Study Number:	ARQ-151-202
NCT #:	NCT03764475
Official Title:	A Phase 2, Multicenter, Open-Label Extension Study of the Long-Term Safety of ARQ-151 Cream 0.3% in Adult Subjects With Chronic Plaque Psoriasis Who Have Completed Preceding Study ARQ-151-201 Phase 2 Randomized Controlled Trial (Cohort 1) and Non-ARQ-151-201 Subjects (Cohort 2)
Protocol Date:	12-Apr-2019

Protocol ARQ-151-202

A Phase 2, Multicenter, Open-Label Extension Study of the Long-Term Safety of ARQ-151 Cream 0.3% in Adult Subjects with Chronic Plaque Psoriasis who have Completed Preceding Study ARQ-151-201 Phase 2 Randomized Controlled Trial (Cohort 1) and non-ARQ-151-201 Subjects (Cohort 2)

ORIGINAL ISSUE DATE: **November 21, 2018**

AMENDMENT 1: **April 12, 2019**

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

Study Number:	ARQ-151-202
NCT #:	NCT03764475
Official Title:	A Phase 2, Multicenter, Open-Label Extension Study of the Long-Term Safety of ARQ-151 Cream 0.3% in Adult Subjects With Chronic Plaque Psoriasis Who Have Completed Preceding Study ARQ-151-201 Phase 2 Randomized Controlled Trial (Cohort 1) and Non-ARQ-151-201 Subjects (Cohort 2)
Protocol Date:	12-Apr-2019

1 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

TITLE:	"**A Phase 2, Multicenter, Open-Label Extension Study of the Long-Term Safety of ARQ-151 Cream 0.3% in Adult Subjects with Chronic Plaque Psoriasis who have Completed Preceding Study ARQ-151-201 Phase 2 Randomized Controlled Trial (Cohort 1) and non-ARQ-151-201 Subjects (Cohort 2)**"
PROTOCOL NUMBER:	**ARQ-151-202**
SPONSOR:	Arcutis, Inc. [redacted]
ORIGINAL ISSUE DATE:	November 21, 2018
AMENDMENT 1:	April 12, 2019
SPONSOR'S REPRESENTATIVE:	[redacted]
PRINCIPAL INVESTIGATO AND CLINICAL SITE:	[redacted]

SITE INVESTIGATOR SIGNATURE PAGE

TITLE: **"A Phase 2, Multicenter, Open-Label Extension Study of the Long-Term Safety of ARQ-151 Cream 0.3% in Adult Subjects with Chronic Plaque Psoriasis who have Completed Preceding Study ARQ-151-201 Phase 2 Randomized Controlled Trial (Cohort 1) and non-ARQ-151-201 Subjects (Cohort 2)"**

PROTOCOL NUMBER: **ARQ-151-202**

SPONSOR: Arcutis, Inc.
[redacted]

ORIGINAL ISSUE DATE: November 21, 2018

AMENDMENT 1: April 12, 2019

I have received and read the investigator's brochure for ARQ-151.

I have read this protocol and commit to conduct the study as outlined herein, in accordance with the current Good Clinical Practices (cGCPs). Any deviations will be agreed to in writing between the Sponsor/CRO and me.

I agree that I or my designee will completely inform all subjects in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with cGCPs and regulatory authority requirements.

I will be responsible for maintaining each subject's consent form in the study file and providing each subject with a signed copy of the consent form.

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

[redacted] _____

[redacted] _____

[redacted]

PROTOCOL REVISION HISTORY

Version/Date	Description
ARQ-151-202 Version 1 November 21, 2018	Original protocol
ARQ-151-202 Amendment 1 April 12, 2019	• Added protocol revision history section • Updated Sponsor address • Added I-IGA and mPASI to secondary endpoints throughout • Added Cohort 2 (non ARQ-151-201) subjects throughout • Added phone visits at Weeks 18, 30 and 44 and added instructions for the subject to call the site prior to restarting study medication • Added additional inclusion and exclusion criteria for Cohorts 1 and 2 • Updated exclusion criteria to exclude moderate to severe liver impairment (Child-Pugh B or C) • Added Screening visit for non-ARQ-151-201 subjects including the Screening C-SSRS • Added Table 2, Wash out period for Medications and Treatments for Cohort 2 • Added Appendix 1 Columbia-Suicide Severity Rating Scale (C-SSRS) Baseline/Screening Version • Updated Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit Version to Appendix 2 and updated 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 to Appendix 3 • Editorial and administrative changes throughout the protocol to clarify language and formatting to improve readability.

2 KEY CONTACTS FOR THE STUDY

Sponsor Contact for Serious Adverse Event Reporting	[redacted]
Medical Monitor	[redacted]
Managing CRO	[redacted]
Certified Clinical Laboratory	[redacted]
Data Management / Statistical Analysis	[redacted]

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4 SYNOPSIS

Compound	ARQ-151 cream 0.3%
IND	135,681
Clinical Indication	Chronic Plaque Psoriasis
Study Phase and Type	• Phase 2 (2b) • 52 week, long-term safety study of ARQ-151 cream 0.3%
Study Objectives	To assess long-term safety in a multicenter, open-label, 52-week study in subjects treated with ARQ-151 cream 0.3% after completing a 12-week Phase 2b study (ARQ-151-201) Cohort 1 and non-ARQ-151-201 subjects (Cohort 2).
Study Endpoints	Primary Endpoints • Occurrence of treatment emergent AEs (TEAEs) • Occurrence of Serious Adverse Events (SAEs) Secondary Endpoints • Proportion (%) of subjects achieving an Investigator Global Assessment (IGA) of clear or almost clear, as observed at Week 12 and subsequent scheduled visits. • Proportion (%) of subjects who achieve 'clear' IGA, I-IGA (if applicable) **and** mPASI (Modified Psoriasis Area Severity Index) score and stop treatment to all lesions, time to re-starting study drug (duration of response). • Proportion (%) of applicable subjects with intertriginous area involvement, 'I-IGA' score of 'clear' or 'almost clear' at week 12 and subsequent visits. • Proportion of subjects who achieve a 75% reduction in mPASI at Week 12 and subsequent scheduled visits as compared to baseline.
Summary of Study Design	Open-label, long-term safety study of ARQ-151 cream 0.3% in subjects with chronic plaque psoriasis involving up to 25% total BSA. Cohort 1 eligible subjects will enroll into the long-term safety study on the same day as the Week 12 visit for the previous study (ARQ-151-201). Cohort 2 eligible subjects will enroll on Day 1 of this study. Study medication will be applied by the qualifying subjects topically QD for 52 weeks at home. Periodic clinic visits will include assessments for clinical safety, application site reactions evaluated in the clinic using the method of Berger and Bowman, and disease improvement or progression.

Blinding	• This study is open label • All participants will receive ARQ-151 cream 0.3%
Countries:	United States and Canada
Number of sites	Approximately 30 sites
Study Population	Subjects who have completed the 12 week treatment period in study ARQ-151-201 and are willing to enroll in this 52-week extension study (Cohort 1) and qualified non-ARQ-151-201 subjects (Cohort 2).
Inclusion Criteria All Subjects	1. Participants legally competent to sign and give informed consent 2. Males and females ages 18 years and older 3. Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at all study visits. In addition, sexually active FOCBP must agree to use at least one form of highly effective contraception throughout the trial. Highly effective forms of contraception include: oral/implant/injectable/transdermal contraceptives, intrauterine device, or partner's vasectomy. If barrier methods are used (e.g., condom with spermicide, diaphragm with spermicide), then 2 forms of 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. 4. Post-menopausal women with spontaneous amenorrhea for at least 12 months or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy).
Inclusion Criteria Cohort 1 Only	5. Subjects with chronic plaque psoriasis who met eligibility criteria for ARQ-151-201, successfully completed ARQ-151-201 through Week 12, and are able to enroll into this long-term safety study on the Week 12 visit of the previous study (ARQ-151-201).
Inclusion Criteria Cohort 2 Only	6. Clinical diagnosis of psoriasis vulgaris of at least 6 months duration as determined by the Investigator. 7. Psoriasis vulgaris on the face, extremities, trunk, and/or intertriginous areas involving 2% to 25% of BSA (excluding the scalp, palms and soles). 8. An Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') at Day 1.
Exclusion Criteria All Subjects	1. Subjects that use any Excluded Medications and Treatments (see Table 1). 2. Subjects currently taking lithium or antimalarial drugs. 3. Planned initiation or changes to concomitant medication that could,

	in the opinion of the Investigator, affect psoriasis vulgaris (e.g. beta blockers, ACE inhibitors). 4. Current diagnosis of guttate, erythrodermic/exfoliative, palmoplantar, or pustular psoriasis. 5. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound safety or efficacy measurements. 6. Known allergies to excipients in ARQ-151 cream [redacted] 7. 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 during the study period. 8. Subjects who cannot discontinue the use of strong P-450 cytochrome inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, and rifampin during the study period. 9. Subjects who have received oral roflumilast (Daxas®, Daliresp®) within the past 4 weeks. 10. Known or suspected: • severe renal insufficiency or moderate to severe liver impairment (Child-Pugh B or C) • hypersensitivity to component(s) of the investigational products • history of severe depression, suicidal ideation 11. Females who are pregnant, wishing to become pregnant during the study, or are breast-feeding. 12. 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. 13. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of study medication. 14. History of and/or concurrent condition of serious hypersensitivity (anaphylactic shock or anaphylactoid reaction) to PDE-4 inhibitors. 15. 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.

	16. Subjects who are unable to communicate, read or understand the local language, or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation.
Exclusion Criteria Cohort 1 Only	17. Subjects who experienced an ARQ-151 treatment-related AE or a serious AE (SAE) that precluded further treatment with ARQ-151 cream in Study ARQ-151-201.
Exclusion Criteria Cohort 2 Only	18. Subjects who cannot discontinue medication and treatments prior to the Day 1 visit according to Excluded Medications and Treatments (Table 2).
Number of Subjects	Up to approximately 300 subjects (Cohort 1) Up to approximately 100 subjects (Cohort 2)
Duration of Participation for Subjects	Approximately 52 weeks
Study Products	ARQ-151 drug product will be supplied as a 0.3% cream in a squeezable tube.
Planned Dose Level	• Subjects with up to 25% total BSA of psoriatic lesions will receive ARQ-151 cream 0.3% to be applied QD topically to all lesions. • Application will be to all areas affected including the face and intertriginous/genital regions (except for the scalp). • Subjects may stop treatment to lesions/areas that have cleared and completely resolved. Treatment may resume in these or new areas should psoriatic lesions emerge during the study. • If treatment is judged by the Investigator as being ineffective, then the subject may be withdrawn from the study at any time.
Safety Assessments	Safety will be monitored through application site assessments in the clinic using the method of Berger and Bowman, clinical laboratory testing, 12-lead ECGs, PHQ-8, C-SSRS and AEs.
Safety Analysis	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. Physical Examinations Vital signs will be collected at all study visits. Physical examinations and 12-lead ECGs will be collected periodically throughout the study. Clinical Laboratory Results Routine blood chemistries will be obtained at all study visits. Urine

	pregnancy tests will be collected periodically throughout the study. Patient Health Questionnaires PHQ-8 and C-SSRS questionnaires will be completed by the subjects at all study visits. 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.
Efficacy Analysis	The efficacy endpoints will be defined as: • Proportion (%) of subjects achieving an Investigator Global Assessment (IGA) of clear or almost clear, as observed at Week 12 and subsequent scheduled visits. • In subjects who achieve 'clear' IGA, I-IGA and MPASI scores and stop treatment to all lesions, time to re-starting study drug (duration of response) • Proportion (%) of applicable subjects with intertriginous area involvement, 'I-IGA' score of 'clear' or 'almost clear' at week 12 and subsequent visits • Proportion (%) of subjects achieving a 75% reduction from Baseline of Modified Psoriasis Area Severity Index-75 (mPASI-75) at weeks 12, 24, 36 and 52 as compared to Baseline.
Power and Sample Size	Up to approximately 300 subjects are planned for Cohort 1 and up to approximately100 subjects are planned for Cohort 2. The sample size will provide a sufficient population size to evaluate the long-term safety of ARQ-151 cream 0.3% at 52 weeks.
Statistical Analysis:	This study is not intended to assess efficacy, but rather the IGA, I-IGA and mPASI are included to determine the need for treatment and subsequent re-treatment after treatment course in Study ARQ-151-201 or Study ARQ-151-202. Certain efficacy data and endpoints will, however, be summarized. Descriptive statistics will be presented for the endpoint data collected in the clinical trial. For analysis of the proportion (%) of subjects achieving an IGA of clear or almost clear at week 52, as observed, no imputation for missing data will be performed. The proportion of successes for the secondary variables of I-IGA and 75% reduction in mPASI will be tabulated. The duration of response will be analyzed using the Kaplan-Meier method. No formal inferential statistics will be performed on safety assessments. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data.

5 SCHEDULE OF VISITS AND ASSESSMENTS

STUDY EVENTS FLOW CHART:

Study Procedure	Washout Cohort 2	Day 1 (Cohort 2)	Wk 4	Wk 12	Wk 18	Wk 24	Wk 30	Wk 36	Wk 44	Wk 52
Visit	**Screening**	**Visit 7 (Week 12) of ARQ-151-201 Study (Cohort 1)**	**1**	**2**	**Phone Visit**	**3**	**Phone Visit**	**4**	**Phone Visit**	**5**
Visit Window	-35 days		+/- 3 days	+/- 5 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days	+/- 7 days
Informed consent	X[i]	X[i]								
Physical examination[a]		X[h]				X				X
I/E criteria	X	X								
Hematology, Serum Chemistries, and Urine Analysis	X	X[h]	X	X		X		X		X
12 lead ECG	X	X[h]				X				X
Vital signs, height, weight[b]		X[h]	X	X		X		X		X
IGA[c], I-IGA, mPASI and BSA[c]	X	X[h]	X	X		X		X		X
C-SSRS, PHQ-8	X	X[h]	X	X		X		X		X
Urine pregnancy test[d]	X	X[h]	X	X		X		X		X
Local Tolerability Assessment[e]		X[h]	X	X		X		X		X
Dispense study medication kit[f]		X	X	X		X		X		
Dispense/review diary		X	X	X		X		X		X
Weigh study medication		X	X	X		X		X		X
Adverse event assessment[g]	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X

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

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

[c] IGA 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 at each visit. A body diagram should be used to record areas of psoriasis involvement.

[d] 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.

[e] Local tolerability will be assessed by the clinic using the method of Berger and Bowman.

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

[g] 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.

[h] For Cohort 1, this data will be obtained from Week 12 of ARQ-151-201 Study and used as the Day 1 data for this long-term safety study (ARQ-151-202). If after ARQ-151-201 completion, subjects should complete the screening visit procedures. The Baseline values for Safety tabulations will be taken from the day that the subject received their first active study drug (across studies ARQ-151-201 and ARQ-151-202). Baseline values for efficacy will be those recorded on Day 1 of Study ARQ-151-201. For Cohort 2, Baseline evaluations will be obtained for all procedures and the Baseline/Screening version of the C-SSRS will be utilized at Screening. For Cohort 2, labs that are collected within 14 days of Baseline do not need to be repeated.

[i] For Cohort 1, the consent will be signed after completion of Week 12 in ARQ-151-201. Cohort 2 will sign consent prior to any study-related procedures at the Screening Visit.

6 ABBREVIATIONS

Acronym	Full Name
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
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
IND	Investigational New Drug
IRB	Institutional Review Board
LED	Light Emitting Device
IWRS	Interactive Web Response System
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

Acronym	Full Name
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

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. The study sponsor is conducting nonclinical studies in which roflumilast is applied dermally to supplement the information available through the registration and labeling of

oral roflumilast and specifically to support dermal clinical trials. Summaries of these new data from dermal studies and existing data from the prior oral/systemic studies follow. In addition, since roflumilast N-oxide is a major active metabolite, some studies were conducted on the metabolite.

The dermal nonclinical program for ARQ-151 cream followed current International Conference on Harmonisation (ICH) guidelines. [redacted]

7.2.1 Repeat-Dose Toxicity

[redacted]

[redacted]

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

7.2.3 Reproductive Toxicity

[redacted]

[redacted]

7.2.4 Genotoxicity

[redacted]

7.2.5 Carcinogenicity

[redacted]

7.2.6 Special Toxicity: Local Tolerance of Topical Formulation

[redacted]

7.2.7 Conclusions on Toxicity Findings

[redacted]

[redacted]

[redacted]

7.3 Clinical Studies

7.3.1 Topical Roflumilast Cream

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

7.3.2 Phase 1/2a Study of Topical ARQ-151 Cream

[redacted]

[redacted]

- [redacted]

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

- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

7.3.3 Phase 2b Study of Topical ARQ-151 Cream

[redacted]

7.3.4 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 clinical trials and also during post-marketing experience (Michalski 2012).

[redacted]

7.4 Rationale for Development

[redacted]

[redacted]

7.4.1 Dose Selection

[redacted]

7.4.2 Risks and/or Benefits to Subjects

[redacted]

8 STUDY OBJECTIVE AND ENDPOINTS

8.1 Study Objective

The objective of this study is to assess long-term safety in a multicenter, open-label, 52-week study in subjects treated with ARQ-151 cream 0.3% after completing a 12-week Phase 2b study (ARQ-151-201) Cohort 1 and non ARQ-151-201 subjects (Cohort 2).

8.2 Study Endpoints

8.2.1 Primary Endpoint

The primary endpoint will be analysis of safety monitored through application site assessments in the clinic using the method of Berger and Bowman, clinical laboratory testing, 12-lead ECGs, PHQ-8, C-SSRS and adverse events. Two primary endpoint analyses are planned:

- Occurrence of Treatment Emergent Adverse Events
- Occurrence of Serious Adverse Events

8.2.2 Secondary Endpoints

The secondary endpoints are related to efficacy and will include:

- Proportion (%) of subjects achieving an Investigator Global Assessment (IGA) of clear or almost clear, as observed at Week 12 and subsequent scheduled visits.
- In subjects who achieve 'clear' scores for IGA, I-IGA (if applicable **and** mPASI (Modified Psoriasis Area Severity Index) and stop treatment to all lesions, time to re-starting study drug (duration of response).
- Proportion (%) of applicable subjects with intertriginous area involvement, 'I-IGA' score of 'clear' or 'almost clear' at week 12 and subsequent visits
- Proportion (%) of subjects achieving a 75% reduction from Baseline of Modified Psoriasis Area Severity Index-75 (mPASI-75) at weeks 12, 24, 36 and 52 as compared to Baseline.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is an open-label, long-term safety study of ARQ-151 cream 0.3% in subjects with chronic plaque psoriasis involving between 0 and 25% BSA. Eligible subjects will enroll into the long-term safety study on the same day as the Week 12 visit for the previous study (ARQ-151-201) for Cohort 1 and on Day 1 for non ARQ-151-201 subjects in Cohort 2. Study medication will be applied by the subjects topically QD for 52 weeks at home.

A total of up to approximately 300 subjects (Cohort 1) and up to approximately 100 non ARQ-151-201 subjects (Cohort 2) 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. Periodic clinic visits will include assessments for clinical safety, application site reactions evaluated in the clinic using the method of Berger and Bowman, disease improvement or progression, and IGA.

9.2 Subject Participation

Subject participation involves a minimum of five clinic visits at Week 4, Week 12, Week 24, Week 36 and Week 52 of treatment. There will be three phone visits conducted at Weeks 18, 30 and 44. The Day 1 visit of this study will be Week 12 of the ARQ-151-201 study (Cohort 1) and Day 1 for Cohort 2. The Baseline values for Safety tabulations will be taken from the day that the subject received their first active study drug. Baseline values for efficacy will be those recorded on Day 1 of Study ARQ-151-201. The anticipated maximum duration of subject participation is about 52 weeks. Subjects in the ARQ-151-201 study that choose to participate in the long-term extension study will transition directly into the ARQ-151-202 study at the Day 1 visit (Week 12 of Study ARQ-151-201).

9.3 Randomization

This is an open-label study and all subjects will be treated with ARQ-151 cream 0.3% QD to psoriatic plaques up to a maximum application area of 25% BSA.

9.4 Numbering of Subjects

All screened subjects enrolled will retain their unique five-digit subject ID number previously assigned during the ARQ-151-201 study (Cohort 1). For Cohort 2 subjects will be numbered with the 2 digit site number and a three digit subject number starting with 500.

The clinical site is responsible for maintaining a current log of subject ID number assignments and study drug kits 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.).

9.5 Blinding

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

9.6 Selection of Patient Population

9.6.1 Inclusion Criteria

All Subjects

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

1. Participants legally competent to sign and give informed consent
2. Males and females ages 18 years and older
3. Females of childbearing potential (FOCBP) must have a negative urine pregnancy test at all study visits. In addition, sexually active FOCBP must agree to use at least one form of 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.

4. Post-menopausal women with spontaneous amenorrhea for at least 12 months or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy).

Cohort 1 Only

5. Subjects with chronic plaque psoriasis who met eligibility criteria for ARQ-151-201, successfully completed ARQ-151-201 through Week 12, and enroll into this long-term safety study on the Week 12 visit of the previous study (ARQ-151-201).

Cohort 2 Only

6. Clinical diagnosis of psoriasis vulgaris of at least 6 months duration as determined by the Investigator.
7. Psoriasis vulgaris on the face, extremities, trunk, and/or intertriginous areas involving 2% to 25% of BSA (excluding the scalp, palms and soles).
8. An Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') at Day 1.

9.6.2 Exclusion Criteria

All Subjects

1. Subjects who experienced an ARQ-151 treatment-related AE or a serious AE (SAE) that precluded further treatment with ARQ-151 cream in Study ARQ-151-201.
2. Subjects that use any Excluded Medications and Treatments (see Table 1).
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, or pustular psoriasis.
6. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound safety or 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 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 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 moderate to severe liver impairment (Child-Pugh B or C)
    - 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. 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.
14. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of study medication.
15. History of and/or concurrent condition of serious hypersensitivity (anaphylactic shock or anaphylactoid reaction) to PDE-4 inhibitors.
16. 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.
17. Subjects who are unable to communicate, read or understand the local language, or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation.

Cohort 1 Only

18. Subjects who experienced an ARQ-151 treatment-related AE or a serious AE (SAE) that precluded further treatment with ARQ-151 cream in Study ARQ-151-201.

Cohort 2 Only

19. Subjects who cannot discontinue medication and treatments prior to the Day 1 visit Excluded Medications and Treatments (Table 2).

9.6.3 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 or intentionally trying to lose weight 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.
8. Subject's repeated failure to comply with protocol requirements or study related procedures.
9. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

9.7 Study Restrictions

9.7.1 Prohibitions and Concomitant Therapy

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

Generally, the addition of new medications, including nonprescription medications, during the course of the study is discouraged. However, it is recognized that this is a 52-week study and subjects may be required to start chronic medications for health benefits. The use of such chronic medications may be authorized by the Investigator. The Investigator must make the decision to authorize the use of any such 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. Short-term medications, such as antibiotics to treat acute infections, are allowed. 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 already been used chronically by subjects, in particular statins and anti-hypertensives, are allowed for use during the study.

Table 1. Excluded Medications and Treatments

Excluded Medications and Treatments
Systemic treatment with biological therapies with a possible effect on psoriasis vulgaris
Systemic treatment with all other therapies with a possible effect on psoriasis vulgaris (eg, oral corticosteroids, retinoids, apremilast, methotrexate, cyclosporine and other systemic immunosuppressants
Topical anti-psoriasis medications (e.g., corticosteroids, vitamin D analogs, prescription shampoos) (except for emollients)
PUVA phototherapy
UVB
Investigational drugs (except ARQ-151 cream)
Note: • Eye drop and nasal corticosteroid preparations are allowed. • Inhaled corticosteroid preparations are allowed if used for a stable condition and at a stable dose for > 28 days before Day 1, and are continued at the same dose throughout the study. • Non-medicated emollients, moisturizers and sunscreens will be allowed as used normally by the subjects. These can be applied to non-treated areas as needed. Study medication should be applied at least 20 minutes before going to bed and no other emollients or moisturizers should be applied to the treated area. • A tar-containing or a dandruff shampoo (zinc pyrithione or selenium sulfide) shampoo is allowed for treatment of the scalp.

Table 2. Wash Out Period for Medications and Treatments (Cohort 2)

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 enrollment:	
Etanercept	4 weeks
Adalimumab, infliximab	8 weeks
All other biologics	12 weeks
• 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)

9.8 Investigational Product and Treatment

9.8.1 Drug Supplies, Packaging and Labeling

ARQ-151 cream 0.3% will be provided in 45 gram squeeze tubes. The tubes will be packaged in kits, each containing 8 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 ten. The kits and tubes will be labeled including a location to record the subject ID on the label.

The Sponsor will supply sufficient quantities of the study drug (ARQ-151 cream 0.3%,) 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.

9.8.2 Treatment Administration

At the Day 1 visit, subjects will be instructed to apply study medication once daily. All subjects should apply medication each evening at least 15 minutes after showering or bathing (if they take an evening shower/bath) and then not wash areas where ARQ-151 cream has been applied until 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 active psoriasis lesions including any new plaques that develop during the study. A Body Diagram should be used to record existing and new areas of psoriasis involvement that are subject to treatment.

Psoriasis plaques that have completely resolved, in the opinion of the investigator, do not require continued treatment. If psoriasis plaques appear to resolve at some time between study visits, study medication should continue to be applied until the next scheduled visit. At that visit, the Investigator will perform an assessment and determine whether or not to discontinue treatment.

Study medication will be weighed prior to dispensing at all visits where study medication is dispensed.. Study medication, both empty and full tubes, must be returned by subjects at each study visit and will be weighed.

9.8.3 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).

Compliance will be assessed by review of the dosing diary. Weight of study medication applied will be measured for reporting purposes. Compliance will be documented in source and in eCRF.

10 STUDY PROCEDURES

10.1 Safety Assessments

The Schedule of Visits and Assessments (see 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 long-term safety of ARQ-151 cream 0.3%. Safety will be monitored through application site assessments in the clinic using the method of Berger and Bowman, physical examination, clinical laboratory testing, 12-lead ECGs, 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 Investigator.

Screening Visit (Cohort 2)

Within 35 days prior to the first dosing, non ARQ-151-201 subjects will be provided details of study requirements and sign an informed consent. 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.

Screening should occur for Cohort 1 subjects if they have completed ARQ-151-201 previously.

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

Day 1 Visit

At Day 1 (Week 12 of the ARQ-151-201 study or Day 1 for non ARQ-151-201) ARQ-151-201 subjects will be provided details of study requirements and sign an informed consent. Medical history and demographic data, psoriatic plaque assessments (IGA, I-IGA, mPASI and BSA), physical examination, vital sign measurements (blood pressure, heart rate, and temperature), PHQ-8, C-SSRS, laboratory tests: hematology, chemistry, urinalysis and a pregnancy test for female subjects of child bearing potential will be obtained at Week 12 visit of study ARQ-151-201 and will serve as the Day 1 for ARQ-151-201 subjects (Cohort 1). Cohort 2 Day 1 assessments for this long-term safety study (ARQ-151-202) will be completed within 35 days of Screening. The Baseline values for Safety tabulations will be taken from the day that the subject received their first active study drug (across studies ARQ-151-201 and ARQ-151-202). Baseline values for efficacy will be those recorded on Day 1 of Study ARQ-151-201 (Cohort 1) and Day 1 of ARQ-151-202 for non ARQ-151-201 subjects (Cohort 2).

Cohort 2 subjects must meet the required wash out period for any excluded medications and treatments according to Table 2.

All Cohort 1 subjects will retain their Subject ID from the previous study which will be entered into the electronic subject tracking system for this long-term safety study. Cohort 2 subject study numbers will include the 2 digit site number and the three digit subject number will begin with 500.

Scheduled Visits (Day 1 and Visits 1 – 5)

10.1.1 Physical Examination

Physical examinations will be performed as follows:

Day 1, Week 24, and Week 52.

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

10.1.2 Vital Signs, Height and Weight

Vital signs will be collected at timepoints noted below:

Blood pressure, heart rate, and temperature will be measured at all study visits.

Height will be collected at Day 1 only.

Weight will be collected at all study visits. 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.

10.1.3 12-lead ECGs

12-lead ECGs will be performed as follows:

Day 1, Week 24 and Week 52.

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.

10.1.4 Laboratory Tests

All tests listed below will be performed as follows:

Day 1, Weeks 4, 12, 24, 36, 52.

All tests listed below will be performed according to the Study Events Flow Chart unless otherwise noted. The collection of specimens will be in a non-fasting state. In addition, laboratory safety tests may be performed at various unscheduled timepoints, if deemed necessary by the Investigator.

Hematology

- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count with indices and morphology
- Platelet count

Serum Chemistry

- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase
- Aspartate aminotransferase
- Alanine aminotransferase
- Albumin
- Sodium
- Potassium
- Chloride
- Glucose
- Creatinine

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 Day 1, Weeks 4, 12, 24, 36 and 52 for FOCBP only

10.1.5 Patient Health Questionnaire depression scale (PHQ-8)

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

Day 1, Weeks 4, 12, 24, 36, and 52

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)

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

C-SSRS Assessments will be performed as follows:

Day 1, Weeks 4, 12, 24, 36, and 52

On all visits, the Since Last Visit version (Appendix 1) will be used for Cohort 1.

Cohort 2 will use the Baseline/Screening version (Appendix 2) for Day 1 and Since Last Visit version for all remaining visits.

- 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.

Clinical study staff that administer the C-SSRS 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.

10.1.7 Local Tolerability Assessments

The Investigator Local Tolerability Assessment will be performed as follows:

Day 1, Weeks 4, 12, 24, 36, and 52

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-Day 1 visit, should be differentiated from the preexisting inflammation associated with the subject's psoriasis.

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

10.1.8 Adverse Events

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

Day 1, Weeks 4, 12, 24, 36, and 52

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.

A psoriasis flare will be considered an AE in this study. For further details on Adverse Events please see Section 10.6.

10.1.9 Phone Visits

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

Subjects will call the site when psoriasis returns prior to restarting application of study drug.

10.2 Efficacy Evaluations

10.2.1 Investigator's Global Assessment (IGA)

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

Day 1, Weeks 4, 12, 24, 36, and 52

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.

Unlike the Phase 2b study, an Intertriginous-IGA will not be done in this open-label extension study. However, study medication should be applied to intertriginous areas if affected.

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

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

- **IGA will be assessed at clinic visits prior to the subject applying Investigational Product at home.**

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 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 Day 1 (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 4, 12, 24, 36 and 52.

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 4, 12, 24, 36 and 52

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:

Day 1, Weeks 4, 12, 24, 36, and 52

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 or BSA assessments. The scalp is not treated and will not be counted towards any assessments.

10.3 Final Study Visit – End of Study

The final study visit will occur approximately at the end of week 52 of overall involvement in the study. The procedures performed during this visit are as described in Section 10.1 and Section 10.2 and the Schedule of Events for the Week 52 visit (Section 5). A 7 day scheduling leeway period is allowed for this visit. In addition to the listed procedures to be performed, adverse events will be recorded as reported by the participant or as observed and followed to resolution as necessary (see Section 10.1.8).

10.4 Early Termination Visit

If a subject is withdrawn or wishes to exit the study, a termination visit will be scheduled. This visit should include the procedures and assessments that would be performed at the final study visit (End of Study visit; see Section 10.3).

10.5 Unscheduled Visit

Subjects that clear between scheduled visits should return for an unscheduled visit for the investigator to confirm IGA, I-IGA (if applicable) and mPASI are clear and subject may stop application of study drug. Unscheduled visits may be necessary for the purpose of measuring time to restarting study drug for those subjects that stopped application of study medication due to resolution of psoriasis plaques. Subjects will call the site when psoriasis returns prior to restarting application of study drug. Unscheduled visits also may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted in the judgement of the Investigator.

The following information will be collected for all subjects:

- Concomitant medications/procedures
- AEs

The following information will be collected for those subjects that had stopped study medication but are experiencing a reoccurrence of psoriasis plaques:

- Time between stopping study medication and restarting application
- Investigator's Global Assessment (IGA) of psoriasis severity
- Body Surface Area (BSA) of psoriasis involvement (not palms, soles, or scalp)

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

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

10.6 Adverse Events

10.6.1 Adverse Event Definition

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

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

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

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

10.6.2 Serious Adverse Event

The definitions and reporting requirements of Health Canada/the Food and Drug Administration (FDA)/ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A will be adhered to. If any AEs are serious, as defined by ICH Guidelines for Clinical Safety, required procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within 24 hours of becoming aware of the event, whether or not the 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 history 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.

10.6.3 Suspected Unexpected Serious Adverse Reaction (SUSAR)

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

10.6.4 Safety Review

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

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the 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).

10.6.5 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 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).

10.7 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 10.6.2. 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.

10.8 Treatment Stopping Rules

For subjects that clear (i.e. have an IGA score of 0 (Clear), an I-IGA (if applicable) of 0 (Clear) **and** an mPASI of 0) treatment may be stopped. The subject will be instructed to document in their diary when they resume treatment with study drug if psoriasis returns. If the subject clears between study visits they should be scheduled for an unscheduled visit for the Investigator to confirm the subject has cleared.

Subjects will call the site when psoriasis returns prior to restarting application of study drug.

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 2 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 can 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.

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

Missing efficacy and/or safety data will remain missing and will not be estimated.

11.1.1 Baseline Definition

Cohort 1 baseline value for each parameter will be defined as the last observation prior to first dose of ARQ-151 cream 0.3% or ARQ-151 cream 0.15%. For subjects receiving either active study drug in ARQ-151-201, the baseline values from ARQ-151-201 will be considered the baseline values for calculations in ARQ-151-202. For subjects receiving Vehicle in ARQ-151-201, baseline values will most commonly be from the Week 12/study exit visit of ARQ-151-201. If subjects choose to enroll in this study, study procedures will not be repeated; study sites will carry over the information from the ARQ-151-201 study (Week 12 visit) to the Day 1 visit for this study. Baseline values for IGA, however, will be taken from Day 1 of Study ARQ-151-201 for all subjects.

Cohort 2 baseline value for each parameter will be collected on Day 1.

11.1.2 Determination of Sample Size

A sample size of approximately 300 subjects is planned for Cohort 1 and up to approximately100 subjects in Cohort 2 is planned for the study. This sample size will provide a sufficient population size to evaluate the long-term safety of ARQ-151 cream 0.3% at 52 weeks.

11.1.3 Subjects to Analyze

All analyses will be performed using the Safety Population which includes all subjects who are enrolled and received at least one confirmed dose of ARQ-151 cream 0.15% or ARQ-151 cream 0.3% study medication either in the Phase 2b Study (ARQ-151-201) or this extension study (ARQ-151-202). The number of patients included in the Safety Population will be summarized.

11.1.4 Interim Analysis

No interim efficacy analyses are planned.

11.1.5 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 subjects will be presented in a by-subject listing.

11.1.6 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 using summary statistics (mean, SD, median, minimum, and maximum), and categorically.

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

11.2.1 Adverse Events

All treatment-emergent AEs occurring during the study will be recorded and classified on the basis of MedDRA terminology for the safety population. Treatment-emergent AEs are those AEs with an onset on or after the date of study treatment. All treatment-emergent AEs will be

summarized by scheduled study visit, the number of subjects reporting treatment-emergent AEs, system organ class, preferred term, severity, relationship, and seriousness.

Serious adverse events (SAEs) will be listed by subject. SAEs will be summarized by severity and relationship to study treatment. Each subject will be counted only once within a system organ class or a preferred term using the event with the greatest relationship and greatest severity.

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

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 listed by subject.

11.2.2 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.

11.2.3 Clinical Laboratory Results and Vital Signs/Weight Measurements

Vital signs will be tabulated by scheduled study visit.

Routine blood chemistries and urinalysis will be obtained throughout the study and the results summarized by parameter and at scheduled study visits.

All clinical laboratory results and vital signs measurements and their change from baseline will be summarized along with timepoint 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.

11.2.4 ECG:

ECGs will be tabulated by scheduled study visit.

11.2.5 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.

11.2.6 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)

11.2.7 C-SSRS

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

11.2.8 Prior and Concomitant Medications

Prior and concomitant medication information for all 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.

11.3 Efficacy Evaluation

This study is not intended to assess efficacy, but rather the IGA, I-IGA and mPASI are included to determine the need for treatment and subsequent re-treatment after treatment course in Study ARQ-151-201 or Study ARQ-151-202. Certain efficacy data and endpoints will, however, be summarized.

Descriptive statistics will be used to summarize the assessment of efficacy. IGA scores will be summarized at Baseline Visit of Study ARQ-151-201 and every scheduled visit through end of the study (Day 1 and Weeks 4, 12, 24, 36, and 52). The efficacy variable in this study is success in Investigator Global Assessment (IGA) of disease severity, defined as an IGA of 'Clear' or 'Almost Clear'. The number and percentage of patients who achieve treatment success at the scheduled study visits will be tabulated. The proportion of successes for the secondary variables of I-IGA and 75% reduction in mPASI will be tabulated in a similar manner.

The number of treatment free days until the first retreatment (relapse) will be calculated and analyzed. For rollover subjects previously treated with Vehicle Cream, the number of treatment free days will be the number of days between the end of the initial treatment in study ARQ-151-202 and the start of the next treatment in study ARQ-151-202 if one should be needed or the end of the subject's participation in study ARQ-151-202. For rollover subjects previously treated

with ARQ-151 cream 0.3% or ARQ-151 cream 0.15%, the number of treatment free days will be the number of days between the last treatment that began in Study ARQ-151-201 and the start of the next treatment in study ARQ-151-202 if one should be needed or the end of the subject's participation in the study ARQ-151-202. There may be additional analyses comparing subjects that were previously treated with ARQ-151 cream 0.3% and ARQ-151 cream 0.15% in the ARQ-151-201 study.

Descriptive statistics for retreatment rates will be presented. The time (number of days) to relapse will be analyzed using the Kaplan–Meier method. The median time to relapse will be calculated in addition to other appropriate descriptive statistics. Patients who discontinue study ARQ-151-202 without relapse will be considered censored in the Kaplan–Meier analysis.

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.

12.4 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.

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14 APPENDICES

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

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

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

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

Appendix 2. Columbia-Suicide Severity Rating Scale (C-SSRS) Since Last Visit Version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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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* _____

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Appendix 3. 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 andFEV_1 <80% predicted after bronchodilator
Dyspnea	Does not interfere with usual and social activities	Interferes with usual and social activities, no treatment	Prevents daily and usual social activity or requires treatment
Nasal discharge (rhinitis infective per **CTCAE 4.0**)	-	Localized; local intervention indicated (e.g. topical antibiotic, antifungal, or antiviral)	-
Pharyngitis **(CTCAE 4.0)**	-	Localized; local intervention indicated (e.g. topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated
Pneumonitis (rales or rhonchi) **(CTCAE 4.0)**	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated
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

[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.

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

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
Albumin	LO g/L	<30-28	<28-25	<25

Blood, Serum, or Plasma Chemistries [a]	LO/HI/N [b]	Mild (Grade 1) [c]	Moderate (Grade 2)	Severe (Grade 3)
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.