baseline
C_{max}	Maximum Concentration
Cm	Centimeter
CDLQI	Children's Dermatology Life Quality Index
CMH	Cochran-Mantel-Haenszel
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
EASI	Eczema Area and Severity Index
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
HCA	Alpha-Hydroxycinnamaldehyde
HPRT	Hypoxanthine-guanine Phosphoribosyl Transferase
Hr	Hour
IB	Investigational Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IDQoL	Infant Dermatology Quality of Life Index
IL	Interleukin
IND	Investigational New Drug

Abbreviation	Definition
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
Kg	Kilogram
LED	Light Emitting Device
LoE	Lack of efficacy
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
MH	Mantel-Haenszel
Min	Minute
mL	Milliliter
MMRM	Mixed Model Repeated Measures
MTD	Maximum Tolerated Dose
MUSE	Maximal Use Systemic Exposure
NCI	National Cancer Institute
NIH	National Institutes of Health
Ng	Nanogram
NOAEL	No Observed Adverse Effect Level
NRS	Numeric Rating Score
NSAID	Nonsteroidal Anti-Inflammatory Drug
P-450	Cytochrome P450
PDE-4	Phosphodiesterase 4
PDMP	Protocol Deviation Management Plan
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
QD	Once Daily ("quaque die")
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation

Abbreviation	Definition
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBD	To Be Determined
TCPS	Tri-Council Policy Statement
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

4. BACKGROUND AND RATIONALE

4.1. Introduction

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

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.

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.

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 a fear of using steroids termed corticosteroid phobia or corticophobia that has been documented in both healthcare providers and patients (Bos 2019).

More recently, Eucrisa® (crisaborole), a PDE-4 inhibitor was approved for the topical treatment of mild to moderate atopic dermatitis in patients 3 months of age and older. 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).

4.2. Nonclinical Studies

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 (DALIRESP PI 2020).

To support the development of ARQ-151 topical cream a GLP-compliant dermal toxicity program has been conducted. To date, no new risks have been identified through the dermal toxicity program. In 13-week dermal toxicity studies in mice and minipigs, and a 39-week dermal toxicity study in minipigs, no evidence of systemic toxicity was observed. The NOAEL in both studies was the 1% concentration of ARQ-151 (20 mg/kg), the highest dose administered and the maximum feasible concentration. Local tolerance studies demonstrated ARQ-151 is not a skin sensitizer or eye irritant, and it does not have phototoxic potential.

4.3. Toxicity Summary

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 is safe.

4.4. Clinical Studies

Topical ARQ-151 cream has been evaluated in both plaque psoriasis (through Phase 3 ongoing) and atopic dermatitis (through Phase 2). The 0.3% concentration is used in psoriasis and the 0.15% and 0.05% concentration is used in atopic dermatitis. The safety data from the psoriasis studies are relevant to the atopic dermatitis development program.

4.4.1. 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 was treated with a single dose application of ARQ-151 cream 0.5% to a 25 cm2 area of psoriatic plaque on the trunk or extremities (not on the face, genital area, palms or soles. Local tolerability and systemic safety labs were monitored. PK assessments were made 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:

- [redacted]

4.4.2. 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]

4.4.3. 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]

4.4.4. 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 consists 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. This cohort of the study is ongoing.

Preliminary Study Results

[redacted]

4.4.5. 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]

[redacted]

4.4.6. 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.

4.5. 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), ARQ-151 cream 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 with mild to moderate atopic dermatitis.

4.5.1. Dose Selection

In ARQ-151-212 (conducted in adult and adolescent subjects), 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 percent 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 further studies of adult and adolescent subjects with mild to moderate AD. [redacted]

4.5.2. Risks and/or Benefits to Subjects

A favorable local and systemic benefit-risk profile has been observed in prior studies of ARQ-151 cream. Subjects 2 to 5 years of age enrolled in this study, randomized to active treatment, may see an improvement in their atopic dermatitis with ARQ-151 cream 0.05%, based on the activity of doses tested in atopic dermatitis (0.05% and 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 of ARQ-151 cream based on a potentially moisturizing effect of the formulation.

Oral roflumilast has been used for almost a decade in the treatment of COPD exacerbations and its safety profile is well-documented. The known adverse effects of oral treatment in the COPD population (nausea, vomiting, diarrhea, weight loss, psychiatric AEs (see Section 4.4.6) can 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, and AE reporting). In addition, parents/caregivers of these subjects 2 to 5 years old will be advised to promptly report any changes in behavior that could signal psychological distress or emotional distress.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1. Study Objectives

5.1.1. Primary Objective

To assess the safety and efficacy of ARQ-151 cream 0.05% vs vehicle administered QD x 4 weeks to children with atopic dermatitis.

5.2. Study Endpoints

5.2.1. Primary Efficacy Endpoints

IGA Success, defined as a vIGA-AD score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at Week 4.

5.2.2. Secondary Efficacy Endpoints

- In subjects with vIGA-AD score of 'Moderate' at randomization, IGA Success at Week 4
- Achievement of at least 75% reduction in the Eczema Area and Severity Index (EASI-75) at Week 4
- vIGA-AD score of 'clear' or 'almost clear' at Week 4

- vIGA-AD Success at Week 2
- vIGA-AD of 'clear' or 'almost clear' at Week 2
- vIGA-AD success at Week 1
- vIGA-AD of 'clear' or 'almost clear' at Week 1

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design and Plan

This is a Phase 3, parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.05% 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 0.05% cream or matching vehicle cream. The randomization will be stratified by vIGA-AD score at baseline ('Mild' vs. 'Moderate'), and by study site.

Caregivers will apply ARQ-151 cream 0.05% or vehicle cream QD to all AD affected areas and any newly appearing AD lesions that arise during the study, except on the scalp. 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/Day 29.

Subject participation involves a minimum of 5 clinic visits including Screening, Baseline/Day 1, Week 1/Day 8, Week 2/Day 15, and Week 4/Day 29. The interval between the Screening and Baseline/Day 1 visits could be up to 30 days, therefore the anticipated maximum duration of subject participation is approximately 8 weeks.

At the Week 4/Day 29 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 and 0.05% QD. All subjects will have the option to enroll into the ARQ-151-313.

6.2. Study Population

Subjects will be male and female children (2-5 years old, inclusive). 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 have a vIGA-AD score of '2'(Mild).

6.3. Number of Subjects

Approximately 650 subjects are planned to be randomized at approximately 109 study sites in the US, Canada, and Poland. During the conduct of the study, additional countries and/or sites may be added if necessary. To test the secondary endpoint of IGA success in subjects with a vIGA-AD score of 'Moderate' at randomization, approximately 490 of the subjects to be accrued

will have vIGA-AD score of 'Moderate' at randomization. Randomization will be stratified by Baseline/Day 1 vIGA-AD score ('Mild' vs. 'Moderate'), and by study site.

6.4. 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.

Randomization will take place at the Baseline/Day 1 visit after the Investigator confirms that the subject meets all eligibility criteria listed in Section 6.6.

Subjects will be randomly assigned to apply ARQ-151 cream 0.05 % QD, or matching vehicle QD. Assignment of drug or vehicle will be made at a 2:1 ratio (drug:vehicle) and stratified by Baseline/Day 1 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.

6.5. Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the Investigator may obtain treatment assignment directly from the IWRS system for that subject. Refer to the current version of the ARQ-151-315 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/parent/caregiver.

6.6. Selection of Study Population

6.6.1. Inclusion Criteria

1. Informed consent of parent(s) or legal guardian as required by local laws.
2. Males and females, ages 2 to 5 years old (inclusive) at time of signing informed consent (Screening) and at Baseline/Day 1.
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 [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 6 weeks as determined by the Investigator through subject interview. Stable disease for the past 4 weeks with no significant flares in atopic dermatitis before screening.
5. EASI Score ≥5 at Baseline/Day1. EASI is evaluated for the entire body except the scalp, palms, and soles.
6. vIGA-AD score of 'Mild' ('2') or '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 at Baseline/Day1 (excluding the scalp, palms, soles).
8. In good health as judged by the Investigator, based on medical history, physical examination, vital signs, serum chemistry labs, and hematology values.
9. 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.

6.6.2. 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.
2. Subjects who cannot discontinue medications and treatments prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 2).
3. Has unstable AD or any consistent requirement for high potency topical steroids to manage AD signs or symptoms.
4. 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 and during the study.
5. Subjects who are unwilling to refrain from prolonged sun exposure for 4 weeks prior to Baseline/Day 1 and during the study.
6. 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.
7. Subjects with known genetic dermatological conditions that overlap with AD, such as Netherton syndrome.
8. Known allergies to excipients in ARQ-151 cream [redacted]

9. 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 visit and during the study period.
10. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, and rifampin and carbamazepine for 2 weeks prior to the baseline visit and during the study period.
11. Subjects who have received oral roflumilast (Daxas®, Daliresp®) within the past 4 weeks prior to Baseline/Day 1.
12. 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)
13. Previous treatment with ARQ-151.
14. 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.
15. Subjects with any serious known medical condition or clinically significant laboratory abnormality that would prevent study participation or place the subject at significant risk, as determined by the Investigator.
16. 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.
17. Any history of cancer.
18. Parent(s)/legal guardian(s) who are unable to communicate, read, or understand the local language(s). Subjects who display any condition which in the Investigator's opinion, makes them unsuitable for clinical study participation.
19. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members of enrolled subjects (subjects enrolled in other studies of ARQ-151) living in the same house.

6.7. Removal of Subjects from Study Treatment or from the Study

6.7.1. Removal of Subjects from Study Treatment

A subject may discontinue study treatment for any of the following reasons:

1. Occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements for investigational product as per the Protocol.
2. Adverse Events as described in Section 7.7. The Investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
3. Parent/Caregiver decision to discontinue treatment with study drug.

6.7.2. Removal of Subjects from the Study

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

- Subject death.
- Parent/Caregiver 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.
- Requirement for use of prohibited concomitant medication after consultation with the Sponsor and Medical Monitor.
- Parent/Caregiver repeated failure to comply with protocol requirements or study related procedures.
- Parent/Caregiver interrupts trial study drug application for more than 50% of scheduled doses.
- Termination of the study by the Sponsor, FDA, or other regulatory authorities

6.8. Replacement of Subjects that Withdraw or are Discontinued from the Study

Subjects that withdraw or are discontinued from the study will not be replaced.

6.9. 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.

Emollients and Moisturizers: 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 (after the shower/bath). The non-medicated emollient or moisturizer can then be applied but only to other untreated areas of the subject's skin (see Section 6.10.3 for additional details).

Table 2: Excluded Medications and Treatments

Excluded Medications and Treatment	**Washout Period Prior to Baseline/Day 1**
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. • 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
Strong cytochrome P-450 CYP3A4 inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin	2 weeks

Table 2: Excluded Medications and Treatments (Continued)

Excluded Medications and Treatment	Washout Period Prior to Baseline/Day 1
Strong cytochrome P-450 CYP3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin, and carbamazepine	2 weeks
Systemic antibiotics	≤15 days
Oral roflumilast (Daxas®, Daliresp®)	4 weeks
All other investigational drugs	4 weeks or 5 half-lives, whichever is longer

Notes:

- 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.
- 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 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.

6.10. Treatment

6.10.1. 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.

6.10.2. 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 = 5 and XX is this study site number such as 01, 02, etc.) and the subject number (YYY). It will be assigned in numerical order, by site, 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.).

6.10.3. Treatment Administration

Initial treatment with the IP will occur on Day 1. ARQ-151 cream 0.05% 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 parent(s)/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 parent(s)/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 parent/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).

Parents/caregivers will be instructed to apply investigational product once daily to all treatment areas identified by the Investigator at Baseline and any new lesions at subsequent visits using a Body Diagram (see Appendix 1).

Note:

- All subjects should receive 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.
- 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 (after the shower/bath). The non-medicated emollient or moisturizer can then be applied but only to other untreated areas of the subject's skin.
- Parents/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 parent/caregiver will be retrained on the study drug application technique.

6.10.4. Treatment Compliance

Investigational product tubes will be weighed at each clinic visit.

Parents/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 Parent/Caregiver 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.

7. STUDY PROCEDURES

The Schedule of Visits and Assessments (Section 2) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below.

7.1. 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, and AEs as outlined in the Schedule of Visits and Assessments (Section 2).

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

7.1.1. Screening

Before a subject's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the subject's parent(s) or legal guardian(s) 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 is completely signed.

During the study, if a subject changes age group, the subject will continue with the assessments specific to their age group at the time of consent at Screening.

The following procedures/assessments will be performed at the Screening Visit (within 30 days 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:
    a. Always burns easily; never tans (sensitive)
    b. Always burns easily; tans minimally (sensitive)
    c. Burns moderately; tans gradually (light brown) (normal)
    d. Burns minimally; always tans well (moderate brown) (normal)
    e. Rarely burns; tans profusely (dark brown) (insensitive)
    f. Never burns, deeply pigmented (insensitive)
- Laboratory tests: hematology and chemistry
- Completion of WI-NRS, CDLQI, IDQoL, DFI, and POEM
- Collection of concomitant medications and serious adverse events

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

7.1.2. 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.

7.1.3. Physical Examination

Physical examinations will be performed according to the Schedule of Visits and Assessments (Section 2). The physical exam will be limited to skin, lungs and heart only.

7.1.4. Vital Signs, Height and Weight

Vital signs will be performed according to the Schedule of Visits and Assessments (Section 2). 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 remove any objects of significant weight (i.e., jackets, outerwear, shoes, cell phones/tablets, 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, 25.1 kilograms). Weight should be measured in triplicate and the average weight reported in EDC. An unexplained, clinically significant weight loss should be reported to the Medical Monitor.

Height will be measured at Screening and Week 4/Day 29.

7.1.5. Laboratory Tests

All tests listed below will be performed according to the Schedule of Visits and Assessments (Section 2) 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.

Hematology	**Serum Chemistry**
Hemoglobin	Blood Urea Nitrogen
Hematocrit	Bilirubin (total and direct)
Total and differential leukocyte count	Alkaline phosphatase
Red blood cell count with indices and morphology	Aspartate aminotransferase
Platelet count	Alanine aminotransferase
	Albumin
	Sodium
	Potassium
	Chloride
	Glucose
	Creatinine (including GFR (Schwartz) or Schwartz creatinine clearance)

7.1.6. Local Tolerability Assessment

The Investigator Local Tolerability Assessment will be performed according to the Schedule of Visits and Assessments (Section 2).

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 sub-investigator 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 2).

The parent/caregiver will assess for the subject 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 Week 4/Day 29, Parents/Caregivers will provide a recall assessment of burning/stinging experienced post drug application on the previous day (Day 28)

7.1.7. Adverse Events

Adverse events (AEs) will be collected and assessed throughout the study according to the Schedule of Visits and Assessments (Section 2). The Investigator is responsible for ensuring that all adverse events observed by the clinical staff or reported by the Parent/Caregiver 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 Parent/Caregiver 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 7.7.1).

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 to Section 7.7 for further details on Adverse Events.

7.2. 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.

7.2.1. Validated Investigator Global Assessment Scale for Atopic Dermatitis (vIGA-AD)

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 2). 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 2). 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, SCORAD).

- **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 Investigational Product application at the site.**

7.2.2. Eczema Area and Severity Index (EASI)

EASI scores (Hanifin 2001) will be performed according to the Schedule of Visits and Assessments (Section 2).

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:

$$EASI = 0.2\,(E_h + I_h + E_{xh} + L_h)\,A_h + 0.2\,(E_u + I_u + E_{xu} + L_u)\,A_u + 0.3\,(E_t + I_t + E_{xt} + L_t)\,A_t + 0.3\,(E_l + I_l + E_{xl} + L_l)\,A_l$$

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, SCORAD, or BSA assessments. EASI is evaluated for the entire body except the scalp, palms, and soles.

7.2.3. 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 parent/caregiver 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").

Date (DD/MMM/YYYY): _____/_____/_____ Time (HH:MM): _____:_____ ☐ AM ☐ PM

Please rate your itching severity by circling the number that best describes your worst level of itching in the past 24 hours:

0 1 2 3 4 5 6 7 8 9 10

0 = No itch **10 = Worst itch imaginable**

WI-NRS Assessments will be performed according to the Schedule of Visits and Assessments (Section 2) starting 7 days prior to the Baseline/Day 1 clinic visit (during the 7 days prior to Baseline/Day 1, the parent/caregiver will record the WI-NRS value every day).

Parents/guardians will be reminded not to review responses from the previous days when completing the WI-NRS. Parent and/or guardian will be trained at the screening visit in the accurate completion of the WI-NRS.

7.2.4. Children's Dermatology Life Quality Index (CDLQI)

CDLQI will be performed according to the Schedule of Visits and Assessments (Section 2). The Children's Dermatology Life Quality Index (CDLQI; ≥4 years old) allows a simple, compact and uniform assessment of patients with skin diseases in general, in which higher scores indicate poorer disease-related quality of life. Parents/caregivers will complete the CDLQI.
See Appendix 3 for the CDLQI.

7.2.5. Infants' Dermatitis Quality of Life Index (IDQOL)

IDQOL will be performed according to the Schedule of Visits and Assessments (Section 2). The Infants' Dermatitis Quality of Life Index questionnaire (Appendix 4) is designed to assess the impact of atopic dermatitis on the quality of life of infants below the age of four years.

It is self-explanatory and should be completed by the child's parent(s) or regular caregiver.

7.2.6. 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 (Appendix 5).

7.2.7. 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.

7.3. Other Evaluations

7.3.1. Body Surface Area (BSA)

BSA assessments will be performed according to the Schedule of Visits and Assessments (Section 2).

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).

7.3.2. 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 (pruritus and insomnia, etc.). See Appendix 6.

7.3.3. 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 7. 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).

7.4. 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 2). 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).

7.5. 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.

7.6. 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)

However, if an unscheduled visit is required for reasons other than safety (e.g. procedures such as labs or images that were either missed at the regular subject visit or need to be repeated), the vIGA-AD and EASI, BSA affected with AD, and Local Tolerability assessment (by Investigator) are not required.

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

7.7. Adverse Events

7.7.1. 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 (e.g., worsening hypertension for a subject with pre-existing hypertension). A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

Progression of treatment 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.

7.7.2. Serious Adverse Event

The definitions and reporting requirements of the Food and Drug Administration (FDA)/ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A will be adhered to. 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.

7.7.3. 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.

7.7.4. 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).

7.7.5. Adverse Event Reporting

The Investigator is responsible for recording all adverse events, observed by the clinic staff or reported by the subject that occur after the first application of investigational product through the end of the study. All SAEs should be reported 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 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 symptoms or value(s) return to normal, or acceptable level, as judged by the PI

(if the subject is continuing into the ARQ-151-313 OLE study, then AEs from this study, ARQ-151-315, will only be followed until they exit from this study).

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]

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 (modified for pediatric subjects) 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. • Definitely not related to drug. • Temporal sequence of an AE onset relative to administration of drug not reasonable. • Another obvious cause of an AE.
Unlikely	• Time sequence is unreasonable. • There is another more likely cause for an AE.
Possibly	• Corresponds to what is known about the drug. • Time sequence is reasonable. • Could have been due to another equally, likely cause.
Probably	• Is a known effect of the drug. • Time sequence from taking drug is reasonable. • Ceases on stopping the drug. • 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). • Time sequence from taking drug is reasonable. • 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. • 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.
AEs will be coded using the most current MedDRA® version 23.0 or later.

7.8. 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 8 and the Laboratory Toxicity Grading section in the appendix for more information).

Parents/caregivers will be advised to promptly report any changes in behavior that could signal psychological distress or emotional distress.

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 6.5). Contact the Medical Monitor and the Sponsor promptly.

8. 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.

8.1. 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.

8.1.1. Determination of Sample Size

Approximately 650 subjects are planned to be randomized in this study. To test the secondary endpoint of IGA success in subjects with a vIGA-AD score of 'Moderate' at randomization, approximately 490 of the subjects to be accrued will have vIGA-AD score of 'Moderate' at randomization. Randomization will be stratified by Baseline vIGA-AD score ('Mild' vs. 'Moderate'), and study site.

This study is designed to differentiate between a vehicle cream treatment that has an IGA success rate of 22% or less and ARQ-151 cream treatment with an IGA success rate of 37% or more. The hypothesis is that the IGA success rate among subjects treated with ARQ-151 cream 0.05% is significantly greater than the IGA success rate among subjects treated with vehicle cream.

This sample size provides more than 90% power to detect 15% difference between treatment groups on vIGA-AD success at Week 4 at α=0.025 using a 2-sided stratified Cochran-Mantel-Haenszel test. The results from a recent Phase 2 study (ARQ-151-212) of ARQ-151 cream 0.05% compared to vehicle treatment were used to estimate the treatment difference. The vIGA-AD success rate at Week 4 was approximately 38% in the ARQ-151 cream 0.05% group compared to 22% in the vehicle. Similarly, approximately 37% of subjects demonstrated vIGA-AD success at Week 4 in the ARQ-151 cream 0.15% group. This sample size also

provides more than 80% power to detect an overall 15% difference between treatment groups on IGA success at Week 4 in 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.

8.1.2. Subjects to Analyze

The analysis populations are defined as follows:

- Intent-to-Treat (ITT) population will include all subjects who are randomized.
- Per protocol (PP) population will include all subjects in the ITT population, who are at least 80% compliant with study medication application, have a vIGA-AD assessment within the Week 4 visit window, and show no major deviations from the study protocol that would affect the interpretation of efficacy.
- vIGA-AD Moderate ITT population will be a subset of the ITT population with vIGA-AD score 'moderate' at randomization.
- The WI-NRS population will be a subset of the ITT population who:
  - Parent/caregiver completed at least 4 of 7 evaluable daily WI-NRS questionnaires during the last 7 days of the Screening period;
  - Have a mean baseline WI-NRS score ≥4.0, defined as the average of all non-missing scores reported during the last 7 days of the Screening period.
- Safety population will include all subjects who are enrolled and received at least one confirmed dose of study medication.

8.1.3. 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.

8.1.4. Investigational Product Application 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.

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.

8.2. Efficacy Evaluation

8.2.1. Statistical Methods

Subjects will be stratified by Baseline vIGA-AD score and by study site, however due to a very low number of subjects in many sites, the analysis model will only stratify by vIGA-AD score stratum.

The primary endpoint will be tested using ITT population.

The primary estimand is described by the following attributes:

Treatment: Roflumilast cream 0.05%

Population: Subjects aged 2-5 years with Atopic Dermatitis

Endpoint: vIGA-AD success at Week 4

Handling of Intercurrent Events: A hybrid strategy will be used for handling intercurrent events. For events other than discontinuation due to AE or lack of efficacy (LoE), the occurrence of the intercurrent event will be considered irrelevant in defining the treatment effect of interest, i.e., the value for the variable of interest is used regardless of whether the intercurrent event occurs. This is the treatment policy strategy. Discontinuation due to an AE or LoE is considered to be informative about the subject's outcome and is incorporated into the definition of the variable. To that end, subjects who discontinue due to LoE or AE will be treated as non-responders for an analysis visit if the study day of the subject's last dose day falls within or prior to the relevant analysis visit window. Analysis visit windows will be defined in the SAP. This is a composite variable strategy.

Population-level Summary: The ratio of the odds of achieving vIGA-AD success after 4 weeks of using roflumilast cream 0.05%, relative to the odds of success after 4 weeks using a matching vehicle cream in the ITT population.

Missing data will be handled with multiple imputation methods (MI). A Cochran-Mantel-Haenszel (CMH) test stratified by the baseline vIGA-AD score used for randomization, will be performed separately for each of the multiply imputed analysis data sets, and results will be combined into one multiple imputation inference. The CMH test will not be stratified by study site as the 650 subjects will be randomized by over 90 sites leading to a low subject to site ratio. The common Mantel-Haenszel (MH) odds ratio and common MH proportion difference, adjusted for baseline vIGA-AD score used for randomization, will be provided along with their associated 97.5% and 95% CIs. Statistical significance will be concluded at the 2.5% significance level (2-sided).

To control for the familywise type I error at level of 0.025, the remaining secondary endpoints will be tested sequentially at an alpha level of 0.025 upon successful demonstration of statistical significance for the primary endpoint. The endpoints listed below will be tested in ITT population unless otherwise noted.

- In subjects with a vIGA-AD score of 'Moderate' at randomization, IGA Success at Week 4
- Achievement of at least 75% reduction in the Eczema Area and Severity Index (EASI-75) at Week 4
- vIGA-AD score of 'clear' or 'almost clear' at Week 4
- vIGA-AD Success at Week 2
- vIGA-AD of 'clear' or 'almost clear' at Week 2
- vIGA-AD success at Week 1
- vIGA-AD of 'clear' or 'almost clear' at Week 1

The ITT population will be used for the primary and secondary efficacy analyses endpoints except the endpoint for subjects with vIGA-AD score of 'Moderate' at baseline, in which vIGA-AD Moderate ITT population will be used.

A supplemental analysis of observed data for the PP population will also be performed for the primary endpoint, vIGA-AD success at Week 4. Descriptive statistics for continuous variables will include mean, median, standard deviation, Q1, Q3, min, max. Descriptive statistics for categorical variables will include frequencies and percentages. For missing data, the primary imputation method and sensitivity methods will be detailed in the SAP. The secondary endpoint of vIGA-AD success in subjects with vIGA-AD of 'Moderate' at randomization will be analyzed with a chi-square test .

Other categorical efficacy endpoints will be analyzed in the same manner as the primary endpoint.

8.2.2. Children's Dermatology Life Quality Index (CDLQI), Infant Dermatology Quality of Life Index (IDQoL), SCORAD and POEM

Children's Dermatology Life Quality Index (CDLQI), the Infant Dermatology Quality of Life Index (IDQoL), 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.

8.3. Safety Evaluation

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.

8.3.1. Adverse Events

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

8.3.2. 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.

8.3.3. 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.

8.3.4. Clinical Laboratory Results and Vital Signs

Clinical safety labs at Week 4 were removed from the study by protocol amendment 1. All clinical laboratory results collected prior to amendment 1 and vital signs measurements, 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 $\geq$5% body weight over the course of the study.

8.3.5. 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.

9. STUDY ADMINISTRATION

9.1. Ethics

9.1.1. 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.

9.1.2. 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).

9.1.3. Subject Information and Consent

The investigator is responsible for obtaining written informed consent from each individual participating and/or their parents/caregivers 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 will be read, appropriately signed and dated by 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.

Parents/caregivers will be given a signed copy of the signed ICF.

9.2. 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.

9.3. Study Completion/Termination

9.3.1. 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.

9.3.2. 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.

9.4. 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.

9.5. 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.

9.6. 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 and Protocol Deviation Management Plan (PDMP).

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 and PDMP.

9.7. 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.

9.8. 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.

9.9. 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).

9.10. 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.

10. REFERENCES

Baumer W, Hoppmann J, Rundfeldt C, et al. Highly selective phosphodiesterase 4 inhibitors for the treatment of allergic skin diseases and psoriasis. *Inflamm Allergy Drug Targets.* 2007;6:17-26.

Berger RS, Bowman JP. A reappraisal of the 21-day Cumulative Irritation Test in man. *J. Toxicol Ot & Ocular Toxicol*. 1982:1(2);109–115.

Bos B, Antonescu I, Osinga H, et al. Corticosteroid phobia (corticophobia) in parents of young children with atopic dermatitis and their health care providers. *Pediatr Dermatol.* 2019;36(1):100-104.

DALIRESP (roflumilast) tablets [package insert]. AstraZeneca Pharmaceuticals LP, Wilmington, DE USA; 2020.

Dastidar SG, Rajagopal D, Ray A. Therapeutic benefit of PDE4 inhibitors in inflammatory diseases. *Curr Opin Investig Drugs*. 2007;8:364–372.

DAXAS (roflumilast) film-coated tablets [product monograph]. AstraZeneca Canada, Inc., Mississauga, Ontario Canada; 2017.

EUCRISA™ (crisaborole) ointment, 2%, for topical use [package insert]. Pfizer Laboratories Div. Pfizer Inc, NY, USA; 2017.

Furue M, Kitahara Y, Akama H, et al. Safety and efficacy of topical E6005, a phosphodiesterase 4 inhibitor, in Japanese adult patients with atopic dermatitis: results of a randomized, vehicle controlled, multicenter clinical trial. *J Dermatol*. 2014;41:577–585.

Grewe SR, Chan SC, Hanifin JM. Elevated leukocyte cyclic AMP-phosphodiesterase in atopic disease: a possible mechanism for cy- clic AMP-agonist hyporesponsiveness. *J Allergy Clin Immunol*. 1982;70:452–457.

Hanifin J.M. and Rajka G. Diagnostic features of atopic dermatitis. *Acta Derm Venereol Suppl (Stockh)*. 1980;92:44–47.

Hanifin JM, Chan SC, Cheng JB, et al. Type 4 phosphodiesterase inhibitors have clinical and in vitro anti-inflammatory effects in atopic dermatitis. *J Invest Dermatol*. 1996;107:51–56.

Hanifin JM, Thurston M, Omoto M, et al. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol*. 2001;10:11–18.

Hatzelmann A, Morcillo EJ, Lungarella G, et al. The preclinical pharmacology of roflumilast – a selective, oral phosphodiesterase 4 inhibitor in development for chronic obstructive pulmonary disease. *Pulm Pharmacol Ther*. 2010;23:235–256.

Investigator's Brochure, Edition 4.0, 22 January 2021.

Michalski JM, Golden G, Ikari J, et al. PDE4: A Novel Target in the Treatment of Chronic Obstructive Pulmonary Disease. *Clin. Pharmacol. Ther*. 2012;91:134–142.

Murrell DF, Gebauer K, Spelman L, et al. Crisaborole topical ointment, 2% in adults with atopic dermatitis: a phase 2a, vehicle- controlled, proof-of-concept study. *J Drugs Dermatol*. 2015;14:1108–1112.

Nazarian R, Weinberg JM. AN-2728, a PDE4 inhibitor for the potential topical treatment of psoriasis and atopic dermatitis. *Curr Opin Investig Drugs*. 2009;10:1236–1242.

Newton et al., Exploring Content and Psychometric Validity of Newly Developed Assessment Tools for Itch and Skin Pain in Atopic Dermatitis. *Journal of Patient-Reported Outcomes*. 2019;3:42.

Nygaard U, Deleuran M, Vestergaard C. Emerging treatment options in atopic dermatitis: topical therapies. *Dermatology*. 2017;233:333–343.

OTEZLA® (apremilast) tablets, for oral use [package insert]. Celgene Corporation, Summit, NJ USA; 2017.

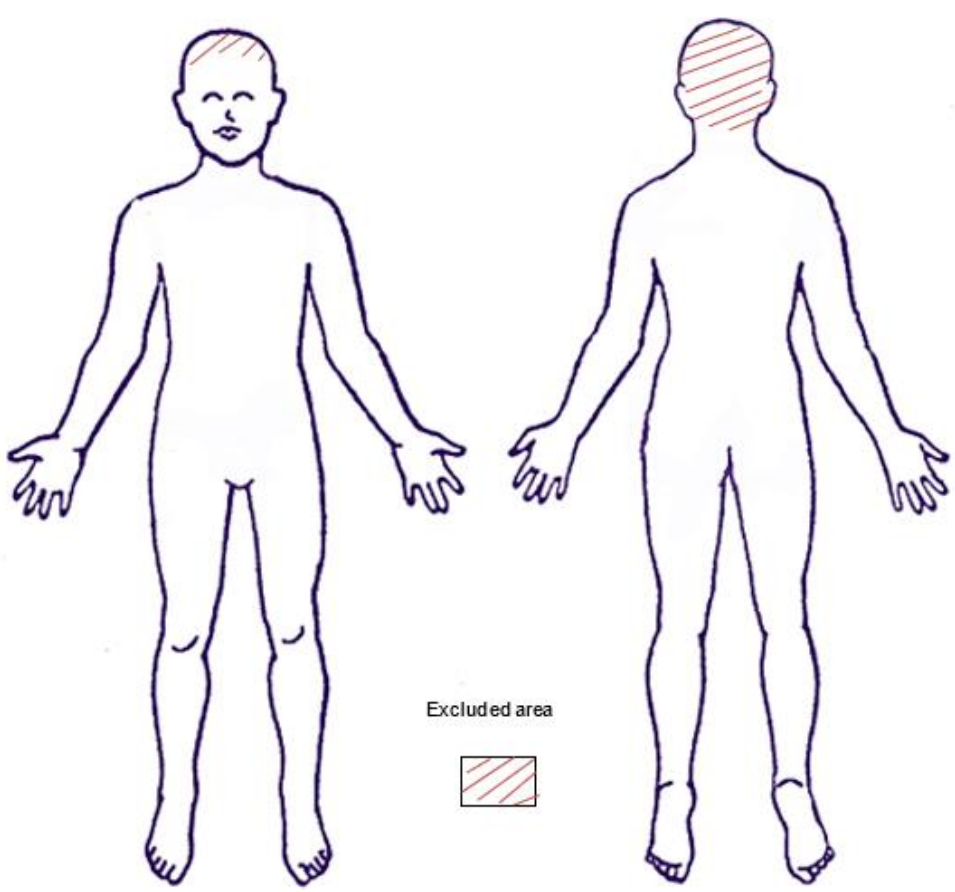
Wedzicha JA, Calverley PMA, Klaus FR. Roflumilast: a review of its use in the treatment of COPD. *Int. J. Chron. Obstruct. Pulmon. Dis.* 2016;11:81–90.

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

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

APPENDIX 4. INFANTS' DERMATITIS QUALITY OF LIFE INDEX (IDQOL)

Name: **Date:** **IDQOL SCORE** ☐
Address:

The aim of this chart is to record how your child's dermatitis has been. Each question concerns THE LAST WEEK ONLY. Please could you answer every question.

Dermatitis Severity

Over the last week, **how severe** do you think your child's dermatitis has been?; i.e. how red, scaly, inflamed or widespread.	Extremely severe	☐
	Severe	☐
	Average	☐
	Fairly good	☐
	None	☐

Life Quality Index

1.	Over the last week, how much has your child been **itching and scratching**?	All the time	☐
		A lot	☐
		A little	☐
		None	☐
2.	Over the last week, what has your child's **mood** been?	Always crying, extremely difficult	☐
		Very fretful	☐
		Slightly fretful	☐
		Happy	☐
3.	Over the last week approximately how much **time** on average has it taken **to get your child off to sleep** each night?	More than 2 hrs	☐
		1 - 2 hrs	☐
		15mins - 1 hr	☐
		0-15mins	☐
4.	Over the last week, what was the **total time** that your child's **sleep was disturbed** on average each night?	5 hrs or more	☐
		3 - 4 hrs	☐
		1 - 2 hrs	☐
		Less than 1 hour	☐
5.	Over the last week, has your child's eczema interfered with **playing or swimming**?	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
6.	Over the last week, has your child's eczema interfered with your child **taking part in** or **enjoying other family activities**?	Very much	☐
		A lot	☐
		A little	☐
		Not at all	☐
7.	Over the last week, have there been problems with your child at **mealtimes** because of the eczema?	Very much	☐
		A lot	☐
		A little	☐
		None	☐

8.	Over the last week, have there been problems with your child caused by the **treatment**?	Very much A lot A little None	□ □ □ □
9.	Over the last week, has your child's eczema meant that **dressing and undressing** the child has been **uncomfortable**?	Very much A lot A little None	□ □ □ □
10.	Over the last week how much has your child having eczema been a problem at **bathtime**?	Very much A lot A little None	□ □ □ □

Please can you check that you have answered every question.

APPENDIX 5. 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.

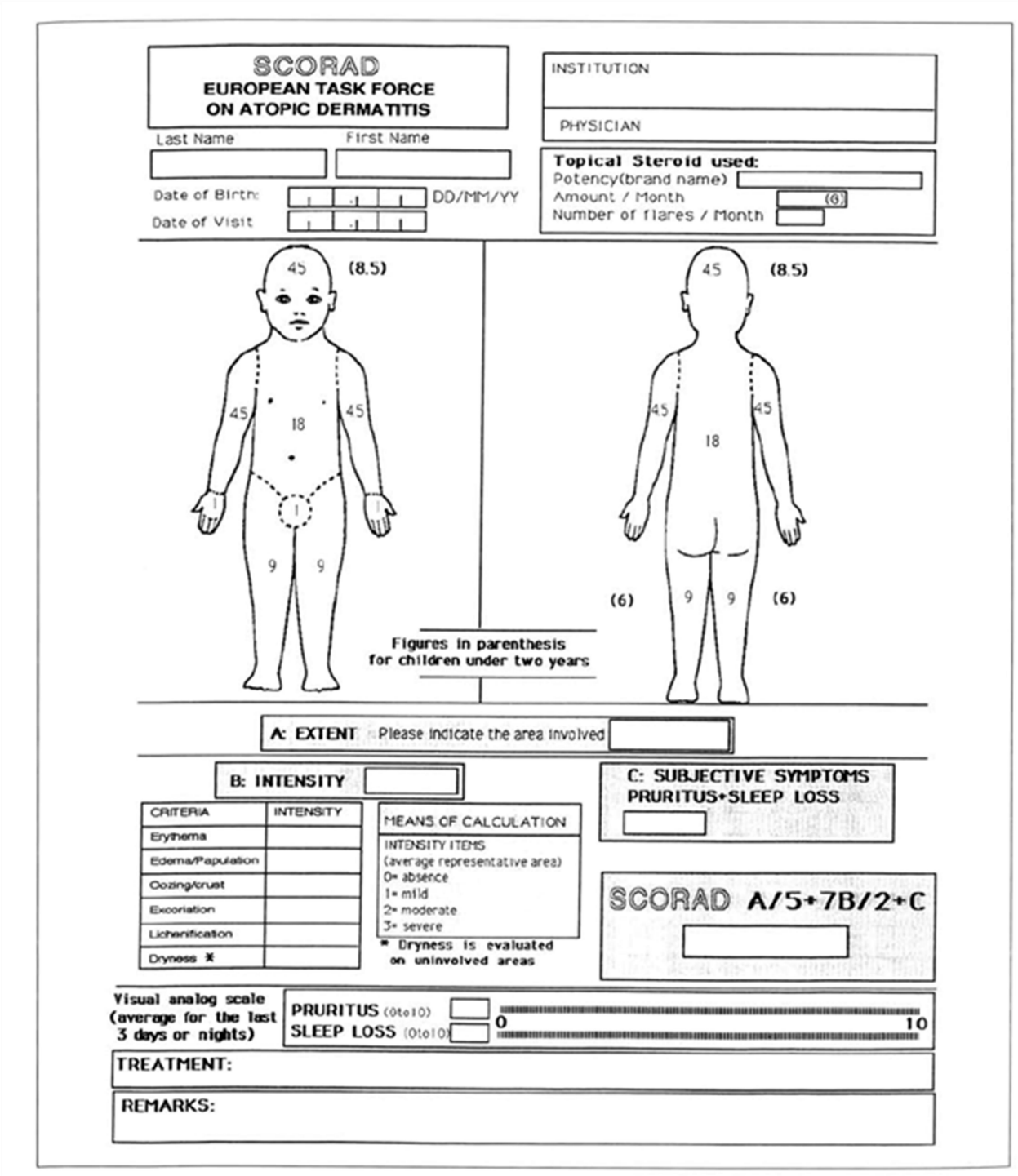
1.	Over the last week, how much effect has your child having eczema had on **housework**, e.g. washing, cleaning.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
2.	Over the last week, how much effect has your child having eczema had on **food preparation** and **feeding**.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
3.	Over the last week, how much effect has your child having eczema had on the **sleep of others in family**.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
4.	Over the last week, how much effect has your child having eczema had on **family leisure activities**, eg swimming.	Very much A lot A little Not at all	❒ ❒ ❒ ❒
5.	Over the last week, how much effect has your child having eczema had on **time spent on shopping for the family.**	Very much A lot A little Not at all	❒ ❒ ❒ ❒
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 A lot A little Not at all	❒ ❒ ❒ ❒
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 A lot A little Not at all	❒ ❒ ❒ ❒
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 A lot A little Not at all	❒ ❒ ❒ ❒

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 A lot A little Not at all	❒ ❒ ❒ ❒
10.	Over the last week, how much effect has **helping with your child's treatment** had on the main carer's life.	Very much A lot A little Not at all	❒ ❒ ❒ ❒

Please check you have answered EVERY question. Thank you

APPENDIX 6. SCORAD

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



APPENDIX 7. 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 8. NIAID DMID TOXICITY TABLE

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, DIVISION OF MICROBIOLOGY AND INFECTIOUS DISEASES (DMID) Toxicity Table for Use in Trials - 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)[1] or QTcB (Bazett's correction)	Asymptomatic, QTc interval 450-479 ms, *OR* Increase in interval<30 ms above baseline	Asymptomatic, QTc interval 480-499 ms, *OR* Increase in interval 30-59 ms above baseline	Asymptomatic, QTc interval ≥500 ms, *OR* 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 FEV_1 < 80% predicted before bronchodilator	Minimal normalization with bronchodilator andFEV_1 <80% predicted after bronchodilator
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities, no treatment	Prevents daily and usual social activity or requires treatment

[1] Inclusion dependent upon protocol requirements

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

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

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

Reactogenicity	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Systemic reactions (Continued)			
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
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 and/or modified for pediatric subjects)

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

Blood, Serum, or Plasma Chemistries [a]	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
Creatinine	N	115-151 (µmol/L)	152-177 (µmol/L)	> 177 (µmol/L)
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

[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.