ARQ-151-212

NCT03916081

Protocol Amendment 2, 05-Aug-2019

Protocol ARQ-151-212

A Phase 2, 4-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.05% and ARQ-151 Cream 0.15% Administered QD in Adolescent and Adult Subjects with Atopic Dermatitis

Sponsor: Arcutis, Inc.
[redacted]

Sponsor Representative: [redacted]

IND Number: 135681

Protocol Version: Amendment 2.0

Date: 05 August 2019

GCP Statement

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

Confidentiality Statement

PROTOCOL REVISION HISTORY

Version/Date	Description
ARQ-151-212 March 27, 2019	Original Protocol
ARQ-151-212 Amendment 1.0 April 15, 2019	• Added Protocol Revision History section. • Updated Inclusion Criterion #8 requiring an additional 1 week of contraception following the last application of study drug. • Updated Exclusion Criterion #11 to clarify exclusion of subjects with moderate to severe liver impairment (Child-Pugh B or C). • Added footnote "n" to the Schedule of Visits and Assessments to clearly note that on Day 29, only the 24-hour PK sample will be collected. No further IP will be applied or dispensed in the study. • Added footnote "o" to the Schedule of Visits and Assessments to clearly note that on Day 8, dispensing of IP is optional. Site should review subject's IP supply to ensure sufficient IP is available until the next visit and only dispense additional IP if needed. • Editorial and administrative changes throughout the protocol to clarify language and formatting to improve readability.
ARQ-151-212 Amendment 2.0 August 05, 2019	• Updated Inclusion Criteria, increasing allowable range of baseline BSA to 1.5% to 35% • Updated Inclusion Criteria, decreasing acceptable history of AD to 4 months, and stable disease for the past 3 weeks with no significant flares in atopic dermatitis before screening • Updated Exclusion Criteria, removing restriction on prior ARQ-151 exposure • Updated Exclusion Criteria, decreasing time since major surgery from 8 weeks to 4 weeks • Updated washout periods, decreasing washout from 2 weeks to 1 week for topical corticosteroids, topical products containing urea, sedating antihistamines, topical antibacterials, calcineurin inhibitors, and Eucrisa®

	(crisaborole) • Revised PK testing plan to include only trough PK sampling for all new subjects enrolled under this amendment • Updated number of sites to approximately 30 • Revised efficacy analysis removing vIGA-AD analyses • Editorial and administrative changes throughout the protocol to clarify language and formatting to improve readability, removed Sponsor and Coordinating PI signature page to a separate standalone document.

1 SITE INVESTIGATOR SIGNATURE PAGE

TITLE: "A Phase 2, 4-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.05% and ARQ-151 Cream 0.15% Administered QD in Adolescent and Adult Subjects with Atopic Dermatitis"

PROTOCOL NUMBER: ARQ-151-212

SPONSOR:	Arcutis, Inc. [redacted]
ORIGINAL ISSUE DATE:	March 27, 2019
AMENDMENT 1.0:	April 15, 2019
AMENDMENT 2.0:	August 05, 2019

I have received and read the investigator's brochure for ARQ-151.

I have read this protocol and commit to conduct the study as outlined herein, in accordance with the current Good Clinical Practices (cGCPs). Any deviations will be agreed to in writing between the Sponsor/CRO and me.

I agree that I or my designee will completely inform all subjects in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with cGCPs and regulatory authority requirements.

I will be responsible for maintaining each subject's consent form in the study file and providing each subject with a signed copy of the consent form.

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

Investigational Site Name: _____ [redacted]

Print Investigator Name: _____

Investigator Signature: [redacted] Date: [redacted]

2 ADDITIONAL KEY CONTACTS FOR THE STUDY

Sponsor Contact for Serious Adverse Event Reporting	
Medical Monitor	
Managing CRO	
Certified Clinical Laboratory	
Bioanalytical Laboratory	
Pharmacokinetic Analysis	
Statistical Analysis	

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4 SYNOPSIS

Compound:	ARQ-151 cream 0.05% and ARQ-151 cream 0.15%
IND	135681
Clinical Indication:	Atopic Dermatitis
Study Phase and Type:	Phase 2 proof of concept study of the safety and efficacy of ARQ-151 cream 0.05% and 0.15% administered QD in adolescent and adult subjects with atopic dermatitis
Study Objectives:	• To assess the safety and efficacy of ARQ-151 cream 0.05% vs ARQ-151 cream 0.15% vs vehicle administered QD x 4 weeks to adolescent and adult subjects with mild to moderate atopic dermatitis. • To evaluate the systemic exposure and characterize the plasma pharmacokinetic (PK) profile of ARQ-151 cream 0.05% and 0.15% and its major N-oxide metabolite, in adolescent and adult subjects with mild to moderate atopic dermatitis.
Summary of Study Design:	This is a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.05% or ARQ-151 cream 0.15% or vehicle is applied QD x 4 weeks to adolescent and adult subjects with atopic dermatitis. A subset of subjects that consented under the previous amendment will have serial PK testing, while only trough PK sampling will be performed for all new subjects enrolled under this amendment.
Blinding:	This study is double blind and vehicle-controlled
Countries:	Canada and United States (for all subjects)
Number of sites:	Approximately 30 sites in the US and Canada
Study Population:	Subjects will be male and female adolescents (12-17 y/o) and adults (≥18 y/o). Subjects will have atopic dermatitis involvement with a vIGA-AD score of '2' (mild) or '3' (moderate) for study entry.
Inclusion Criteria	1. Participants legally competent to sign and give informed consent or, in the case of adolescents, assent with consent of a parent(s) or legal guardian, as required by local laws. 2. Males and females ages 12 years and older (inclusive) at the time of consent. 3. Clinical diagnosis of active atopic dermatitis according to the criteria of Hanifin and Rajka (1980). Subjects must have at least 3 of the 4 basic features (1. Pruritus; 2. Typical morphology and distribution [flexural lichenification in adults and facial and extensor eruptions in infants and children]; 3. Chronic or chronically relapsing dermatitis; or 4. Personal or family history of atopy), in addition to at least 3 minor criteria.

	4. History of AD for at least 4 months as determined by the Investigator through subject interview. Stable disease for the past 3 weeks with no significant flares in atopic dermatitis before screening. 5. BSA involvement of at least 1.5% (excluding the scalp, palms, and soles) but no more than 35%, at Baseline (Visit 2). 6. vIGA-AD score of 'mild' ('2') or 'moderate ('3') at Baseline (Visit 2). vIGA-AD is evaluated for the entire body except the scalp, palms, and soles. 7. Subject has an EASI score of ≥ 5 at Baseline (Visit 2). EASI is evaluated for the entire body except the scalp, palms, and soles. 8. Females of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at Baseline (Visit 2). In addition, sexually active FOCBP must agree to use at least one form of highly effective contraception throughout the duration of the trial and for one week after application of the last dose. Highly effective forms of contraception include: oral/implant/ injectable/transdermal contraceptives, intrauterine device, and partner's vasectomy. If barrier methods are used (e.g., condom with spermicide, diaphragm with spermicide), then 2 forms of contraception are required in association with spermicide. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a lifestyle choice and an acceptable backup method has been identified if the subject becomes sexually active. 9. Females of non-childbearing potential must either be pre-menarchal, or post-menopausal with spontaneous amenorrhea for at least 12 months (post-menopausal status should be confirmed with FSH testing) or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy). 10. Subjects in good health as judged by the Investigator, based on medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), serum chemistry labs, hematology values, and urinalysis. 11. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule, according to the judgment of the Investigator.
Exclusion Criteria	1. Subjects with any serious medical condition or clinically significant laboratory, ECG, 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. Subjects who have 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, 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 (Visit 2). 5. Subjects who are unwilling to refrain from using a tanning bed or other LEDs as well as outdoor tanning or excessive sun exposure for 4 weeks prior to Baseline (Visit 2) 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. 7. Subject has a known or suspected allergy to ARQ-151 or to excipients in ARQ-151 crea [redacted] 8. Subjects who cannot discontinue the use of strong P-450 cytochrome inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin for two weeks prior to the baseline visit and during the study period. 9. Subjects who cannot discontinue the use of strong P-450 cytochrome inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin, and carbamazepine for two weeks prior to the Baseline (Visit 2) and during the study period. 10. Subjects who have received oral roflumilast (Daxas®, Daliresp®) within the past 4 weeks. 11. Known or suspected: • severe renal insufficiency or moderate to severe liver impairment (Child-Pugh B or C) • history of chronic infectious disease (e.g., hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)) • within last 5 years, a history of severe depression, suicidal ideation 12. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.

	13. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of study medication. 14. History of and/or concurrent condition of serious hypersensitivity (anaphylactic shock or anaphylactoid reaction) to PDE-4 inhibitors. 15. Current or a history of cancer within 5 years with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix. 16. Subjects with a history of a major surgery within 4 weeks prior to Baseline (Visit 2) or has a major surgery planned during the study. 17. Subjects who are unable to communicate, read or understand the local language, or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation. 18. Subjects that are family members of the clinical study site, clinical study staff, or sponsor, or family members of enrolled subjects.
Number of Subjects:	Approximately 90 to 105 subjects; randomized 1:1:1 to ARQ-151 cream 0.05% : ARQ-151 cream 0.15% : vehicle and stratified based on IGA score of '2' (mild) or '3' (moderate).
Duration of Participation for Subjects:	Screening (up to 4 weeks) + Treatment phase (4 weeks) for a total of approximately 8 weeks
Study Products:	• ARQ-151 will be supplied as a 0.05% emollient cream and a 0.15% emollient cream • Matching vehicle will contain only excipients of ARQ-151 cream
Planned Dose Level:	Subjects will receive ARQ-151 cream 0.05% QD or ARQ-151 cream 0.15% QD or matching vehicle QD to be applied to all AD affected areas and any newly appearing AD lesions that arise during the study, except the scalp. 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.
Safety Assessments:	• Safety will be monitored through local tolerability assessments, vital signs, safety labs, 12 lead ECGs and AEs. • After obtaining consent, all AEs and TEAEs should be collected. • The investigator, or designee, will perform local tolerability assessments at Baseline (Visit 2), and weeks 1, 2, and 4 (Visits 4, 5, and 7). Subjects will have vital signs measured at each study visit, except for the 24-hour PK sampling visits (Visit 3 and 6) for subjects who agree to serial PK samples collected during the study. Height will be collected at Visit 1 only (Screening).

	• A limited physical exam (skin, lungs, and heart only) will be performed at Visit 1-Screening, Visit 2-Baseline and Visit 7-Day 29. An ECG will be obtained at Visit 1-Screening and Visit 7-Day 29. Blood and urine samples for routine safety laboratory tests (hematology, serum chemistry, and urinalysis) will be obtained at Visit 1-Screening, Visit 2-Baseline and Visit 7-Day 29. For all female subjects of childbearing potential, a urine pregnancy test will be administered at all clinic visits, except for the 24-hour PK sampling visits (Visit 3 and 6) for subjects who agree to serial PK samples collected during the study, and except for Visit 1 (Screening) where a serum pregnancy test will be performed. A negative pregnancy result is required for continued participation in the study, and results (of the urine pregnancy test) must be available prior to dispensing of study drug at study visits. • Safety will also be monitored by PHQ-8 and C-SSRS.
Safety Analysis:	The following analyses will be performed; however, no formal inferential statistics will be done on safety assessments. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. All subjects who are randomized and receive at least one confirmed dose of study drug will be included in the safety population. **Adverse Events:** All adverse events (AEs) reported during the study will be recorded and classified based on MedDRA terminology. Treatment-emergent adverse events (TEAEs) are defined as those AEs with an onset on or after the time of the first study drug application, or AEs that started before but worsened after first drug application. All reported TEAEs will be summarized by the number of subjects reporting TEAEs, system organ class, preferred term, severity, relationship to study drug, and as local to the study drug administration site or as a non-local TEAE. When summarizing TEAEs by severity or relationship to study drug, each subject will be counted only once within a system organ class or a preferred term by using the event with the greatest severity or causality, respectively, within each category. Serious adverse events (SAEs) will be summarized by the number of subjects reporting SAEs, system organ class, preferred term, severity, and relationship to study drug. All information pertaining to AEs reported during the study will be listed by subject, detailing verbatim term given by the Investigator, preferred term, system organ class, start date, stop date, seriousness, severity, action taken regarding study drug, corrective treatment, outcome, and relationship to study drug. In addition, a list of subjects who prematurely discontinued from the study due to an adverse event

	will also be provided. Subset analysis by age group (adolescents and adults) will be conducted. **Medical History, Physical Examinations, Vital Signs, Safety Labs and ECGs:** Medical history will be listed by subject. Clinically significant physical examination parameters will be captured as adverse events. Safety laboratory parameters and vital signs will be summarized at each visit using descriptive statistics or frequencies and percentages, as appropriate. Changes from baseline in laboratory values and vital signs will also be summarized by visit. In addition, changes from baseline in weight and laboratory values will be summarized using shift tables according to normal ranges. For ECGs, interval measurements will be summarized by time point using descriptive statistics. Changes from screening in interval measures will also be summarized. Any ECG abnormalities not present at Baseline will be identified in a listing of ECG abnormalities. Subset analysis by age group (adolescents and adults) will be conducted.
Efficacy Analysis	**The Primary Efficacy Endpoint will be defined as**: • Change from baseline in Eczema Area and Severity Index (EASI) Total Score at Week 4 **The Secondary Efficacy Endpoints will include**: • Percent change from baseline in EASI Total Score at each study visit • Change from baseline in EASI Total Score at Weeks 1 and 2 • Achievement of a 75% or greater improvement in Eczema Area and Severity Index (EASI75) score from baseline to each study visit • Achievement of a 50% or greater improvement in Eczema Area and Severity Index (EASI50) score from baseline to each study visit • Change from baseline in BSA involvement at each study visit • Change from baseline in WI-NRS pruritus score at each study visit • Achievement of a ≥ 4-point improvement from Baseline in WI-NRS pruritus score at each study visit for subjects with a Baseline WI-NRS ≥ 4 Subset analysis by age group (adolescents and adults) will be

	conducted.
Power and Sample Size	There are approximately 90-105 subjects planned for this study. Approximately 30-35 subjects will receive ARQ-151 cream 0.05% QD; approximately 30-35 subjects will receive ARQ-151 cream 0.15% QD; approximately 30-35 subjects will receive vehicle QD. A sample size of 27 per arm will provide at least 80% power to detect a difference in the mean change from baseline in EASI Total Score of 35% at week 4 (for each ARQ-151-treated group versus vehicle-treated group), assuming a pooled standard deviation of 40%, with a two-sided $\alpha = 0.05$. This is based on a 2-sample t-test. This includes P value adjustment for multiplicity using Bonferroni correction. With a 10-25% dropout rate, the sample size for the study would be increased to 30-35 subjects per arm (90-105 subjects total). Change from baseline in EASI Total Score at Week 4 is expected to provide more statistical power than percent change from baseline in EASI Total Score at this timepoint (which is a secondary endpoint) and has been chosen as the primary endpoint.
Pharmacokinetic Sample Collection:	• = For all subjects enrolling under this amendment: • A single pre-dose PK sample will be collected on Days 1 and 29 (trough). For a subset of subjects: • Subjects who consented to optional collection of serial PK samples under the previous amendment will participate in serial PK sampling.

Statistical Analysis:	Four analysis populations will be defined: • Safety population will include all subjects who are enrolled and received at least one confirmed dose of study medication; this population will be defined separately for each cohort. • Intent-to-Treat (ITT) population will include all randomized subjects. • Per-Protocol (PP) Population will include all subjects who are in the safety population, were at least 80% compliant with study medication, and showed no other serious deviations from the study protocol. • PK population will include all subjects receiving the active drug with sufficient plasma concentrations of roflumilast to define a profile, as determined by the pharmacokineticist. <u>Pharmacokinetics Assessment</u> Plasma levels of circulating roflumilast and its major N-oxide metabolite will be measured at the following time points: • Prior to study drug application on Days 1 and 29 • Pre-dose, 1, 2, 4, 6 and 24 hours post-dose administration on Days 1 and 15 (PK subset only for subjects enrolled under the previous amendment) <u>Efficacy Assessment</u> Descriptive statistics for continuous variables will include mean, median, standard deviation, min, max. Descriptive statistics for categorical variables will include frequencies and percents. For missing data, a multiple imputation technique will be detailed in the SAP. The primary endpoint 'EASI CFB' will be analyzed with Mixed Model Repeated Measures (MMRM) analysis with subject as a random effect and vIGA-AD strata, visit, treatment, visit by treatment interaction as fixed effects and baseline as a covariate. The week 4 treatment group comparison will be provided using the appropriate contrast. Continuous secondary efficacy analysis will be analyzed in the same manner as the primary endpoint. Categorical variables (such as proportion with EASI50) will be analyzed using Cochran-Mantel-Haenszel test adjusting for vIGA-AD strata.

5 SCHEDULE OF VISITS AND ASSESSMENTS

STUDY EVENTS FLOW CHART:

Study Procedure	Screen	Baseline Day 1	Day 2, 24-hour PK Collection	Wk 1 Day 8	Wk 2 Day 15	Day 16, 24-hour PK Collection	Wk 4 Day 29
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Window	**-4 weeks**			**+/- 3 days**	**+/- 3 days**		**+/- 3 days**
Informed consent	X						
Demographics	X						
Medical and surgical history	X						
Physical examination[a]	X	X					X
I/E criteria	X	X					
Hematology, Serum Chemistries, and Urine Analysis	X	X					X
12 lead ECG	X						X
Vital signs, height, weight[b]	X	X		X	X		X
vIGA-AD[c], EASI[c], BSA[c]	X	X		X	X		X
WI-NRS pruritus[d]	X	X		X	X		X
Local Tolerability Assessment[e]		X		X	X		X
PHQ-8, C-SSRS	X	X		X	X		X
Optional photography[f]		X		X			X
Serum pregnancy test	X						
Urine pregnancy test[g]		X		X	X		X
PK draws[h]		X	X		X	X	X
Drug/vehicle application in clinic[i]		X		X	X		
Dispense study medication kit[j]		X		X	X		
Dispense/review diary		X		X[o]	X		X[n]
Weigh study medication kit[k]		X		X	X		X
Compliance calculation[l]		X		X	X		X
Adverse event assessment[m]	X	X	X	X	X	X	X
Concomitant medications	X	X		X	X		X

[a] Limited physical examination: skin, lungs, and heart only

[b] Height will be collected at Screening only. Weight will be collected at all study visits. Subject to void prior to weight being taken. Remove any jackets, outerwear and shoes. Remove any objects of significant weight (i.e. cell phones, wallet, key chains). A 5% weight loss should be reported to the medical monitor.

[c] vIGA-AD 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. vIGA-AD should be completed prior to other physician assessments.

[d] Subjects will complete the WI-NRS pruritus questionnaire.

[e] 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.

[f] Photography of AD lesion(s) selected by the Investigator will be performed at some investigational sites. Photography will be optional. All efforts will be made to de-identify the subjects.

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

[h] For the subset of subjects who enrolled under the previous amendment and agreed to the serial PK: on the first day of dosing, PK draws will be done pre-dose (within 1-hour) and at 1, 2, 4, 6 (all ± 20 min) and 24 hours (± 2 hr) post-dose administration. On Day 15, PK draws will be taken at pre-dose (within 1-hour), 1, 2, 4, 6 (all ± 20 min) and 24 hours (± 2 hr) post dose administration. For other subjects: PK draws will be collected at Days 1 and 29. The draws will be pre-dose, ≤ 60 minutes before drug application in the clinic. Ensure study medication is not applied in the area where PK will be drawn. Note: Day 2 and Day 16 visits for 24-hour PK collection only apply to the subset of subjects who agree to the serial PK.

[i] Subjects to apply assigned IP in clinic at every visit.

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

[k] The entire kit should be weighed and recorded at every visit. See IP Handling Manual for details.

[l] Compliance calculation is described in the IP Handling Manual

[m] Any emergent AEs will be followed in the clinic for up to one month at the Investigator's discretion until resolved or otherwise judged as clinically stable.

[n] On Day 29, no further IP will be applied or dispensed.

[o] On Day 8, 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.

6 ABBREVIATIONS

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
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
EASI	Eczema Area and Severity Index
FDA	U.S. Food and Drug Administration
FOCBP	Female of Child Bearing Potential
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
IL	Interleukin
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat

Abbreviation	Definition
kg	Kilogram
LED	Light Emitting Device
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mITT	Modified Intent to Treat
mL	Milliliter
MMRM	Mixed Model Repeated Measures
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
ng	Nanogram
P-450	Cytochrome P450
PDE-4	Phosphodiesterase 4
PHQ-8	Patient Health Questionnaire-8
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
QD	Once Daily ("quaque die")
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
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

7 BACKGROUND AND RATIONALE

7.1 Introduction

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

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

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

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

7.2 Preclinical Studies

Roflumilast was initially developed as a 500 µg tablet for oral therapy in patients with COPD, and as such has been thoroughly evaluated in nonclinical studies. The safety profile is well-established, and the results of those studies are relevant to the dermal roflumilast (ARQ-151 cream) development program. In addition, since roflumilast N-oxide is a major active metabolite, some studies were conducted on the metabolite. [redacted]

[redacted]

7.2.1 Repeat-Dose Toxicity

[redacted]

[redacted]

[redacted]

7.2.2 Reproductive Toxicity

[redacted]

7.2.3 Genotoxicity

[redacted]

7.2.4 Carcinogenicity

[redacted]

7.2.5 Special Toxicity: Local Tolerance of Topical Formulation

Eye Irritation Study

[redacted]

Skin Sensitization Study

[redacted]

Photosensitization Study

[redacted]

7.2.6 Conclusions on Toxicity Findings

[redacted]

[redacted]

7.3 Clinical Studies

7.3.1 Topical Roflumilast Cream

ARQ-151 cream 0.5% and 0.15% have been studied in a Phase 2a study (protocol ARQ-151-101; NCT03392168) in patients with mild to moderate chronic plaque psoriasis in the United States and Canada. The study included two cohorts. Cohort 1 was a single dose study to 25 cm^2 of psoriatic plaque(s) in 8 psoriasis subjects to determine skin permeation. Cohort 1 subjects were then enrolled, if they met entry criteria, into Cohort 2 of the study. Cohort 2 was a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.5%, ARQ-151 cream 0.15% or vehicle cream was applied QD for 28 days to 89 subjects with 0.5% to 5.0% BSA of chronic plaque psoriasis. Cohort 2 subjects had at least one target plaque of psoriasis of at least 9 cm^2 Target Plaque Area (TPA) in size and with a Target Plaque Severity Score (TPSS) ≥ 4. However, all body psoriasis plaques were treated except for the face, scalp, intertriginous areas and palms/soles. Only safety and pharmacokinetics were evaluated for the single dose Cohort 1 subjects.

In the parallel group assessment (Cohort 2), the Primary Efficacy Endpoint was:

- Difference in mean percent change from baseline at week 4 in the product of TPSS x TPA between each dose concentration level of ARQ-151 cream and vehicle control. This was assessed as a sum of up to 3 target plaques per subject.

Efficacy and safety results of ARQ-151-101 are as follows:

- [redacted]

[redacted]

[redacted]

7.3.2 Oral Roflumilast Tablet

Oral roflumilast (DALIRESP®, a 500 µg tablet) 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, other than hypersensitivity to components of the product, is in patients with moderate to severe liver impairment (Child-Pugh B or C), where systemic levels of roflumilast may become highly elevated.

7.4 Rationale for Development

Atopic dermatitis is currently treated with topical calcineurin inhibitors and/or topical corticosteroids in combination with emollients. In 2016, Eucrisa® (crisaborole), a less potent PDE-4 inhibitor than roflumilast, was approved for the topical treatment of atopic dermatitis. Topical calcineurin inhibitors block the activation of T-lymphocytes and diminish inflammation, but are accompanied by a 'black box' warning for the development of lymphomas and other lymphoproliferative diseases. Topical corticosteroids can cause skin atrophy and hypothalamic-pituitary axis suppression, and their use is often accompanied by poor adherence due to corticophobia (fear of using corticosteroids in patients or doctors). Eucrisa provides precedence for the effectiveness of topical PDE-4 inhibitors in atopic dermatitis, but it is a twice-daily ointment, its efficacy is modest, and its use is often accompanied by burning, stinging, and local skin reactions. [redacted]

The study here will evaluate the safety, efficacy, and PK of ARQ-151 cream 0.15% and ARQ-151 cream 0.05% in adolescent and adult subjects with mild to moderate atopic dermatitis.

7.4.1 Dose Selection

[redacted]

[redacted]

7.4.2 Risks and/or Benefits to Subjects

[redacted]

The safety monitoring practices employed in this protocol (i.e., physical examinations, vital signs/weight, 12-lead ECGs, local skin toleration assessments, hematology, serum chemistry, urinalysis, mood disorder questionnaires, and AE questioning) are adequate to protect the subjects' safety and will detect expected AEs.

Oral roflumilast has now been used for almost a decade in the treatment of COPD exacerbations and its safety record has been well-documented. The known adverse effects of oral treatment in the COPD population (nausea, vomiting, diarrhea, weight loss, psychiatric AEs; see Section 7.3.2) are readily monitorable. The current protocol is designed to detect these adverse events and others should they occur, and provides guidance for their management, as necessary, to ensure patient safety.

8 STUDY ENDPOINTS AND OBJECTIVES

8.1 Study Objectives

8.1.1 Primary Objectives

To assess the safety and efficacy of ARQ-151 cream 0.05% vs ARQ-151 cream 0.15% vs vehicle administered QD x 4 weeks to adolescent and adult subjects with mild to moderate atopic dermatitis.

To evaluate the systemic exposure and characterize the plasma pharmacokinetic (PK) profile of ARQ-151 cream 0.05% and 0.15% and its major N-oxide metabolite, in adolescent and adult subjects with mild to moderate atopic dermatitis.

8.2 Study Endpoints

8.2.1 Primary Endpoints

The Primary Efficacy Endpoint will be:

- Change from baseline in Eczema Area and Severity Index (EASI) Total Score at Week 4

8.2.2 Secondary Endpoints

The Secondary Efficacy Endpoints will include:

- Percent change from baseline in EASI Total Score at each study visit
- Change from baseline in EASI Total Score at Weeks 1 and 2
-
-
- Achievement of a 75% or greater improvement in Eczema Area and Severity Index (EASI75) score from baseline to each study visit
- Achievement of a 50% or greater improvement in Eczema Area and Severity Index (EASI50) score from baseline to each study visit
- Change from baseline in BSA involvement at each study visit
- Change from baseline in WI-NRS pruritus score at each study visit
- Achievement of a ≥4-point improvement from Baseline in WI-NRS pruritus score at each study visit for subjects with a Baseline WI-NRS ≥ 4

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a phase 2, parallel group, double blind, vehicle-controlled study of ARQ-151 cream 0.15% and ARQ-151 cream 0.05% QD applied for 4 weeks to adolescent and adult subjects with 1.5% to 35% BSA of mild to moderate atopic dermatitis. A subset of subjects that consented under the previous amendment will have serial PK testing, while only trough PK sampling will be performed for all new subjects enrolled under this amendment.

A total of up to approximately 90 to 105 subjects will be enrolled at approximately 30 study sites in the United States and Canada. Subjects will be adolescent (12-17 y/o) or adult (≥18 y/o) males or females with atopic dermatitis. Subjects must have an Investigator's Global Assessment of disease severity (vIGA-AD) of Mild ('2') or Moderate ('3') at Baseline. Subjects must have at least 1.5% and no more than 35% BSA of atopic dermatitis (excluding scalp, palms, and soles). 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).

9.2 Subject Participation

Subject participation involves a minimum of 5 clinic visits including Screening, Baseline, Week 1, Week 2, and Week 4. For the subset of subjects enrolled under the previous amendment and consented to participate in serial PK sampling, 2 additional clinic visits include 24 hour PK collection after Baseline on Day 2 and 24 hour PK collection after Week 2 on Day 16. The interval between the Screening and Baseline visits could be up to 4 weeks, therefore the anticipated maximum duration of subject participation is ~8 weeks.

9.3 Randomization

Subjects will apply ARQ-151 cream 0.15% QD or ARQ-151 cream 0.05% QD or vehicle cream QD. Assignment of drug or vehicle will be made at a 1:1:1 ratio and stratified based on vIGA-AD score of '2' (mild) or '3' (moderate) according to a computer-generated randomization list. Randomization will take place at Baseline after the patient has been found to be fully eligible for participation. 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.

9.4 Numbering of Subjects

All screened subjects will be identified by a unique five-digit subject ID number. The first two digits correspond to the site number (assigned by the Sponsor, e.g., 01 to 15), the next three digits correspond to the sequential order in which the subject is screened for the study (e.g., Subject ID 05001: Site 5, subject number 1 screened by that site).

The clinical site is responsible for maintaining a current log of subject ID number assigned to that subject. The subject ID number 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.).

9.5 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 has received.

9.6 Selection of Study Population

9.6.1 Inclusion Criteria

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

1. Participants legally competent to sign and give informed consent or, in the case of adolescents, assent with consent of a parent(s) or legal guardian, as required by local laws.
2. Males and females ages 12 years and older (inclusive) at the time of consent.
3. Clinical diagnosis of active atopic dermatitis according to the criteria of Hanifin and Rajka (1980). Subjects must have at least 3 of the 4 basic features (1. Pruritus; 2. Typical morphology and distribution [flexural lichenification in adults and facial and extensor eruptions in infants and children]; 3. Chronic or chronically relapsing dermatitis; or 4. Personal or family history of atopy), in addition to at least 3 minor criteria.
4. History of AD for at least 4 months as determined by the Investigator through subject interview. Stable disease for the past 3 weeks with no significant flares in atopic dermatitis before screening.
5. BSA involvement of at least 1.5% (excluding the scalp, palms, and soles) but no more than 35%, at Baseline (Visit 2).
6. vIGA-AD score of 'mild' ('2') or 'moderate ('3') at Baseline (Visit 2). vIGA-AD is evaluated for the entire body except the scalp, palms, and soles.
7. Subject has an EASI score of ≥ 5 at Baseline (Visit 2). EASI is evaluated for the entire body except the scalp, palms, and soles.
8. Females of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at Baseline (Visit 2). In addition, sexually active FOCBP must agree to use at least one form of highly effective contraception throughout the duration of the trial and for one week after application of the last dose. Highly effective forms of contraception include: oral/implant/injectable/transdermal contraceptives, intrauterine device, and partner's vasectomy. If barrier methods are used (e.g., condom with spermicide, diaphragm with spermicide), then 2 forms of conception are required in association with spermicide. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a lifestyle choice and an acceptable backup method has been identified if the subject becomes sexually active.

9. Females of non-childbearing potential must either be pre-menarchal, or post-menopausal with spontaneous amenorrhea for at least 12 months (post-menopausal status should be confirmed with FSH testing) or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy).
10. Subjects in good health as judged by the Investigator, based on medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), serum chemistry labs, hematology values, and urinalysis.
11. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule, according to the judgment of the Investigator.

9.6.2 Exclusion Criteria

1. Subjects with any serious medical condition or clinically significant laboratory, ECG, 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. Subjects who have 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, 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 (Visit 2).
5. Subjects who are unwilling to refrain from using a tanning bed or other LEDs as well as outdoor tanning or excessive sun exposure for 4 weeks prior to Baseline (Visit 2) 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.
7. Subject has a known or suspected allergy to ARQ-151 or to excipients in ARQ-151 cream [redacted]
8. Subjects who cannot discontinue the use of strong P-450 cytochrome inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin for two weeks prior to the baseline visit and during the study period.
9. Subjects who cannot discontinue the use of strong P-450 cytochrome inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin,

rifampin, and carbamazepine for two weeks prior to the Baseline (Visit 2) and during the study period.

10. Subjects who have received oral roflumilast (Daxas®, Daliresp®) within the past 4 weeks.
11. Known or suspected:
    - severe renal insufficiency or moderate to severe liver impairment (Child-Pugh B or C)
    - history of chronic infectious disease (e.g., hepatitis B, hepatitis C, or human immunodeficiency virus (HIV))
    - within last 5 years, a history of severe depression, suicidal ideation
12. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.
13. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of study medication.
14. History of and/or concurrent condition of serious hypersensitivity (anaphylactic shock or anaphylactoid reaction) to PDE-4 inhibitors.
15. Current or a history of cancer within 5 years with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix.
16. Subjects with a history of a major surgery within 4 weeks prior to Baseline (Visit 2) or has a major surgery planned during the study.
17. Subjects who are unable to communicate, read or understand the local language, or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation.
18. Subjects that are family members of the clinical study site, clinical study staff, or sponsor, or family members of enrolled subjects

9.7 Removal of Subjects from the Study

Subject participation in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the Protocol.

2. Occurrence of a treatment-emergent adverse event (TEAE) or considerable worsening of an AE that, in the opinion of the investigator in consultation with the Medical Monitor and Sponsor, represents an unacceptable risk to the subject if he/she continues in the study. The investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
3. Pregnancy.
4. Subject's decision to withdraw.
5. Weight loss of >5% if not dieting and after consultation with the Sponsor, at the Investigator's discretion.
6. C-SSRS indicative of suicidal ideation or a PHQ-8 score ≥15, after consultation with a mental health professional, the Sponsor, and at the Investigator's discretion.
7. Requirement for use of prohibited concomitant medication after consultation with the Sponsor and Medical Monitor.
8. Subject's repeated failure to comply with protocol requirements or study related procedures.
9. The subject interrupts trial study drug application for more than 50% of scheduled doses.
10. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

9.8 Replacement of Subjects that Withdraw or are Discontinued from the Study

Subjects that withdraw or are discontinued from the study prior to Final Study Visit (see Section 10.4), may be replaced.

9.9 Prohibitions and Concomitant Therapy

Prohibited medications and products are detailed in Table 1 (Excluded Medications and Treatments).

Table 1. Excluded Medications and Treatments

Excluded Medications and Treatments	Washout Period Prior to Day 1
Biologics including dupilumab and investigational biologics	12 weeks or 5 half-lives, whichever is longer
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 in a stable regimen is allowed.	4 weeks
PUVA or NBUVB phototherapy	4 weeks
Topical products containing urea	1 week
Sedating antihistamines	1 week
Topical corticosteroids, calcineurin inhibitors, or Eucrisa®. Topical antibacterial medications or products, including soaps, bleach baths, or sodium hypochlorite-based products anywhere on the body.	1 week
Strong P-450 cytochrome inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin	2 weeks
Strong P-450 cytochrome inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin, and carbamazepine	2 weeks
Systemic antibiotics	2 weeks
Tanning beds, other light emitting devices	4 weeks
Oral roflumilast (Daxas®, Daliresp®)	4 weeks
All other investigational drugs	4 weeks or 5 half-lives, whichever is longer

Note:

- 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, moisturizers and sunscreens will be allowed once daily in a stable regimen as normally used by the subjects and applied at least 2 hours after application of randomized study drug to untreated areas only.
- Concomitant other medications for chronic conditions (eg, NSAIDs, statins, anti-hypertensives) are permitted unless specifically prohibited in the Protocol.
- Topical antibiotics or any other topical agents are not allowed to be applied to treated areas. Only study drug should be applied to treated areas.

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. 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 Case Report Forms. Medications which have been used chronically by subjects, in particular statins and anti-hypertensives, are allowed for use during the study, except as prohibited in 'Exclusions' (Table 1).

9.10 Treatment

9.10.1 Drug Supplies, Packaging and Labeling

ARQ-151 cream or vehicle cream will be in squeeze tubes that dispense approximately 45 grams of cream. 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 AD. 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 (ARQ-151 cream 0.15%, ARQ-151 cream 0.05%, and matching vehicle cream) 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 unused study drugs will be returned to the Sponsor or designee, or destroyed, as per Sponsor instructions.

9.10.2 Treatment Administration

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

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

Subjects will be instructed to apply study medication once daily to all treatment areas identified by the investigator at Baseline using a Body Diagram (see Appendix 1).

Note:

- All subjects should apply medication each evening (except on clinic visit days) at least 15 minutes after showering or bathing (if they take an evening shower/bath) and then not wash areas where ARQ-151 cream or vehicle has been applied until at least 4 hours after study drug application and preferably not until the following morning. Study medication should be applied at least 20 minutes before going to bed.
- 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 Day 29.
- 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 study medication tube will be weighed prior to dispensing at the baseline visit or subsequent visits. Study medication tubes must be returned by subjects at each study visit, both empty and full, and will be weighed. If the subject's actual use is substantially different than the expected use for the subject's BSA (see IP Handling Plan), the subject will be retrained on the study drug application technique.

9.10.3 Treatment Compliance

Study medication tubes will be weighed at each follow-up clinic visit.

Subjects will complete a daily diary recording the date and time of each dose applied, any missed doses, and a comment section should the subjects have a comment, e.g., record potential AEs. Site personnel will review the diaries and use the information to question the subject regarding compliance and AEs and then record appropriate information in source documents and complete Case Report Forms (CRFs). If a subject misses a dose, they should be instructed to return to the protocol study medication administration schedule (i.e. if subject forgets a dose they should wait until that evening and apply as usual).

A subject will be considered compliant with the dosing regimen if the subject applies at least 80% of the expected applications during the study drug application period and does not miss more than 3 consecutive doses.

Compliance will be assessed by review of the dosing diary. Weight of study medication applied will be measured for reporting purposes.

If the diary shows less than 80% of expected use, the subject is using too little study drug and retraining must be conducted and documented.

Compliance will be documented in source and in eCRF.

10 STUDY PROCEDURES

10.1 Safety Assessments

The Schedule of Visits and Assessments (Section 5) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI and/or the Sponsor for reasons related to subject safety.

This study assesses the safety, efficacy, and pharmacokinetics of ARQ-151 cream. Safety will be determined by evaluating physical examinations, 12-lead ECGs, local tolerability assessments, vital signs/weight, clinical laboratory parameters and AEs as outlined in the Schedule of Visits and Assessments (Section 5). If deemed necessary, additional safety assessments will be performed at the discretion of the PI.

10.1.1 Screening

Within 4 weeks prior to the first dosing, subjects will be provided details of study requirements and sign an informed consent. Medical history and demographic data including sex, age, race, ethnicity, body weight (kg), and height (cm) will be recorded. Each subject will undergo atopic dermatitis assessments, a physical examination, ECG, vital sign measurements (blood pressure, heart rate, and temperature) and laboratory tests: hematology, chemistry, urinalysis and a pregnancy test for female subjects of child bearing potential. Abnormal or questionable serum chemistry tests may be repeated at the discretion of the Investigator.

All screened subjects will receive a screening number and be entered into the study tracking document.

10.1.2 Physical Examination

Physical examinations will be performed as follows: Screening, Baseline, and Week 4.

The physical exam will be limited to skin, lungs and heart only.

10.1.3 Vital Signs, Height and Weight

Vital signs will be collected (in seated position after 5 mins) at timepoints noted below:

Weight, blood pressure, heart rate, and temperature will be measured at Screening, Baseline, Week 1, Week 2, and Week 4.

Height will be measured at Screening only.

10.1.4 12-lead ECGs

12-lead ECGs will be performed as follows: Screening and Week 4.

ECGs will be performed on subjects after 5 minutes in the supine position. All ECG tracings and readouts will be reviewed by the central reader at the ECG laboratory.

10.1.5 Laboratory Tests

All tests listed below will be performed as follows:

Screening, Baseline, and Week 4.

All tests listed below will be performed according to the Study Events Flow Chart unless otherwise noted. The collection of specimens will be in a non-fasting state (no food restrictions). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Hematology

- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count with indices and morphology
- Platelet count

Serum Chemistry

- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Albumin
- Sodium
- Potassium
- Chloride
- Glucose
- Creatinine

Urinalysis

- pH
- Specific gravity
- Protein*
- Glucose
- Ketones
- Bilirubin
- Blood*
- Nitrite*
- Urobilinogen
- Leukocyte esterase*

Additional Tests

- Urine pregnancy test**
  (for females of child bearing potential only)
- Serum pregnancy test (hCG)***
- FSH test, if indicated

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

** At baseline, Week 1, Week 2, and Week 4 for FOCBP only

*** At screening only

10.1.6 Patient Health Questionnaire Depression Scale (PHQ-8)

The 8 item PHQ-8 Assessment (see Appendix 3) will be performed as follows: Screening, Baseline, Week 1, Week 2, and Week 4.

A subject with a PHQ-8 score of '15' or above should be referred promptly to a mental health care professional and, if currently applying study drug, consideration be given to discontinuation from study drug.

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

Five severity categories of depression are defined as follows:

- None – Minimal depression (1 to 4)
- Mild depression (5 to 9)
- Moderate depression (10 to 14)
- Moderately severe depression (15 to 19)
- Severe depression (20 to 27)

10.1.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

C-SSRS Assessments will be performed as follows: Screening, Baseline, Weeks 1, 2, and 4.

The administration schedule of the C-SSRS will be:

- The Baseline-Screening version (Appendix 5) will be used at Screening to provide a pre-treatment assessment baseline.
    - If a subject has a score greater than 0 in suicidal ideation, this is important and may indicate the need for mental health intervention. The investigator should give consideration to not enrolling the subject in the study.

- On all subsequent visits, the Since Last Visit version (Appendix 6) will be used.
    - Any score greater than 0 in the suicidal ideation score is important and may indicate the need for mental health intervention and consideration be given to discontinuation from study drug. This should result in prompt referral to a mental health professional and/or possibly the emergency room. The Medical Monitor should be contacted.

Subjects will complete the C-SSRS.

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

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

10.1.8 Local Tolerability Assessment

Investigator Local Tolerability Assessment will be performed as follows: Baseline, Week 1, Week 2, and Week 4.

Application site reactions will be graded at the timepoints outlined in the Schedule of Visits and Assessments (Section 5). 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 AD.

The investigator assessments will be conducted by the 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 as follows: Baseline, Week 1, Week 2.

This assessment will be administered by the site 10 to 15 minutes after study drug application in the clinic at Baseline and at Weeks 1 and 2.

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

10.1.9 Adverse Events

Adverse events (AEs) will be collected beginning at informed consent signature.

Any treatment emergent AEs will be followed in the clinic for up to one month at the Investigator's discretion until resolved or otherwise judged as clinically stable.

For further details on Adverse Events please see Section 10.7.

10.2 Efficacy Evaluations

10.2.1 Eczema Area and Severity Index (EASI)

EASI scores (Hanifin, et al. 2001) will be performed as follows: Screening, Baseline, Week 1, Week 2, and Week 4.

The EASI is a static assessment to measure the severity and extent of AD. EASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease).

The body is divided into four sections (head (h) (10% of a person's skin); arms (a) (20%); trunk (t) (30%); legs (l) (40%)). Each of these areas is scored by itself, and then the four scores are combined into the final EASI.

For each section, the percent of area (A) of skin involved is estimated and then transformed into a grade from 0 to 6 (A):

0. 0% of involved area
1. < 10% of involved area
2. 10–29% of involved area
3. 30–49% of involved area
4. 50–69% of involved area
5. 70–89% of involved area
6. 90–100% of involved area

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

Within each area, the severity is estimated by four clinical signs: Redness (erythema, inflammation), Thickness (induration, papulation, swelling – acute eczema), Scratching (excoriation), and Lichenification (lined skin, furrowing, prurigo nodules – chronic eczema). Severity parameters are measured on a scale of 0 to 3, from none to severe.

To calculate the EASI, the sum of the severity rating for the four clinical signs are multiplied with the numerical value of the area affected and with the various percentages of the four body areas (see Appendix 4).

10.2.2 Validated Investigator Global Assessment scale for Atopic Dermatitis

Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD) assessments will be performed as follows: Screening, Baseline, Week 1, Week 2, and Week 4.

The vIGA-AD should be completed prior to other physician assessments.

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 Table below). 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).

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:

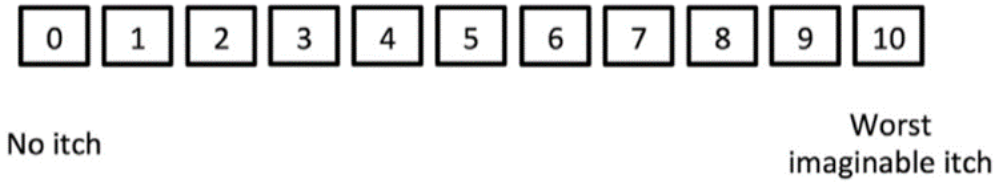
- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*

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

10.2.3 Worst Itch Numerical Rating Scale (WI-NRS)

WI-NRS Assessments will be performed as follows: Screening, Baseline, Week 1, Week 2, and Week 4.

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



10.3 Other Evaluations

10.3.1 Body Surface Area (BSA)

BSA Assessments will be performed as follows: Screening, Baseline, Week 1, Week 2, and Week 4.

The BSA affected by 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 (BSA).

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, IGA, BSA).

Body Diagram

The body diagram (see Appendix 1) will be completed as follows: Baseline.

A copy of the body diagram will be provided to the subject for study drug application at home.

10.3.2 Pharmacokinetics Assessment

PK draws will be performed as follows for all subjects at all sites:

- For the serial PK subset enrolled under the previous amendment: On the first day of dosing, PK draws will be done pre-dose and at 1, 2, 4, 6 and 24 hours post-dose administration. On Day 15, PK draws will be taken at pre-dose, 1, 2, 4, 6, and 24 hours post-dose administration
- For all subsequent subjects enrolled under this amendment: PK draws will be collected at Days 1 and 29. The single draw will be pre-dose drug application in the clinic.

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

10.4 Final Study Visit

The approximate final study visit will occur at Week 4 (Day 29). The procedures performed during these visits are as described in Schedule of Events (Section 5). A 3-day scheduling leeway period is allowed for this visit.

10.5 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 visit (Day 29).

10.6 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

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

10.7 Adverse Events

10.7.1 Adverse Event Definition

An AE means 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.

AEs will be collected following informed consent of the subject until one month after treatment.

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.

Application site reactions will be considered adverse events if they require intervention, suspension or discontinuation of study drug.

10.7.2 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. If any AEs are serious, as defined by ICH Guidelines for Clinical Safety, required procedures will be followed. All 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. 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.

An SAE is any AE that in the view of either the PI or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE that in the view of the PI or Sponsor, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

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 elsewhere in the current IND.

If a SAE occurs to a subject on this study, contact the Sponsor personnel listed in Section 2 within one business day of knowledge of event.

10.7.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

This 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.

10.7.4 Safety Review with Subject

At each follow-up 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 up 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 PI.

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).

10.7.5 Adverse Event Reporting

The PI will review each event and assess its relationship to drug treatment (unrelated, unlikely, possibly, probably, likely). Each sign or symptom reported will be graded on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5). The date and time of onset, time relationship to drug dosing, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted.

- The relationship of each AE to the study drug 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.
* Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

10.8 Reporting Pregnancy

During the study, all subjects should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, the subject will be withdrawn from the study and followed until the pregnancy comes to term.

The investigator is responsible for reporting all available pregnancy information on the pregnancy report within 24 hours of becoming aware of the event, although pregnancy itself is not considered an AE. Study treatment must be discontinued immediately in the event of a pregnancy. The subject should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Monitoring of the subject should continue until the conclusion of the pregnancy. Follow-up information detailing the outcome of the pregnancy and the health of the newborn should be reported as it becomes available.

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

Any pregnancy complication or premature terminations including miscarriage, spontaneous abortion or elective termination of a pregnancy for medical reasons will be reported as an SAE, as described in Section 10.7.2. Should the pregnancy result in a congenital abnormality or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality. In addition,

any infant death that occurs after the 30-day reporting period that the investigator suspects are related to the in-utero exposure to the study treatment should also be reported.

10.9 Treatment Stopping Rules

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

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 severe (Grade 3) laboratory abnormality (confirmed by repeat sample and considered related to study drug).

Dosing of study drug for an individual subject may be suspended for safety concerns other than those described above, at the discretion of the investigator if he/she feels the subject's safety may be threatened.

A subject with a PHQ-8 score of '15' or above should be referred promptly to a mental health care professional and consideration be given to discontinuation from study drug.

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

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

Treatment should be interrupted:

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

Treatment should be discontinued:

- If the 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.

11 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.

11.1 Statistical Methods

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

All statistical processing will be performed using SAS® (Version 9.4 or later) unless otherwise stated. No interim efficacy analyses are planned.

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

11.1.1 Pharmacokinetics Assessment

Plasma levels of circulating roflumilast and its major N-oxide metabolite will be measured at the following time points:

- Prior to study drug application on Days 1 and 29
- Pre-dose, 1, 2, 4, 6 hrs post dose on Days 1 and 15, and 24 hrs post dose on Days 2 and 16 (serial PK subgroup enrolled under previous amendment only)

11.1.2 Pharmacokinetic Parameters

All subjects who are enrolled and receive at least one application of study drug, and have sufficient pharmacokinetic assessments will be included in the pharmacokinetic population.

When possible, the exposure of roflumilast and its major N-oxide metabolite will be calculated based on plasma concentrations versus time profile data and compared between the treatment groups.

A detailed description of the PK analysis will be presented in the SAP.

11.1.3 Safety Analysis

The following analyses will be performed; however, no formal inferential statistics will be done on safety assessments.

Descriptive statistics will be presented by visit for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. Summaries of local tolerability will be presented by visit.

Adverse Events:

All treatment-emergent AEs occurring during the study will be recorded and classified on the basis of MedDRA terminology for the safety population. Treatment-emergent AEs are those AEs with an onset on or after application of study medication at the Baseline visit or were present at treatment initiation but worsened during treatment, through study completion. All treatment-emergent AEs will be summarized by treatment group, the number of subjects reporting treatment-emergent AEs, system organ class, preferred term, severity, relationship, and seriousness.

Comparisons between treatment groups will be made by tabulating the frequency of subjects with one or more treatment-emergent AEs (classified into MedDRA terms) during the study.

Serious adverse events (SAEs) will be listed by subject. SAEs will be summarized by severity, and relationship to study treatment. Each subject will be counted only once within a system organ class or a preferred term using the event with the greatest relationship and greatest severity.

All information pertaining to AEs noted during the study will be listed by subject, detailing the verbatim description given by the Investigator, preferred term, system organ class, start date, stop date, severity, action taken regarding study drug, corrective treatment, outcome, and drug relatedness. The event onset will also be shown relative (in number of days) to date of first application. In addition, a list of subjects who prematurely discontinue from the study due to adverse events will also be provided.

A subject-by-subject treatment-emergent AE (TEAE) data listing, including verbatim term, preferred term, treatment, severity, and relationship to study drug, will be provided.

Medical history will be listed by subject. Physical examinations performed at Screening, Baseline and Week 4, and 12-lead ECGs will be performed at Screening and Week 4. Both physical examination and ECG results will be listed by subject.

Vital signs will be tabulated by visit and treatment group.

ECGs will be tabulated by visit and treatment group.

Laboratory testing will be obtained throughout the study and the results summarized by parameter, visit and treatment group.

11.1.4 Determination of Sample Size

The sample size will be approximately 90 to 105 subjects. A subset of subjects enrolled under the previous amendment will receive serial PK sampling.

A sample size of 27 per arm will provide at least 80% power to detect a difference in the mean change from baseline in EASI Total Score of 35% at week 4 (for each ARQ-151-treated group versus vehicle-treated group), assuming a pooled standard deviation of 40%, with a two-sided $\alpha = 0.05$. This is based on a 2-sample t-test. This includes P value adjustment for multiplicity using Bonferroni correction. With a 10-25% dropout rate, the sample size for the study would be increased to 30-35 subjects per arm (90-105 subjects total). Change from baseline in EASI Total Score at week 4 is expected to provide more statistical power than percent change from baseline in Total EASI Score at this timepoint (which is a secondary endpoint) and has been chosen as the primary endpoint.

This sample size is considered adequate for PK and safety evaluation.

11.1.5 Subjects to Analyze

Four analysis populations will be defined:

- Safety population will include all subjects who are enrolled and received at least one confirmed dose of study medication; this population will be defined separately for each cohort.
- Intent-to-Treat (ITT) population will include all randomized subjects.
- Per-Protocol (PP) Population will include all subjects who are in the safety population, were at least 80% compliant with study medication, and showed no other serious deviations from the study protocol.
- PK population will include all subjects receiving the active drug with sufficient plasma concentrations of roflumilast and its major N-oxide metabolite to define a profile, as determined by the pharmacokineticist.

11.1.6 Interim Analysis

No interim efficacy analyses are planned.

11.1.7 Background and Demographic Characteristics

Descriptive statistics will be used to summarize demographic characteristics (age, sex, ethnicity, and race) and background characteristics for the enrolled subjects. Past/coexistent medical history information and physical examination observations and vital signs information for all randomized subjects will be presented in a by-subject listing.

11.1.8 Study Medication Compliance

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

The amount of study medication received by each subject based on kit weight will be summarized by treatment using summary statistics (mean, SD, median, minimum, and maximum), and categorically.

11.2 Efficacy Evaluation

11.2.1 Primary Endpoint

The Primary Efficacy Endpoint will be:

- Change from baseline in Eczema Area and Severity Index (EASI) Total Score at Week 4

The primary efficacy endpoint will be analyzed using a MMRM analysis on change-from-baseline EASI with subject as a random effect and vIGA-AD strata, visit, treatment group, and interaction term for treatment-by-visit as fixed effects and the baseline as a covariate. Comparison between treatment groups at Week 4 will be done using the appropriate contrast. An unstructured variance-covariance matrix will be used. Additional interaction terms will also be included in supportive statistical models and will be detailed in the SAP. For missing data, a multiple imputation technique will be detailed in the SAP.

The primary efficacy analysis will be done using the ITT (Intent to Treat) population (all randomized subjects)and the PP population will be used as supportive analysis.

11.2.2 Secondary Endpoints

The Secondary Efficacy Endpoints will include:

- Percent change from baseline in EASI Total Score at each study visit
- Change from baseline in EASI Total Score at Weeks 1 and 2

- Achievement of a 75% or greater improvement in Eczema Area and Severity Index (EASI75) score from baseline to each study visit
- Achievement of a 50% or greater improvement in Eczema Area and Severity Index (EASI50) score from baseline to each study visit
- Change from baseline in BSA involvement at each study visit
- Change from baseline in WI-NRS pruritus score at each study visit
- Achievement of a ≥ 4-point improvement from Baseline in WI-NRS pruritus score at each study visit for subjects with a Baseline WI-NRS ≥ 4

A similar analysis approach as outlined for the primary endpoint will be used for all secondary continuous efficacy endpoints.

For categorical efficacy endpoints involving proportions (e.g. proportion of patients with vIGA-AD score of 'clear' or 'almost clear' at each study visit), a Cochran-Mantel-Haenszel test (CMH) controlling for the stratification variables will be performed.

11.3 Safety Evaluation

The following analyses will be performed; however, no formal inferential statistics will be performed on safety assessments.

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

11.3.1 Adverse Events

The assessment of safety will be based mainly on the frequency and percent of subjects who reported treatment-emergent AEs.

Adverse events will be coded using the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Treatment emergent adverse events (i.e. events with onset dates on or after the start of study drug or with missing onset dates) will be summarized by presenting for each treatment group, the number and percentage of subjects having any AE, having an AE in an individual body system, and having an AE in an individual preferred term. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

11.3.2 Local Tolerance Assessment

For the Investigator's assessment the numeric application site reaction scores will be summarized individually by using number and percentage of subjects by visit.

11.3.3 Medical History and Physical Examinations

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

Physical examination findings for all subjects will be presented. Clinically significant changes in physical examinations will be reported as AEs and will be described in the text of the final report.

11.3.4 Clinical Laboratory Results and Vital Signs

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

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

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

11.3.5 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.

11.4 Pharmacokinetic Analysis

All subjects who are enrolled and receive at least one application of study drug, and have sufficient pharmacokinetic assessments will be included in the pharmacokinetic population.

For all subjects, blood samples for the determination of roflumilast and its N-oxide metabolite will be collected at scheduled time points as delineated in the Schedule of Visits and Assessments (Section 5). Plasma drug concentrations at each time point will be summarized using descriptive statistics, reporting n, mean, standard deviation, median, minimum, and maximum.

Where possible, the exposure of roflumilast and its major N-oxide metabolite (as evidenced by the Cmax and AUC) will be calculated based on plasma concentrations obtained within 1 hour prior to study drug application, and 1, 2, 4, 6 and 24 hours post-dose administration following application on Days 1 and 15 (for serial PK subset subjects enrolled under previous amendment only).

A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

12 STUDY ADMINISTRATION

12.1 Ethics

12.1.1 Ethics Review Board

Before enrollment of patients into the study, the current protocol and ICF 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.

12.1.2 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).

12.1.3 Subject Information and Consent/Assent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to screening and will be assured that they may withdraw from the study at any time without jeopardizing their medical care. Adolescents will provide written assent and their parent(s) or legal guardian(s) will provide consent, as required by local law.

Subjects will be given a signed copy of their ICF.

12.2 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 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 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.

12.3 Study Completion/Termination

12.3.1 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.

12.3.2 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.

12.4 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 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges etc. Corrections are made prior to database lock.

12.5 Data Handling and Record Keeping

During the clinical study, the Investigator will maintain adequate records, including medical records, records detailing the progress of the study for each subject, laboratory reports, signed informed consent forms, investigational product 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.

12.6 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.

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.

12.7 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).

12.8 Publication Policy

The Sponsor is supportive of publishing clinical trial findings. The process of coordinating publication efforts is detailed in the Clinical Trial Agreement.

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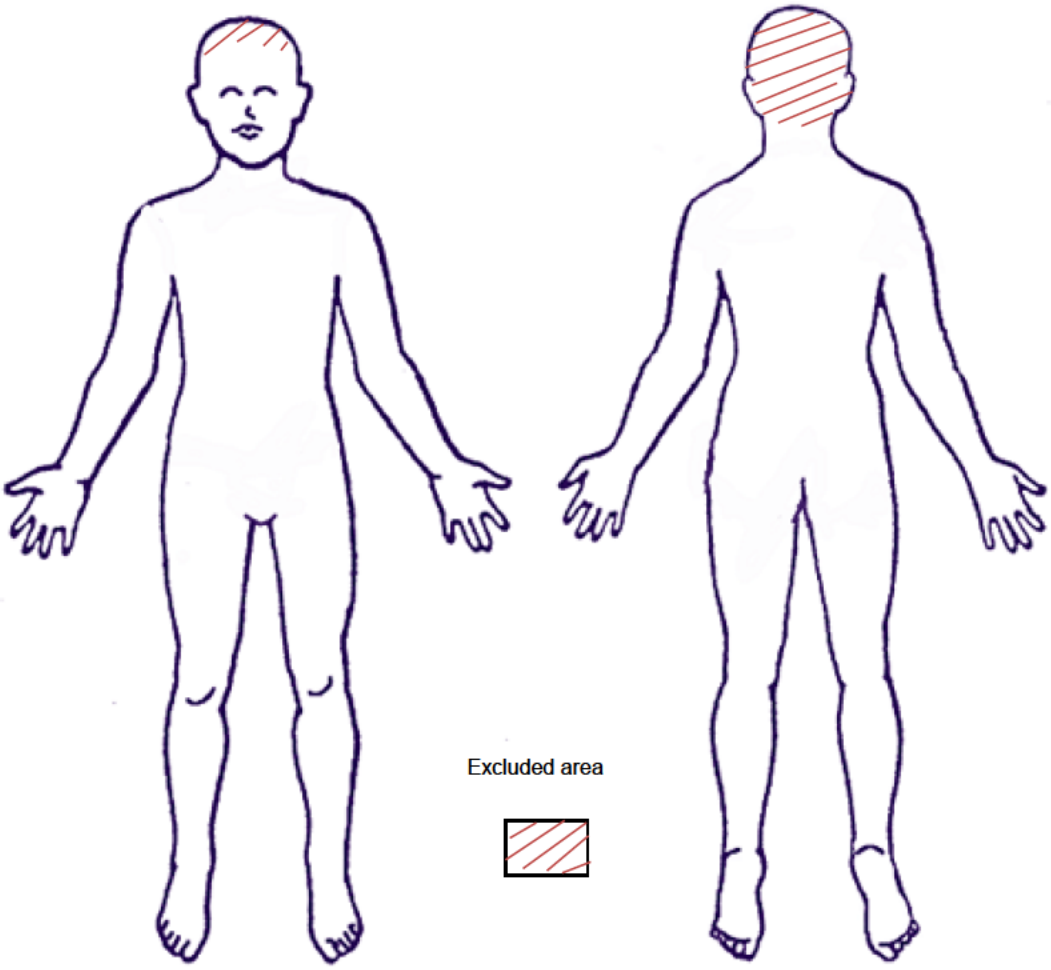
14 APPENDICES

Appendix 1. Body Diagram

Site personnel to mark treatable areas identified by 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. Hanifin and Rajka Diagnostic Criteria for Atopic Dermatitis (AD)

Major criteria: Must have three or more of:

1. Pruritus
2. Typical morphology and distribution
    - Flexural lichenification or linearity in adults
    - Facial and extensor involvement in infants and children
3. Chronic or chronically-relapsing dermatitis
4. Personal or family history of atopy (asthma, allergic rhinitis, atopic dermatitis)

Minor criteria: Should have three or more of:

1. Xerosis
2. Ichthyosis, palmar hyperlinearity, or keratosis pilaris
3. Immediate (type 1) skin-test reactivity
4. Raised serum IgE
5. Early age of onset
6. Tendency toward cutaneous infections (especially *S aureus* and herpes simplex) or impaired cell-mediated immunity
7. Tendency toward non-specific hand or foot dermatitis
8. Nipple eczema
9. Cheilitis
10. Recurrent conjunctivitis
11. Dennie-Morgan infraorbital fold
12. Keratoconus
13. Anterior subcapsular cataracts
14. Orbital darkening
15. Facial pallor or facial erythema
16. Pityriasis alba
17. Anterior neck folds
18. Itch when sweating
19. Intolerance to wool and lipid solvents
20. Perifollicular accentuation
21. Food intolerance
22. Course influenced by environmental or emotional factors
23. White dermographism or delayed blanch

Appendix 3. Patient Health Questionaire-8 (PHQ-8)

SMRC Self-Management Resource Center

Personal Health Questionnaire Depression Scale (PHQ-8)

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

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

Scoring

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

Appendix 4. EASI Scoring Tool

Eczema Area and Severity Index (EASI) case report form - age≥8 years

Area of Involvement: Each body region has potentially 100% involvement. Score **0 to 6** based on the following table:

% involvement	0	1-9%	10 - 29%	30 - 49%	50 - 69%	70 - 89%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs: Grade the severity of each sign on a scale of **0 to 3**:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved area.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)

Scoring table:

Body region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Region score (0-6)	Multiplier	Score per body region
Head/neck	(+	+	+	)	x	X 0.1	
Trunk	(+	+	+	)	x	X 0.3	
Upper extremities	(+	+	+	)	x	X 0.2	
Lower extremities	(+	+	+	)	x	X 0.4	
The final EASI score is the sum of the 4 region scores:							_____ (0-72)

Appendix 5. Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes No**	**Yes No**
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e g , *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes No**	**Yes No**
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period This is different than a specific plan with time, place or method details worked out (e g thought of method to kill self but not a specific plan) Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes No**	**Yes No**
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes No**	**Yes No**
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes No**	**Yes No**
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) Past X Months - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***)	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself Intent does not have to be 100% If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt ***There does not have to be any injury or harm***, just the potential for injury or harm If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e g , gunshot to head, jumping from window of a high floor/story) Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** Total # of Attempts _____ **Yes No**	**Yes No** Total # of Attempts _____ **Yes No**
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting Once they ingest any pills, this becomes an attempt rather than an interrupted attempt Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger Once they pull the trigger, even if the gun fails to fire, it is an attempt Jumping: Person is poised to jump, is grabbed and taken down from ledge Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** Total # of interrupted _____	**Yes No** Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** Total # of aborted _____	**Yes No** Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt This can include anything beyond a verbalization or thought, such as assembling a specific method (e g , buying pills, purchasing a gun) or preparing for one's death by suicide (e g , giving things away, writing a suicide note) ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No**	**Yes No**
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No**	**Yes No**

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

Appendix 6. Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

Since Last Visit

1. Wish to be Dead — **Yes** **No**

Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up

Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

2. Non-Specific Active Suicidal Thoughts — **Yes** **No**

General, non-specific thoughts of wanting to end one's life/commit suicide (e g , *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period

Have you actually had any thoughts of killing yourself?

If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act — **Yes** **No**

Subject endorses thoughts of suicide and has thought of at least one method during the assessment period This is different than a specific plan with time, place or method details worked out (e g , thought of method to kill self but not a specific plan) Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it...and I would never go through with it."*

Have you been thinking about how you might do this?

If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan — **Yes** **No**

Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*

Have you had these thoughts and had some intention of acting on them?

If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent — **Yes** **No**

Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out

Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

INTENSITY OF IDEATION

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

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency — ____

How many times have you had these thoughts?

(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

Duration — ____

When you have the thoughts, how long do they last?

(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

Controllability — ____

Could/can you stop thinking about killing yourself or wanting to die if you want to?

(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

Deterrents — ____

Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?

(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

Reasons for Ideation — ____

What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?

(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

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

Appendix 7. NIAID DMID Toxicity Table

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

ABBREVIATIONS USED IN FOLLOWING TABLES:

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

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

ESTIMATING SEVERITY GRADE

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

GRADE 1 **Mild**: Transient or mild discomfort (<48 hours); no medical intervention/therapy required

GRADE 2 **Moderate**: Mild to moderate limitation in activity - some assistance may be needed; no or minimal medical intervention/therapy required

GRADE 3 **Severe**: Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalizations possible.

LABORATORY RANGES

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

CLINICAL ADVERSE EVENTS

Cardiovascular	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Arrhythmia		Asymptomatic, transient signs, no Rx required	Recurrent/persistent; symptomatic Rx required
Hemorrhage, blood loss	Estimated blood loss ≤100 mL	Estimated blood loss >100 mL, no transfusion required	Transfusion required
QTcF (Fridericia's correction)[a] or QTcB (Bazett's correction)	Asymptomatic, QTc interval 450-479 ms, *OR* 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
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

[a] Inclusion dependent upon protocol requirements

Respiratory (continued)	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Lung infection (**CTCAE 4.0**)	-	Moderate symptoms; oral intervention indicated (e.g. antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated
Gastrointestinal	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Nausea	No interference with activity	Some interference with activity	Prevents daily activities
Vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity or requires IV hydration
Diarrhea	2-3 loose or watery stools or <400 g/24 hours	4-5 loose or watery stools or 400-800 g/24 hours	6 or more loose or watery stools or >800 g/24 hours or requires IV hydration
Urinary Tract	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Urinary tract infection (**CTCAE 4.0)**	-	Localized; local intervention indicated (e.g.oral or topical antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated
Reactogenicity	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Local reactions			
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity
Tenderness	Discomfort only to touch	Discomfort with movement	Significant discomfort at rest
Erythema/redness [b]	2.5-5 cm	5.1-10 cm	>10 cm
Induration/swelling [c]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity

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

Reactogenicity (continued)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Systemic reactions			
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema or anaphylaxis
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
All other conditions	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention

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

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

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

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

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

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