ARQ-154-309

A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-154 Foam 0.3% Administered QD in Subjects with Scalp and Body Psoriasis (ARRECTOR)

Sponsor:	Arcutis Biotherapeutics, Inc. 3027 Townsgate Road, Suite 300 Westlake Village, CA 91361
Sponsor Representative:	[redacted]
IND Number:	[redacted]
Protocol Version:	Amendment 3
Date:	29 July 2022

GCP Statement

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

Confidentiality Statement

SITE INVESTIGATOR SIGNATURE PAGE

ARQ-154-309

A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-154 Foam 0.3% Administered QD in Subjects with Scalp and Body Psoriasis

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

ISSUE DATE: 12 MAY 2022

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 foam 0.3% 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.

SUMMARY OF CHANGES

The following sections have been changed in Amendment 3 of the ARQ-154-309 protocol:

Section	Summary of Changes
Amendment 3	
Synopsis	Updated to align with changes made within the protocol.
Secondary Endpoints (3.2.2)	Revised PSD-related endpoints, adding new endpoints to the list of secondary endpoints and removing others.
Secondary Endpoints (5.2.8)	Added The PSD includes items related to Itching (question 1), Pain (question 9) and Scaling (question 11).
Secondary Endpoint (6.3.2)	Family 1 added or '$\alpha = 0.015$'. Updated the multiple testing strategy to reflect the change in the PSD secondary endpoints. Moved SI-NRS change from baseline at Day 1 endpoint from Family 1 to Family 3 in the multiple testing strategy. Family 3 added 'or 0.015 or 0.025'.
Editorial changes made throughout to improve accuracy or readability.	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
AMP	Adenosine Monophosphate
B-IGA	Body-Investigator Global Assessment of Disease
BSA	Body Surface Area
C_{max}	Maximum Concentration
CDLQI	Children's Dermatology Life Quality Index
CFB	Change from Baseline
COPD	Chronic Obstructive Pulmonary Disease
eCRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
EDC	Electronic Data Capture
ERB	Ethics Review Board
FDA	U.S. Food and Drug Administration
FOCBP	Female of Childbearing Potential
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practices
HC	Health Canada
IB	Investigational Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IGA	Investigator Global Assessment
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
IWRS	Interactive Web Response System
kg	Kilogram
LED	Light Emitting Device

Abbreviation	Definition
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
Min	Minute
mITT	Modified Intent to Treat
mL	Milliliter
NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
NRS	Numeric Rating Score
P-450	Cytochrome P450
PASI	Psoriasis Area and Severity Index
PASI-75	Psoriasis Area and Severity Index-75; subjects who achieve a 75% reduction in PASI from Baseline
PDE-4	Phosphodiesterase 4
PHQ-8	Patient Health Questionnaire
PHQ-A	Modified Patient Health Questionnaire for Adolescents
PI	Principal Investigator
PK	Pharmacokinetics
PSD	Psoriasis Symptoms Diary
PSSI	Psoriasis Scalp Severity Index
PSSI-75	Psoriasis Scalp Severity Index-75; subjects who achieve a 75% reduction in PSSI from Baseline
QD	Once Daily ("quaque die")
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
S-IGA	Scalp-Investigator Global Assessment of Disease
SI-NRS	Scalp Itch-Numeric Rating Scale
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper Limit of Normal
WI-NRS	Worst Itch-Numeric Rating Scale

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Arcutis Biotherapeutics, Inc.		
Protocol Number: ARQ-154-309	**Phase:** 3	**IND:** 142047
Protocol Title: A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-154 Foam 0.3% Administered QD in Subjects with Scalp and Body Psoriasis		
Clinical Indication: Scalp and Body Psoriasis		
Investigational Product: ARQ-154 foam investigational product (IP) will be supplied as ARQ-154 foam 0.3%. The active ingredient in ARQ-154 foam is roflumilast, a phosphodiesterase 4 (PDE-4) inhibitor. Matching vehicle foam will contain only excipients of ARQ-154 foam. Subjects will be randomized 2:1 to receive ARQ-154 foam 0.3% or matching vehicle foam once daily (QD) applied to all areas of scalp and body psoriasis. Areas of application will be all areas affected including face, scalp, trunk, or intertriginous/genital regions, with a maximum overall body surface area (BSA) of 25% (including a maximum non-scalp BSA of 20%). Subjects should continue to apply IP to all treatment areas for the duration of the study regardless of whether treatable areas of psoriasis clear. New lesions that appear during the treatment period should also be treated.		
Study Design: This is a parallel group, double blind, vehicle-controlled study in which ARQ-154 foam 0.3% or vehicle foam is applied QD x 8 weeks to subjects with scalp and body psoriasis. Total BSA affected and treated will not exceed 25% (not including palms/soles).		
Primary Objective: The purpose of this study is to assess the safety and efficacy of ARQ-154 foam 0.3% administered once daily (QD) vs. vehicle foam for 8 weeks in adolescent and adult subjects with scalp and body psoriasis.		
Study Sites: Approximately 45 sites in North America		
Number of Subjects (planned): Approximately 420		
Study Population: Subjects will be male and female adolescents (12-17 y/o) and adults (≥18 y/o). Subjects will have a minimum Scalp Investigator Global Assessment (S-IGA) = 'Moderate' (3) and a minimum rest of the Body Investigator Global Assessment (B-IGA) = 'Mild' (2) for study entry. Randomization will be stratified by study site, Baseline S-IGA (3 vs. 4), and Baseline B-IGA (2 vs. ≥3).		

Duration of Participation for Subjects: Screening (up to 4 weeks) + Treatment phase (8 weeks) for a total of up to approximately 12 weeks.

Main Criteria for Inclusion:

1. For adult subjects: Participants legally competent to read, write, and sign and give informed consent. For adolescent subjects: Informed consent of a parent(s) or legal guardian, and assent by the subjects, as required by local laws.
2. Males and females ages 12 years and older (inclusive) at the time of consent or assent.
3. Scalp psoriasis with a Scalp-Investigator Global Assessment of Disease (S-IGA) severity of at least Moderate ('3') at Baseline.
4. Extent of scalp psoriasis involving ≥ 10% of the total scalp at Baseline.
5. A Psoriasis Scalp Severity Index (PSSI) of at least 6 at Baseline.
6. An IGA of body (i.e., non-scalp) psoriasis (B-IGA) of at least Mild ('2') at Baseline.
7. A PASI score of at least 2 (excluding palms and soles) at Baseline.
8. Clinical diagnosis of psoriasis vulgaris of at least 6 months duration at Screening as determined by the Investigator. Stable disease for the past 4 weeks.
9. Total overall psoriasis involvement on scalp and non-scalp areas ≤ 25% BSA (not including palms/soles) at Baseline. Total non-scalp BSA should not exceed 20%.
10. Female subject of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening (Visit 1) and negative urine pregnancy test at Baseline (Visit 2). In addition, sexually active FOCBP must agree to use at least one form of highly effective contraception or a barrier method of contraception throughout the study according to Contraception Requirements (Figure 1).
11. Females of non-childbearing potential must either be premenarchal, post-menopausal with spontaneous amenorrhea for at least 12 months (post-menopausal status will be confirmed with FSH testing) or have undergone surgical sterilization according to Contraception Requirements. Prepubescent females must agree to be abstinent during the study (Figure 1).
12. Subjects in good health as judged by the Investigator, based on medical history, physical examination, vital signs, serum chemistry labs, hematology values, and urinalysis.
13. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule according to the Investigator judgment.

Main Criteria for Exclusion:

1. Subjects who cannot discontinue treatment with therapies for the treatment of psoriasis vulgaris prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 1).
2. Planned excessive exposure to treated area(s) to either natural or artificial sunlight, tanning bed, or other LED.
3. Subjects currently taking lithium or antimalarial drugs.
4. Planned initiation or changes to concomitant medication that could, in the opinion of the Investigator, affect psoriasis vulgaris (e.g., beta blockers or ACE inhibitors if not on stable dose for at least 8 week).
5. Current diagnosis of non-plaque forms of psoriasis (e.g., guttate, erythrodermic/ exfoliative, palmoplantar only involvement, or pustular psoriasis). Current diagnosis of drug-induced psoriasis.
6. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements.
7. Known allergies or hypersensitivity to component(s) of the investigational product [redacted]
8. 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) for two weeks prior to the Baseline visit and during the study period.
9. Known or suspected:
   - Known HIV infection
   - Severe renal insufficiency as evidenced by calculated creatinine clearance <30 mL/min or estimated glomerular filtration rate <30mL/min/1.73cm^2
   - Moderate to severe hepatic disorders (Child-Pugh B or C)
10. Liver functions tests results that exceed:
    - AST or ALT > 2x ULN
    - Total bilirubin:
      - > 1.5 x ULN or
      - > ULN and ≤ 1.5 x ULN AND direct bilirubin is > 35% of total bilirubin
    - ALP ≥ 2x ULN

11. Subjects with PHQ-8 (≥18 years old, inclusive) or modified PHQ-A (adolescents, 12 to 17 years old, inclusive) score ≥10 at Screening or Baseline visits.
12. History of severe depression, suicidal ideation or behavior, Baseline/Screening C-SSRS (for adolescents and adults 12 years old and older) indicative of suicidal ideation or behavior, whether lifetime or recent/current.
13. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.
14. Previous treatment with ARQ-151 or ARQ-154.
15. Subjects who have received oral roflumilast (Daliresp®, Daxas®), or apremilast (Otezla®) within the past 4 weeks prior to Baseline.
16. 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.
17. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of the investigational product.
18. Subjects who had a major surgery within 4 weeks prior to Baseline or have a major surgery planned during the study.
19. 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. Parent(s)/legal guardian(s) of adolescent subjects who are unable to communicate, read, or understand the local language.
20. Subjects with a current or a history of cancer within 5 years, with the exception of fully treated cutaneous basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix.
21. Subjects with active infection that required oral or intravenous administration of antibiotics, antifungals, or antiviral agents within 7 days of Baseline.
22. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members residing in the same household of enrolled subjects.
23. Subjects unable to apply product to the scalp (and/or psoriasis elsewhere) due to physical limitations.
24. Any condition that in the Investigator's assessment would preclude the subject from participating in the study.

Key Assessments: Safety will be monitored through application site assessments, vital signs/weight, physical examinations, safety labs, and Adverse Events (AEs). Safety will also be monitored by C-SSRS, and PHQ-8 (in adults) or modified PHQ-A (adolescents 12-17 y/o) assessments.

All AEs that occur after the first application of IP through the end of the study should be collected. All SAEs should be collecting starting at Screening.

Efficacy assessments will be evaluated utilizing:

- Scalp-IGA (S-IGA)
- Body-IGA (B-IGA)
- Psoriasis Scalp Severity Index (PSSI)
- Extent of Scalp Involvement
- Body Surface Area (BSA)
- Psoriasis Area and Severity Index (PASI)
- Worst Itch-Numeric Rating Scale (WI-NRS)
- Scalp Itch-Numeric Rating Scale (SI-NRS)
- Scalpdex
- Dermatology Life Quality Index (DLQI) in subjects ≥ 17 years old
- Children's Dermatology Life Quality Index (CDLQI) in subjects 12-16 years old
- PSD (Psoriasis Symptom Diary) in subjects ≥ 18 years old

Study Endpoints:

The co-Primary Efficacy Endpoints will be:

- S-IGA Success, defined as achievement of Scalp-IGA (S-IGA) score of 'Clear' or 'Almost Clear' plus a 2-grade improvement from Baseline
- B-IGA Success, defined as achievement of Body-IGA (B-IGA) score of 'Clear' or 'Almost Clear' plus a 2-grade improvement from Baseline

The Secondary Efficacy Endpoints will include:

- For subjects with Baseline Scalp Itch (SI) NRS score ≥4, achievement of ≥4-point improvement from Baseline in SI-NRS at Week 8 ("SI-NRS Success at Week 8")
- SI-NRS Success at Week 4
- SI-NRS Success at Week 2
- SI-NRS Change from Baseline (CFB) at Week 1
- SI-NRS CFB at 72 hours

- SI-NRS CFB at Day 1
- For subjects with Baseline WI-NRS score ≥4, achievement of ≥4-point improvement from Baseline in WI-NRS at Week 8 ("WI-NRS Success at Week 8")
- PASI-75 at Week 8
- CFB in PSD Items related to Itching, Pain, and Scaling (Questions 1, 9, and 11) aggregate score at Week 8
- PSD Item related to Scaling (Question 11) = 0 at Week 8
- PSD Item related to Itching (Question 1) = 0 at Week 8
- PSD Item related to Pain (Question 9) = 0 at Week 8
- PSSI-75 at Week 8
- S-IGA score of 'Clear' at Week 8
- S-IGA Success at Week 4
- CFB in PASI at Week 2
- S-IGA Success at Week 2
- PSD Total Score = 0 at Week 8

Statistical Methods:

[redacted]

The co-primary endpoints of 'S-IGA Success at Week 8' and 'B-IGA Success at Week 8' will be analyzed using a Cochran-Mantel-Haenszel test stratified by Baseline S-IGA (3 vs. 4), Baseline B-IGA (2 vs. ≥3), and study site. The analysis will be performed on the Intention to Treat (ITT) population and missing data will be imputed using multiple imputation.

Continuous secondary and exploratory endpoints will be analyzed using Analysis of Covariance with treatment and stratification factors as independent variables. The ITT population will be used, and missing data will be imputed using multiple imputation. Binary secondary and exploratory endpoints will be analyzed similarly to the primary endpoint. To control for multiple comparisons among the secondary endpoints, the following testing plan will be used:

Upon demonstration of statistical significance for S-IGA Success at Week 8 at the 2.5% level and statistical significance of B-IGA Success at Week 8 at the 2.5% level, the testing scheme described below will be used to test the secondary endpoints. This testing scheme will control the overall type 1 error at the 0.025 level.

The overall α level of 0.025 will be split to test 3 families of secondary endpoints.

Family 1 (α=0.01):

- SI-NRS Success at Week 8
- SI-NRS Success at Week 4
- SI-NRS Success at Week 2
- SI-NRS CFB at Week 1
- SI-NRS CFB at 72 hours

Family 2 (α=0.005):

- WI-NRS Success at Week 8
- PASI-75 at Week 8
- CFB in PSD Items related to Itching, Pain, and Scaling (Questions 1, 9, and 11) aggregate score at Week 8
- PSD Item related to Scaling (Question 11) = 0 at Week 8
- PSD Item related to Itching (Question 1) = 0 at Week 8
- PSD Item related to Pain (Question 9) = 0 at Week 8
- PSSI-75 at Week 8

Family 3 (α=0.01):

- S-IGA score of 'clear' at Week 8
- S-IGA Success at Week 4
- CFB in PASI at Week 2
- S-IGA Success at Week 2
- PSD Total Score = 0 at Week 8
- SI-NRS CFB at Day 1

The Fallback Method will be used to pass unused alpha. The Families will be tested in this order: Family 2, Family 1, Family 3. Testing will be sequential within Family 2 and Family 1, with the order of testing within each family as listed above. Testing within Family 3 will be implemented with a Holm's procedure.

To start, Family 2 will be tested, sequentially within Family 2, at the α=0.005 level. Should the testing succeed through all seven endpoints in Family 2, the α=0.005 will remain unused, and will be passed to Family 1.

The testing of the five SI-NRS endpoints in Family 1 will be sequential, either at the α=0.01 level (assumes Family 2 had an unsuccessful test), or the α=0.015 level (assumes all endpoints in Family 2 were successful at the α=0.005 level).

Family 3 contains six endpoints. Family 3 has initially been allocated α=0.01. This creates three possible testing alpha levels for Family 3 endpoints:

- If all tests in Family 1 (α=0.01) and Family 2 (α=0.005) are successful, then α=0.005+0.01=0.015 is unused, and the α=0.015 will be carried to Family 3, allowing Family 3 endpoints to be tested at the full 0.025 level.
- If the α=0.005 in Family 2 is used, but the subsequent α=0.01 allocated to Family 1 is not used, then Family 3 endpoints will be tested at the α=0.01+0.01=0.02 level.
- If the α=0.01 in Family 1 is used, and the α=0.005 in Family 2 is also used, then Family 3 endpoints will be tested at α=0.01.

Descriptive statistics will be presented for endpoint and safety data collected in the clinical study. 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.

All subjects who are randomized and receive at least one confirmed dose of investigational product will be included in the safety population.

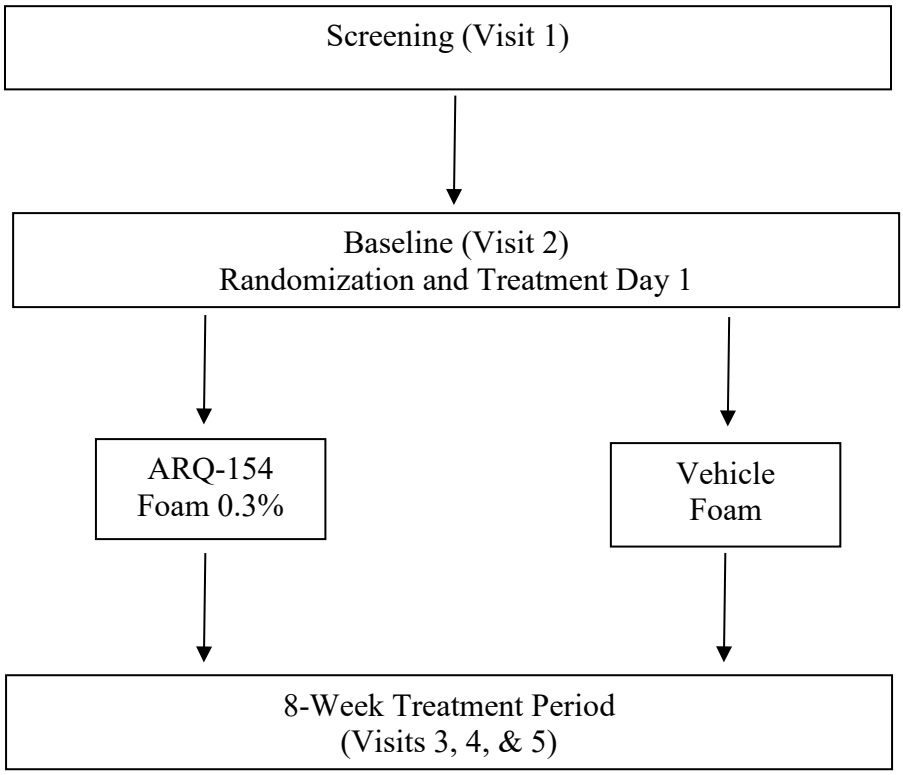
Adverse events (AEs) will be summarized by preferred term, system organ class, and treatment group for all treatment-emergent AEs, serious AEs, related AEs, AEs leading to withdrawal from investigational product.

Safety laboratory parameters and vital signs will be summarized at each visit using descriptive statistics or frequencies and percentages, as appropriate. Changes from Baseline and percent changes from Baseline in laboratory values and vital signs will also be summarized by visit. In addition, changes from Baseline and percent changes from Baseline in weight and laboratory values will be summarized using shift tables.

Descriptive statistics will be calculated for the PHQ-8 (adults) and Modified PHQ-A (adolescents). The C-SSRS will be analyzed per the Scoring and Data Analysis Guide from the Columbia Lighthouse Project.

[redacted]

1.2. Study Schema



A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-154 Foam 0.3% Administered in Subjects with Scalp and Body Psoriasis

Approximately 420 adolescent and adult subjects with scalp and body psoriasis will be randomized 2:1 to receive either:

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

1.3. Schedule of Visits and Assessments

Study Procedure	Screening	Baseline Day 1	Week 2 Day 15	Week 4 Day 29	Week 8[a] Day 57
Visit	**1**	**2**	**3**	**4**	**5**
Visit Window	**-4 Weeks**		**± 3 Days**	**± 5 Days**	**± 5 Days**
Informed consent/assent	X				
Medical/surgical history, demography	X				
Physical examination[b]	X	X			X
Fitzpatrick Skin Type	X				
I/E criteria	X	X			
Randomization		X			
Hematology, Chemistry, and Urinalysis[c]	X	X		X	X
Vital signs, weight, height[d]	X	X	X	X	X
S-IGA[e], B-IGA[e], PSSI[e], BSA[f], Extent of Scalp Involvement[g], PASI	X	X	X	X	X
DLQI/CDLQI[h], Scalpdex[h], PSD[h]	X	X	X	X	X
Daily SI-NRS and WI-NRS[i] at home (non-clinic)	Day -7 through Day 57				
Application Site Reaction Assessment/ Local Tolerability[j]		X	X	X	X
C-SSRS, PHQ-8/PHQ-A[k]	X	X		X	X
Medical Photography[l]		X	X	X	X
Follicle Stimulating Hormone (FSH) [m]	X				
Serum pregnancy test[m]	X				
Urine pregnancy test[n]		X		X	X
[redacted]				[redacted]	[redacted]
IP application and subject/family training[p]		X	X	X	
Dispense investigational product kit[q]		X	X	X	
Dispense / review dosing diary		X	X	X	X
Weigh investigational product[r]		X	X	X	X
Compliance calculation[s]			X	X	X
Adverse event assessment[t]	X	X	X	X	X
Concomitant medications	X	X	X	X	X

***Footnotes from table above*:**

a. Subjects that terminate early should return to the study site for the Week 8 assessments.
b. Limited physical examination: skin (including assessment of Fitzpatrick Skin Type at Screening only), lungs, and heart only.
c. For subjects <18 years of age, if the Baseline/Day 1 visit occurs within 3 weeks of Screening, the Screening lab results may be utilized.
d. Height will be collected at Screening and Week 8. Weight will be collected at all study visits. Subjects should void prior to weight being taken and remove any objects of significant weight (i.e., jackets, outerwear, shoes, cell phones, wallet, key chains, etc.). A 5% unintentional weight loss from Baseline should be reported to the medical monitor.
e. S-IGA will be a 5-point scale ranging from clear (0) to severe (4) and is evaluated for the scalp only. B-IGA will use the same scale as S-IGA but will evaluate the entire body (except the scalp, palms, and soles). PSSI is scored on a 0-72 scale and evaluates the scalp only. PASI assessment should exclude palms and soles. **S-IGA and B-IGA should be completed prior to other Investigator assessments and every effort should be made for the same evaluator to complete at each study visit.**
f. Total BSA affected by scalp and body psoriasis 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. Scalp will be included in total BSA measurement, but palms and soles will be excluded. The total scalp (ie, 100% of the total scalp surface area) can be considered to be approximately 4% BSA.
g. Extent of scalp involvement will be the extent of psoriasis involved, expressed as a percentage of total scalp.
h. The DLQI will be completed by subjects ≥17 years of age. The CDLQI will be completed for subjects 12 to 16 years old, inclusive. Scalpdex will be completed by all subjects. PSD will be completed by subjects ≥ 18 years of age.
i. Subjects/parents/caregivers will complete the SI-NRS and WI-NRS daily at home starting 7 days prior to the Baseline/Day 1 visit to Day 57 (Week 8) visit. Daily SI-NRS and WI-NRS will be completed in the evening prior to IP application (except at Baseline and Week 2 when IP is applied at the clinic). **The SI-NRS should be completed first and then WI-NRS.**
j. Local tolerability assessments include both investigator and subject assessments. The Investigator assessment of skin irritation (Berger and Bowman skin irritation score) is to be recorded prior to IP application.
Note for Investigator tolerability assessments: reactions at the site of IP application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's psoriasis. The subject's '0-3' burning/stinging assessment is to be recorded 10-15 minutes post IP application for the subject's '0-3' burning/stinging assessment. **At Week 8, subjects will provide a recall assessment of burning/stinging experienced post IP application on the day prior to the clinic visit.**
k. All subjects will complete the C-SSRS. Adults will complete the PHQ-8. Adolescents (ages 12 to 17 inclusive) will complete the PHQ-A (PHQ-9 modified). Refer screen failures due to score ≥10 to a mental health professional. For Scores 10-14 at all visits, refer subject promptly to a mental health professional. For scores ≥15 at all visits, refer subject promptly to a mental health professional and consider interruption of IP.
l. Medical photography will be obtained for target lesions by all sites. All efforts will be made to de-identify the subjects.
m. A serum pregnancy test will be administered to all females of child-bearing potential at the Screening visit only. Follicle Stimulating Hormone (FSH) will be performed at Screening (if indicated) to confirm post-menopausal status.
n. A urine pregnancy test will be performed at the Baseline, 4, and 8 to all females of child-bearing potential. A negative result is required for continued participation in the study, and results must be available at each visit prior to dispensing of IP.
[redacted].
p. Subjects/parents/caregivers to apply assigned IP in the study site at every designated visit.
q. Kits will be dispensed based on % BSA. See IP Handling Plan for details.
r. Each IP canister in the Kit should be weighed and recorded at every visit. See IP Handling Plan for details.
s. Compliance calculation is described Section 4.8.3 and in the IP Handling Plan.

***Footnotes from table above*:**

t. All AEs should be collected starting after the first application of the IP through the end of the study. All SAEs should be collected starting after the signing of the informed consent through 30 days after the last day of the IP application or the end of the study (whichever is later). Any 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 to 30 days after end of treatment or until symptoms or value(s) return to subject's Baseline, or acceptable level, as judged by the PI.

2. BACKGROUND AND RATIONALE

2.1. 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.

Psoriasis is a chronic inflammatory skin disease characterized by raised, well-demarcated, erythematous oval plaques with adherent silvery scales. Numerous past reports have suggested a deficiency of cyclic AMP-dependent protein kinases in human psoriatic skin (Brion 1986). More recently, various cytokines produced by Th1 and Th17 cells have been shown to play a crucial role in the pathogenesis of psoriasis. It has been postulated that the anti-inflammatory effects of PDE-4 inhibitors may provide a beneficial therapeutic intervention in the treatment of chronic plaque psoriasis, and Otezla® (apremilast) a PDE-4 inhibitor has been approved for the oral treatment of chronic plaque psoriasis.

The scalp is a common area of psoriasis involvement, and often the first area on the body to be affected. The scalp is considered an underdiagnosed, undertreated, and difficult to manage area for psoriasis. Scalp psoriasis may be associated with pruritus, pain, flaking, and hair loss, and may disproportionately impact quality of life relative to psoriasis elsewhere. Treatment of scalp psoriasis is often limited to topical therapy, unless there are sufficient additional non-scalp psoriasis to merit systemic treatment. Intralesional therapy represents another approach. Current treatment options for scalp psoriasis include topical steroids, vitamin D derivatives, tar preparations, and salicylic acid products, but considerable unmet need remains for safe and effective products (Blakely 2016, Schlager 2016, Wang 2017, Merola 2018, Kivelevitch 2018). Given the scalp is a hair-bearing site, choice of formulation is critical, and foams are a favored option.

The past 15 years have witnessed a transformation in the systemic treatment of moderate to severe psoriasis with the advent of biological therapies. However, for patients with milder forms of disease, best treated with topical options, the therapeutic landscape has not significantly changed in several decades. Similarly, topical treatment options for the scalp have also not significantly changed in several decades. Topical steroids come in all shapes and forms, but the lower potency steroids are not effective and the higher potency steroids are beset with issues of local skin atrophy and the potential for hypothalamic-pituitary axis suppression when applied over larger body surface areas and for prolonged periods of time. Vitamin D has been the other staple of topical psoriasis treatment, but it is irritating, not suitable for use on the face or intertriginous areas, and its efficacy is rather modest. Hence, there is substantial medical need for additional topical approaches in the treatment of psoriasis, on the scalp and rest of body.

[redacted]

2.2. Conclusions on Toxicity Findings

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

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

[redacted]

2.3. Clinical Studies

2.3.1. Scalp and Body Psoriasis Phase 2b

ARQ-154-204 (NCT 04128007) was a Phase 2b, parallel group, double blind, vehicle-controlled study that evaluated ARQ-154 foam 0.3% for the treatment of psoriasis involving the scalp, face, and/or body. ARQ-154 foam 0.3% or matching vehicle was applied once daily (QD) for eight weeks to male and female adolescents and adults (≥ 12 y/o). The minimum psoriatic scalp involvement was a Scalp-IGA (S-IGA) of 'Moderate' (3) for study entry. Subjects were also required to have psoriasis elsewhere on the body, with a minimum body (i.e., non-scalp)-IGA (B-IGA) of 'Mild' (2) for study entry. The scalp psoriasis had to involve ≥10% of the total scalp. The total BSA affected with psoriasis (scalp + rest of body) could not exceed 25% BSA (not including palms/soles). A total of 304 subjects were randomized at a ratio of 2:1 to receive ARQ-154 foam 0.3% or matching vehicle foam. All randomized subjects were included in both the safety and intent-to-treat (ITT) populations.

2.4. Rationale for Development

The development plan for ARQ-154 foam will leverage experience to date with ARQ-15 [redacted] Given the unmet need for new medical therapies for scalp and body psoriasis and the results of a phase 2b study of ARQ-154 foam 0.3% in scalp and body psoriasis, the Sponsor is pursuing development of ARQ-154 foam 0.3% for the treatment of scalp and body psoriasis in this phase 3 study. [redacted]

2.4.1. Dose Selection

ARQ-154 foam at 0.3% was selected for this study to match the dose of ARQ-154 foam from the phase 2a study ARQ-154-204. The 0.3% dose is also consistent with the dose of the related roflumilast cream formulation (ARQ-151 cream 0.3%) which was evaluated in phase 3 for plaque psoriasis. The 0.3% dose for ARQ-151 cream was selected based on results of the phase 2b study plaque psoriasis study ARQ-151-201, in which the 0.3% concentration demonstrated greater efficacy that the 0.15% concentration. In that phase 2b study, there were no differences in the safety profiles of the two doses, supporting that it was not necessary to evaluate doses less than 0.3% in scalp and body psoriasis. The Sponsor expects similar doses to be safe and effective in scalp and body psoriasis, as supported by the phase 2b scalp and body psoriasis study ARQ-154-204.

[redacted]

2.4.2. Risks and/or Benefits to Subjects

Based on efficacy data from the phase 2b study ARQ-154-204, it is expected that subjects in the present study ARQ-154-309 will experience improvement in their scalp and body psoriasis. Subjects randomized to the vehicle treatment group may also see some improvement as the formulation of ARQ-154 may have a moisturizing effect.

[redacted]

[redacted]

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

The primary objective of this study is to assess the safety and efficacy of ARQ-154 foam 0.3% administered once daily (QD) vs. vehicle foam for 8 weeks in adolescent and adult subjects with scalp and body psoriasis.

3.2. Study Endpoints

3.2.1. Co-Primary Endpoints

The co-primary efficacy endpoints in this study are

- S-IGA Success, defined as achievement of Scalp-IGA (S-IGA) score of 'Clear' or 'Almost Clear' plus a 2-grade improvement from Baseline.
- B-IGA Success, defined as Achievement of Body-IGA (B-IGA) score of 'Clear' or 'Almost Clear' plus a 2-grade improvement from Baseline.

3.2.2. Secondary Endpoints

The Secondary Efficacy Endpoints will include:

- For subjects with Baseline Scalp Itch (SI) NRS score ≥4, achievement of ≥4-point improvement from Baseline in SI-NRS at Week 8 ("SI-NRS Success at Week 8")
- SI-NRS Success at Week 4
- SI-NRS Success at Week 2
- SI-NRS Change from Baseline (CFB) at Week 1
- SI-NRS CFB at 72 hours
- SI-NRS CFB at Day 1
- For subjects with Baseline WI-NRS score ≥4, achievement of ≥4-point improvement from Baseline in WI-NRS at Week 8 ("WI-NRS Success at Week 8")
- PASI-75 at Week 8
- CFB in PSD Items related to Itching, Pain, and Scaling (Questions 1, 9, and 11) aggregate score at Week 8

- PSD Item related to Scaling (Question 11) = 0 at Week 8
- PSD Item related to Itching (Question 1) = 0 at Week 8
- PSD Item related to Pain (Question 9) = 0 at Week 8
- PSSI-75 at Week 8
- S-IGA score of 'Clear' at Week 8
- S-IGA Success at Week 4
- CFB in PASI at Week 2
- S-IGA Success at Week 2
- PSD Total Score = 0 at Week 8

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a phase 3, parallel group, double blind, vehicle-controlled study in which ARQ-154 foam 0.3% or vehicle foam is applied QD x 8 weeks to adolescent and adult subjects with a minimum Scalp Investigator Global Assessment (S-IGA) of 'Moderate' (3) and a minimum rest of the Body Investigator Global Assessment (B-IGA) of 'Mild' (2).

4.2. Number of Sites and Subjects

A total of up to approximately 420 subjects will be enrolled at approximately 45 study sites in North America. Additional countries or study sites may be added, as necessary. Subjects will be male and female adolescents (12 – 17 y/o) and adults (≥18 y/o). Subjects must have no more than 25% BSA total across scalp and body psoriasis not including palm/soles (non-scalp BSA must not exceed 20%). All lesions on a subject will be treated including the scalp, face, trunk, and intertriginous areas.

4.3. Subject Participation

Subject participation involves a minimum of 5 clinic visits, including Screening, Baseline/Day 1, Week 2, Week 4, and Week 8. The interval between Screening and Baseline visits may take up to 4 weeks, the anticipated maximum duration of subject participation is approximately 12 weeks.

4.4. Subject Identification Number Assignment

All subjects who sign an informed consent or assent (adolescents) form will be assigned a unique 5-digit subject identification (ID) number by the interactive web response system (IWRS). The first 2 digits correspond to the site number (assigned by the Sponsor), the next 3 digits (starting with 900) correspond to the sequential order in which the subject is screened for the

study (e.g., Subject ID <11900>: Site 11, subject number 900, as the first subject screened by that site). The subject ID will remain the same in the event the subject is rescreened.

The study site is responsible for maintaining a current log of subject ID number assigned to each subject. The subject ID number will be used to identify the subject throughout the study and is required to be entered on all clinical study documentation (e.g., case report forms, labeling of clinical materials and sample containers, investigational product accountability logs, etc.).

4.5. Selection of Study Population

4.5.1. Inclusion Criteria

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

1. For adult subjects: Participants legally competent to read, write, and sign and give informed consent. For adolescent subjects: Informed consent of a parent(s) or legal guardian, and assent by the subjects, as required by local laws.
2. Males and females ages 12 years and older (inclusive) at the time of consent or assent.
3. Scalp psoriasis with a Scalp-Investigator Global Assessment of Disease severity (S-IGA) of at least Moderate ('3') at Baseline.
4. Extent of scalp psoriasis involving ≥ 10% of the total scalp at Baseline.
5. A Psoriasis Scalp Severity Index (PSSI) of at least 6 at Baseline.
6. An IGA of body (i.e., non-scalp) psoriasis (B-IGA) of at least Mild ('2') at Baseline.
7. A PASI score of at least 2 (excluding palms and soles) at Baseline.
8. Clinical diagnosis of psoriasis vulgaris of at least 6 months duration at Screening as determined by the Investigator. Stable disease for the past 4 weeks.
9. Total overall psoriasis involvement on scalp and non-scalp areas ≤ 25% BSA (not including palms/soles) at Baseline. Total non-scalp BSA should not exceed 20%.
10. Female subject of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening (Visit 1) and negative urine pregnancy test at Baseline (Visit 2). In addition, sexually active FOCBP must agree to use at least one form of highly effective contraception or a barrier method of contraception throughout the study according to Contraception Requirements (Figure 1).
11. Females of non-childbearing potential must either be premenarchal, post-menopausal with spontaneous amenorrhea for at least 12 months (post-menopausal status will be confirmed with FSH testing) or have undergone surgical sterilization according to Contraception Requirements. Prepubescent females must agree to be abstinent during the entire course of the study (Figure 1).
12. Subjects in good health as judged by the Investigator, based on medical history, physical examination, vital signs, serum chemistry labs, hematology values, and urinalysis.

13. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule according to the Investigator judgment.

4.5.2. Exclusion Criteria

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

1. Subjects who cannot discontinue treatment with therapies for the treatment of psoriasis vulgaris prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 1).
2. Planned excessive exposure to treated area(s) to either natural or artificial sunlight, tanning bed, or other LED.
3. Subjects currently taking lithium or antimalarial drugs.
4. Planned initiation or changes to concomitant medication that could, in the opinion of the Investigator, affect psoriasis vulgaris (e.g., beta blockers or ACE inhibitors if not on stable dose for at least 8 weeks).
5. Current diagnosis of non-plaque forms of psoriasis (e.g., guttate, erythrodermic/ exfoliative, palmoplantar only involvement, or pustular psoriasis). Current diagnosis of drug-induced psoriasis.
6. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements.
7. Known allergies or hypersensitivity to component(s) of the investigational product [redacted]
8. 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) for two weeks prior to the Baseline visit and during the study period.
9. Known or suspected:
    a. Known HIV infection
    b. Severe renal insufficiency as evidenced by calculated creatinine clearance <30 mL/min or estimated glomerular filtration rate <30mL/min/1.73cm^2
    c. Moderate to severe hepatic disorders (Child-Pugh B or C)
10. Liver functions tests results that exceed:
    - AST or ALT > 2x ULN
    - Total bilirubin:
        - > 1.5 x ULN or
        - > ULN and ≤ 1.5 x ULN AND direct bilirubin is > 35% of total bilirubin
    - ALP ≥ 2x ULN

11. Subjects with PHQ-8 (≥18 years old, inclusive) or modified PHQ-A (adolescents, 12 to 17 years old, inclusive) score ≥10 at Screening or Baseline visits.
12. History of severe depression, suicidal ideation or behavior, Baseline/Screening C-SSRS (for adolescents and adults 12 years old and older) indicative of suicidal ideation or behavior, whether lifetime or recent/current.
13. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.
14. Previous treatment with ARQ-151 or ARQ-154.
15. Subjects who have received oral roflumilast (Daliresp®, Daxas®), or apremilast (Otezla®) within the past 4 weeks prior to Baseline.
16. 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.
17. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of the investigational product.
18. Subject had a major surgery within 4 weeks prior to Baseline or have a major surgery planned during the study.
19. Subjects with 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. Parent(s)/legal guardian(s) of adolescent subjects who are unable to communicate, read, or understand the local language.
20. Subjects with a current or a history of cancer within 5 years, with the exception of fully treated Cutaneous basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix.
21. Subjects with active infection that required oral or intravenous administration of antibiotics, antifungals, or antiviral agents within 7 days of Baseline.
22. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members residing in the same household of enrolled subjects.
23. Subjects unable to apply product to the scalp (and/or psoriasis elsewhere) due to physical limitations.
24. Any condition that in the Investigator's assessment would preclude the subject from participating in the study.

4.6. Randomization

Randomization will take place at the Baseline (Day 1) visit after the Investigator confirms the subject to be fully eligible for participation as outlined in Section 4.5. Subjects will be randomly assigned to apply ARQ-154 foam 0.3% QD or vehicle foam QD. Assignment of ARQ-154 or vehicle will be made at a 2:1 ratio and will be stratified by study site, Baseline S-IGA (3 vs. 4),

and Baseline B-IGA (2 vs. ≥ 3) according to a computer-generated randomization list. Kits containing canisters of IP will be assigned to each subject using the IWRS. A subject may receive more than one kit for the treatment period. The kits and canisters are blinded and each kit is numbered with a unique kit number.

4.7. Prohibitions and Concomitant Therapy

Prohibited medications and products are detailed in Table 1.

Generally, the addition of new medications, including nonprescription medications, during 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 'Excluded Medications and Treatments' (Table 1).

Table 1: Excluded Medications and Treatments

Excluded Medications and Treatments	**Wash Out Period Prior to Baseline (Day 1)**
Etanercept	4 weeks
Adalimumab, infliximab	8 weeks
All other Biologics	12 weeks or 5 half-lives, whichever is longer
Systemic corticosteroids, retinoids, apremilast, roflumilast, methotrexate, cyclosporine, fumarates, and other systemic immunosuppressants	4 weeks
Shampoos containing coal tar, keratolytics including salicylic acid, antifungals, zinc pyrithione, selenium sulfide, or medical devices	1 week
Topical medications used on the scalp for conditions besides psoriasis, e.g., use of topical minoxidil for androgenetic alopecia	2 weeks
Topical anti-psoriasis medications (e.g., topical corticosteroids including corticosteroid shampoos, vitamin D analogs)	2 weeks
Strong systemic P-450 cytochrome inhibitors (e.g. indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin)	2 weeks
PUVA or UVB phototherapy	4 weeks

Table 1: Excluded Medications and Treatments (Continued)

Excluded Medications and Treatments	Wash Out Period Prior to Baseline (Day 1)
Investigational drugs	12 weeks (biologics) or 5 half-lives, whichever is longer; 5 half-lives (orals); 2 weeks (topical)
Sedating antihistamines including over the counter products containing sedating antihistamines Note: Systemic treatments with nonsedating antihistamines (e.g., cetirizine, desloratadine, loratadine) in a stable regimen is allowed.	1 week

Note:

1. 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.
2. Non-medicated emollients, moisturizers and sunscreens will be allowed as used normally by the subjects. These can be applied to non-treated areas as needed and should not be used within 12 hours of a study visit.
3. No emollients or moisturizers should be applied on treated areas.

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

4.8. Treatment

4.8.1. IP Supplies, Packaging, and Labeling

ARQ-154 foam 0.3% or vehicle foam will be provided in a canister containing approximately 60 grams of foam. Two canisters of IP will be packed in kits. The number of kits dispensed to a subject will be based on the BSA involvement. The kits and canisters will be labeled with a unique number to maintain blinding.

The Sponsor will supply sufficient quantities of the IP (ARQ-154 foam 0.3%, and matching vehicle) to each site to allow for completion of this study. The matching vehicle foam will contain only excipients of ARQ-154 foam.

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

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

4.8.2. Treatment Administration

Initial treatment with the IP will occur on Baseline/Day 1. At the randomization visit (Baseline), the study staff will demonstrate to the subject/parent(s)/caregiver(s) how to apply ARQ-154 foam 0.3% or vehicle foam using the first canister from the kit that is assigned to the subject at randomization. Study site staff will be trained to ensure a proper amount is dispensed from the foam can and applied to psoriasis lesion(s) as a thin film and rubbed in thoroughly but gently, until the 'white' has disappeared. **For scalp lesions, special attention should be given to ensuring adequate investigational product is applied to scalp skin and not rubbed off on hair**. The subject/parent(s)/caregiver(s) will then practice dispensing a similar amount of investigational product and applying to scalp and body psoriasis lesion(s). The study staff will confirm that the subject's application technique is correct.

Subjects/parent(s)/caregiver(s) will be instructed to apply IP QD in the evening (except at Baseline and Week 2, in which case IP will be applied at the study site) to areas of scalp and body psoriasis lesions identified by the Investigator at Baseline using a Body and Scalp Diagram (see Appendix 1). 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 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.

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 IP to all treatment areas for the duration of the study regardless of whether treatable areas of psoriasis clear. New lesions that appear during the treatment period should also be treated. Application will be to all areas affected including the face, scalp, and intertriginous areas. A Body and Scalp Diagram (see Appendix 1) should be used to record existing and new areas of scalp and body psoriasis involvement that are subject to treatment.

4.8.3. Treatment Compliance

Weight of the IP applied will be measured for reporting purposes. Each IP canister will be weighed individually prior to dispensing at the Baseline visit or subsequent visits. IP canisters must be returned by subjects at each study visit (both empty and full) and will be weighed individually. Record IP canister weight 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 AEs or reason for missed dose. Site personnel will review the diaries and use the information to question the subject regarding compliance and AEs and then record appropriate information in source documents and complete eCRFs. 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 entire IP application period (Baseline to Week 8) and does not miss more than 3 consecutive doses.

Compliance will be assessed by review of the dosing diary. Re-training will be conducted at subsequent visits as needed, i.e., if the returned canister weighs substantially different than the expected weight, the diary shows less than 80% of expected use, or more than 3 consecutive doses are missed.

Compliance will be documented in the source and eCRF.

4.8.4. Blinding

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

4.8.5. Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the Investigator may obtain treatment assignment directly from the IWRS system for that subject. Refer to the current version of the ARQ-154-309 IWRS Plan for details on unblinding. Treatment assignment should, however, remain blinded unless the assignment knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the eCRF, along with the date on which the treatment assignment was obtained. The Investigator is requested to contact the Medical Monitor promptly in the event of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical study and therefore, if a subject's treatment assignment is disclosed to the Investigator, the subject will have the study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

4.8.6. Removal of Subjects from Investigational Product

A subject may discontinue from receiving the IP 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 IP administration as per the Protocol.
- Occurrence of or considerable worsening of an AE (described in Section 5.7) 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.

- IP application must be discontinued immediately in the event of a female subject's pregnancy.
- Subject's decision to withdraw from receiving IP.
- Weight loss of >5% from Baseline, if not dieting or intentionally trying to lose weight, at the Investigator's discretion and after consultation with the Medical Monitor and Sponsor.
- C-SSRS indicative of suicidal ideation
- PHQ-8/PHQ-A score ≥15 if determined by Investigator in consultation with a mental health professional.
- Requirement for use of prohibited concomitant medication (Table 1) after consultation with the Sponsor and Medical Monitor.
- Subjects repeated failure to comply with protocol requirements or study related procedures.

4.8.7. Removal of Subjects from the Study

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

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

5. STUDY PROCEDURES

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

5.1. Safety Assessments

This study assesses the safety and efficacy of ARQ-154 foam 0.3%. Safety will be determined by evaluating physical examinations, vital signs/weight, local tolerability assessments, clinical laboratory parameters, PHQ-8/PHQ-A, C-SSRS, and AEs as outlined in the Schedule of Visits and Assessments (Section 1.3). If deemed necessary, additional safety assessments will be performed at the discretion of the Investigator.

5.1.1. Screening

Before a subject's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the subject or written assent from adolescent subjects and consent from their parent(s) or legal guardian(s) after adequate explanation of the study design, anticipated benefits, and the potential risks. Informed consent must be obtained before completion of any non-standard of care study-specific procedures. Procedures that are part of standard of care are not considered study-specific and, therefore, may be performed prior to obtaining consent and used to confirm eligibility provided they occur within the time allowance outlined in the Schedule of Visits and Assessments (Section 1.3). A subject is considered a participant of the study once the informed consent form (ICF) (and written assent for an adolescent subject) is completely signed.

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

- Review of medical and surgical history
- Review of childbearing potential (female subjects) and contraceptive use (Section 5.1.2)
- Collection of demographic data including age, sex, race, ethnicity
- Limited physical examination of skin (including assessment of Fitzpatrick Skin Type at Screening only), lungs, heart
- Vitals signs including temperature, heart rate, blood pressure
- Collection of height (cm) and body weight (kg)
- Laboratory tests: hematology, chemistry, urinalysis, serum pregnancy (for female subjects of childbearing potential) and FSH (to confirm post-menopausal status)
- Scalp and body psoriasis assessments: S-IGA, B-IGA, PSSI, BSA, PASI
- Completion of DLQI/CDLQI, Scalpdex, PSD
- C-SSRS, PHQ-8/PHQ-A
- Collection of prior and concomitant medication

All screened subjects will receive a subject identification number (see Section 4.4) and be entered into the eCRF. Subjects that fail to meet the eligibility criteria will be designated as a screen failure and entered in the IWRS and eCRF as such. Subjects who are unable to enroll within the screening window will be rescreened.

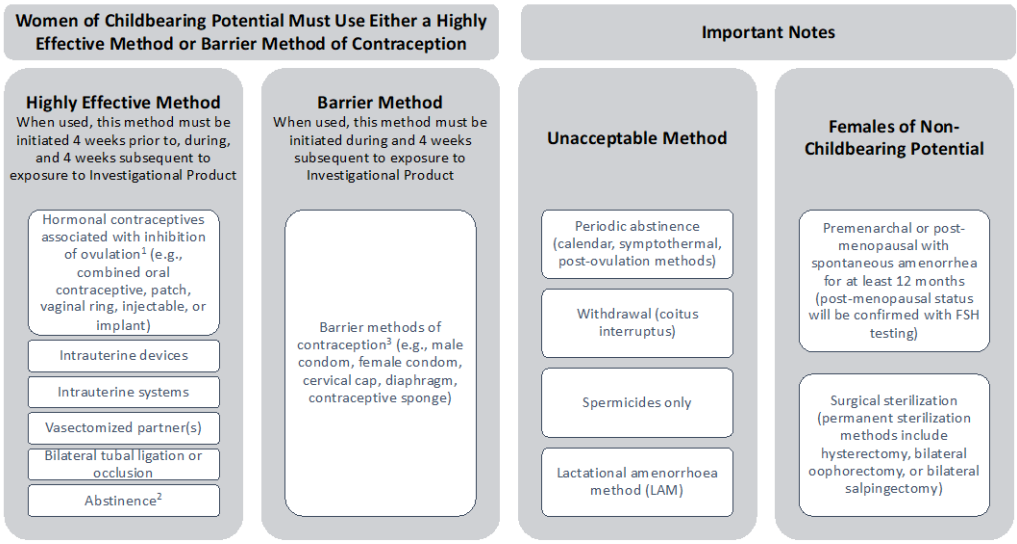
Subjects may be re-screened one time. The original assigned subject ID number will be used for re-screening.

Subjects who consent but do not proceed with enrollment will be considered a screen fail.

5.1.2. Contraception Requirements

Females of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at Baseline (Visit 2), Week 4 (Visit 4) and Week 8 (Visit 5). In addition, sexually active FOCBP must agree to use at least one form of a highly effective or barrier method of contraception throughout the study according to Contraception Requirements for Female Subjects. Prepubescent females must agree to be abstinent during the entire course of the study (Figure 1).

Figure 1: Contraception Requirements for Female Subjects



[1]Subjects using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Day 1.
[2]The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.
[3]Female condom and male condom should not be used together.

5.1.3. Baseline

Each subject will undergo Baseline assessments outline in the Schedule of Visits and Assessments (Section 1.3). For subjects <18years, if the Baseline (Day 1) visit occurs within 3 weeks of Screening, the Screening lab results may be utilized.

Randomization and IP kit assignment will take place via IWRS after the subject has been found to be fully eligible for participation. A subject will be considered enrolled into the study upon the first IP application.

5.1.4. Physical Examination

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

Fitzpatrick skin phototype assessment will be rated as follows:

I. Always burns easily; never tans (sensitive)
II. Always burns easily; tans minimally (sensitive)
III. Burns moderately; tans gradually (light brown) (normal)
IV. Burns minimally; always tans well (moderate brown) (normal)
V. Rarely burns; tans profusely (dark brown) (insensitive)
VI. Never burns; deeply pigmented (insensitive)

5.1.5. Vital Signs, Height and Weight

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

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

Height will be collected at Screening and Week 8.

Subjects should void prior to weight being taken and remove any objects of significant weight (i.e., jackets, outerwear, shoes, cell phones, wallet, key chains, etc.). A 5% unintentional weight loss from Baseline should be reported to the medical monitor.

5.1.6. Laboratory Tests

All tests listed in Table 2 will be performed according to the Schedule of Visits and Assessments (Section 1.3) unless otherwise noted. For subjects <18 years old, Screening safety lab results collected within 3 weeks of the Baseline visit may be utilized as the Baseline safety lab assessment. No food restrictions are required for the collection of specimens. In addition, laboratory safety tests may be performed at 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, shipping, 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)*** • FSH**** • Pharmacokinetic (PK) assessments

*If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.
** Baseline, Weeks 4, and 8, for FOCBP only
*** At Screening, for FOCBP only
****At Screening, for postmenopausal females only

5.1.7. Patient Health Questionnaire Depression Scale (PHQ-8)

The PHQ-8 Assessment (see Appendix 2) will be completed by adult subjects according to the Schedule of Visits and Assessments (Section 1.3).

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

Five severity categories of depression are defined as follows:

- None – Minimal depression (1 to 4)
- Mild depression (5 to 9)
- Moderate depression (10 to 14)
- Moderately severe depression (15 to 19)
- Severe depression (20 to 24)

Subjects with a PHQ-8 score of 10-14 should be referred to a mental health professional for evaluation, regardless of the reason for their change in score.

Subjects with a PHQ-8 score of ≥15 should be immediately referred to a mental healthcare professional and Investigators in consultation with the mental health professional should consider interruption or discontinuation of the investigational product.

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

The Modified PHQ-A Assessment (Appendix 3) will be completed by adolescent subjects (12-17 years old, inclusive) according to the Schedule of Visits and Assessments (Section 1.3).

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)

Subjects with a modified PHQ-A score of 10-14 should be referred to a mental health professional for evaluation, regardless of the reason for their change in score.

Subjects with a modified PHQ-A score ≥15 should be immediately referred to a mental health professional, and Investigators in consultation with the mental health professional should consider interruption or discontinuation of the investigational product.

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

C-SSRS Assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3).

The administration schedule of the C-SSRS will be:

- The Baseline-Screening version (Appendix 4) will be used at Screening to provide a pre-treatment assessment Baseline. The timeframe for the Baseline-Screening version is the past 6 months for suicidal ideation and past 5 years for suicidal behavior.
- On all subsequent visits, the Since Last Visit version (Appendix 5) will be used.
- A score greater than 0 at the Screening or Baseline visit in suicidal ideation may indicate the need for mental health intervention. The Investigator should not enroll the subject in the study.
- Any score greater than 0 in the suicidal ideation score may indicate the need for mental health intervention. The Investigator should give consideration for the subject to discontinue from the IP and prompt referral to a mental health professional and/or possibly the emergency room. The Medical Monitor should be contacted.

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

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

5.1.10. Local Tolerability Assessment

The Investigator Local Tolerability Assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3).

Application site reasons will be graded at each timepoint. Irritation reactions are graded using the scale detailed in the following section (Berger 1982). **Reactions at the site of product application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's psoriasis**.

For the Baseline, Weeks 2, 4 and 8 visits, when IP is applied in the clinic, the Investigator assessments will be conducted by the Investigator prior to IP application.

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 erythema
5 = erythema, edema and papules
6 = vesicular eruption
7 = strong reaction spreading beyond application site

The Subject Local Tolerability Assessment will be performed according to the Schedule of Visits and Assessments (Section 1.3).

This assessment will be administered by the site 10 to 15 minutes after IP application in the clinic at Baseline and Weeks 2 and 4, and a recall assessment at Week 8.

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

5.1.11. Adverse Events

Adverse events (AEs) will be collected and assessed throughout the study according to the Schedule of Visits and Assessments (Section 1.3). The Investigator is responsible for ensuring that all adverse events observed by the clinical staff or reported by the subject that occur after the first application of investigational product and treated and/or followed up for up to 30 days after end of treatment or until the symptoms or value(s) return to the subject's Baseline value, or acceptable levels, as judged by the Investigator, are recorded in the subject's medical record and the eCRF.

The Investigator is responsible for ensuring that all serious adverse events observed by the clinical staff or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the application of the investigational product or the end of study (whichever is later) are recorded in the subject's medical record and are submitted per SAE reporting requirements (Section 5.7.2).

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 30 days after end of treatment or until the symptoms or value(s) return to the subject's Baseline value, or acceptable levels, as judged by the Investigator.

Refer to Section 5.7 for further details on Adverse Events.

5.2. Efficacy Evaluations

Investigators will be trained in the administration of rating scales. A training certificate is issued upon successful completion of the training and will be valid for 12 months, unless compliance issues are identified that warrant retraining.

Note: Palms and soles may be treated with the IP in this study, but will not be counted towards IGA, PASI or BSA assessments.

5.2.1. Scalp (S-IGA) and Body (B-IGA) Investigator Global Assessments

Investigator Global Assessments (S-IGA and B-IGA) will be performed according to the Schedule of Visits and Assessments (Section 1.3). The S-IGAs should be completed prior to any other physician assessments. The B-IGA will be the second efficacy assessment performed at clinic visits (after the S-IGA).

The IGAs are static evaluations of qualitative overall psoriasis severity. The global assessment scales are ordinal scales 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 S-IGA and B-IGA for the subject at every study visit, particularly for Baseline and Week 8.

5.2.1.1. Scalp - Investigator Global Assessment of Disease (S-IGA)

The Scalp-IGA (S-IGA) will be the first efficacy assessment performed at clinic visits. As with other efficacy assessments, the S-IGA should be performed prior to the application of any Investigational Product.

Scale	Grade	Description
0	Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling Erythema = none (no residual red coloration but post-inflammatory hyperpigmentation may be present)
1	Almost Clear	Plaque thickening = none or possible thickening but difficult to ascertain if there is a slight elevation above normal skin level Scaling = none or residual surface drying and scaling Erythema = light pink coloration
2	Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering the lesions Erythema = light red coloration
3	Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red coloration
4	Severe	Plaque thickening = marked or very marked elevation typically with hard or sharp edges Scaling = non-tenacious or thick tenacious scale, covering most or all of lesions Erythema = very bright red coloration; extreme red coloration; deep red coloration

5.2.1.2. Body - Investigator Global Assessment of Disease (B-IGA, i.e. non-scalp)

The Body-IGA (B-IGA) will be the second efficacy assessment performed at clinic visits (after the S-IGA). As with other efficacy assessments, the B-IGA should be performed prior to the application of any Investigational Product. In assessing B-IGA, the scalp, palms, and soles should not be considered.

Scale	Grade	Description
0	Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling Erythema = none (no residual red coloration but post-inflammatory hyperpigmentation may be present)
1	Almost Clear	Plaque thickening = none or possible thickening but difficult to ascertain if there is a slight elevation above normal skin level Scaling = none or residual surface drying and scaling Erythema = light pink coloration
2	Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering the lesions Erythema = light red coloration
3	Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red coloration
4	Severe	Plaque thickening = marked or very marked elevation typically with hard or sharp edges Scaling = non-tenacious or thick tenacious scale, covering most or all of lesions Erythema = very bright red coloration; extreme red coloration; deep red coloration

5.2.2. Extent of Scalp Involvement

The extent of scalp involvement assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3).

The extent of scalp involvement will measure the extent of the scalp affected by psoriasis, expressed as the percentage of total scalp surface area. For this assessment, the subject's thumb approximates 1% of the total scalp surface area.

5.2.3. Body Surface Area (BSA)

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

The BSA affected by psoriasis 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. The

BSA assessment includes the scalp, but it does not include the palms and soles. The total scalp (ie, 100% of the total scalp surface area) can be considered to be approximately 4% BSA.

5.2.4. Psoriasis Scalp Severity Index (PSSI)

PSSI assessments will be performed at study visits according to the Schedule of Visits and Assessments (Section 1.3).

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

The PSSI is used for the measurement of severity of psoriasis.

PSSI combines the assessment of the severity of scalp lesions and the area of scalp affected into a single score in the range 0 (no disease) to 72 (maximal disease).

The extent of scalp affected is scored based on the following:

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

The severity is estimated by three clinical signs: erythema ('E'; redness), induration ('T'; thickness) and desquamation ('S'; scaling). Severity parameters are measured on a scale of 0 to 4, from none to maximum severity possible:

0. absent
1. slight
2. moderate
3. severe
4. severest possible

To calculate the PSSI, the sum of the severity rating for the three main signs are multiplied with the numerical value of the area affected:

PSSI = Sum of scores for erythema, induration and desquamation x involved area (range 0–72)

5.2.5. Psoriasis Area and Severity Index (PASI)

Assessments will be performed as single assessments at each timepoint, from which PASI will be calculated.

PASI assessments will be performed at study visits according to the Schedule of Visits and Assessments (Section 1.3).

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

Psoriasis Area and Severity Index (PASI) is used for the measurement of severity of psoriasis.

PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease).

The body is divided into four sections (head (h) (10% of a person's skin); arms (a) (20%); trunk (t) (30%); legs (l) (40%)). Each of these areas is scored by itself, and then the four scores are combined into the final PASI. For each section, the percent of area (A) of skin involved is estimated and then transformed into a grade from 0 to 6 (A):

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

Note: Palms and soles may be treated with the IP in this study, but will not be counted towards IGA, PASI or BSA assessments.

Within each area, the severity is estimated by three clinical signs: erythema ('E'; redness), induration ('T'; thickness) and desquamation ('S'; scaling). Severity parameters are measured on a scale of 0 to 4, from none to maximum severity possible.

To calculate the PASI, the sum of the severity rating for the three main signs are multiplied with the numerical value of the area affected and with the various percentages of the four body areas. These values are then added to complete the formula as follows:

PASI = 0.1 (Eh + Th + Sh) Ah + 0.2 (Ea + Ta + Sa) Aa + 0.3 (Et + Tt + St)

At + 0.4 (El + Tl + Sl) Al

5.2.6. Scalp Itch-NRS (SI-NRS)

The Scalp Itch-NRS is a single-item scale to assess the patient-reported severity of their symptom at the highest intensity of scalp itching over the past 24 hours. Scalp Itch-NRS will be determined by asking the subject's assessment of worst itching of the **scalp** over the past **24 hours**. The scale is from '0' to '10' ('no scalp itch' to 'worst scalp itch imaginable'). Subjects will complete the Scalp Itch-NRS assessment (Wang 2019).

SI-NRS Assessment will be performed by subjects **daily** at home according to the Schedule of Visits and Assessments (Section 1.3) starting 7 days prior to the scheduled Baseline/Day 1 visit up to the Week 8/Day 57 visit.

The SI-NRS should be completed first and then WI-NRS.

SCALP ITCH NUMERIC RATING SCALE

Please rate the itching severity of your **scalp** due to your psoriasis by circling the number that best describes your **worst** level of itching in the **past 24 hours**.

0	1	2	3	4	5	6	7	8	9	10
0 = No scalp itch										10 = Worst scalp itch imaginable

5.2.7. Worst Itch-Numerical Rating Scale (WI-NRS)

Given that itch is an important symptom of psoriasis, a WI-NRS assessment is included in the present study. The WI-NRS 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 Assessment will be performed by subjects **daily** at home according to the Schedule of Visits and Assessments (Section 1.3) starting 7 days prior to the scheduled Baseline/Day 1 visit up to the Week 8/Day 57 visit.

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 be asked on a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?

5.2.8. Psoriasis Symptom Diary (PSD)

The PSD will be performed at study visits according to the Schedule of Visits and Assessments (Section 1.3). The PSD includes items related to Itching (question 1), Pain (question 9) and Scaling (question 11).

Only adult subjects will complete the PSD. See Appendix 6 for the PSD.

5.2.9. Scalpdex

The Scalpdex (Appendix 7) will be performed by subjects according to the Schedule of Visits and Assessments (Section 1.3).

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

The DLQI (ages 17+ years) and CDLQI (ages 12-16 years, inclusive) will be performed according to the Schedule of Visits and Assessments (Section 1.3). The DLQI/CDLQI is a simple, self-administered and user-friendly validated questionnaire. The DLQI/CDLQI is designed to measure the health-related quality of life of patients suffering from a skin disease. The DLQI/CDLQI consists of 10 questions concerning patients' perception of the impact of skin diseases on different aspects of their health-related quality of life over the last week.

1. The DLQI (Appendix 8) will be completed by subjects ages 17 years and older. The CDLQI (Appendix 9) will be completed by caregivers of subjects ages 12-16 years. If a subject is 16 years old and turns 17 during the study, they will continue to complete the CDLQI.

5.3. Other Evaluations

[redacted]

5.3.2. Dermal Imaging

Medical photography as supportive evidence of clinical outcome will be conducted by all sites using Canfield equipment. Photos will be obtained according to the Schedule of Visits and Assessments (Section 1.3). Photography should be focused on single lesions or specific body sections (e.g., scalp). Body or half body photos should only be taken if necessary. Every effort should be made to prioritize obtaining a photograph of the scalp lesion(s). All efforts will be made to de-identify the subjects. Subjects who are unwilling to participate in the medical photography will be allowed to opt out of this procedure and documented on the informed consent. Refer to the current Photography Manual for instructions regarding photography.

5.4. Final Study Visit

The approximate final study visit will occur at Week 8 (Day 57). The procedures performed during this visit are described in the Schedule of Visits and Assessments (Section 1.3). A 5-day scheduling window is allowed for this visit. Adverse events will be recorded as reported by the subject and followed to resolution (as necessary) as outlined in Section 5.7.

5.5. Early Termination Visit

If a subject is withdrawn from the study, an early termination visit will be scheduled. This visit should include the procedures and assessments that would be performed at the Week 8 visit (Day 57). Subjects who withdraw consent from study participation, will not be required to perform an early termination visit.

5.6. Unscheduled Visit

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

The following information will be collected for all subjects:

- Concomitant medications/procedures
- AEs

5.7. Adverse Events

5.7.1. Adverse Event Definition

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

The definition of AEs includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. When recording such events, provide descriptions that the pre-existing condition has changed (e.g., worsening hypertension for a subject with pre-existing hypertension). A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

Progression of treatment indication including new or worsening of anticipated clinical signs or symptoms, which are collected as clinical efficacy variables and assessed as unequivocally associated with the disease progression and /or lack of efficacy, should NOT be reported as adverse events unless the disease progression is greater than anticipated in the natural course of the disease.

In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as AEs. However, abnormal laboratory findings that result in new or worsening clinical sequelae, or that require therapy or adjustment in current therapy, are considered AEs. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.

5.7.2. Serious Adverse Event

The definitions and reporting requirements of the Food and Drug Administration (FDA)/ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A will be adhered to. Mandatory reporting of all serious unexpected adverse drug reactions (SUSARs) to Health Canada [as per C.05.014 (1) of the FDR] will be adhered. If any AEs are serious, as defined by ICH Guidelines for Clinical Safety, required procedures will be followed.

An SAE is defined as any AE that, in the view of either the PI or Sponsor, meets at least 1 of the following serious criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity/disability
- Congenital anomaly/birth defect
- Other important medical events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition

Hospitalization does not include the following:

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

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

- Admission for treatment of a preexisting condition that did not worsen
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the Baseline documentation for the individual subject
- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

Unexpected is defined as an AE that is not listed in the Investigator Brochure (IB) or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or study documentation.

5.7.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

SUSAR is defined as a serious adverse reaction, the nature or severity of which is not consistent with the known study treatment information. A serious event or reaction is not defined as a SUSAR when: 'it is serious but expected' or it does not fit the definition of an SAE, whether expected or not.

5.7.4. Safety Review with Subject

At each subsequent clinic visit after the Screening visit, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?' Additionally, the study staff will review subject diaries and, if it appears that a potential AE was recorded, study staff will query the subject and determine if an AE occurred.

5.7.5. Adverse Event Reporting

The Investigator is responsible for recording all adverse events, observed by the clinic staff, or reported by the subject that occur after the first application of investigational product through 30 days after end of treatment are recorded in the subject's medical record and the eCRF. Serious adverse events observed by the clinic staff or reported by the subject after signing the informed consent form will be recorded.

All adverse events that meet the criteria for "serious" (i.e., SAEs) will be reported to the Sponsor via fax or e-mail to [redacted].com within 24 hours of becoming aware of the event, whether or not the serious events are deemed IP-related.

All serious event reporting will adhere to ICH E6: Guideline for Good Clinical Practice and ICH E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. The Institutional Review Board (IRB) will be notified of the Alert Reports as per FDA, ICH and the IRB's policies and procedures.

The Sponsor, or delegate, will be responsible for reporting SAEs to health authorities per local reporting requirements. The Investigator will be responsible for reporting events to their respective IRBs/ Ethics Review Board (ERB) in accordance with the IRB/ERB requirements.

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI and treated and/or followed for 30 days after end of treatment until the symptoms or value(s) return to the subject's Baseline value, 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).

The Investigator will review each adverse event and assess its relationship to Investigational Product (unrelated, unlikely, possibly, probably, likely). Each sign or symptom reported will be graded on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5). The date and time of onset, time relationship to drug dosing, duration, and outcome) of each event will be noted.

The relationship of each AE to the Investigational Product will be assessed using the following definitions:

Unrelated	The AE must clearly be caused by the subject's clinical state, or the study procedure/conditions. Definitely not related to drug. Temporal sequence of an AE onset relative to administration of drug not reasonable. Another obvious cause of an AE.
Unlikely	Time sequence is unreasonable. There is another more likely cause for an AE.
Possibly	Corresponds to what is known about the drug. Time sequence is reasonable. Could have been due to another equally, likely cause.
Probably	Is a known effect of the drug. Time sequence from taking drug is reasonable. Ceases on stopping the drug. Cannot be reasonably explained by the known characteristics of the subject's clinical state.
Likely	Is a known effect of the drug (e.g., listed in Physicians' Desk Reference, Compendium of Pharmaceuticals and Specialties, IB). Time sequence from taking drug is reasonable. Event stops upon stopping drug, event returns upon restarting drug.

The following CTCAE toxicity grading scale 5-point severity scale definitions for rating maximum severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.*
Grade 3	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.** Note**:** An experience may be severe but may not be serious, e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Footnotes from table above:

Note: A semi-colon indicates 'or' within the description of the grade.
* Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

5.8. Reporting Pregnancy

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

The Investigator is responsible for reporting all available pregnancy information on the pregnancy report to [redacted] 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.

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

5.9. Treatment Stopping Rules

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

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

- A SAE or a clinically significant non-serious AE which in the opinion of the Principal Investigator or Medical Monitor warrants discontinuation from the study for that subject's well-being
- A treatment-emergent severe (Grade 3) laboratory abnormality (confirmed by repeat sample) which in the opinion of the Principal Investigator or Medical Monitor warrants discontinuation from the study for that subject's well-being

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

- Subjects with a PHQ-8 or modified PHQ-A score of 10-14 should be referred to a mental health professional for evaluation, regardless of the reason for their change in score

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, IP must be discontinued immediately in the event of a female subject's pregnancy.

IP 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.

IP Treatment should be discontinued:

- If the reaction reoccurs. IP should be discontinued permanently, and the subject followed until the reaction resolves.

For cases of suspected allergic contact dermatitis, the medical monitor and sponsor should be notified and there should be discussion about performing patch testing to further evaluate. Patch testing is encouraged in such cases.

In the event of a medical emergency where unblinding is required to provide medical care to the subject, refer to the most current IWRS Plan and Breaking Treatment Codes (Section 4.8.5). Contact the Medical Monitor and the Sponsor promptly.

6. DATA ANALYSIS

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

6.1. Statistical Methods

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

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

Subjects will be stratified by study site, Baseline S-IGA (3 vs. 4), and Baseline B-IGA (2 vs. ≥3).

6.1.1. Determination of Sample Size

A sample size of up to approximately 420 subjects is planned for the study.

The randomization scheme will be 2:1 (ARQ-154 foam 0.3% QD: matching vehicle QD). Approximately 280 subjects will receive ARQ-154 foam 0.3% QD; approximately 140 subjects will receive vehicle foam QD.

This sample size provides more than 99% power to detect an overall 35% difference between treatment groups on S-IGA success at Week 8 and an overall 25% difference between treatment groups on B-IGA success at Week 8 at α=0.025 using a 2-sided stratified (B-IGA at randomization, S-IGA at randomization and study site) Cochran-Mantel-Haenszel test. The results from a recent phase 2 study (ARQ-154-204) of ARQ-154 foam 0.3% compared to vehicle treatment were used to estimate the treatment difference.

The number of subjects to be enrolled will also provide at least 90% power for most of the secondary endpoint analyses. Additionally, the larger study size is included in order to provide additional/sufficient numbers of subjects on ARQ-154 treatment for a safety database.

6.1.2. Interim Analysis

No interim analyses are planned.

6.1.3. Background and Demographic Characteristics

Descriptive statistics will be presented for the subject disposition, demographics, Baseline characteristics, treatment compliance, efficacy endpoints and safety data collected in the clinical study. 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.

6.1.4. Study Disposition

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

6.1.5. Protocol Deviations and Eligibility Deviations

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

6.1.6. Investigational Product Application Compliance

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

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

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

[redacted]

6.2. Safety Analysis

Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. The safety population will be used for these analyses.

6.2.1. Adverse Events

Adverse events (AEs) will be summarized by preferred term, system organ class, and treatment group for all AEs, serious AEs, related AEs, AEs leading to withdrawal from investigational product, and AEs leading to withdrawal from study.

6.2.2. Clinical Laboratory Results

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

6.2.3. Vital Signs

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

6.2.4. Local Tolerance Assessments

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

6.2.5. Medical History and Physical Examinations

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

Clinically significant changes observed during physical examination will be captured as adverse events and included in AE tabulations.

6.3. Efficacy Evaluation

Efficacy analyses will be conducted in the Intent-to-Treat (ITT) population. [redacted]

[redacted]

6.3.1. Co-Primary Endpoints

The co-primary efficacy endpoints in this study are

1. S-IGA Success, defined as achievement of Scalp-IGA (S-IGA) score of 'Clear' or 'Almost Clear' plus a 2-grade improvement from Baseline.
2. B-IGA Success, defined as Achievement of Body-IGA (B-IGA) score of 'Clear' or 'Almost Clear' plus a 2-grade improvement from Baseline.

The primary estimands are the odds of achieving S-IGA success at 8 weeks and the odds of achieving B-IGA success at 8 weeks; that is, the ratio of the odds of achieving S-IGA success at 8 weeks roflumilast foam 0.3% relative to the odds of success at 8 weeks of using a matching vehicle cream (similarly for B-IGA). In the course of the 8-week randomized treatment period, subjects may be exposed to possible known or unknown intercurrent events that could possibly impact the estimand, such as treatment discontinuation due to a specific adverse effect or perhaps a lack of effect. The "Treatment Policy Strategy" has been adopted for handling all known or unknown intercurrent events in this study. To this end, the ITT principle will serve as the analytical basis for interpreting the estimand. In other words, the odds ratio of achieving S-IGA Success and the odds ratio of achieving B-IGA Success for roflumilast foam 0.3% relative to vehicle at 8 weeks will be evaluated regardless of the occurrence of any such intercurrent event. This estimand shall be estimated using the CMH approach. This approach produces an estimate that is the combined odds ratio resulting from adjusting for the possible effects of 3 classification factors: pooled site group, baseline S-IGA category (3 vs. 4) and baseline B-IGA category (2 vs. $\geq$3). S-IGA and B-IGA will be tested separately, but both endpoints must be statistically significant at the 2.5% level for the study to be considered a success.

6.3.2. Secondary Endpoint

Continuous secondary and exploratory endpoints will be analyzed using Analysis of Covariance with treatment and the stratification factors as independent variables. The ITT population will be used, and missing data will be imputed using multiple imputation. Binary secondary and exploratory endpoints will be analyzed similarly to the primary endpoint. To control for multiple comparisons among the secondary endpoints, the following testing plan will be used:

Upon demonstration of statistical significance for S-IGA Success at Week 8 at the 2.5% level and statistical significance of B-IGA Success at Week 8 at the 2.5% level, the testing scheme described below will be used to test the secondary endpoints. This testing scheme will control the overall type 1 error at the 0.025 level.

The overall α level of 0.025 will be split to test 3 families of secondary endpoints, and the Fallback Method will be applied.

Family 1 (α=0.01 or α = 0.015):

- For subjects with Baseline Scalp Itch (SI) NRS score ≥4, achievement of ≥4-point improvement from Baseline in SI-NRS at Week 8 ("SI-NRS Success at Week 8")
- SI-NRS Success at Week 4
- SI-NRS Success at Week 2
- SI-NRS Change from Baseline (CFB) at Week 1
- SI-NRS CFB at 72 hours

Family 2 (α=0.005):

- For subjects with Baseline WI-NRS score ≥4, achievement of ≥4-point improvement from Baseline in WI-NRS at Week 8 ("WI-NRS Success at Week 8")
- PASI-75 at Week 8
- CFB in PSD Items related to Itching, Pain, and Scaling (Questions 1, 9, and 11) aggregate score at Week 8
- PSD Item related to Scaling (Question 11) = 0 at Week 8
- PSD Item related to Itching (Question 1) = 0 at Week 8
- PSD Item related to Pain (Question 9) = 0 at Week 8
- PSSI-75 at Week 8

Family 3 (α=0.01 or 0.015 or 0.025):

- S-IGA score of 'clear' at Week 8
- S-IGA Success at Week 4
- CFB in PASI at Week 2
- S-IGA Success at Week 2
- PSD Total Score = 0 at Week 8
- SI-NRS CFB at Day 1

The Fallback Method will be used to pass unused alpha across the Families. The Families will be tested in this order: Family 2, Family 1, Family 3. Testing will be sequential within Family 2 and Family 1, with the order of testing of each endpoint within each family as listed above.

Testing within Family 3 will be implemented with Holm's procedure.

To start, Family 2 will be tested, sequentially within Family 2, each endpoint at the α=0.005 level. Should the testing succeed through all seven endpoints in Family 2, the α=0.005 will remain unused, and will be passed to Family 1.

The testing of the five SI-NRS endpoints in Family 1 will be sequential, either at the α=0.01 level (assumes Family 2 had an unsuccessful test), or the α=0.015 level (assumes all endpoints in Family 2 were successful at the α=0.005 level).

Family 3 contains six endpoints. Family 3 has initially been allocated α=0.01. This creates three possible testing alpha levels for the Family 3 endpoints:

- If all tests in Family 1 (α=0.01) and Family 2 (α=0.005) are successful, then α=0.005+0.01=0.015 is unused, and the α=0.015 will be carried to Family 3, allowing Family 3 endpoints to be tested at the full 0.025 level.
- If the α=0.005 in Family 2 is used, but the subsequent α=0.01 allocated to Family 1 is not used, then Family 3 endpoints will be tested at the α=0.01+0.01=0.02 level.
- If the α=0.01 in Family 1 is used, and the α=0.005 in Family 2 is also used, then Family 3 endpoints will be tested at α=0.01.

Descriptive statistics will be presented for endpoint and safety data collected in the clinical study. 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.

All subjects who are randomized and receive at least one confirmed dose of investigational product will be included in the safety population.

Adverse events (AEs) will be summarized by preferred term, system organ class, and treatment group for all treatment-emergent AEs, serious AEs, related AEs, AEs leading to withdrawal from investigational product.

Safety laboratory parameters and vital signs will be summarized at each visit using descriptive statistics or frequencies and percentages, as appropriate. Changes from Baseline and percent changes from Baseline in laboratory values and vital signs will also be summarized by visit. In addition, changes from Baseline and percent changes from Baseline in weight and laboratory values will be summarized using shift tables.

Descriptive statistics will be calculated for the PHQ-8 (adults) and Modified PHQ-A (adolescents). The C-SSRS will be analyzed per the Scoring and Data Analysis Guide from the Columbia Lighthouse Project.

7. STUDY ADMINISTRATION

7.1. Ethics

7.1.1. Ethics Review Board

Before screening of subjects into the study, the current protocol, ICF/assent, and any accompanying material to be provided to the subjects will be reviewed and approved by an appropriate IRB/ERB, as required by FDA (21 CFR § 56) or Health Canada and ICH GCP regulations. A letter documenting the IRB approval must be received by the Sponsor before the

initiation of the study at a study site. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator, Sponsor, or designee will submit a progress report at least once yearly to the IRB. However, the frequency of these reports will depend on IRB requirements. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB per the IRB requirements, and in compliance with FDA and ICH GCP guidelines.

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

7.1.2. Ethical Conduct of the Study

This research will be conducted in accordance with the protocol, the principles of the Tri-Council Policy Statement, the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 (R2), December 2016).

7.1.3. Subject Information and Consent/Assent

The Investigator is responsible for obtaining written informed consent or assent (for adolescents) from everyone participating in this study after adequate explanation (in non-technical terms) of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The Investigator must use the most current IRB or ERB-approved consent/assent forms for documenting written informed consent and assent (for adolescents). Subjects will be assured that they may withdraw from the study at any time without jeopardizing their medical care. Each informed consent (or assent as applicable) will be read, appropriately signed, and dated by the subject or the subject's legally authorized representative and the person conducting the consent discussion, and by an impartial witness if required by the IRB/ERB local requirements.

Subjects will be given a copy of their ICF/assent.

7.2. Study Completion and Termination

7.2.1. Study Completion

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

7.2.2. Study Termination

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study 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 a study site by the Sponsor or Investigator may include but are not limited to:

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

7.3. Study Monitoring

Prior to the initiation of the clinical investigation, Sponsor representatives or designees may visit the study 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 study site at appropriate intervals as required to ensure compliance with the protocol and to verify the accuracy and completeness of data reported on the eCRFs. The Study Director or designees shall be available for consultation with the Investigator and serve as liaisons between the study site and the Sponsor.

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

7.4. Data Quality Assurance

To ensure the collection of adequate, consistent, complete, and reliable data during this clinical investigation, Sponsor representatives or designees may conduct audits of participating sites at appropriate intervals throughout the study. The results of these periodic site audits may be subject to review by independent auditors at completion of the clinical investigation.

All clinical data will undergo a quality control check prior to clinical database lock. Edit checks are performed for appropriate databases as a validation routine to check for missing data, data inconsistencies, data ranges etc. Corrections are made prior to database lock.

7.5. Data Handling and Record Keeping

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

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 IP. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

7.6. Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the Investigator or Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the Investigator and Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the Investigator and Sponsor. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s)/IEC(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/IEC, 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)/IEC(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

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

7.7. Confidentiality and Privacy

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

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

7.8. Conflict of Interest

All study Investigators will provide documentation of their financial interest or arrangements with Arcutis Biotherapeutics Inc., or proprietary interests in the investigational product under study. This documentation must be provided prior to the Investigator's participation in the study. Any change to the Investigator's financial interest during the study and up to one year after study completion will be reported to the Sponsor. All Investigators with reported conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study.

7.9. Report Format

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

7.10. Publication Policy

The Sponsor is supportive of publishing clinical study 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.

8. REFERENCES

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

Blakely K, Gooderham M. Management of scalp psoriasis: current perspectives. *Psoriasis (Auckl)*. 2016;6:33-40. Published 2016 Mar 29. Doi: 10.2147/PTT.S85330.

Brion DE, Raynaud F, Plet A, et al. Deficiency of cyclic AMP dependent protein kinases in human psoriasis. *Proc. Natl. Acad. Sci*. 1986;83:5272-5276.

DALIRESP (roflumilast) tablets [package insert]. AstraZeneca Pharmaceuticals LP, Wilmington, DE USA; 2018.

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

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

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

Kimball AB, Naegeli AN, Edson-Heredia E, et al. Psychometric properties of the Itch Numeric Rating Scale in patients with moderate-to-severe plaque psoriasis. *Br. J. Dermatol.* 2016;175(1):157-162. doi:10.1111/bjd.1446.

Kivelevitch D, Frieder J, Watson I, et al. Pharmacotherapeutic approaches for treating psoriasis in difficult-to-treat areas. *Expert Opin Pharmacother.* 2018;19(6):561-575.

Merola JF, Qureshi A, Husni ME. Underdiagnosed and undertreated psoriasis: Nuances of treating psoriasis affecting the scalp, face, intertriginous areas, genitals, hands, feet, and nails. *Dermatol Ther.* 2018;31(3):e12589.

Naegeli AN, Flood E, Tucker J, et al. The Worst Itch Numeric Rating Scale for patients with moderate to severe plaque psoriasis or psoriatic arthritis. *Int J Dermatol*. 2015;54(6):715–22.

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

Schlager JG, Rosumeck S, Werner RN, et al. Topical treatments for scalp psoriasis: summary of a Cochrane Systematic Review. *Br. J. Dermatol.* 2016;176(3):604-614.

Wang TS, Tsai TF. Managing Scalp Psoriasis: An Evidence-Based Review. *Am J Clin Dermatol.* 2017;18(1):17-43.

Wang Y, Coyne K, Sofen H, et al. Qualitative analysis and reproducibility assessment of the Scalp Itch Numeric Rating Scale among patients with moderate to severe plaque psoriasis of the scalp. *Journal of Dermatological Treatment.* 2019. DOI: 10.1080/09546634.2019.1577546.

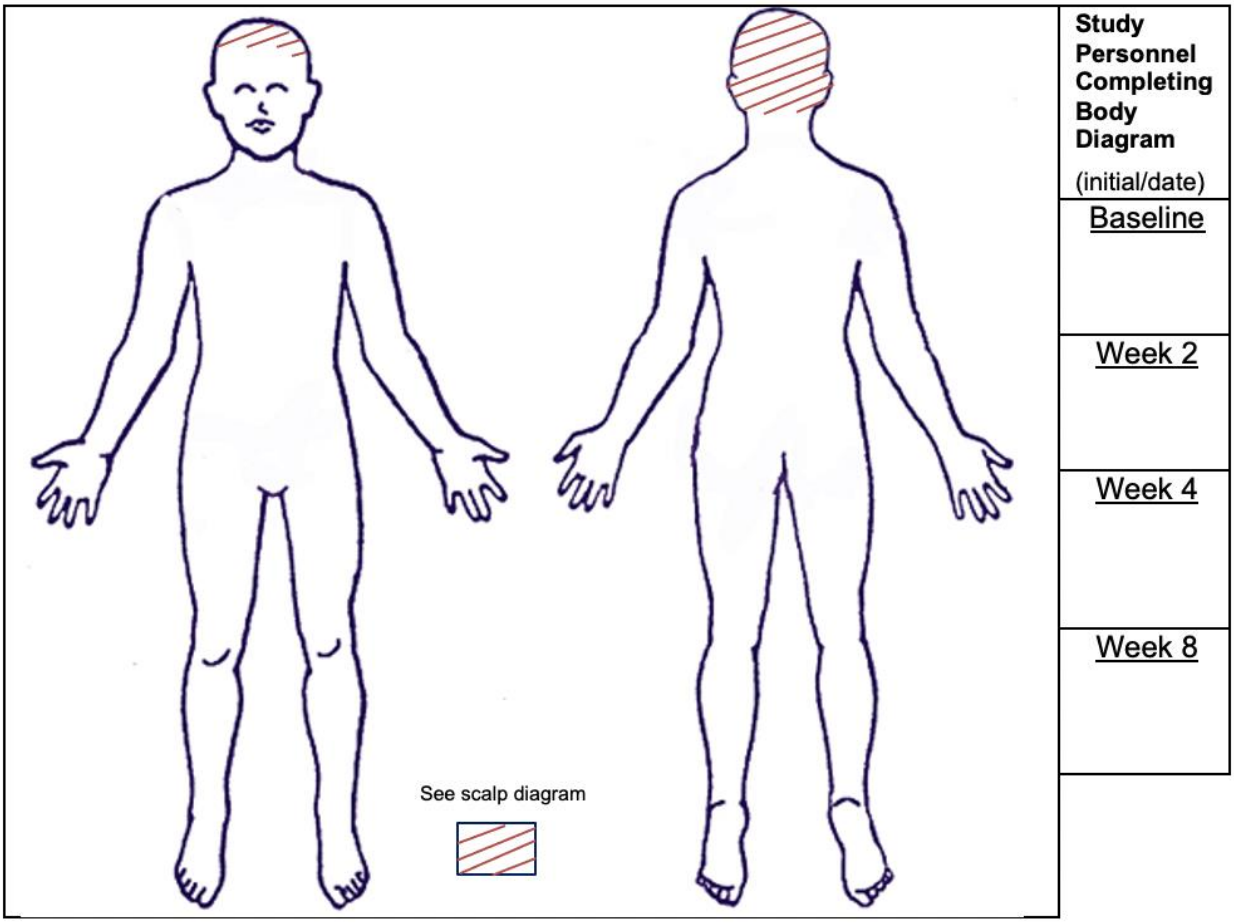
Yosipovitch, G, et al. Peak Pruritis Numerical Rating Scale: psychometric validation and responder definition for assessing itch in moderate-to-severe atopic dermatitis. *Br J Dermatol*. 2019;181(4):761-769. doi:10.1111/bjd.17744.

9. APPENDICES

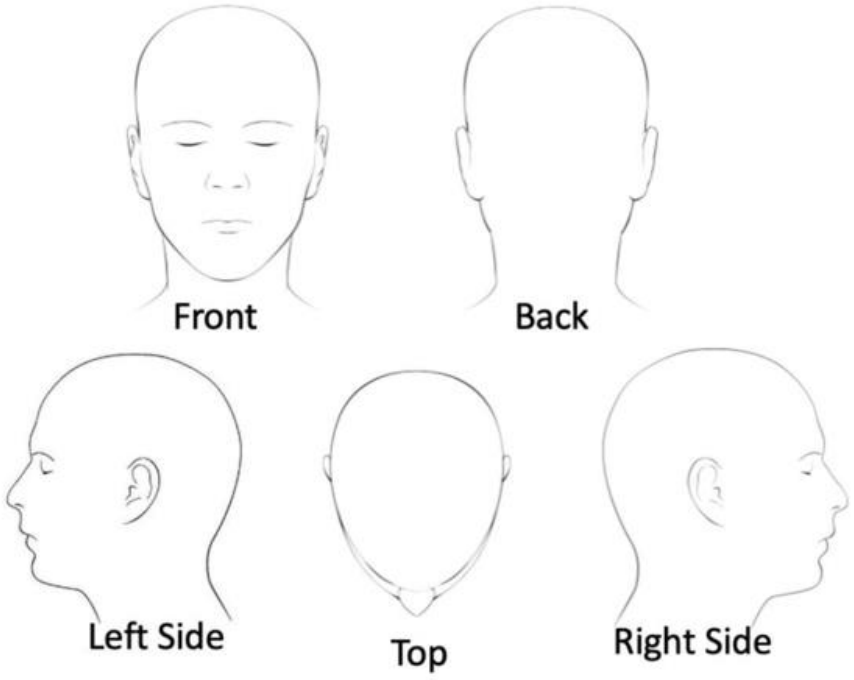
APPENDIX 1. BODY & SCALP DIAGRAM

Site personnel to mark treatable areas identified by the Investigator.

Reminder: Application will be all areas affected including scalp, face, trunk and/or intertriginous/genital regions. Subject should continue to apply even if area(s) clears and treat new lesions.



ARQ-154-309 BODY & SCALP DIAGRAM



APPENDIX 2. 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 3. MODIFIED PATIENT HEALTH QUESTIONNAIRE DEPRESSION SCALE (PHQ-A)

Instructions: How often have you been bothered by each of the following symptoms during the past **two weeks**? For each symptom put an "**X**" in the box beneath the answer that best describes how you have been feeling.				
	(0) Not at all	**(1) Several days**	**(2) More than half the days**	**(3) Nearly every day**
1. Feeling down, depressed, irritable, or hopeless?				
2. Little interest or pleasure in doing things?				
3. Trouble falling asleep, staying asleep, or sleeping too much?				
4. Poor appetite, weight loss, or overeating?				
5. Feeling tired, or having little energy?				
6. Feeling bad about yourself – or feeling that you are a failure, or that you have let yourself or your family down?				
7. Trouble concentrating on things like school work, reading, or watching TV?				
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you were moving around a lot more than usual?				

APPENDIX 4. 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

Please note: The timeframe for the Baseline-Screening version is the past 6 months for suicidal ideation and past 5 years for suicidal behavior.

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

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

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

C-SSRS—Baseline/Screening (Version 1/14/09)
Page 2 of 2

APPENDIX 5. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) SINCE LAST VISIT VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

Since Last Visit

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

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

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

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

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

INTENSITY OF IDEATION

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

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

Most Severe

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

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

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

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

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

SUICIDAL BEHAVIOR *(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* _____

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

APPENDIX 6. PSORIASIS SYMPTOM DIARY

Psoriasis Symptom Diary (PSD)

1	Overall, how <u>severe</u> was your psoriasis-related itching over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		No itching										**Itching as bad as you can imagine**
2	Overall, how <u>bothered</u> were you by your psoriasis-related itching over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		Not bothered at all										**As bothered as you can imagine**
3	Overall, how <u>severe</u> was your psoriasis-related stinging over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		No stinging										**Stinging as bad as you can imagine**
4	Overall, how <u>bothered</u> were you by your psoriasis-related stinging over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		Not bothered at all										**As bothered as you can imagine**
5	Overall, how <u>severe</u> was your psoriasis-related burning over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		No burning										**Burning as bad as you can imagine**

6	Overall, how bothered were you by your psoriasis-related burning over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		Not bothered at all										**As bothered as you can imagine**
7	Overall, how severe was your psoriasis-affected skin cracking over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		No pain										**Pain as bad as you can imagine**
8	Overall, how bothered were you by your psoriasis-affected skin cracking over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		Not bothered at all										**As bothered as you can imagine**
9	Overall, how severe was your psoriasis-related pain over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		No pain										**Pain as bad as you can imagine**
10	Overall, how bothered were you by your psoriasis-related pain over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		Not bothered at all										**As bothered as you can imagine**
11	Overall, how severe was your psoriasis scaling over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		No scaling										**Scaling as bad as you can imagine**

12 Overall, how bothered were you by your psoriasis scaling over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	Not bothered at all										**As bothered as you can imagine**
13 Overall, how noticeable did you think the color of your psoriasis-affected skin was over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	Not at all noticeable										**As noticeable as you can imagine**
14 Overall, how much did you try to hide your psoriasis-affected skin over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	Did not try to hide at all										**Totally avoided being seen by others**
15 Overall, how much did your psoriasis cause you to avoid activities with other people over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	You did not avoid other people										**Avoided other people as much as you ever have**
16 Overall, how embarrassed were you because of your psoriasis over the past 24 hours?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
	No embarrassment										**As embarrassed as you can imagine**

APPENDIX 7. 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 8. DERMATOLOGY LIFE QUALITY INDEX (DLQI)

DLQI Score: ☐

Site No: Date:
Name:
Address: Diagnosis:

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

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

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

Please check you have answered EVERY question. Thank you.

APPENDIX 9. CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX (CDLQI)

Subject Number: Diagnosis: CDLQI
Age: Date: SCORE: ☐

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

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

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

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

APPENDIX 10. COVID-19 STUDY SITE GUIDANCE

BACKGROUND

As the impact of coronavirus disease 2019 (COVID-19) continues to develop, Premier Research Inc. and Arcutis Biotherapeutics Inc. have collated the following guidelines in response for study sites participating in the ARQ-154-309. While it is ideal for subjects to perform all protocol-specific assessments at the study site, both Premier and Arcutis are focused on prioritizing subject safety and data integrity. Therefore, the following guidelines will identify challenges and mitigation strategies while operating clinical trials remotely.

REMOTE DATA COLLECTION

In the event subjects are unable to complete protocol-specific assessments onsite, study sites may collect data from subjects remotely via telephone and/or by traditional mail or email. The method used for data collection must be clearly documented in the source. Whenever possible, sites should adhere to the protocol visit window for remote data collection. Screening and Baseline (Day 1) visits/assessments must be performed in the clinic and must NOT be completed remotely. If necessary, these visits can be delayed ensuring they are conducted in the clinic and not remotely.

Data collection by phone may be performed. Subjects are contacted via telephone and site staff will collect data verbally for all critical data points applicable. Subject responses should be recorded in the site source documents. Data collected remotely should be entered into the Electronic Data Capture (EDC) system (iMedidata Rave).

Data collection by mail or email may also be performed for applicable assessments. Site staff will contact subjects via traditional mail or email to collect data using paper versions of study questionnaires. C-SSRS cannot be collected by mail/email as this requires subject interview by site staff.

Investigator assessments and subject questionnaires normally completed during on-site visits should be completed on the appropriate paper source documents and entered in the EDC. The following subject assessments/questionnaires are approved to be collected via telemedicine/remotely:

- C-SSRS
- WI-NRS/SI-NRS
- PHQ-8/PHQ-A
- Subject Local Tolerability
- Adverse Events
- Concomitant medication

The following Investigator assessments cannot be completed via telemedicine/remotely:

- S-IGA
- B-IGA
- PASI
- PSSI
- BSA
- Investigator Local Tolerability
- Subject Weight

GUIDELINES FOR REMOTE DATA COLLECTION

1. Highest priorities: the subject safety and preserving integrity of data are critical
2. Study visits and procedures must be followed per protocol whenever possible. Any specific changes in study conduct that deviate from the protocol should be communicated to the IRB and Sponsor (via reporting to your site assigned CRA). All protocol deviations which occurred as a result of COVID-19 disruptions (e.g., visits out of window, missed assessments, etc.) should be differentiated from other PDs. It is prudent to receive IRB guidance or approval if a deviation is known to occur in advance (i.e., extending IP application or changing assessment windows, etc.).
3. If, despite all efforts, a planned clinic visit is absolutely not possible due to a COVID-19 related issue (e.g., site has closed, subject prohibited from coming to the study site, etc.), Sponsor's strong preference is a delayed clinic visit. If the subject can come to clinic within a reasonable amount of time considering the protocol allowed visit window. If a delayed clinic visit cannot be completed within 14 days of the protocol specified visit window, please contact the Medical Monitor for additional guidance.
4. It is critical to ensure subjects have enough IP in the event timely clinic visit(s) is/are not possible. It is also critical to ensure subjects are instructed to continue to apply IP per protocol for the duration of their participation in the study. Subjects should also be reminded to complete their daily diaries and IP compliance should be assessed via phone if clinic visits are not possible or are delayed.
5. It is critical for preserving data integrity to make every effort possible to have a subject return to clinic for the Week 8 visit. For visits conducted in the clinic, it is critical to ensure Rater consistency for all efficacy assessments (e.g., IGA, etc.). If absolutely necessary, it is preferred to have several missed visits and a delayed Week 8 visit versus having no Week 8 visit. If it is not possible for a subject to return on-site within window for the Week 8 visit, sites should:
    a. Ensure the subject has signed the most current IRB approved ICF.
    b. Contact subjects to discuss continue administration of IP and continue to complete their dosing diaries per regular IP administration instructions.

c. Subjects are approved to continue applying IP post Week 8 as long as the following have been discussed with the subject:
   - Site should confirm the subject has adequate IP to continue dosing and if not ask the subject to return to the site to pick up additional IP or refer to the current IP Handling Plan for instructions on shipment of IP from site to subject.
   - Confirm the subject has no AEs that would warrant discontinuation of the IP.
   - Site should discuss any new or ongoing conmed(s) and determine if the use of any warrant having the subject stop IP application or not.
   - For any female subject of childbearing potential the site should discuss and confirm the subject has continued her methods of ensuring pregnancy does not occur. Any deviation from these methods should be discussed further and the site should determine if IP should be halted or contact the medical monitor or Arcutis if they have any questions. A urine pregnancy test should be performed at the next onsite visit (this is applicable to prior visits being missed due to COVID-19 as well).
   - Subjects are approved to continue dosing for up to 14 days past their Week 8 visit. After this, sites should reach out to the Medical Monitor and/or Arcutis directly for approval to have subjects continue dosing.
   - All the above discussions must be documented in the source.

d. If available, home health nurse visits could be considered for collection of Vital Signs and Clinical Labs.
e. In the event a subject is quarantined, has symptoms, or is confirmed positive for COVID-19, it is the Sponsor's opinion that IP can continue, assuming no other contraindications.