



Protocol ARQ-151-306

A Phase 3, Multicenter, Open-Label Extension Study of the Long-Term Safety of ARQ-151 Cream 0.3% in Subjects with Chronic Plaque Psoriasis

Sponsor:

[REDACTED]

Sponsor Representative:

[REDACTED]

Medical Monitor:

[REDACTED]

IND Number:

135681

Protocol Version:

Amendment 2

Date:

25 October 2022

GCP Statement

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

Confidentiality Statement

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SITE INVESTIGATOR SIGNATURE PAGE

ARQ-151-306

A Phase 3, Multicenter, Open-Label Extension Study of the Long-Term Safety of ARQ-151
Cream 0.3% in Subjects with Chronic Plaque Psoriasis

SPONSOR:



ISSUE DATE:

25 October 2022

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

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

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

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

Investigational Study Site Name:



Print Investigator Name:



Investigator Signature:



Date:



SUMMARY OF CHANGES

The following sections have been changed in Amendment 2 of the ARQ-151-306 protocol:

Version/Date	Description
27 November 2019	Original protocol
Amendment 1 May 6, 2020	- Added protocol revision history section. - Added Cohort 2 (naïve 2 to 17 year old subjects). - Increased site number to up to approximately 100 sites. - Increased subject number to up to approximately 300 subjects. - Added language to allow caregivers to complete diary and apply investigational product. - Added one SAE from the ARQ-151-201 study. - Updated Inclusion and Exclusion Criteria for Cohort 2. - Modified language specifying subjects will roll over from ARQ-151-301 and ARQ-151-302 to allow subjects successfully completing a prior ARQ-151 cream study. - Included Parent version of CDI-2 which will be collected from parents for subjects 6-11 years old (inclusive). - Clarified the WI-NRS will be collected from all subjects; subjects 8 years and older will self-report, and caregivers will report if subjects are younger than 8 years. - Added CDI-2 raw total score of 34 as a reason to remove subjects from Investigational Product after consultation with a mental health professional, the Sponsor, and at the Investigator's discretion. - Clarified details for assigning the subject number. - Statistical Methods updated. - Editorial and administrative changes throughout the protocol to clarify language and formatting to improve readability.
Amendment 2 25 October 2022	- Updated Medical Monitor and contact details. - Updated Sponsor Contact, Medical Monitor and contact details. - Study sites to add the Dominican Republic and during the conduct of the study, additional countries and/or sites may be added if necessary. - Increased subject number to up to approximately 330 subjects - Removed laboratory assessments at Weeks 4, 12 and 24/ET post Amendment 2. - Inclusion Criteria 2 updated to note 'Subjects enrolled post Amendment 2 will be 2 to <12 years old only'.

Version/Date	Description
	• Section 5.1 Introduction added: ‘Zoryve™ was approved July 2022 in the United States for topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older.’ • Section 5.2.1 Toxicology Summary was updated to reflect the GLP-compliant dermal toxicity study was completed. • Section 7.8.1 Investigational Product updated to include 60 gram tubes and note that kits will contain multiple tubes. • Section 7.8.2 Treatment Administration updated to include ‘For Cohort 2 initial IP application, the study staff will demonstrate to the subject/caregiver(s) how to apply ARQ-151 cream using the first tube from the kit that is assigned to the subject. Study site staff will be trained to ensure a unit dose (a pea size unit of ARQ-151 cream will cover approximately 1% BSA) is properly squeezed from the tube and applied to all active psoriasis lesion(s) as a thin film and rubbed in using the index and middle finger, rubbing in thoroughly but gently, until the ‘white’ has disappeared. The parent(s)/caregiver will then practice squeezing a similar amount onto their index and middle finger and apply a thin film to other areas to be treated. The study staff will ensure that the subject/caregiver’s application technique is correct and that a thin layer is applied as instructed. Re-training will be conducted at subsequent visits as needed.’ • Section 9.1.4 updated to ‘Changes associated with protocol amendment 2 will result in the final analyses of this study, and no further interim analyses are planned.’ • Deleted Appendix 3. • Updated Appendix 4 to Appendix 3. • Editorial and administrative changes throughout the protocol to clarify language and formatting to improve readability.

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2. SYNOPSIS

Protocol Title:	A Phase 3, Multicenter, Open-Label Extension Study of the Long-Term Safety of ARQ-151 Cream 0.3% in Subjects with Chronic Plaque Psoriasis
Investigational Product:	ARQ-151 investigational product will be supplied as a 0.3% cream
Planned Dose Level:	Subjects will receive ARQ-151 cream 0.3% QD applied to all psoriatic lesions up to and including an area of 25% BSA. Application will be to all areas affected including the face and intertriginous/genital regions (except for the scalp).
IND:	135681
Clinical Indication:	Chronic Plaque Psoriasis
Study Design:	This is a phase 3, open-label, single arm study in which ARQ-151 cream 0.3% is applied QD for 24 weeks to subjects with chronic plaque psoriasis involving up to 25% BSA. Subjects will stop application after the Investigator confirms IGA, I-IGA and PASI/mPASI assessments are clear. Subject/caregiver will phone the clinical study site and complete the subject diary if psoriasis returns and application of IP is resumed.
Study Objectives:	To assess long-term safety in a multicenter, open-label, single-arm 24-week study in subjects treated with ARQ-151 cream 0.3%.
Study Sites:	Up to approximately 100 sites in Canada, the United States and the Dominican Republic. During the conduct of the study, additional countries and/or sites may be added if necessary.
Study Population:	Up to approximately 330 subjects. Subjects will be male and female 2 years and older.
Inclusion Criteria:	1. Participants legally competent to sign and give informed consent or informed consent of legal guardian, and, if age appropriate, assent by the subject, as required by local laws. 2. Males and females ages 2 years and older. Note, Subjects enrolled post Amendment 2 will be 2 to < 12 years old only. 3. Subjects with chronic plaque psoriasis who meet eligibility criteria and: a. Successfully completed a prior ARQ-151 cream study in psoriasis (Cohort 1) or b. Are naïve to treatment with ARQ-151 cream (Cohort 2) 4. 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 (eg, 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. 5. Females of non-childbearing potential must either be pre-menarchal, or post-menopausal with spontaneous amenorrhea for at least 12 months or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy).
Inclusion Criteria Cohort 2 Only:	1. Clinical diagnosis of psoriasis vulgaris of at least 3 months duration as determined by the Investigator. 2. Psoriasis vulgaris on the face, extremities, trunk, and/or intertriginous areas involving 2% to 25% of BSA (excluding the scalp, palms and soles). 3. An Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') at Day 1.
Exclusion Criteria:	1. Subjects who experienced an ARQ-151 treatment-related AE or a serious AE (SAE) that precluded further treatment with ARQ-151 cream in a prior ARQ-151 cream study (Cohort 1). 2. Planned excessive exposure of treated area(s) to either natural or artificial sunlight, tanning bed or other LED. 3. Subjects that use any Excluded Medications and Treatments (see Table 1). 4. Subjects currently taking lithium or antimalarial drugs. 5. Planned initiation or changes to concomitant medication that could, in the opinion of the Investigator, affect psoriasis vulgaris (eg, beta blockers, ACE inhibitors). 6. Current diagnosis of non-plaque form of psoriasis (eg, guttate, erythrodermic/exfoliative, palmoplantar only involvement, or pustular psoriasis). Current diagnosis of drug-induced psoriasis. 7. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound safety or efficacy measurements. 8. Known allergies to excipients in ARQ-151 cream [REDACTED] 9. Subjects who cannot discontinue the use of strong P-450 cytochrome inhibitors eg, indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin during the study period.

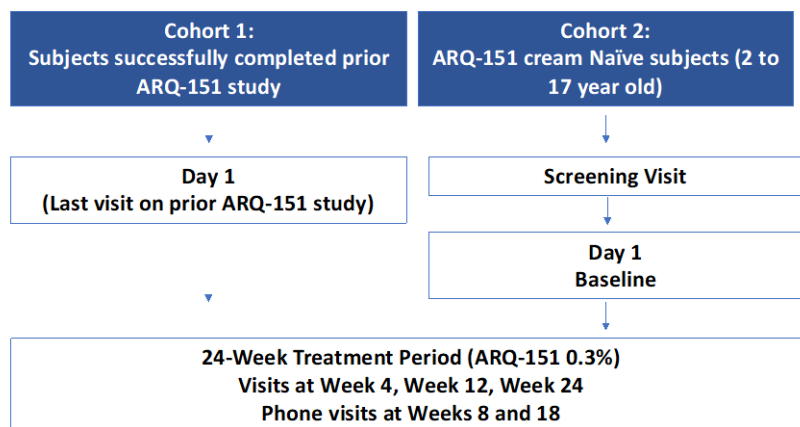
	10. Subjects who cannot discontinue the use of strong P-450 cytochrome inducers eg, efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, and rifampin during the study period. 11. Known or suspected: • severe renal insufficiency, or moderate to severe hepatic disorders (Child-Pugh B or C) • known HIV infection • hypersensitivity to component(s) of the investigational product • 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. 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. 17. Subjects who are family members of the clinical study site, clinical study staff, or sponsor.
Exclusion Criteria Cohort 2 Only:	1. Subjects who cannot discontinue medication and treatments prior to the Day 1 visit according to Excluded Medications and Treatments (Table 1). 2. Baseline/Screening C-SSRS (12years and older) indicative of suicidal ideation, whether lifetime or recent/current. Subjects with or modified PHQ-A (12 to 17 y/o) >10 at Screening or Baseline visits. Subjects (6 to 11 years old, inclusive) with a CDI-2 (parent report) raw score >20 at Screening/Baseline.
Duration of Participation for Subjects:	Approximately 24 weeks
Key Assessments:	Safety will be monitored through application site assessments in the clinic using the method of Berger and Bowman, vital signs, physical examinations, clinical laboratory testing, either PHQ-8 (in adults) or a modified version of the PHQ-A (in adolescents), CDI-2 parent report (Children's Depressive Index-2 for children 6 to 11 years old, inclusive), C-SSRS in subjects ≥12 years old, and AEs.

	Efficacy assessments will include IGA, I-IGA, PASI/mPASI, BSA, WI-NRS. The WI-NRS will be collected from all subjects; subjects 8 years and older will self-report, and caregivers will report if subjects are younger than 8 years.
Study Endpoints:	<u>Primary Endpoints</u> • Occurrence of treatment emergent AEs (TEAEs) • Occurrence of Serious Adverse Events (SAEs) <u>Secondary Endpoints</u> • Achievement of an Investigator Global Assessment (IGA) of ‘clear’ or ‘almost clear’ over time. • In subjects who achieve a 'clear' IGA, I-IGA and PASI/mPASI scores and stop treatment to all lesions, time to re-starting investigational product (duration of response). • Achievement of a 50% reduction in PASI over time • Achievement of a 75% reduction in PASI over time • Achievement of a 90% reduction in PASI over time • Achievement of a 100% reduction in PASI over time • Achievement of an I-IGA of ‘clear’ or ‘almost clear’, as observed over time. • Change in WI-NRS score over time
Statistical Considerations:	Up to approximately 330 subjects are planned for this study. The sample size will provide a sufficient population size to evaluate the long-term safety of ARQ-151 cream 0.3% over 24 weeks of treatment, and in combination with other studies provide the development program with sufficient numbers of subjects to meet ICH exposure goals. Descriptive statistics will be presented for the endpoint and safety data collected in the clinical trial. This includes the number and percentage of subjects for binary endpoints/categorical data, and mean, SD, median, minimum, and maximum for continuous data. <u>Adverse Events</u> For the primary endpoints, the occurrence of treatment-emergent AEs (TEAEs) and the occurrence of Serious Adverse Events (SAEs) will be tabulated by preferred term and system organ class. In addition, summary tables of TEAEs by severity, by relationship to investigational product, and those leading to withdrawal from investigational product will be created. <u>Vital Signs</u> Descriptive statistics will be calculated for vital signs and change from baseline in vital signs over time.

	<u>Clinical Laboratory Results</u> Descriptive statistics of the laboratory parameters will be calculated at each scheduled time point. Change from baseline will be summarized at each scheduled time point. Shifts from baseline will be tabulated. Post Amendment 2, laboratory assessments at Weeks 4, 12 and 24/ET have been removed. <u>Patient Health Questionnaires</u> PHQ-8 (in adults) or a modified version of the PHQ-A (in adolescents) (PHQ-A = PHQ-9 modified for Adolescents) or CDI-2 parent report (Children's Depressive Index-2 for children 6 to 11 years old), and C-SSRS (12 years and older) questionnaires will be completed by the subjects at all study visits. Descriptive statistics will be calculated for the PHQ-8 and Modified PHQ-A. The C-SSRS will be analyzed per the Scoring and Data Analysis Guide from the Columbia Lighthouse Project. Descriptive statistics will be presented for the efficacy data collected in the clinical trial for the subjects who enroll in this study and receive at least one day of investigational product. For the binary endpoints related to IGA, I-IGA, and PASI/mPASI, the proportions of subjects achieving each endpoint will be tabulated at each scheduled visit. For subjects who withdraw from study due to lack of efficacy, their data will be imputed using a non-responder imputation method.
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2.1. Study Schema

A Phase 3, Multicenter, Open-Label Extension Study of the Long-Term Safety of ARQ-151 Cream 0.3% in Subjects with Chronic Plaque Psoriasis



Up to approximately 300 subjects with chronic plaque psoriasis will receive ARQ-151 cream 0.3%.

3. SCHEDULE OF VISITS AND ASSESSMENTS

STUDY EVENTS FLOW CHART

Study Procedure	Washout ^k (Cohort 2)	Day 1	Wk 4	Wk 8	Wk 12	Wk 18	Wk 24/ ET
Visit	Screening	Completion of ARQ-151 Study or Baseline for Naïve (Cohort 2)	1	Phone Visit	2	Phone Visit	3
Visit Window	-35 days		+/- 3 days	+/- 5 days	+/- 5 days	+/- 5 days	+/- 7 days
Informed consent/assent	X ⁱ	X ⁱ					
Physical examination ^a		X ^h					X
I/E criteria	X	X					
Hematology, Serum Chemistries, and Urine Analysis	X	X ^h					
Vital signs, height, weight ^b		X ^h	X		X		X
IGA ^c , I-IGA ^c , PASI/mPASI ^c , BSA ^c	X	X ^h	X		X		X
C-SSRS (≥12 years), PHQ-8 (adults), PHQ-A (adolescents), CDI-2 (6-11 years old)	X	X ^h	X		X		X
WI-NRS ^j	X	X ^h	X		X		X
Urine pregnancy test ^d		X ^h	X		X		X
Local Tolerability Assessment ^e		X ^h	X		X		X
Dispense study medication kit ^f		X	X		X		
Dispense/review diary		X	X		X		X
Weigh study medication		X	X		X		X
Adverse event assessment ^g	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X

^a Limited physical examination: skin, lungs, and heart only.

^b Height will be collected at Day 1 and Week 24/ET. 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](#) on Page 1.

^c IGA (based on whole body involvement) will be a 5-point scale ranging from clear (0) to severe (4). **IGA should be completed prior to other physician assessments and by the same Evaluator at each study visit.** Total BSA affected by psoriasis will be determined by the subject's hand method, where the subject's hand (including fingers) surface area is assumed to equal 1% of the BSA. PASI/mPASI will be determined by standard methods. NOTE: while palms and soles will be treated with IP, they are not counted towards IGA, PASI/mPASI, or BSA assessments.

Intertriginous area involvement will be recorded using the same IGA scale but evaluating intertriginous areas ONLY and NOT whole body involvement. **This 'intertriginous area IGA' should be done AFTER the 'standard whole body IGA' (primary endpoint).**

Footnotes from table above:

- mPASI will be collected for Cohort 1 subjects only if collected in previous ARQ-151 cream study (i.e., only if subject has a baseline value from a prior study).
- ^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 investigational product at each visit.
- ^e Local tolerability will be assessed by the clinic using the method of Berger and Bowman. **Reactions at the site of investigational product application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's Psoriasis.**
- ^f Kits will be dispensed based on %BSA affected. Each IP tube should be weighed and recorded at every visit. 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 This data will be obtained from completion visit of prior ARQ-151 cream study and used as the Day 1 data for this long-term safety study (ARQ-151-306).
For Cohort 1, the consent will be signed after completion visit of prior ARQ-151 cream study. Cohort 2 will sign consent prior to any study-related procedures at the Screening Visit.
- ^j The WI-NRS will be collected from all subjects; subjects 8 years and older will self-report, and caregivers will report if subjects are younger than 8 years.
- ^k See [Table 2](#) for washout requirements.

4. ABBREVIATIONS

Abbreviations	Definition
AE	Adverse Event
AMP	Adenosine Monophosphate
AUC	Area Under the Curve
BSA	Body Surface Area
C _{max}	Maximum Concentration
CDI-2	Children Depression Inventory, Second Edition
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
ERB	Ethics Review Board
FDA	U.S. Food and Drug Administration
FOCBP	Female of Child Bearing Potential
GCP	Good Clinical Practices
HC	Health Canada
IB	Investigational Brochure
IC ₅₀	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA	Investigator Global Assessment
I-IGA	Intertriginous IGA
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent to Treat
LED	Light Emitting Device
IWRS	Interactive Web Response System
µg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
mL	Milliliter

Abbreviations	Definition
MMRM	Mixed effect Model Repeat Measurement
mPASI	Modified Psoriasis Area and Severity Index
NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
ng	Nanogram
PASI	Psoriasis Area and Severity Index
PASI-75	Psoriasis Area and Severity Index-75; subjects who achieve a 75% reduction in PASI from Baseline
PASI-90	Psoriasis Area and Severity Index-90; subjects who achieve a 90% reduction in PASI from Baseline
PDE-4	Phosphodiesterase 4
PHQ-A	Modified PHQ-9 for Adolescents
PHQ-8	Patient Health Questionnaire depression scale
PI	Principal Investigator
PK	Pharmacokinetics
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
WI-NRS	Worst Itch – Numeric Rating Score

5. BACKGROUND AND RATIONALE

5.1. 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. ZoryveTM was approved July 2022 in the United States for topical treatment of plaque psoriasis, including intertriginous areas, in patients 12 years of age and older. 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). IC₅₀ 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 2 results suggest that ARQ-151 may be a highly efficacious and well-tolerated topical treatment for psoriasis.

5.2. Nonclinical Studies

5.2.1. Toxicology Summary

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

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

To support the development of ARQ-151 topical cream, a GLP-compliant dermal toxicity program was conducted. To date, no new risks have been identified through the dermal toxicity program. In 13-week dermal toxicity studies in mice and minipigs and a 39-week dermal toxicity study in minipigs, no evidence of systemic toxicity was observed. Histopathological evaluation of skin in the mouse included minimal to mild epidermal hyperplasia and/or inflammation which was observed with low incidence and severity, and as such, was not considered adverse. The NOAEL in each of these studies was the 1% concentration of ARQ-151 (20 mg/kg), the highest dose administered and the maximum feasible concentration.

Local tolerance studies were conducted in support of the dermal program and results demonstrate ARQ-151 was not an eye irritant or dermal sensitizer, and it did not demonstrate phototoxic potential in vitro.

Across the dermal and systemic toxicology programs, the exposure to parent drug and N-oxide metabolite differs by route and species; however, when considered as a whole, the NOAELs across routes and species provide assurance that the anticipated exposures in this planned Phase 3 study will be safe (see [Section 5.4.1](#), Dose Selection). While the anticipated exposure to roflumilast and its active metabolite in this Phase 3 study is likely to exceed that of the approved dose of oral roflumilast, there is sufficient coverage for both parent and N-oxide from the oral and dermal toxicity studies.

Refer to the current ARQ-151 Investigator's Brochure (IB) for the most current nonclinical and clinical information.

5.3. Clinical Studies

5.3.1. Topical Roflumilast Cream

Phase 2a

ARQ-151 cream 0.5% and 0.15% have been studied in a Phase 2a study (ARQ-151-101; NCT03392168) in adult patients with mild to moderate chronic plaque psoriasis in the United States and Canada. The study included two cohorts. Cohort 1 was a single dose study to 25 cm² of psoriatic plaque(s) in 8 psoriasis subjects. Cohort 1 subjects were then enrolled, if they met entry criteria, into Cohort 2 of the study. Cohort 2 was a parallel group, double blind, vehicle-controlled study in which ARQ-151 cream 0.5%, ARQ-151 cream 0.15% or vehicle

cream was applied QD for 28 days to 89 subjects with at least 0.5% BSA of chronic plaque psoriasis; area for application was not to exceed 5.0% BSA. Cohort 2 subjects had at least one target plaque of psoriasis of at least 9 cm² Target Plaque Area (TPA) in size and with a Target Plaque Severity Score (TPSS) ≥ 4 . However, all body psoriasis plaques were treated except for the face, scalp, intertriginous areas and palms/soles. Only safety and pharmacokinetics were evaluated for the single dose Cohort 1 subjects.

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

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

[REDACTED]	
1	[REDACTED]
2	[REDACTED]
3	[REDACTED]
4	[REDACTED]
5	[REDACTED]
6	[REDACTED]
7	[REDACTED]
8	[REDACTED]
9	[REDACTED]
10	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Phase 2b

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

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

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

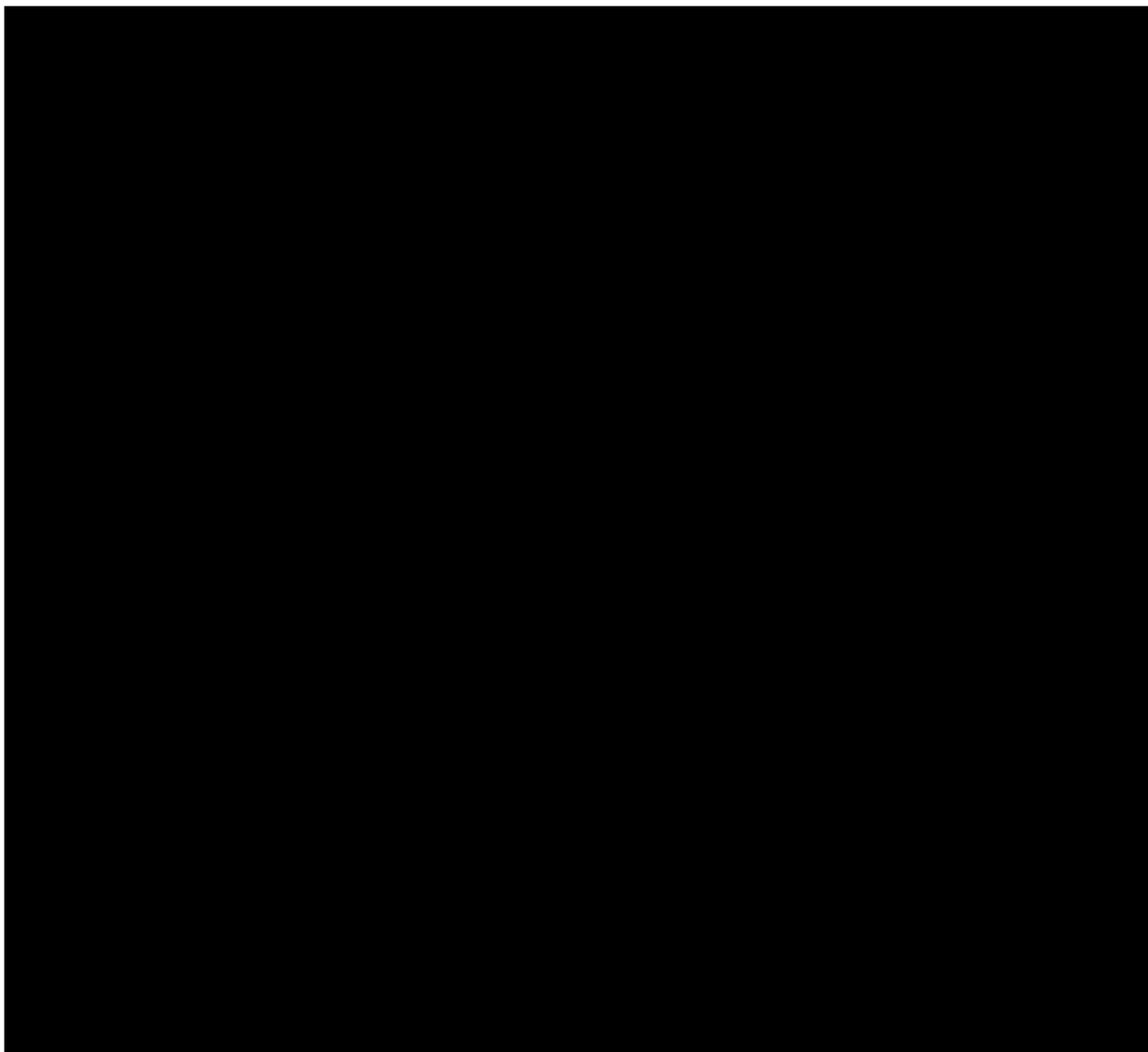
[REDACTED]

I [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



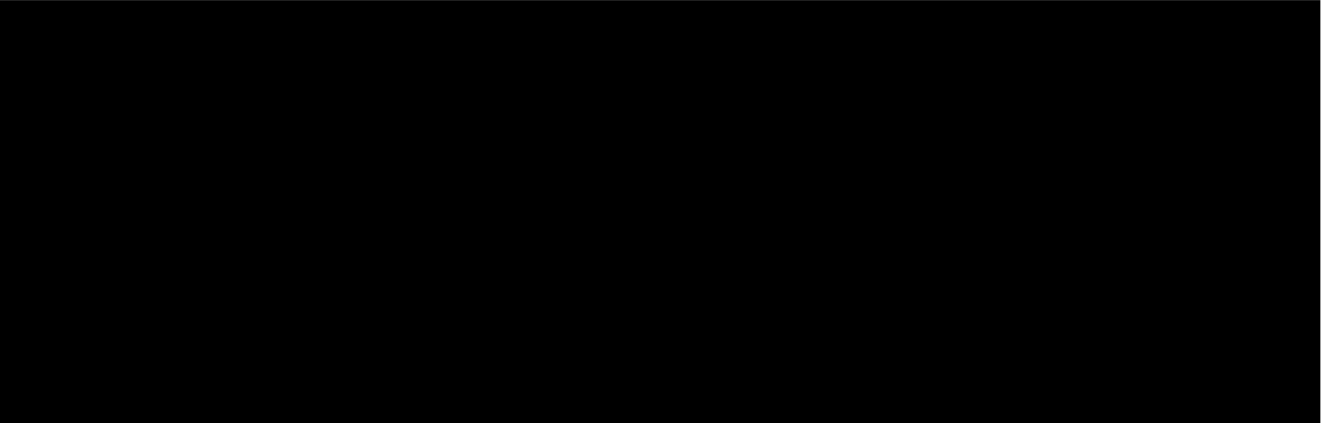
[Redacted text line]

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5.3.2. Oral Roflumilast Tablet

Oral roflumilast (DALIRESP[®], DAXAS[®], a 500 µg tablet) has been approved globally for the treatment of COPD and has been evaluated in nine Phase III/IV randomized double-blind clinical trials ([Wedzicha 2016](#)). Overall, the safety of oral roflumilast has been well established in its targeted population of mostly middle- and upper-aged individuals who currently smoke cigarettes or have smoked them extensively in the past. Adverse events (AEs) reported with roflumilast tablets have been consistent with those expected for oral PDE-4 inhibitors. In a pooled analysis of safety data from 6-month and 1-year clinical trials (N=8630), the most common AEs were diarrhea, weight loss and nausea. Other AEs reported more frequently with roflumilast treatment than with placebo were back pain, influenza, insomnia and decreased appetite ([Michalski 2012](#), [Wedzicha 2016](#)).

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

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

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

5.4. Rationale for Development

Given the approval of OTEZLA as an oral treatment for moderate to severe psoriasis, PDE-4 inhibition is a well validated approach to the treatment of psoriasis.



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

The safety monitoring practices employed in this protocol (i.e., physical examinations, vital signs/weight, local skin toleration assessments, hematology, serum chemistry, urinalysis, (post Amendment 2, laboratory assessments at Weeks 4, 12 and 24/ET have been removed), PHQ-8 (adults), Modified PHQ-A(adolescents), C-SSRS and AE questioning) are adequate to protect the subjects' safety and should detect AEs.

Oral roflumilast has now been used for almost a decade in the treatment of COPD exacerbations and its safety record has been well-documented. The known adverse effects of oral treatment in the COPD population (nausea, diarrhea, weight loss, psychiatric AEs; see [Section 5.3.2](#)) are

monitorable, the current protocol is designed to detect these adverse events and others should they occur, and provides guidance for management, as necessary, to ensure patient safety.

Furthermore, the safety profiles of ARQ-151 at doses ranging from 0.15% to 0.5% in the preceding Phase 2a and 2b studies in psoriasis suggests that ARQ-151 0.3% will be similarly well tolerated in the present study.



6. STUDY OBJECTIVE AND ENDPOINTS

6.1. Study Objective

The objective of this study is to assess long-term safety in a multicenter, open-label, single arm 24-week study in subjects treated with ARQ-151 cream 0.3%.

6.2. Study Endpoints

6.2.1. 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 (post Amendment 2, laboratory assessments at Weeks 4, 12 and 24/ET have been removed) , PHQ-8, Modified PHQ-A or CDI-2 parent report (Children's Depressive Index-2 for children 6 to 11 years old), C-SSRS and adverse events. Two primary endpoint analyses are planned:

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

6.2.2. Secondary Endpoints

The secondary endpoints are related to efficacy and will include:

- Achievement of an Investigator Global Assessment (IGA) of 'clear' or 'almost clear' over time.
- In subjects who achieve a 'clear' IGA, I-IGA and PASI scores and stop treatment to all lesions, time to re-starting investigational product (duration of response).
- Achievement of a 50% reduction in PASI over time
- Achievement of a 75% reduction in PASI over time

- Achievement of a 90% reduction in PASI over time
- Achievement of a 100% reduction in PASI over time
- Achievement of an I-IGA of ‘clear’ or ‘almost clear’ over time
- Change in WI-NRS score over time

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design and Plan

This is an open-label, single-arm, long-term safety study of ARQ-151 cream 0.3% in subjects with chronic plaque psoriasis involving between 0 and 25% BSA. For Cohort 1, eligible subjects will enroll into the long-term safety study on the same day as the last visit of a prior ARQ-151 cream study. Cohort 2 will be ARQ-151 naïve 2 to 17 year old subjects. Study medication will be applied by the subjects/caregivers topically QD for 24 weeks at home.

Up to approximately 330 subjects will be enrolled at up to approximately 100 clinical study sites in the United States, Canada and the Dominican Republic. Subjects will be adolescent and adult 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, I-IGA, PASI/mPASI, BSA and WI-NRS.

7.2. Subject Participation

Subject participation for Cohort 1 involves a minimum of 3 clinic visits at Week 4, Week 12, and Week 24, and 2 phone visits at Weeks 8 and 18. Cohort 2 will also include a screening visit. For Cohort 1 the Day 1 visit of this study will be the last visit of the preceding ARQ-151 cream study. Cohort 1 Baseline values for Safety tabulations will be taken from the day that the subject received first investigational product in this study. Baseline values for efficacy will be those recorded on Day 1 of prior ARQ-151 cream study for Cohort 1. The anticipated maximum duration of subject participation is about 24 weeks.

7.3. Randomization

This is a single-arm 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.

7.4. Numbering of Subjects

Subject numbers are 3 digit site numbers and 3 digit subject number. The site number is assigned based on the ARQ-151 parent study in which the site participated in. The subject number is assigned based on sequence in which the subject is enrolled at the site. The first parent study site numbers start with 100 (i.e., 101-001 is first subject at first site in the study). The second study site numbers begin with 200 and 3 digit subject numbers (i.e., 201-001 is the first subject at the first site in the study). The next study site numbers will begin with 300 (i.e., first subject at first

site will be 301-001). The next study site numbers will begin with 400, the next will begin with 500, etc.

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

7.5. Blinding

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

7.6. Selection of Patient Population

7.6.1. Inclusion Criteria

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

All subjects

1. Participants legally competent to sign and give informed consent or informed consent of legal guardian, and, as age appropriate, assent by the subject, as required by local laws.
2. Males and females ages 2 years and older. Note, subjects enrolled post Amendment 2 will be 2 to < 12 years old only.
3. Subjects with chronic plaque psoriasis who meet eligibility criteria and;
 - a. Successfully completed prior ARQ-151 cream study in psoriasis (Cohort 1) or
 - b. Are naïve to treatment with ARQ-151 cream (Cohort 2).
4. 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 (eg, 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.
5. Females of non-childbearing potential must either be pre-menarchal, or post-menopausal with spontaneous amenorrhea for at least 12 months or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy).

Cohort 2 only

1. Clinical diagnosis of psoriasis vulgaris of at least 3 months duration as determined by the Investigator.
2. Psoriasis vulgaris on the face, extremities, trunk, and/or intertriginous areas involving 2% to 25% of BSA (excluding the scalp, palms and soles).
3. An Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') at Day 1.

7.6.2. 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 a prior ARQ-151 cream study (Cohort 1).
2. Planned excessive exposure of treated area(s) to either natural or artificial sunlight, tanning bed or other LED.
3. Subjects that use any Excluded Medications and Treatments (see [Table 1](#)).
4. Subjects currently taking lithium or antimalarial drugs.
5. Planned initiation or changes to concomitant medication that could, in the opinion of the Investigator, affect psoriasis vulgaris (eg, beta blockers, ACE inhibitors).
6. Current diagnosis of non-plaque form of psoriasis (eg, guttate, erythrodermic/exfoliative, palmoplantar only involvement, or pustular psoriasis). Current diagnosis of drug-induced psoriasis.
7. Subjects with any condition on the treatment area which, in the opinion of the Investigator, could confound safety or efficacy measurements.
8. Known allergies to excipients in ARQ-151 cream [REDACTED]
9. Subjects who cannot discontinue the use of strong P-450 cytochrome inhibitors eg, indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin during the study period.
10. Subjects who cannot discontinue the use of strong P-450 cytochrome inducers eg, efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, and rifampin during the study period.
11. Known or suspected:
 - severe renal insufficiency, or moderate to severe hepatic disorders (Child-Pugh B or C)
 - known HIV infection

- hypersensitivity to component(s) of the investigational product
 - 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. 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.
 17. Subjects who are family members of the clinical study site, clinical study staff, or sponsor.

Cohort 2 only

1. Subjects who cannot discontinue medication and treatments prior to the Day 1 visit according to Excluded Medications and Treatments ([Table 1](#)).
2. Baseline/Screening C-SSRS (12years and older) indicative of suicidal ideation, whether lifetime or recent/current. Subjects with PHQ-8 (18 y/o and older) or modified PHQ-A (12 to 17 y/o) >10 at Screening or Baseline visits. Subjects (6 to 11 years old, inclusive) with a CDI-2 (parent report) raw score >20 at Screening/Baseline.

7.6.3. Removal of Subjects from Investigational Product

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

- Occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes the subject to substantial risk and/or does not allow the subject to adhere to investigational product per the requirements of the protocol.
- Occurrence of a treatment-emergent adverse event (TEAE) or considerable worsening of an AE that, in the opinion of the Investigator in consultation with the Medical Monitor and Sponsor, represents an unacceptable risk to the subject if he/she continues with the investigational product. The Investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
- Pregnancy.
- Subject's decision to withdraw from investigational product.

- Weight loss of >5% if not dieting or intentionally trying to lose weight and after consultation with the Sponsor, at the Investigator's discretion.
- C-SSRS indicative of suicidal ideation, PHQ-8 or PHQ-A score ≥ 15 or CDI-2 raw total score of 34, after consultation with a mental health professional, the Sponsor, and at the Investigator's discretion.
- Requirement for use of prohibited concomitant medication after consultation with the Sponsor and Medical Monitor.
- Subject's repeated failure to comply with protocol requirements or study related procedures.

7.6.4. Removal of Subjects from Study

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

7.7. Study Restrictions

7.7.1. 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 24-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 (eg, corticosteroids, vitamin D analogs, prescription shampoos) (except for emollients)	
PUVA phototherapy	
UVB	
Investigational drugs (except ARQ-151 cream)	
Antihistamines – if prescribed for pruritus associated with psoriasis	
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 (eg, 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)

7.8. Treatment

7.8.1. Investigational Product Supplies, Packaging and Labeling

ARQ-151 cream 0.3% will be provided in 45 or 60 gram squeeze tubes. The tubes will be packaged in kits, each containing multiple 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 two. 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 investigational product (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 investigational product supplied. At the conclusion of the study, any unused investigational product will be returned to the Sponsor or designee, or destroyed, as per Sponsor instructions.

Refer to the current version of the IP Handling Manual for details on the accountability, storage, and management of the IP.

7.8.2. Treatment Administration

Psoriasis plaques that have completely resolved, in the opinion of the Investigator, do not require continued treatment. At every clinic visit the Investigator will determine if the IGA, I-IGA and PASI/mPASI are considered 'clear' and subject will stop investigational product. The subject will contact the clinical study site and document in diary when psoriasis returns prior to restarting investigational product. Subjects that clear between scheduled visits should return for an unscheduled visit for the Investigator to confirm IGA, I-IGA, and PASI/mPASI scores are considered 'clear'.

Unless otherwise instructed by the Investigator subjects/caregivers will apply investigational product once daily. Investigational product should be applied 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. Investigational product should be applied at least 20 minutes before going to bed.

Subjects/caregivers should continue to apply investigational product to all active psoriasis lesions including any new plaques that develop during the study unless otherwise instructed by the Investigator. Application will be to all areas affected including the face and intertriginous/genital regions (except for the scalp).

For Cohort 2 initial IP application, the study staff will demonstrate to the subject/caregiver(s) how to apply ARQ-151 cream using the first tube from the kit that is assigned to the subject. Study site staff will be trained to ensure a unit dose (a pea size unit of ARQ-151 cream will cover approximately 1% BSA) is properly squeezed from the tube and applied to all active psoriasis lesion(s) as a thin film and rubbed in using the index and middle finger, rubbing in thoroughly but gently, until the 'white' has disappeared. The parent(s)/caregiver will then practice squeezing a similar amount onto their index and middle finger and apply a thin film to other areas to be treated. The study staff will ensure that the subject/caregiver's application

technique is correct and that a thin layer is applied as instructed. Re-training will be conducted at subsequent visits as needed.

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

7.8.3. 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, eg, 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.

8. STUDY PROCEDURES

8.1. Safety Assessments

The Schedule of Visits and Assessments (see [Section 3](#)) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the 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, vital signs, physical examination, clinical laboratory testing (post Amendment 2, laboratory assessments at Weeks 4, 12 and 24/ET have been removed), either PHQ-8 (in adults) or Modified PHQ-A (in adolescents), C-SSRS (in subject 12 years and older), and AEs as outlined in the Schedule of Visits and Assessments ([Section 3](#)). 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, Cohort 2 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-A/CDI-2, C-SSRS (if 12 years or older), and laboratory tests: hematology, chemistry, urinalysis and a pregnancy test for female subjects of childbearing potential.

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

Day 1 Visit

At Day 1 (Cohort 1 will be final visit of prior ARQ-151 cream study), subjects will be provided details of study requirements and sign an informed consent. Medical history and demographic data, psoriatic plaque assessments (IGA, I-IGA, PASI/mPASI [will be collected for Cohort 1 subjects only if collected in previous ARQ-151 cream study] and BSA), physical examination including weight, vital sign measurements (blood pressure, heart rate, and temperature), PHQ-8 (adults), Modified PHQ-A (adolescents), CDI-2 (6-11 years, inclusive), C-SSRS (12 years and older), laboratory tests: hematology, chemistry, urinalysis and a pregnancy test for female subjects of child bearing potential will be obtained at the final visit of prior ARQ-151 cream study and will serve as the Day 1 assessments for this long-term safety study (ARQ-151-306).

All subjects will be assigned a subject number, which will be entered into the electronic subject tracking system for this long-term safety study.

Scheduled Visits (Day 1 and Visits 1 – 3)

8.1.1. Physical Examination

Physical examinations will be performed as follows:

- Day 1, Week 24

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

8.1.2. 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 and Week 24/ET.

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% unintentional weight loss should be reported to the medical monitor.

8.1.3. Laboratory Tests

All tests listed below will be performed on Day 1. In addition, urine pregnancy test will be performed at Week 4, 12, and 24 for FOCBP only.

All tests listed [Table 3](#) below will be performed according to the Schedule of Visits and Assessments ([Section 3](#)) 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.

Table 3: Laboratory Tests

Hematology	Serum Chemistry
• Hemoglobin • Hematocrit • Total and differential leukocyte count • Red blood cell count with indices and morphology • Platelet count	• Blood Urea Nitrogen • Bilirubin (total and direct) • Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Albumin • Sodium • Potassium • Chloride • Glucose • Creatinine
Urinalysis	Additional Tests
• pH • Specific gravity • Protein* • Glucose • Ketones • Bilirubin • Blood* • Nitrite* • Urobilinogen • Leukocyte esterase*	• Urine pregnancy test** (for females of child bearing potential only)

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

** Baseline/D1, Weeks 4, 12 and 24 for FOCBP only

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

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

- Day 1, Weeks 4, 12, and 24

Adult subjects will complete PHQ-8 questionnaire.

A subject with a PHQ-8 score of '15' or above should be referred promptly to a mental health care professional and, if currently applying 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)
- Severe depression (20 to 24)

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

The 8 item Modified PHQ-A Assessment will be performed in adolescent subjects (12 – 17 years old, inclusive) as follows:

- Day 1, Weeks 4, 12, and 24

Only adolescent subjects will complete PHQ-A questionnaire.

A subject with a PHQ-A 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 investigational product.

Modified PHQ-A

Name: _____ Clinician: _____ Date: _____

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

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

Five severity categories of depression are defined as follows:

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

8.1.6. Children's Depression Inventory 2

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

- Screening, Baseline, Week 4, Week 12 and Week 24

The CDI-2 quantifies depressive symptomatology using reports from children/adolescents, teachers, and parents or caregivers. This study will use the CDI Parent Report Form. An example of the Parent report form is presented in [Appendix 3](#).

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

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

- Day 1, Weeks 4, 12, and 24

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

Cohort 2 (adolescent subjects only) 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 investigational product. This should result in prompt referral to a mental health professional and/or possibly the emergency room. The Medical Monitor should be contacted.

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.

8.1.8. Local Tolerability Assessments

The Investigator Local Tolerability Assessment will be performed as follows:

- Day 1, Weeks 4, 12, and 24

Application site reactions will be graded at the timepoints outlined in the Schedule of Visits and Assessments ([Section 3](#)). Irritation reactions are graded using the scale detailed in the following section ([Berger 1982](#)). **Reactions at the site of investigational product application, which may occur post-Day 1 visit, should be differentiated from the preexisting inflammation associated with the subject's psoriasis.**

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

Dermal Response

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

Other Effects

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

8.1.9. Adverse Events

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

- Day 1, Weeks 4, 12, and 24, and phone calls at Weeks 8 and 18

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 8.6](#).

8.1.10. Phone Visits

Phone visits -- Weeks 8 and 18 -- will be conducted for all subjects to review any adverse event or concomitant medication changes.

Subjects/caregivers will call the site when psoriasis returns prior to restarting application of investigational product.

8.2. Efficacy Evaluations

8.2.1. Investigator Global Assessment (IGA)

Investigator 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, and 24

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

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

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.**

An IGA (using the IGA scale shown above but evaluating intertriginous areas ONLY and NOT whole body involvement) for the intertriginous region alone (I-IGA) will be recorded at Weeks 4, 12, and 24.

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

8.2.2. Psoriasis Area and Severity Index (PASI) and Modified Psoriasis Area and Severity Index (mPASI)

Assessments will be performed as single assessments at each timepoint, from which both PASI’s and mPASI’s will be calculated. The mPASI will be collected for Cohort 1 subjects only if collected in previous ARQ-151 cream study.

PASI/mPASI Assessments will be performed as follows:

- Day 1, Weeks 4, 12, and 24

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

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

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

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

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

mPASI: for subjects with < 10% of an involved anatomic area, the mPASI will be calculated using the actual percentage of the anatomical area involved (eg, 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, PASI/mPASI, or BSA assessments.

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

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

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

8.2.3. Body Surface Area (BSA)

BSA Assessments will be performed as follows:

- Day 1, Weeks 4, 12, and 24

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

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

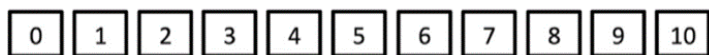
8.2.4. Worst Itch Numerical Rating Scale (WI-NRS)

WI-NRS Assessments will be performed as follows:

- Day 1, Weeks 4, 12 and 24

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

The WI-NRS will be collected from all subjects; subjects 8 years and older will self-report, and caregivers will report if subjects are younger than 8 years.



No itch

Worst
imaginable itch

8.3. Final Study Visit – End of Study

The final study visit will occur approximately at the end of Week 24 of overall involvement in the study. The procedures performed during this visit are as described in Schedule of Events for the Week 24 visit ([Section 3](#)). 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 8.6](#)).

8.4. 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 8.3](#)). It will be noted in the database which subjects have completed the study and which were early terminations.

8.5. Unscheduled Visit

Subjects that clear between scheduled visits should return for an unscheduled visit for the Investigator to confirm IGA, I-IGA and PASI/mPASI are clear and subject will stop application of investigational product after Investigator confirmation. Subjects will call the site when psoriasis returns prior to restarting application of investigational product. 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. These subjects may have an unscheduled visit (although an unscheduled visit is not required as subjects only need to call the site when psoriasis returns prior to restarting application of investigational product:

- Time between stopping study medication and restarting application
- IGA, I-IGA, PASI/mPASI
- 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.

8.6. Adverse Events

8.6.1. 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 investigational product through study completion.

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

8.6.2. 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 (or delegate) via fax or e-mail within 24 hours of becoming aware of the event, whether or not the serious events are deemed IP-related.

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

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

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

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities or respite care (eg, 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 Medical Monitor within one business day of knowledge of event.

8.6.3. 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.

8.6.4. 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).

8.6.5. Adverse Event Reporting

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

The Investigator will review each event and assess its relationship to investigational product treatment (unrelated, unlikely, possibly, probably, likely). Each sign or symptom reported will be graded on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5). The date and time of onset, time relationship to 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 investigational product will be assessed using the following definitions:

Unrelated	• The AE must clearly be caused by the subject's clinical state, or the study procedure/conditions. • Definitely not related to drug. • Temporal sequence of 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 (eg, 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, eg, 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 (eg, 21.0 or higher).

8.7. Reporting Pregnancy

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

The Investigator is responsible for reporting all available pregnancy information on the pregnancy report and submitting to the Medical Monitor within 24 hours of becoming aware of the event, although pregnancy itself is not considered an AE. Follow-up information detailing the outcome of the pregnancy and the health of the newborn should be reported as it becomes available. Any pregnancy resulting in a congenital abnormality or birth defect of the newborn, or neonatal death occurring within 30 days of the birth must be reported as a SAE, regardless of causality. Any infant death that occurs after the 30 day reporting period that the Investigator suspects is related to Investigational Product must also be reported as an SAE.

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

9. 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.

9.1. Statistical Methods

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

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

Descriptive statistics will be used to provide an overview of the 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 safety data will remain missing and will not be estimated. For subjects who withdraw from study due to lack of efficacy will have their data imputed as non-response for the secondary efficacy endpoints. Missing data due to other reasons will not be imputed.

9.1.1. Baseline Definition

For subjects in Cohort 1, the baseline value for safety and efficacy parameters will be defined as the last observation prior to the first dose of ARQ-151 cream in either the ARQ-151 parent study, or this study. Sensitivity analyses will be performed where the baseline value for subjects in cohort 1 is defined as the last observation prior to the first dose of ARQ-151 cream in this study. If subjects choose to enroll in this study, study procedures will not be repeated; study sites will carry over the information from the prior ARQ-151 cream study to the Day 1 visit for this study.

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

9.1.2. Determination of Sample Size

A sample size of up to approximately 330 subjects 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% over 24 weeks of treatment, and in the combination with other studies provide the development program with sufficient numbers of subjects to meet ICH exposure goals.

9.1.3. 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 0.3% in this extension study. The number of patients included in the Safety Population will be summarized.

9.1.4. Interim Analysis

Changes associated with protocol amendment 2 will result in the final analyses of this study, and no further interim analyses are planned.

9.1.5. Background and Demographic Characteristics

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

9.1.6. Study Disposition

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

9.1.7. Protocol Deviations and Eligibility Deviations

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

9.1.8. Investigational Product Compliance

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

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

Investigational product compliance will be calculated based on number of applications and amount of IP used divided by the expected number (amount) of study medication for each subject. Compliance will be summarized descriptively.

9.2. Safety Evaluation

Descriptive statistics will be calculated for safety data and 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.

9.2.1. 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 earliest date of investigational product in this study. All treatment-emergent AEs will be summarized by the number of subjects reporting treatment-emergent AEs, system organ class, preferred term, severity, relationship, and seriousness. As indicated in [Section 8.1.1](#) additional summaries of adverse events will be generated in which the baseline value (for subjects receiving ARQ-151 in studies ARQ-151 parent studies) is defined by the baseline value in studies ARQ-151 parent studies and in which the incidence of adverse events is tabulated across the safety data in both the parent study and this study.

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

For AE tables, 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 listing of subjects who prematurely discontinue from the study drug due to adverse events will also be provided.

9.2.2. Medical History and Physical Examinations

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

9.2.3. Clinical Laboratory Results and Vital Signs/Weight Measurements

All clinical laboratory results and vital signs measurements and their change from baseline will be summarized along with timepoint of collection. Post Amendment 2, laboratory assessments at Weeks 4, 12 and 24/ET have been removed.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results. Shift tables will summarize the number of subjects who gain or lose >5% or >10% body weight over the course of the study.

9.2.4. 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.

9.2.5. PHQ-8 and Modified PHQ-A

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

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

9.2.6. C-SSRS

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

9.2.7. Prior and Concomitant Medications

Summary tables will be presented by World Health Organization-Anatomical Therapeutic Chemical Classification System (WHO-ATC) therapeutic category and product.

9.3. Efficacy Evaluation

The IGA, I-IGA and PASI/mPASI are included to determine the need for treatment and subsequent re-treatment after treatment course in parent study or ARQ-151-306. 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 parent study and every scheduled visit through end of the study (Day 1 and Weeks 4, 12, and 24). 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 50%, 75%, 90%, and 100% reductions in PASI and mPASI will be tabulated in a similar manner.

Duration of IGA Success, defined as the time from the first observation of IGA success to the last time a subjects' disease response meets the criteria for IGA success will be summarized. The duration of IGA success for subjects who end treatment in IGA success will be censored at the last disease assessment date.

In subjects who achieve 'clear' scores for IGA, I-IGA, PASI, and mPASI and stop treatment to all lesions, time to restarting study drug (treatment-free interval) will be summarized. Subjects with continual clearance will be censored at their date of last contact. Subjects may have multiple treatment free intervals and each interval will be counted separately.

10. STUDY ADMINISTRATION

10.1. Ethics

10.1.1. Ethics Review Board

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

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

The Investigator, the Sponsor, or designee shall promptly notify the IRB or IEC of any SAEs, SUSARs, or any other information that may affect the safe use of the 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.

10.1.2. 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).

10.1.3. Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date a current version of the IRB/EC approved ICF summarizing the discussion prior to enrollment 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.

10.2. Study Completion and Termination

10.2.1. Study Completion

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

10.2.2. Study Termination

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

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

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

10.3. Study Monitoring

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

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

10.4. Data Quality Assurance

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

The Clinical Study Report will be audited by the Clinical Research Organization's Quality Assurance (QA) department and the QA audit certificate will be included in the study report.

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

10.5. Data Handling and Record Keeping

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

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

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

10.6. Protocol Amendments and Deviations

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

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

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

10.7. Confidentiality and Privacy

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

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

10.8. Conflict of Interest

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

10.9. Report Format

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

10.10. Publication Policy

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

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12. APPENDICES

APPENDIX 1. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) SINCE LAST VISIT VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

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APPENDIX 2. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS) BASELINE/SCREENING VERSION

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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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, <i>as a result of act</i> . Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is <i>any</i> 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 ☐	Yes ☐	No ☐
		Total # of Attempts		Total # of Attempts	
		_____		_____	
Has subject engaged in Non-Suicidal Self-Injurious Behavior?		Yes ☐	No ☐	Yes ☐	No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self injurious act (<i>if not for that, actual attempt would have occurred</i>). 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 ☐	Yes ☐	No ☐
		Total # of interrupted		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 ☐	Yes ☐	No ☐
		Total # of aborted		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, <i>medical</i> 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, <i>medical</i> 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	
		_____	_____	_____	

APPENDIX 3. CHILDREN'S DEPRESSION INVENTORY 2 (PARENT REPORT)

By Maria Kovacs, Ph.D.



Child's Name/ID: _____

Parent's Name/ID: _____

Relationship to Child: _____

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

Child's Sex: ☐ Male ☐ Female
Circle One

Date of Birth: ____/____/____
Year Month Day

Today's Date: ____/____/____
Year Month Day

Instructions:

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

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

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

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