ARQ-154-214

A Phase 2, Multicenter, Open-Label Study of the Long-Term Safety of ARQ-154 Foam 0.3% in Subjects with Seborrheic Dermatitis

Sponsor:	Arcutis Biotherapeutics, Inc. [redacted]
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]
IND Number:	142047
Protocol Version:	Amendment 2
Protocol Date:	04 November 2021

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

A Phase 2, Multicenter, Open-Label Study of the Long-Term Safety of ARQ-154 Foam 0.3% in Subjects with Seborrheic Dermatitis

ARQ-154-214

SPONSOR: Arcutis Biotherapeutics, Inc.
[redacted]

ISSUE DATE: 04 November 2021

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

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

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

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

Investigational Site Name: _____

Print Investigator Name: _____

Investigator Signature: _____ Date: _____

SUMMARY OF CHANGES

The following sections have been changed from the Amendment 1 edition of the ARQ-154-214 protocol:

Section	Summary of Changes
Amendment 2.0	
Title page and Site Investigator Signature Page	Updated Sponsor contact
1.1 Synopsis	Updated to align with changes made within the protocol.
5.4.2 Exclusion Criteria	Transferred exclusion criterion for subjects that have previously participated in this study from Cohort 2 to Cohort 1.
5.6.3 Treatment Administration	Specified Cohort 1 Group 2 will apply last IP for ARQ-154-116 on Week 2 and IP dose for ARQ-154-214 will begin on Day 2.
6.1.3 Table 2 Laboratory Test	Added *Malassezia* Testing for Cohort 1 Group 2 and specified footnotes.
6.1.13 *Malassezia* Testing	Added new section for *Malassezia* Testing
6.6.5 Adverse Event Reporting Appendix 6	Revised to reference the most current version of the CTCAE and removed Appendix 6 which is the outdated version of the CTCAE.
7. Data Analysis	Added percent change from baseline for lab, vital sign, and related endpoint summary. Added Q1, Q3 to the summary statistics provided for continuous variables.
7.1 Statistical Method	Added that subjects in Cohort 1 Group 2 will be summarized in listing only. Removed primary analysis and added that final analysis will be performed once subjects in Cohort 1 Group 1 and Cohort 2 finish treatment. Removed imputation. Only observed values will be used in the analysis. Removed the language with regard to the analysis for Cohort 2 of IGA success. Details will be included in the SAP instead.
7.4.6 Pharmacokinetic Analysis	Added new section for Pharmacokinetic Analysis
8.1.2 Ethical Conduct of the Study	Revised to align with current guidelines
9. References	Revised with Investigator's Brochure version 4
Editorial changes made throughout to improve accuracy or readability.	

Section	Summary of Changes
Amendment 1.0	
Title page and Site Investigator Signature Page	Updated Sponsor address
1.1 Synopsis	Updated to align with changes made within the protocol.
1.3 Schedule of Visits and Assessments	Added clinic visits Week 36 and 52 and phone visits Week 30 and 44. Added a pharmacokinetic sample collection at the Week 4 visit for subjects age 9 – 16 years old.
5.2 Number of Sites and Subjects	Increased approximate total number of subjects enrolled from 375 up to approximately 410.
6.1.11 Pharmacokinetic Assessment	Added new section for the pharmacokinetic sample collection.
Table 1 Excluded Medications and Treatments	Clarified excluded investigational products does not refer to ARQ-154.
Throughout protocol as appropriate	Modified language specifying subjects will roll over from ARQ-154-203 to allow subjects successfully completing a prior ARQ-154 foam study.
Visits and treatment period	Added clinic visits at Weeks 36 and 52 and phone visits at Weeks 30 and 44. Extended treatment period to up to 52 weeks.
Cohort 1	Updated age range to 9 years and older
Schedule of Visits and Assessments	Included CDQ-2 parent report for children 9-11 years old, inclusive.
Inclusion Criteria # 4	Added females of non-childbearing potential must be either premenarchal.
Exclusion Criteria #5	Clarified this criterion is for systemic P-450 inhibitors.
Exclusion Criteria #12	Amended to allow siblings in the same household to participate if qualified
Exclusion Criteria #18	Added to exclude subjects that have previously participated in this study.
5.4.3 Removal of Subjects from Investigational Product	Clarified for PHQ if determined by Investigator in consultation with a mental health professional. Added CDI-2 raw score of ≥32 if determined by Investigator in consultation with a mental health professional.
	Statistical methods updated.
Editorial changes made throughout to improve accuracy or readability.	

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:	A Phase 2, Multicenter, Open-Label Study of the Long-Term Safety of ARQ-154 Foam 0.3% in Subjects with Seborrheic Dermatitis
Investigational Product:	ARQ-154 investigational product will be supplied as a 0.3% foam
IND:	142047
Clinical Indication:	Seborrheic dermatitis
Study Design:	ARQ-154-214 is an open-label, single-arm, long-term safety study of ARQ-154 foam 0.3% in subjects with seborrheic dermatitis involving up to 20% total BSA. Cohort 1 eligible subjects will enroll into the long-term safety study on the same day as the final visit for a previous ARQ-154 study. Cohort 1 Group 1 will be subjects who rolled over from the previous ARQ-154-203 study. Group 2 will be subjects who rolled over from the previous ARQ-154-116 study. Cohort 2 eligible subjects will enroll on Day 1 of this study. Investigational product will be applied by the eligible subjects topically QD for up to 52 weeks at home. Periodic clinic visits will include assessments for clinical safety, application site reactions evaluated in the clinic using the method of Berger and Bowman, and disease improvement or progression. Final analysis will be performed when subjects in Cohort 1 Group 1 and Cohort 2 (approximately 400 subjects) finish up to 52 weeks of treatment. Subjects in Cohort 1 Group 2 (approximately 10 subjects) will only be summarized in the listings and will be updated once all Group 2 subjects finish up to 52 weeks of treatment. A CSR addendum will be provided based on the updated Cohort 1 Group 2 listing.
Study Objectives:	To assess long-term safety in a multicenter, open-label, single-arm 52-week study in subjects with seborrheic dermatitis treated with ARQ-154 foam 0.3%.
Study Sites:	Up to approximately 40 sites in North America
Study Population:	Up to approximately 410 subjects total will be enrolled across Cohorts 1 and 2. For Cohort 1, subjects will be male and female adolescents (9-17 y/o) and adults (≥18 y/o) who have completed the treatment period in a prior ARQ-154 study and immediately enroll in this safety study. Cohort 1 Group 1 subjects will be the ones who rolled over from ARQ-154-203. Cohort 1 Group 2 subjects will be the ones who rolled over from ARQ-154-116. For Cohort 2, subjects will be male and female adolescents (12 – 17 y/o) and adults (≥18 y/o) subjects who may or may not have participated in a prior ARQ-154 study, i.e. either de novo subjects who did not participate in ARQ-154-203

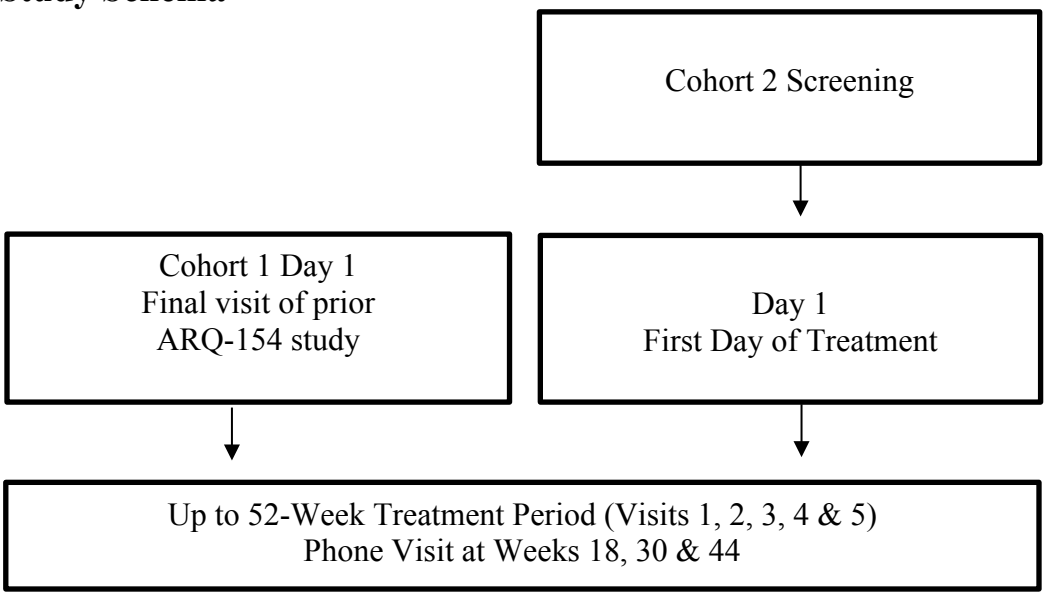
	or subjects who completed a ARQ-154 study prior to initiation of the current ARQ-154-214 study.
Inclusion Criteria: All Subjects	1. Participants legally competent to sign and give informed consent or (for adolescents) assent. 2. Males and females ages 9 years and older (inclusive) at the time of consent. 3. Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at all study visits. In addition, sexually active FOCBP must agree to use at least one form of an acceptable effective contraception throughout the trial. Acceptable effective forms of contraception may include: oral/implant/injectable/ transdermal contraceptives, intrauterine device, or partner's vasectomy. If barrier methods are used (e.g., condom with spermicide, diaphragm with spermicide), then 2 forms of contraception 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. 4. Females of non-childbearing potential must be either premenarchal or post-menopausal women 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).
Inclusion Criteria: Cohort 1 Only	5. Subjects with seborrheic dermatitis who met eligibility criteria for a prior ARQ-154 study, successfully completed a prior ARQ-154 study through the final visit and are able to immediately enroll into this long-term safety study on the final visit of a previous ARQ-154 study.
Inclusion Criteria: Cohort 2 Only	For subjects that have not participated in a prior ARQ-154 study: 6. Clinical diagnosis of seborrheic dermatitis of at least 3 months duration as determined by the Investigator. Stable disease for the past 4 weeks. 7. Seborrheic dermatitis of the scalp and/or face and/or trunk and/or intertriginous areas up to ≤20% BSA involvement. 8. An Investigator Global Assessment (IGA) of disease severity of at least Moderate ('3') at Day 1. 9. Overall Assessment of Erythema and Overall Assessment of Scaling scores of Moderate ('2') at Day 1. For subjects that have completed a prior ARQ-154 study prior to initiation of the current ARQ-154-214 study: 10. Clinical diagnosis of seborrheic dermatitis of at least 3 months duration as determined by the Investigator. 11. Seborrheic dermatitis of the scalp and/or face and/or trunk and/or intertriginous areas up to ≤20% BSA involvement.

Exclusion Criteria: All Subjects	1. Planned excessive exposure of treated area(s) to either natural or artificial sunlight, tanning bed or other LED. 2. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound safety or efficacy measurements. 3. Subjects unable to apply investigational product to the scalp due to physical limitation. 4. Known allergies to excipients in ARQ-154 foam [redacted] 5. Subjects who cannot discontinue the use of strong, systemic P-450 cytochrome inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin during the study period. 6. Known or suspected: • severe renal insufficiency, or moderate to severe hepatic disorders (Child-Pugh B or C) • history of severe depression, suicidal ideation or C-SSRS (for adolescents and adults 12 years old and older) indicative of suicidal ideation, whether lifetime or recent/current 7. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding. 8. Subjects with any serious medical condition or laboratory abnormality that would prevent study participation or place the subject at significant risk, as determined by the Investigator. 9. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of investigational product. 10. Current or a history of cancer within 5 years with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix. 11. 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. 12. Subjects who are family members of the clinical study site, clinical study staff, or Sponsor.
Exclusion Criteria: Cohort 1 Only	13. Subjects who experienced an ARQ-154 treatment-related AE or a serious AE (SAE) that precluded further treatment with ARQ-154 foam in prior ARQ-154 study. 14. Subjects that use any Excluded Medications and Treatments (Table 1).

Exclusion Criteria: Cohort 2 Only	17. Previous participation in this ARQ-154-214 study. 15. Subjects who cannot discontinue treatment with therapies for the treatment of seborrheic dermatitis prior to the Day 1 visit and during the study according to Excluded medications and Treatment (Table 1). 16. Subjects with PHQ-8 >10 or modified PHQ-A >10 at Screening or Day 1. For subjects that have completed a prior ARQ-154 study prior to initiation of the current ARQ-154-214 study: 18. Subjects who experienced an ARQ-154 treatment-related AE or a serious AE (SAE) that precluded further treatment with ARQ-154 foam.
Duration of Participation for Subjects:	Up to approximately 52 weeks
Key Assessments:	Safety will be monitored through application site assessments, safety labs, vital signs, physical examinations, clinical laboratory testing, and Adverse Events (AEs). Safety will also be monitored by C-SSRS (for adolescents and adults 12 years old and older), Children's Depression Inventory 2 (CDI-2, parent report for children 9-11 years old, inclusive), PHQ-8 (in adults) and modified PHQ-A (in adolescents 12-17 years old, inclusive) assessments. Efficacy assessments will include IGA, Overall Assessment of Erythema, Overall Assessment of Scaling, WI-NRS, Scalpdex, and BSA.
Study Endpoints:	Primary Endpoints • Occurrence of treatment emergent AEs (TEAEs) • Occurrence of Serious Adverse Events (SAEs) Secondary Endpoints • Achievement of an Investigator Global Assessment (IGA) of 'completely clear' or 'almost clear', as observed over time • A 2-grade improvement in IGA from Baseline (see Section 7.1.1) as observed over time • 'IGA Success', defined as achievement of an IGA of 'completely clear' or 'almost clear' plus a 2-grade improvement in IGA from Baseline (see Section 7.1.1) as observed over time • Duration of IGA Success, defined as the time from the first observation of IGA Success to the last time a subject's disease response meets the criteria for IGA success. The duration of IGA Success for subjects who end treatment in IGA Success will be censored at the last disease assessment date

	• Treatment-free interval, defined among subjects who achieve a 'completely clear' IGA and stop treatment to all lesions as the time from attainment of a score of ‘completely clear’ to re-starting IP.
Statistical Considerations:	Up to approximately 410 subjects total across Cohorts are planned for this study. The sample size will be sufficient to evaluate the long-term safety of ARQ-154 foam 0.3% up to 52 weeks of treatment. Descriptive statistics will be presented for the 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, Q1, Q3, minimum, and maximum for continuous data. <u>Adverse Events</u> For the primary endpoints, the occurrence of treatment-emergent AEs (TEAEs) and the occurrence of Serious Adverse Events (SAEs) will be tabulated by preferred term and system organ class. In addition, summary tables of TEAEs by severity, by relationship to investigational product, and those leading to withdrawal from investigational product will be created. <u>Vital Signs</u> Descriptive statistics will be calculated for vital signs and change from baseline and percent change from baseline in vital signs over time. <u>Clinical Laboratory Results</u> Descriptive statistics of the laboratory parameters will be calculated at each scheduled time point. Change from Baseline and percent change from Baseline will be summarized at each scheduled time point. Shifts from Baseline will be tabulated. <u>Patient Health Questionnaires</u> PHQ-8/PHQ-A/CDI-2 and C-SSRS questionnaires will be completed by the subjects at all study visits. Descriptive statistics will be calculated for the PHQ-8/PHQ-A/CDI-2. The C-SSRS will be analyzed per the Scoring and Data Analysis Guide from the Columbia Lighthouse Project. Descriptive statistics will be presented for the efficacy data collected in the clinical trial for the subjects who enroll in this study and receive at least one day of IP. For the binary endpoints related to IGA, the proportions of subjects achieving each endpoint will be tabulated at each scheduled visit. For subjects who withdraw from study due to lack of efficacy. The duration of response and treatment-free interval will be analyzed using the Kaplan-Meier method.

1.2. Study Schema



A Phase 2, Multicenter, Open-Label Study of the Long-Term Safety of ARQ-154 Foam 0.3% in Subjects with Seborrheic Dermatitis

Up to Approximately 410 subjects total across two cohorts with seborrheic dermatitis will be receive ARQ-154 foam 0.3%. Cohort 1 will consist of roll over subjects from a prior ARQ-154 study on the final visit and Cohort 2 will consist of subjects that may or may not have participated on in a prior ARQ-154 study.

1.3. Schedule of Visits and Assessments

Study Procedure	Washout Cohort 2	Day 1 (Cohort 2)	Wk 4 D 29	Wk 12 D 85	Wk 18 D 127	Wk 24 D 169	Wk 30 D 211	Wk 36 D 253	Wk 44 D 309	Wk 52/ ET D 365
Visit	**Screening**	**Final Visit of prior ARQ-154 Study l (Cohort 1)**	**1**	**2**	**Phone Visit**	**3**	**Phone Visit**	**4**	**Phone Visit**	**5**
Visit Window	**-35 days**		**+/- 3 days**	**+/- 5 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**
Informed consent/assent	X[k]	X[k]								
Physical examination[a]	X	X[l]				X				X
Medical history	X									
I/E criteria	X	X								
Hematology, Serum Chemistries, and Urine Analysis	X	X[l]	X	X		X		X		X
Vital signs, height, weight[b]	X	X[l]	X	X		X		X		X
IGA[c], Overall Assessment of Erythema[c], Overall Assessment of Scaling[c] , WI-NRS, Scalpdex	X	X[l]	X	X		X		X		X
BSA	X	X[l]				X		X		X
C-SSRS, PHQ-8/ PHQ-A/CDI-2[d]	X	X[l]	X	X		X		X		X
Pregnancy test[e]	X	X[l]	X	X		X		X		X
Local Tolerability Assessment[f]		X[l]	X	X		X		X		X
Pigmentation Assessment[g]	X	X[l]	X	X		X		X		X
Medical Photography[h]		X	X	X		X		X		X
Dispense study medication kit[i]		X	X	X		X		X		
IP application at the study site		X								
Dispense/review diary		X	X	X		X		X		X

Study Procedure	Washout Cohort 2	Day 1 (Cohort 2)	Wk 4 D 29	Wk 12 D 85	Wk 18 D 127	Wk 24 D 169	Wk 30 D 211	Wk 36 D 253	Wk 44 D 309	Wk 52/ ET D 365
Visit	**Screening**	**Final Visit of prior ARQ-154 Study l (Cohort 1)**	**1**	**2**	**Phone Visit**	**3**	**Phone Visit**	**4**	**Phone Visit**	**5**
Visit Window	**-35 days**		**+/- 3 days**	**+/- 5 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**	**+/- 7 days**
Weigh study medication		X	X	X		X		X		X
Adverse event assessment[j]	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X
PK Sampling[m]			X							
Malassezia test[n]			X	X		X		X		X

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

[b] Height will be collected at Day 1, Week 24 and Week 52/ET only. Weight will be collected at all study visits. Subject to void prior to weight being taken. Remove any jackets, outerwear and shoes. Remove any objects of significant weight (i.e. cell phones, wallet, key chains). A 5% unintentional weight loss from Baseline should be reported to the medical monitor.

[c] IGA will be a 5-point scale ranging from completely 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. Total BSA affected by seborrheic dermatitis will be determined at each visit. A body diagram should be used to record areas of seborrheic dermatitis involvement.

[d] Adolescents and adults will complete the C-SSRS (12 years of age and older). Adults will complete the PHQ-8. Adolescents (ages 12 -17, inclusive) will complete the modified PHQ-A. Parents/caregivers will complete CDI-2 (parent report) for children 9-11 years of age, inclusive.

[e] 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 for Cohort 2. A urine pregnancy test will be performed at Day 1, Weeks 4, 12, 24, 36 and 52. A negative result is required for continued participation in the study, and results must be available prior to dispensing of IP at each visit.

[f] Local tolerability will be assessed prior to IP application in the clinic for the Investigator assessment of skin (Berger and Bowman skin irritation score) and 10-15 minutes post IP application for the subject's '0-3' burning/stinging assessment at Baseline. Note for Investigator tolerability assessments: **reactions at the site of product application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's seborrheic dermatitis**. At Weeks 4, 12, 24, 36, and 52 will be a recall assessment of burning/stinging experienced post drug application on the previous day of the clinic visit.

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

[h] 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.

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

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

[k] For Cohort 1, the consent will be signed after completion of the final visit in prior ARQ-154 study. Cohort 2 will sign consent prior to any study-related procedures at the Screening Visit.

[l] For Cohort 1, this data will be obtained from the final visit of the prior ARQ-154 Study and used as the Day 1 data for this long-term safety study (ARQ-154-214). If after the prior ARQ-154 study completion, subjects should complete the screening visit procedures. The Baseline values for Safety tabulations will be taken from the day that the subject received their first active IP (across prior ARQ-154 studies and ARQ-154-214). Baseline values for efficacy will be those recorded on Day 1 of the prior ARQ-154 Study. For Cohort 2, Baseline evaluations will be obtained for all procedures and the Baseline/Screening version of the C-SSRS will be utilized at Screening. For Cohort 2, Screening labs that are collected within 14 days of Day 1 do not need to be repeated.

[m] For Cohort 2 adolescent subjects PK samples will be collected on Week 4 for adolescent subjects between 12 – 16 years old. Collect PK sample with the safety lab collection. Ensure PK will not be drawn on the area where investigational product is applied.

[n] At select sites, the Investigator will collect samples for *Malassezia* testing on Cohort 1 Group 2 subjects at Weeks 4, 12, 24, 36, and 52. Samples will be collected from treated and untreated areas by swabbing the skin surface. Samples should be collected from the same areas as samples collected during the ARQ-154-116 Baseline visit.

2. ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AMP	Adenosine Monophosphate
AUC	Area Under the Curve
BSA	Body Surface Area
C_{max}	Maximum Concentration
CDI	Children's Depression Inventory
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
FDA	U.S. Food and Drug Administration
FOCBP	Female of Child Bearing Potential
GCP	Good Clinical Practices
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
mL	Milliliter
NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
Ng	Nanogram

Abbreviation	Definition
NRS	Numerical Rating Score
PASI	Psoriasis Area and Severity Index
PDE-4	Phosphodiesterase 4
PHQ-A	Modified PHQ-9 for Adolescents
PHQ-8	Patient Health Questionnaire depression scale
PI	Principal Investigator
PK	Pharmacokinetics
QD	Once Daily ("quaque die")
SAE	Serious Adverse Event
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to reach maximum concentration
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.

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). Additionally, a case report documented several subjects with recalcitrant seborrheic dermatitis successfully treated with apremilast (Cohen 2020).

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. 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 2 open-label safety 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, [redacted]

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.

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

[redacted]

[redacted]

3.3. Clinical Studies

3.3.1. Topical Roflumilast Cream

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

3.3.1.1. Psoriasis Phase 2a

ARQ-151 cream 0.5% and 0.15% have been studied in a Phase 2a study (ARQ-151-101; NCT03392168) in adult patients with mild to moderate chronic plaque psoriasis in the United States and Canada. The study included two cohorts. Cohort 1 was a single dose study to 25 cm^2 of psoriatic plaque(s) in 8 psoriasis subjects. Cohort 1 subjects were then enrolled, if they met entry criteria, into Cohort 2 of the study. Cohort 2 was a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.5%, ARQ-151 cream 0.15% or vehicle cream was applied QD for 28 days to 89 subjects with at least 0.5% BSA of chronic plaque psoriasis; area for application was not to exceed 5.0% BSA. Cohort 2 subjects had at least one target plaque of psoriasis of at least 9 cm^2 Target Plaque Area (TPA) in size and with a Target Plaque Severity Score (TPSS) ≥ 4. However, all body psoriasis plaques were treated except for the face, scalp, intertriginous areas and palms/soles. Only safety and pharmacokinetics were evaluated for the single dose Cohort 1 subjects.

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

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

[redacted]

[redacted]

3.3.1.2. Psoriasis Phase 2b

ARQ-151 has also been evaluated in a Phase 2b study (ARQ-151-201; NCT03638258) in adult patients with chronic plaque psoriasis. ARQ-151-201 was a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.15%, ARQ-151 cream 0.3%, or vehicle cream was applied QD for 12 weeks to over 300 adult subjects with 2% to 20% BSA of chronic plaque psoriasis and baseline IGA of Mild or greater.

In ARQ-151-201, the Primary Efficacy Endpoint was:

- Achievement of IGA score of 'clear' or 'almost clear' at Week 6

[redacted]

[redacted]

3.3.1.3. Atopic Dermatitis Phase 1

ARQ-151 has also been evaluated in a 15-day, open label, phase 1, PK and safety study in [redacted]

3.3.1.4. Atopic Dermatitis Phase 2

A parallel group, double blind, vehicle-controlled, Phase 2 study (ARQ-151-212; NCT03916081) has recently completed and evaluated ARQ-151 cream 0.05% and 0.15% in the treatment of mild to moderate atopic dermatitis in adolescents and adults with 1.5 to 35% BSA of involvement. [redacted]

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

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

The development plan for ARQ-154 foam will leverage experience to date with ARQ-151 cream, which has been safe, well tolerated, and effective in Phase 2 for the treatment of psoriasis, and safe and well tolerated in a small PK study for atopic dermatitis. [redacted] 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.

3.4.1. [redacted]

[redacted]

[redacted]

3.4.2. [redacted]

[redacted]

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

Oral roflumilast has now been used for almost a decade in the treatment of COPD exacerbations and its safety record has been well-documented. The known adverse effects of oral treatment in the COPD population (nausea, diarrhea, weight loss, psychiatric AEs; see Section 3.3.2) are monitorable, the current protocol is designed to detect these adverse events and others should they occur, and provides guidance for management, as necessary, to ensure patient safety.

[redacted]

4. STUDY ENDPOINTS AND OBJECTIVES

4.1. Study Objective

The objective of this study is to assess long-term safety in a multicenter, open-label, single-arm up to 52-week study in subjects with seborrheic dermatitis treated with ARQ-154 foam 0.3%.

4.2. Study Endpoints

4.2.1. Primary Endpoints

The primary endpoint will be analysis of safety monitored through application site assessments in the clinic using the method of Berger and Bowman, clinical laboratory testing, PHQ-8, Modified PHQ-A, CDI-2, C-SSRS and adverse events. Two primary endpoint analyses are planned:

- Occurrence of treatment emergent AEs (TEAEs)
- Occurrence of Serious Adverse Events (SAEs)

4.2.2. Secondary Endpoints

The secondary endpoints are related to efficacy and will include:

- Achievement of an Investigator Global Assessment (IGA) of 'completely clear' or 'almost clear', as observed over time
- A 2-grade improvement in IGA from Baseline (see Section 7.1.1) as observed over time
- 'IGA Success', defined as achievement of an IGA of 'completely clear' or 'almost clear' plus a 2-grade improvement in IGA from Baseline (see Section 7.1.1) as observed over time
- Duration of IGA Success, defined as the time from the first observation of IGA Success to the last time a subject's disease response meets the criteria for IGA Success. The duration of IGA Success for subjects who end treatment in IGA Success will be censored at the last disease assessment date
- Treatment-free interval, defined among subjects who achieve a 'completely clear' IGA and stop treatment to all lesions, as the time from attainment of a score of 'completely clear' to re-starting investigational product.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design and Plan

This is an open-label, single-arm, long-term safety study of ARQ-154 foam 0.3% in subjects with seborrheic dermatitis involving up to 20% total BSA. Cohort 1 eligible subjects will enroll into the long-term safety study on the same day as the final visit for a previous ARQ-154 study. For Cohort 1, subjects will be male and female adolescents (9-17 y/o) and adults (≥18 y/o) with seborrheic dermatitis. Cohort 1 Group 1 will be subjects who rolled over from the prior ARQ-154-203 study and Cohort 1 Group 2 will be subjects who rolled over from the prior ARQ-154-116 study.

Cohort 2 eligible subjects will enroll on Day 1 of this study. For Cohort 2, subjects will be male and female adolescents (12 – 17 y/o) and adults (≥18 y/o) subjects who may or may not have participated in a prior ARQ-154 study, i.e., either de novo subjects who did not participate in ARQ-154-203 or subjects who completed ARQ-154-203 prior to initiation of the current study, ARQ-154-214.

For each Cohort, investigational product will be applied by the qualifying subjects topically QD for up to 52 weeks. Periodic clinic visits will include assessments for clinical safety, application site reactions evaluated in the clinic using the method of Berger and Bowman, and disease improvement or progression.

Final analysis will be performed when subjects in Cohort 1 Group 1 and Cohort 2 (approximately 400 subjects) finish up to 52 weeks.

Subjects in Cohort 1 Group 2 (approximately 10 subjects) will only be summarized in the listings and will be updated once all Group 2 subjects finish up to 52 weeks of treatment. A CSR addendum will be provided based on the updated Cohort 1 Group 2 listing.

5.2. Number of Sites and Subjects

A total of up to approximately 410 subjects total across both Cohorts will be enrolled at approximately 40 study sites in North America. Additional countries or study sites may be added as necessary. Subjects in Cohort 1 will be male and female adolescents (9-17 y/o) and adults (≥18 y/o) with seborrheic dermatitis. Subjects in Cohort 2 will be adolescent and adult males or females with seborrheic dermatitis that may or may not have participated in a prior ARQ-154 study. Subjects in Cohort 2 that have not participated in a prior ARQ-154 study (i.e., de novo subjects) must have an IGA of disease severity of at least Moderate (‘3’) at Baseline. Subjects that completed a prior ARQ-154 study prior to initiation of the current ARQ-154-214 study may be eligible to enroll in Cohort 2 of the present study, and these subjects may have any IGA at Day 1 of the present study. All subjects in each Cohort 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.

5.3. Subject Participation

Subject participation involves a minimum of 5 clinic visits at Week 4, Week 12, Week 24, Week 36 and Week 52 and phone visits at Week 18, Week 30 and Week 44. The Day 1 visit of this study will be the final visit of a preceding ARQ-154 study for Cohort 1 and Day 1 of this study for Cohort 2. The anticipated duration of subject participation up to approximately 52 weeks.

5.3.1. Numbering of Subjects

Cohort 1 subjects enrolled may retain their unique five-digit subject ID number previously assigned during the prior ARQ-154 study or may be assigned a unique ID. Cohort 2 subjects will be numbered with the 2-digit site number and a three-digit subject number starting with 500.

The clinical site is responsible for maintaining a current log of subject ID number assignments and the investigational product kit numbers assigned to that subject and entering into the IRT system. 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.).

5.4. Selection of Study Population

5.4.1. Inclusion Criteria

All Subjects

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

1. Participants legally competent to sign and give informed consent or (for adolescents) assent.
2. Males and females ages 9 years and older (inclusive) at the time of consent.
3. Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at all study visits. In addition, sexually active FOCBP must agree to use at least one form of an acceptable effective contraception throughout the trial. Acceptable effective forms of contraception may include: oral/implant/injectable/transdermal contraceptives, intrauterine device, or partner's vasectomy. If barrier methods are used (e.g., condom with spermicide, diaphragm with spermicide), then 2 forms of contraception 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.
4. Female of non-childbearing potential must be either pre-menarchal or post-menopausal women 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).

Cohort 1 Only

5. Subjects with seborrheic dermatitis who met eligibility criteria for a prior ARQ-154 study, successfully completed a prior ARQ-154 study through the final visit and are able to immediately enroll into this long-term safety study on the final visit of a previous ARQ-154 study.

Cohort 2 Only

For subjects that have not participated in a prior ARQ-154 study:

6. Clinical diagnosis of seborrheic dermatitis of at least 3 months duration as determined by the Investigator. Stable disease for the past 4 weeks.
7. Seborrheic dermatitis of the scalp and/or face and/or trunk and/or intertriginous areas up to ≤20% BSA involvement.
8. An Investigator Global Assessment (IGA) of disease severity of at least Moderate ('3') at Day 1.
9. Overall Assessment of Erythema and Overall Assessment of Scaling scores of at least Moderate ('2') at Day 1.

For subjects that have completed a prior ARQ-154 study prior to initiation of the current ARQ-154-214 study:

10. Clinical diagnosis of seborrheic dermatitis of at least 3 months duration as determined by the Investigator.
11. Seborrheic dermatitis of the scalp and/or face and/or trunk and/or intertriginous areas up to ≤20% BSA involvement.

5.4.2. Exclusion Criteria

All Subjects

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

1. Planned excessive exposure of treated area(s) to either natural or artificial sunlight, tanning bed or other LED.
2. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound safety or efficacy measurements.
3. Subjects unable to apply investigational product to the scalp due to physical limitation.
4. Known allergies to excipients in ARQ-154 foam [redacted]
5. Subjects who cannot discontinue the use of strong systemic P-450 cytochrome inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin during the study period.

6. Known or suspected:
    - severe renal insufficiency, or moderate to severe hepatic disorders (Child-Pugh B or C)
    - history of severe depression, suicidal ideation or C-SSRS (for adolescents and adults 12 years old and older) indicative of suicidal ideation, whether lifetime or recent/current
7. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.
8. Subjects with any serious medical condition or laboratory abnormality that would prevent study participation or place the subject at significant risk, as determined by the Investigator.
9. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of investigational product.
10. Current or a history of cancer within 5 years with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix.
11. 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.
12. Subjects who are family members of the clinical study site, clinical study staff, or Sponsor.

Cohort 1 Only

13. Subjects who experienced an ARQ-154 treatment-related AE or a serious AE (SAE) that precluded further treatment with ARQ-154 foam in a prior ARQ-154 study.
14. Subjects that use any Excluded Medications and Treatments (Table 1).
17. Previous participation in this ARQ-154-214 study.

Cohort 2 Only

15. Subjects who cannot discontinue treatment with therapies for the treatment of seborrheic dermatitis prior to the Day 1 visit and during the study according to Excluded medications and Treatment (Table 1).
16. Subjects with PHQ-8 $\geq$10 or modified PHQ-A $\geq$10 at Screening or Day 1.

For subjects that have completed a prior ARQ-154 study prior to initiation of the current ARQ-154-214 study:

18. Subjects who experienced an ARQ-154 treatment-related AE or a serious AE (SAE) that precluded further treatment with ARQ-154 foam.

5.4.3. Removal of Subjects from Investigational Product

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

- Occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements for investigational product administration as per the protocol.
- 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.
- Pregnancy.
- Subject's decision to withdraw from administration of the investigational product.
- Weight loss of >5% from Baseline if not dieting or intentionally trying to lose weight and after consultation with the Sponsor, at the Investigator's discretion.
- C-SSRS indicative of suicidal ideation.
- PHQ-8 or modified PHQ-A score ≥15 if determined by Investigator in consultation with a mental health professional.
- CDI-2 raw score of ≥32 if determined by Investigator in consultation with a mental health professional.
- Requirement for use of prohibited concomitant medication (see Table 1) after consultation with the Sponsor and Medical Monitor.
- Subject's repeated failure to comply with protocol requirements or study related procedures.

5.4.4. Removal of Subjects from the Study

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

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

5.5. Study Restrictions

5.5.1. 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 Day 1
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
Strong systemic P-450 cytochrome inhibitors (e.g. indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin)	2 weeks
Phototherapy, tanning beds, other light emitting devices	4 weeks
Investigational drugs (other than ARQ-154)	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 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.

5.6. Treatment

5.6.1. IP Supplies, Packaging and Labeling

ARQ-154 foam 0.3% will be provided in a dispense Can containing approximately 60 grams of foam. The Cans will be packaged in Kits. The number of Kits dispensed to a subject will be based on the BSA involvement. The Kit(s) and Cans will be labeled including a location to record the subject ID on the label.

The Sponsor will supply sufficient quantities of the investigational product (ARQ-154 foam 0.3%) 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 foam.

5.6.2. Blinding

This is an open-label study and no blinding is planned.

5.6.3. Treatment Administration

Seborrheic dermatitis lesions that have completely resolved, in the opinion of the Investigator, do not require continued treatment. At every clinic visit the Investigator will determine if the IGA are considered ‘clear’ and the subject will stop applying the investigational product. The subject will contact the clinical study site and document in diary when seborrheic dermatitis returns prior to restarting investigational product. Subjects that clear between scheduled visits should return for an unscheduled visit for the Investigator to confirm IGA score are considered ‘clear’.

Unless otherwise instructed by the Investigator, subjects will apply investigational product once daily. At the Day 1 visit, the study staff will demonstrate to the subject how to apply ARQ-154 foam using the first Can from the Kit that is provided to the subject at Day 1. 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 layer and rubbed in thoroughly but gently, until the foam 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. Cohort 1 Group 2 subjects will apply the last dose of IP for ARQ-154-116 Week 2 (Day 15) study visit; subjects will enroll in ARQ-154-214 on the same day but will start applying IP the following day (Day 2). The study staff will review with the subject the appropriate IP

dispensing and application technique for the ARQ-154-214 study during the Baseline visit (Day 1).

IP will be applied in the evening 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 IP into scalp skin. As the IP is applied, the subject should move any hair away to ensure that sufficient foam is actually applied directly to the affected skin on the scalp. Subjects should not use other hair products for at least an hour before or after application.

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

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

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

Subjects should continue to apply investigational product to all active seborrheic dermatitis lesions including any new lesions that develop during the study unless otherwise instructed by the Investigator. Application will be to all areas affected including the face, scalp and intertriginous areas. A Body and Scalp Diagram should be used to record existing and new areas of seborrheic dermatitis involvement that are subject to treatment.

Each IP Can will be weighed prior to dispensing at the Day 1 visit or subsequent visits. IP Cans must be returned by subjects at each study visit, both empty and full, and will be weighed individually. 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.

5.6.4. Treatment Compliance

Weight of the IP applied will be measured for reporting purposes. Each IP Can will be weighed individually at each follow-up clinic visit and 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 scheduled dose, they should be instructed to return to the protocol IP administration schedule (i.e. if subject forgets a dose they should wait until that evening and apply as usual).

A subject will be considered compliant with the dosing regimen if the subject applies at least 80% of the expected applications during the 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.

6. STUDY PROCEDURES

6.1. 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/PHQ-A/CDI-2, C-SSRS and AEs as outlined in the Schedule of Visits and Assessments (Section 1.3). If deemed necessary, additional safety assessments will be performed at the discretion of the Investigator.

Screening Visit (Cohort 2)

Within 35 days prior to the first dosing (Day 1), 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/PHQ-A, C-SSRS, and laboratory tests: hematology, chemistry, urinalysis and serum pregnancy tests for female subjects of childbearing potential.

All screened subjects will receive a screening number according to Section 5.3.1 and be entered into the IRT system 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.

Day 1 Visit

For Cohort 1, at Day 1 (Final visit of the prior ARQ-154 study) subjects will be provided details of study requirements and sign an informed consent. Each subject will undergo seborrheic dermatitis assessments, a physical examination, vital sign measurements (blood pressure, heart rate, and temperature), PHQ-8/PHQ-A/CDI-2, C-SSRS, and laboratory tests: hematology, chemistry, urinalysis and urine pregnancy tests for female subjects of child bearing potential will be obtained at the final visit of the prior ARQ-154 study and will serve as Day 1 for Cohort 1 subjects. Cohort 2 Day 1 assessments for this long-term safety study (ARQ-154-214) will be completed within 35 days of Screening.

For Cohort 2, if the Day 1 visit occurs within 14 days of Screening, the Screening lab results may be utilized. Cohort 2 subjects must meet the required wash out period for any excluded medications and treatment according to Table 1.

IP will be dispensed at the Day 1 visit (via IWRS) after the Investigator confirms the subject to be fully eligible for participation based on the study criteria listed in Section 5.4.1 and Section 5.4.2. A subject is considered enrolled into the study upon the first IP application.

6.1.1. Physical Examination

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

6.1.2. Vital Signs, Height and Weight

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

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

Height will be collected at Day 1, Week 24 and end of study Week 52/Early Termination.

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% unintentional weight loss from Baseline should be reported to the medical monitor.

6.1.3. 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. No food restrictions are required for the collection of specimens. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator. 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

Table 2: Laboratory Tests (Continued)

Urinalysis	Additional Tests
• pH • Specific gravity • Protein* • Glucose • Ketones • Bilirubin • Blood* • Nitrite* • Urobilinogen • Leukocyte esterase*	• Urine pregnancy test • (for females of childbearing potential only) • Serum pregnancy test (hCG)** • Pharmacokinetic (PK) assessments • *Malassezia* Test***

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

** At Screening only

*** Samples collected for Cohort 1 Group 2 subjects only and may be used for *Malassezia* testing.

6.1.4. Patient Health Questionnaire depression scale (PHQ-8)

The 8 item PHQ-8 Assessment (see Appendix 1) will be completed by adult subjects according to the Schedule of Visits and Assessments (Section 1.3).

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 >10 at Screening (Cohort 2 only) or Day 1 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)

6.1.5. Patient Health Questionnaire depression scale (Modified PHQ-A)

The 8 item Modified PHQ-A Assessment (see Appendix 2 will be completed by adolescent subjects (12-17 years old, inclusive) according to the Schedule of Visits and Assessments (Section 1.3).

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

Subjects with PHQ-A >10 at Screening (Cohort 2 adolescents only) or Day 1 will be excluded from the study.

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

Five severity categories of depression are defined as follows:

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

6.1.6. Children's Depression Inventory 2

The CDI-2 Assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3) for subjects 9 to 11 years old, inclusive.

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

This study will use the CDI Parent Report Form. An example of the Parent Report Form is presented in Appendix 6.

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

A subject with a CDI-2 raw score of $\geq$ 32 should be immediately referred to a mental health professional, and Investigators in consultation with the mental health professional should consider interruption or discontinuation of the IP.

6.1.7. Columbia-Suicide Severity Rating Scale (C-SSRS)

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

On all visits, the Since Last Visit version (Appendix 4) will be used for Cohort 1. Cohort 2 will use the Baseline-Screening version (Appendix 3) for Screening and Since Last Visit version (Appendix 4) for Day 1 and all remaining visits.

If a subject has a score greater than 0 in suicidal ideation at Screening (Cohort 2 only) or Day 1, this is important and may indicate the need for mental health intervention. The investigator should not enroll the subject in the study.

Any score greater than 0 in the suicidal ideation score 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.

6.1.8. Local Tolerability Assessments

The Investigator Local Tolerability Assessment will be an overall assessment of local tolerability.

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 at the timepoints outlined in the Schedule of Visits and Assessments (Section 1.3).

This assessment will be administered on Day 1 at the site 10 to 15 minutes after IP application at the study site. Assessments at the study site during Weeks 4, 12, 24, 36 and 52 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

6.1.9. Pigmentation Assessment

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

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

6.1.10. Adverse Events

Adverse events (AEs) will be collected beginning at informed consent and assessed at the following visits and throughout the study according to the Schedule of Visits and Assessments (Section 1.3).

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.

Refer to Section 6.6 for further details on Adverse Events.

6.1.11. Phone Visits

Phone visits at Weeks 18, 30 and 44 will be conducted for all subjects to review any adverse event or concomitant medication changes.

6.1.12. Pharmacokinetic Assessment

An optional pharmacokinetic sample will be collected during the Week 4 visit for Cohort 2 subjects between 12 – 16 years of age. Adolescent subjects must give assent and the parent/legal guardian give consent for the PK collection. Collect the PK sample while the subject is having safety laboratory samples drawn. Ensure the PK sample is not drawn on the area where IP is applied.

6.1.13. *Malassezia* Testing

Samples will be collected at select sites by an Investigator from treated and untreated areas of Cohort 1 Group 2 subjects by swabbing the skin surface according to the Schedule of Visits and Assessments (Section 1.3). The collected samples may be used for *Malassezia* testing. Samples should be collected from the same areas as those collected during the ARQ-154-116 Baseline visit. Refer to the *Malassezia* sample collection instruction manual for details.

6.2. Efficacy Evaluations

6.2.1. Investigator Global Assessment (IGA)

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

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

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

Investigator Global Assessment of Disease (IGA)

Score	Description
0	**Completely clear:** [redacted]
1	**Almost clear:** [redacted]
2	**Mild:** [redacted]
3	**Moderate:** [redacted]
4	**Severe:** [redacted]

6.2.2. Overall Assessment of Erythema

Overall Assessment of Erythema will be performed at the timepoints outlined in the Schedule of Visits and Assessments (Section 1.3).

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

Every effort must be made for the same Evaluator to complete the Overall Assessment of Erythema for the subject at every study visit.

Overall Assessment of Erythema

Symptom	Score	Description
Erythema	**0**	**None:** [redacted]
	1	**Mild:** [redacted]
	2	**Moderate:** [redacted]
	3	**Severe:** [redacted]

6.2.3. Overall Assessment of Scaling

Overall Assessment of Scaling will be performed at the timepoints outlined in the Schedule of Visits and Assessments (Section 1.3).

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

Every effort must be made for the same Evaluator to complete the Overall Assessment of Scaling for the subject at every study visit.

Overall Assessment of Scaling

Symptom	Score	Description
Scaling	**0**	**None:** [redacted]
	1	**Mild:** [redacted]
	2	**Moderate:** [redacted]
	3	**Severe:** [redacted]

6.2.4. Body Surface Area (BSA)

BSA Assessments will be performed at the timepoints outlined in the Schedule of Visits and Assessments (Section 1.3).

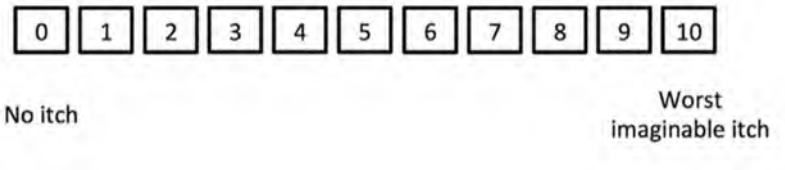
The BSA affected by seborrheic dermatitis will be determined by the subject's hand method, where the subject's hand (including fingers) surface area is assumed to equal 1% of body surface area (BSA).

6.2.5. 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 at the timepoints outlined in the Schedule of Visits and Assessments (Section 1.3).

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.



6.2.6. Scalpdex

The Scalpdex will be completed at the timepoints outlined in the Schedule of Visits and Assessments (Section 1.3).

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

6.2.7. Dermal Imaging

Medical photography will be performed at selected sites at Day 1, Weeks 4, 12, 24, 36 and 52 using Canfield photography equipment. Photography should be focused on single lesions or specific body sections (e.g. forehead). 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.

6.3. Final Study Visit

The approximate final study visit will occur at the end of Week 52 of overall involvement in the study. The procedures performed during this visit is described in the Schedule of Visits and Assessments (Section 1.3). A 7-day scheduling window is allowed for this visit. Adverse events will be recorded as reported by the subject or followed to resolution as outlined in Section 6.6.5.

6.4. Early Termination Visit

If a subject is withdrawn from the study, a termination visit will be scheduled. This visit should include the procedures and assessments that would be performed at the Week 52 visit. It will be noted in the database which subjects have completed the study and which were early terminations.

6.5. Unscheduled Visit

Subjects that clear between scheduled visits should return for an unscheduled visit for the Investigator to confirm IGA score are considered 'clear' and subject will stop application of investigational product after Investigator confirmation. Subjects will call the site when seborrheic dermatitis returns prior to restarting application of investigational product. Unscheduled visits may also 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.

The following information will be collected for all subjects:

- AEs
- Concomitant medications/procedures

The following information will be collected for those subjects that had stopped study medication but are experiencing a reoccurrence of seborrheic dermatitis. These subjects may have an unscheduled visit (although an unscheduled visit is not required as subjects only need to call the site) when seborrheic dermatitis returns prior to restarting application of investigational product:

- IGA

An updated Body Diagram of seborrheic dermatitis involvement should be provided to the subject.

6.6. Adverse Events

6.6.1. 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 Day 1 visit through study completion.

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

6.6.2. 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 IRB will be notified of the Alert Reports as per FDA, ICH and the IRB's policies and procedures.

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

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

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition that did not worsen
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the Day 1 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.

6.6.3. 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.

6.6.4. 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.

6.6.5. 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 most current version of the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5). The date and time of onset, time relationship to drug dosing, duration, and outcome of each event will be noted.

The relationship of each AE to the 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).

6.7. 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. 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.

6.8. Treatment Stopping Rules

If a subject has non-cutaneous adverse events of concern, clinically significant laboratory values or any condition that the Investigator determines could possibly be related to the 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).

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 or modified PHQ-A 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 with a CDI-2 raw total score of 32 or above should be referred to a mental health professional, and Investigators in consultation with the mental health professional should consider interruption or discontinuation of the IP.

- Subjects with a CDI-2 raw score of 21 or above in females and 22 or above in males should be referred to a mental health professional for evaluation

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

As noted above, 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.

7. 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.

7.1. 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 safety and efficacy 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, Q1, Q3, minimum, and maximum.

No missing efficacy or safety data will be imputed unless specified otherwise. The observed values will be used in the analysis.

The final analysis will be conducted after all treated subjects in Cohort 1 Group 1 and Cohort 2 have had the opportunity to be followed to the Week 52 assessment. Once all treated subjects in Cohort 1 Group 2 have had the opportunity to be followed to the Week 52 assessment, listings for these subjects will be provided for the CSR addendum.

7.1.1. Baseline Definition

For subjects in Cohort 1, the baseline value for safety and efficacy parameters will be defined as the last observation prior to the first dose of ARQ-154 foam 0.3% in either the prior ARQ-154 study or this study (See Section 7.2.1 for the definition of a treatment emergent event). Additional analyses will be performed where in the baseline value for subjects in Cohort 1 is defined as the last observation prior to the first dose of ARQ-154 foam 0.3% in this study. For the purpose of these latter analyses, study procedures will not be repeated; the information from the prior ARQ-154 study final visit will be carried over to the Day 1 visit for this study.

For subjects in Cohort 2, baseline values for efficacy and safety will be defined as the last observation prior to the first dose of ARQ-154 foam 0.3% in this study.

7.1.2. Determination of Sample Size

A sample size of up to approximately 410 subjects is planned for the study. This sample size will provide a sufficient population size to evaluate the long-term safety of ARQ-154 foam 0.3% over 52 weeks of treatment, and in the combination with other studies provide the development program with sufficient numbers of subjects to meet ICH exposure goals.

7.1.3. Subjects to Analyze

All analyses will be performed using the Safety Population which includes all subjects who are enrolled and received at least one confirmed dose of ARQ-154 foam 0.3% in this safety study. The number of subjects included in the Safety Population will be summarized.

Subjects in Cohort 1 Group 2 will be summarized in listings only.

7.1.4. Interim Analysis

No interim analysis will be performed.

7.1.5. Background and Demographic Characteristics

Baseline disease characteristics and vital sign information will be summarized descriptively for all enrolled subjects.

7.1.6. Study Disposition

Number of subjects enrolled, receiving investigational product, completing study, and withdrawing prematurely (with reason for withdrawal) will be summarized.

7.1.7. Protocol Deviations and Eligibility Deviations

The number of subjects with important protocol deviations and/or eligibility deviations will be summarized.

7.1.8. Investigational Product Compliance

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

The amount of investigational product used by each subject based on Can weight will be summarized using descriptive statistics.

Investigational product compliance will be calculated based on number of applications and amount of IP used divided by the expected number (amount) of study medication for each subject. Compliance will be summarized descriptively.

7.2. Safety Evaluation

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

7.2.1. 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 first date of study treatment in this study. 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.

7.2.2. 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.

7.2.3. 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.

7.2.4. PHQ-8 and Modified PHQ-A

Data for PHQ-8 and Modified PHQ-A 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)

7.2.5. C-SSRS

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

7.2.6. Clinical Laboratory Results and Vital Signs/Weight Measurements

All clinical laboratory results and vital signs measurements and their change from baseline and percent change from Baseline, 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.

7.2.7. 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.

7.3. Patient Reported Outcomes Analyses

7.3.1. WI-NRS

Change from baseline and percent 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 ≥ 4 at baseline, the proportion of subjects with a 4-point reduction in WI-NRS pruritus score at Weeks 4, 12, and 24 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 Section 4.2.2, Secondary Endpoints).

7.3.2. Scalpdex

The Scalpdex will be analyzed as change from Day 1 in total score as assessed at Weeks 4, 12, and 24 using an analysis of covariance with treatment, baseline score, and the stratification factors as independent variables.

7.4. Efficacy Endpoints

7.4.1. Achievement of IGA 'Completely Clear' or 'Almost Clear'

The subject incidence of an IGA Assessment will be tabulated for each assessment.

7.4.2. Achievement of IGA 'Completely Clear' or 'Almost Clear' plus a 2-grade Improvement from Baseline

The subject incidence of IGA of 'Completely Clear' or 'Almost Clear' plus a 2-grade improvement from Baseline will be tabulated for each assessment

7.4.3. Achievement of a 2-grade improvement in IGA from Baseline

The subject incidence of a 2-grade improvement in IGA from Baseline will be tabulated for each assessment.

7.4.4. Duration of IGA Success

Duration of IGA Success will be analyzed with the Kaplan-Meier method. The rate of subjects remaining in IGA Success over time will be summarized descriptively.

7.4.5. Treatment-free Interval

The time to re-starting IP will be analyzed with the Kaplan-Meier method. The rate of subjects remaining off treatment over time will be summarized descriptively.

7.4.6. Pharmacokinetic Analysis

For Cohort 2 adolescent subjects, blood samples for the determination of roflumilast and its N-oxide metabolite will be collected as delineated in the Schedule of Visits and Assessments (Section 1.3). Plasma drug concentrations at Week 4 will be summarized using descriptive statistics.

8. STUDY ADMINISTRATION

8.1. Ethics

8.1.1. Ethics Review Board

Before enrollment of subjects into the study, the current protocol, ICF, and any accompanying material to be provided to the subjects will be reviewed and approved by an appropriate IRB 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.

8.1.2. 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 E6 (R2), December 2016.

8.1.3. Subject Information and Consent

The Investigator is responsible for obtaining written informed consent from each individual participating in this study and/or parent(s)/legal guardians, 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. Subject and/or parent(s)/legal guardian(s) must provide their written informed consent prior to enrollment in a clinical trial and

before any protocol-specific procedures are performed. The Investigator must use the most current approved consent form for documenting written informed consent. Subjects and/or parent(s)/legal guardian(s) 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 and/or parent(s)/legal guardian(s), the Investigator conducting the consent discussion, and by an impartial witness if required by local requirements.

Adolescents will provide written assent and their parent(s) or legal guardian(s) will provide consent, as required by local laws.

Subjects and/or parent(s)/legal guardian(s) will be given a signed copy of their Consent/Assent.

8.2. Study Completion and Termination

8.2.1. 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.

8.2.2. 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

8.3. 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.

8.4. 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.

8.5. Data Handling and Record Keeping

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

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

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

8.6. 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.

8.7. 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.

8.8. Conflict of Interest

All study investigators will provide documentation of their financial interest or arrangements with Arcutis Biotherapeutics Inc., or proprietary interests in the 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.

8.9. 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).

8.10. Publication Policy

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

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10. APPENDICES

APPENDIX 1. PATIENT HEALTH QUESTIONNAIRE DEPRESSION SCALE (PHQ-8)

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

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

APPENDIX 2. PATIENT HEALTH QUESTIONNAIRE DEPRESSION SCALE (MODIFIED PHQ-A)

Modified PHQ-A

Name: _____ **Clinician:** _____ **Date:** _____

Instructions: How often have you been bothered by each of the following symptoms during the past **two weeks**? For each symptom put an **"X"** in the box beneath the answer that best describes how you have been feeling.

	(0) Not at all	(1) Several days	(2) More than half the days	(3) Nearly every day
1. Feeling down, depressed, irritable, or hopeless?				
2. Little interest or pleasure in doing things?				
3. Trouble falling asleep, staying asleep, or sleeping too much?				
4. Poor appetite, weight loss, or overeating?				
5. Feeling tired, or having little energy?				
6. Feeling bad about yourself – or feeling that you are a failure, or that you have let yourself or your family down?				
7. Trouble concentrating on things like school work, reading, or watching TV?				
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you were moving around a lot more than usual?				

APPENDIX 3. 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: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

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

APPENDIX 4. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) SINCE LAST VISIT VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

Since Last Visit

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

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

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

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

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

INTENSITY OF IDEATION

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

Most Severe Ideation: ____ _____ — Most Severe

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

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

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

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

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

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

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, ***as a result of act.*** Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	**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* _____

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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. CHILDREN'S DEPRESSION INVENTORY 2 (PARENT REPORT)

By Maria Kovacs, Ph.D.

CDI 2 PARENT

Child's Name/ID: _____ Child's Sex: Male Female (Circle One)

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

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

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

Instructions:

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

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

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

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