Protocol ARQ-151-101

A Phase 1/2a Single Dose and 28-day Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety, Pharmacokinetics and Efficacy of ARQ-151 Cream 0.5% and 0.15% in Adults with Mild to Moderate Chronic Plaque Psoriasis

NCT03392168

GCP Statement

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

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

Version/Date	Description
ARQ-151-101 17 October 2017	Original Protocol
ARQ-151-101 Amendment 1.0 06 December 2017	• Added Protocol Revision History section. • Added footnote “k” to the Study Events Flowchart for Cohort 2 under Schedule of Visits and Assessments to allow a window for follow-up visits. • Revised Inclusion Criterion #7 to more completely define Women of Non-Child Bearing Potential to include those who are post-menopausal and surgically sterile. • Revised Exclusion Criterion #12 to clarify the washout period for excluded biologic medications and to update the washout period for investigational medications. • Updated Ethics Review Board information to include information relevant to clinical studies performed in the US. • Editorial and administrative changes throughout the protocol to clarify language and formatting to improve readability.
ARQ-151-101 Amendment 1.1 27 February 2018	• This amendment applies only to the US site to add optional dermal imaging assessment (photography). • Revised Study Events Flowchart for Cohort 2 under Schedule of Visits and Assessments to show optional photography for Baseline, Visit 3, Visit 4, and Visit 6 for US site. • Revised footnote “c” of the Study Events Flowchart for Cohort 2 under Schedule of Visits and Assessments to show photography assessment visits for Canadian (Baseline and Visit 6 only) and US sites (Baseline, Visit 3, Visit 4, and Visit 6). • Revised section 8.13.2 Dermal Imaging to show photography assessment visits for Canadian (Baseline and Visit 6 only) and US sites (Baseline, Visit 3, Visit 4, and Visit 6).
ARQ-151-101 Amendment 2.0 19 March 2018	• This amendment increases the number of optional dermal photography assessments from two to four and applies to all sites participating in dermal imaging (both Canadian and US). • Revised Study Events Flowchart for Cohort 2 under Schedule of Visits and Assessments to show optional photography for Baseline, Visit 3, Visit 4, and Visit 6 for all sites. • Revised section 8.12.1 Screening to indicate four rather than three investigational centers participating in dermal imaging. • Revised section 8.13.2 Dermal Imaging to show photography assessment visits for all photography sites at Baseline, Visit 3, Visit 4, and Visit 6.

2 PRINCIPAL INVESTIGATOR AND SPONSOR – SIGNATORIES

A Phase 1/2a Single Dose and 28-day Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety, Pharmacokinetics and Efficacy of ARQ-151 Cream 0.5% and 0.15% in Adults with Mild to Moderate Chronic Plaque Psoriasis

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5 SYNOPSIS

Compound:	ARQ-151 cream 0.15 % and ARQ-151 cream 0.5%
Clinical Indication:	Chronic Plaque Psoriasis
Study Phase and Type:	A Phase 1/2a Single Dose and 28-day Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety, Pharmacokinetics and Efficacy of ARQ-151 cream 0.5% and 0.15% in Adults with Mild to Moderate Chronic Plaque Psoriasis
Study Objectives:	1. To assess the safety and PK of a single dose application of ARQ-151 cream 0.5% to 25 cm^2 of psoriatic plaque(s) (Cohort 1) 2. To assess the safety, pharmacokinetics and efficacy of ARQ-151 cream 0.5% vs. vehicle and ARQ-151 cream 0.15% vs vehicle applied QD x 28 days to individuals with 0.5% to 5.0% BSA of chronic plaque psoriasis (Cohort 2)
Summary of Study Design:	There are 2 cohorts of subjects. Cohort 1 is a single dose study to 25 cm^2 of psoriatic plaque(s) in 8 psoriasis subjects. Cohort 1 subjects will then be enrolled, if they meet entry criteria, into Cohort 2 of the study. Cohort 2 is a parallel group, double blind, vehicle controlled study in which ARQ-151 cream 0.5%, ARQ-151 cream 0.15% or vehicle cream is applied QD x 28 days to subjects with at least 0.5% BSA of chronic plaque psoriasis; area for application will not exceed 5.0% BSA.
Blinding:	The single dose assessment (Cohort 1) to 25 cm^2 of psoriatic plaque(s) is open label. The parallel group study (Cohort 2) is double blind and vehicle controlled.
Countries:	Canada (Cohorts 1 and 2) and United States (Cohort 2 only)
Number of sites:	7 sites in Canada; 1 site in the United States.
Study Population:	Subjects will be adults, male and female (>18 y/o). Cohort 1 subjects will have at least 25 cm^2 of chronic plaque psoriasis; Cohort 2 subjects will have 0.5 – 5.0% total BSA of chronic plaque psoriasis and at least one target plaque of psoriasis at least 9 cm^2 in size and with a TPSS ≥ 4.
Number of Subjects:	1. Cohort 1 = Up to 8 subjects 2. Cohort 2 (can include Cohort 1 subjects) = 84 subjects; randomized 1:1:1 to ARQ-151 cream 0.5%: ARQ-151 cream 0.15%: vehicle/placebo. Total subjects in both cohorts = 84-92.

Duration of Participation for Subjects:	1. Cohort 1: 22 days (Screening, Day 1, Day 2 and Day 8). If subjects roll into Cohort 2, then total study duration prior to start of Cohort 2 is approximately 22 days. Screening is up to 2 weeks. 2. Cohort 2 (not in Cohort 1): Screening (up to 6 weeks) + Treatment phase and follow-up (5 weeks), 77 days.
Study Products:	ARQ-151 cream drug product will be supplied as a 0.15% and 0.5% cream. Matching vehicle cream will contain only excipients of ARQ-151 cream.
Planned Dose Level:	Cohort 1 subjects will receive ARQ-151 cream 0.5% applied to 25 cm^2 of psoriatic plaque(s). Cohort 2 subjects will receive ARQ-151 cream 0.15% or 0.5% or matching vehicle cream applied to all psoriatic lesions up to an area of 5.0% BSA (if subject rolled over from Cohort 1, lesions treated in Cohort 1 can also be treated in Cohort 2).
Safety Assessments:	Safety will be monitored through application site assessments, safety labs and AEs.
Safety Analysis:	The following analyses will be performed; however, no formal inferential statistics will be done on safety assessments. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. **Adverse Events:** A subject-by-subject treatment-emergent AE (TEAE) data listing, including verbatim term, preferred term, treatment, severity, and relationship to study drug, will be provided. The number of subjects experiencing AEs and number of AEs will be summarized by treatment using frequency counts. **Medical History and Physical Examinations:** Medical history will be listed by subject. Physical examinations will be performed at screening, baseline and end-of-study. **Clinical Laboratory Results:** Routine blood chemistries and 12-lead ECGs will be obtained throughout the study.

Efficacy Analysis	The single dose Cohort 1 will have analyses only for safety and pharmacokinetics. The parallel group assessment (Cohort 2) will have analyses for safety, pharmacokinetics, and efficacy. In the parallel group assessment (Cohort 2), the Primary Efficacy Endpoint will be: • Difference in mean percent change from baseline at week 4 in the product of: [Target Plaque Severity Score (TPSS) x Target Plaque Area (TPA)] (TPSS x TPA) between each dose concentration level of ARQ-151 cream and vehicle control. This will be assessed as a sum of up to 3 target plaques per subject. The secondary efficacy endpoints will include: 1. Difference in mean percent change from baseline at weeks 1, 2 and 3 in TPSS x TPA between each dose concentration level of ARQ-151 cream and vehicle control. This will be assessed as a sum of up to 3 target plaques per subject. 2. Difference in mean percent change from baseline at weeks 1, 2, 3 and 4 in TPSS between each dose concentration level of ARQ-151 cream and vehicle control. This will be assessed as a sum of up to 3 target plaques per subject. 3. Difference in mean percent change from baseline at weeks 1, 2, 3, and 4 in TPA between each dose concentration level of ARQ-151 cream and vehicle control. This will be assessed as a sum of up to 3 target plaques per subject.
Pharmacokinetic Sample Collection: **(Cohort 1 n = up to 8; Cohort 2 n = 45)**	1. Cohort 1: PK draws will be done at 1, 2, 4, 6 and 24 hours after ARQ-151 cream 0.5% application to 25 cm^2 of psoriatic plaques 2. Cohort 2: PK draws will be done on day 1: 1, 2, 4 and 6 hours; day 14: pre-dose (trough) and 1-hour post-dose; and day 28: pre-dose (trough), 1, 2, 4, 6 and 24 hours post-dose

Statistical Analysis:	Four analysis populations will be defined: • Safety population will include all subjects who are enrolled and received at least one confirmed dose of study medication; this population will be defined separately for each cohort. • Modified Intent-to-Treatment (mITT) population will include all subjects who are in the safety population for Cohort 2 with at least one post-baseline efficacy evaluation. • Per-Protocol (PP) Population will include all subjects who are in the safety population for Cohort 2, were at least 80% compliant with study medication, and showed no other serious deviations from the study protocol. • PK population will include all subjects receiving the active drug with sufficient plasma concentrations of ARQ-151 cream to define a profile, as determined by the pharmacokineticist; this population will be defined separately for each cohort. The primary endpoint of mean percent change from baseline at Week 4 in TPSS x TPA will be analyzed using a mixed model for repeated measures (MMRM). The difference between treatment groups in TPSS x TPA at Weeks 1, 2, and 3 will also be analyzed using the MMRM. Descriptive statistics will be provided for observed and percent change from baseline in TPSS x TPA at Weeks 1, 2, 3, and 4. A comparison of changes in TPSS and TPA between treatment groups will be analyzed similarly to TPSS x TPA.

6 SCHEDULE OF VISITS AND ASSESSMENTS

STUDY EVENTS FLOW CHART: COHORT 1; SINGLE DOSE APPLICATION TO 25 cm^2

Study Procedure **Days**	**Screening**	**Day 1**	**Day 2**	**Day 8**
Weeks	**2 weeks**			
Informed consent	X			
Medical history	X			
Physical examination[a]	X	X		
Hematology, Serum Chemistries, and Urine Analysis	X		X	
Urine Drug Screen	X			
I/E criteria	X	X		
Vital signs, height, weight	X	X		
Urine pregnancy test[b]	X	X		
Resting 12-lead ECG	X			
ARQ-151 cream application[c]		X		
PK sampling[d]		X	X	
Application Site Reaction Assessment		X	X	
Adverse events assessments		X	X	
Concomitant medications	X	X	X	
Telephone Follow-up[e]				X

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

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

[c] ARQ-151 cream application to 25 cm^2 of target plaque(s)

[d] PK sampling: 1, 2, 4, 6 (±10 minutes for 1, 2, 4 and 6 hour collections) and 24 hours (± 1 hour) after ARQ-151 cream application to 25 cm^2 of psoriatic plaque(s)

[e] Telephone call to the subjects for follow up on any continuing adverse events related to study drug. Telephone call will also assess any emergent adverse event post Day 1 ARQ-151 cream application. Any emergent AEs will be followed in the clinic at the investigator's discretion for up to one month until resolved or otherwise judged as clinically stable.

STUDY EVENTS FLOW CHART: COHORT 2; 28 DAY APPLICATION TO 0.5 – 5% BSA; DOUBLE BLIND, PLACEBO CONTROLLED

Study Procedure	Screen Visit 1	Baseline Day 1 Visit 2	Week 1 Day 7[k] Visit 3	Week 2 Day 14[k] Visit 4	Week 3 Day 21[k] Visit 5	Week 4 Day 28[k] Visit 6	Week 4 Day 29[k] Visit 7	Week 5 Day 35[k]
Weeks	**-6**	**0**	**1**	**2**	**3**	**4**		
Informed consent	X							
Medical history	X							
Physical examination[a]	X	X				X		
I/E criteria	X	X						
Hematology, Serum Chemistries, and Urine Analysis	X	X		X		X		
Urine Drug Screen	X							
Vital signs, weight, height	X	X	X	X	X	X		
TPSS x TPA measurements[b]	X	X	X	X	X	X		
Application Site Reaction Assessment		X	X	X	X	X		
Depressive Symptomatology Questionnaire	X			X		X		
Optional Photography[c]		X[c]	X[c]	X[c]		X[c]		
Urine pregnancy test[d]	X	X	X	X	X	X		
Resting 12-lead ECG	X	X				X		
PK sampling[e]		X		X		X	X	

STUDY EVENTS FLOW CHART: COHORT 2; 28 DAY APPLICATION TO 0.5 – 5% BSA; DOUBLE BLIND, PLACEBO CONTROLLED (Continued)

Study Procedure	Screen Visit 1	Baseline Day 1 Visit 2	Week 1 Day 7 [k] Visit 3	Week 2 Day 14 [k] Visit 4	Week 3 Day 21 [k] Visit 5	Week 4 Day 28 [k] Visit 6	Week 4 Day 29 [k] Visit 7	Week 5 Day 35 [k]
Weeks	**-6**	**0**	**1**	**2**	**3**	**4**		
Vehicle Application in Clinic (subject training)[f]			X[f]		X[f]			
Drug/Vehicle Application in Clinic[g]		X[g]		X[g]		X[g]		
ARQ-151 cream/Vehicle application at home		X	X	X[h]	X	X[h]		
Dispense study medication		X	X	X	X			
Weigh study medication		X	X	X	X	X		
Dispense/Review Diary		X	X	X	X	X	X[l]	
Adverse events assessments		X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X		
Optional Skin biopsy[i]						X		
Telephone follow up [j]								X

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

[b] Target Plaque Severity Score: Sum of erythema, induration, and scaling each scored 0-4 (maximum score = 12). Target plaque area = Longest diameter (cm) x Widest perpendicular diameter (cm). Up to three target plaques will be chosen, each at least 9 cm^2. The target plaques must each have a TPSS ≥4. Subjects much have at least one target plaque.

[c] Photography will be at selected investigational sites. Photography will be optional and confined to the target lesions. All efforts will be made to de-identify the subjects.

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

STUDY EVENTS FLOW CHART: COHORT 2; 28 DAY APPLICATION TO 0.5 – 5% BSA; DOUBLE BLIND, PLACEBO CONTROLLED (Continued)

[e] PK draws on day 1: 1, 2, 4 and 6 hours (± 10 minutes for 1, 2, 4 and 6 hour collections); day 14: pre-dose (trough) and 1-hour (± 10 minutes) post-dose; and day 28: pre-dose (trough), 1, 2, 4, 6 (± 10 minutes for 1, 2, 4 and 6 hour collections); and 24 hours (± 1 hour) post-dose for analysis. PKs will be collected from at least 45 volunteer subjects; PK collections will continue until PKs have been collected from 15 subjects in each treatment group.

[f] Vehicle application training post baseline will be conducted as needed on Visits 3 (week 1) and 5 (week 3).

[g] Drug or vehicle will be applied in clinic.

[h] Visits 4 (week 2) and 6 (week 4) only: ARQ-151 cream or vehicle application will be done at home in the morning of Days 13 and 27 and in the morning at the clinic on PK collection Days 1, 14 and 28. ARQ-151 cream or vehicle will not be applied in the evening of Days 13 and 27.

[l] 4 mm skin punch biopsy for analysis of Roflumilast and metabolites (n = 15 for analysis). Tissue will be collected from at least 15 volunteer subjects; tissue collection will continue until samples have been collected from 5 subjects in each treatment group.

[j] Telephone call to the subjects for follow up on any continuing adverse events related to study drug. Telephone call will also assess any emergent adverse event post Visit 6. 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.

[k] Follow-up visits should occur within +/- 1 day of the targeted date.

[l] For those subjects participating in the PK assessment, diary is completed by subject and reviewed by study staff during visit (Possible Side Reactions / Comments Section of the diary).

7 ABBREVIATIONS

AE	Adverse Event
AMP	Adenosine Monophosphate
AUC	Area Under the Curve
BSA	Body Surface Area
C_{max}	Maximum Concentration
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
ECG	Electrocardiography
ERB	Ethics Review Board
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practices
HC	Health Canada
HCA	Alpha-Hydroxycinnamaldehyde
HPRT	Hypoxanthine-guanine Phosphoribosyl Transferase
IB	Investigational Brochure
IC50	Half Maximal Inhibitory Concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IGA	Investigator Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
IVRT	In Vitro Release Testing
mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MMRM	Mixed Model for Repeated Measures
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
NDA	New Drug Application
ng	Nanogram
PDE-4	Phosphodiesterase 4
PK	Pharmacokinetics

QD	Once Daily ("quaque die")
SAE	Serious Adverse Event
Th1	Type 1 T Helper Cell
Th17	Type 17 T Helper Cell
T_{max}	Time to reach maximum concentration
TPA	Target Plaque Area
TPSS	Target Plaque Severity Score
TPSS x TPA	Target Plaque Severity Score x Target Plaque Area
V79	Chinese hamster cell line

8 BACKGROUND AND RATIONALE

8.1 Introduction

Roflumilast is a phosphodiesterase 4 (PDE-4) inhibitor approved globally to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations associated with chronic bronchitis. Roflumilast and its active metabolite, roflumilast N-oxide, are high affinity selective inhibitors of PDE-4 (a major cyclic-3′,5′-adenosine monophosphate (cyclic AMP)-metabolizing enzyme), whose activity leads to accumulation of intracellular cyclic AMP. There are four different subtypes of PDE-4: PDE-4a, PDE-4b, PDE-4c, and PDE-4d, each with several isoforms (splicing variants). 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.

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 treatment but it is irritating, not suitable for use on the face, and its efficacy is rather modest. Hence, there is substantial medical need for additional topical approaches in the treatment of psoriasis.

8.1.1 Preclinical Studies

Roflumilast was initially developed as a 500 mcg tablet for oral therapy in patients with COPD, and as such has been thoroughly evaluated in nonclinical studies. The safety profile is well-established and the results of those studies are relevant to the dermal roflumilast (ARQ-151 cream) development program. Oral roflumilast (500 mcg tablet) was approved by Health Canada as DAXAS® in December 2010 and by the US FDA as DALIRESP® in February 2011 for the treatment of COPD. The study sponsor is conducting nonclinical studies in which roflumilast is applied dermally to supplement the information available through the registration and labeling of oral roflumilast and specifically to support initial dermal clinical trials. Summaries of these new data from dermal studies and existing data from the prior oral/systemic studies follow. In addition, since roflumilast N-oxide is a major active metabolite, some studies were conducted on the metabolite also.

The dermal nonclinical program for ARQ-151 cream followed current International Conference on Harmonisation (ICH) guidelines. A dermal toxicology program was initiated that included a 13-week dermal toxicity study in minipigs (with a 28-day interim sacrifice to support Phase 1 studies), a skin sensitization study in guinea pigs, a phototoxicity study and an eye irritation study.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.1.2 Clinical Studies

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

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

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

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

The only contraindication to oral roflumilast, other than hypersensitivity to components of the product, is in patients with moderate to severe liver impairment (Child-Pugh B or C), where systemic levels of roflumilast may become highly elevated.

8.2 Rationale

In 2016, Snape and colleagues performed a phase 1 randomized clinical trial to assess the effect on skin infiltrate thickness and tolerability of topical phosphodiesterase inhibitors, including roflumilast, in the treatment of psoriasis vulgaris using a modified psoriasis plaque test. The products evaluated were the active comparators calcipotriol 0.005% and betamethasone valerate 0.1% (both in their marketed cream formulations), and investigational cream formulations of roflumilast 0.5%, TAK-084 0.5% and 5%. A vehicle cream was used as a control (the vehicle cream and roflumilast formulations in this study were different from the ARQ-151 cream formulation). Each treatment was applied daily to different test sites located on a single psoriasis plaque of an individual for 3 weeks. Fifteen patients with psoriasis were studied. The primary endpoint of mean change from baseline in skin infiltrate thickness after 3 weeks of treatment

showed statistically significant improvements for all treatments: betamethasone valerate (-286.9 µm), the selective PDE-4 inhibitors roflumilast 0.5% (-237.1 µm), TAK-084 0.5% (-153.6 µm), TAK-084 5% (-216.7 µm) and calcipotriol 0.005% (-187.7 µm) when compared with vehicle cream control (all $p < 0.001$) (Snape 2016).

The above data indicated to us that topical roflumilast, in an appropriate market image vehicle, could provide an important addition to the dermatologist's armamentarium in treating chronic plaque psoriasis.

8.2.1 Dose Selection

The ARQ-151 cream 0.5% dose concentration was selected because of the efficacy observed in the Snape, et al study described above (Snape 2016). [redacted]
The dose concentration of ARQ-151 cream 0.15% was selected to determine whether lower ARQ-151 cream doses are effective and whether systemic exposure is also reduced.

Cohort 1 will involve application of ARQ-151 cream 0.5% to 25 cm^2 of psoriatic plaque(s). It is well known that cutaneous disease states can alter drug permeability as compared to normal human skin. Since psoriatic skin is known to have different drug permeability characteristics than normal skin (Tang-Liu 1999), we do not believe there is anything to be gained by prior application of topical drug to normal human volunteers. [redacted]

8.2.2 Risks and/or Benefits to Subjects

Subjects in Cohort 1 will not be expected to see an improvement in their psoriasis since it is a single dose of drug product and the purpose of Cohort 1 is PK analysis to justify the escalation in the area treated in Cohort 2.

Subjects randomized to active treatment in Cohort 2 may see an improvement in their psoriasis with the use of ARQ-151 cream at either or both dose levels. Subjects randomized to the vehicle arm may also see an improvement as the excipients in the vehicle may have a moisturizing effect on the subject's psoriatic plaques. ARQ-151 cream is an unprecedented treatment for psoriasis and if efficacious, would add substantially to the dermatologist's armamentarium in treating patients with this disease.

The safety monitoring practices employed in this protocol (i.e., physical examinations, application site reaction assessments, hematology, serum chemistry, urinalysis, and AE questioning) are adequate to protect the subjects' safety and should detect expected AEs. [redacted]

8.3 Study Objectives

8.3.1 Primary Objectives

1. To assess the safety and PK of a single dose application of ARQ-151 cream 0.5% to 25 cm^2 of psoriatic plaque(s) (Cohort 1).

2. To assess the safety, pharmacokinetics and efficacy of ARQ-151 cream 0.5% and ARQ-151 cream 0.15% vs. vehicle applied QD x 28 days to individuals treated with up to 5.0% BSA of chronic plaque psoriasis (Cohort 2).

8.4 Efficacy Endpoints

8.4.1 Primary Endpoint

The single dose Cohort 1 will have analyses only for safety and pharmacokinetics.

The parallel group assessment (Cohort 2) will have analyses for safety, pharmacokinetics, and efficacy.

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

- Difference in mean percent change from baseline at week 4 in the product of: [Target Plaque Severity Score (TPSS) x Target Plaque Area (TPA)] (TPSS x TPA) between each dose concentration level of ARQ-151 cream and vehicle control. This will be assessed as a sum of up to 3 target plaques per subject.

8.4.2 Secondary Endpoints

The secondary efficacy endpoints in the parallel group (Cohort 2) assessment will include:

1. Difference in mean percent change from baseline at weeks 1, 2, and 3 in TPSS x TPA between each dose concentration level of ARQ-151 cream and vehicle control. This will be assessed as a sum of up to 3 target plaques per subject.
2. Difference in mean percent change from baseline at weeks 1, 2, 3, and 4 in TPSS between each dose concentration level of ARQ-151 cream and vehicle control. This will be assessed as a sum of up to 3 target plaques per subject.
3. Difference in mean percent change from baseline at weeks 1, 2, 3, and 4 in TPA between each dose concentration level of ARQ-151 cream and vehicle control. This will be assessed as a sum of up to 3 target plaques per subject.

8.5 Overall Study Design and Plan

There are 2 cohorts of subjects:

Cohort 1 is a single dose study to 25 cm^2 of psoriatic plaque(s) in up to up to 8 psoriasis subjects. Cohort 1 subjects may then be enrolled into Cohort 2 of the study if all admission criteria are met at the Baseline Visit (Day 1, Visit 2, per Cohort 2). In this case, the same plaque(s) treated in the Cohort 1 study may also be treated in Cohort 2.

Cohort 2 is a parallel group, double blind, vehicle controlled study in which ARQ-151 cream 0.5%, ARQ-151 cream 0.15% or vehicle cream is applied QD x 28 days to subjects with between 0.5% to 5.0% BSA of chronic plaque psoriasis.

Including both Cohorts, a total of up to 92 subjects will be enrolled at 7 study sites in Canada and 1 site in the U.S. Subjects will be adult (≥18 y/o) males or females with chronic plaque psoriasis. For inclusion into Cohort 2, subjects must have at least 1 target plaque of at least 9 cm^2 in size with TPSS ≥4. While 1 target plaque is minimally acceptable, it is strongly recommended that 2 or 3 target plaques be identified, if present, meeting these criteria. Target plaques may be on the knees and/or elbows, but priority should be given to identifying target lesions in other areas. All psoriasis lesions on a subject will be treated in this Cohort except for those on the face, scalp, intertriginous areas, palms and soles.

Subject Participation

Cohort 1: This cohort involves a minimum of three clinic visits including Screening, Baseline, one follow-up visit (24 hours after the baseline visit) and one follow up telephone call 7 days after the follow up visit. Subjects may be asked to return for additional visits(s) if an adverse reaction occurs. The interval between the Screening and Baseline visits could be up to 14 days, therefore the anticipated maximum duration of subject participation in Cohort 1 is 22 days.

Cohort 2: This cohort involves a minimum of seven clinic visits including Screening, Baseline and four visits at Week 1, Week 2, Week 3 and Week 4 of treatment and a day 29 visit for a final PK collection. A follow-up telephone call with subjects will occur at week 5 to assess any reactions to discontinuing drug product and will decide upon disposition of any ongoing adverse events.

The interval between the Screening and Baseline visits could be up to 6 weeks, therefore the anticipated maximum duration of subject participation in Cohort 2 is 77 days.

8.6 Randomization

Cohort 1: Cohort 1 is an open label single dose application of ARQ-151 cream 0.5% to 25 cm^2 of psoriatic plaque(s) in up to eight (8) subjects. Cohort 1 subjects may enroll in Cohort 2 if the eligibility criteria for Cohort 2 are met.

Cohort 2: Subjects will apply ARQ-151 cream 0.5% or ARQ-151 cream 0.15% or vehicle to psoriatic plaques that will not exceed an application area of 5% BSA. Assignment of drug or vehicle will be made at a 1:1:1 ratio according to a computer generated randomization list. Randomization will take place at Baseline after the patient has been found to be fully eligible for participation. A kit containing ten (10) tubes of study medication will be assigned to each subject. Each kit has a unique kit number (randomization number).

8.7 Numbering of Subjects

All treated subjects will be identified by a unique four-digit subject ID number. The first two digits correspond to the site number (assigned by the Sponsor), the next three digits correspond to the sequential order in which the subject was enrolled into the study. Screen failures will not be assigned a number.

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

8.8 Blinding

Cohort 1: This is an open label Cohort, therefore both the subjects and the clinical personnel will be aware that ARQ-151 cream 0.5% will be applied to 25 cm^2 of psoriatic plaque(s).

Cohort 2: This is a double-blind Cohort, therefore neither the subjects nor the clinical personnel will be aware of which treatment an individual has received.

8.9 Selection of Study Population

8.9.1 Inclusion Criteria

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

1. Participants legally competent to sign and give informed consent
2. Cohort 1: Adult male and female subjects aged ≥18 years with at least 25 cm^2 of chronic plaque psoriasis (diagnosed by a dermatologist).
3. Cohort 2: Adult male and female subjects aged ≥18 years with chronic plaque psoriasis (diagnosed by a dermatologist) covering 0.5% to 5.0% of total BSA excluding the face, scalp, intertriginous areas, palms and soles.

4. Subjects must have at least one target plaque, of at least 9 cm^2 in size with a TPSS ≥4. Target plaques may be on the knees and/or elbows, but priority should be given to identifying target lesions in other areas. All psoriasis lesions on a subject will be treated in this study except for those on the face, scalp, intertriginous areas, palms and soles.
5. Psoriasis disease duration of ≥6 months at the baseline visit.
6. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test at Screening (Visit 1). In addition, sexually active WOCBP must agree to use at least one form of highly effective contraception throughout the trial. Highly effective forms of contraception include: oral/implant/injectable/transdermal contraceptives, intrauterine device, and partner's vasectomy. If barrier methods are used (e.g., condom with spermicide, diaphragm with spermicide), then 2 forms of conception are required.
7. Women of non-childbearing potential (WONCBP) must either be post-menopausal with spontaneous amenorrhea for at least 12 months with a serum follicle stimulating hormone (FSH) level of ≥ 30 mIU/mL or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, hysteroscopic sterilization, bilateral tubal ligation or bilateral salpingectomy).
8. In good health as judged by the Investigator, based on medical history, physical examination, 12-lead electrocardiogram (ECG), serum chemistry labs, hematology values, and urinalysis.
9. Subjects agree not to have prolonged sun exposure during the course of the study. Tanning bed use is not allowed.
10. Subjects are considered reliable and capable of adhering to the Protocol and visit schedule, according to the judgment of the Investigator.

8.9.2 Exclusion Criteria

1. Subjects with non-plaque forms of psoriasis (erythrodermic, guttate, pustular or palmo-plantar psoriasis)
2. Subjects with drug-induced psoriasis
3. Evidence of skin conditions at the time of Screening Visit other than psoriasis that would interfere with evaluations of the effect of the study medication on psoriasis, as determined by the Investigator
4. Subjects with any serious medical condition or laboratory abnormality, that would prevent study participation or place the subject at significant risk, as judged by the investigator
5. Subjects with any psychiatric illness that would prevent study participation or place the subject at significant risk, as judged by the investigator
6. Pregnant or lactating women or women planning to become pregnant during the study and / or within 28 days following the last dose of study medication
7. Known allergies to excipients in ARQ-151 cream (petrolatum, isopropyl palmitate, methylparaben, propylparaben, Diethylene Glycol Monoethyl Ether, hexylene glycol, cetylstearyl alcohol, dicetyl phosphase and ceteth-10 phosphate)

8. Subjects who cannot discontinue the use of strong P-450 cytochrome inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, and rifampin for two weeks prior to the baseline visit and during the study period.
9. Subjects who cannot discontinue the use of strong P-450 cytochrome inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, suboxone and telithromycin for two weeks prior to the baseline visit and during the study period.
10. Subjects who are unwilling to refrain from using a tanning bed for 2 weeks prior to baseline and during the study
11. Subjects who have received oral roflumilast (Daxas®, Daliresp®) within the past 4 weeks
12. Subjects who cannot discontinue systemic therapies and/or topical therapies for the treatment of psoriasis prior to the baseline visits and during the study period according to the table below:

Excluded Medications and treatments	**Wash out period prior to Day 1**
Topical psoriasis medications (corticosteroids, calcipotriene, topical vitamin D derivatives, retinoids, anthralin, coal tar)	Cohort 1: 48 hours Cohort 2: 14 days
Systemic non-biologic treatments for psoriasis (apremilast, methotrexate, cyclosporine, azathioprine, corticosteroids)	Cohort 1: 48 hours Cohort 2: 28 days
UVB or PUVA phototherapy	Cohort 1: 48 hours Cohort 2: 28 days
Systemic retinoids	Cohort 1: 48 hours Cohort 2: 12 weeks
All biologics	Cohort 1: 48 hours Cohort 2: 12 weeks
Investigational drugs	Cohort 1: 48 hours Cohort 2: 12 weeks (biologics); 5 half-lives (orals); 2 weeks (topical)
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 screening, and are continued at the same dose throughout the study. Non-medicated emollients, moisturizers and sunscreens will be allowed as normally used by the subjects.	

13. Subjects with a history of chronic alcohol or drug abuse within 6 months of initiation of study medication.
14. History of and/or concurrent condition of serious hypersensitivity (anaphylactic shock or anaphylactoid reaction) to PDE-4 inhibitors.
15. Current or a history of cancer within 5 years with the exception of fully excised skin basal cell carcinoma, cutaneous squamous cell carcinoma or carcinoma in situ of the cervix.
16. Subjects with active infection that required oral or intravenous administration of antibiotics, antifungal or antiviral agents within 7 days of Baseline/Day 1
17. Subjects who are unable to communicate, read or understand the local language, or who display another condition, which in the Investigator's opinion, makes them unsuitable for clinical study participation.

8.9.3 Removal of Subjects from the Study

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

1. Occurrence of any medical condition or circumstance that, in the opinion of the Investigator, exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the Protocol.
2. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that occurs which the Investigator determines continued participation is not in the best interest of the subject.
3. Subject's decision to withdraw.
4. Requirement for use of prohibited concomitant medication.
5. Subject's repeated failure to comply with protocol requirements or study related procedures.
6. The subject interrupts trial study drug application for more than 50% of scheduled doses.
7. Termination of the study by the Sponsor, FDA, or other regulatory authorities.

8.10 Study Restrictions

8.10.1 Prohibitions and Concomitant Therapy

Prohibited medications and products are detailed in the exclusion criteria (Section 8.9.2).

Generally, the addition of new medications, including nonprescription medications, during the course of the study is discouraged. However, the short-term use of a medication may be authorized by the Investigator. The Investigator must make the decision to authorize the use of any such a medication only after consideration of the clinical situation, the potential for masking symptoms of a more significant underlying event, and whether the use of the medication will compromise the outcome or validity of the clinical investigation. If medication is required, the name, strength, frequency, duration of use, and reason for use will be recorded in source documents and transcribed to Case Report Forms.

8.11 Treatments

8.11.1 Drug Administration

Cohort 1: ARQ-151 cream 0.5% will be applied by site personnel to 25 cm^2 of psoriatic plaque(s) (more than one plaque may be identified for a total area of 25 cm^2).

The study sponsor or its representative will ensure the study staff can demonstrate proper dosing for Cohort 1 at the Site Initiation Visit. Study staff will be trained to ensure a unit dose (a pea-sized amount of ARQ-151 cream vehicle) is properly squeezed from the vehicle training tube and applied as a thin film and rubbed in using the index and middle finger, rubbing in thoroughly but gently, until the 'white' has disappeared.

Cohort 2: At the randomization visit, the study staff will demonstrate to the subject how to apply ARQ-151 cream or vehicle using the first tube from the kit that is assigned to the subject at randomization. The study staff will demonstrate application to the subject according to the technique described above. The subject will then practice squeezing a similar amount onto their index and middle finger and apply a thin film to areas to be treated. The study staff will confirm that the subject's application technique is correct.

Re-training will be conducted at subsequent visits (visits 3 and 5) as needed using a vehicle training tube (i.e., if a returned tube weighs substantially more or less than the expected weight).

Subjects will be instructed to apply study medication each evening at least 15 minutes after showering or bathing (if they take an evening shower/bath) and then to not wash areas where ARQ-151 cream or vehicle have been applied until the following morning. Study medication should be applied at least 10 minutes before going to bed.

Each study medication tube will be weighed prior to dispensing at the baseline visit and each follow up visit. Study medication tubes returned by subjects will also be weighed and compliance will be assessed. If the subject's actual use is substantially greater than or less than the expected use, the subject will retrained on the study drug application technique.

8.11.2 Treatment Stopping Rules

Any topically applied product may irritate the skin. If a subject develops an application site reaction with the clinical appearance of an 'irritation reaction', and with a severity of a Dermal Response Score of 5 (erythema, edema and papules) or greater on the scale of Berger and Bowman (8.12.6), treatment should be discontinued for up to one week and may then be resumed if the reaction has, in the opinion of the Investigator, adequately resolved. If the reaction reoccurs, treatment should be discontinued permanently and the subject followed until the reaction resolves.

8.11.2.1 Unblinding Due to Application Site Reactions

If a subject is terminated from the study due to non-resolution or reoccurrence of a skin reaction after having undergone up to a one-week treatment interruption, the Sponsor's Chief Medical Officer (CMO) may be unblinded as to treatment assignment of that subject. The determination of whether or not to unblind will be made by the CMO taking into account the severity of the reactions, the number of subjects involved, and the number of discontinuations.

8.11.3 Treatment Compliance

Study medication tubes will be weighed at each follow-up clinic visit. Additionally, subjects will complete a daily diary recording the date and time of each dose applied, any missed doses, and a comment section should the subjects have a comment, e.g., record potential AEs. Site personnel will review the diaries and use the information to question the subject regarding compliance and AEs and then record appropriate information in source documents and complete Case Report Forms (CRFs). If a subject misses a dose, they should be instructed to return to the per protocol study medication administration schedule.

8.12 Safety Assessments

The Schedule of Visits and Assessments (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI and/or the Sponsor for reasons related to subject safety.

This study assesses the safety and efficacy of ARQ-151 cream. Safety will be determined by evaluating physical examinations, application site reaction assessments, vital signs, ECGs, clinical laboratory parameters, and AEs as outlined in the Schedule of Visits and Assessments (Section 6). If deemed necessary, additional safety assessments will be performed at the discretion of the PI.

8.12.1 Screening

Within 14-42 days (depending on which Cohort the subject is enrolled) prior to the first dosing, subjects will be provided details of study requirements and sign an informed consent. Medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), and height (cm) will be recorded. Each subject will undergo psoriatic plaque assessments, a physical examination, vital sign measurements (blood pressure, heart rate, and temperature), 12-lead ECG, dermal photography (at four investigational centers), and laboratory tests of hematological, hepatic and renal function, urinalysis, urine drug screen and a pregnancy test for female subjects.

8.12.2 Physical Examination

Physical examinations will be performed as follows:

Cohort 1 at Screening and Day 1.

Cohort 2 at Screening, Baseline, and Week 4.

For both Cohorts, the physical exam will be limited to skin, lungs and heart only.

8.12.3 Vital Signs and Weight

Blood pressure, heart rate, temperature, and weight will be measured at every visit for both Cohorts.

8.12.4 ECG Monitoring

Single 12-lead ECGs will be performed at Screening for both Cohorts and at Baseline and Week 4 for Cohort 2.

ECGs will be performed on subjects in the supine position. All ECG tracings and readouts will be reviewed by the Study Physician or his/her designee.

8.12.5 Laboratory Tests

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

All tests listed below will be performed as follows:

Cohort 1: Screening and Day 2

Cohort 2 and Cohort 1 subjects who rollover into Cohort 2: Screening, Baseline, Week 2, and Week 4.

The collection of specimens will be in a non-fasting state. In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI.

Hematology

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

Serum Chemistry

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

Urinalysis

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

Additional Tests

- Urine drug screen**
  - Amphetamines
  - Barbiturates
  - Benzodiazepine
  - Cocaine
  - Cannabinoid
  - Methadone
  - Opiates
  - PCP
  - Propoxyphene
- Urine pregnancy test***
  (for females 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.

** Only at Screening visit

*** All visits for both Cohorts except Day 2 for Cohort 1

8.12.6 Application Site Reaction Assessment (Cohorts 1 and Cohort 2)

Application Site Reaction Assessments will be performed as follows:

Cohort 1: Day 1 and Day 2

Cohort 2: Baseline (Visit 2), Visit 3, Visit 4, Visit 5 and Visit 6

Application site reactions will be graded at the timepoints outlined in the Schedule of Visits and Assessments (Section 6). Irritation reactions are graded using the scale detailed in the following section (Berger-1982). Reactions at the site of product application, which may occur post-Baseline, should be differentiated from the preexisting inflammation associated with the subject's psoriasis. Changes in Dermal Response scores, consistent with disease fluctuation, will only be recorded as an AE if the Investigator considers the change to be worse than normal fluctuation.

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 covering all or part of the patch site

F = small petechial erosions and/or scabs

G = no other effects

8.13 Efficacy Evaluations (Cohort 2 Only)

8.13.1 Product of the Target Plaque Severity Score (TPSS) and the Target Plaque Area (TPA)

Target Plaque Severity Score (TPSS) will be determined for each target plaque on each subject as the sum of erythema (graded 0-4), thickness (graded 0-4), and scaling (graded 0-4) using the descriptors listed below.

Erythema

0 = none (includes hyperpigmentation)

1 = Mild - faint redness

2 = Moderate - red

3 = Severe - Bright red / dark red

4 = Very Severe - Extremely dark red / purple

Thickness

0 = none - no elevation over normal skin

1 = Mild - slight elevation

2 = Moderate - moderate elevation with rough or sloped edges

3 = Severe - marked elevation with hard or sharp edges

4 = Very Severe - very marked elevation with hard and sharp edges

Scaling

0 = none

1 = Mild - fine scale that covers part (≤ 50%) of the lesion

2 = Moderate - fine to rough scale that covers a large part (>50%) of the lesion

3 = Severe - rough, thick scale that covers almost all the lesion

4 = Very Severe - very rough, very thick scale that completely covers the lesion

Target plaque area (cm^2) is determined by multiplying the longest diameter (cm) of the target plaque by the widest perpendicular diameter (cm) (perpendicular to the longest diameter of the target plaque). The same plaque(s) will be measured at each applicable visit. If a plaque is resolved after baseline with a score of 0 for all descriptors (i.e., Erythema, Thickness and Scaling), then the TPSS x TPA should be recorded as 0.

Values for TPSS and measurement of the Target Plaque Area will be calculated at Screening, Baseline, Visit 3, Visit 4, Visit 5 and Visit 6.

Investigators should aim to identify up to 3 target plaques of at least 9 cm^2 in size with TPSS ≥4. One or two target plaques are acceptable, but only if a subject does not have three plaques meeting the criteria of at least 9 cm^2 with a TPSS ≥4. Target plaques may be on the knees and/or elbows, but priority should be given to identifying target lesions in other areas.

Whenever possible, the same individual who performs the target plaque analyses for a subject at baseline should continue to perform the analyses for that subject during the course of the study.

Changes in Target Plaque Severity Scores consistent with disease fluctuation, will only be recorded as an AE if the Investigator considers the change to be worse than normal fluctuation.

8.13.2 Dermal Imaging

Photography will be performed at four centers only during the following visits: Baseline, Visit 3, Visit 4, and Visit 6.

8.14 Depressive Symptomatology Questionnaire (Cohort 2 Only)

Depressive Symptomatology Questionnaire will be administered at Screening, Week 2 and Week 4.

8.15 Pharmacokinetic Assessment

Cohort 1: Plasma PK assessments will be performed on all subjects.

Cohort 2: Plasma PK assessments will be performed on 45 subjects. Tissue metabolite assessments will be performed on 15 subjects.

8.15.1 Blood and Skin Sampling and Processing

Blood samples for pharmacokinetic evaluation will be performed as follows:

Cohort 1: PK draws will be done at 1, 2, 4, 6, and 24 hours after ARQ-151 cream 0.5% application to 25 cm^2 of psoriatic plaque(s).

Cohort 2: PK draws will be done on day 1: 1, 2, 4 and 6 hours; day 14: pre-dose (trough) and 1-hour post-dose; and Day 28: pre-dose (trough), 1, 2, 4, 6 and 24 hours. On days 1, 14, and 28, study medication will be applied in the clinic and blood draws performed subsequently. Subjects will be contacted on days 12 and 26 and reminded to apply their study medication in the morning of days 13 and 27. Study medication will not be applied in the evening of days 13 and 27.

An optional 4 mm diameter punch biopsy will be collected from a target plaque at the Day 28 Visit. The punch biopsy will include the epidermis, dermis, and sub-cutaneous skin layers.

8.16 Adverse Events

8.16.1.1 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.

8.16.1.2 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 ICH Guidelines for Clinical Safety, required procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within 24 hours of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to ICH E6: Guideline for Good Clinical Practice and ICH E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.: The ERB/IRB will be notified of the Alert Reports as per HC, FDA, ICH and the 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.

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.

If a SAE occurs to a subject on this study, contact the Sponsor personnel listed in Section 3.

8.16.1.3 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.

Treatment of SAEs will be performed by a physician. 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).

8.16.1.4 Reporting

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

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

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

The following definitions for rating maximum severity will be used:

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

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

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

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

AEs will be coded using the most current MedDRA® available at Premier Research (e.g., 18.1 or higher).

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 for Cohort 2. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

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

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

P-values of less than 0.05 will be considered statistically significant based on a two-sided test unless otherwise specified.

9.1.1 Determination of Sample Size

A sample size of 24 per arm (72 total) will provide 80% power to detect a difference of 23% in the mean percent change from baseline in TPSS x target plaque area (cm^2) between the ARQ-151 cream and the matching vehicle arms, with a standard deviation for the change of 25%. This is based on a one-way analysis of variance (ANOVA) at the $\alpha = 0.025$ significance level. With a 16% dropout rate, the sample size for the study would be increased to 84 subjects.

9.1.2 Subjects to Analyze

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

The Modified Intent-to-Treatment (mITT) population will include all subjects who are in the safety population for Cohort 2 with at least one post-baseline efficacy evaluation.

Per-Protocol (PP) Population will include all subjects who are in the safety population for Cohort 2, were at least 80% compliant with study medication, and showed no other serious deviations from the study protocol.

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

9.1.3 Interim Analysis

No interim efficacy analyses are planned.

9.1.4 Background and Demographic Characteristics

Descriptive statistics will be used to summarize demographic characteristics (age, sex, and race) and background characteristics for the enrolled subjects in Cohort 1 and the randomized subjects in Cohort 2. Past/coexistent medical history information and physical examination observations and vital signs information for all randomized subjects will be presented in a by-subject listing.

9.1.5 Study Medication Compliance

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

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

9.2 Efficacy (Cohort 2)

Efficacy will be assessed for Cohort 2 only.

9.2.1 Primary Efficacy Endpoint

In the parallel group assessment (Cohort 2), the Primary Efficacy Endpoint will be the Difference in mean percent change from baseline at week 4 in TPSS x TPA between each dose concentration level of ARQ-151 cream and vehicle control. This will be assessed as a sum of up to 3 target plaques per subject.

The primary endpoint will be analyzed using a mixed model for repeated measures (MMRM), with center, treatment, study visit, and study visit-by-treatment interaction as fixed effects and baseline TPSS x TPA score as a covariate. An unstructured covariance structure will be used, unless the model does not converge; in that case, the appropriate covariance structure will be investigated. The Bonferroni method will be used to control for multiplicity, where the significance level for each of the two comparisons of active versus placebo is $\alpha=0.025$.

Descriptive statistics for absolute and percent change from baseline at Week 4 will be provided.

9.2.2 Secondary Efficacy Endpoints

1. Difference in mean percent change from baseline at weeks 1, 2, and 3 in TPSS x TPA between each dose concentration level of ARQ-151 cream and vehicle control. This will be assessed as a sum of up to 3 target plaques per subject.

2. Difference in mean percent change from baseline at weeks 1, 2, 3, and 4 in TPSS between each dose concentration level of ARQ-151 cream and vehicle control. This will be assessed as a sum of up to 3 target plaques per subject.

3. Difference in mean percent change from baseline at weeks 1, 2, 3, and 4 in TPA between each dose concentration level of ARQ-151 cream and vehicle control. This will be assessed as a sum of up to 3 target plaques per subject.

All secondary endpoints will be analyzed similarly to the primary endpoint; however, adjustments for multiplicity will not occur and all analyses will be conducted at the $\alpha=0.05$ level.

9.3 Safety Evaluation

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

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

Adverse Events:

The assessment of safety will be based mainly on the frequency and percent of subjects who reported treatment-emergent AEs.

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) Version 18.1 or higher. Treatment emergent adverse events (i.e. events with onset dates on or after the start of study drug or with missing onset dates) will be summarized by presenting for each treatment group, the number and percentage of subjects having any AE, having an AE in an individual body system, and having an AE in an individual preferred term. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

Application Site Reaction

The numeric application site reaction scores will be summarized individually by using number and percentage of subjects by visit.

Medical History and Physical Examinations:

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

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

Clinical Laboratory Results, Electrocardiograms and Vital Signs Measurements:12

All clinical laboratory results, 12-lead ECGs and vital signs measurements and their change from baseline (pre-dose), will be summarized along with time point of collection.

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

Prior and Concomitant Medications:

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

Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR):

The total score of the QIDS-SR (i.e., the sum of the 16 individual item scores) will be summarized by visit. Additionally, the number and percentage of subjects meeting the criteria for each severity level based on total score (i.e., normal, mild, moderate, moderate to severe, and severe) will be presented by visit.

9.4 Pharmacokinetic Analysis

Pharmacokinetic parameter estimates for roflumilast will be calculated by a standard noncompartmental method of analysis; these may include AUC_{0-t}, AUC_{0-inf}, C_{max}, t_{max}, and others, as data permit. Pharmacokinetic parameters will be summarized using appropriate descriptive statistics. Time to reach maximum concentration (t_{max}) will be summarized using n, mean, standard deviation, median, minimum, and maximum. All other PK parameters will also be summarized using geometric mean and coefficient of variation.

For all subjects, blood samples for the determination of roflumilast and its metabolites will be collected at scheduled time points as delineated in the Schedule of Visits and Assessments (Section 6).

Note: the sample times for PK collection are in relation to the start of drug application.

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

STUDY ADMINISTRATION

9.5 Ethics

9.5.1 Ethics Review Board

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

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

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

9.5.2 Ethical Conduct of the Study

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

9.5.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a signed copy of their ICF.

9.6 Study Monitoring

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

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

9.7 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 Premier Research's Quality Assurance (QA) department and the QA audit certificate will be included in the study report.

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

9.8 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of the study drug (ARQ-151 cream 0.5% and ARQ-151 cream 0.15%) and placebo (matching vehicle cream) to each site to allow for completion of this study.

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

9.9 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 CRFs using black ballpoint pen. Any change of data will be made by marking out the original value with a single line, recording the revised value, the date of the change, and the initials of the party making the change alongside the corrected value. Liquid correction (i.e., “white out”) and erasing are not permitted on CRFs.

9.10 Report Format

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

9.11 Publication Policy

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

10 REFERENCES

Berger, RS, Bowman JP. A reappraisal of the 21-day Cumulative Irritation Test in man. J. Toxicol Ot & Ocular Toxicol 1982:1(2);109-115.

Bethke, TD, Lahu, G. High absolute bioavailability of the new oral phosphodiesterase-4 inhibitor roflumilast. Int. J Clin Pharmacol Ther. 2011; 49:51-57.

Brion DE, Raynaud F, Plet A, Laurent P, Leduc B, and Anderson W. Deficiency of cyclic AMP-dependent protein kinases in human psoriasis. Proc. Natl. Acad. Sci. 1986; 83:5272-5276.

DALIRESP (roflumilast) tablets [package insert]. AstraZeneca Pharmaceuticals LP, Wilmington, DE USA; 2017.

DAXAS (roflumilast) film-coated tablets [product monograph]. AstraZeneca Canada, Inc., Mississauga, Ontario Canada; 2017.

Hatzelmann A, Morcillo EJ, Lungarella G, Adnot S, Sanjar S, Beume R, et al. The preclinical pharmacology of roflumilast – a selective, oral phosphodiesterase 4 inhibitor in development for chronic obstructive pulmonary disease. Pulm Pharmacol Ther. 2010; 23:235–256.

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Michalski, J. M., Golden, G., Ikari, J. and Rennard, S. I. (2012), PDE4: A Novel Target in the Treatment of Chronic Obstructive Pulmonary Disease. Clinical Pharmacology & Therapeutics, 91: 134–142

Snape SD, Wigger-Alberti W, Goehring, UM. A phase I randomized trial to assess the effect on skin infiltrate thickness and tolerability of topical phosphodiesterase inhibitors in the treatment of psoriasis vulgaris using a modified psoriasis plaque test. Br J Dermatol. 2016; 175:479-486.

Tang-Liu DD, Matsumoto RM, Usansky JI. Clinical pharmacokinetics and drug metabolism of tazarotene: a novel topical treatment for acne and psoriasis. Clin Pharmacokinet. 1999; 37:273-287.

Wedzicha, JA, Calverley, PMA, Klaus, FR. Roflumilast: a review of its use in the treatment of COPD. International Journal of Chronic Obstructive Pulmonary Disease (2016) 11:81-90.

Appendix 1: Target Plaque Severity Score (TPSS)

Rating	Erythema	Thickness (induration)	Scaling (desquamation)
0 = None	none (includes hyperpigmentation)	no elevation over normal skin	none
1 = Mild	faint redness	slight elevation	fine scale that covers part (≤ 50%) of the lesion
2 = Moderate	red	moderate elevation with rough or sloped edges	fine to rough scale that covers a large part (>50%) of the lesion
3 = Severe	Bright red / dark red	marked elevation with hard or sharp edges	rough, thick scale that covers almost all the lesion
4 = Very severe	Extremely dark red / purple	very marked elevation with hard and sharp edges	very rough, very thick scale that completely covers the lesion

Target Plaque Severity Score			
0 = None 1 = Mild 2 = Moderate 3 = Severe 4 = Very Severe			
	Target Lesion 1	**Target Lesion 2**	**Target Lesion 3**
Locations of target Lesions *(i.e. R. forearm)*			
Erythema (E)			
Induration (I)			
Scaling (S)			
Total Each Column			
Dimensions and Areas of Target Lesions			
	Target Lesion 1	**Target Lesion 2**	**Target Lesion 3**
Longest Diameter (cm)			
Widest Perpendicular diameter (cm)			
Target Plaque Area, cm^2 (Longest diameter x widest perpendicular diameter)			

Appendix 2 Depressive Symptomatology Questionnaire