Study Number:	ARQ-151-201
NCT #:	NCT03638258
Official Title:	A Phase 2b 12-Week Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety, Efficacy and Pharmacokinetics of ARQ-151 Cream 0.3% and ARQ-151 Cream 0.15% Administered QD in Subjects with Chronic Plaque Psoriasis
Protocol Date:	02-Aug-2018

Protocol ARQ-151-201

Amendment 1

A Phase 2b 12-Week Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety, Efficacy and Pharmacokinetics of ARQ-151 Cream 0.3% and ARQ-151 Cream 0.15% Administered QD in Subjects with Chronic Plaque Psoriasis

GCP Statement

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

Confidentiality Statement

1 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Phase 2b 12-Week Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety, Efficacy and Pharmacokinetics of ARQ-151 Cream 0.3% and ARQ-151 Cream 0.15% QD in Subjects with Chronic Plaque Psoriasis

AMENDMENT 1

SPONSOR: Arcutis, Inc.

[redacted]

SPONSOR'S REPRESENTATIVE: [redacted]

[redacted]

12 NOV 2018

Signature Date

PRINCIPAL INVESTIGATOR AND CLINICAL SITE: Kim Papp, MD, PhD, FRCPC
K. Papp Clinical Research, Inc.
135 Union Street East
Waterloo, Ontario, Canada
N2J 1C4

[redacted] 12 Nov 2018

Signature Date

PROTOCOL REVISION HISTORY

Version/Date	Description
ARQ-151-201 Version 1 August 2, 2018	Original protocol
ARQ-151-201 Amendment 1.0 November 8, 2018	• Added protocol revision history section. • Added the Dermatology Life Quality Index (DLQI) to visits 1 through 7. • Updated modified Intent to Treat (mITT) population to Intent to Treat (ITT) population. • Added footnote "b" in the Study Events Flowchart to clarify routine blood chemistries if Baseline is within 14 days of Screening, the Screening results may be utilized for Baseline. The other footnotes were updated accordingly. • Footnote "m" has been revised to include collection of the tube weight prior to the application and after the application. • Added footnote "r" to the Study Events Flowchart to update the duration of subject participation for the study. Subjects who enroll into the open label extension study (ARQ-151-202) will complete the study at Week 12; subjects that do not enroll into ARQ-151-202 will return at Week 16 to complete the study. • Revised Inclusion Criterion #8 to more completely define Females of Non-Child Bearing Potential to include those who are post-menopausal or surgically sterile. • Revised Exclusion Criterion #5 to clarify subjects with palmoplantar only involvement are to be excluded. • Clarified the optional PK draws will be applicable only to subjects who enter the 4-week follow up period. • Added text in Data Analysis section relevant to the PSD and addition of the DLQI; changed primary analysis population from mITT to ITT per FDA advice; rearranged order of subsections under Data Analysis to improve organization. • Editorial and administrative changes throughout the protocol to clarify language and formatting to improve readability.

2 ADDITIONAL KEY CONTACTS FOR THE STUDY

Sponsor Contact for Serious Adverse Event Reporting	[redacted]
Medical Monitor	[redacted]
Managing CRO	Cu-Tech, LLC 333 US Highway 46 West Mountain Lakes, NJ 07046 [redacted]
Certified Clinical Laboratory	ACM Global Laboratories 160 Elmgrove Park Rochester, NY 14624, USA [redacted]
Bioanalytical Laboratory	Q Squared Solutions BioSciences, LLC 19 Brown Road Ithaca, NY 14850 [redacted]
Pharmacokinetic Analysis	ADME Solutions, Inc. [redacted]

ADDITIONAL KEY CONTACTS FOR THE STUDY (Cont.)

Data Management / Statistical Analysis	QST Consultations, Ltd. 11275 Edgewater Drive Allendale, MI 49401 [redacted]

3 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

4 SYNOPSIS

Compound:	ARQ-151 cream 0.3% and ARQ-151 cream 0.15%
IND	135681
Clinical Indication:	Chronic Plaque Psoriasis
Study Phase and Type:	Phase 2b Parallel Group, Double Blind, Vehicle-Controlled Study
Study Objectives:	To assess the safety and efficacy of ARQ-151 cream 0.3% and ARQ-151 cream 0.15% vs. vehicle administered QD for 84 days to individuals with 2 - 20% BSA of chronic plaque psoriasis.
Summary of Study Design:	This is a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.3% or ARQ-151 cream 0.15% or vehicle cream is applied QD for 84 days to subjects with chronic plaque psoriasis involving between 2 and 20% BSA.
Blinding:	This study is double blind and vehicle controlled
Countries:	Canada and United States
Number of sites:	Approximately 30 sites
Study Population:	Subjects will be male and female adults (≥18 y/o). Subjects will have 2% to 20% total BSA of chronic plaque psoriasis. Subjects will have a minimum IGA of 'Mild' (2) for study entry. Subjects with an IGA of 'Mild' (2) will be limited to 20% of total enrollment and subjects with IGA of 'Severe" (4) will be limited to 15% of total enrollment.
Main Inclusion Criteria	1. Participants legally competent to sign and give informed consent 2. Males and females ages 18 years and older 3. Clinical diagnosis of psoriasis vulgaris of at least 6 months duration as determined by the Investigator 4. Psoriasis vulgaris on the face, extremities, trunk, and/or intertriginous areas involving 2% to 20% of BSA (excluding the scalp, palms and soles) 5. An Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') at Baseline 6. A mPASI score of at least 2 (excluding the scalp, palms and soles) at Baseline 7. Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at Screening (Visit 1) and Baseline (Visit 2). In addition, sexually active FOCBP must agree to use at least one form of highly effective contraception throughout the trial. Highly effective forms of contraception include: oral/implant/injectable/transdermal contraceptives, intrauterine device, and partner's vasectomy. If barrier methods are used (e.g., condom with spermicide, diaphragm with spermicide), then 2 forms of conception are required. The use of abstinence as a contraceptive measure is acceptable as long as this is a

	consistent part of a lifestyle choice and an acceptable backup method has been identified if the subject becomes sexually active. 8. Females of non-childbearing potential should be post-menopausal with spontaneous amenorrhea for at least 12 months or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy).
Main Exclusion Criteria	1. Subjects who cannot discontinue medication and treatments prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 1). 2. Planned excessive exposure of treated area(s) to either natural or artificial sunlight, tanning bed or other LED. 3. Subjects currently taking lithium or antimalarial drugs. 4. Planned initiation or changes to concomitant medication that could, in the opinion of the Investigator, affect psoriasis vulgaris (e.g. beta blockers, ACE inhibitors). 5. Current diagnosis of guttate, erythrodermic/exfoliative, palmoplantar only involvement, or pustular psoriasis. 6. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements. 7. Known allergies to excipients in ARQ-151 cream [redacted] 8. Subjects who cannot discontinue the use of strong P-450 cytochrome inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin) for two weeks prior to the baseline visit and during the study period. 9. Subjects who cannot discontinue the use of strong P-450 cytochrome inducers (e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, and rifampin) for two weeks prior to the baseline visit and during the study period. 10. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding. 11. Previous treatment with ARQ-151. 12. Subjects who have received oral roflumilast (Daliresp®, Daxas®) or other PDE4 inhibitors (apremilast)) within the past 4 weeks. 13. Known or suspected: • severe renal insufficiency or severe hepatic disorders • hypersensitivity to component(s) of the investigational products • history of severe depression, suicidal ideation 14. Subjects who are unable to communicate, read or understand the local language, or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation.

Number of Subjects:	Approximately 300 subjects; randomized 1:1:1 to ARQ-151 cream 0.3% QD : ARQ-151 cream 0.15% QD : vehicle QD
Duration of Participation for Subjects:	All subject will participate in Screening (up to 5 weeks) and Treatment phases (12 weeks). Upon completion of this study, participants may have the opportunity, subject to regulatory approval, to participate in an open-label extension study of up to 12 months, receiving the 0.3% concentration of drug product (ARQ-151-202). For subjects who enroll in ARQ-151-202, the week 12 visit will complete this study. Subjects who do not enroll in ARQ-151-202 will return for a follow-up visit (4 weeks post-treatment completion).
Study Products:	• ARQ-151 drug product will be supplied as a 0.3% and 0.15% cream • Matching vehicle cream will contain only excipients of ARQ-151 cream
Planned Dose Level:	Subjects will receive ARQ-151 cream 0.3% QD or ARQ-151 cream 0.15% QD or matching vehicle cream QD applied to all psoriatic lesions up to and including an area of 20% BSA. Application will be all areas affected including the face and intertriginous/genital regions (except for the scalp).
Safety Assessments:	Safety will be monitored through application site assessments, safety labs, 12-lead ECGs, PHQ-8, C-SSRS and AEs.
Safety Analysis:	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. Descriptive statistics will be calculated for the PHQ-8. The C-SSRS will be analyzed per the Scoring and Data Analysis Guide from the Columbia Lighthouse Project. **Adverse Events:** A subject-by-subject treatment-emergent AE (TEAE) data listing, including verbatim term, preferred term, treatment, severity, and relationship to study drug, will be provided. The number of subjects experiencing AEs and number of AEs will be summarized by treatment using frequency counts. **Medical History and Physical Examinations:** Medical history will be listed by subject. Physical examinations and 12-lead ECGs will be performed at screening, Week 4 and end-of-study. Vital signs will be collected at all study visits. **Clinical Laboratory Results:** Routine blood chemistries will be obtained at screening, baseline, week 4 and week 12. If Baseline is within 14 days of Screening, the Screening results may be utilized. Urine pregnancy tests will be obtained at screening, baseline, weeks 4, 8, and 12.

Efficacy Analysis	The Primary Efficacy Endpoint will be an IGA score of 'clear' or 'almost clear' at week 6. The secondary efficacy endpoints will include: • IGA score of 'clear' or 'almost clear' at weeks 4, 8 and 12. • Percent reduction in mPASI at weeks 4, 6, 8, and 12 as compared to Baseline. • Decrease in percent BSA affected at weeks 4, 6, 8, and 12 as compared to baseline. • IGA score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at weeks 4, 6, 8 and 12. • For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (intertriginous IGA (I-IGA) ≥2) at Baseline, 'I-IGA' score of 'clear' or 'almost clear' at weeks 4, 6, 8 and 12. • Reduction in WI-NRS pruritus score at weeks 4, 6, 8, and 12 as compared to Baseline. • In subjects with WI-NRS pruritus score ≥ 6 at baseline, a 4-point reduction in WI-NRS pruritus score at weeks 4, 6, 8, and 12 as compared to Baseline. • Modified Psoriasis Area Severity Index-75 (mPASI-75; subjects who achieve a 75% reduction in mPASI from Baseline) improvement at weeks 4, 6, 8, and 12 as compared to Baseline. • Modified Psoriasis Area Severity Index-90 (mPASI-90; subjects who achieve a 90% reduction in mPASI from Baseline) improvement at weeks 4, 6, 8, and 12 as compared to Baseline. • Total PSD at weeks 4, 6, 8, and 12 as compared to Baseline. • Reduction in Itch-related Sleep Loss score at weeks 4, 6, 8, and 12 as compared to Baseline. • Reduction in Dermatology Life Quality Index (DLQI) score at weeks 4, 6, 8, and 12 as compared to Baseline. • Responses to the questions of PSD analyzed as improvement at weeks 4, 6, 8, and 12 as compared to Baseline. Exploratory Endpoints are as follows: • Reduction in Fatigue NRS score at weeks 4, 6, 8, and 12 as compared to Baseline. • Reduction in WPAI score at weeks 4, 6, 8, and 12 as compared to Baseline.

Power and Sample Size	Approximately 300 subjects are planned for this study. Approximately 100 subjects will receive ARQ-151 cream 0.3% QD; approximately 100 subjects will receive ARQ-151 cream 0.15% QD; approximately 100 subjects will receive matching vehicle cream QD. The randomization scheme will be 1:1:1 (ARQ-151 cream 0.3% QD : ARQ-151 cream 0.15% QD : matching vehicle QD. The sample size was not powered based on data for the primary endpoint to provide statistical significance because of the absence of previous primary endpoint data. However, based on efficacy data from the proof of concept study, this Phase 2b study is expected to provide reliable information regarding the efficacy and safety of the drug products.
Pharmacokinetic Sample Collection:	PK draws will be done on days 1 (baseline), 29 (week 4) and 85 (week 12) pre-dose (trough) for all subjects. Approximately 30 subjects who enter the 4 week follow up period with greater than or equal to 5% BSA involvement will have the option to have additional PK draws at 72 hr (3 days), 120 hr (5 days), 168 hr (7 days), and 216 hr (9 days) after the last dose of drug. For the 72 hour timepoint, the PK draw should be +/- 2 hours of the last study drug application. The 5, 7 and 9 day draws should be completed in the morning before noon at the site.
Statistical Analysis:	Four analysis populations will be defined: • Safety population will include all subjects who are enrolled and received at least one confirmed dose of study medication; this population will be defined separately for each cohort. • Intent-to-Treatment (ITT) population will include all randomized subjects. • Per-Protocol (PP) Population will include all subjects who are in the safety population, were at least 80% compliant with study medication, and showed no other serious deviations from the study protocol. • PK population will include all subjects receiving the active drug with quantifiable plasma concentrations of roflumilast. Descriptive statistics will be presented for the endpoint data collected in the clinical trial. Missing efficacy data will be estimated by a mixture of linear interpolation and last observation carried forward for the cases were linear interpolation is not computationally possible. The week 6 'IGA success' endpoint will be analyzed with a logistic regression. Statistical comparison between the active treatment arms and vehicle arms will be facilitated by using contrasts.

5 SCHEDULE OF VISITS AND ASSESSMENTS

STUDY EVENTS FLOW CHART:

Study Procedure	Screen	Baseline Day 1	Wk 2 Day 15	Wk 4 Day 29	Wk 6 Day 43	Wk 8 Day 57	Wk 12 Day 85	Wk 16 Day 113
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Visit Window	**-35 days**		**+/- 3 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 7 days**	**+/- 7 days**
Informed consent	X							
Medical history	X							
Physical examination[a]	X	X					X	
I/E criteria	X	X						
Hematology, Serum Chemistries, and Urine Analysis[b]	X	X		X			X	
12-lead ECG	X			X			X	
Vital signs, height, weight[c]	X	X	X	X	X	X	X	X
IGA[d], BSA[d], mPASI[d]	X	X	X	X	X	X	X	X
Intertriginous area IGA (I-IGA)[e]		X	X	X	X	X	X	X
WI-NRS[f], Fatigue NRS[g], WPAI[h], Itch-related sleep loss and DLQI[i]	X	X	X	X	X	X	X	
Local Tolerability Assessments[j]		X		X		X	X	
C-SSRS, PHQ-8	X	X		X		X	X	
PSD	X	X	X	X	X	X	X	X
Optional Photography[k]		X		X	X	X	X	
Urine pregnancy test[l]	X	X		X		X	X	
PK draws[m]		X		X			X	
IP application in clinic[n]		X	X	X	X	X	X	
Assign study medication kit[o]		X						
Dispense/review diary		X	X	X	X	X	X	
Weigh study medication tubes[p]		X	X	X	X	X	X	
Compliance calculation[p]		X	X	X	X	X	X	
Adverse event assessment[q]	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Study Exit[r]								X

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

[b] To be collected at Screening, Baseline, Week 4 and Week 12. If Baseline is within 14 days of Screening, the Screening results may be utilized.

[c] Height will be collected at Baseline only. Weight will be collected at baseline, week 4, 6, 8 and 12. Subject to void prior to weight being taken. Remove any jackets, outerwear and shoes. Remove any objects of significant weight (i.e. cell phones, wallet, key chains). A 5% weight loss should be reported to the medical monitor.

[d] IGA (based on whole body involvement) will be a 5-point scale ranging from clear (0) to severe (4). **IGA should be completed prior to other physician assessments.** Total BSA affected by psoriasis will be determined. mPASI will be determined by standard PASI methods for subjects with ≥ 10% BSA involvement; for subjects with < 10% BSA involvement the mPASI will be calculated using the actual percentage of the anatomical area involved (e.g. for 5% of an anatomical area involved 0.5 would be used for the calculation). PASI-75 and PASI-90 responses will be determined.

[e] For subjects with intertriginous area involvement of at least 'mild' severity by IGA (IGA≥2) at Baseline (using the IGA scale but evaluating intertriginous areas ONLY and NOT whole body involvement), an IGA for the intertriginous region alone (I-IGA) will be recorded at weeks 2, 4, 6, 8, 12 and 14. **This 'intertriginous area IGA' should be done AFTER the 'standard whole body IGA' (primary endpoint) in subjects who qualify.**

[f] Subjects will complete WI-NRS pruritus assessment.

[g] Subjects will complete Fatigue NRS assessment.

[h] Subjects will complete WPAI (work impairment) assessment.

[i] Subjects will complete Itch-related sleep loss assessment and DLQI.

[j] Tolerability assessments should be recorded prior to study drug application for Investigator assessment (Berger and Bowman skin irritation score) and 10-15 minutes post-drug application for subject '0-3' burning/stinging assessment.

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

[l] 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 at each visit.

[m] PK draws will be collected from all subjects at Days 1, 29 and 85. The draws will be pre-dose drug application in the clinic (i.e., trough levels). The tube weight will be collected prior to the application and after the application. Ensure study medication is not applied in the area where PK will be drawn. Approximately 30 subjects, continuing to the Week 16 visit, with greater than or equal to 5% BSA involvement, will have additional PK draws at 72 hr (3 days), 120 hr (5 days), 168 hr (7 days), and 216 hr (9 days) timepoints post the last treatment application. For the 72 hour timepoint, the PK draw should be +/- 2 hours of the last study drug application. The 5, 7 and 9 day draws should be completed in the morning, before noon at the site.

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

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

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

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

[r] Subjects who enroll into the open label extension study (ARQ-151-202) will complete the study at Week 12; subjects that do not enroll into ARQ-151-202 will return at Week 16 to complete the study.

6 ABBREVIATIONS

AE	Adverse Event
AMP	Adenosine Monophosphate
AUC	Area Under the Curve
BSA	Body Surface Area
C_{max}	Maximum Concentration
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic Acid
ERB	Ethics Review Board
FDA	U.S. Food and Drug Administration
FOCBP	Female of Child Bearing Potential
GCP	Good Clinical Practices
HC	Health Canada
HCA	Alpha-Hydroxycinnamaldehyde
HPRT	Hypoxanthine-guanine Phosphoribosyl Transferase
IB	Investigational Brochure
IC_{50}	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA	Investigator Global Assessment
I-IGA	Intertriginous IGA
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to Treat
IWRS	Interactive Web Response System
LED	Light Emitting Device
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
mL	Milliliter
MMRM	Mixed effect Model Repeat Measurement
mPASI	Modified Psoriasis Area and Severity Index
mPASI-75	Modified Psoriasis Area and Severity Index-75; subjects who achieve a 75% reduction in mPASI from Baseline
mPASI-90	Modified Psoriasis Area and Severity Index-90; subjects who achieve a 90% reduction in mPASI from Baseline

MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
ng	Nanogram
NRS	Numerical Rating Score
PASI	Psoriasis Area and Severity Index
PDE-4	Phosphodiesterase 4
PHQ-8	Patient Health Questionnaire depression scale
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PSD	Psoriasis Symptoms Diary
QD	Once Daily ("quaque die")
SAE	Serious Adverse Event
TEAE	Treatment Emergent Adverse Event
Th1	Type 1 T Helper Cell
Th17	Type 17 T Helper Cell
T_{max}	Time to reach maximum concentration
V79	Chinese hamster cell line
WPAI	Work Productivity and Activity Impairment Questionnaire
WI-NRS	Worst Itch – Numeric Rating Score

7 BACKGROUND AND RATIONALE

7.1 Introduction

Roflumilast is a phosphodiesterase 4 (PDE-4) inhibitor approved globally to reduce the risk of exacerbations in patients with severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis. Roflumilast and its active metabolite, roflumilast N-oxide, are high affinity selective inhibitors of PDE-4 (a major cyclic-3′,5′-adenosine monophosphate (cyclic AMP)-metabolizing enzyme), whose activity leads to accumulation of intracellular cyclic AMP. There are four different subtypes of PDE-4: PDE-4a, PDE-4b, PDE-4c, and PDE-4d, each with several isoforms (splicing variants). IC_{50} values of both roflumilast and roflumilast N-oxide for the different PDE-4 isoforms and subtypes are mostly sub-nanomolar and single digit nanomolar (Hatzelmann 2010). The PDE-4 family of enzymes are the most prevalent phosphodiesterases in immune cells and inhibition of PDE-4 subtypes has been associated with anti-inflammatory effects in many biological systems.

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

The past 15 years have witnessed a transformation in the systemic treatment of moderate to severe psoriasis with the advent of biological therapies. However, for patients with milder forms of disease, best treated with topical options, the therapeutic landscape really has not changed in several decades. Topical steroids come in all shapes and forms, but the lower potency steroids are not effective and the higher potency steroids are beset with issues of local skin atrophy and the potential for hypothalamic-pituitary axis suppression when applied over larger body surface areas and for prolonged periods of time. Vitamin D has been the other staple of topical psoriasis treatment but it is irritating, not suitable for use on the face or intertriginous areas, and its efficacy is rather modest. Hence, there is substantial medical need for additional topical approaches in the treatment of psoriasis. The study sponsor is developing a topical formulation of roflumilast for the treatment of chronic plaque psoriasis. Our Phase 2a results suggest that ARQ-151 may be a highly efficacious and well-tolerated topical treatment for psoriasis.

7.2 Preclinical 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. Oral roflumilast (500 µg tablet) was approved by Health Canada as DAXAS® in December 2010 and by the US FDA as DALIRESP® in February 2011 for the treatment of COPD. [redacted]

[redacted]

Based on the data from this study, the NOAEL in this strain of mice is the 20 mg/kg dose (2 mL/kg of a 1% w/w formulation).

7.2.2 Oral (Systemic) Studies of Roflumilast and N-Oxide Metabolite

The repeat-dose toxicity studies of roflumilast has been evaluated in five animal species, with the longest duration being 6 months in mice, 6 months in rats, 3 months in hamsters, 12 months in dogs and 9-months in monkeys. The N-oxide metabolite has been studied for 6 months in mice, 1 month in rats and 12 months in dogs. Below is a summary of the drug-related effects seen in these studies.

Dose-related changes in rodent olfactory mucosa consisted of disorganization and degeneration accompanied by basal cell hyperplasia and inflammatory changes of Bowman's capsule and submucosa. The rat was the most sensitive species (NOAEL of 0.8 mg/kg/day), while mice and hamsters were less sensitive (NOAEL of 4 mg/kg/day). No equivalent changes were observed in the olfactory mucosa of dogs and monkeys, despite high systemic exposures to roflumilast and roflumilast N-oxide. Nasal mucosa lesions in the olfactory region are attributed to a rodent-specific metabolite. Humans do not have the corresponding olfactory-specific enzyme.

Gastrointestinal effects in rats (erosion, ulceration and/or inflammation) were seen primarily in the 4-week studies with roflumilast and roflumilast N-oxide at the highest doses. Gastrointestinal effects seen in monkeys (inflammation in the pyloric region) were minimal and transient as they occurred after one month of treatment, but were absent after 9 months of dosing. In relation to the approved 500 µg dose, the safety margins (plasma AUC of free drug fraction) for any potential gastrointestinal effects are 3.7- and 7.4-fold for rats, and 15- and 9.3-fold for monkeys, for roflumilast and roflumilast N-oxide, respectively. For mice, hamsters and dogs, the safety margins at the highest dose tested are 628-, 22- and 47-fold for roflumilast and 249-, 56- and 3.8-fold for roflumilast N-oxide, respectively. While these margins based on AUC may be somewhat less with topical administration if exposure to roflumilast and roflumilast N-oxide is increased with topical administration at high BSAs, gastrointestinal effects are likely to be C_{max}-mediated and thus should be mitigated by a lower, and slower ascent to, C_{max} that occurs with topical administration.

Epididymal spermiogenic granuloma as well as tubular dilation and degeneration of the testes were observed in rats treated with roflumilast and roflumilast N-oxide at doses >0.8 mg/kg/day or >1.2 mg/kg/day, respectively. No drug-related changes in the testis or epididymis were noted in the other species.

Cardiac lesions such as focal hemorrhages, hemosiderin deposits and lympho-histiocytic cell infiltration in the right atria/auricles were found in repeat dose toxicity with roflumilast and roflumilast N-oxide in dogs. In a 6-month study in mice, peri-arteritis was seen in 1-2/40 mice at doses > 12 mg/kg/day. In a 1-month study in monkeys, myocarditis was seen in 1/3 monkeys at 0.25 mg/kg/day, but was not seen in a subsequent 9-month study at 0.5 mg/kg/day. The effects seen in the latter two species are not considered treatment related.

Decreased food consumption, reduced body weight gain and adrenal hypertrophy (in mice accompanied by a premature involution of the juxtamedullary x-zone) occurred in mice, rats and hamsters at high doses of roflumilast that produced exposure ratios exceeding 9- to 650-fold the human plasma levels of unbound roflumilast and roflumilast N-oxide compared to the 500 µg oral dose..

7.2.3 Reproductive Toxicity

Roflumilast was not teratogenic in rats and rabbits following oral administration up to the highest doses of 1.8 mg/kg/day in rats and 0.8 mg/kg/day in rabbits. Administered at the same doses, roflumilast has been shown to induce mild retardation of embryo-fetal development (incomplete ossification) in the rat, but not in the rabbit. Exposure of pregnant rats to unbound roflumilast and roflumilast N-oxide was 1.7 and 10.8 times higher, respectively, than exposure of women at the 500 µg oral roflumilast dose. In one of three rat studies on fertility and embryo-fetal development, post-implantation losses were observed at oral doses of 0.8 mg/kg/day. Post-implantation losses were not seen in rabbits up to doses of 0.8 mg/kg/day. Rat and rabbit fetuses were exposed to roflumilast and the permeability of the placental barrier for drug-related material increased with the progression of pregnancy. Prolongation of gestation was seen in mice due to a potential tocolytic effect.

There was no effect on female fertility up to the highest roflumilast dose of 1.5 mg/kg/day in rats. Slight reduction in male fertility was seen in conjunction with epididymal toxicity in rats dosed with 1.8 mg/kg/day. This finding is not considered relevant to humans.

7.2.4 Genotoxicity

Roflumilast tested positive in an *in vivo* mouse micronucleus test, but negative in the following assays: Ames test for bacterial gene mutation, in vitro chromosome aberration assay in human lymphocytes, in vitro HPRT test with V79 cells, in vitro micronucleus test with V79 cells, DNA adduct formation assay in rat nasal mucosa, liver and testes, and in vivo mouse bone marrow chromosome aberration assay. Roflumilast N-oxide was negative in the Ames test and the in vitro micronucleus test with V79 cells.

7.2.5 Carcinogenicity

In a 2-year carcinogenicity study in mice, roflumilast was administered by gavage at doses up to 18 mg/kg/day in males and 12 mg/kg/day in females. No compound-related tumors occurred. In the two 2-year carcinogenicity studies in hamsters, roflumilast was administered by gavage at doses up to 16 mg/kg/day. Nasal neoplasms (undifferentiated carcinomas of the olfactory epithelium and adenocarcinoma of Bowman's gland) were observed at the high doses of roflumilast. No other treatment-related neoplastic findings were observed. Overall, the tumor-free level in the animals was 4 mg/kg/day. The significance of this finding to humans is unknown.

7.2.6 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2.7 Conclusions on Toxicity Findings

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

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

[redacted]

[redacted]

7.3 Clinical Studies

7.3.1 Topical Roflumilast Cream

This will be the second study of topical ARQ-151 cream in the human population.

ARQ-151 cream 0.5% and 0.15% have been studied in a Phase 2a study (protocol # ARQ-151-101; NCT03392168) in patients with mild to moderate chronic plaque psoriasis in the United States and Canada. The study included two cohorts. Cohort 1 was a single dose study to 25 cm^2 of psoriatic plaque(s) in 8 psoriasis subjects. Cohort 1 subjects were then enrolled, if they met entry criteria, into Cohort 2 of the study. Cohort 2 was a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.5%, ARQ-151 cream 0.15% or vehicle cream was applied QD for 28 days to 89 subjects with at least 0.5% BSA of chronic plaque psoriasis; area for application was not to exceed 5.0% BSA. Cohort 2 subjects had at least one target plaque of psoriasis of at least 9 cm^2 Target Plaque Area (TPA) in size and with a Target Plaque Severity Score (TPSS) $\geq$ 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.

Efficacy and safety results of ARQ-151-101 are as follows:

- Figure 1 shows evaluation of the primary efficacy endpoint at Weeks 1, 2, 3 and 4, with p values and standard error bars:

[redacted]

[redacted]

Day 28 pharmacokinetic results of ARQ-151-101 are as follows:

[redacted]

7.3.2 Oral Roflumilast Tablet

Oral roflumilast (DALIRESP®, DAXAS®, a 500 µg tablet) 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, other than hypersensitivity to components of the product, is in patients with moderate to severe liver impairment (Child-Pugh B or C), where systemic levels of roflumilast may become highly elevated.

7.4 Rationale for Development

In 2016, Snape and colleagues performed a Phase 1 randomized clinical trial to assess the effect on skin infiltrate thickness and tolerability of topical phosphodiesterase inhibitors, including roflumilast, in the treatment of psoriasis vulgaris using a modified psoriasis plaque test. The products evaluated were the active comparators calcipotriol 0.005% and betamethasone valerate 0.1% (both in their marketed cream formulations), and investigational cream formulations of roflumilast 0.5%, TAK-084 0.5% and 5%. A vehicle cream was used as a control (the vehicle cream and roflumilast formulations in this study were different from the ARQ-151 cream formulation). Each treatment was applied daily to different test sites located on a single psoriasis plaque of an individual for 3 weeks. Fifteen patients with psoriasis were studied. The primary endpoint of mean change from baseline in skin infiltrate thickness after 3 weeks of treatment showed statistically significant improvements for all treatments: betamethasone valerate (-286.9 μm), the selective PDE-4 inhibitors roflumilast 0.5% (-237.1 μm), TAK-084 0.5% (-153.6 μm), TAK-084 5% (-216.7 μm) and calcipotriol 0.005% (-187.7 μm) when compared with vehicle cream control (all $p < 0.001$) (Snape 2016).

[redacted]

[redacted]

7.4.1 Dose Selection

[redacted]

[redacted]

7.4.2 Risks and/or Benefits to Subjects

Based on the Phase 2a study results, subjects randomized to active treatment groups are likely to see an improvement in their psoriasis with ARQ-151 cream at both the 0.3% and 0.15% dose levels. Subjects randomized to the vehicle arm may also see some improvement as the excipients in the vehicle appeared to have some benefit, likely because of a moisturizing effect on the subject's psoriatic plaques.

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, PHQ-8, C-SSRS and AE questioning) are adequate to protect the subjects' safety and should detect expected AEs.

Oral roflumilast has now been used for almost a decade in the treatment of COPD exacerbations and its safety record has been well-documented. The known adverse effects of oral treatment in the COPD population (nausea, diarrhea, weight loss, psychiatric AEs; see Section 7.3.2) are monitorable, the current protocol is designed to detect these adverse events and others should they occur, and provides guidance for management, as necessary, to ensure patient safety.

8 STUDY ENDPOINTS AND OBJECTIVES

8.1 Study Objectives

8.1.1 Primary Objectives

To assess the safety, pharmacokinetics and efficacy of ARQ-151 cream 0.3% and ARQ-151 cream 0.15% vs. vehicle applied QD for 12 weeks to individuals treated with 2 to 20% (inclusive) BSA of chronic plaque psoriasis.

8.2 Efficacy Endpoints

8.2.1 Primary Endpoint

The parallel groups will have analyses for safety, pharmacokinetics, and efficacy.

The Primary Efficacy Endpoint will be:

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

Investigator Global Assessment of Disease (IGA)

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

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

8.2.2 Secondary Endpoints

The secondary efficacy endpoints will include:

- IGA score of 'clear' or 'almost clear' at weeks 4, 8 and 12.
- Percent reduction in mPASI at weeks 4, 6, 8, and 12 as compared to Baseline.
- Decrease in Percent BSA affected at weeks 4, 6, 8, and 12 as compared to Baseline.
- IGA score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at weeks 4, 6, 8 and 12.
- For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (I-IGA≥2) at Baseline, 'I-IGA' score of 'clear' or 'almost clear' at weeks 4, 6, 8 and 12.
- Reduction in WI-NRS pruritus score at weeks 4, 6, 8, and 12 as compared to Baseline.
- In subjects with WI-NRS pruritus score ≥ 6 at baseline, a 4-point reduction in WI-NRS pruritus score at 4, 6, 8, and 12 weeks as compared to Baseline.
- Modified Psoriasis Area Severity Index-75 (mPASI-75) improvement at weeks 4, 6, 8, and 12 as compared to Baseline.
- Modified Psoriasis Area Severity Index-90 (mPASI-90) improvement at weeks 4, 6, 8, and 12 as compared to Baseline.
- Total PSD at weeks 4, 6, 8, and 12 as compared to Baseline
- Reduction in Itch-related Sleep Loss score at weeks 4, 6, 8, and 12 as compared to Baseline.
- Reduction in Dermatology Life Quality Index (DLQI) score at weeks 4, 6, 8, and 12 as compared to Baseline.
- Responses to the questions of PSD analyzed as improvement at weeks 4, 6, 8, and 12 as compared to Baseline.

8.2.3 Exploratory Endpoints

Exploratory Endpoints are as follows:

- Reduction in Fatigue NRS score at weeks 4, 6, 8, and 12 as compared to Baseline.
- Reduction in WPAI score at weeks 4, 6, 8, and 12 as compared to Baseline.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.3%, ARQ-151 cream 0.15% or vehicle cream QD is applied for 84 days to subjects with between 2% to 20% (inclusive) BSA of chronic plaque psoriasis.

A total of up to approximately 300 subjects will be enrolled at approximately 30 study sites in the United States and Canada. Subjects will be adult (≥18 y/o) males or females with chronic plaque psoriasis. Subjects must have an Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') at Baseline. Subjects with an IGA of 'Mild' (2) will be limited to 20% of total enrollment. Subjects with an IGA of 'Severe' (4) will be limited to 15% of total enrollment. Subjects must have at least 2% and no more than 20% Body Surface Area (BSA) of chronic plaque psoriasis. All psoriasis lesions on a subject will be treated including the face, trunk, genitals/skin folds, or limbs (excluding the scalp). The palms and soles will be treated but will not be counted towards any measurements of efficacy (IGA, BSA, mPASI). For subjects with intertriginous area involvement, and with severity of the intertriginous area lesions at least 'mild' (IGA≥2) at Baseline, 'I-IGA' score will be recorded at weeks 4, 6, 8 and 12. The same IGA used for the primary endpoint (whole body) will also be used for 'intertriginous area lesion IGA score' (I-IGA)), but only intertriginous areas will be evaluated for I-IGA, not the rest of the body.

9.2 Subject Participation

Subject participation involves a minimum of seven clinic visits:eight clinic visits including Screening, Baseline and five visits at Week 2, Week 4, Week 6, Week 8 and Week 12 of treatment and a week 14 follow-up visit (2 weeks after last dose). The interval between the Screening and Baseline visits could be up to 35 days, therefore the anticipated maximum duration of subject participation is ~19 weeks.

Upon completion of this study, participants may have the opportunity, subject to regulatory approval, to participate in an open-label extension study of up to 12 months, receiving the 0.3% concentration of drug product. The week 12 visit will be the Day 1 visit for ARQ-151-202.

For subjects who do not enter ARQ-151-202 there will be a minimum of eight clinic visits: Screening, Baseline, five visits at Week 2, Week 4, Week 6, Week 8 and Week 12 of treatment, and a week 16 follow-up visit (4 weeks after last dose). The interval between the Screening and Baseline visits could be up to 35 days, therefore the anticipated maximum duration of subject participation is ~21 weeks.

9.2.1 Randomization

Subjects will apply ARQ-151 cream 0.3% QD or ARQ-151 cream 0.15% QD or vehicle cream QD to psoriatic plaques of 2% BSA up to a maximum application area of 20% BSA.

Assignment of drug or vehicle will be made at a 1:1:1 ratio according to a computer-generated randomization list.

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

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

9.2.2 Numbering of Subjects

All screened subjects will be identified by a unique five-digit subject ID number. The first two digits correspond to the site number (assigned by the Sponsor), the next three digits correspond to the sequential order in which the subject is screened for the study (e.g., Subject ID 10001: Site 10, first subject screened 001 for that site). Site number 10 will be the first site in the study.

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

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

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

1. Participants legally competent to sign and give informed consent
2. Males and females ages 18 years and older (inclusive)
3. Clinical diagnosis of psoriasis vulgaris of at least 6 months duration as determined by the Investigator
4. Psoriasis vulgaris on the face, extremities, trunk, and/or intertriginous areas involving 2-20% (inclusive) of BSA (excluding the scalp, palms and soles).
5. An Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') at Baseline.
6. A mPASI score of at least 2 (excluding the scalp, palms and soles) at Baseline.

7. Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at Screening (Visit 1) and Baseline (Visit 2). In addition, sexually active FOCBP must agree to use at least one form of highly effective contraception throughout the trial. Highly effective forms of contraception include: oral/implant/injectable/transdermal contraceptives, intrauterine device, and partner's vasectomy. If barrier methods are used (e.g., condom with spermicide, diaphragm with spermicide), then 2 forms of conception are required. The use of abstinence as a contraceptive measure is acceptable as long as this is a consistent part of a lifestyle choice and a backup method has been identified if the subject becomes sexually active.
8. Females of non-childbearing potential should be post-menopausal with spontaneous amenorrhea for at least 12 months or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy).
9. In good health as judged by the Investigator, based on medical history, physical examination, serum chemistry labs, hematology values, and urinalysis.
10. Subjects agree not to have prolonged sun exposure during the course of the study. Tanning bed use or use of other LEDs is not allowed.
11. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule, according to the judgment of the Investigator.

9.3.2 Exclusion Criteria

1. Subjects who cannot discontinue medications and treatments prior to the Baseline visit and during the study according to Excluded Medications and Treatments (Table 1).
2. Planned excessive exposure of treated area(s) to either natural or artificial sunlight, tanning bed or other LED.
3. Subjects currently taking lithium or antimalarial drugs.
4. Planned initiation or changes to concomitant medication that could, in the opinion of the Investigator, affect psoriasis vulgaris (e.g. beta blockers, ACE inhibitors).
5. Current diagnosis of guttate, erythrodermic/exfoliative, palmoplantar only involvement, or pustular psoriasis.
6. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound efficacy measurements.
7. Known allergies to excipients in ARQ-151 cream [redacted]
8. Subjects who cannot discontinue the use of strong P-450 cytochrome inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin for two weeks prior to the baseline visit and during the study period.

9. Subjects who cannot discontinue the use of strong P-450 cytochrome inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, and rifampin for two weeks prior to the baseline visit and during the study period.
10. Subjects who have received oral roflumilast (Daxas®, Daliresp®) within the past 4 weeks.
11. Known or suspected:
    - severe renal insufficiency or severe hepatic disorders
    - hypersensitivity to component(s) of the investigational products
    - history of severe depression, suicidal ideation
12. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding.
13. Previous treatment with ARQ-151.
14. Subjects with any serious medical condition or laboratory abnormality that would prevent study participation or place the subject at significant risk, as determined by the Investigator.
15. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of study medication.
16. History of and/or concurrent condition of serious hypersensitivity (anaphylactic shock or anaphylactoid reaction) to PDE-4 inhibitors.
17. 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.
18. Subjects with active infection that required oral or intravenous administration of antibiotics, antifungal or antiviral agents within 7 days of Baseline/Day 1.
19. Subjects who are unable to communicate, read or understand the local language, or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation.

9.3.3 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.

5. Weight loss of >5% if not dieting and after consultation with the Sponsor, at the Investigator's discretion.
6. C-SSRS indicative of suicidal ideation or a PHQ-8 score ≥15, after consultation with a mental health professional, the Sponsor, and at the Investigator's discretion.
7. Requirement for use of prohibited concomitant medication 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.

9.4 Study Restrictions

9.4.1 Prohibitions and Concomitant Therapy

Prohibited medications and products are detailed in Table 1.

Table 1: Excluded Medications and Treatments

Excluded Medications and treatments	Wash out period prior to Day 1
• Systemic treatment with biological therapies with a possible effect on psoriasis vulgaris within the following time periods prior to randomization	
etanercept	4 weeks
adalimumab, infliximab	8 weeks
All other biologics	12 weeks
• Systemic treatment with all other therapies with a possible effect on psoriasis vulgaris	
Oral corticosteroids, retinoids, apremilast, methotrexate, cyclosporine and other systemic immunosuppressants	4 weeks
Topical anti-psoriasis medications (e.g., topical corticosteroids, vitamin D analogs, prescription shampoos) (except for emollients)	2 weeks
PUVA phototherapy	4 weeks
UVB	2 weeks
Systemic retinoids	12 weeks
Investigational drugs	12 weeks (biologics); 5 half-lives (orals); 2 weeks (topical)
Notes: (1) Eye drop and nasal corticosteroid preparations are allowed. Inhaled corticosteroid preparations are allowed if used for a stable condition and at a stable dose for > 28 days before screening, and are continued at the same dose throughout the study. (2) Non-medicated emollients, moisturizers and sunscreens will be allowed as used normally by the subjects. These can be applied to non-treated areas as needed and should not be used within 12 hours of a study visit. (3) Study medication should be applied at least 20 minutes before going to bed. No emollients or moisturizers should be applied on treated areas. (4) A tar-containing or dandruff shampoo (zinc pyrithione or selenium sulfide) is allowed for treatment of the scalp.	

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

9.5 Treatment

9.5.1 Drug Supplies, Packaging and Labeling

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

The Sponsor will supply sufficient quantities of the study drug (ARQ-151 cream 0.3%, ARQ-151 cream 0.15%, and matching vehicle cream) to each site to allow for completion of this study.

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

9.5.2 Blinding

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

9.5.3 Treatment Administration

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

Re-training will be conducted at subsequent visits (weeks 2, 4, 6 and 8) as needed (i.e., if the returned tube(s) weighs substantially different than the expected weight).

Subjects will be instructed to apply study medication once daily. 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 or vehicle has been applied until at least 4 hours after study drug application and preferably not until the following morning. Study medication should be applied at least 20 minutes before going to bed.

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

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

9.5.4 Treatment Compliance

Study medication tubes will be weighed at each follow-up clinic visit.

Subjects will complete a daily diary recording the date and time of each dose applied, any missed doses, and a comment section should the subjects have a comment, e.g., record potential AEs. 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 study medication 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 regiment 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 study medication applied 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.

10 STUDY PROCEDURES

10.1 Safety Assessments

The Schedule of Visits and Assessments (Section 5) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI and/or the Sponsor for reasons related to subject safety.

This study assesses the safety and efficacy of ARQ-151 cream. Safety will be determined by evaluating physical examinations, 12-lead ECGs, local tolerability assessments, vital signs/weight, clinical laboratory parameters, PHQ-8, C-SSRS and AEs as outlined in the Schedule of Visits and Assessments (Section 5). If deemed necessary, additional safety assessments will be performed at the discretion of the PI.

10.1.1 Screening

Within 35 days prior to the first dosing, subjects will be provided details of study requirements and sign an informed consent. Medical history and demographic data including sex, age, race, ethnicity, body weight (kg), and height (cm) will be recorded. Each subject will undergo psoriatic plaque assessments, a physical examination, vital sign measurements (blood pressure, heart rate, and temperature), PHQ-8, C-SSRS, and laboratory tests: hematology, chemistry, urinalysis and a pregnancy test for female subjects of child bearing potential.

All screened subjects will receive a screening number and be entered into the electronic subject tracking system.

10.1.2 Physical Examination

Physical examinations will be performed as follows:

Screening, Baseline and Week 12.

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

10.1.3 Vital Signs, Height and Weight

Vital signs will be collected at timepoints noted below:

Blood pressure, heart rate, and temperature will be measured at Screening, Baseline, Weeks 2, 4, 6, 8, 12 and 16 (if applicable).

Height will be collected at Baseline only.

Weight will be collected at Baseline, Weeks 4, 6, 8 and 12. Subject to void prior to weight being taken and remove any jackets, outerwear and shoes. Remove any objects of significant weight (i.e. cell phones, wallet, key chains). A 5% weight loss should be reported to the medical monitor.

10.1.4 12-Lead ECGs

12-lead ECGs will be performed as follows:

Screening, Week 4 and 12.

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.

10.1.5 Laboratory Tests

All tests listed below will be performed as follows:

Screening, Baseline, Weeks 4 and 12.

All tests listed in Table 2 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. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Table 2.: Laboratory Tests

Hematology	**Serum Chemistry**
• Hemoglobin • Hematocrit • Total and differential leukocyte count • Red blood cell count with indices and morphology • Platelet count	• Blood Urea Nitrogen • Bilirubin (total and direct) • Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Albumin • Sodium • Potassium • Chloride • Glucose • Creatinine

Laboratory Tests, continued

Urinalysis

- pH
- Specific gravity
- Protein*
- Glucose
- Ketones
- Bilirubin
- Blood*
- Nitrite*
- Urobilinogen
- Leukocyte esterase*

Additional Tests

- Urine pregnancy test**
  (for females of child bearing potential only)

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

** At screening, baseline, Weeks 4, 8 and 12 for FOCBP only

10.1.6 Patient Health Questionnaire depression scale (PHQ-8)

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

Screening, Baseline, Weeks 4, 8, and 12

Subjects will complete PHQ-8 questionnaire.

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

The PHQ-8

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

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

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

Five severity categories of depression are defined as follows:

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

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

C-SSRS Assessments will be performed as follows:

Screening, Baseline, Weeks 4, 8, and 12.

The administration schedule of the C-SSRS will be:

- The Baseline-Screening version (Appendix 2) will be used at Screening to provide a pre-treatment assessment baseline.
    - If a subject has a score greater than 0 in suicidal ideation, this is important and may indicate the need for mental health intervention. The investigator should give consideration to not enrolling the subject in the study.
- On all subsequent visits, the Since Last Visit version (Appendix 3) will be used.
    - Any score greater than 0 in the suicidal ideation score is important and may indicate the need for mental health intervention and consideration be given to discontinuation from study drug. This should result in prompt referral to a mental health professional and/or possibly the emergency room. The Medical Monitor should be contacted.

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

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

10.1.8 Local Tolerability Assessments

The Investigator Local Tolerability Assessment will be performed as follows:

Baseline, Weeks 4, 8 and 12

Application site reactions will be graded at the timepoints outlined in the Schedule of Visits and Assessments (Section 5). Irritation reactions are graded using the scale detailed in the following section (Berger-1982). Reactions at the site of product application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's psoriasis.

The investigator assessments will be conducted by the investigator prior to 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

The Subject Local Tolerability Assessment will be performed as follows:

Baseline, Weeks 4, 8 and 12

This assessment will be administered by the site 10 to 15 minutes after study drug application in the clinic at Baseline and at Weeks 4, 8 and 12.

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

10.1.9 Adverse Events

Adverse events (AEs) will be collected beginning at informed consent and assessed as follows:

Screening, Baseline, Weeks 2, 4, 6, 8, 12 and 16 (if applicable)

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

For further details on Adverse Events please see Section 10.4.

10.2 Efficacy Evaluations

10.2.1 Investigator's Global Assessment (IGA)

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

Screening, Baseline, Weeks 2, 4, 6, 8, 12 and 16 (if applicable)

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

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

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

Investigator Global Assessment of Disease (IGA)

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

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

For subjects with intertriginous area involvement of at least 'mild' severity by IGA (I-IGA≥2) at Baseline (using the IGA scale shown above but evaluating intertriginous areas ONLY and NOT whole body involvement), an IGA for the intertriginous region alone (I-IGA) will be recorded at weeks 2, 4, 6, 8, 12 and 16 (if applicable).

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

10.2.2 Modified Psoriasis Area and Severity Index (mPASI)

mPASI Assessments will be performed as follows:

Screening, Baseline, Weeks 2, 4, 6, 8, 12 and 16 (if applicable)

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

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

mPASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease).
The body is divided into four sections (head (h) (10% of a person's skin); arms (a) (20%); trunk (t) (30%); legs (l) (40%)). Each of these areas is scored by itself, and then the four scores are combined into the final 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 - see below for Modified PASI (mPASI) for this grade
2. 10–29% of involved area
3. 30–49% of involved area
4. 50–69% of involved area
5. 70–89% of involved area
6. 90–100% of involved area

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

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

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

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

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

10.2.3 Body Surface Area (BSA)

BSA Assessments will be performed as follows:

Screening, Baseline, Weeks 2, 4, 6, 8, 12 and 16 (if applicable)

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

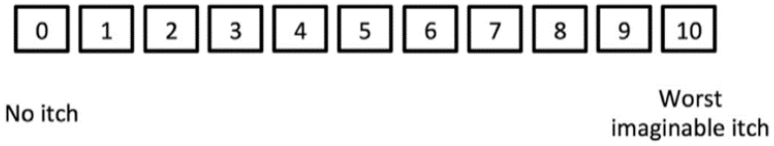
Note: Palms and soles will be treated with study medication, but will not be counted towards IGA, mPASI, or BSA assessments.

10.2.4 Worst Itch Numerical Rating Scale (WI-NRS)

WI-NRS Assessments will be performed as follows:

Screening, Baseline, Weeks 2, 4, 6, 8 and 12

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). The WI-NRS will be determined by asking the subject's assessment of worst itch over the past 24 hours. The scale is from '0 to 10' ("no itch" to "worst imaginable itch"). Subjects will complete the WI-NRS pruritus assessment.



10.2.5 Fatigue NRS

Fatigue NRS Assessments will be performed as follows:

Screening, Baseline, Weeks 2, 4, 6, 8 and 12

Subjects will complete circle the number on the Fatigue NRS assessment that best fits their fatigue severity. Fatigue severity will be measured using a unidimensional 11-point numeric rating scale (NRS) with anchors of 0 (No Fatigue) and 10 (Fatigue as bad as it can be) for the intensity during the previous 24-hour period. The words 'no fatigue' and 'Fatigue as bad as it can be' corresponding to the anchors 0 and 10, respectively, will be placed under the NRS scale.

No fatigue — Fatigue as bad as it can be

10.2.6 Work Productivity and Activity Impairment (WPAI)

WPAI Assessments will be completed at the following:

Screening, Baseline, Weeks 2, 4, 6, 8 and 12

Subjects will complete the WPAI questionnaire. Please see Appendix 1 for the WPAI.

10.2.7 Itch-Related Sleep Loss

Itch-Related Sleep Loss Assessments will be performed as follows:

Screening, Baseline, Weeks 2, 4, 6, 8 and 12

Subjects will complete the itch-related sleep loss numerical rating scale (NRS) assessment. Itch-related sleep loss severity will be measured using a unidimensional rating scale (NRS) with anchors at 0 (no itch-related sleep loss) and 10 (itch-related sleep loss as bad as it could be) for the intensity during the previous 24-hour period. The words 'no itch-related sleep loss' and 'itch-related sleep loss as bad as it could be' correspond to the anchors or 0 and 10, respectively, and will be placed on the NRS scale.

No itch-related sleep loss — Sleep loss as bad as it can be

10.2.8 Psoriasis Symptom Diary (PSD)

The PSD will be completed as follows:

Screening, Baseline, Weeks 2, 4, 6, 8, 12 and 16 (if applicable)

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

10.2.9 Dermatology Life Quality Index (DLQI)

The DLQI will be completed as follows:

Screening, Baseline, Weeks 2, 4, 6, 8 and 12

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

10.2.10 Dermal Imaging

Optional photography will be performed at selected centers only at Baseline, Weeks 4, 6, 8 and 12.

10.3 Pharmacokinetics Assessment

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

Baseline, Weeks 4 and 12

Plasma PK assessments will be performed on all subjects.

PK draws will be collected while the subject is having serum chemistries drawn. The draws will be pre-dose drug application in the clinic. The tube weight will be collected prior to the application and after the application. Ensure study medication is not applied in the area where PK will be drawn.

Approximately 30 subjects, continuing to the Week 16 visit, with greater than or equal to 5% BSA at the Baseline visit, will have the option to participate in additional PK draws at 72 hours (3 days), 120 hours (5 days), 168 hours (7 days) and 216 hours (9 days) post the last treatment application. For the 72 hour timepoint, the PK draw should be +/- 2 hours of the last study drug application. The 5, 7 and 9 day draws should be completed in the morning, before noon at the site.

10.4 Adverse Events

10.4.1 Adverse Event Definition

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

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

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

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

10.4.2 Serious Adverse Event

The definitions and reporting requirements of Health Canada/the Food and Drug Administration (FDA)/ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A will be adhered to. If any AEs are serious, as defined by ICH Guidelines for Clinical Safety, required procedures will be followed. All SAEs will be reported to the Sponsor 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 ERB/IRB will be notified of the Alert Reports as per HC, FDA, ICH and the IRB/ERB's policies and procedures.

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

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

Hospitalization does not include the following:

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

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

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

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

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

If a SAE occurs to a subject on this study, contact the Sponsor personnel listed in Section 2 within one business day of knowledge of event.

10.4.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

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

10.4.4 Safety Review

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

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

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

10.4.5 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 (e.g., 21.0 or higher).

10.5 Reporting Pregnancy

During the study, all subjects should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, 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.

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

Any pregnancy complication or premature terminations including miscarriage, spontaneous abortion or elective termination of a pregnancy for medical reasons will be reported as an SAE, as described in Section 10.4.2. Should the pregnancy result in a congenital abnormality or birth defect, a separate 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 is related to the in-utero exposure to the study treatment should also be reported.

10.6 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 6 for details.

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.

A subject with a PHQ-8 score of '15' or above should be referred promptly to a mental health care professional and consideration be given to discontinuation from 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. Given the excellent local toleration in the Phase 1/2a study, such reactions are possible, but unlikely.

10.6.1 Emergency Unblinding

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

11 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.

11.1 Statistical Methods

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

All statistical processing will be performed using SAS® (Version 9.4) unless otherwise stated. No interim efficacy analyses are planned.

Descriptive statistics will be used to provide an overview of the efficacy, safety and pharmacokinetic results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentage will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics

will include n (number of subjects), mean, standard deviation (SD), median, minimum, and maximum.

Missing efficacy data will be estimated by a mixture of linear interpolation and last observation carried forward for the cases were linear interpolation is not computationally possible.

P-values of less than 0.05 will be considered statistically significant based on a two-sided test unless otherwise specified. No adjustment will be made for multiplicity.

11.1.1 Determination of Sample Size

A sample size of approximately 300 subjects are planned for the study.

Approximately 100 subjects will receive ARQ-151 cream 0.3% QD; approximately 100 subjects will receive ARQ-151 cream 0.15% QD; and approximately 100 subjects will receive matching vehicle cream QD. The randomization scheme will be 1:1:1 (ARQ-151 cream 0.3% QD: ARQ-151 cream 0.15% QD: matching vehicle QD).

The sample size was not powered based on data for the primary endpoint to provide statistical significance because of the absence of previous primary endpoint data. However, based on efficacy data from the Phase 1/2a study, this Phase 2b study is expected to provide reliable information regarding the efficacy and safety of the drug products.

11.1.2 Subjects to Analyze

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

The Intent-to-Treatment (ITT) population will include all randomized subjects.

Per-Protocol (PP) Population will include all subjects who are in the safety population, were at least 80% compliant with study medication application, and showed no other serious deviations from the study protocol.

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

11.1.3 Interim Analysis

No interim efficacy analyses are planned.

11.1.4 Background and Demographic Characteristics

Descriptive statistics will be used to summarize demographic characteristics (age, sex, and race) and background characteristics for the enrolled subjects. Past/coexistent medical history information and physical examination observations and vital signs information for all randomized subjects will be presented in a by-subject listing.

11.1.5 Study Medication Compliance

The number of study drug applications by each subject based on diary data will be summarized using summary statistics (mean, standard deviation [SD], median, minimum, and maximum), and categorically.

The amount of study medication used by each subject based on tube weight will be summarized by treatment using summary statistics (mean, SD, median, minimum, and maximum), and categorically.

11.2 Efficacy Evaluation

11.2.1 Primary Efficacy Endpoint

The primary efficacy variable in this study is success in Investigator Global Assessment (IGA) of disease severity, defined as an IGA of 'Clear' or 'Almost Clear' at Week 6.

The primary endpoint will be analyzed with a logistic regression with a factor of treatment group. Statistical comparison between the active treatment arms and vehicle arms will be facilitated by using contrasts.

11.2.2 Secondary Endpoints

The secondary efficacy endpoints will include:

- IGA score of 'clear' or 'almost clear' at weeks 4, 8 and 12.
- Percent reduction in mPASI at weeks 4, 8, and 12 as compared to Baseline.
- Decrease in Percent BSA affected at weeks 4, 6, 8, and 12 as compared to baseline.
- IGA score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at weeks 4, 6, 8 and 12.
- For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (I-IGA≥2) at Baseline, 'I-IGA' score of 'clear' or 'almost clear' at weeks 4, 6, 8 and 12.
- Reduction in WI-NRS pruritus score at weeks 4, 6, 8, and 12 as compared to Baseline.
- In subjects with WI-NRS pruritus score ≥ 6 at baseline, a 4-point reduction in WI-NRS pruritus score at 4, 6, 8, and 12 weeks as compared to Baseline.
- Modified Psoriasis Area Severity Index-75 (mPASI-75) improvement at weeks 4, 6, 8, and 12 as compared to Baseline.
- Modified Psoriasis Area Severity Index-90 (mPASI-90) improvement at weeks 4, 6, 8, and 12 as compared to Baseline.
- Total PSD at weeks 4, 6, 8, and 12 as compared to Baseline.

- Reduction in Itch-related Sleep Loss score at weeks 4, 6, 8, and 12 as compared to Baseline.
- Reduction in Dermatology Life Quality Index (DLQI) score at weeks 4, 6, 8, and 12 as compared to Baseline.
- Responses to the questions of PSD analyzed as improvement at weeks 4, 6, 8, and 12 as compared to Baseline.

The dichotomized IGA analyses will be analyzed with logistic regression similar to the primary endpoint. The remainder of the endpoints will be considered continuous and analyzed with an analysis of variance with a factor of treatment group. Statistical comparison between the active treatment arms and vehicle arms will be facilitated by using contrasts.

mPASI will be analyzed for all subjects with the modification that, for subjects with < 10% of an involved anatomic area, the actual percentage of the anatomical area involved is used rather than a '0' or '1' (e.g. for 5% area involved, 0.5 would be used for the calculation).

11.2.3 Exploratory Endpoints

Exploratory Endpoints are as follows:

- Reduction in Fatigue NRS score at weeks 4, 6, 8, and 12 as compared to Baseline.
- Reduction in WPAI score at weeks 4, 6, 8, and 12 as compared to Baseline.

Only descriptive statistics will be used to analyze these endpoints.

11.3 Safety Evaluation

The following analyses will be performed; however, no formal inferential statistics will be done on safety assessments.

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

11.3.1 Adverse Events

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

Comparisons between treatment groups will be made by tabulating the frequency of subjects with one or more treatment-emergent AEs (classified into MedDRA terms) during the study.

Serious adverse events (SAEs) will be listed by subject. SAEs will be summarized by treatment group, 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.

A subject-by-subject treatment-emergent AE (TEAE) data listing, including verbatim term, preferred term, treatment, severity, and relationship to study drug, will be provided.

Medical history will be listed by subject. Physical examinations and 12-lead ECGs will be performed at screening, baseline and end-of-study which will be listed by subject.

Vital signs will be tabulated by visit and treatment group.

ECGs will be tabulated by visit and treatment group.

Routine blood chemistries will be obtained throughout the study and the results summarized by parameter, visit and treatment group.

11.3.2 Local Tolerance Assessments

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

11.3.3 Medical History and Physical Examinations

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

Physical examination findings for all subjects will be presented in a by-subject listing. Changes in physical examinations will be described in the text of the final report.

11.3.4 PHQ-8

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

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

11.3.5 C-SSRS

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

11.3.6 Clinical Laboratory Results and Vital Signs/Weight Measurements

All clinical laboratory results and vital signs measurements and their change from baseline (pre-dose), will be summarized 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.

11.3.7 Prior and Concomitant Medications

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

11.4 Patient Reported Outcomes Analyses

11.4.1 WI-NRS, Fatigue NRS, Itch-Related Sleep Loss

The NRS scales will be analyzed for change from baseline in itch severity (WI-NRS), fatigue NRS, and itch-related sleep loss.

11.4.2 Work Productivity and Activity Impairment (WPAI) Questionnaire

The WPAI yields four types of scores:

1. Absenteeism (work time missed)

2. Presenteeism (impairment at work / reduced on-the-job effectiveness)

3. Work productivity loss (overall work impairment / absenteeism plus presenteeism)

4. Activity Impairment

11.4.3 Dermatology Life Quality Index (DLQI)

The DLQI will be analyzed by evaluation of the reduction in total score at weeks 4, 6, 8, and 12 as compared to Baseline.

11.4.4 Psoriasis Symptom Diary (PSD)

The PSD will be analyzed as the improvement in responses to the questions of PSD weeks 4, 6, 8, and 12 as compared to Baseline.

11.5 Pharmacokinetic Analysis

Plasma drug concentrations at pre-dose will be summarized using descriptive statistics, reporting n, mean, standard deviation, median, minimum, and maximum.

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 5).

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

12 STUDY ADMINISTRATION

12.1 Ethics

12.1.1 Ethics Review Board

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

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

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

12.1.2 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).

12.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date 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.

Subjects will be given a signed copy of their ICF.

12.2 Study Monitoring

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

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

12.3 Data Quality Assurance

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

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

12.3.1 Verification of Blinding

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

12.4 Data Handling and Record Keeping

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

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

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

12.5 Protocol Amendments and Deviations

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

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

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

12.6 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).

12.7 Publication Policy

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

13 REFERENCES

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14 APPENDICES

Appendix 1: Work Productivity and Activity Impairment Questionnaire (WPAI)

Work Productivity and Activity Impairment Questionnaire:
Specific Health Problem V2.0 (WPAI:SHP)

The following questions ask about the effect of your psoriasis on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your psoriasis? *Include hours you missed on sick days, times you went in late, left early, etc., because of your psoriasis. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your psoriasis affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If psoriasis affected your work only a little, choose a low number. Choose a high number if psoriasis affected your work a great deal.

   Consider only how much psoriasis affected productivity while you were working.

Psoriasis had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	Psoriasis completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your psoriasis affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If psoriasis affected your activities only a little, choose a low number. Choose a high number if psoriasis affected your activities a great deal.

Consider only how much psoriasis affected your ability
to do your regular daily activities, other than work at a job.

Psoriasis had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	Psoriasis completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

Appendix 2: Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

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

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

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

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

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

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION

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

Since Last Visit

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

Yes ☐ No ☐

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

Yes ☐ No ☐

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

Yes ☐ No ☐

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

Yes ☐ No ☐

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

Yes ☐ No ☐

INTENSITY OF IDEATION

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

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

Most Severe

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

____

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

____

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

____

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

____

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

____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

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

Appendix 4: Psoriasis Symptom Diary (PSD)

Psoriasis Symptom Diary (PSD)

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

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

12 Overall, how bothered were you by your psoriasis scaling over the past 24 hours?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6 7 8 9 10

Not bothered at all — **As bothered as you can imagine**

13 Overall, how noticeable did you think the colour of your psoriasis-affected skin was over the past 24 hours?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6 7 8 9 10

Not at all noticeable — **As noticeable as you can imagine**

14 Overall, how much did you try to hide your psoriasis-affected skin over the past 24 hours?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6 7 8 9 10

Did not try to hide at all — **Totally avoided being seen by others**

15 Overall, how much did your psoriasis cause you to avoid activities with other people over the past 24 hours?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6 7 8 9 10

You did not avoid other people — **Avoided other people as much as you ever have**

16 Overall, how embarrassed were you because of your psoriasis over the past 24 hours?

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6 7 8 9 10

No embarrassment — **As embarrassed as you can imagine**

Appendix 5: Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX

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

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

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

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

Please check you have answered EVERY question. Thank you.

Appendix 6: National Institute of Allergy and Infectious Diseases, Division of Microbiology and Infectious Diseases (DMID) Toxicity Table for Use in Trials Enrolling Healthy Adults (2014) Modified

ABBREVIATIONS USED IN FOLLOWING TABLES:

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

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

ESTIMATING SEVERITY GRADE

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

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

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

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

LABORATORY RANGES

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

CLINICAL ADVERSE EVENTS

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

[a] Inclusion dependent upon protocol requirements

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

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

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

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

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

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

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

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

[a] Low, High, Not Graded.
[b] If initial boundary of grade 1 has gap from reference range or eligibility range, calculations based on the New England Journal of Medicine (NEJM) reference ranges.

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

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