Protocol ARQ-151-301

A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.3% Administered QD in Subjects with Chronic Plaque Psoriasis

Sponsor:	Arcutis, Inc. [redacted]
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]
IND Number:	135681
Protocol Version:	Amendment 1
Final for Release:	11 September 2019
Final:	31 October 2019
Amendment 1:	21 February 2020

GCP Statement

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

Site Investigator Signature Page

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ARQ-151-301

SPONSOR: Arcutis, Inc. [redacted]

FINAL ISSUE DATE: 31 October 2019

Amendment 1: 21 February 2020

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

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Arcutis, Inc. I will discuss the material with them to ensure that they are fully informed about ARQ-151 and the study.

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

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

Investigational Study Site Name: [redacted]

Print Investigator Name: [redacted]

Investigator Signature: [redacted] Date: [redacted]

SUMMARY OF CHANGES

The following sections have been changed in the Final edition of the ARQ-151-301 protocol:

Section	Summary of Changes
Final	
SUMMARY OF CHANGES	Added protocol revision history section
Study Population	Removed limits for mild and severe populations
Exclusion Criteria	Corrected typo for exclusion criteria 14 to confirm Subjects with PHQ-8 or modified PHQ-A ≥10 at Screening or Baseline visits
Exclusion Criteria	Remove criteria #20 History of and/or concurrent condition of serious hypersensitivity (anaphylactic shock or anaphylactoid reaction) to PDE-4 inhibitors.
Numbering of Subjects 6.2.2	Updated site numbers from 2 digits to 3 digits and subject numbers from 5 digits to 6 digits
Section 9.4	Updated to Clinical Research Organization and removed QST
Adverse Event Definition 7.4.1	Added text to clarify adverse event definition
Pregnancy reporting 7.5	Updated section to clarify pregnancy reporting
	Editorial and administrative changes throughout the protocol to clarify language and formatting to improve readability.

The following sections have been changed in Amendment 1 of the ARQ-151-301 protocol:

Section	Summary of Changes
Amendment 1	
Study population	Added children (2 -11 y/o)
C-SSRS, PHQ-8 / modified PHQ-A	Will be collected for subjects 12 years and older
CDI-2	Parent version will be collected from parents for subjects 6-11 y/o (inclusive)
Screening	Added therapies the subject has used in the last twelve months for psoriasis will be recorded.
Removal of Subjects from Investigational Product	Added CDI-2 raw total score of 34, after consultation with a mental health professional, the Sponsor, and at the Investigator's discretion
Subject tolerability assessments	Added parents may rate for children
Appendix 5	Updated to include pediatric values
Appendix 6	Added Appendix 6 Children's Depression Inventory 2 (Parent Report)
	Editorial and administrative changes throughout the protocol to clarify language and formatting to improve readability

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1 PROTOCOL SYNOPSIS

Protocol Title:	A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.3% Administered QD in Subjects with Chronic Plaque Psoriasis
Investigational Product:	ARQ-151 investigational product will be supplied as a 0.3% cream Matching vehicle cream will contain only excipients of ARQ-151 cream
Planned Dose Level:	Subjects will be randomized 2:1 to receive ARQ-151 cream 0.3% QD or matching vehicle cream QD applied to all psoriatic lesions up to and including an area of 20% BSA. Application will be to all areas affected including the face and intertriginous/genital regions (except for the scalp).
IND:	135681
Clinical Indication:	Chronic Plaque Psoriasis
Study Design:	This is a phase 3, randomized, parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.3% or vehicle cream is applied QD for 8 weeks to subjects with chronic plaque psoriasis involving between 2 and 20% BSA
Study Objectives:	To assess the safety and efficacy of ARQ-151 cream 0.3% vs. vehicle administered QD for 8 weeks to individuals with 2 - 20% BSA of chronic plaque psoriasis.
Study Sites:	Approximately 40 sites in Canada and United States
Study Population:	Approximately 400 subjects; randomized 2:1 to ARQ-151 cream 0.3% QD or vehicle QD. Subjects will be male and female children (2 -11 y/o), adolescents (12-17 y/o) and adults ($\geq$18 y/o). Subjects will have 2% to 20% total BSA of chronic plaque psoriasis. Subjects will have a minimum IGA of 'Mild' (2) for study entry.
Main Inclusion Criteria	1. Participants legally competent to sign and give informed consent and if age appropriate (for children and adolescents) assent, as required by local laws 2. Males and females ages 2 years and older 3. Clinical diagnosis of psoriasis vulgaris of at least 6 months duration (3 months for children) as determined by the Investigator. Stable disease for the past 4 weeks. 4. Psoriasis vulgaris on the face, extremities, trunk, and/or intertriginous areas involving 2% to 20% of BSA (excluding the scalp, palms and soles) 5. An Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') at Baseline 6. A PASI score of at least 2 (excluding the scalp, palms and soles) at Baseline 7. Females of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test

	at Baseline (Visit 2). In addition, sexually active FOCBP must agree to use at least one form of highly effective contraception throughout the trial. Highly effective forms of contraception include: oral/implant/injectable/transdermal contraceptives, intrauterine device, and partner's vasectomy. If barrier methods are used (e.g., condom with spermicide, diaphragm with spermicide), then 2 forms of conception are required. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a lifestyle choice and an acceptable backup method has been identified if the subject becomes sexually active. 8. Females of non-childbearing potential must either be premenarchal or post-menopausal with spontaneous amenorrhea for at least 12 months or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy). 9. In good health as judged by the Investigator, based on medical history, physical examination, serum chemistry labs, hematology values, and urinalysis. 10. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule, according to the judgment of the Investigator.
Main Exclusion Criteria	1. Subjects who cannot discontinue medication and treatments prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 1). 2. Planned excessive exposure of treated area(s) to either natural or artificial sunlight, tanning bed or other LED. 3. Subjects 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, ACE inhibitors). 5. Current diagnosis of non-plaque form 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 to excipients in ARQ-151 cream [redacted] 8. Subjects who cannot discontinue the use of strong P-450 cytochrome inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin) for two weeks prior to the baseline visit and during the study period. 9. Subjects who cannot discontinue the use of strong P-450 cytochrome inducers (e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, and rifampin) for two weeks prior to the baseline visit and during the study period.

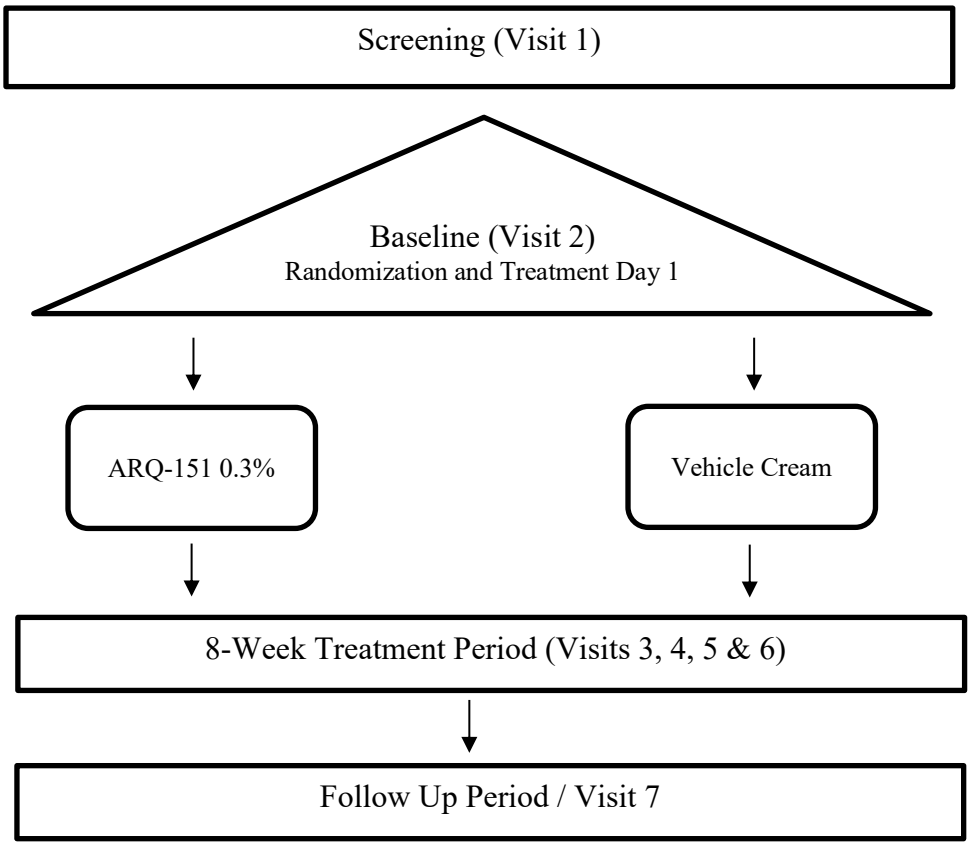
	10. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding. 11. Previous treatment with ARQ-151 or ARQ-154. 12. Subjects who have received oral roflumilast (Daliresp®, Daxas®) or other PDE4 inhibitors (apremilast) within the past 4 weeks. 13. Known or suspected: • severe renal insufficiency or moderate to severe liver impairment (Child-Pugh B or C) • known HIV infection • hypersensitivity to component(s) of the investigational products • history of severe depression, suicidal ideation, Baseline/Screening C-SSRS (12 years and older) indicative of suicidal ideation, whether lifetime or recent/current 14. Subjects with PHQ-8 (18 y/o and older) or modified PHQ-A (12 to 17 y/o) ≥10 at Screening or Baseline visits. Subjects (6 to 11 years old, inclusive) with a CDI-2 (parent report) raw score >20 at Screening/Baseline 15. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of study medication. 16. Subjects with a history of a major surgery within 4 weeks prior to Baseline (Visit 2) or has a major surgery planned during the study. 17. Subjects who are unable to communicate, read or understand the local language, or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation. 18. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members that live in the same house of enrolled subjects. 19. 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. 20. Current or a history of cancer within 5 years with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix. 21. Subjects with active infection that required oral or intravenous administration of antibiotics, antifungal or antiviral agents within 7 days of Baseline/Day 1.
Duration of Participation for Subjects:	Screening (up to 5 weeks), Treatment phases (8 weeks), and a follow up (1 week post-treatment completion) for subjects who do not enroll in ARQ-151-306. Upon completion of the treatment phase of this study (week 8), subjects may have the opportunity, subject to regulatory approval, to participate in an open-label extension study (ARQ-151-306) of up to 6 months.

Key Assessments:	Safety will be monitored through AEs, application site assessments, vital signs, physical examinations, safety labs, C-SSRS (12 years and older), either PHQ-8 (in adults), modified version of the PHQ-A (in adolescents) or Children's Depression Inventory 2 (CDI-2), parent report for children (6-11 years old, inclusive), assessments. Efficacy assessments will include IGA, I-IGA, PASI/mPASI, BSA, WI-NRS (12 years and older), PSD (adults only), and DLQI (≥17 years of age)/CDLQI (subjects 2 to 16 inclusive). Pharmacokinetic (PK) samples will be collected at pre-dose (trough) on days 1 (baseline), 29 (week 4), and 57 (week 8) for all subjects. Refer to the Schedule of Visits and Assessments (Section 2) for detailed schedules of the study assessments.
Study Endpoints	The Primary Efficacy Endpoint is IGA success, defined as an IGA score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at week 8. The secondary efficacy endpoints will include: • Achievement of Psoriasis Area Severity Index 75 (PASI-75; subjects who achieve a 75% reduction in PASI from Baseline) at week 8 • For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (intertriginous IGA (I-IGA) ≥2) at Baseline, achievement of 'I-IGA' score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at week 8. • In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 8 • In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 4 • In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 2 • Change from Baseline in total Psoriasis Symptoms Diary (PSD) score at week 8. • Change from Baseline in PSD score at week 4. • Time to achieving Psoriasis Area Severity Index-50 (PASI-50) • For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (I-IGA ≥2) at Baseline, achievement of 'I-IGA' score of 'clear' at week 8. • Achievement of Psoriasis Area Severity Index-90 (PASI-90; subjects who achieve a 90% reduction in PASI from Baseline) at week 8.
Statistical Considerations:	Approximately 400 subjects are planned for this study. Approximately 267 subjects will receive ARQ-151 cream 0.3% QD; approximately 133 subjects will receive matching vehicle cream QD. The randomization scheme will be 2:1 (ARQ-151 cream 0.3% QD : matching vehicle QD) stratified by study site, baseline IGA (IGA=2 vs. IGA≥3), and intertriginous involvement at baseline (I-IGA≥2, yes vs no). This sample size provides >99% power to detect a 22.4% difference between treatment groups on IGA success at α=0.05 using a 2-sided Chi-squared test. The results from a recent phase 2b study (ARQ-151-201) of ARQ-151

	compared to vehicle treatment were used to estimate the treatment difference. Specifically, in the phase 2b trial, 32.2% of subjects demonstrated IGA success in the ARQ-151 0.3% group and 9.8% of subjects demonstrated IGA success in the vehicle group. The number of subjects to be enrolled will also provide sufficient power for the first 5 secondary endpoints. Additionally, the larger study size is included in order to provide additional/sufficient numbers of subjects on ARQ-151 treatment for a safety database. Descriptive statistics will be presented for the endpoint and safety data collected in the clinical trial. This includes the number and percentage of subjects for binary endpoints/categorical data, and mean, SD, median, minimum, and maximum for continuous data. The primary endpoint of 'IGA success at week 8' will be analyzed using a Cochran-Mantel-Haenszel test stratified by study site, IGA at baseline, and intertriginous involvement at baseline. The analysis will be performed on the Intention-to-Treat (ITT) population and missing data will be imputed using multiple imputation. Continuous secondary endpoints will be analyzed using Analysis of Covariance with treatment and stratification factors as independent variables. The ITT population will be used and missing data will be imputed using multiple imputation. Binary secondary endpoints will be analyzed similarly to the primary endpoint. Time-to-event endpoints will be analyzed using the Kaplan-Meier estimator. Treatment group comparisons will be performed using the log-rank statistic. Secondary endpoints will only be tested statistically if the primary endpoint is considered statistically significant. To control for multiple comparisons among the secondary endpoints, the following multiplicity procedure will be used: • Upon successful testing of the primary endpoint, the alpha will be partitioned to test secondary endpoints families 1 and 2 (partition 1) and to test additional WI-NRS timepoints (partition 2) • Partition 1 of alpha = 0.03 will be allocated to test secondary endpoint family 1 and secondary endpoint family 2. The endpoints in family 1 will be tested independently using a Bonferroni split of the alpha; the next 5 secondary endpoints (secondary endpoint family 2) will be tested using the alpha available after testing endpoint family 1. The Holm procedure will be used to control for multiple comparisons in secondary endpoint family 2. • Partition 2 of alpha = 0.02 will be allocated to sequentially test WI-NRS success at week 4 and WI-NRS success at week 2. All subjects who are randomized and receive at least one confirmed dose of investigational product or vehicle cream 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, and AEs leading to withdrawal from study.

	Safety laboratory parameters and vital signs will be summarized at each visit using descriptive statistics or frequencies and percentages, as appropriate. Changes from baseline in laboratory values and vital signs will also be summarized by visit. In addition, changes from baseline in weight and laboratory values will be summarized using shift tables. Descriptive statistics will be calculated for the PHQ-8 (adults) or Modified PHQ-A (adolescents) and CDI-2 (children). The C-SSRS will be analyzed per the Scoring and Data Analysis Guide from the Columbia Lighthouse Project.

1.1 Study Schema



A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.3% Administered QD in Subjects with Chronic Plaque Psoriasis

Approximately 400 subjects with chronic plaque psoriasis will be randomized 2:1 to receive either:

- ARQ-151 cream 0.3%,
- Vehicle cream

2 SCHEDULE OF VISITS AND ASSESSMENTS

Study Procedure	Screen	Baseline Day 1	Wk 2 Day 15	Wk 4 Day 29	Wk 6 Day 43	Wk 8[r] Day 57	Wk 9 Day 64
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Window	**-35 days**		**+/- 3 days**	**+/- 5 days**	**+/- 5 days**	**+/- 7 days**	**+/- 7 days**
Informed consent/assent	X						
Medical history	X						
Physical examination[a]	X	X				X	
I/E criteria	X	X					
Hematology, Serum Chemistries, and Urine Analysis[b]	X	X		X		X	
Vital signs, height, weight[c]	X	X	X	X	X	X	X
IGA[d], BSA[d], PASI/mPASI[d]	X	X	X	X	X	X	X
Intertriginous area IGA (I-IGA)[e]		X	X	X	X	X	X
WI-NRS[f]	X	X	X	X	X	X	
DLQI/CDLQI[g]	X	X	X	X		X	
Local Tolerability Assessments[h]		X		X		X	
C-SSRS, PHQ-8 / modified PHQ-A (12 years and older)	X	X		X		X	
CDI-2 parent report (6-11 y/o inclusive)	X	X		X		X	
PSD[i]	X	X	X	X	X	X	
Photography[j]		X	X	X	X	X	
Serum pregnancy test	X						
Urine pregnancy test[k]		X		X		X	
PK draws[l]		X		X		X	
IP application in clinic[m]		X	X	X	X	X	
Assign investigational product kit[n]		X					
Dispense/review diary		X	X	X	X	X	
Weigh investigational product tubes[n]		X	X	X	X	X	
Compliance calculation[o]		X	X	X	X	X	
Adverse event assessment[p]	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Study Exit[q]							X

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

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

[c] Height will be collected at Baseline only. Weight will be collected at every visit. Subject to void prior to weight being taken. Remove any jackets, outerwear and shoes. Remove any objects of significant weight (i.e. cell phones, wallet, key chains). A 5% unintentional weight loss should be reported to the medical monitor on Page 1.

[d] IGA (based on whole body involvement) will be a 5-point scale ranging from clear (0) to severe (4). **IGA should be completed prior to other physician assessments and by the same Evaluator at each study visit.** Total 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 the BSA. PASI/mPASI will be determined by standard methods. NOTE: while palms and soles will be treated with IP, they are not counted towards IGA, PASI/mPASI, or BSA assessments.

[e] For subjects with intertriginous area involvement of at least 'mild' severity by IGA (IGA≥2) at Baseline (using the IGA scale but evaluating intertriginous areas ONLY and NOT whole body involvement), an IGA for the intertriginous region alone

(I-IGA) will be recorded. **This 'intertriginous area IGA' should be done AFTER the 'standard whole body IGA' (primary endpoint) in subjects who qualify.**

[f] Subjects 12 years and older will complete WI-NRS pruritus assessment.

[g] Subjects ≥17 years of age will complete DLQI. For subjects 2-16 years of age, CDLQI will be completed.

[h] Tolerability assessments should be recorded prior to investigational product application for Investigator assessment (Berger and Bowman skin irritation score) and 10-15 minutes post-investigational product application for subject '0-3' burning/stinging assessment. Parents may report for children. **Note for investigator tolerability assessments: reactions at the site of product application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's Psoriasis.**

[I] Adult subjects only

[j] Photography will be performed using Canfield equipment on all subjects at all sites. 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. See Photography Manual for details.

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

[l] PK draws will be collected from all subjects at Days 1, 29 and 57. The draws will be pre-dose investigational product application in the clinic (i.e., trough levels). Ensure investigational product is not applied in the area where PK will be drawn.

[m] Subjects to apply assigned IP in clinic at every visit. The time of application will be documented.

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

[o] Each IP tube should be weighed and recorded at every visit. See IP Handling Manual for details.

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

[q] Subjects who consent to/enroll into the open label extension study (ARQ-151-306) will complete the study at Week 8; subjects that do not consent to/enroll into ARQ-151-306 will return at Week 9 to complete the study.

[r] Subjects that terminate early should return to the clinic for the week 8 assessments.

3 ABBREVIATIONS

AE	Adverse Event
AMP	Adenosine Monophosphate
AUC	Area Under the Curve
BSA	Body Surface Area
C_{max}	Maximum Concentration
CDI-2	Children's Depression Inventory 2
CDLQI	Children's Dermatology Life Quality Index
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic Acid
ERB	Ethics Review Board
FDA	U.S. Food and Drug Administration
FOCBP	Female of Child Bearing Potential
GCP	Good Clinical Practices
HC	Health Canada
HCA	Alpha-Hydroxycinnamaldehyde
HPRT	Hypoxanthine-guanine Phosphoribosyl Transferase
IB	Investigational Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA	Investigator Global Assessment
I-IGA	Intertriginous IGA
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to Treat
IWRS	Interactive Web Response System
LED	Light Emitting Device
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
mL	Milliliter
MMRM	Mixed effect Model Repeat Measurement
mPASI	Modified Psoriasis Area and Severity Index
MTD	Maximum Tolerated Dose

NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
Ng	Nanogram
NRS	Numerical Rating Score
PASI	Psoriasis Area and Severity Index
PASI-75	Psoriasis Area and Severity Index-75; subjects who achieve a 75% reduction in PASI from Baseline
PASI-90	Psoriasis Area and Severity Index-90; subjects who achieve a 90% reduction in PASI from Baseline
PASI-100	Psoriasis Area and Severity Index-100; subjects who achieve a 100% reduction in PASI from Baseline
PDE-4	Phosphodiesterase 4
PHQ-A	Modified PHQ-9 for Adolescents
PHQ-8	Patient Health Questionnaire depression scale
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PSD	Psoriasis Symptoms Diary
QD	Once Daily ("quaque die")
SAE	Serious Adverse Event
TEAE	Treatment Emergent Adverse Event
Th1	Type 1 T Helper Cell
Th17	Type 17 T Helper Cell
T_{max}	Time to reach maximum concentration
V79	Chinese hamster cell line
WI-NRS	Worst Itch – Numeric Rating Score

4 BACKGROUND AND RATIONALE

4.1 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 recently Otezla® (apremilast) a PDE-4 inhibitor has been approved for the oral treatment of chronic plaque psoriasis.

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. 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. The study sponsor is developing a topical formulation of roflumilast for the treatment of chronic plaque psoriasis. Our Phase 2 results suggest that ARQ-151 may be a highly efficacious and well-tolerated topical treatment for psoriasis.

4.2 Nonclinical Studies

4.2.1 Toxicology Summary

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

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

4.3 Clinical Studies

4.3.1 Topical Roflumilast Cream

Phase 2a

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

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

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

[redacted]

Phase 2b

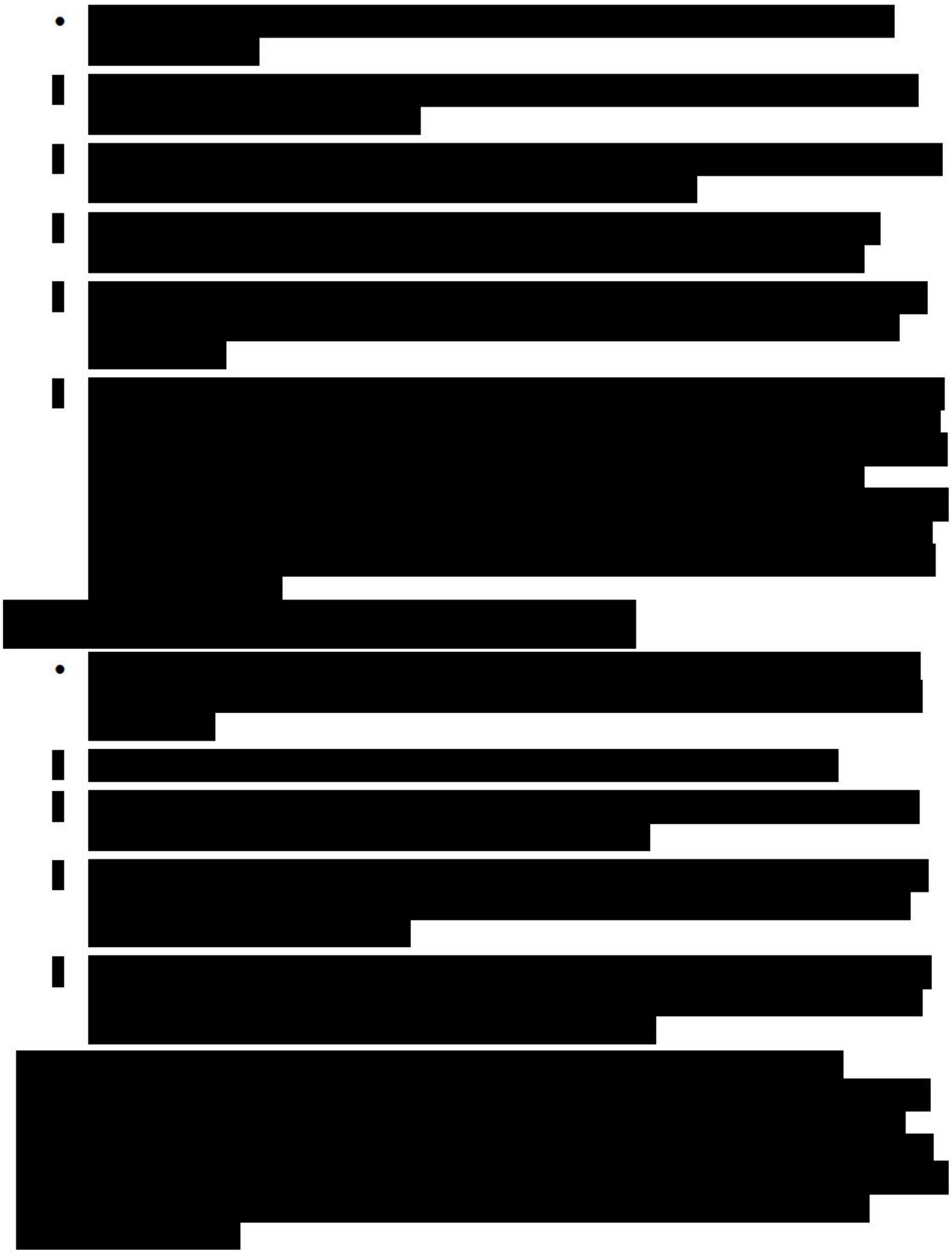
ARQ-151 has also been evaluated in a Phase 2b study (ARQ-151-201; NCT03638258) in adult patients with chronic plaque psoriasis. ARQ-151-201 was a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.15%, ARQ-151 cream 0.3%, or vehicle cream was applied QD for 12 weeks to 332 adult subjects with 2% to 20% BSA of chronic plaque psoriasis and baseline IGA of Mild or greater.

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

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

[redacted]

[redacted]



4.3.2 Oral Roflumilast Tablet

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

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

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

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

4.4 Rationale for Development

Given the approval of OTEZLA as an oral treatment for moderate to severe psoriasis, PDE4 inhibition is a well validated approach to the treatment of psoriasis.

[redacted]

The safety monitoring practices employed in this protocol (i.e., physical examinations, vital signs/weight, local skin toleration assessments, hematology, serum chemistry, urinalysis, PHQ-8 (adults)/modified PHQ-A (adolescents), C-SSRS (12 years and older) or Children's Depression Inventory 2 (CDI-2), parent report for children (6-11 years old, inclusive) and AE questioning) are adequate to protect the subjects' safety and should detect expected AEs.

Oral roflumilast has now been used for almost a decade in the treatment of COPD exacerbations and its safety record has been well-documented. The known adverse effects of oral treatment in the COPD population (nausea, diarrhea, weight loss, psychiatric AEs; see Section 4.3.2) are monitorable, the current protocol is designed to detect these adverse events and others should they occur, and provides guidance for management, as necessary, to ensure patient safety. Furthermore, the safety profiles of ARQ-151 at doses ranging from 0.15% to 0.5% in the preceding Phase 2a and 2b studies in psoriasis suggests that ARQ-151 0.3% will be similarly well tolerated in the present study.

[redacted]

[redacted]

5 STUDY ENDPOINTS AND OBJECTIVES

5.1 Study Objectives

5.1.1 Primary Objectives

To assess the safety and efficacy of ARQ-151 cream 0.3% vs. vehicle administered QD for 8 weeks to individuals with 2-20% BSA of chronic plaque psoriasis.

5.2 Efficacy Endpoints

5.2.1 Primary Endpoint

The Primary Efficacy Endpoint is achievement of IGA Success defined as:

- An IGA score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at week 8

Investigator Global Assessment of Disease (IGA)

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

This IGA (whole body) will be the first efficacy endpoint measured at clinic visits and <u>prior to</u> the application of any Investigational Product.

5.2.2 Secondary Endpoints

The secondary efficacy endpoints will include:

- Achievement of Psoriasis Area Severity Index 75 (PASI-75; subjects who achieve a 75% reduction in PASI from Baseline) at week 8.
- For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least ‘mild’ (intertriginous IGA (I-IGA) ≥2) at Baseline, achievement of ‘I-IGA’ score of ‘clear’ or ‘almost clear’ PLUS a 2-grade improvement from Baseline at week 8.
- In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 8 as compared to Baseline.
- In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 4 as compared to Baseline.
- In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 2 as compared to Baseline.

- Change from Baseline in total Psoriasis Symptoms Diary (PSD) score at week 8.
- Change from Baseline in total PSD score at week 4.
- Time to achieving Psoriasis Area Severity Index-50 (PASI-50; subjects who achieve a 50% reduction in PASI from Baseline).
- For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (intertriginous IGA (I-IGA) ≥2) at Baseline, achievement of 'I-IGA' score of 'clear' at week 8.
- Psoriasis Area Severity Index-90 (PASI-90; subjects who achieve a 90% reduction in PASI from Baseline) at week 8.

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan

This is a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.3% or vehicle cream QD is applied for 8 weeks to subjects with between 2% to 20% (inclusive) BSA of chronic plaque psoriasis.

Approximately 400 subjects will be enrolled at approximately 40 study sites in the United States and Canada. Subjects will be children, adolescent and adult males or females with chronic plaque psoriasis. Subjects must have an Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') at Baseline. Subjects must have at least 2% and no more than 20% Body Surface Area (BSA) of chronic plaque psoriasis. All psoriasis lesions on a subject will be treated including the face, trunk, genitals/skin folds, or limbs (excluding the scalp). The palms and soles will be treated but will not be counted towards any measurements of efficacy (IGA, BSA, PASI/mPASI). For subjects with intertriginous area involvement, and with severity of the intertriginous area lesions at least 'mild' (IGA≥2) at Baseline, 'I-IGA' score will be recorded at subsequent visits. The same IGA used for the primary endpoint (whole body) will also be used for 'intertriginous area lesion IGA score' (I-IGA), but only intertriginous areas will be evaluated for I-IGA, not the rest of the body.

6.2 Subject Participation

Upon completion of this study, participants may have the opportunity, subject to regulatory approval, to participate in an open-label extension study (ARQ-151-306) of up to 6 months. The Week 8 visit of the present study would be the Day 1 visit for ARQ-151-306 and there would not be a Week 9 follow-up visit.

For subjects who do not enter ARQ-151-306 there will be a minimum of 7 clinic visits, including Screening, Baseline, Week 2, Week 4, Week 6, and Week 8 of treatment, as well as a Week 9 follow-up visit (1 week after last dose). Since the interval between the Screening and Baseline visits may be up to 35 days, the anticipated maximum duration of subject participation is ~14 weeks.

6.2.1 Randomization

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

Assignment of drug or vehicle will be made at a 2:1 ratio to ARQ-151 cream 0.3% or vehicle cream QD according to a computer-generated randomization list. Randomization will be stratified by study site, baseline IGA (IGA=2 vs. IGA≥3), and intertriginous involvement at baseline (I-IGA≥2, yes vs no).

Kits containing tubes of investigational product will be assigned to each subject using an internet-based randomization system (IWRS). A subject may receive more than one kit for the treatment period. The kits and tubes are blinded and each kit is assigned a unique kit number.

Subjects will apply ARQ-151 cream 0.3% QD or vehicle cream QD to psoriatic plaques of 2% BSA up to a maximum application area of 20% BSA.

6.2.2 Numbering of Subjects

All subjects who are randomized will be assigned a unique six-digit subject ID number by the IWRS system. The first three digits correspond to the site number (assigned by the Sponsor), the next three digits correspond to the sequential order in which the subject is screened for the study (e.g., Subject ID 101001: Site 101, first subject screened 001 for that site). Site number 101 will be the first site in the study.

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

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

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

1. Participants legally competent to sign and give informed consent and, if age appropriate (for children and adolescents) assent, as required by local laws.
2. Males and females ages 2 years and older (inclusive).
3. Clinical diagnosis of psoriasis vulgaris of at least 6 months duration (3 months for children) as determined by the Investigator. Stable disease for the past 4 weeks.
4. Psoriasis vulgaris on the face, extremities, trunk, and/or intertriginous areas involving 2% to 20% BSA (excluding the scalp, palms and soles).

5. An Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') at Baseline.
6. A PASI score of at least 2 (excluding the scalp, palms and soles) at Baseline.
7. Females of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening (Visit 1) and a negative urine pregnancy test at Baseline (Visit 2). In addition, sexually active FOCBP must agree to use at least one form of highly effective contraception throughout the trial. Highly effective forms of contraception include: oral/implant/injectable/transdermal contraceptives, intrauterine device, and partner's vasectomy. If barrier methods are used (e.g., condom with spermicide, diaphragm with spermicide), then 2 forms of conception are required. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a lifestyle choice and a backup method has been identified if the subject becomes sexually active.
8. Females of non-childbearing potential must either be premenarchal or post-menopausal with spontaneous amenorrhea for at least 12 months or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy).
9. In good health as judged by the Investigator, based on medical history, physical examination, serum chemistry labs, hematology values, and urinalysis.
10. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule, according to the judgment of the Investigator.

6.3.2 Exclusion Criteria

1. Subjects who cannot discontinue medications and treatments prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 1).
2. Planned excessive exposure of treated area(s) to either natural or artificial sunlight, tanning bed or other LED.
3. Subjects 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, ACE inhibitors).
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 to excipients in ARQ-151 cream [redacted]
8. Subjects who cannot discontinue the use of strong P-450 cytochrome inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin) for two weeks prior to the baseline visit and during the study period.

9. Subjects who cannot discontinue the use of strong P-450 cytochrome inducers (e.g., efavirenz, nevirapine, glucocorticoids, barbiturates including phenobarbital, phenytoin, and rifampin) for two weeks prior to the baseline visit and during the study period.
10. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.
11. Previous treatment with ARQ-151 or ARQ-154.
12. Subjects who have received oral roflumilast (Daxas®, Daliresp®) or other PDE4 inhibitors (apremilast) within the past 4 weeks.
13. Known or suspected:
    - severe renal insufficiency or moderate to severe liver impairment (Child-Pugh B or C)
    - known HIV infection
    - hypersensitivity to component(s) of the investigational products
    - history of severe depression, suicidal ideation, Baseline/Screening C-SSRS indicative of suicidal ideation, whether lifetime or recent/current
11. Subjects with PHQ-8 (18 y/o and older) or modified PHQ-A (12 to 17 y/o) $\geq$10 at Screening or Baseline visits. Subjects (6 to 11 years old, inclusive) with a CDI-2 (parent report) raw score >20 at Screening/Baseline
14. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of investigational product.
15. Subjects with a history of a major surgery within 4 weeks prior to Baseline (Visit 2) or has a major surgery planned during the study.
16. 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.
17. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members that live in the same household of enrolled subjects.
18. 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.
19. Current or a history of cancer within 5 years with the exception of fully treated skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix.
20. Subjects with active infection that required oral or intravenous administration of antibiotics, antifungal or antiviral agents within 7 days of Baseline (Visit 2).

6.3.3 Removal of Subjects from Investigational Product

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

- Occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements for investigational product as per the protocol.
- Occurrence of a treatment-emergent adverse event (TEAE) or considerable worsening of an AE that, in the opinion of the investigator in consultation with the Medical Monitor and Sponsor, represents an unacceptable risk to the subject if he/she continues investigational product. The investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
- Pregnancy.
- Subject's decision to withdraw from investigational product.
- Weight loss of >5% if not dieting and after consultation with the Sponsor, at the Investigator's discretion.
- C-SSRS indicative of suicidal ideation or a PHQ-8 or modified PHQ-A score ≥15, after consultation with a mental health professional, the Sponsor, and at the Investigator's discretion.
- CDI-2 raw total score of 34, after consultation with a mental health professional, the Sponsor, and at the Investigator's discretion.
- Requirement for use of prohibited concomitant medication after consultation with the Sponsor and Medical Monitor.
- Subject's repeated failure to comply with protocol requirements or study related procedures.
- The subject interrupts trial investigational product application for more than 50% of scheduled doses.

6.3.4 Removal of Subjects from Study

1. Subject death.
2. Subject's decision to withdraw from study.
3. 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.
4. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

6.4 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 the investigational product.

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

- Experiences a serious adverse event (SAE) or a clinically significant non-serious AE which in the opinion of the Principal Investigator or Medical Monitor warrants discontinuation from the investigational product for that subject's well-being.
- A severe (Grade 3) laboratory abnormality (confirmed by repeat sample and considered related to investigational product).
    - See Appendix 5 for details.

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

A subject with a PHQ-8 or Modified PHQ-A score of '15'or above, CDI-2 raw total score of 34 and/or is experiencing suicidal ideation or behavior, should be referred promptly to a mental health care professional and consideration be given to discontinuation from investigational product.

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

Treatment should be interrupted:

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

Treatment should be discontinued:

- If the reaction reoccurs, treatment should be discontinued permanently, and the subject followed until the reaction resolves. Given the excellent local toleration in the Phase 1/2a and Phase 2b studies, such reactions are possible, but unlikely.

6.5 Study Restrictions

6.5.1 Prohibitions and Concomitant Therapy

Prohibited medications and products are detailed in Table 1.

Table 1. Excluded Medications and Treatments

Excluded Medications and treatments	Washout period prior to Day 1
Systemic treatment with biological therapies with a possible effect on psoriasis vulgaris within the following time periods prior to randomization	
Etanercept	4 weeks
Adalimumab, infliximab	8 weeks
All other biologics	12 weeks or 5 half-lives, whichever is longer
Systemic treatment with all other therapies with a possible effect on psoriasis vulgaris	
Oral/systemic corticosteroids, retinoids, apremilast, methotrexate, cyclosporine and other systemic immunosuppressants	4 weeks
Topical anti-psoriasis medications (e.g., topical corticosteroids, vitamin D analogs, prescription shampoos) (except for emollients)	2 weeks
PUVA or UVB phototherapy	4 weeks
Investigational drugs	12 weeks or 5 half-lives, whichever is longer (biologics); 5 half-lives (orals); 2 weeks (topical)
Antihistamines – if prescribed for pruritus associated with psoriasis	2 weeks
Strong P-450 cytochrome inhibitors and strong P-450 cytochrome inducers	2 weeks
Notes: (1) Eye and ear drop and nasal corticosteroid preparations are allowed. Inhaled corticosteroid preparations are allowed if used for a stable condition and at a stable dose for > 28 days before screening, and are continued at the same dose throughout the study. (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) Investigational product should be applied at least 20 minutes before going to bed. No emollients or moisturizers should be applied on treated areas. (4) A tar-containing or dandruff shampoo (zinc pyrithione or selenium sulfide) is allowed for treatment of the scalp.	

Generally, the addition of new medications, including nonprescription medications, during the course of the study is discouraged. However, the short-term use of a medication may be authorized by the Investigator. The Investigator must make the decision to authorize the use of any such a medication only after consideration of the clinical situation, the potential for masking symptoms of a more significant underlying event, and whether the use of the medication will compromise the outcome or validity of the clinical investigation. If medication is required, the name, strength, frequency, duration of use, and reason for use will be recorded in source documents and transcribed to Case Report Forms. Medications which have been used chronically by subjects, in particular statins and anti-hypertensives, are allowed for use during the study, except as prohibited in 'Exclusions' (Table 1).

6.6 Treatment

6.6.1 Investigational Product Supplies, Packaging and Labeling

ARQ-151 cream 0.3% or vehicle cream will be in 45 gram squeeze tubes. The tubes will be packaged in kits, each containing 4 tubes of investigational product. The number of kits dispensed to a subject will be based on the BSA involvement of psoriasis. It is anticipated that the maximum number of kits dispensed to a subject will be four. The kits and tubes will be labeled in a blinded manner. The kit(s) dispensed to a subject/caregiver will be labeled with a unique number.

The Sponsor will supply sufficient quantities of the investigational product (ARQ-151 cream 0.3%, and matching vehicle cream) to each site to allow for completion of this study.

Records will be made of the receipt and dispensing of the 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 current version of the IP Handling Manual for details on the accountability, storage, and management of the IP.

6.6.2 Blinding

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

6.6.3 Treatment Administration

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

Re-training will be conducted at subsequent visits (weeks 2, 4, and 6) as needed (i.e., if the returned tube(s) weighs substantially different than the expected weight).

Subjects/caregivers will be instructed to apply investigational product once daily. All subjects should apply investigational product each evening (except on clinic visit days) at least 15 minutes after showering or bathing (if they take an evening shower/bath) and then not wash areas where ARQ-151 cream or vehicle has been applied until at least 4 hours after investigational product application and preferably not until the following morning. Investigational product should be applied at least 20 minutes before going to bed.

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

Each investigational product tube will be weighed prior to dispensing at the baseline visit and subsequent visits. Investigational product tubes must be returned by subjects at each study visit, both empty and full, and will be weighed. If the subject's actual use is substantially different than the expected use for the subject's BSA (see IP Manual), the subject will be retrained on the investigational product application technique.

6.6.4 Treatment Compliance

Investigational product tubes will be weighed at each follow-up clinic visit.

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

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

Compliance will be assessed by review of the dosing diary. Weight of investigational product applied will be measured for reporting purposes. The site will document the weight of the tube prior to dispensing to the subject and the weight of the tube when the subject returns for the next visit.

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

Compliance will be documented in source and in eCRF.

7 STUDY PROCEDURES

7.1 Safety Assessments

The Schedule of Visits and Assessments (Section 2) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI and/or the Sponsor for reasons related to subject safety.

This study assesses the safety and efficacy of ARQ-151 cream. Safety will be determined by evaluating physical examinations, local tolerability assessments, vital signs/weight, clinical laboratory parameters, either PHQ-8 (adults)/modified PHQ-A (adolescents)) or Children's Depresssion Inventory 2 (CDI-2), C-SSRS (12 years and older) and AEs as outlined in the Schedule of Visits and Assessments (Section 2). If deemed necessary, additional safety assessments will be performed at the discretion of the PI.

7.1.1 Screening

Within 35 days prior to the first dosing, subjects will be provided details of study requirements and sign a current IRB/EC approved informed consent/assent (if appropriate). Medical history and demographic data including sex, age, race, ethnicity, body weight (kg), and height (cm) will be recorded. Each subject will undergo psoriatic plaque assessments, a physical examination, vital sign measurements (blood pressure, heart rate, and temperature), PHQ-8 (adults)/modified PHQ-A (adolescents) or CDI-2 (children), C-SSRS (12 years and older), and laboratory tests: hematology, chemistry, urinalysis and serum (Screening) and urine (Baseline) pregnancy tests for female subjects of child bearing potential.

Therapies the subject has used in the last twelve months prior to the Screening (Visit 1) for psoriasis will be recorded.

All screened subjects will be entered into the electronic IWRS system at the time of informed consent.

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

7.1.2 Physical Examination

Physical examinations will be performed as follows:

Screening, Baseline and Week 8.

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

7.1.3 Vital Signs, Height and Weight

Vital signs will be collected at timepoints noted below:

Blood pressure, heart rate, and temperature will be measured at Screening, Baseline, Weeks 2, 4, 6, 8, and 9 (if applicable).

Height will be collected at Baseline only.

Weight will be collected at Baseline, Weeks 2, 4, 6, 8 and 9 (if applicable). Subject to void prior to weight being taken and remove any jackets, outerwear and shoes. Remove any objects of significant weight (i.e. cell phones, wallet, key chains). A 5% unintentional weight loss should be reported to the medical monitor.

7.1.4 Laboratory Tests

All tests listed below will be performed as follows and sent to ACM the central laboratory for the study for processing:

Screening, Baseline, Weeks 4 and 8. If the Baseline visit occurs within 14 days of Screening, the Screening lab results may be utilized.

All tests listed in Table 2 below will be performed according to the Schedule of Visits and Assessments (Section 2) unless otherwise noted. The collection of specimens will be in a non-fasting state. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Table 2. Laboratory Tests

Hematology		**Serum Chemistry**
• Hemoglobin • Hematocrit • Total and differential leukocyte count • Red blood cell count with indices and morphology • Platelet count		• Blood Urea Nitrogen • Bilirubin (total and direct) • Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Albumin • Sodium • Potassium • Chloride • Glucose • Creatinine
Urinalysis		**Additional Tests**
• pH • Specific gravity • Protein* • Glucose • Ketones • Bilirubin • Blood* • Nitrite* • Urobilinogen • Leukocyte esterase*		• Urine pregnancy test** (for females of child bearing potential only) • Serum pregnancy test (hCG)***
* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed. ** Baseline, Weeks 4, and 8, for FOCBP only *** At Screening, for FOCBP only		

7.1.5 Children's Depression Inventory 2

The CDI-2 Assessment will be performed only for subjects 6-11 years old (inclusive) as follows:

- Screening, Baseline, Week 4, and Week 8

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

CDI-2 is available as a self report long and short form, and a parent report form:

- CDI 2: Self-Report (Short) version (CDI 2:SR[S]). The CDI 2:SR(S) Form is an efficient screening measure that contains 12 items and takes about half the time of the full-length version to administer (5-10 minutes).The CDI 2:SR(S) has excellent psychometric properties and yields a Total Score that is generally very comparable to the one produced by the full-length version.

- CDI: Parent (CDI:P) Forms consist of items that correspond to the self-report version and are suitably rephrased. Item selection for the parent form was guided to maximize validity, and thus focused on observable manifestations of depression.

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

7.1.6 Patient Health Questionnaire depression scale (PHQ-8)

The 8 item PHQ-8 Assessment will be performed in adult subjects as follows:

Screening, Baseline, Weeks 4 and Week 8

Only adult subjects will complete PHQ-8 questionnaire.

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

The 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

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

Five severity categories of depression are defined as follows:

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

7.1.7 Patient Health Questionnaire depression scale (Modified PHQ-A)

The 8 item Modified PHQ-A Assessment will be performed in adolescent subjects as follows:

Screening, Baseline, Weeks 4 and Week 8

Only adolescent subjects will complete the Modified PHQ-A questionnaire.

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

Modified PHQ-A

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

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

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

Office use only: **Severity score:** _____

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)

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

C-SSRS Assessments will be performed for subjects 12 and older as follows:

Screening, Baseline, Week 4 and Week 8.

The administration schedule of the C-SSRS will be:

- The Baseline-Screening version (Appendix 1) will be used at Screening to provide a pre-treatment assessment baseline.
    - If a subject has a score greater than 0 in suicidal ideation, this is important and may indicate the need for mental health intervention. The investigator should give consideration to not enrolling the subject in the study.
- On all subsequent visits, the Since Last Visit version (Appendix 2) will be used.
    - Any score greater than 0 in the suicidal ideation score is important and may indicate the need for mental health intervention and consideration be given to discontinuation from investigational product. This should result in prompt referral to a mental health professional and/or possibly the emergency room. The Medical Monitor should be contacted.

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

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.

7.1.9 Local Tolerability Assessments

The Investigator Local Tolerability Assessment will be performed as follows:

Baseline, Weeks 4, and 8

Application site reactions will be graded at the timepoints outlined in the Schedule of Visits and Assessments (Section 2). 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.

The investigator assessments will be conducted by the investigator prior to investigational product application in the clinic.

Dermal Response

0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definite erythema, readily visible; minimal edema or minimal papular response
3 = erythema and papules
4 = definite edema
5 = erythema, edema and papules
6 = vesicular eruption
7 = strong reaction spreading beyond application site

Other Effects

A = slight glazed appearance
B = marked glazing
C = glazing with peeling and cracking
D = glazing with fissures
E = film of dried serous exudates
F = small petechial erosions and/or scabs
G = no other effects

The Subject Local Tolerability Assessment will be performed as follows:

Baseline, Weeks 4, and 8

This assessment will be administered by the site 10 to 15 minutes after investigational product application in the clinic at Baseline and at Weeks 4, and 8. Parents may report for children.

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

7.1.10 Adverse Events

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

Screening, Baseline, Weeks 2, 4, 6, 8, and 9 (if applicable)

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

For further details on Adverse Events please see Section 7.4.

7.2 Efficacy Evaluations

7.2.1 Investigator Global Assessment (IGA)

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

Screening, Baseline, Weeks 2, 4, 6, 8, and 9 (if applicable)

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

Note: Palms and soles will be treated in this study with investigational product, but will not be counted towards IGA, PASI/mPASI, or BSA assessments.

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

Investigator Global Assessment of Disease (IGA)

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

The standard 'whole body' IGA shown above will be recorded for every subject in the study.

For subjects with intertriginous area involvement of at least 'mild' severity by IGA (I-IGA≥2) at Baseline (using the IGA scale shown above but evaluating intertriginous areas ONLY and NOT

whole body involvement), an IGA for the intertriginous region alone (I-IGA) will be recorded at weeks 2, 4, 6, 8, and 9 (if applicable).

This 'intertriginous area IGA' (I-IGA) should be done AFTER the 'standard whole body IGA' (primary endpoint) in subjects who qualify.

7.2.2 Psoriasis Area and Severity Index (PASI) and Modified Psoriasis Area and Severity Index (mPASI)

Assessments will be performed as single assessments at each timepoint, from which both PASIs and mPASIs will be calculated.

PASI/mPASI assessments will be performed as follows:

Screening, Baseline, Weeks 2, 4, 6, 8, 9 (if applicable)

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

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

PASI/mPASI 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/mPASI. 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

mPASI: for subjects with < 10% of an involved anatomic area, the mPASI will be calculated using the actual percentage of the anatomical area involved (e.g. 0.1 for 1%, 0.2 for 2%, 0.3 for 3%, … 0.9 for 9%), corresponding to the actual percentage of that particular anatomical area of involvement.

Note: Palms and soles may be treated with investigational product in this study, but will not be counted towards IGA, PASI/mPASI, 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/mPASI, 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:

$$PASI = 0.1 (Eh + Th + Sh) Ah + 0.2 (Ea + Ta + Sa) Aa + 0.3 (Et + Tt + St) At + 0.4 (El + Tl + Sl) Al$$

7.2.3 Body Surface Area (BSA)

BSA Assessments will be performed as follows:

Screening, Baseline, Weeks 2, 4, 6, 8, and 9 (if applicable)

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 (BSA).

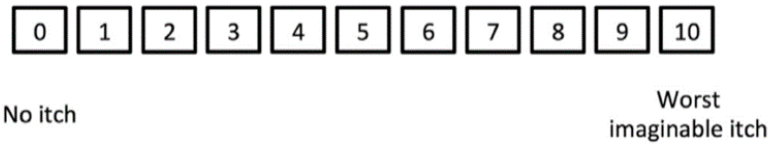
Note: Palms and soles will be treated with investigational product, but will not be counted towards IGA, PASI/mPASI, or BSA assessments.

7.2.4 Worst Itch Numerical Rating Scale (WI-NRS)

WI-NRS Assessments will be performed for subjects 12 years and older as follows:

Screening, Baseline, Weeks 2, 4, 6, 8 and 9 (if applicable)

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



7.2.5 Psoriasis Symptom Diary (PSD)

The PSD will be completed, by adult subjects (≥18 years old at Screening), as follows:

Screening, Baseline, Weeks 2, 4, 6 and 8

Subjects will complete the PSD. See Appendix 3 for the PSD.

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

The DLQI (age ≥17 years) and CDLQI (age 2-16 years) will be completed as follows:

Screening, Baseline, Weeks 2, 4, and 8

Subjects/caregivers will complete the CDLQI/DLQI. See Appendix 4 for the DLQI and CDLQI.

7.2.7 Dermal Imaging

Medical photography will be performed at all sites using Canfield photography equipment at Baseline, Weeks 2, 4, 6, and 8.

Photography should be focused on single lesions or specific body sections (e.g. arm). Subjects with intertriginous involvement will have also photos of the intertriginous area.

Body or half body photos should only be taken if necessary. All efforts will be made to de-identify the subjects. Subjects who are unwilling to participate in the medical photography will be allowed to opt out of this procedure and documented on the informed consent.

Refer to the current Photography Manual for instructions regarding photography.

7.3 Pharmacokinetics Assessment

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

Baseline, Weeks 4 and 8

Plasma PK assessments will be performed on all subjects.

PK draws will be collected while the subject is having serum chemistries drawn. The draws will be pre-dose investigational product application in the clinic. Ensure investigational product is not applied in the area where PK will be drawn.

7.4 Adverse Events

7.4.1 Adverse Event Definition

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

A treatment emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.

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.

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.

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

7.4.2 Serious Adverse Event

The definitions and reporting requirements of Health Canada/the Food and Drug Administration (FDA)/ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A will be adhered to. If any AEs are serious, as defined by ICH Guidelines for Clinical Safety, required procedures will be followed.

All SAEs will be reported to the Sponsor (or delegate) via fax or e-mail 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 ERB/IRB will be notified of the Alert Reports as per HC, FDA, ICH and the IRB/ERB's policies and procedures.

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

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

Hospitalization does not include the following:

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

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

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

Unexpected is defined as an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current IND/CTA.

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

7.4.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

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

7.4.4 Safety Review

At each follow-up visit, subjects will be queried with an open-ended question such as: ‘How have you been feeling since your last visit?’ Additionally, the study staff will review

subject diaries and, if it appears that a potential AE was recorded, study staff will query the subject and determine if an AE occurred.

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI and treated and/or followed up for up to one month after end of treatment until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI.

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

7.4.5 Adverse Event Reporting

AEs will be collected following informed consent of the subject through subject study completion.

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

The relationship of each AE to the investigational product will be assessed using the following definitions:

Unrelated	• The AE must clearly be caused by the subject's clinical state, or the study procedure/conditions. • Definitely not related to investigational product. • Temporal sequence of an AE onset relative to administration of investigational product 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 investigational product. • Time sequence is reasonable. • Could have been due to another equally, likely cause.
Probably	• Is a known effect of the investigational product. • Time sequence from taking investigational product is reasonable. • Ceases on stopping the investigational product.

	• Cannot be reasonably explained by the known characteristics of the subject's clinical state.
Likely	• Is a known effect of the investigational product (e.g., listed in Physicians' Desk Reference, Compendium of Pharmaceuticals and Specialties, IB). • Time sequence from taking investigational product is reasonable. • Event stops upon stopping investigational product, event returns upon restarting investigational product.

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

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

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

AEs will be coded using the most current MedDRA® version available at the start of the study (e.g., 21.0 or higher).

7.5 Reporting Pregnancy

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

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

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

7.5.1 Emergency Unblinding

If the situation requires emergency unblinding this will be done by investigator using the study IWRS system after discussion with Medial Monitor and the Sponsor's CMO.

8 DATA ANALYSIS

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

8.1 Statistical Methods

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

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

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

Missing IGA scores will be imputed using multiple imputation.

8.1.1 Determination of Sample Size

A sample size of approximately 400 subjects are planned for the study.

Approximately 267 subjects will receive ARQ-151 cream 0.3% QD; approximately 133 subjects will receive vehicle cream QD. The randomization scheme will be 2:1 (ARQ-151 cream 0.3% QD: matching vehicle QD).

This sample size provides >99% power to detect a 22.4% difference between treatment groups on IGA success at α=0.05 using a 2-sided Chi-squared test. The results from a recent phase 2b study (ARQ-151-201) of ARQ-151 compared to vehicle treatment were used to estimate the treatment difference. Specifically, in this trial 32.2% of subjects reported IGA success in the ARQ-151 0.3% group and 9.8% of subjects reported IGA success in the vehicle group.

The number of subjects to be enrolled will also provide sufficient power for the first 5 secondary endpoints. Additionally, the larger study size is included in order to provide additional/sufficient numbers of subjects on ARQ-151 treatment for a safety database.

8.1.2 Subjects to Analyze

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

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

The I-IGA population is a subset of the ITT population and includes subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (intertriginous IGA (I-IGA) ≥2) at Baseline. This population will be used for the analysis of I-IGA endpoints.

The Pruritis population is a subject of the ITT population and includes subjects with WI-NRS pruritus score ≥ 4 at Baseline. This population will be used for the analysis of achievement of a 4-point reduction in WI-NRS pruritus score as compared to Baseline.

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

8.1.3 Interim Analysis

No interim efficacy analyses are planned.

8.1.4 Background and Demographic Characteristics

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

8.1.5 Study Disposition

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

8.1.6 Protocol Deviations and Eligibility Deviations

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

8.1.7 Investigational Product Application Compliance

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

The amount of investigational product used by each subject based on tube weight will be summarized by treatment using descriptive statistics, and categorically.

Investigational product application compliance will be calculated based on number of applications divided by the expected number (amount) of investigational product applications for each subject. Compliance will be summarized descriptively by treatment group.

8.2 Efficacy Evaluation

8.2.1 Primary Efficacy Endpoint

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

The primary endpoint will be analyzed using a Cochran-Mantel-Haenszel test stratified by site, baseline IGA, and baseline intertriginous involvement. Statistical significance will be concluded at the 5% significance level (2-sided).

Missing IGA scores will be imputed using multiple imputation.

8.2.2 Secondary Endpoints

The secondary efficacy endpoints will include:

- Achievement of Psoriasis Area Severity Index-75 (PASI-75; subjects who achieve a 75% reduction in PASI from Baseline) at week 8.
- For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (intertriginous IGA (I-IGA) ≥2) at Baseline, achievement of 'I-IGA' score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at week 8.
- In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 8.
- In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 4.
- In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 2.
- Change from Baseline in total Psoriasis Symptoms Diary (PSD) score at week 8.
- Change from Baseline in total PSD score at week 4.
- Time to achieving Psoriasis Area Severity Index-50 (PASI-50).

- For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (I-IGA ≥2) at Baseline, achievement of 'I-IGA' score of 'clear' at week 8.
- Achievement of PASI-90 (subjects who achieve a 90% reduction in PASI from Baseline) at week 8.

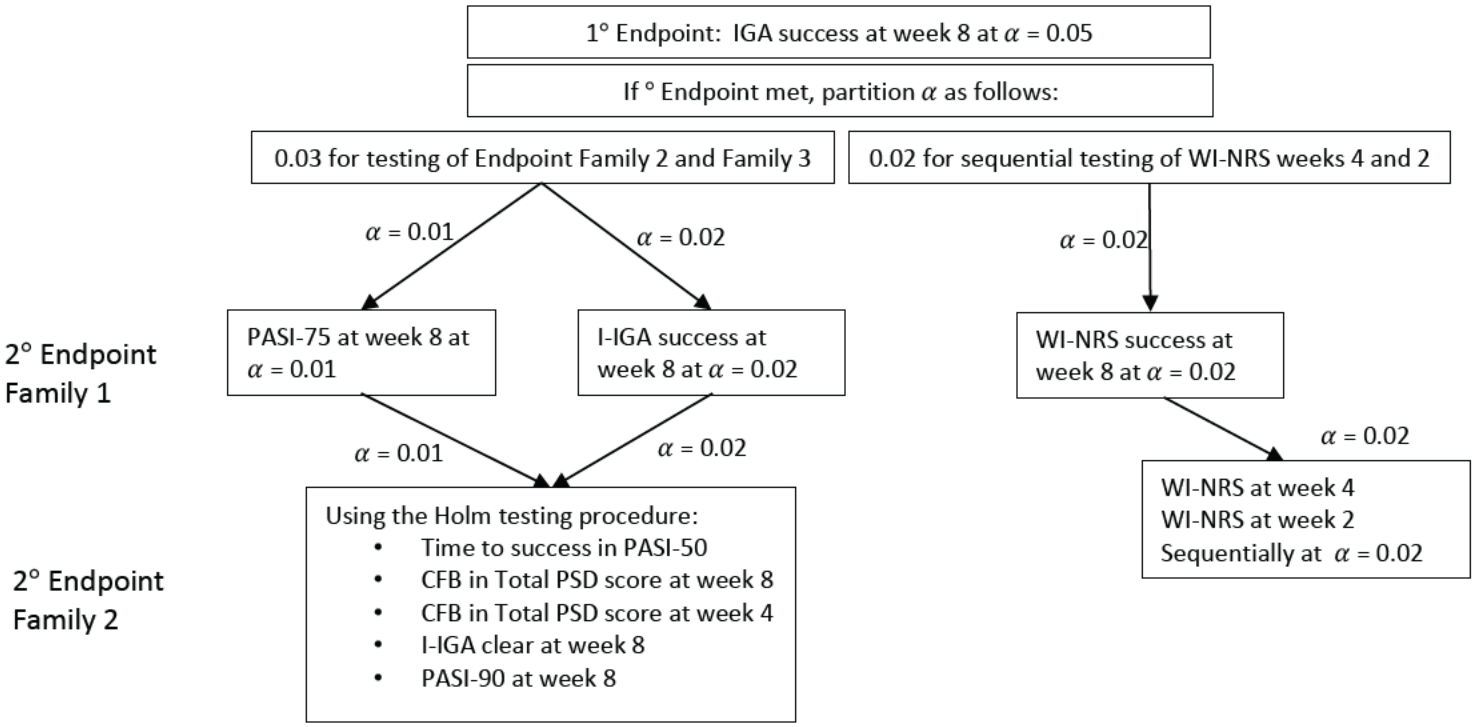
Secondary endpoints will only be tested statistically if the primary endpoint is considered statistically significant. To control for multiple comparisons among the secondary endpoints, the following multiplicity procedure will be used:

Upon successful testing of the primary endpoint the alpha will be partitioned to test secondary endpoints families 1 and 2 (partition 1) and to test additional WI-NRS timepoints (partition 2)

Partition 1 of alpha = 0.03 will be allocated to test secondary endpoint family 1 and secondary endpoint family 2. The endpoints in family 1 will be tested independently using a Bonferroni split of the alpha; the next 5 secondary endpoints (secondary endpoint family 2) will be tested using the alpha available after testing endpoint family 1. The Holm procedure will be used to control for multiple comparisons in secondary endpoint family 2.

Partition 2 of alpha = 0.02 will be allocated to sequentially test WI-NRS success at week 4 and WI-NRS success at week 2.

Figure 3. Secondary Endpoint Testing



Achievement of IGA success is a score of 'clear' or 'almost clear' plus a 2 grade improvement from baseline.
I-IGA success is an I-IGA score of 'clear' or 'almost clear' plus a 2 grade improvement from baseline among subjects with I-IGA ≥ 2 at baseline.
WI-NRS success is a 4 point reduction in WI-NRS among subjects with WI-NRS ≥ 4 at baseline.
CFB – Change from baseline
I-IGA clear at week 8 is evaluated among subjects with I-IGA ≥ 2 at baseline.

The binary endpoints will be analyzed using a Cochran-Mantel-Haenszel test stratified by site, baseline IGA, and baseline intertriginous involvement, similar to the primary endpoint.

The continuous endpoints will be analyzed using an analysis of covariance with treatment, and the stratification factors including site, baseline IGA, and baseline intertriginous involvement, and baseline value as independent variables. Statistical comparison between the active treatment arm and vehicle arm will be facilitated by using contrasts.

Time-to-event endpoints will be analyzed using the Kaplan-Meier estimator. Treatment group comparisons will be performed using the log-rank statistic.

8.3 Safety Evaluation

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

8.3.1 Adverse Events

All treatment-emergent AEs occurring during the study will be recorded and classified on the basis of MedDRA terminology for the safety population. Treatment-emergent AEs are those AEs with an onset on or after the date of study treatment. All treatment-emergent AEs will be summarized by treatment group, the number of subjects reporting treatment-emergent AEs, system organ class, preferred term, severity, relationship, and seriousness.

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

For AEs, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest relationship and greatest severity.

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

8.3.2 Local Tolerance Assessments

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

8.3.3 Medical History and Physical Examinations

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

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

8.3.4 PHQ-8 and Modified PHQ-A

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

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

8.3.5 C-SSRS

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

8.3.6 Clinical Laboratory Results and Vital Signs/Weight Measurements

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

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

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

8.3.7 Prior and Concomitant Medications

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

8.4 Patient Reported Outcomes Analyses

8.4.1 WI-NRS

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

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

Both the DLQI and CDLQI will be analyzed by evaluation of the reduction in total score at weeks 2, 4, and 8 as compared to Baseline.

8.4.3 Psoriasis Symptom Diary (PSD)

The PSD will be analyzed as the change from baseline in responses to the questions of PSD weeks 2, 4, and 8 as compared to Baseline.

8.5 Pharmacokinetic Analysis

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

For all subjects, blood samples for the determination of roflumilast and its N-oxide metabolite will be collected at scheduled time points as delineated in the Schedule of Visits and Assessments (Section 2).

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

9 STUDY ADMINISTRATION

9.1 Ethics

9.1.1 Ethics Review Board

Before enrollment of patients into the study, the current protocol and ICF will be reviewed and approved by an appropriate IRB or IEC, as required by FDA (21 CFR § 56), Health Canada, and ICH GCP regulations. A letter documenting the IRB or IEC approval must be received by the Sponsor (or delegate) before the initiation of the study at a clinical site. Amendments to the protocol will be subject to the same requirements as the original protocol.

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

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

9.1.2 Ethical Conduct of the Study

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

9.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date a current version of the IRB/EC approved ICF/assent (if appropriate) summarizing the discussion prior to screening and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a signed copy of their ICF.

9.2 Study Completion and Termination

9.2.1 Study Completion

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

9.2.2 Study Termination

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

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

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

9.3 Study Monitoring

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

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

9.4 Data Quality Assurance

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

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

9.4.1 Verification of Blinding

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

9.5 Data Handling and Record Keeping

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

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

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

9.6 Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the investigator or Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator and Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and Sponsor. Institutional review board approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.

No deviation from the protocol will be made except to protect the life or physical well-being of a subject in an emergency. Except in such emergencies, prior approval of the Sponsor, and the IRB, is required before deviations from the planned protocol. All protocol deviations that occur during the study will be documented and reported to Sponsor and to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

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.

9.7 Confidentiality and Privacy

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

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

9.8 Conflict of Interest

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

9.9 Report Format

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

9.10 Publication Policy

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

10 REFERENCES

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11 APPENDICES

Appendix 1. Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e g , *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period This is different than a specific plan with time, place or method details worked out (e g thought of method to kill self but not a specific plan) Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, 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. <u>Lifetime</u> - ***Most Severe Ideation:*** _____ (***Type # (1-5)***) _____ (***Description of Ideation***) <u>Past X Months</u> ***- 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	____	

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

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 2. 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: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting Once they ingest any pills, this becomes an attempt rather than an interrupted attempt Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger Once they pull the trigger, even if the gun fails to fire, it is an attempt Jumping: Person is poised to jump, is grabbed and taken down from ledge Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt This can include anything beyond a verbalization or thought, such as assembling a specific method (e g , buying pills, purchasing a gun) or preparing for one's death by suicide (e g , giving things away, writing a suicide note) ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐
Suicide:	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0 No physical damage or very minor physical damage (e g , surface scratches) 1 Minor physical damage (e g , lethargic speech; first-degree burns; mild bleeding; sprains) 2 Moderate physical damage; medical attention needed (e g , conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel) 3 Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e g , comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures) 4 Severe physical damage; *medical* hospitalization with intensive care required (e g , comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area) 5 Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over) 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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

Appendix 3. Psoriasis Symptom Diary (PSD)

Psoriasis Symptom Diary (PSD)

1	Overall, how severe 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 bothered 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 severe 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 bothered 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 severe 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 4. Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI)

DERMATOLOGY LIFE QUALITY INDEX

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

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

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

	your skin been a problem at **work** or **studying**?	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.

CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX

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**,		Very much ☐ Quite a lot ☐ Only a little ☐

	bullying, **asking questions** or **avoiding you**?	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 5. National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Toxicity Table for Use in Trials Enrolling Healthy Adults (2014) Modified

ABBREVIATIONS USED IN FOLLOWING TABLES:

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

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

ESTIMATING SEVERITY GRADE

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

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

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

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

LABORATORY RANGES

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

For pediatric subjects the National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (2007)

https://www.niaid.nih.gov/sites/default/files/dmidpedtox.pdf

CLINICAL ADVERSE EVENTS

Cardiovascular	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Arrhythmia		Asymptomatic, transient signs, no Rx required	Recurrent/persistent; symptomatic Rx required
Hemorrhage, blood loss	Estimated blood loss ≤100 mL	Estimated blood loss >100 mL, no transfusion required	Transfusion required
QTcF (Fridericia's correction) [a] or QTcB (Bazett's correction)	Asymptomatic, QTc interval 450-479 ms, *OR* Increase in interval<30 ms above baseline	Asymptomatic, QTc interval 480-499 ms, *OR* Increase in interval 30-59 ms above baseline	Asymptomatic, QTc interval ≥500 ms, *OR* Increase in interval ≥60 ms above baseline
PR interval (prolonged)	PR interval 0.20-0.25 s	PR interval >0.25 s	Type II 2nd degree AV block *OR* Ventricular pause >3.0 s
Respiratory	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Cough	Transient-no treatment	Persistent cough	Interferes with daily activities
Bronchospasm, acute	Transient wheeze; no treatment;	Requires treatment; normalizes with bronchodilator and FEV_1 < 80% predicted before bronchodilator	Minimal normalization with bronchodilator and FEV_1 <80% predicted after bronchodilator
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities, no treatment	Prevents daily and usual social activity or requires treatment
Nasal discharge (rhinitis infective per **CTCAE 4.0**)	-	Localized; local intervention indicated (e.g. topical antibiotic, antifungal, or antiviral)	-
Pharyngitis **(CTCAE 4.0)**	-	Localized; local intervention indicated (e.g. topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated
Pneumonitis (rales or rhonchi) **(CTCAE 4.0)**	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated
Lung infection **(CTCAE 4.0)**	-	Moderate symptoms; oral intervention indicated (e.g. antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated

[a] Inclusion dependent upon protocol requirements

Gastrointestinal	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Nausea	No interference with activity	Some interference with activity	Prevents daily activities
Vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity or requires IV hydration
Diarrhea	2-3 loose or watery stools or <400 g/24 hours	4-5 loose or watery stools or 400-800 g/24 hours	6 or more loose or watery stools or >800 g/24 hours or requires IV hydration
Urinary Tract	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Urinary tract infection **(CTCAE 4.0)**	-	Localized; local intervention indicated (e.g., oral or topical antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated
Reactogenicity	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Local reactions			
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity
Tenderness	Discomfort only to touch	Discomfort with movement	Significant discomfort at rest
Erythema/redness [a]	2.5-5 cm	5.1-10 cm	>10 cm
Induration/swelling [b]	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity
Systemic reactions			
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema or anaphylaxis
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity

All other conditions	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention

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

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

Blood, Serum, or Plasma Chemistries [a]	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
Sodium (mEq/L or mmol/L)	LO	131-<LLN	130	<130
	HI	>ULN-148	149-150	>150
Potassium (mEq/L or mmol/L)	LO	<LLN-3.2	<3.2-3.1	<3.1
	HI	>ULN-5.6	>5.6-5.7	>5.7
Glucose (mg/dL)	LO mmol/L	<LLN-3.0	<3.0-2.2	<2.2
	HI mmol/L	>ULN-8.9	>8.9-13.9	>13.9
Blood urea nitrogen	HI mmol/L	>8.9-17.8	>17.8-35.5	>35.5
Creatinine	N	115-151 (µmol/L)	152-177 (µmol/L)	> 177 (µmol/L)
Calcium **(CTCAE 4.0)**	LO mmol/L	<LLN-2.0	<2.0-1.75	<1.75
	HI mmol/L	>ULN-2.9	>2.9-3.1	>3.1
Magnesium **(CTCAE 4.0)**	LO mmol/L	<LLN-0.5	<0.5-0.4	<0.4
Phosphorous **(CTCAE 4.0)**	LO mmol/L	<LLN-0.8	<0.8-0.6	<0.6
Creatine kinase (CPK or CK) **(CTCAE 4.0)**	HI	>ULN-2.5xULN	>2.5xULN-5xULN	>5xULN

Blood, Serum, or Plasma Chemistries [a]	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
Albumin	LO g/L	<30-28	<28-25	<25
Total protein	LO g/L	<LLN-52	<52-50	<50
Alkaline phosphatase (U/L) **(CTCAE 4.0)**	HI	>ULN-2.5xULN	>2.5xULN-5xULN	>5xULN
AST (U/L) **(CTCAE 4.0)**	HI	>ULN-3xULN	>3xULN-5xULN	>5xULN
ALT (U/L) **(CTCAE 4.0)**	HI	>ULN-3xULN	>3xULN-5xULN	>5xULN
Bilirubin, serum total (mmol/L) **(CTCAE 4.0)**	HI mmol/L	>ULN-1.5xULN	>1.5xULN-3xULN	>3xULN
Bilirubin, serum total (mg/dL) when ALT ≥105 (Hy's law)	HI	1.3-1.5	1.6-2.0	>2.0
Bilirubin, serum direct (mmol/L) (CTCAE 4.0)	HI mmol/L	>ULN-1.5xULN	>1.5xULN-3xULN	>3xULN
Amylase (U/L) **(CTCAE 4.0)**	HI	>ULN-1.5xULN	>1.5xULN-2xULN	>2xULN
Lipase (U/L) **(CTCAE 4.0)**	HI	>ULN-1.5xULN	>1.5xULN-2xULN	>2xULN
Uric acid (mg/dL/mmol/L) **(CTCAE 4.0)**	HI	>ULN – 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN – 10 mg/dL (0.59 mmol/L) with physiologic consequences

[a] Depending upon the laboratory used, references ranges, eligibility ranges and grading may be split out by sex and/or age.
[b] Low, High, Not Graded (N).
[c] If initial boundary of grade 1 has gap from reference range or eligibility range, calculations based on the New England Journal of Medicine (NEJM) reference ranges.

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

[a] Low, High, Not Graded.

[b] If initial boundary of grade 1 has gap from reference range or eligibility range, calculations based on the New England Journal of Medicine (NEJM) reference ranges.

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

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

Appendix 6. Children's Depression Inventory 2 (Parent Report)

By Maria Kovacs, Ph.D.

CDI 2 PARENT

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

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

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

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

Instructions:

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

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

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

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