Protocol ARQ-154-203

A Phase 2a, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-154 Foam 0.3% Administered QD in Subjects with Seborrheic Dermatitis

Sponsor:	Arcutis, Inc.
Sponsor Contact	[redacted]
Medical Monitor	[redacted]
IND Number:	142047
Protocol Version:	Amendment 1
Protocol Date:	07 January 2020

GCP Statement

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

Confidentiality Statement

SITE INVESTIGATOR SIGNATURE PAGE

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ARQ-154-203

SPONSOR: Arcutis, Inc.
[redacted]

ISSUE DATE: 07 January 2020

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

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

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

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

Investigational Site Name: [redacted]

Print Investigator Name: [redacted]

Investigator Signature: [redacted] Date: [redacted]

SUMMARY OF CHANGES

The following sections have been changed in Amendment 1 of the ARQ-154-203 protocol.

Section	Summary of Changes
Protocol Title	Update protocol title from Phase 2b to Phase 2a throughout the protocol as applicable
Synopsis	Updated to align with changes made within the body of the protocol
3.3.1.2 Psoriasis Phase 2b	Updated Figures 1 and 2
4.2 Number of Subjects	Increase the number of subjects to be enrolled in the study to 184. Remove the limit of 20% total enrollment for IGA of 'Severe'
4.4.1 Inclusion Criteria	Clarified inclusion 6 to include at least Moderate scores for Overall Assessments of Erythema and Scaling at Baseline
4.4.2 Exclusion Criteria	Previous exclusion 8: remove exclusion criteria for hypersensitivity to PDE-4 inhibitors. Exclusion 9: clarify exclusion criteria for suicidal ideation. Exclusion 10: specified 4 week washout period for subjects with a history of a major surgery. Exclusion 12: specified physical limitations for subjects with scalp involvement. Exclusion 16: specified family members of enrolled subjects residing in the same household are excluded from the study.
5.1.1 Screening	Revised to allow subjects to re-screen one time
5.1.2 Baseline	Allow Screening lab results to be used for Baseline lab assessments if the Baseline visit occurs within 14 days of Screening
5.1.4 Vital Signs, Height, Weight	Specified blood pressure to be collected while the subject is sitting/resting for at least 5 minutes
5.2 Efficacy Evaluations	Clarify every effort must be made for the same evaluator to complete the IGA, Overall Assessments of Erythema and Scaling
5.8 Reporting Pregnancy	Clarify guidance for pregnancy reporting.
6.1.3 Interim Analysis	Add an interim analysis for futility
6.3.3 Exploratory Endpoints	Add an exploratory endpoint for IGA
Appendix 5	Added image for Scalpdex.
Appendix 6	Move Toxicity Table from Appendix 5 to 6
Editorial changes made throughout to improve accuracy or readability	

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:	A Phase 2a, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-154 Foam 0.3% Administered QD in Subjects with Seborrheic Dermatitis
Investigational Product:	ARQ-154 foam investigational product will be supplied at a concentration of 0.3%. Matching vehicle foam will contain only excipients of ARQ-154 foam. Subjects will be randomized 2:1 to receive ARQ-154 foam 0.3% or matching vehicle foam QD applied to all areas of seborrheic dermatitis. Areas of application will be all areas affected including the face, scalp, trunk, or intertriginous/genital regions, with a maximum BSA of 20%. Subjects should maintain treatment of areas with investigational product for the duration of the study regardless of whether treatable areas of seborrheic dermatitis clear. New lesions that appear during the treatment period should also be treated.
IND	142047
Clinical Indication:	Seborrheic dermatitis
Study Design:	This is a parallel group, double blind, vehicle-controlled study in which ARQ-154 foam 0.3% or vehicle foam is applied QD x 8 weeks to adult subjects with at least moderate seborrheic dermatitis affecting the scalp and/or rest of body
Study Objectives:	To assess the safety and efficacy of ARQ-154 foam 0.3% administered once daily (QD) vs vehicle foam x 8 weeks in adult subjects with seborrheic dermatitis
Study Sites:	Multicenter study with approximately 20 sites
Study Population:	Subjects will be male and female adults. Subjects will have a minimum Investigator Global Assessment (IGA) = 'Moderate' (3) for study entry. Randomization will be stratified by study site and baseline disease severity (IGA = 3 or IGA = 4).
Inclusion Criteria	1. Participants legally competent to sign and give

	informed consent. 2. Males and females ages 18 years and older (inclusive) at the time of consent. 3. Clinical diagnosis of seborrheic dermatitis of at least 3 months duration as determined by the Investigator. Stable disease for the past 4 weeks. 4. Seborrheic dermatitis of the scalp and/or face and/or trunk and/or intertriginous areas up to ≤20% BSA involvement. 5. An Investigator Global Assessment (IGA) of disease severity of at least Moderate ('3') at Baseline. 6. Overall Assessment of Erythema and Overall Assessment of Scaling scores of at least Moderate ('2') at Baseline. 7. 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 trial. 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. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a lifestyle choice and a backup method has been identified if the subject becomes sexually active. 8. Females of non-childbearing potential must either be post-menopausal with spontaneous amenorrhea for at least 12 months or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy). 9. Subjects in good health as judged by the Investigator, based on medical history, physical examination, vital signs, serum chemistry labs, hematology values, and urinalysis. 10. Subjects are considered reliable and capable of adhering

	to the Protocol and visit schedule according to the Investigator judgment.
Exclusion Criteria	1. Subjects who cannot discontinue treatment with therapies for the treatment of seborrheic dermatitis prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 1). 2. Planned excessive exposure of treated area(s) to either natural or artificial sunlight, tanning bed or other LED. 3. 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 (Visit 2) and during the study. 4. 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 (Visit 2) and during the study. 5. Subjects with PHQ-8 $\geq$10 at Screening or Baseline visits. 6. Previous treatment with ARQ-151 cream. 7. Subjects who have received oral roflumilast (Daliresp®, Daxas®) or other PDE-4 inhibitors (apremilast) within the past 4 weeks. 8. Known allergies to excipients in ARQ-154 foam [redacted] 9. Known or suspected: • severe renal insufficiency or moderate to severe hepatic disorders • hypersensitivity to component(s) of the investigational products • history of severe depression, suicidal ideation or Screening/Baseline C-SSRS indicative of suicidal ideation, whether lifetime or recent/current 10. Subjects with a history of a major surgery within 4 weeks prior to Baseline (Visit 2) or has a major surgery

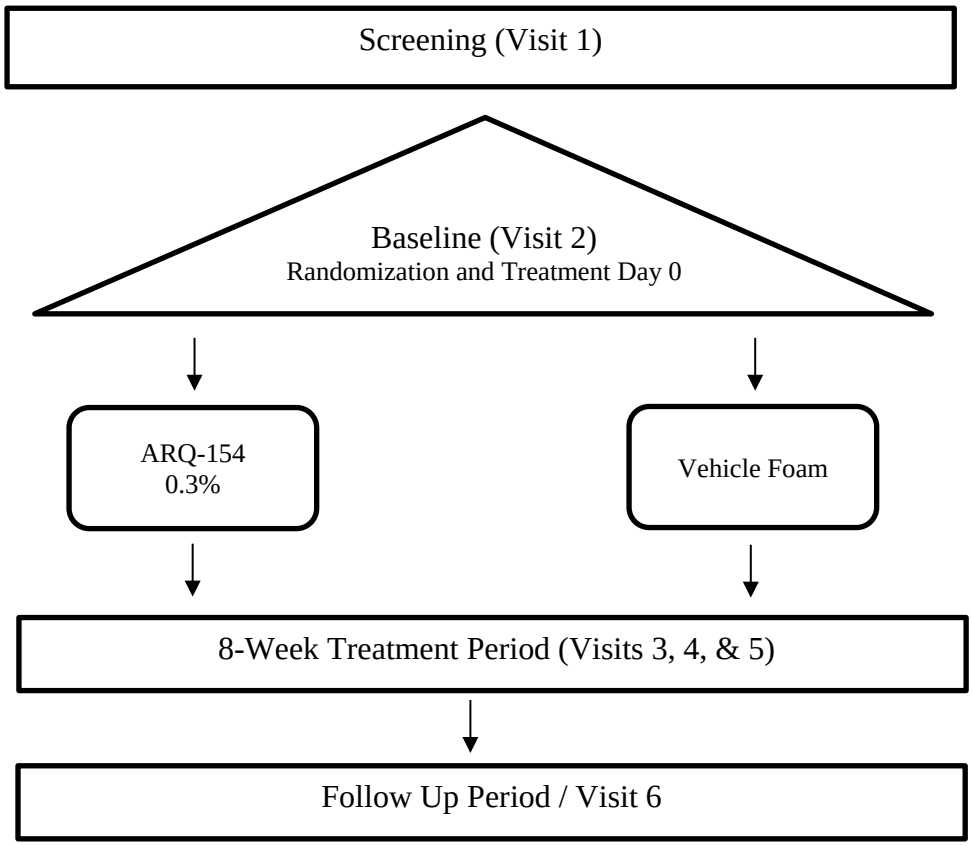
	planned during the study. 11. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements. 12. Subjects unable to apply product to the scalp due to physical limitations if the subject has current or history of seborrheic dermatitis involving the scalp. 13. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding. 14. A clinically relevant history of abuse of alcohol or other drugs, at the discretion of the Investigator. 15. 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. 16. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members residing in the same household of enrolled subjects. 17. Any condition that in the Investigator's assessment would preclude the subject from participating in the study.
Duration of Participation for Subjects:	Screening (up to 4 weeks) + Treatment phase (8 weeks) and follow-up (1 week post-treatment completion) for a total of up to approximately 13 weeks
Key Assessments:	Safety will be monitored through application site assessments, safety labs, and Adverse Events (AEs). Safety will also be monitored by C-SSRS and PHQ-8 assessments. Efficacy assessments will include IGA, Overall Assessment of Erythema, Overall Assessment of Scaling, WI-NRS, Scalpdex, and DLQI. Pharmacokinetic samples will be collected at pre-dose for all subjects. Refer to the Schedule of Visits and Assessments (Section 1.3) for detailed schedules of the study assessments.
Study Endpoints	The Primary Efficacy Endpoint will be defined as: • Achievement of an IGA score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at week 8

	The Secondary Efficacy Endpoints will include: • Achievement of an IGA score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at weeks 2 and 4 • Change from Baseline in Overall Assessment of Erythema score at weeks 2, 4, and 8 • Change from Baseline in Overall Assessment of Scaling score at weeks 2, 4, and 8 • Achievement of an Overall Assessment of Erythema (0-3 scale) score of 0 or 1 PLUS a 2-grade improvement from Baseline at weeks 2, 4, and 8 • Achievement of an Overall Assessment of Scaling (0-3 scale) score of 0 or 1 PLUS a 2-grade improvement from Baseline at weeks 2, 4, and 8 • Change in WI-NRS pruritus score at weeks 2, 4, and 8, as compared to Baseline • In subjects with a Baseline WI-NRS pruritus score of ≥4, achievement of a ≥4-point improvement from Baseline in WI-NRS pruritus score at weeks 2, 4, and 8. Exploratory Endpoints will include: • Change in Scalpdex total score from Baseline at weeks 2, 4, and 8 • Achievement of an Overall Assessment of Erythema (0-3 scale) score of 0 or 1 at weeks 2, 4, and 8 • Achievement of an Overall Assessment of Scaling (0-3 scale) score of 0 or 1 at weeks 2, 4, and 8 • Achievement of an Overall Assessment of Erythema (0-3 scale) score of 0 at weeks 2, 4, and 8 • Achievement of an Overall Assessment of Scaling (0-3 scale) score of 0 at weeks 2, 4, and 8 • In subjects with a Baseline WI-NRS pruritus score of ≥4, achievement of a ≥4-point improvement from Baseline in WI-NRS pruritus score at weeks 2, 4, and 8 • Change from Baseline in DLQI at weeks 2, 4, and 8 • Change from Baseline in BSA affected at week 8 • A 2-grade improvement in IGA from Baseline

Statistical Considerations:	There are approximately 184 subjects planned for this study; randomized 2:1 to ARQ-154 foam 0.3% : vehicle QD, stratified by study site and baseline disease severity. A sample size of 184 subjects will provide approximately 90% power to detect an active response of at least 55.8%, assuming 159 (86%) subjects complete the study and a vehicle response of 30%, based on two-group X^2 test of equal proportions (without continuity correction, using a 2-sided alpha of 0.10). One interim futility analysis is planned when the first 60 subjects randomized have had the opportunity to complete the 8 week disease assessment. This futility analysis will be non binding and will be used for decision making on further expansion of the clinical development program in seborrheic dermatitis. Accrual to this study will not be held during the conduct and interpretation of this futility analysis. Descriptive statistics will be presented for endpoint and safety data collected in the clinical trial. This includes the number and percentage of subjects for binary endpoints/categorical data, and mean, SD, median, minimum, and maximum for continuous data. The primary endpoint of 'IGA success at week 8' will be analyzed using a Cochran-Mantel-Haenszel test stratified by the stratification factors study site and baseline disease severity. The analysis will be performed on the Intention-to-Treat (ITT) population and missing data will be imputed using multiple imputation. Continuous secondary endpoints will be analyzed using Analysis of Covariance with treatment and stratification factor as independent variables. The ITT population will be used, and missing data will be imputed using multiple imputation. Binary secondary endpoints will be analyzed similarly to the primary endpoint. All subjects who are randomized and receive at least one confirmed dose of IP will be included in the safety population. Adverse events (AEs) will be summarized by preferred

	term, system organ class, and treatment group for all treatment-emergent AEs, serious AEs, related AEs, AEs leading to withdrawal from investigational product. 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.

1.2 Study Schema



A Phase 2a, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-154 Foam 0.3% Administered QD in Subjects with Seborrheic Dermatitis

Approximately 184 adult subjects with seborrheic dermatitis will be randomized 2:1 to receive either:

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

1.3 Schedule of Visits and Assessments

Study Procedure	Screen	Baseline Day 0	Wk 2 Day 14	Wk 4 Day 28	Wk 8 Day 56	Wk 9 Day 63
Visit	1	2	3	4	5	6
Visit Window	-4 weeks		+/- 3 day	+/- 5 days	+/- 5 days	+/-5 days
Informed consent/assent	X					
Medical history	X					
Physical examination[a]	X	X			X	
I/E criteria	X	X				
Randomization		X				
Hematology, Serum Chemistries, and Urine Analysis	X	X			X	
Vital signs, height, weight[b]	X	X	X	X	X	X
IGA[c], Overall Assessment of Erythema[c], Overall Assessment of Scaling[c]	X	X	X	X	X	X
WI-NRS, DLQI, Scalpdex	X	X	X	X	X	
BSA	X	X			X	
Application Site Reaction Assessment/Local Tolerability[d]		X		X	X	
Pigmentation Assessment[e]	X	X	X	X	X	X
C-SSRS, PHQ-8	X	X		X	X	
Medical Photography[f]		X	X	X	X	
Pregnancy test[g]	X	X		X	X	
PK draws[h]		X		X	X	
IP/vehicle application at the study site[i]		X	X			
Dispense study medication kit[j]		X	X	X		
Dispense/review diary		X	X	X	X	
Weigh study medication kit[k]		X	X	X	X	
Compliance calculation[l]		X	X	X	X	
Adverse event assessment	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X

Footnotes:

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

[b] Height will be collected at Baseline and Week 8. 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 from Baseline should be reported to the medical monitor.

[c] IGA will be a 5-point scale ranging from clear (0) to severe (4). IGA should be completed prior to other physician assessments. Overall assessment of erythema (0-3 scale) and overall assessment of scaling (0-3 scale) will be completed.

[d] Local tolerability Assessments: The Investigator local tolerability assessment of skin irritation (Berger and Bowman skin irritation score) should be performed prior to the investigational product application at Baseline, and at Weeks 4 and 8. Reactions at the site of product application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's seborrheic dermatitis. Subjects will perform the local tolerability assessment 10-15 minutes post-drug application at Baseline, and recall assessments at Weeks 4 and 8 for the subject's '0-3' burning/stinging assessment.

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

[f] At selected sites, medical photography will be obtained for target lesions. All efforts will be made to de-identify the subjects. Subjects who are unwilling to participate in the medical photography will be allowed to opt out of this procedure.

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

[h] PK draws (trough / pre-dose) will be collected at Days 0, 28 and 56. At baseline, this draw will be pre-dose relative to drug application in the clinic. Ensure study medication is not applied in the area where PK will be drawn.

[i] Subjects to apply assigned IP at the study site at every designated visit, to confirm understanding of instruction on how to apply initially.

[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

2 ABBREVIATIONS

AE	Adverse Event
AMP	Adenosine Monophosphate
AUC	Area Under the Curve
BSA	Body Surface Area
C_{max}	Maximum Concentration
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic Acid
ERB	Ethics Review Board
FDA	U.S. Food and Drug Administration
FOCBP	Female of Child Bearing Potential
GCP	Good Clinical Practices
HC	Health Canada
HCA	Alpha-Hydroxycinnamaldehyde
HPRT	Hypoxanthine-guanine Phosphoribosyl Transferase
IB	Investigational Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA	Investigator Global Assessment
I-IGA	Intertriginous IGA
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to Treat
IWRS	Interactive Web Response System
LED	Light Emitting Device
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
mL	Milliliter
MMRM	Mixed effect Model Repeat Measurement
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level

Ng	Nanogram
NRS	Numerical Rating Score
PASI	Psoriasis Area and Severity Index
PDE-4	Phosphodiesterase 4
PHQ-8	Patient Health Questionnaire depression scale
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
QD	Once Daily ("quaque die")
SAE	Serious Adverse Event
TEAE	Treatment Emergent Adverse Event
Th1	Type 1 T Helper Cell
Th17	Type 17 T Helper Cell
T_{max}	Time to reach maximum concentration
V79	Chinese hamster cell line
WI-NRS	Worst Itch – Numeric Rating Scale

3 BACKGROUND AND RATIONALE

3.1 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.

The Sponsor is developing topical roflumilast in several formulations (ARQ-151 cream and ARQ-154 foam) and indications. To date, ARQ-151 cream has been evaluated in studies in psoriasis and atopic dermatitis. Additionally, two PDE-4 inhibitors have been marketed for dermatologic indications in the US and elsewhere, including OTEZLA® as an oral therapy for moderate to severe plaque psoriasis in adults and EUCRISA® as a topical therapy for mild to moderate atopic dermatitis in individuals 2 years of age and older. The present study will be the first study of ARQ-154 foam.

Seborrheic dermatitis is a common, chronic inflammatory skin disease characterized by erythematous, scaly plaques, often with a yellowish, oily, moist, and/or greasy appearance, affecting areas of sebaceous gland abundance. Frequently involved sites include the scalp (including retroauricular areas), eyebrows, ears, nasolabial folds, eyelids, trunk, and intertriginous areas. There may be associated pruritus and/or pigmentary changes. Seborrheic dermatitis affects about 2% of the adult population (Borda 2015, Dessinioti 2013) and occurs in the adolescent population as well. It may be associated with certain medications and conditions such as Parkinson's disease and other neurologic conditions, Down syndrome, and HIV infection. Seborrheic dermatitis is generally a clinical diagnosis. The exact cause of seborrheic dermatitis remains unknown. Treatment of seborrheic dermatitis may vary by location on the body involved, eg, scalp or non-scalp and periocular or not. For the scalp, anti-dandruff shampoos are often used such as anti-fungals, zinc products, selenium sulfide, salicylic acid, or tar. Topical corticosteroid products may also be used. Scalp lesions of seborrheic dermatitis can present a particular treatment challenge and form thick crusts which may not respond to topical steroids or antifungals. On non-scalp regions such as the face, topical antifungals or low potency topical corticosteroids are typically used. However, importantly, topical antifungals may demonstrate limited efficacy and topical steroids may demonstrate tachyphylaxis and cause important adverse events, particularly on the face, such as telangiectasias, acne, atrophy, rosacea, and ocular complications. Since seborrheic dermatitis is a chronic condition, treatment with topical steroids is particularly problematic due to the need for prolonged treatment duration, which may result in side effects. Other medications which have been used for seborrheic

dermatitis include topical sulfur/sulfonamide products, topical calcineurin inhibitors, and oral retinoids.

Literature reports suggest that PDE-4 inhibition can be effective in the treatment of seborrheic dermatitis. Indeed, crisaborole (Eucrisa®), a PDE-4 inhibitor marketed in the U.S. for the treatment of atopic dermatitis, has been reported to be effective in the treatment of chronic nasolabial fold seborrheic dermatitis (Liu 2018).

Given the unmet need for new medical therapies for seborrheic dermatitis, the efficacy and safety demonstrated to date in Phase 2 studies of topical roflumilast (ARQ-151 cream) in psoriasis, and the precedent of topical anti-inflammatory agents as treatments for seborrheic dermatitis, the Sponsor is pursuing development of ARQ-154 foam for the treatment of seborrheic dermatitis, with the present study being the first. Relative to topical formulations such as a cream or gel, the foam formulation in the present study is expected to be well suited for the treatment of the scalp, where seborrheic dermatitis may predominate and be most difficult to treat. Foams have the ability to access skin lesions in hair-bearing areas and have commonly been used for treating scalp psoriasis (e.g., Olux® and Luxiq® foams) and seborrheic dermatitis (e.g., Extina® foam). In this Phase 2a proof-of-concept study, Arcutis will evaluate ARQ-154 foam 0.3% for the treatment of seborrheic dermatitis involving the scalp, face, and body areas.

The composition of ARQ-154 topical roflumilast foam includes minimal qualitative or quantitative changes relative to the composition of ARQ-151 topical roflumilast cream. Compared to ARQ-151, ARQ-154 foam also involves addition of a propellant that is eliminated at delivery, avoiding gas bubbles in the foam. Since the composition of ARQ-154 foam is very close to the composition of ARQ-151 cream, Arcutis plans to rely on the nonclinical development program for ARQ-151 topical cream, as detailed below, in order to support the ARQ-154 foam development program.

3.2 Preclinical Studies

3.2.1 Toxicity Summary

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

[redacted]

[redacted]

[redacted]

[redacted]

3.3 Clinical Studies

3.3.1 Topical Roflumilast Cream

Although the present study will be the first clinical study with ARQ-154 foam, the related formulation of topical roflumilast, ARQ-151 cream, has been evaluated in both psoriasis (through Phase 2b) and atopic dermatitis (Phase 1).

3.3.1.1 Psoriasis Phase 2a

[redacted]

[redacted]

[redacted]

[redacted]

3.3.1.2 Psoriasis Phase 2b

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

3.3.1.3 Atopic Dermatitis Phase 1

[redacted]

3.3.2 Oral Roflumilast Tablet

Oral roflumilast (DALIRESP®, DAXAS®) has been approved globally for the treatment of COPD and has been evaluated in nine Phase III/IV randomized double-blind clinical trials (Wedzicha 2016). Overall, the safety of oral roflumilast has been well established in its targeted population of mostly middle- and upper-aged individuals who currently smoke cigarettes or have smoked them extensively in the past. Adverse events (AEs) reported with roflumilast tablets have been consistent with those expected for oral PDE-4 inhibitors. In a pooled analysis of safety data from 6-month and 1-year clinical trials (N=8630), the most common AEs were diarrhea, weight loss and nausea. Other AEs reported more frequently with roflumilast treatment than with placebo were back pain, influenza, insomnia and decreased appetite (Michalski 2012, Wedzicha 2016).

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

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

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

3.4 Rationale for Development

[redacted]

3.4.1 Dose Selection

[redacted]

3.4.2 Risks and/or Benefits to Subjects

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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

4.2 Number of Subjects

A total of up to approximately 184 subjects will be enrolled at approximately 20 study sites in the United States and Canada. Additional countries or study sites may be added as necessary. Subjects will be adult males or females with seborrheic dermatitis. Subjects must have an IGA of disease severity of at least Moderate ('3') at Baseline. Subjects must have no more than 20% Body Surface Area (BSA) of seborrheic dermatitis. All lesions on a subject will be treated including the scalp, face, trunk, and intertriginous areas.

4.3 Subject Participation

There will be a minimum of 6 clinic visits, including Screening, Baseline, Week 2, Week 4, and Week 8 of treatment, as well as a Week 9 follow-up visit (1 week after last dose). Since the

interval between the Screening and Baseline visits may be up to 4 weeks, the anticipated maximum duration of subject participation is ~13 weeks.

4.3.1 Randomization

Subjects will be randomly assigned to apply ARQ-154 foam 0.3% QD or vehicle foam QD to lesions of seborrheic dermatitis up to a maximum application area of 20% BSA.

Assignment of active drug or vehicle will be made at a 2:1 ratio according to a computer-generated randomization list. Randomization will be stratified by study site and baseline disease severity (IGA = 3 or IGA = 4).

Randomization will take place at Baseline after the subject has been found to be fully eligible for participation. Kits containing investigational product (IP) will be assigned to each subject using an internet-based randomization system (IWRS). A subject may receive more than one kit for the treatment period.

The kits and foam cans are blinded and each kit is numbered with a unique kit number.

4.3.2 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), the next three digits correspond to the sequential order in which the subject is screened for the study (e.g., Subject ID 10001: Site 10, first subject screened 001 for that site). Site number 10 will be the first site in the study.

The clinical site is responsible for maintaining a current log of subject ID number assignments and the kit 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.).

4.4 Selection of Study Population

4.4.1 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.
2. Males and females ages 18 years and older (inclusive) at the time of consent.
3. Clinical diagnosis of seborrheic dermatitis of at least 3 months duration as determined by the Investigator. Stable disease for the past 4 weeks.
4. Seborrheic dermatitis of the scalp and/or face and/or trunk and/or intertriginous areas up to ≤20% BSA involvement.
5. An Investigator Global Assessment (IGA) of disease severity of at least Moderate (‘3’) at Baseline.

6. Overall Assessment of Erythema and Overall Assessment of Scaling scores of at least Moderate (‘2’) at Baseline.
7. 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 trial. 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. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a lifestyle choice and a backup method has been identified if the subject becomes sexually active.
8. Females of non-childbearing potential must either be post-menopausal with spontaneous amenorrhea for at least 12 months or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy).
9. Subjects in good health as judged by the Investigator, based on medical history, physical examination, vital signs, serum chemistry labs, hematology values, and urinalysis.
10. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule according to the Investigator judgment.

4.4.2 Exclusion Criteria

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

1. Subjects who cannot discontinue treatment with therapies for the treatment of seborrheic dermatitis prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 1).
2. Planned excessive exposure of treated area(s) to either natural or artificial sunlight, tanning bed or other LED.
3. 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.
4. 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.
5. Subjects with PHQ-8 $\geq$10 at Screening or Baseline visits.
6. Previous treatment with ARQ-151 cream.
7. Subjects who have received oral roflumilast (Daliresp®, Daxas®) or other PDE-4 inhibitors (apremilast) within the past 4 weeks.

8. Known allergies to excipients in ARQ-154 foam [redacted]
9. Known or suspected:
    - severe renal insufficiency or moderate to severe hepatic disorders
    - hypersensitivity to component(s) of the investigational products
    - history of severe depression, suicidal ideation or Screening/Baseline C-SSRS indicative of suicidal ideation, whether lifetime or recent/current
10. 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.
11. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements.
12. Subjects unable to apply product to the scalp due to physical limitations if the subject has current or history of seborrheic dermatitis involving the scalp.
13. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.
14. A clinically relevant history of abuse of alcohol or other drugs, at the discretion of the Investigator.
15. 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.
16. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members residing in the same household of enrolled subjects.
17. Any condition that in the Investigator's assessment would preclude the subject from participating in the study.

4.4.3 Removal of Subjects from Investigational Product

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

1. Occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements for investigational product administration as per 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 from administration of the investigational product.

5. Weight loss of >5% from baseline 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 (see Table 1) 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 investigational product application for more than 50% of scheduled doses.

4.4.4 Removal of Subjects from the Study

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

1. Subject's decision to withdraw from the study.
2. Subject is lost to follow up.
3. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

4.5 Study Restrictions

4.5.1 Prohibitions and Concomitant Therapy

Prohibited medications and products are detailed in Table 1.

Table 1: Excluded Medications and Treatments

Excluded Medications and Treatments	Wash out period prior to Baseline (Day 0)
Biologics	12 weeks or 5 half-lives, which is longer
Systemic treatment with antifungal agents, corticosteroids, immunosuppressive therapies, retinoids, roflumilast, or Otezla®	4 weeks
Topical antifungals, corticosteroids, calcineurin inhibitors, sulfur-based treatments, medical devices, Eucrisa®, azelaic acid, or metronidazole	2 weeks
Medicated shampoos (e.g., coal tar, keratolytics including salicylic acid, antifungals, zinc pyrithione, selenium sulfide, corticosteroids, medical devices)	2 weeks
Topical medications used on the scalp for conditions besides seborrheic dermatitis, e.g., use of topical minoxidil for androgenetic alopecia	4 weeks
Phototherapy, tanning beds, other light emitting devices	4 weeks
Investigational drugs	12 weeks (biologics) or 5 half-lives, whichever is longer; 5 half-lives (orals); 2 weeks (topical)
Note: Eye drop and nasal corticosteroid preparations are allowed. Inhaled corticosteroid preparations are allowed if used for a stable condition and at a stable dose for > 28 days before screening and are continued at the same dose throughout the study. Non-medicated emollients, moisturizers and sunscreens will be allowed once daily as normally used by the subjects and applied at least 3 hours after application of randomized investigational product to untreated areas only.	

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

Only non-medicated shampoos are permitted. Medicated shampoos (e.g., coal tar, keratolytics including salicylic acid, antifungals, zinc pyrithione, selenium sulfide, corticosteroids, medical devices) are prohibited. Subjects should not use other hair products for at least an hour before or after application of investigational product.

4.6 Treatment

4.6.1 IP Supplies, Packaging and Labeling

ARQ-154 foam 0.3% or vehicle foam will be provided in a dispense can containing approximately 60 grams of foam. The cans will be packaged in kits, each containing two cans. The number of kits dispensed to a subject will be based on the BSA involvement. It is anticipated that the maximum number of kits dispensed to a subject will be two. The kits and cans 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 investigational product (ARQ-154 foam 0.3%, and matching vehicle) to each site to allow for completion of this study.

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

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

4.6.2 Blinding

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

4.6.3 Treatment Administration

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

IP will be applied QD in the evening (except at Baseline and Week 2, in which case IP will be applied at the study site) to areas of lesions of seborrheic dermatitis. IP will be applied at least 20 minutes before going to bed.

For Scalp Lesions: IP will be applied when the skin and hair on the scalp is dry. Subjects should dispense IP on their fingers, then part hair where there are lesions and rub in. Subjects should not use other hair products for at least an hour before or after application. Subjects should maintain treatment of areas with the IP for the duration of the study regardless of whether treatable areas of seborrheic dermatitis clear.

For Non-scalp Lesions: IP should be applied QD to affected areas and rubbed in until disappeared. Subjects should maintain treatment of areas with IP for the duration of the study regardless of whether treatable areas of seborrheic dermatitis clear.

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

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

Subjects should continue to apply the IP to all treatment areas identified by the Investigator at Baseline using a Body Diagram even if that area has cleared during the treatment period. New plaques that develop during the study should be treated as well.

Each IP can will be weighed prior to dispensing at the baseline visit or subsequent visits. IP cans 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 Manual), the subject will be retrained on the IP application technique.

4.6.4 Treatment Compliance

Weight of the IP applied will be measured for reporting purposes. IP cans will be weighed at each follow-up clinic visit. The weight of the IP can will be collected prior to the IP application

and after the IP application at Baseline and Week 2. Weight of the IP applied and the IP cans will be recorded in the source notes and in the eCRF.

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 Adverse Events (AEs). Site personnel will review the diaries at each clinic visit 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 IP administration schedule (i.e. if subject forgets a dose they should wait until that evening and apply as usual).

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

Compliance will be assessed by review of the dosing diary. If the diary shows less than 80% of expected use, the subject is using too little IP and retraining must be conducted and documented.

Compliance will be documented in source and in eCRF.

5 STUDY PROCEDURES

5.1 Safety Assessments

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

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

5.1.1 Screening

Within 4 weeks prior to the first dosing (Baseline visit), 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 seborrheic dermatitis assessments, a physical examination, vital sign measurements (blood pressure, heart rate, and temperature), PHQ-8, C-SSRS, and laboratory tests: hematology, chemistry, urinalysis and serum (Screening) and urine (Baseline) pregnancy tests for female subjects of child bearing potential.

All screened subjects will receive a screening number according to Section 4.3.2 and be entered into the IWRS and eCRF. Subjects that fail to meet the eligibility criteria will be designated as a screen failure and entered into the IWRS and eCRF as such.

Subjects may be re-screened one time, the original assigned Subject ID screening number will be used for re-screening.

5.1.2 Baseline

Randomization will take place at the Baseline visit after the subject has been found to be fully eligible for participation. The subject is considered enrolled into the study once randomization occurs and the subject has been assigned to one of the treatment groups.

If the Baseline visit occurs within 14 days of Screening, the Screening lab results may be utilized.

5.1.3 Physical Examination

Physical examinations will be performed as follows:

Screening, Baseline and Week 8.

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

5.1.4 Vital Signs, Height and Weight

Vital signs will be collected at timepoints noted below:

Blood pressure, heart rate, and temperature will be measured at Screening, Baseline, Weeks 2, 4, 8, and 9.

Height will be collected at Baseline and Week 8.

Weight will be collected at Screening, Baseline, Weeks 2, 4, 8, and 9. Subject to void prior to weight being taken and remove any jackets, outerwear and shoes. Remove any objects of significant weight (i.e. cell phones, wallet, key chains). A 5% weight loss from Baseline should be reported to the medical monitor. Blood pressure will be collected while the subject is sitting/resting for at least 5 minutes.

5.1.5 Laboratory Tests

All tests listed in Table 2 below will be performed according to the Schedule of Visits and Assessments (Section 1.3), unless otherwise noted. The collection of specimens will be in a non-fasting state. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator. Laboratory samples will be sent to the central lab. Refer to the most current Central Laboratory Manual for collection, processing, ship, and report receipt instructions.

Table 2: Laboratory Tests

Hematology		**Serum Chemistry**
• Hemoglobin • Hematocrit • Total and differential leukocyte count • Red blood cell count with indices and morphology • Platelet count		• Blood Urea Nitrogen • Bilirubin (total and direct) • Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Albumin • Sodium • Potassium • Chloride • Glucose • Creatinine
Urinalysis		**Additional Tests**
• pH • Specific gravity • Protein* • Glucose • Ketones • Bilirubin • Blood* • Nitrite* • Urobilinogen • Leukocyte esterase*		• Urine pregnancy test** (for females of child bearing potential only) • Serum pregnancy test (hCG)***
* 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. ** Baseline, Weeks 4, and 8, for FOCBP only *** At Screening, for FOCBP only		

5.1.6 Patient Health Questionnaire depression scale (PHQ-8)

The 8 item PHQ-8 Assessment (see Appendix 1) will be completed by the subject at the following visits:

Screening, Baseline, Week 4, and Week 8

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 investigational product, consideration should be given to discontinuation from investigational product.

Subjects with PHQ-8 $\geq$10 at Screening or Baseline will be excluded from the study.

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

Five severity categories of depression are defined as follows:

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

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

C-SSRS Assessments will be performed as follows:

Screening, Baseline, Week 4, and Week 8.

The administration schedule of the C-SSRS will be:

- The Baseline-Screening version (Appendix 2) 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 3) 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 IP. This should result in prompt referral to a mental health professional and/or possibly the emergency room. The Medical Monitor should be contacted.

The trained administrator will conduct the C-SSRS. The C-SSRS administrator 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.

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

5.1.8 Local Tolerability Assessments

The Investigator Local Tolerability Assessment will be an overall assessment of local tolerability and performed as follows:

Baseline, Weeks 4 and 8

Application site reactions will be graded at the timepoints outlined in the Schedule of Visits and Assessments (Section 1.3). Irritation reactions are graded using the scale detailed in the following section (Berger 1982). Reactions at the site of product application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's seborrheic dermatitis.

The Investigator assessments will be conducted by the Investigator prior to any investigational product application in the study site.

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 an overall assessment of local tolerability and performed as follows:

Baseline, Weeks 4 and 8

This assessment will be administered at Baseline by the site 10 to 15 minutes after IP application at the study site. Assessments at the study site during Weeks 4 and 8 will be a recall assessment of the subject's experience 10-15 minutes after IP application since the last study visit.

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

5.1.9 Pigmentation Assessment

The Investigator will assess for pigmentation in areas affected previously and/or currently by seborrheic dermatitis at the following visits:

Screening, Baseline, Weeks 2, 4, 8 and 9.

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

5.1.10 Adverse Events

Adverse events (AEs) will be collected beginning at informed consent and assessed at the following visits and throughout the study:

Screening, Baseline, Weeks 2, 4 and 8, and 9

AE collection will end upon completion of study participation for subjects who complete or early terminate from the study without any new or ongoing AEs. Subjects with new or ongoing related AEs upon study completion or early termination will be followed for up to one month after the end of treatment until the symptoms or clinically significant abnormal laboratory test value(s) return to normal or acceptable levels, as judged by the Investigator.

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, see Section 5.7.

5.2 Efficacy Evaluations

5.2.1 Investigator Global Assessment (IGA)

Investigator's Global Assessments ('whole body' and 'intertriginous area') will be performed at the study visits listed below. The IGA should be completed prior to any other physician assessments.

Screening, Baseline, Weeks 2, 4, 8, and 9

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

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

Investigator Global Assessment of Disease (IGA)

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

5.2.2 Overall Assessment of Erythema

Overall Assessment of Erythema will be performed at the following study visits:

Screening, Baseline, Weeks 2, 4, 8, and 9

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

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

Overall Assessment of Erythema

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

5.2.3 Overall Assessment of Scaling

Overall Assessment of Scaling will be performed at the following study visits:

Screening, Baseline, Weeks 2, 4, 8, and 9

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

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

Overall Assessment of Scaling

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

5.2.4 Body Surface Area (BSA)

BSA Assessments will be performed as follows:

Screening, Baseline, and Week 8

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

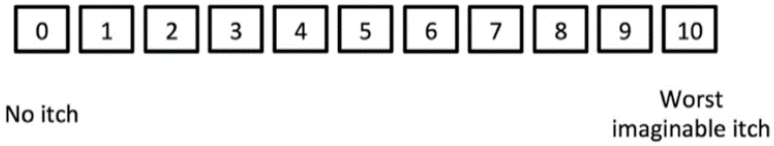
5.2.5 Worst Itch Numerical Rating Scale (WI-NRS)

Given that itch is an important symptom of seborrheic dermatitis, a WI-NRS assessment is included in the present study. A responder analysis will be performed to evaluate achievement of a 4-point reduction of WI-NRS, which has been described as optimal for demonstrating a level of clinically meaningful improvement in itch severity in other skin conditions, including other forms of eczema (Yosipovitch 2019) and psoriasis (Kimball 2016).

WI-NRS Assessments will be performed as follows:

Screening, Baseline, Weeks 2, 4, and 8

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.



5.2.6 Scalpdex

The Scalpdex will be completed as follows:

Screening, Baseline, Weeks 2, 4, and 8

Subjects will complete the Scalpdex. See Appendix 5 for the Scalpdex.

5.2.7 Dermatology Life Quality Index (DLQI)

The DLQI will be completed as follows:

Screening, Baseline, Weeks 2, 4, and 8

Subjects will complete the DLQI. See Appendix 4 for the DLQI.

5.2.8 Dermal Imaging

Medical photography will be performed at selected sites at Baseline, Weeks 2, 4, and 8 using Canfield photography equipment. Photography should be focused on single lesions or specific body sections (e.g. arm). Body or half body photos should only be taken if necessary. All efforts will be made to de-identify the subjects. Subjects who are unwilling to participate in the medical photography will be allowed to opt out of this procedure and documented on the informed consent. Refer to the current Photography Manual for instructions regarding photography.

5.3 Pharmacokinetics Assessment

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

Baseline, Weeks 4 and 8

PK draws will be collected while the subject is having serum chemistries drawn. At Baseline, the draws will be pre-dose drug application in the clinic. Ensure the IP is not applied in the area where PK will be drawn.

5.4 Final Study Visit

The approximate final study visit will occur at Week 9. The procedures performed during these visits are described in the Schedule of Visits and Assessments (Section 1.3). A 5-day scheduling window is allowed for this visit. Adverse events will be recorded as reported by the participant or followed to resolution as outlined in Section 5.1.10.

5.5 Early Termination Visit

If a subject is withdrawn or wishes to exit the study, a termination visit will be scheduled. This visit should include the procedures and assessments that would be performed at the Week 9 visit (Day 63).

5.6 Unscheduled Visit

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

5.7 Adverse Events

5.7.1 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 through subject study completion.

A treatment emergent adverse event (TEAE) is defined as an AE that started post application of IP at the Baseline visit through study completion.

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

5.7.2 Serious Adverse Event

The definitions and reporting requirements of Health Canada/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 SAEs are deemed drug-related. Refer to the Safety Reporting Instructions for details on how to submit the SAE Report. 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 ERB/IRB will be notified of the Alert Reports as per HC, FDA, ICH and the IRB/ERB'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/CTA.

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

5.7.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

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.

5.7.4 Safety Review

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 Investigator 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 Investigator.

Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

5.7.5 Adverse Event Reporting

The Investigator 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 IP 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 (e.g., 21.0 or higher).

5.8 Reporting Pregnancy

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

The Investigator is responsible for reporting all available pregnancy information on the pregnancy report and submitting to the Medical Monitor within 24 hours of becoming aware of the event, although pregnancy itself is not considered an AE. Follow-up information detailing the outcome of the pregnancy and the health of the newborn should be reported as it becomes available. Any pregnancy complication must be reported as a SAE. In addition, any pregnancy resulting in a congenital abnormality or birth defect of the newborn, or neonatal death occurring within 30 days of the birth must be reported as a SAE, regardless of causality. Any infant death that occurs after the 30 day reporting period that the Investigator suspects is related to the Investigational Product must also be reported as a SAE.

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

5.9 Treatment Stopping Rules

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

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

- Experiences a serious adverse event (SAE) or a clinically significant non-serious AE which in the opinion of the Principal Investigator or Medical Monitor warrants discontinuation from the IP for that subject's well-being.
- A severe (Grade 3) laboratory abnormality (confirmed by repeat sample and considered related to IP).
    - See Appendix 6 for details.

Dosing of IP 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 IP.

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

As noted above, 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. Given the excellent local toleration in the Phase 1/2a study, such reactions are possible, but unlikely.

5.9.1 Emergency Unblinding

Treatment assignment should remain blinded unless the knowledge is necessary to determine emergency medical care, as determined by the Investigator. Emergency unblinding will be done using the study IWRS system in consultation with the Medical Monitor and the Sponsor's CMO. Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the Investigator, the subject will have the IP discontinued.

6 DATA ANALYSIS

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

6.1 Statistical Methods

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

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

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

P-values of less than 0.10 will be considered statistically significant based on a two-sided test unless otherwise specified. No adjustments for multiplicity are planned.

6.1.1 Determination of Sample Size

A sample size of approximately 184 subjects are planned for the study.

The randomization scheme will be 2:1 (ARQ-154 foam 0.3% QD: matching vehicle QD). Randomization will be stratified by site and baseline disease severity (IGA = 3 or IGA = 4). Approximately 121 subjects will receive ARQ-154 foam 0.3% QD; approximately 63 subjects will receive vehicle foam QD.

A sample size of 184 subjects will provide approximately 90% power to detect an active response of at least 58.5%, assuming 159 subjects complete the study and a vehicle response of 30%, based on two-group X^2 test of equal proportions (without continuity correction), using a 2-sided alpha of 0.10.

6.1.2 Subjects to Analyze

Safety population will include all subjects who are enrolled and received at least one confirmed dose of IP. This population will be used for all safety analyses.

The Intention-to-Treat (ITT) population will include all randomized subjects. This population will be the primary analysis population for the analysis of efficacy endpoints.

Per-Protocol (PP) Population will include all subjects who are in the safety population, were at least 80% compliant with IP application, and showed no other serious deviations from the study protocol. This population will be used as a sensitivity analysis of primary and secondary efficacy endpoints.

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

6.1.3 Interim Analysis

One interim futility analysis is planned when the first 60 subjects randomized have had the opportunity to complete the 8 week disease assessment. This futility analysis will be non binding and will be used for decision making on further expansion and timing of the clinical development program in seborrheic dermatitis. Accrual to this study will not be held during the conduct and interpretation of this futility analysis. To maintain the integrity of the remaining

data to be collected, only sponsor staff responsible for planning further development in the seborrheic dermatitis program will be provided with results. This futility analysis will use a stopping rule defined by the rho family with parameter = 0.1.

6.1.4 Background and Demographic Characteristics

Demographic and baseline disease characteristics and vital sign information will be summarized descriptively for all randomized subjects.

6.1.5 Study Disposition

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

6.1.6 Protocol Deviations and Eligibility Deviations

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

6.1.7 Investigational Product Compliance

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

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

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

6.2 Study Objective

6.2.1 Primary Objective

To assess the safety and efficacy of ARQ-154 foam 0.3% administered QD vs vehicle x 8 weeks in adults with seborrheic dermatitis.

6.3 Efficacy Evaluation

6.3.1 Primary Efficacy Endpoint

The primary efficacy variable in this study is success in Investigator Global Assessment (IGA) of disease severity, defined as an IGA score of ‘Clear’ or ‘Almost Clear’ plus a 2-grade improvement from Baseline at Week 8.

The primary endpoint will be analyzed using a Cochran-Mantel-Haenszel test stratified by the stratification factors study site and baseline disease severity. Statistical significance will be concluded at the 5% significance level (2-sided).

Missing IGA scores will be imputed using multiple imputation.

6.3.2 Secondary Endpoints

The Secondary Efficacy Endpoints will include:

- Achievement of an IGA score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at weeks 2 and 4
- Change from Baseline in Overall Assessment of Erythema score at weeks 2, 4, and 8
- Change from Baseline in Overall Assessment of Scaling score at weeks 2, 4, and 8
- Achievement of an Overall Assessment of Erythema (0-3 scale) score of 0 or 1 PLUS a 2-grade improvement from Baseline at weeks 2, 4, and 8
- Achievement of an Overall Assessment of Scaling (0-3 scale) score of 0 or 1 PLUS a 2-grade improvement from Baseline at weeks 2, 4, and 8
- Change in WI-NRS pruritus score at weeks 2, 4, and 8, as compared to Baseline
- In subjects with a Baseline WI-NRS pruritus score of ≥4, achievement of a ≥4-point improvement from Baseline in WI-NRS pruritus score at weeks 2, 4, and 8

The binary endpoints will be analyzed using a Cochran-Mantel-Haenszel test stratified by study site and baseline disease severity similar to the primary endpoint.

The continuous endpoints will be analyzed using an analysis of covariance with treatment, study site, baseline disease severity, and baseline value as independent variables. Statistical comparison between the active treatment arm and vehicle arm will be facilitated by using contrasts.

The endpoints measuring change from baseline in overall assessment of erythema and scaling will be statistically tested using CMH row-mean scores test.

6.3.3 Exploratory Endpoints

Exploratory Endpoints will include:

- Change in Scalpdex total score from Baseline at Weeks 2, 4, and 8
- Achievement of an Overall Assessment of Erythema (0-3 scale) score of 0 or 1 at weeks 2, 4, and 8
- Achievement of an Overall Assessment of Scaling (0-3 scale) score of 0 or 1 at weeks 2, 4, and 8
- Achievement of an Overall Assessment of Erythema (0-3 scale) score of 0 at weeks 2, 4, and 8

- Achievement of an Overall Assessment of Scaling (0-3 scale) score of 0 at weeks 2, 4, and 8
- In subjects with a Baseline WI-NRS pruritus score of ≥4, achievement of a ≥4-point improvement from Baseline in WI-NRS pruritus score at weeks 2, 4, and 8
- Change from Baseline in DLQI at weeks 2, 4, and 8
- Change from Baseline in BSA affected at week 8
- A 2-grade improvement in IGA from Baseline

6.4 Safety Evaluation

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

6.4.1 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 the date of study treatment. 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.

Serious adverse events (SAEs) will be listed by subject. SAEs will be summarized by treatment group, severity, and relationship to study treatment.

For AEs, 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 IP, 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 listing of subjects who prematurely discontinue from the IP due to adverse events will also be provided.

6.4.2 Local Tolerance Assessments

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

6.4.3 Medical History and Physical Examinations

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

Clinically significant changes observed during physical examination will be captured as adverse

events and included in AE tabulations.

6.4.4 PHQ-8

Data for PHQ-8 will be analyzed by a shift in state of severity using the following scoring system:

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

6.4.5 C-SSRS

The C-SSRS will be analyzed per the Columbia–Suicide Severity Rating Scale Scoring and Data Analysis Guide.

6.4.6 Clinical Laboratory Results and Vital Signs/Weight Measurements

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

A shift table summarizing out-of-normal range shifts from baseline by treatment group will be provided for clinical laboratory results.

Shift tables (from baseline) by treatment group will summarize the number of subjects who gain or lose >5% body weight over the course of the study, as well as subjects who gain or lose >10% body weight over the course of the study.

6.4.7 Prior and Concomitant Medications

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

6.5 Patient Reported Outcomes Analyses

6.5.1 WI-NRS

Change from baseline in itch severity will be analyzed by treatment group and over time using the WI-NRS scale. For subjects with WI-NRS pruritus score ≥ 6 at baseline, the proportion of subjects with a 4-point reduction in WI-NRS pruritus score at weeks 2, 4, and 8 as compared to Baseline will be calculated by treatment group and analyzed using a Cochran-Mantel-Haenszel test stratified by study site and baseline disease severity (see secondary endpoints).

6.5.2 Dermatology Life Quality Index (DLQI)

Change from baseline in DLQI total score will be analyzed at weeks 2, 4, and 8 using an analysis of covariance with treatment, baseline score, and the stratification factors as independent variables.

6.5.3 Scalpdex

The Scalpdex will be analyzed as change from Baseline in total score as assessed at weeks 2, 4, and 8 using an analysis of covariance with treatment, baseline score, and the stratification factors as independent variables.

6.6 Pharmacokinetic Analysis

Plasma drug concentrations at pre-dose will be summarized using descriptive statistics.

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 1.3).

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

7 STUDY ADMINISTRATION

7.1 Ethics

7.1.1 Ethics Review Board

Before enrollment of patients into the study, the current protocol, ICF, and any accompanying material to be provided to the subjects will be reviewed and approved by an appropriate IRB or IEC, as required by FDA (21 CFR § 56), Health Canada, and ICH GCP regulations. A letter documenting the IRB or IEC 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 or IEC. However, the frequency of these reports will depend on IRB or IEC requirements. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB or IEC per the IRB or IEC requirements, and in compliance with FDA and Health Canada regulations and ICH GCP guidelines.

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

7.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, the principles of the Tri-Council Policy Statement (TCPS), the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

7.1.3 Subject Information and Consent

The Investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation (in non-technical terms) of the purpose of the study, the procedures to be carried out and the potential hazards before undertaking any study-related procedures. The Investigator must use the most current approved consent form for documenting written informed consent. Subjects will be assured that they may withdraw from the study at any time without jeopardizing their medical care. Each informed consent will be read, appropriately signed and dated by the subject, the Investigator conducting the consent discussion, and by an impartial witness if required by local requirements.

Subjects will be given a signed copy of their ICF.

7.2 Study Completion and Termination

7.2.1 Study Completion

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

7.2.2 Study Termination

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

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

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

7.3 Study Monitoring

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

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

7.4 Data Quality Assurance

In order to ensure the collection of accurate, consistent, complete, and reliable data during this clinical investigation, Sponsor representatives or designees may conduct audits of participating sites at appropriate intervals throughout the study. The results of these periodic site audits may be subject to review by independent auditors at completion of the clinical investigation. The Clinical Study Report will be audited by the Premier Research's Quality Assurance (QA) department and the QA audit certificate will be included in the study report.

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 to check for missing data, data inconsistencies, data ranges etc. Corrections are made prior to database lock.

7.4.1 Verification of Blinding

The treatment assignments for all enrolled subjects will be unblinded only after the conclusion of the study. Specifically, the blind will be broken only after all data are verified, entered into the database, and validated; subject evaluability assessments are performed and entered into the database; and the database is locked.

7.5 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 ERB/IRB and Study Monitor/Sponsor, AE reports, and information regarding subject discontinuation and completion of the clinical investigation.

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

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

7.6 Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the Investigator or Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the Investigator and Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the Investigator and Sponsor. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.
No deviation from the protocol will be made except to protect the life or physical well-being of a subject in an emergency. Except in such emergencies, prior approval of the Sponsor, and the IRB, is required before deviations from the planned protocol. All protocol deviations that occur during the study will be documented and reported to Sponsor and to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

No waivers to inclusion/exclusion criteria will be granted; subjects need to meet all criteria, exactly as specified, to be enrolled. Additionally, prospective deviations from the protocol or investigational plan are not permitted except to protect the life or physical well-being of a subject in an emergency. Deviations that occur unintentionally or are the result of action by the subject must be documented and reported to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

7.7 Confidentiality and Privacy

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

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

disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

7.8 Conflict of Interest

All study investigators will provide documentation of their financial interest or arrangements with Arcutis Inc., or proprietary interests in the IP under study. This documentation must be provided prior to the Investigator's participation in the study. All investigators with reported conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study.

7.9 Report Format

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

7.10 Publication Policy

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

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9 APPENDICES

Appendix 1: Patient Health Questionnaire depression scale (PHQ8)

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

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

Appendix 2: 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	____	____

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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:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**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* _____

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Appendix 3: Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

Since Last Visit

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
If yes, describe:

Yes ☐ No ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period.
Have you actually had any thoughts of killing yourself?
If yes, describe:

Yes ☐ No ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?
If yes, describe:

Yes ☐ No ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
If yes, describe:

Yes ☐ No ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
If yes, describe:

Yes ☐ No ☐

INTENSITY OF IDEATION

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

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

Most Severe

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

____

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

____

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

____

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

____

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

____

C-SSRS—Since Last Visit (Version 1/14/09)
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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:	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**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 4: Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX

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

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

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

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

Please check you have answered EVERY question. Thank you.

Appendix 5: Scalpdex

Scalpdex

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

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

Appendix 6: 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 and FEV_1 <80% predicted after bronchodilator
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities, no treatment	Prevents daily and usual social activity or requires treatment
Nasal discharge (rhinitis infective per **CTCAE 4.0**)	-	Localized; local intervention indicated (e.g. topical antibiotic, antifungal, or antiviral)	-
Pharyngitis **(CTCAE 4.0)**	-	Localized; local intervention indicated (e.g. topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated
Pneumonitis (rales or rhonchi) **(CTCAE 4.0)**	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated
Lung infection (**CTCAE 4.0**)	-	Moderate symptoms; oral intervention indicated (e.g. antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated

[a] Inclusion dependent upon protocol requirements

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 [a]	2.5-5 cm	5.1-10 cm	>10 cm
Induration/swelling [b]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity
Systemic reactions			
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema or anaphylaxis
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
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

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

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

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