Protocol ARQ-151-215

An Open Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in Pediatric Subjects (ages 6 to 11 years old) with Plaque Psoriasis

Sponsor:	Arcutis Biotherapeutics, Inc. [redacted]
Sponsor Representative:	[redacted]
IND Number:	135681
Protocol Version:	Amendment 1 Final
Date:	22 January 2021

GCP Statement

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

Confidentiality Statement

This document contains confidential information. It contains proprietary information of Arcutis, Biotherapeutics, Inc. Any viewing or disclosure of such information that is not authorized in writing by Arcutis, Biotherapeutics, Inc. is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

SITE INVESTIGATOR SIGNATURE PAGE

An Open Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in Pediatric Subjects (ages 6 to 11 years old) with Plaque Psoriasis

ARQ-151-215

SPONSOR: Arcutis Biotherapeutics, Inc.
[redacted]

ISSUE DATE: 22 Jan 2021

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

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

Print Investigator Name: _____

Investigator Signature: _____ Date: _____

SUMMARY OF CHANGES

The following sections have been changed in Amendment 1 of the ARQ-151-215 protocol:

Section	Summary of Changes
Title Page	Sponsor address, protocol version and date updated.
1 Synopsis	Synopsis updated throughout to reflect changes in the body of the protocol and summarized herein. The number of study sites was updated to reflect approximately 10 to 15 study sites planned. The planned countries were updated to include the Dominican Republic.
1.1 Study Schema	Schema updated to remove reference to serial PK collection.
2 Schedule of Visits and Assessments	Updated the visits and associated footnote for PK sampling to remove references to pre-dose PK collection at Baseline/Day 1, serial PK collection at Baseline/Day 1, and serial PK collection at Week 2.
3 Abbreviations	Removed references to abbreviations not included in the body of the protocol.
6.1 Overall Study Design and Plan	Edited to remove references to serial PK collection. Updated the definition of PK evaluable subjects in the maximal usage subset.
6.5.1 Inclusion Criteria	Updated inclusion criterion 6 to remove reference to serial PK collection.
7.1.5 Laboratory Tests	Clarified that if the Baseline visit is within 3 weeks of Screening, the Screening laboratory results will be used for Baseline.
7.1.8 Adverse Events	Clarified the timepoint when adverse events will be collected.
7.3.2 Pharmacokinetics Sample Collection	Edited to remove references to pre-dose and serial PK collection at Baseline/Day 1, and serial PK collection at Week 2. The section title was updated.
8.1.1 Pharmacokinetics Assessment	Edited to remove duplicative description of PK collection timepoints.
8.1.2 Pharmacokinetic Parameters	Updated to remove reference to treatment groups.
Appendix 6 COVID-19 Study Site Guidance	COVID-19 study site guidance added as an appendix. This guidance provides mitigation strategies to sites in the event subjects are unable to complete protocol-specific assessments onsite.
Editorial changes made throughout to improve accuracy or readability	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

[redacted]

LIST OF APPENDICES

1 SYNOPSIS

Protocol Title:	An Open Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in Pediatric Subjects (ages 6 to 11 years old) with Plaque Psoriasis
Investigational Product:	ARQ-151 cream 0.3%
IND:	135681
Clinical Indication:	Plaque Psoriasis
Study Objectives:	• To evaluate the systemic exposure and characterize the plasma pharmacokinetic (PK) profile of ARQ-151 cream 0.3% and its major N-oxide metabolite, in pediatric subjects with plaque psoriasis involving body surface areas (BSA) of at least 3%, under maximal usage conditions. • To evaluate the safety of ARQ-151 cream 0.3% applied QD to pediatric subjects with plaque psoriasis involving BSA of at least 2%. • To explore the efficacy of ARQ-151 cream 0.3% applied QD for 4 weeks to pediatric subjects with plaque psoriasis involving BSA of at least 2%.
Summary of Study Design:	This is a phase 2, open label, maximal usage PK and safety study of ARQ-151 cream 0.3% in pediatric subjects (ages 6 to 11 years old) with plaque psoriasis: • At entry, subjects will have at least 2% BSA involvement (excluding the scalp, palms, soles), except for a subset of evaluable subjects who consent to a PK sample for maximal usage evaluation that will have at least 3% BSA involvement (excluding the scalp, palms, soles), and both groups of subjects will have a minimum IGA of Mild ('2'). • Subjects who discontinue the study may be replaced. • Subjects/caregivers will apply ARQ-151 cream 0.3% QD for 28 days to all affected areas of plaque psoriasis and any newly appearing plaque psoriasis lesions that arise during the study, except on the scalp. • Subjects/caregivers should maintain treatment of these areas with study drug for the duration of the study regardless of whether treatable areas of psoriasis clear prior to Week 4.

Countries:	Planned for the United States, Canada, and the Dominican Republic.
Number of Sites:	Approximately 10 to 15 sites planned
Study Population:	Approximately 20 male and female subjects ages 6 to 11 years old with plaque psoriasis: • All subjects must have at least 2% BSA psoriasis involvement at Baseline • However, a subset of 6 evaluable subjects who consent to a PK sample for maximal usage evaluation will have at least 3% BSA involvement (excluding the scalp, palms, soles) at Baseline o PK evaluable subjects (in the maximal usage subset) are defined as those that have PK results at Week 2. Unevaluable subjects may be replaced. • All subjects must have at least Mild ('2') psoriasis severity based on IGA at Baseline
Main Inclusion Criteria:	1. Informed consent of parent(s) or legal guardian, and, if age appropriate, assent by the subject, as required by local laws. 2. Males or females, 6 to 11 years old (inclusive). 3. Clinical diagnosis of psoriasis vulgaris of at least 2 months duration as determined by the Investigator or through subject interview. Stable disease for the past 3 weeks. 4. Psoriasis vulgaris on the face, extremities, trunk, and/or intertriginous areas involving at least 2% of BSA (excluding the scalp, palms, and soles). 5. An Investigator Global Assessment of disease severity (IGA) of at least Mild ('2') at Baseline. 6. Subject has adequate venous access for PK sampling in areas not involved by plaque psoriasis and not being treated with ARQ-151 (e.g., back of the hands). 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 duration of the trial and for one week after application of the last dose. Highly effective forms of contraception include: oral/implant/ injectable/transdermal contraceptives, intrauterine device, and partner's vasectomy. If barrier methods are used (e.g., condom with spermicide, diaphragm with spermicide), then 2 forms of contraception are

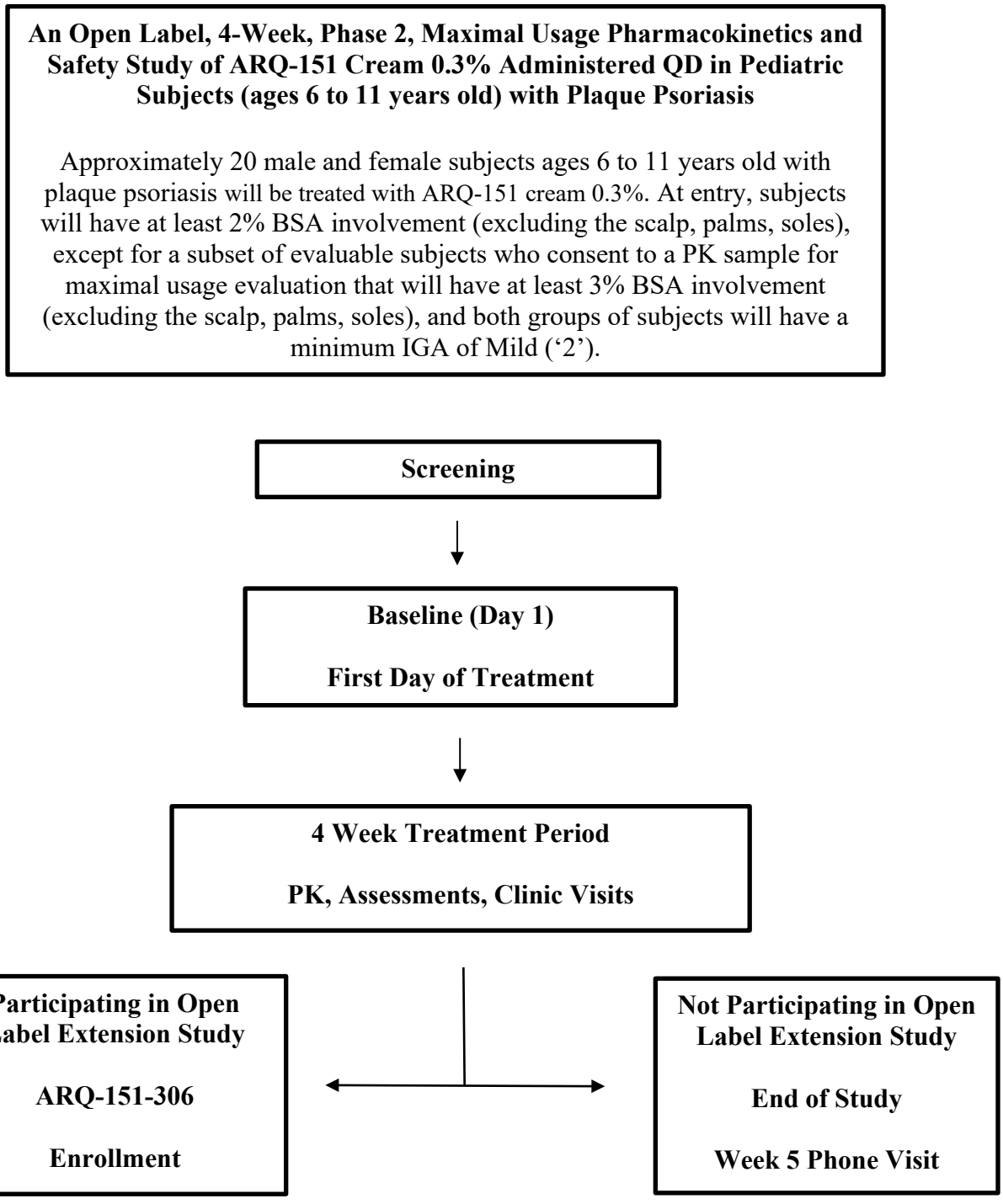
	required in association with spermicide. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a lifestyle choice and an acceptable backup method has been identified if the subject becomes sexually active. 8. Females of non-childbearing potential must be pre-menarchal. 9. In good health as judged by the Investigator, based on medical history, physical examination, 12-lead electrocardiogram (ECG), serum chemistry labs, hematology values, and urinalysis. 10. Subjects and parent(s)/legal guardian(s) 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 with any serious medical or psychiatric condition or clinically significant laboratory, ECG, vital signs, or physical examination abnormality that would prevent study participation or place the subject at significant risk, as judged by the Investigator. 2. Planned initiation or changes to concomitant medication that could, in the opinion of the Investigator, affect psoriasis vulgaris (e.g. beta blockers, ACE inhibitors). 3. 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. 4. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements. 5. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inducers (e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin, and carbamazepine) for 2 weeks prior to Baseline/Day 1 and during the study period. 6. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin) for 2 weeks prior to Baseline/Day 1 and during the study period. 7. Subjects who are unwilling to refrain from prolonged sun exposure and from using a tanning bed or other artificial light emitting devices (LEDs) for 4 weeks prior to Baseline/Day 1 and during the study.

	8. Subjects who cannot discontinue specific systemic therapies and/or topical therapies prior to the Baseline/Day 1 and during the study period according to Table 1. 9. 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. 10. Subjects with any infection requiring oral or intravenous administration of antibiotics, antifungal or antiviral agents within 2 weeks prior to Baseline/Day 1. 11. Known or suspected: a. severe renal insufficiency or moderate to severe hepatic disorders (Child-Pugh B or C) b. history of chronic infectious disease (e.g., hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)) c. hypersensitivity to component(s) of the investigational products 12. Subjects with a CDI-2 (parent report) raw score >20 at Screening/Baseline. 13. Subjects with a history of a major surgery within 4 weeks prior to Baseline/Visit 1 or subjects who have a major surgery planned during the study. 14. Subjects who are family members of the clinical study site, clinical study staff, or sponsor. 15. Parent(s)/legal guardian(s) who are unable to communicate, read, or understand the local language. Subjects who are unable to communicate or understand the local language, or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation.
Duration of Participation for Subjects:	All subjects will participate in screening (up to 3 weeks) and a Treatment phase (4 weeks). Upon completion of this study, participants may have the opportunity, subject to research site participation, to enroll in an open-label extension study of up to 24 weeks, receiving ARQ-151 cream 0.3% concentration (study ARQ-151-306).For subjects who enroll in ARQ-151-306, the Week 4 visit will complete this study. Subjects who do not enroll in ARQ-151-306 will complete this study (ARQ-151-215) with the Week 5 Telephone Visit.
Planned Dose Level:	Subjects will receive ARQ-151 cream 0.3% QD x 28 days.

Key Assessments:	Safety will be monitored through local cutaneous tolerability assessments, vital signs, physical examination, safety labs (blood chemistries/hematology/urinalysis), ECGs, Children's Depression Inventory 2 (CDI-2, parent report), Children's Dermatology Life Quality Index (CDLQI), and reported Adverse Events (AEs). All AEs will be collected starting at Screening after the parent/legal guardian and, as appropriate, the subject has provided assent/informed consent. TEAEs should be recorded starting from the beginning of the treatment period. Efficacy assessments will include IGA, Intertriginous Area-IGA (I-IGA), PASI, WI-NRS, BSA, and CDLQI. PK sample collection: • All enrolled subjects will have a trough PK sample at the Week 4 visit. • A subset of 6 evaluable subjects who consent will have an additional PK sample collected pre-dose at the Week 2 visit. o PK evaluable subjects (in the maximal usage subset) are defined as those that have PK results for Week 2. Unevaluable subjects may be replaced.
Study Endpoints:	• The primary endpoints will be PK, safety and tolerability. • Efficacy will be assessed as exploratory endpoints.
Statistical Considerations:	**Safety** The following analyses will be performed; however, no formal inferential statistics will be done on safety assessments. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. All subjects who receive at least one confirmed dose of study drug will be included in the safety population. **Adverse Events:** A subject-by-subject treatment-emergent adverse event (TEAE) data listing, including verbatim term, preferred term, treatment, severity, and relationship to study drug, will be provided. The number of subjects experiencing adverse events (AEs) and number of AEs will be summarized by cohort using frequency counts. **Medical History, Physical Examinations, Vital Signs, Safety Labs and ECGs:**

	Clinically significant physical examination parameters will be captured as adverse events. Vital signs and safety laboratory parameters 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. ECG data will be summarized with descriptive statistics. **Efficacy** All efficacy analyses will be exploratory. Descriptive statistics will be calculated for absolute and percentage change from baseline in IGA, I-IGA, PASI, WI-NRS, and BSA. The proportion of subjects with 50% and 75% improvement in PASI at post-baseline visits will also be described descriptively.
Study Nuances:	Non-medicated emollients, moisturizers and sunscreens will be allowed as normally used by the subjects, but may only be applied to non-treatment sites.
PK Analysis:	**Pharmacokinetics Assessment** Plasma levels of circulating roflumilast and its major N-oxide metabolite will be measured at the following time points: • All enrolled subjects will have a trough PK sample collected at the Week 4 visit. • A subset of 6 evaluable subjects who consent to a PK sample under maximal usage conditions will have an additional PK sample collected pre-dose at the Week 2 visit. **Pharmacokinetic Parameters** All subjects who are enrolled and receive at least one application of study drug will be included in the pharmacokinetic population. When possible, the exposure or roflumilast and its major N-oxide metabolite will be calculated based on plasma concentrations versus time profile data.

1.1 Study Schema



2 SCHEDULE OF VISITS AND ASSESSMENTS

Study Procedure	Screening	Baseline Day 1	Wk 2 Day 14	Wk 4 Day 28/ET	Wk 5 Day 35
Visit	**1**	**2**	**3**	**4**	**5**
Visit Window	-3 weeks		+/- 1 day	+/- 3 days	+/- 3 days
Informed consent/assent	X				
Demographics	X				
Medical and surgical history	X				
Physical examination[a]	X	X		X	
I/E criteria	X	X			
Hematology, Serum Chemistries, and Urine Analysis[b]	X	X		X	
Vital signs, weight, height[c]	X	X	X	X	
IGA, I-IGA, PASI, BSA, WI-NRS, CDLQI[d]	X	X	X	X	
Local cutaneous tolerability assessment (including Berger & Bowman and subject-rated stinging/burning)[e]		X	X	X	
CDI-2	X	X	X	X	
Serum pregnancy test[f]	X				
Urine pregnancy test[f]		X		X	
Resting 12-lead ECG	X			X	
PK sampling[g]			X	X	
Drug application and subject/family training in clinic[h]		X	X		
Dispense investigational product kit[i]		X	X		
Weigh investigational product tubes[j]		X	X	X	
Dispense/review diary		X	X	X	
Adverse event assessment[k]	X	X	X	X	
Concomitant medications	X	X	X	X	
Optional photography[l]		X	X	X	
Study Exit[m]					X

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

[b] To be collected at Screening, Baseline, and Week 4. If Baseline is within 3 weeks of Screening, the Screening results will be utilized.

[c] Height will be measured at every visit (see Section 7.1.3 for the recommended procedure). Weight will be collected on every visit. Weight should be obtained using a calibrated weight scale and the same scale should be used for a subject throughout the duration of the study. The subject should remove shoes and heavy clothing (sweaters or jackets), and empty pockets. The subject should stand with both feet in the center of the scale with

their arms at their side and hold still. Record the weight to the nearest decimal fraction (for example, 55.5 pounds or 25.1 kilograms). Measure the weight in triplicate and report the average weight in EDC.

[d] BSA, IGA affected by plaque psoriasis will be determined to qualify for study entry (Screening and Baseline) and will be measured at the Week 2 and Week 4 visits. Scalp, palms and soles should be excluded from consideration in these assessments. Additionally, Intertriginous Area-IGA (I-IGA), PASI, and WI-NRS will be evaluated. WI-NRS pruritus assessment will be completed by subjects ≥ 8 years old, or by parent/caregiver for subjects < 8 years old. All other assessments will be performed by the Investigator or study staff, as appropriate.

[e] Local tolerability assessments should be recorded prior to study drug application for the Investigator assessment of skin irritation (Berger and Bowman skin irritation score) and 10-15 minutes post-drug application for the subject's '0-3' burning/stinging assessment (subject-rating completed by the subject or parent/caregiver). At the Week 4 visit, only the Investigator assessment of skin irritation will be performed. Note for investigator tolerability assessments: reactions at the site of product IP application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's psoriasis.

[f] For females that have started menstruation, a serum pregnancy test will be performed during Screening. A urine pregnancy test will be administered to all females of child-bearing potential. A negative result is required for continued participation in the study, and results must be available prior to dispensing of study drug

[g] All enrolled subjects will have a trough PK sample collected at the Week 4 visit. A subset of 6 subjects who consent will provide an additional PK sample pre-dose (within 1 hour) at the Week 2 visit.

[h] Subjects/caregiver to apply assigned IP in clinic at Baseline and Week 2. All Investigator assessments should be completed prior to IP application.

[I] The number of kits to be dispensed is based on %BSA affected. See IP Handling Manual for details. Site should review IP kit to ensure sufficient IP is available until the next visit and only dispense additional IP if needed.

[j] Every tube should be weighed and recorded when dispensed and returned.

[k] Any emergent AEs will be followed in the clinic for up to 1 month at the Investigator's discretion until resolved or otherwise judged as clinically stable.

[l] Photography is planned to be performed at selected investigational sites. Photography will be optional. All efforts will be made to de-identify the subjects.

[m] Subjects who enroll into the open label extension study (ARQ-151-306) will complete the study at Week 4; subjects that do not enroll into ARQ-151-306 will complete the study with a Week 5 Telephone Follow-up. The Week 5 Telephone Follow-up is a call to the subjects to follow-up on any continuing adverse events related to the study drug. Telephone call also assesses any emergent adverse event post-Visit 4. Any emergent AEs will be followed in the clinic for up to 1 month at the Investigator's discretion until resolved or otherwise judged as clinically stable.

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3 ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AMP	Adenosine Monophosphate
AD	Atopic Dermatitis
AUC	Area Under the Curve
BSA	Body Surface Area
C_{max}	Maximum Concentration
cm	Centimeter
CDI 2	Children's Depression Inventory 2
CDLQI	Children's Dermatology Life Quality Index
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
FDA	U.S. Food and Drug Administration
FOCBP	Female of Child Bearing Potential
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
hr	Hour
IB	Investigational Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ID	Identification
IGA	Investigator Global Assessment
I-IGA	Intertriginous Investigator Global Assessment
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
kg	Kilogram
LED	Light Emitting Device
µg	Microgram

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
mL	Milliliter
MUSE	Maximal Use Systemic Exposure
NCI	National Cancer Institute
NIH	National Institutes of Health
ng	Nanogram
NOAEL	No Observed Adverse Effect Level
NSAID	Nonsteroidal Anti-Inflammatory Drug
P-450	Cytochrome P450
PASI	Psoriasis Area and Severity Index
PDE-4	Phosphodiesterase 4
PI	Principal Investigator
PK	Pharmacokinetics
QD	Once Daily ("quaque die")
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCPS	Tri-Council Policy Statement
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Reach Maximum Concentration
TPA	Target Plaque Area
TPSS	Target Plaque Severity Score
US	United States
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. The pathogenesis of pediatric and adult psoriasis is believed to be similar. Numerous past reports have suggested a deficiency of cyclic AMP-dependent protein kinases in human psoriatic skin (Brion 1986). More recently, various cytokines produced by Th1 and Th17 cells have been shown to play a crucial role in the pathogenesis of psoriasis. It has been postulated that the anti-inflammatory effects of PDE-4 inhibitors may provide a beneficial therapeutic intervention in the treatment of chronic plaque psoriasis, and Otezla® (apremilast) a PDE-4 inhibitor has been approved for the oral treatment of chronic plaque psoriasis.

The 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 cream formulation of roflumilast for the treatment of chronic plaque psoriasis. Phase 2 results suggest that ARQ-151 may be a highly efficacious and well-tolerated topical treatment for psoriasis. Accordingly, a phase 3 program is ongoing evaluating ARQ-151 cream 0.3% for the treatment of plaque psoriasis in subjects 2 years of age and older. The present study is a maximal use pharmacokinetic trial with the to-be-marketed formulation. The study is designed to ensure that the expected target patient population for ARQ-151 is properly represented, as well as to ensure that a suitable number of subjects with plaque psoriasis are evaluated and that PK is adequately characterized.

4.2 Nonclinical Studies

Roflumilast was initially developed as a 500 µg tablet for oral therapy in patients with COPD, and as such has been thoroughly evaluated in nonclinical studies. The safety profile is well-established, and the results of those studies are relevant to the dermal roflumilast (ARQ-151 cream) development program. In addition, since roflumilast N-oxide is a major active metabolite, some studies were conducted on the metabolite. The study sponsor is conducting nonclinical studies in which roflumilast is applied dermally to supplement the information available through the registration and labeling of oral roflumilast and specifically to support dermal clinical trials. Summaries of these new data from dermal studies and existing data from the prior oral/systemic studies follow.

[redacted]

4.2.1 Toxicity Summary

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

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

[redacted]

[redacted]

4.3 Clinical Studies

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

4.3.1 Psoriasis Phase 2a

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

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

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

[redacted]

[redacted]

4.3.2 Psoriasis Phase 2b

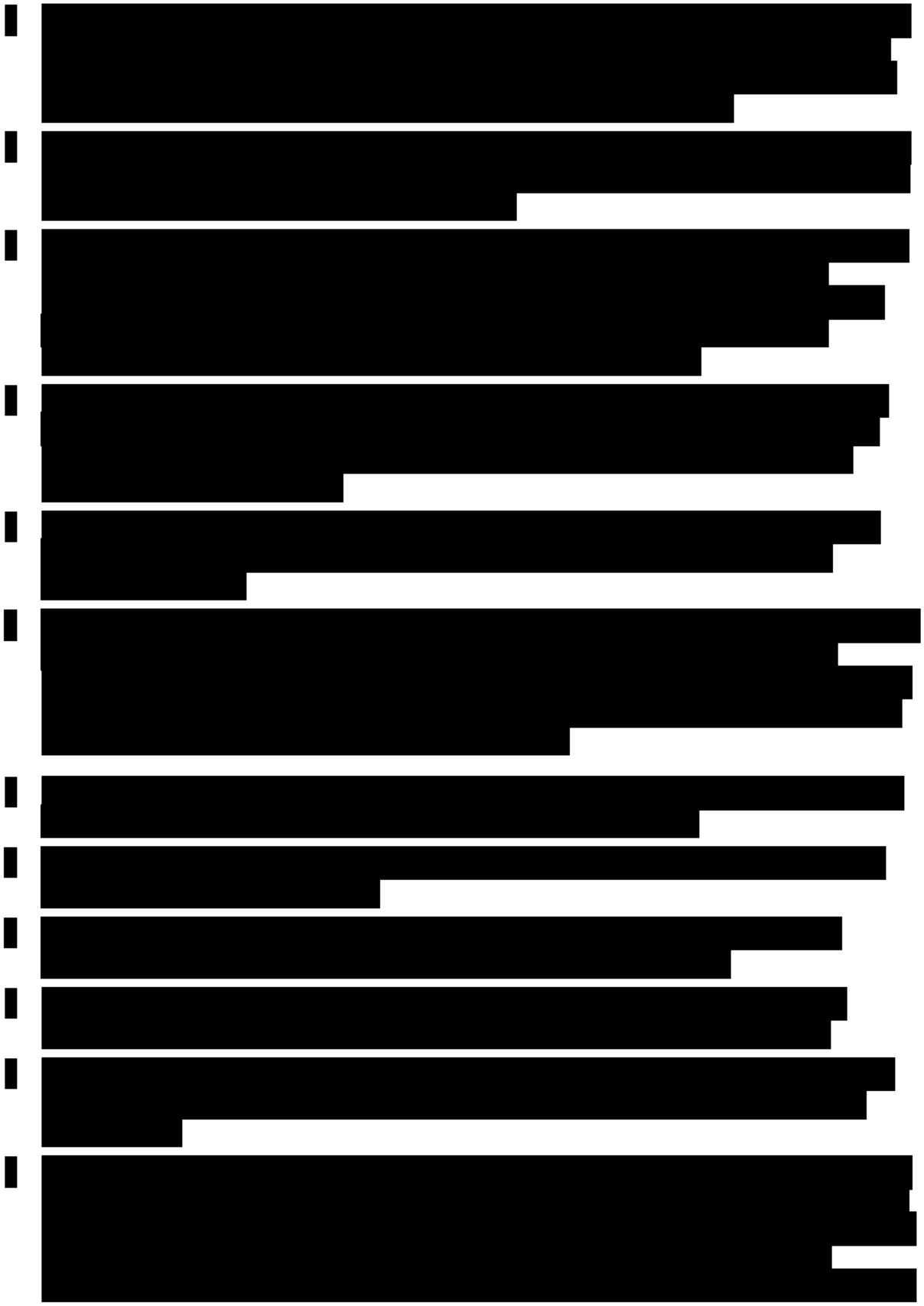
ARQ-151 has also been evaluated in a phase 2b study (ARQ-151-201; NCT03638258) in adult patients with chronic plaque psoriasis. ARQ-151-201 was a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.15%, ARQ-151 cream 0.3%, or vehicle cream was applied QD for 12 weeks to 332 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]



[redacted]

4.3.3 Atopic Dermatitis Phase 1 PK Study

ARQ-151 cream has also been evaluated in a 15 day, open label, phase 1, PK and safety study in 16 adult subjects with mild to moderate AD affecting 4 to 8% BSA (Study ARQ-151-102).

[redacted]

4.3.4 Atopic Dermatitis Phase 2

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

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

4.3.5 Oral Roflumilast Tablet

Oral roflumilast (DALIRESP®) 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 use 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

PDE-4 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, 12-lead ECGs, local skin toleration assessments, hematology, serum chemistry, urinalysis, mood disorder questionnaire, and AE questioning) are adequate to protect the subjects' safety and will detect expected AEs.

Oral roflumilast has now been used for almost a decade in the treatment of COPD exacerbations and its safety record has been well-documented. The known adverse effects of oral treatment in the COPD population (nausea, vomiting, diarrhea, weight loss, psychiatric AEs; see Section 4.3.4) are readily monitorable. The current protocol is designed to detect these

adverse events and others should they occur, and provides guidance for their management, as necessary, to ensure patient safety.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Primary Objectives

To evaluate the systemic exposure and characterize the plasma pharmacokinetic (PK) profile of ARQ-151 cream 0.3% and its major N-oxide metabolite, in pediatric subjects with plaque psoriasis involving body surface areas (BSA) of at least 3%.

To evaluate the safety of ARQ-151 cream 0.3% applied QD to pediatric subjects with plaque psoriasis involving BSA of at least 2%.

To explore the efficacy of ARQ-151 cream 0.3% applied QD for 4 weeks to pediatric subjects with plaque psoriasis involving BSA of at least 2%.

5.2 Study Endpoints

5.2.1 Primary Endpoints

The primary endpoints will be PK, safety and tolerability.

5.2.2 Exploratory Endpoints

Efficacy will be explored with analyses including:

- Change and percent change from baseline in PASI score at each study visit
- Achievement of a 50% or greater and 75% or greater improvement in PASI score from baseline to each study visit
- Change and percent change from baseline in IGA score at each study visit
- Change and percent change from baseline in I-IGA score at each study visit
- Change and percent change from baseline in BSA score at each study visit
- Change and percent change from baseline in WI-NRS score at each study visit

6 INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan

This is a phase 2, open label, maximal usage PK and safety study of ARQ-151 cream 0.3% in pediatric subjects (ages 6 to 11 years old, inclusive) with plaque psoriasis.

At entry, subjects will have at least 2% BSA involvement (excluding the scalp, palms, soles), except for a subset of evaluable subjects who consent to a PK sample for maximal usage evaluation that will have at least 3% BSA involvement (excluding the scalp, palms, soles), and both groups of subjects will have a minimum IGA of Mild ('2').

Subjects who discontinue the study may be replaced.

Subjects/caregivers will apply ARQ-151 cream 0.3% QD for 28 days to all plaque psoriasis affected areas and any newly appearing plaque psoriasis lesions that arise during the study, except on the scalp.

Subjects/caregivers should maintain treatment of areas with study drug for the duration of the study regardless of whether treatable areas clear prior to Week 4. The palms and soles will be treated but will not be counted towards any measurements of efficacy (PASI, IGA, I-IGA, BSA).

Approximately 20 male and female subjects ages 6 to 11 years old with plaque psoriasis:

- All subjects must have at least 2% BSA psoriasis involvement at Baseline
- However, a subset of 6 evaluable subjects who consent to a PK sample for maximal usage evaluation will have at least 3% BSA involvement at Baseline (excluding the scalp, palms, soles).
    - PK evaluable subjects (in the maximal usage subset) are defined as those that have PK results at Week 2. Unevaluable subjects may be replaced.
- All subjects must have at least Mild ('2') psoriasis severity based on IGA at Baseline

6.2 Subject Participation

All subjects will participate in screening (up to 3 weeks) and a Treatment phase (4 weeks).

Upon completion of this study, participants may have the opportunity, subject to research site participation, to enroll in an open-label extension study of up to 24 weeks, receiving ARQ-151 cream 0.3% concentration (study ARQ-151-306).

- For subjects who enroll in ARQ-151-306, the Week 4 visit will complete this study (ARQ-151-215).
- Subjects who do not enroll in ARQ-151-306 will complete this study (ARQ-151-215) with the Week 5 Telephone Visit.

6.3 Numbering of Subjects

All screened subjects will be identified by a unique six-digit subject ID number. The first digit will be "5" while the next two digits correspond to the site number (assigned by the Sponsor, e.g., 01 to 05), the last three digits correspond to the sequential order in which the subject is screened for the study (e.g., Subject ID 505-001: first digit fixed at 5, Site 5 (next two digits), subject number 001 screened by that site [last three digits]).

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

6.4 Blinding

This is an open label study, therefore the subjects, the Investigator and clinical personnel will be aware of the treatment an individual has received.

6.5 Selection of Study Population

6.5.1 Inclusion Criteria

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

1. Informed consent of parent(s) or legal guardian, and, if age appropriate, assent by the subject, as required by local laws.
2. Males or females, 6 to 11 years old (inclusive).
3. Clinical diagnosis of psoriasis vulgaris of at least 2 months duration as determined by the Investigator or through subject interview. Stable disease for the past 3 weeks.
4. Psoriasis vulgaris on the face, extremities, trunk, and/or intertriginous areas involving at least 2% of BSA (excluding the scalp, palms, and soles).
5. An Investigator Global Assessment of disease severity (IGA) of at least Mild ('2') at Baseline.
6. Subject has adequate venous access for PK sampling in areas not involved by plaque psoriasis and not being treated with ARQ-151 (e.g., back of the hands).
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 duration of the trial and for one week after application of the last dose. Highly effective forms of contraception include: oral/implant/ injectable/transdermal contraceptives, intrauterine device, and partner's vasectomy. If barrier methods are used (e.g., condom with spermicide, diaphragm with spermicide), then 2 forms of contraception are required in association with spermicide. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a

lifestyle choice and an acceptable backup method has been identified if the subject becomes sexually active.

8. Females of non-childbearing potential must be pre-menarchal.
9. In good health as judged by the Investigator, based on medical history, physical examination, 12-lead electrocardiogram (ECG), serum chemistry labs, hematology values, and urinalysis.
10. Subjects and parent(s)/legal guardian(s) are considered reliable and capable of adhering to the Protocol and Visit Schedule, according to the judgment of the Investigator.

6.5.2 Exclusion Criteria

1. Subjects with any serious medical or psychiatric condition or clinically significant laboratory, ECG, vital signs, or physical examination abnormality that would prevent study participation or place the subject at significant risk, as judged by the Investigator.
2. Planned initiation or changes to concomitant medication that could, in the opinion of the Investigator, affect psoriasis vulgaris (e.g. beta blockers, ACE inhibitors).
3. 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.
4. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements.
5. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inducers (e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin, and carbamazepine) for 2 weeks prior to Baseline/Day 1 and during the study period.
6. Subjects who cannot discontinue the use of strong cytochrome P-450 CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin) for 2 weeks prior to Baseline/Day 1 and during the study period.
7. Subjects who are unwilling to refrain from prolonged sun exposure and from using a tanning bed or other artificial light emitting devices (LEDs) for 4 weeks prior to Baseline/Day 1 and during the study.
8. Subjects who cannot discontinue specific systemic therapies and/or topical therapies prior to the Baseline/Day 1 and during the study period according to Table 1.
9. 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.
10. Subjects with any infection requiring oral or intravenous administration of antibiotics, antifungal or antiviral agents within 2 weeks prior to Baseline/Day 1.
11. Known or suspected:

a. severe renal insufficiency or moderate to severe hepatic disorders (Child-Pugh B or C)

b. history of chronic infectious disease (e.g., hepatitis B, hepatitis C, or human immunodeficiency virus (HIV))

c. hypersensitivity to component(s) of the investigational products

12. Subjects with a CDI-2 (parent report) raw score >20 at Screening/Baseline
13. Subjects with a history of a major surgery within 4 weeks prior to Baseline/Visit 1 or subjects who have a major surgery planned during the study.
14. Subjects who are family members of the clinical study site, clinical study staff, or sponsor.
15. Parent(s)/legal guardian(s) who are unable to communicate, read, or understand the local language. Subjects who are unable to communicate or understand the local language, or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation.

6.6 Removal of Subjects from the Study

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

1. Occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the Protocol.
2. Occurrence of a treatment-emergent adverse event (TEAE) or considerable worsening of an AE that, in the opinion of the investigator in consultation with the Medical Monitor and Sponsor, represents an unacceptable risk to the subject if he/she continues in the study. The investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
3. Pregnancy
4. Subject's decision to withdraw from the study.
5. Weight loss of >5% if not dieting and after consultation with the Sponsor, at the Investigator's discretion.
6. CDI-2 raw total score of 34, after consultation with a mental health professional, the Sponsor, and at the Investigator's discretion.
7. Requirement for use of prohibited concomitant medication after consultation with the Sponsor and Medical Monitor.
8. Subject's repeated failure to comply with protocol requirements or study related procedures.
9. The subject interrupts trial study drug application for more than 50% of scheduled doses.
10. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

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

Subjects that withdraw or are discontinued from the study prior to the Week 4 Visit, may be replaced.

6.8 Prohibitions and Concomitant Therapy

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

Table 1. Excluded Medications and Treatments

Excluded Medications and Treatments	Washout Period Prior to Baseline
Systemic treatment with biological therapies with a possible effect on psoriasis vulgaris within the following time periods prior to Baseline/Day1	
Etanercept	4 weeks
Adalimumab, infliximab	8 weeks
All other Biologics	12 weeks or 5 half-lives, whichever is longer
All other therapies with a possible effect on psoriasis vulgaris	
Oral/systemic corticosteroids, retinoids, apremilast, methotrexate, cyclosporine and other systemic immunosuppressants	4 weeks
PUVA or NBUVB phototherapy	4 weeks
Sedating antihistamines	1 week
Topical anti-psoriasis medications (e.g., topical corticosteroids, vitamin D analogs, prescription shampoos) (except for emollients)	1 week
Strong cytochrome P-450 CYP3A4 inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin	2 weeks
Strong cytochrome P-450 CYP3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin, and carbamazepine	2 weeks
Tanning beds, other light emitting devices	4 weeks
Investigational drugs	30 days or 5 half-lives, whichever is longer

Note: 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.
Non-medicated emollients, moisturizers and sunscreens will be allowed as used normally by the subjects. These can be applied only to non-treated areas as needed and should not be used within 12 hours of a study visit.
A tar-containing or dandruff shampoo (zinc pyrithione or selenium sulfide) is allowed for treatment of the scalp.
Concomitant other medications for chronic conditions (eg, NSAIDs, statins, anti-hypertensives) are permitted unless specifically prohibited in the Protocol.

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

6.9 Treatment

6.9.1 Drug Supplies, Packaging and Labeling

ARQ-151 cream 0.3% will be in 45 gram (weight of cream) squeeze tubes. The tubes will be packaged in kits, containing multiple tubes of investigational product. The number of kits dispensed to a subject will be based on the BSA involvement of plaque psoriasis. The kits will be labeled in an open-label manner. The kit(s) dispensed to a subject will be labeled with a unique number.

The Sponsor will supply sufficient quantities of the investigational product to each site to allow for completion of this study.

Records will be made of the receipt and dispensing of the investigational products supplied. At the conclusion of the study, any unused investigational products 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.

6.9.2 Treatment Administration

ARQ-151 cream 0.3% is administered once daily as a topical product to cover the skin surface at an application rate of approximately 2 mg/cm^2. Each site and each subject will be provided a digital scale to accurately measure the proper amount of cream to be applied to the psoriatic lesions. Each site will be provided a calculation program that uses the subject's height, weight, and %BSA of plaque psoriasis involvement to calculate the correct amount of ARQ-151 to be applied once a day to the psoriatic lesions.

At the Baseline visit, the **Investigator** will calculate daily IP to be applied in grams using the calculation tool.

- IP tubes will be weighed prior to and immediately after IP application (Cap On)
- IP will be weighed into a plastic dish using the digital scale

Investigator will confirm calculated IP adequately covers the entire involved area of plaque psoriasis. The Investigator can adjust IP usage up or down based on their clinical judgement or may consider the calculated expected IP weight as acceptable. The plastic dish should be reweighed after IP application to determine the actual amount of IP used.

At the Baseline visit, the study staff will demonstrate to the subject and/or parent/caregiver how to use the digital scale to measure the proper amount of ARQ-151 cream to apply. ARQ-151 cream is applied to psoriasis lesions as a thin film and rubbed in using the index and middle finger, thoroughly but gently, until the 'white' has disappeared. The subject or parent/caregiver will then apply the weighed amount of ARQ-151 to the psoriasis lesions once a day.

If a parent/guardian/caregiver helps apply the study medication, they should wash their hands with soap and water when finished.

For days that are a clinic visit, the IP will be applied in the clinic and the subject does not apply any further IP that day. All psoriasis lesions should be treated using the IP amount as noted in the Subject Body Diagram (see Appendix 1), except for the scalp.

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

Note:

- All subjects should apply medication each evening (except on clinic visit days) at least 15 minutes after showering or bathing (if they take an evening shower/bath) and then not wash areas where ARQ-151 cream has been applied until at least 4 hours after study drug application and preferably not until the following morning. Investigational product should be applied at least 20 minutes before going to bed.
- Subjects should maintain treatment of areas with study drug for the duration of the study regardless of whether treatable areas of psoriasis clear prior to Week 4 visit.

New lesions that develop during the study should be treated (except scalp). An unscheduled visit is not required for starting treatment of new lesions.

Each investigational product tube will be weighed prior to dispensing at the Baseline visit and at 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, the subject/parent/caregiver will be retrained on the study drug application technique.

At the final clinic visit, the subject should return all IP (used or unused), the digital scale, and any remaining plastic dishes.

Refer to the Investigational Product (IP) Handling Plan for detailed instructions.

6.9.3 Treatment Compliance

Investigational product tubes will be weighed at each 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 study drug application period and does not miss more than 3 consecutive doses.

Compliance will be assessed by review of the dosing diary. Weight of investigational product applied (via dispensed and returned tube weights) will be measured for reporting purposes.

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

Compliance will be documented in source and in eCRF.

7 STUDY PROCEDURES

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.

7.1 Safety Assessments

This study assesses the safety, efficacy, and pharmacokinetics of ARQ-151 cream. Safety will be determined by evaluating physical examinations, 12-lead ECGs, local tolerability assessments, vital signs/weight, clinical laboratory parameters, Children's Depression Inventory 2 (CDI-2, parent report), 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 Investigator.

7.1.1 Screening

Within 3 weeks prior to the first dosing, subjects/legal guardians will be provided details of study requirements and sign an informed consent form and, when applicable, assent form. Medical history and demographic data including sex, age, race, ethnicity, body weight (kg), and height (cm) will be recorded. Each subject will undergo plaque psoriasis assessments, a physical examination, ECG, vital sign measurements (blood pressure, heart rate, and temperature) and laboratory tests: hematology, chemistry, urinalysis and a pregnancy test for female subjects of

child bearing potential. Abnormal or questionable serum chemistry tests may be repeated at the discretion of the Investigator.

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

7.1.2 Physical Examination

Physical examinations will be performed as follows:

- Screening, Baseline, and Week 4.

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

7.1.3 Vital Signs, Height and Weight

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

- Weight, height, blood pressure, heart rate, and temperature will be measured at Screening, Baseline, Week 2, and Week 4.
    - For both weight and height measurements, the investigator or examiner should be trained in measuring height and weight as well as in calibration procedures
    - Ideally, the same person should measure the subject at every visit
    - Attempts should be made to schedule visits, so that measurements can be taken at approximately the same time throughout the study
    - The parent / caregiver may help with the measurements and to soothe and comfort the child, as needed
    - Explain to the parent/ caregiver the steps in the procedures and that it is important to keep the child still and calm to obtain good measurements, as needed
    - For measuring weight, use a calibrated scale with appropriate range and resolution, and the same scale should be used for a subject throughout the duration of the study
        - Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains
        - Subjects must also remove the contents of their pockets and remain still during measurement of weight
        - Have the child or teen stand with both feet in the center of the scale with their arms at their side and hold still
        - Record the weight to the nearest decimal fraction (for example, 55.5 pounds or 25.1 kilograms)

- For measuring length, a device such as a stadiometer should be used and placed on a flat, stable surface
  - Remove the child or teen's shoes, bulky clothing, and hair ornaments, and unbraid hair that interferes with the measurement
  - Lower the headpiece until it firmly touches the crown of the head.
  - Accurately record the height to the nearest 1/8th inch or 0.1 centimeter
- For both weight and height, three reproducible measurements of both the child's weight and height should be recorded and the average of the 3 recordings will be entered onto the eCRF

7.1.4 12-lead ECGs

12-lead ECGs will be performed as follows:

- Screening and Week 4.

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

7.1.5 Laboratory Tests

All tests listed below will be performed as follows:

- Screening, Baseline (see also Section 2, Schedule of Visits and Assessments footnote "b") and Week 4. If the Baseline visit is within 3 weeks of the Screening, the Screening laboratory results will be used for Baseline.

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

Hematology	**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.
** At baseline and Week 4 for FOCBP only
*** At screening only and only for FOCBP that have started menstruation

7.1.6 Children's Depression Inventory 2

The CDI-2 Assessment will be performed as follows:

- Screening, Baseline, Week 2, and Week 4

The CDI-2 quantifies depressive symptomatology and is recommended for use in initial evaluation and is appropriate when there is a need for an assessment and robust description of a child's depressive symptoms.

This study will use the CDI Parent Report Form. An example of the Parent report form is presented in Appendix 2.

7.1.7 Local Tolerability Assessment

Investigator Local Tolerability Assessment will be performed as follows:

- Baseline, Week 2, and Week 4

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 plaque psoriasis.

The investigator assessments will be conducted by the investigator prior to study drug application in the clinic.

Dermal Response

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

Other Effects

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

Subject Local Tolerability Assessment will be performed as follows:

- Baseline, Week 2

This assessment will be administered by the site 10 to 15 minutes after study drug application in the clinic at Baseline and at Week 2. Response may be by the subject and/or parent/caregiver, as deemed appropriate by the Investigator.

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

7.1.8 Adverse Events

Adverse events (AEs) will be collected starting at Screening after the parent/ legal guardian and, as appropriate, the subject has provided assent/informed consent. TEAEs should be recorded starting from the beginning of the treatment period.

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 7.7.

7.2 Efficacy Evaluations

7.2.1 Investigator Global Assessment (IGA) and Intertriginous Investigator Global Assessment (I-IGA)

IGA

The Investigator Global Assessment (Appendix 3) will be performed at Screening, Baseline, Week 2, and Week 4.

The IGA should be completed prior to other physician assessments.

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 distinct and clinically relevant morphologic description that minimizes inter-observer variability.

Every effort should be made for the same Evaluator to complete the IGA for the subject during Screening and at the Baseline/Day 1 visit.

Investigator Global Assessment of Disease (IGA)

Scale	Grade	Description
0	Clear	[redacted]
1	Almost Clear	[redacted]
2	Mild	[redacted]
3	Moderate	[redacted]
4	Severe	[redacted]

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

I-IGA

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 Screening, Baseline, Week 2, and Week 4.

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

7.2.2 Psoriasis Area and Severity Index (PASI)

Assessments will be performed as single assessments from which PASIs will be calculated.

PASI assessment will be performed at Screening, Baseline/Day 1, Week 2, and Week 4 visits.

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

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

The body is divided into four (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

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

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

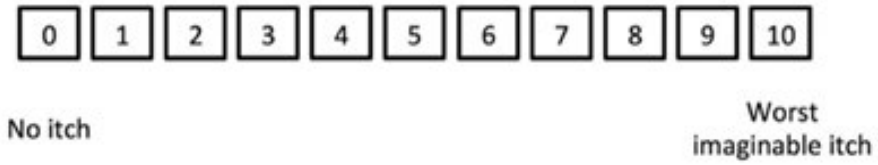
$$PASI = 0.1 (Eh + Th + Sh) Ah + 0.2 (Ea + Ta + Sa) Aa + 0.3 (Et + Tt + St) At + 0.4 (El + Tl + Sl) Al$$

7.2.3 Worst Itch-Numerical Rating Scale (WI-NRS)

WI-NRS Assessments will be performed as follows:

- Screening, Baseline, Week 2, and Week 4

The WI-NRS has been developed as a simple, single item to assess the patient-reported severity of this symptom at its highest intensity during the previous 24-hour period (Naegeli 2015). The WI-NRS will be determined by asking the subject's assessment of worst itch over the past 24 hours. The scale is from '0 to 10' ("no itch" to "worst imaginable itch"). WI-NRS pruritus assessment will be completed by subjects ≥ 8 years old, or by parent/caregiver for subjects < 8 years old.



7.2.4 Children's Dermatology Life Quality Index (CDLQI)

CDLQI (age 2-16 years) will be completed as follows:

- Screening, Baseline, Week 2, and Week 4

The Children's Dermatology Life Quality Index (CDLQI) allows a simple, compact and uniform assessment of patients with skin diseases in general, in which higher scores indicate poorer disease-related quality of life. Subjects/caregivers will complete the CDLQI. See Appendix 4 for the CDLQI.

7.2.5 Dermal Imaging

Medical photography will be performed at participating sites on consenting/assenting subjects as follows:

- Baseline, Week 2, and Week 4

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

Body or half-body photographs 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 document on the informed consent form.

Refer to the current Photography Manual for instructions regarding photography.

7.3 Other Evaluations

7.3.1 Body Surface Area (BSA)

BSA Assessments will be performed as follows:

- Screening, Baseline, Week 2, and Week 4

The BSA affected by plaque 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: All plaque 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 (PASI, IGA, BSA).

Body Diagram

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

- Baseline

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

7.3.2 Pharmacokinetics Sample Collection

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

- All enrolled subjects will have a trough PK sample at the Week 4 visit.
- A subset of 6 subjects who consent will have an additional PK sample collected pre-dose at the Week 2 visit.

Ensure investigational product is not applied in the area where PK will be drawn.

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

7.4 Final Study Visit

The approximate final study visit will occur at Week 4 for those subjects that enroll into the Open Label Extension study (ARQ-151-306), or Week 5 (Day 35 – Telephone Follow-up) for those subjects that do not enroll in ARQ-151-306. See Schedule of Visits and Assessments (Section 2).

7.5 Early Termination Visit

If a subject is withdrawn or wishes to exit the study, a termination visit will be scheduled. This visit should include the procedures and assessments that would be performed at the Week 4 visit (Day 28).

7.6 Unscheduled Visit

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

The following information will be collected for all subjects:

- Concomitant medications/procedures
- AEs

The following information also will be collected:

- IGA/I-IGA and PASI
- BSA affected with plaque psoriasis
- Local tolerability assessment (by Investigator)

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

7.7 Adverse Events

7.7.1 Adverse Event Definition

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

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

A treatment emergent adverse event (TEAE) is defined as an AE that started post application of investigational product at the Baseline visit or was present at treatment initiation but worsened during treatment, through study completion.

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

7.7.2 Serious Adverse Event

The definitions and reporting requirements of the Food and Drug Administration (FDA)/ ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A will be adhered to. If any AEs are serious, as defined by ICH Guidelines for Clinical Safety, required procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within 24 hours of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to ICH E6: Guideline for Good Clinical Practice and ICH E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. The IRB will be notified of the Alert Reports as per FDA, ICH and the IRB's policies and procedures.

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

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

Hospitalization does not include the following:

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

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

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

- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

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

If a SAE occurs to a subject on this study, contact the Sponsor personnel listed in Key Contacts List (provided separately) within one business day of knowledge of event.

7.7.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

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

7.7.4 Safety Review with Subject

At each follow-up visit, subjects and/or caregivers 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).

7.7.5 Adverse Event Reporting

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

- The relationship of each AE to the study drug will be assessed using the following definitions:

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

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

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

Note: A semi-colon indicates 'or' within the description of the grade.

* Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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

7.8 Reporting Pregnancy

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

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

Should the pregnancy result in a congenital abnormality or birth defect, a SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAEs, without regard to causality. In addition, any infant death that occurs after the 30-day reporting period that the investigator suspects are related to the in-utero exposure to the study treatment should also be reported.

7.9 Treatment Stopping Rules

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

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

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

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

CDI-2 raw total score of 34 should be referred promptly to a mental health care professional and consideration be given to discontinuation from study drug.

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

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

Treatment should be interrupted:

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

Treatment should be discontinued:

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

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

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. 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) unless otherwise stated. No interim efficacy analyses are planned.

Descriptive statistics will be used to provide an overview of the safety, efficacy, and pharmacokinetic results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentage will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation (SD), median, minimum, and maximum. No formal inferential statistics will be performed for this open-label study.

8.1.1 Pharmacokinetics Assessment

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). Plasma drug concentrations at each time point will be summarized using descriptive statistics, reporting n, mean, standard deviation, median, minimum, and maximum.

8.1.2 Pharmacokinetic Parameters

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

Pharmacokinetic parameter estimates for roflumilast and its N-oxide metabolite will be calculated by a standard noncompartmental method of analysis; these may include AUC_{last}, C_{max}, T_{max}, and others, as data permit. Pharmacokinetic parameters will be summarized using appropriate descriptive statistics.

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

8.1.3 Determination of Sample Size

The sample size will be approximately 20 subjects.

This sample size is considered adequate for safety and PK evaluation. The sample size was not powered based on data for the efficacy endpoints to provide statistical significance.

8.1.4 Subjects to Analyze

Safety population will include all subjects who are enrolled and received at least one confirmed dose of investigational product. This population will be defined separately for each cohort.

All subjects who are enrolled and receive at least one application of study drug and have evaluable PK data will be included in the pharmacokinetic population.

The MUSE PK subset population will include all evaluable (see Section 8.1.1 above) subjects receiving the active drug with sufficient plasma concentrations of roflumilast to define a profile, as determined by the pharmacokineticist.

8.1.5 Interim Analysis

No interim efficacy analyses are planned. PK and safety data may be reviewed on an ongoing basis.

8.1.6 Background and Demographic Characteristics

Descriptive statistics will be used to summarize demographic characteristics (age, sex, ethnicity, and race) and background characteristics for the enrolled subjects.

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 Exploratory Endpoints

The Exploratory Efficacy Endpoints will include:

- Change and percent change from baseline in PASI score at each study visit
- Achievement of a 50% or greater, 75% or greater improvement in PASI score from baseline to each study visit
- Change and percent change from baseline in IGA score at each study visit
- Change and percent change from baseline in I-IGA score at each study visit
- Change and percent change from baseline in BSA score at each study visit
- Change and percent change from baseline in WI-NRS score at each study visit

Descriptive statistics will be calculated for quantitative efficacy data and frequency counts will be compiled for classification of categorical efficacy data.

8.3 Safety Evaluation

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

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 application of investigational product at the Baseline visit or were present at treatment initiation but worsened during treatment, through study completion. All treatment-emergent AEs will be summarized by cohort, 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 severity, and relationship to study treatment. Each subject will be counted only once within a system organ class or a preferred term using the event with the greatest relationship and greatest severity.

All information pertaining to AEs noted during the study will be listed by subject, detailing the verbatim description given by the Investigator, preferred term, system organ class, start date, stop date, severity, action taken regarding study drug, corrective treatment, outcome, and drug relatedness. The event onset will also be shown relative (in number of days) to date of first

application. In addition, a list of subjects who prematurely discontinue from the study due to adverse events will also be provided.

8.3.2 Local Tolerance Assessment

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

8.3.3 Medical History and Physical Examinations

Physical examinations will be performed at Screening, Baseline and Week 4, and 12-lead ECGs will be performed at Screening and Week 4. Medical history and Physical Examination findings will be listed by subject. Clinically significant physical examination parameters will be captured as adverse events. Changes in physical examinations will be described in the text of the final report.

ECGs will be tabulated by visit within each cohort.

8.3.4 Clinical Laboratory Results and Vital Signs

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

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

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

8.3.5 Prior and Concomitant Medications

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

9 STUDY ADMINISTRATION

9.1 Ethics

9.1.1 Ethics Review Board

Before enrollment of subjects into the study, the current protocol and ICF will be reviewed and approved by an appropriate IRB or EC, as required by FDA (21 CFR § 56), Health Canada, and ICH GCP regulations. A letter documenting the IRB or EC 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 EC. However, the frequency of these reports will depend on IRB or EC requirements. As soon as possible after completion or termination of the study, the Investigator will submit a

final report to the IRB or EC per the IRB or EC 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 EC of any SAEs, SUSARs, or any other information that may affect the safe use of investigational product during the study, per the IRB or EC 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/Assent

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

Subjects will be given a signed copy of their ICF.

9.2 Study Monitoring

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

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

9.3 Study Completion/Termination

9.3.1 Study Completion

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

9.3.2 Study Termination

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

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

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

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.

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

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 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)/EC(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/EC, 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)/EC(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)/EC(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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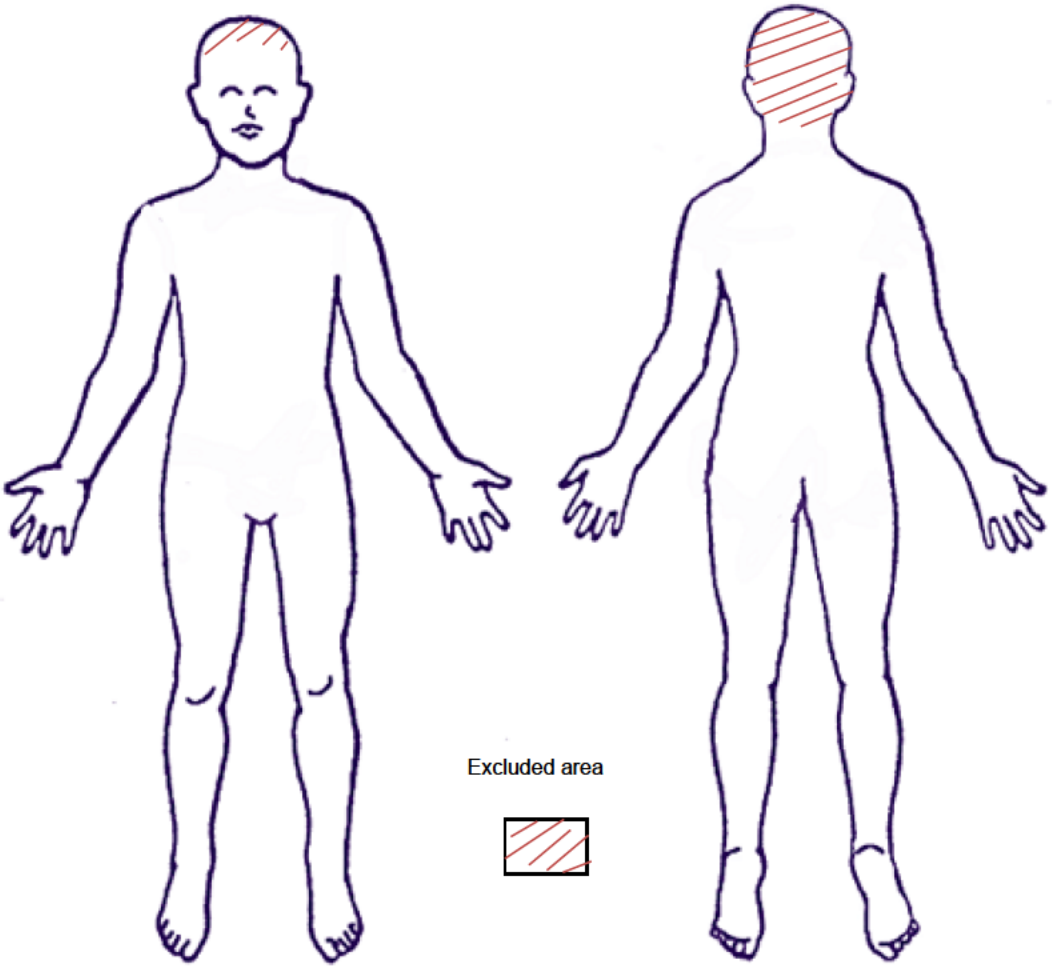
11 APPENDICES

Appendix 1. Body Diagram

Site personnel to mark treatable areas identified by investigator.

(Reminder: Application will be all areas affected (except for the scalp). Continue to apply even if area(s) clears and treat new lesions (except scalp).



Study Personnel Completing Body Diagram (initial/date)
Baseline

Amount of ARQ-151 cream 0.3% to be Weighed and Applied Once a Day to Psoriasis Areas Shown on this Body Diagram
_____ grams

Site to photocopy this page after updating at the Baseline and retain the original in source. Provide the copy to the subject to refer to for study application at home.

Appendix 2. 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.

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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

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Appendix 3. Investigator Global Assessment

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 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

Appendix 4. Children's Dermatology Life Quality Index (CDLQI)

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**, **bullying**, **asking questions** or **avoiding you**?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐

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

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Appendix 5. Toxicity Table

National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Pediatric Toxicity Tables (2007) and Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (2017)

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
TBV	Total Blood Volume
U	Unit
ULN	upper limit of normal

ESTIMATING SEVERITY GRADE

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

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

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

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

LABORATORY RANGES

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

CLINICAL ADVERSE EVENTS

Cardiovascular	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Arrhythmia		Asymptomatic, transient signs, no Rx required	Recurrent/persistent; symptomatic Rx required
Hemorrhage, blood loss	Estimated blood loss ≤ 25% of Total Blood Volume (TBV)	Estimated blood loss >25% TBV, symptomatic, 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)	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block *OR* Ventricular pause >3.0 s
Respiratory	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Cough	Transient-no treatment	Persistent cough	Interferes with daily activities
Bronchospasm, acute	Transient wheeze; no treatment;	Requires treatment; normalizes with bronchodilator and FEV_1 < 80% predicted before bronchodilator	Minimal normalization with bronchodilator andFEV_1 <80% predicted after bronchodilator
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities, no treatment	Prevents daily and usual social activity or requires treatment
Nasal discharge (rhinitis infective per **CTCAE 4.0**)	-	Localized; local intervention indicated (e.g. topical antibiotic, antifungal, or antiviral)	-
Pharyngitis **(CTCAE 4.0)**	-	Localized; local intervention indicated (e.g. topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated
Pneumonitis (rales or rhonchi) **(CTCAE 4.0)**	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated

[a] Inclusion dependent upon protocol requirements

Respiratory (continued)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Lung infection (**CTCAE 4.0**)	-	Moderate symptoms; oral intervention indicated (e.g. antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated
Gastrointestinal	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Nausea	No interference with activity	Some interference with activity	Prevents daily activities
Vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity or requires IV hydration
Diarrhea	2-3 loose or watery stools or <400 g/24 hours	4-5 loose or watery stools or 400-800 g/24 hours, mild dehydration	6 or more loose or watery stools or >800 g/24 hours or requires IV hydration
Urinary Tract	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Urinary tract infection (**CTCAE 4.0**)	-	Localized; local intervention indicated (e.g., oral or topical antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated
Reactogenicity	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Local reactions			
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity
Tenderness	Discomfort only to touch	Discomfort with movement	Significant discomfort at rest
Erythema/redness [b]	≤ 2.5 cm	>2.5 cm with < 50% surface area of the segment area involved 5.1-10 cm	>10 cm
Induration/swelling [c]	≤ 2.5cm and does not interfere with activity	>2.5 cm with < 50% surface area of the segment area involved or interferes with activity	>10 cm or prevents daily activity

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

Reactogenicity (continued)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Systemic reactions			
Allergic reaction	Pruritus without rash	Localized urticaria	Generalized urticaria; angioedema or anaphylaxis
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity
All Other Conditions	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention
Unintentional Weight Loss	-	5 to <9% loss in body weight from baselines	≥9 to 20% loss in body weight from baseline
Underweight	-	WHO BMI or weight-for-height z-score < -2 to -3	WHO BMI or weight-for-height z-score < -3

LABORATORY AND VITAL SIGNS TOXICITY GRADING (Some laboratory values have been modified to be consistent with the normal ranges of the 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-3.0	<3.0-2.5	<2.5
	HI	>ULN-6.0	>6.0-6.5	>6.5
Glucose (mmol/L)	LO	<LLN-3.0	<3.0-2.2	<2.2
	HI	>ULN-8.9	>8.9-13.9	>13.9
Blood urea nitrogen (mmol/L)	HI	>8.9-17.8	>17.8-35.5	>35.5
Creatinine (mg/dL)	HI	0.7-1.0 x ULN	1.1-1.6 x ULN	1.7-2.0 x ULN
Calcium (mmol/L) **(CTCAE 4.0)**	LO	<LLN-2.0	<2.0-1.75	<1.75
	HI	>ULN-2.9	>2.9-3.1	>3.1
Magnesium (mmol/L) **(CTCAE 4.0)**	LO	1.2-1.4	0.9-1.1	0.6-<0.9
Phosphate (mmol/L) **(CTCAE 4.0)**	LO	3.0-<3.5	2.5-<3.0	1.5-<2.5
Creatine kinase (CPK or CK) **(CTCAE 4.0)**	HI	>ULN-2.5xULN	>2.5xULN-5xULN	>5xULN
Albumin (g/L)	LO	<30-28	<28-25	<25
Total protein (g/L)	LO	<LLN-52	<52-50	<50
Alkaline phosphatase (U/L) **(CTCAE 4.0)**	HI	>ULN-2.5xULN	>2.5xULN-5xULN	>5xULN
AST (U/L) **(CTCAE 4.0)**	HI	>ULN-3xULN	>3xULN-5xULN	>5xULN
ALT (U/L) **(CTCAE 4.0)**	HI	>ULN-3xULN	>3xULN-5xULN	>5xULN

Blood, Serum, or Plasma Chemistries [a]	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
Bilirubin, serum total (mmol/L) **(CTCAE 4.0)**	HI mmol/L	>ULN-1.5xULN	>1.5xULN-3xULN	>3xULN
Bilirubin, serum 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) **(CTCAE 4.0)**	HI	>ULN – 10.0 without physiologic consequences	10.0-<12.5	>12.5 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 (g/dL)	LO	9.5-10.4	8.5-<9.5	<8.5
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	<125-100	100-50	<50
Coagulation				
Prothrombin time (PT, seconds)	HI	1.1-1.2 xULN	1.3-1.5 x ULN	1.6 -3.0 x ULN
Partial thromboplastin time (PTT or aPTT, seconds)	HI	1.1-1.6 x ULN	1.7-2.3 x ULN	2.4-3.0 x ULN
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	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 (>6 years) - beats per minute	HI	101-115	116-130	>130 or ventricular dysrhythmias
Tachycardia (≤6 years) - beats per minute		120-130	131-150	>150 or ventricular dysrhythmias
Bradycardia - beats per minute	LO	<60-50 and no symptoms	<60-50 with symptoms	<50
Hypertension (systolic) - mm Hg [d]	HI	>90-95th percentile adjusted for age, height, and gender	≥95-99th percentile adjusted for age, height, and gender	≥99th percentile adjusted for age, height, and gender
Hypertension (diastolic) - mm Hg	HI	>90-95th percentile adjusted for age, height, and gender	≥95-99th percentile adjusted for age, height, and gender	≥99th percentile adjusted for age, height, and gender
Hypotension (systolic) - mm Hg	LO	85-89	80-84	<80
Tachypnea - breaths per minute	HI	31-35	36-40	>40

[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. COVID-19 Study Site Guidance

BACKGROUND

As the impact of coronavirus disease 2019 (COVID-19) continues to develop, Paidion Research Inc. and Arcutis Biotherapeutics Inc. have collated the following guidelines for study sites participating in the ARQ-151-215 study. While it is ideal for subjects to perform all protocol-specific assessments at the study site, both Paidion and Arcutis are focused on prioritizing subject safety and data integrity. Therefore, the following guidelines will identify challenges and mitigation strategies while operating clinical trials remotely.

REMOTE DATA COLLECTION

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

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

Data collection by mail or email may also be performed for applicable assessments. Site staff will contact subjects via traditional mail or email to collect data using paper versions of study questionnaires.

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

- WI-NRS
- CDLQI
- CDI-2
- Subject Local Tolerability
- Adverse Events
- Concomitant medication
- Review of Subject Diary

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

- IGA, I-IGA
- PASI
- BSA
- Investigator Local Tolerability
- Subject Weight

GUIDELINES FOR REMOTE DATA COLLECTION

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

- Site should confirm the subject has adequate IP to continue dosing and if not ask the subject to return to the site to pick up additional IP or refer to the current IP Handling Plan for instructions on shipment of IP from site to subject.
- Confirm the subject has no AEs that would warrant discontinuation of the IP.
- Site should discuss any new or ongoing conmed(s) and determine if the use of any warrant having the subject stop IP application or not.
- For any female subject of childbearing potential that site should discuss and confirm the subject has continued her methods of ensuring pregnancy does not occur. Any deviation from these methods should be discussed further and the site should determine if IP should be halted or contact the medical monitor or Arcutis if they have any questions. A pregnancy test can be performed at the next onsite visit (this is applicable to prior visits being missed due to COVID-19 as well).
- Subjects are approved to continue dosing for up to 14 days past Week 4 until they return the clinic for the Week 4 visit. After this, sites should reach out to the Medical Monitor and/or Arcutis directly for approval to have subjects continue dosing.
- All the above discussions must be documented in the source.

d. If available, home health nurse visits could be considered for collection of Vital Signs and Clinical Labs.

e. In the event a subject is quarantined, has symptoms, or is confirmed positive for COVID-19, it is the Sponsor's opinion that IP can continue, assuming no other contraindications.