Statistical Analysis Plan

Protocol Title	An Open Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in Pediatric Subjects (ages 6 to 11 years old) with Plaque Psoriasis
Protocol Number:	ARQ-151-215
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This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

SAP Document History

Version Number	Author	Date	Change
1	Ryan McBride	23FEB2022	
2	Ryan McBride	2MAR2022	Included summary analysis of PK data. Some minor grammatical edits.

Signatures / Approvals

Mar 4, 2022

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List of Abbreviations

AE	Adverse Event
ATC Class	Anatomical/Therapeutic/Chemical Class
BSA	Body Surface Area
CDI 2	Children's Depression Inventory 2
CDLQI	Children's Dermatology Life Quality Index
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Report
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End of Study
FOCBP	Female of Childbearing Potential
IGA	Investigator Global Assessment
I-IGA	Intertriginous Investigator Global Assessment
ITT	Intent to Treat
LSR	Local Skin Reactions
μg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
PDE-4	Phosphodiesterase 4
PASI	Psoriasis Area and Severity Index
PK	Pharmacokinetics
QD	Once Daily ("quaque die")
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization
WI-NRS	Worst Itch Numeric Rating Score

1. Introduction

Arcutis, Inc. is conducting a study under the protocol name "An Open-Label, 4-Week, Phase 2, Maximal Usage Pharmacokinetics and Safety Study of ARQ-151 Cream 0.3% Administered QD in Pediatric Subjects (aged 6 to 11 years old) with Plaque Psoriasis". The study background, design and subject assessments for the study are described in the study specific protocol.

The statistical methods to be implemented during the analyses of data collected within the scope of this study (ARQ-151-215) will be outlined in this document. The purpose of this plan is to provide specific guidelines from which the statistical analysis will proceed. Any deviations from this plan will be documented in the clinical study report.

This version of the Statistical Analysis Plan (SAP) addresses this study as described in Amendment 1 Final dated 22 January 2021 of the study protocol.

2. Study Rationale and Objectives

2.1. Study Rationale

The past 15 years have witnessed a transformation in the systemic treatment of moderate to severe psoriasis with the advent of biological therapies. However, for patients with milder forms of disease, best treated with topical options, the therapeutic landscape has not significantly changed in several decades. Topical steroids come in all shapes and forms, but the lower potency steroids are not effective and the higher potency steroids are best 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 a substantial medical need for additional topical approaches in the treatment of psoriasis. The study Sponsor is developing a topical cream formulation of roflumilast for the treatment of chronic plaque psoriasis. Phase 2 results suggest that ARQ-151 may be a highly efficacious and well-tolerated topical treatment for psoriasis. Accordingly, a phase 3 program is ongoing evaluating ARQ-151 cream 0.3% for the treatment of plaque psoriasis in subjects 2 years of age and older. The present study is a maximal use pharmacokinetic trial with the to-be-marked formulation. The study is designed to ensure that the expected target patient population for ARQ-151 is properly represented, as well as to ensure that a suitable number of subjects with plaque psoriasis are evaluated and that PK is adequately characterized.

2.2. Study Objectives

2.2.1. Primary Objectives

The primary objectives are:

- To evaluate the systemic exposure and characterize the plasma pharmacokinetic (PK) profile of ARQ-151 cream 0.3% and its major N-oxide metabolite, in pediatric subjects with plaque psoriasis involving body surface areas (BSA) of at least 3%.
- To evaluate the safety of ARQ-151 cream 0.3% applied QD to pediatric subjects with plaque psoriasis involving BSA of at least 2%.
- To explore the efficacy of ARQ-151 cream 0.3% applied QD for 4 weeks to pediatric subjects with plaque psoriasis involving BSA of at least 2%.

3. Study Design

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

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

Subjects who discontinue the study may be replaced.

Subjects/caregivers will apply ARQ-151 cream 0.3% QD for 28 days to all affected areas of plaque psoriasis and any newly appearing plaque psoriasis lesions that arise during the study, except on the scalp. Subjects/caregivers should maintain treatment of these areas with study drug for the duration of the study regardless of whether treatable areas of plaque psoriasis clear prior to Week 4. The palms and soles will be treated but will not be counted towards any measurements of efficacy (PASI, IGA, I-IGA, BSA).

3.1. Schedule of Visits and Assessments

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

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

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

[c] Height will be measured at every visit (see Protocol Section 7.1.3 for the recommended procedure). Weight will be collected on every visit. Weight should be obtained using a calibrated weight scale

and the same scale should beused for a subject throughout the duration of the study. The subject should remove shoes and heavy clothing (sweaters or jackets), and empty pockets. The subject should stand with both feet in the center of the scale with their arms at their side and hold still. Record the weight to the nearest decimal fraction (for example, 55.5 pounds or 25.1 kilograms). Measure the weight in triplicate and report the average weight in EDC.

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

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

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

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

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

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

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

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

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

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

4. Determination of Sample Size

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

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

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

5. Statistical Methods

Summaries may be generated for regulatory interaction prior to the completion of the study and an interim report may be written at that time. The statistical analyses will be reported using summary tables, figures and listings (TFLs). Numbering for TFLs will be based on the recommended numbering convention provided by the International Conference on Harmonisation.

Continuous variables will be summarized with means, standard deviations, medians, minimums and maximums. Categorical variables will be summarized by counts and percent of subjects in corresponding categories. Unless specified otherwise, baseline results will be defined as the closest measurement taken prior to first dose of study medication. When applicable, unscheduled visits will be used in the determination of baseline values. Missing values are not considered for percent calculations, unless stated otherwise. In those cases, footnotes will specify the percent calculation. No formal inferential statistics will be performed for this open-label study.

Individual subject data obtained via the electronic data capture (EDC) system and from external vendors will be presented in by subject listings.

The analyses described in this plan are considered *a priori*, in that they have been defined prior to database lock. Any analysis added after the database lock will be considered *post hoc* and exploratory. *Post hoc* analyses will be labeled as such on the output and identified in the CSR. All analyses and tabulations for the CSR will be performed using

SAS® version 9.4 or higher. Tables will be presented in .rtf and .pdf format. Listings will be presented in .pdf format. Upon completion, all SAS programs will be validated by an independent programmer. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency with tables and consistency between tables and corresponding data listings.

6. Analysis Populations

Subjects who enroll into the study need to sign inform consent and receive at least one confirmed dose of investigational product.

The Safety population will include all subjects who are enrolled and received at least one confirmed dose of investigational product. This population will be used for safety and efficacy analyses.

The Pharmacokinetic (PK) population will include all subjects who have who received at least 1 confirmed dose of IP with sufficient plasma concentrations of roflumilast to define a profile, as determined by the pharmacokinetics.

7. Study Population

7.1. Subject Disposition

Information regarding subject disposition will be summarized for all subjects. Summaries will include the number of the subjects who were screened, who failed the screen, who enrolled into the study, the subject number in each analysis population, the number of the subjects who completed the study and who discontinue the study early. For those who discontinue the study, the primary reason for discontinuation will be summarized.

7.2. Protocol Deviations

Protocol deviations will be collected throughout the duration of the study. Protocol deviations will be assigned a sponsor-defined category type, such as treatment compliance, study adherence, and use of prohibited therapies. Each deviation will be defined as important or minor. A tabular summary of the important deviations will be generated. In addition, a by-subject listing of all the protocol deviations will be produced.

7.3. Demographic and Baseline Characteristics

Demographics and baseline characteristic data will include age, sex, ethnicity, race, body weight (kg), height (cm), and baseline disease characteristics [BSA, BSA group (>=5% or <5%), IGA, I-IGA, PASI, and WI-NRS baseline scores]. Medical history will not be summarized in a table but will be displayed in a listing.

Continuous variables will be summarized using descriptive statistics. Categorical variables will be summarized using counts and percentages. Demographics and baseline characteristics will be summarized for the Safety population.

8. Efficacy Analysis

The Safety population will be used for efficacy analysis. Analyses using the Safety population will be based on treatment received.

8.1. Efficacy Variables

Efficacy will be an exploratory endpoint, with analyses including:

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

8.2. Baseline Values

Unless otherwise noted, baseline is defined as the last non-missing value recorded prior to the first application of study drug. When applicable, unscheduled visits will be used in the determination of baseline values.

For subject local tolerability assessment, baseline is derived as the last non-missing measurement taken on Day 1 of first application of study drug. Baseline investigator local tolerability assessment is the last non-missing assessment prior to the first dose.

8.3. Handling of Dropouts or Missing Data

Subjects that withdraw or are discontinued from the study prior to Week 4 Visit, may be replaced. Unless described otherwise in subsequent sections, analyses will be carried out with the data available using no imputation for missing data. A description of how missing data will be handled for select endpoints is included below.

8.3.1. Coronavirus 19

Due to coronavirus disease 19 (COVID-19) outbreak during the course of the study, there may be several subjects who will have missing assessments which could affect the analysis. Subjects who are unable to attend a study visit due to COVID-19 will be documented in the protocol deviation log. The protocol deviation date will be used as the COVID-19 affected date (or visit). If a subject reports an adverse event of COVID-19,

then the event start date will be used as the affected date. In the event that a subject has an affected COVID-19 date from both sources, the earlier of the dates will be used.

Subjects who were affected by COVID-19 will be summarized in a data listing. The listing will contain the following information: subject number, treatment, gender, age, total study duration, exposure to study treatment, any COVID-19 related adverse events, completion/discontinuation of the study, and reasons for discontinuation.

8.4. Handling of repeat and unscheduled assessments

Unscheduled assessments are used when scheduled assessments are not collected. Unscheduled assessments will be assigned to the associated visit and timepoint based on date and time of assessment. If there are multiple unscheduled assessments assigned to the same visit, then the assessment closest to the scheduled visit will be used for analysis.

8.5. Interim Analysis and Data Monitoring

No interim efficacy analyses are planned. PK and safety data may be reviewed on an ongoing basis. Summaries may be generated for regulatory interaction.

8.6. Multiple Comparison/Multiplicity

No formal statistical comparisons are planned; thus, no adjustment for multiple comparisons is needed.

9. Methods of Efficacy Analysis

9.1. Psoriasis Area and Severity Index (PASI)

Psoriasis Area and Severity Index (PASI) assessment will be summarized at Baseline/Day 1, Week 2, and Week 4 visits. Assessments will be performed as single assessments from which PASIs will be calculated. PASI is used for the measurement of severity of psoriasis. PASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease).

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

0. 0% of involved area
1. < 10% of involved area
2. 10-29% of involved area
3. 30-49% of involved area
4. 50-69% of involved area

5. 70-89% of involved area
6. 90-100% of involved area

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

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

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

Descriptive statistics will be calculated for percent change from baseline and change from baseline in PASI score at each study visit. Improvement in PASI scores will be summarized at each study visit. For example, 75% improvement (PASI75) from baseline is when the percent change from baseline is 75% or greater and 50% or greater improvement (PASI50) from baseline is when percent change from baseline is at least 50%. Frequency counts and percentages will be compiled for PASI75 and PASI50 scores at each study visit.

9.2. Investigator Global Assessment (IGA) and Intertriginous Investigator Global Assessment (I-IGA)

Investigator Global Assessment (IGA) will be summarized at Baseline, Week 2, and Week 4. The IGA should be completed prior to other physician assessments. The IGA is a static evaluation of qualitative overall psoriasis severity. This global assessment scale is an ordinal scale with five severity grades (reported only in integers of 0 to 4). Each grade is defined by a distinct and clinically relevant morphologic description that minimizes inter- observer variability (see Table below). Descriptive statistics will be calculated for change and percent change from baseline in IGA score at each study visit. IGA success is defined as number of subjects who achieved IGA score of "clear" or "almost clear" plus >= 2-grade improvement from baseline. The proportion of subjects who achieved IGA success will be summarized at each visit.

Score	Morphological Description
0 – Clear	Plaque thickening = no elevation or thickening over normal skin Scaling = no evidence of scaling Erythema = none (no residual red coloration but post-inflammatory hyperpigmentation may be present
1 – Almost Clear	Plaque thickening = none or possible thickening but difficult to ascertain if there is a slight elevation above normal skin level Scaling = none or residual surface drying and scaling Erythema = light pink coloration

2 – Mild	Plaque thickening = slight but definite elevation Scaling = fine scales partially or mostly covering the lesions Erythema = light red coloration
3 – Moderate	Plaque thickening = moderate elevation with rounded or sloped edges Scaling = most lesions at least partially covered Erythema = definite red coloration
4 – Severe	Plaque thickening = marked or very marked elevation typically with hard or sharp edges Scaling = non-tenacious or thick tenacious scale, covering most or all of lesions Erythema = very bright red coloration; extreme red coloration; deep red coloration

For subjects with intertriginous area involvement of at least 'mild' severity by IGA (I-IGA ≥ 2) at Baseline (using the IGA scale shown above but evaluating intertriginous areas ONLY and NOT whole body involvement), an IGA for the intertriginous region alone (I-IGA) will be summarized at Baseline, Week 2, and Week 4. Descriptive statistics will be calculated for change and percent change from baseline in I-IGA score at each study visit along with I-IGA score at each visit.

9.3. Body Surface Area (BSA)

Body surface area assessments will be summarized at Baseline, Week 2, and Week 4. The BSA affected by plaque psoriasis will be determined by the subject's hand method, where the subject's hand (including fingers) surface area is assumed to equal 1% of body surface area (BSA). Descriptive statistics will be calculated for change and percent change from baseline at each study visit.

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

WI-NRS Assessments will be summarized at Baseline, Week 2, and Week 4. The WI-NRS has been developed as a simple, single item to assess the patient-reported severity of this symptom at its highest intensity during the previous 24-hour period. (Naegeli 2015). The WI-NRS will be determined by asking the subject's assessment of worst itch over the past 24 hours. The scale is from '0 to 10' ("no itch" to "worst imaginable itch"). WI-NRS pruritis assessment will be completed by subjects ≥ 8 years old, or by parent/caregiver for subjects < 8 years old. Descriptive statistics will be calculated for change and percent change from baseline in WI-NRS pruritus score at each study visit. WI-NRS success is defined as achievement of WI-NRS of 4-point reduction from baseline in subjects who had baseline WI-NRS >=4. The WI-NRS success rate will be summarized at each visit.

9.5. Children's Dermatology Life Quality Index (CDLQI)

The Children's Dermatology Life Quality Index (CDLQI) (age 2-16) will be completed at Screening, Baseline, Week 2, and Week 4. CDLQI allows a simple, compact and uniform assessment of patients with skin diseases in general, in which higher scores indicate poorer disease-related quality of life. Subject/caregivers will complete the CDLQI. CDLQI will be displayed in a by-subject listing.

10. Safety Analysis

All safety analysis will be based on the Safety Population. Analysis using the Safety population will be based on the treatment received.

10.1. Exposure and Compliance

The number of IP applications by each subject based on diary data will be summarized using descriptive statistics appropriate for continuous variables. The amount of IP used by each subject based on tube weight will be summarized descriptively using continuous methods. The number of days on IP will be summarized descriptively.

A subject will be considered compliant with the dosing regimen if the subject applies at least 80% of the expected applications during the IP application period and does not miss more than 3 consecutive doses.

Investigational product application compliance will be calculated based on number of applications divided by the expected number of IP applications. Compliance will be summarized descriptively using the following categories: 100%, ≥ 80% - <100%, < 80%.

10.2. Adverse Events

All the adverse events will be coded based on MedDRA version 23 or higher version.

Treatment emergent adverse events (TEAEs) are those adverse events (AEs) with an onset on or after first application of investigational product or were present at treatment initiation but worsened during treatment, through study completion. Pre-treatment AEs and AEs reported after study completion will be listed but not included in TEAE summaries. If it cannot be determined whether the AE is treatment emergent due to an incomplete (partial) onset date, then the AE will be considered to be treatment emergent.

Overall summary will be presented, which will include the total number of events, and the number and percentage of subjects who experienced TEAE, TEAE by the strongest relationship, TEAE by the maximum severity, treatment-emergent serious AE (TESAE), TEAE leading to study discontinuation, and TEAE leading to death.

Each AE summary will be displayed. Summaries of the following types will be presented:

- Subject count and incidence rate of TEAEs by MedDRA system organ class and preferred term. Summaries will be ordered by descending order of incidence of system organ class and preferred term within each system organ class
- Subject count and incidence rate of TEAEs by MedDRA preferred term in descending order.
- Subject count and incidence rate of TEAEs by MedDRA system organ class, preferred term and maximum severity. At each level of subject summarization, a

subject is classified according to the maximum severity if the subject reported one or more events.

- Subject count and incidence rate of treatment related TEAEs by MedDRA system organ class and preferred term. Related AEs are those reported as “Unrelated”, “Unlikely”, “Possibly”, “Probably”, or “Likely”. A subject is classified according to the closest relationship if the subject reported one or more events. Adverse events with missing relationship will be considered treatment related.
- Subject count and incidence rate of Serious TEAEs by MedDRA system organ class and preferred term. Each subject will be counted only once within a system organ class or a preferred term using the event with maximum severity.
- Subject count and incidence rate of TEAEs leading to study treatment discontinuation by MedDRA system organ class and preferred term if there is any.

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 along with the treatment emergent flag and subjects who prematurely discontinued from study flag. The event onset will also be shown relative (in number of days) to date of first application.

10.3. Local Tolerability Assessment

Investigator Local Tolerability Assessments will be summarized at Baseline, Week 2, and Week 4. Irritation reactions are graded using the following dermal response scale below. The investigator assessments will be conducted by the investigator prior to study drug application in the clinic.

Dermal Response

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

Other Effects

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

The investigator assessments will be conducted by the investigator prior to study drug application in the clinic. Frequency counts and percentages of the numeric application site reaction scores will be summarized at each study visit. Any additional information collected on the investigator's tolerance assessment that are not included in the summaries will be presented in listings.

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

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

10.4. Vital Signs

Vital signs measurements and their change from baseline will be summarized at each study visit. A shift table will identify subjects who gain or lose >5% body weight over the course of the study.

10.5. Physical Examination

Physical examinations will be performed at Screening, Baseline, and Week 4. Clinically significant physical examination parameters will be capture as adverse events. Physical examination and abnormal values will be listed in a listing. No summary tables of physical examination are planned. Changes in physical examination will be described in the text of the final report.

10.6. Prior and Concomitant Medications

Prior and concomitant medication verbatim terms captured via the EDC system will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and Preferred Names using the

World Health Organization (WHO) Drug Dictionary Enhanced version B3 March 2019 or later. Prior medications are any medication with onset prior to first dose of treatment, even if the medication is continued after first dose. Concomitant medications are any medication with first dose on or after the day of first dose of treatment.

Prior and concomitant medications will be summarized by WHO ATC class and preferred name. These summaries will present the number and percent of subjects using each medication. Subjects may have more than one medication per preferred name. A subject is counted once if one or more medications is reported for the subject. Each summary will be ordered by descending order of incidence of ATC class and preferred term.

10.7. Laboratory Tests

Laboratory tests will be summarized at Baseline and Week 4. All tests listed in the table below will be collected in a non-fasting state (no food restrictions). In addition, laboratory safety tests may be performed at various unscheduled timepoints, if deemed necessary by the Investigator. All laboratory tests will be summarized (baseline, observed, change from baseline and percent change from baseline) by presenting descriptive statistics (number of subjects, mean, standard deviation, median, Q1, Q3, minimum, and maximum). A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

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

Nitrite*	
Urobilinogen	
Leukocyte esterase*	
* If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed. ** At baseline and Week 4 for FOCBP only *** At screening only	

10.8. Electrocardiogram

12-lead electrocardiograms (ECGs) will be performed at Screening and Week 4. ECGs will be performed on subjects after 5 minutes in the supine position. ECGs will be summarized with descriptive statistics at each study visit.

10.9. Children's Depression Inventory 2 (CDI-2)

The CDI-2 assessment will be summarized at Baseline, Week 2, and Week 4. The CDI-2 quantifies depressive symptomatology and is recommended for use in initial evaluation and is appropriate when there is a need for an assessment and robust description of a child's depressive symptoms. This study will use the CDI Parent Report Form. The total score is the sum of the responses for the 17 questions. Total score, functional score, and emotional score will be summarized descriptively at each study visit.

CDI-2 total score is a sum of the 17 questions (individual questions scored as much or most of the time=3, often=2, some of the time=1, Not at all=0; range for score 0 to 51).

- CDI-2 emotional problem scale is a sum of 9 questions (Q1, Q3-6, Q8, Q10-12)
- CDI-2 function problem scale is a sum of 8 questions (Q2, Q7, Q9, Q13-17)

10.10. Dermal Imaging

Medical photography will be performed at participating sites on consenting/assenting subjects and summarized at Baseline, Week 2, and Week 4. Subjects who are unwilling to participate in the medical photography will be allowed to opt out of this procedure and document on the informed consent form. Medical photography information will be presented in a by-subject listing.

11. Pharmacokinetics

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

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

PK concentration will be summarized by nominal time point. In addition, PK parameters and concentration listing will be presented as well. A detailed description of the PK analysis will be presented in a separate pharmacokinetics report.

12. Planned Tables, Figures, and Listings

A table of contents for the tables, listings, and figures will be presented in a separate document as the list of summaries or numbering may change after finalization of this document. If additional summaries are added that are not described in this document, then this SAP will be amended, or an addendum will be created.