NCT03392168

16.1.9 Documentation of Statistical Methods

Final Statistical Analysis Plan, Version 1.0, dated 06-May-2018

Sponsor	Arcutis, Inc.
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1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Arcutis, Inc. protocol number 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), dated 19-Mar-2018, Amendment 2.0. Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials[1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association[2] and the Royal Statistical Society[3], for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

The statistical plan described hereafter is an *a priori* plan. It will be submitted to file prior to any unblinded inferential or descriptive analysis of data pertaining to Arcutis, Inc.'s study ARQ-151-101.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objectives are:

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 (PK), and efficacy of ARQ-151 cream 0.5% and ARQ-151 cream 0.15% vs. vehicle applied once daily (QD) x 28 days to individuals in the range of 0.5% to 5.0% body surface area (BSA) of chronic plaque psoriasis (Cohort 2).

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- Treatment emergent adverse events (TEAEs)
- Application site assessments
- Medical history and physical examinations
- Changes in clinical laboratory results
- Changes in 12-lead electrocardiograms (ECGs)
- Changes in vital signs

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

In the parallel group assessment (Cohort 2), the primary efficacy endpoint is:

- 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.

2.2.2.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints in the parallel group (Cohort 2) assessment 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.

2.2.3. Pharmacokinetic Variable(s)

The PK endpoints of the study include plasma concentrations (both cohorts) and tissue concentrations (Cohort 2 substudy) of roflumilast and any metabolites, as follows:

- Mean plasma concentrations and parameters (parameters may include $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, t_{max}, and others as data permit); and

- Mean tissue concentrations.

2.2.4. Other Endpoints

The other endpoint includes changes in depressive symptomatology (Cohort 2).

3. Overall Study Design and Plan

3.1. Overall Design

There are 2 cohorts of subjects:

Cohort 1

Cohort 1 is an open label, single dose study to 25 cm^2 of psoriatic plaque(s) in up to up to 8 subjects with psoriasis. 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; however, a minimum of 14 days of wash-out is required between Cohort 1 drug application and the baseline visit of Cohort 2. This cohort involves a minimum of 3 clinic visits including Screening, Baseline, 1 follow-up visit (24 hours after the baseline visit) and 1 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

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 0.5% to 5.0% BSA of chronic plaque psoriasis, inclusive. This cohort involves a minimum of seven clinic visits including Screening, Baseline and 4 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 AEs. 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.

Including both Cohorts, a total of about 92 subjects will be enrolled at 7 study sites in Canada and 1 site in the U.S. Subjects will be adult (≥18 years old) 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.

3.2. Sample Size and Power

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 TPA (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 1-way analysis of variance (ANOVA) at the $\alpha = 0.025$ significance level. With a 16% dropout rate, the sample size for the study has been increased to 84 subjects.

3.3. Study Population

Subjects in this study are male or female adults (≥18 years old) with chronic plaque psoriasis (at least 25 cm^2 for Cohort 1; covering 0.5% to 5.0% of total BSA excluding the face, scalp, intertriginous areas, palms, and soles for Cohort 2).

3.4. Treatments Administered

All subjects in Cohort 1 will receive ARQ-151 cream 0.5%.

Subjects in Cohort 2 will be randomized to receive ARQ-151 cream 0.5%, ARQ-151 cream 0.15%, or matching vehicle (ie, placebo).

If a subject is terminated from the study due to non-resolution or reoccurrence of a skin reaction after having undergone up to a 1-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.

3.5. Method of Assigning Subjects to Treatment Groups

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 the Baseline Visit after the subject has been found to be fully eligible for participation. A kit containing 10 tubes of study medication will be assigned to each subject. Each kit has a unique kit number (randomization number).

3.6. Blinding and Unblinding

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.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1 and Table 2, for Cohorts 1 and 2, respectively.

Table 1: Schedule of Events (Cohort 1)

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.

Table 2: Schedule of Events (Cohort 2)

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	
Vehicle Application in Clinic (subject training)[f]			X[f]		X[f]			
Drug/Vehicle Application in Clinic[g]		X[g]		X[g]		X[g]		

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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**		
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.

[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.

[i] 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).

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations, except for PK parameter estimation, will be performed primarily using SAS (release 9.4 or higher). All PK parameter estimations will be performed using WinNonlin® version 6.4 or later. If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

For purposes of this SAP, "treatment within cohort" is defined as enrolled subjects ("Overall") for Cohort 1 and treatment group ("ARQ-151 0.5%," "ARQ-151 0.15%," and "Vehicle") for Cohort 2. For background and efficacy summaries for Cohort 2, this will be the randomized (ie, planned) treatment group; for safety summaries, this will be the actual (ie, received) treatment group.

Where possible, data for both cohorts will be summarized in the same output.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment groups within cohort, unless otherwise specified.

The minimum and maximum will be reported with the same degree of precision (ie, the same number of decimal places) as the observed data. Measures of location (mean and median) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

Unless otherwise indicated, all statistical tests will be conducted at the 0.05 significance level using 2-tailed tests, and *p* values will be reported. Corresponding 95% confidence intervals (CIs) will be presented for statistical tests.

4.2. Interim Analysis and Data Monitoring

No interim analyses are planned.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population:** The Safety Population includes all subjects who are enrolled and received at least 1 confirmed dose of study medication in each cohort. This population will be defined separately for each cohort. Analyses using the Safety Population for either cohort will be based on treatment received.
- **Modified Intent-To-Treat (mITT) Population:** The mITT Population includes all subjects who are in the Safety Population for Cohort 2 with at least 1 post-baseline efficacy evaluation. Analyses using the mITT Population will be based on randomized treatment.
- **PK Population:** The PK Population includes all subjects, who consented to PK draws, 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. Analyses using the PK Population will be presented in a separate PK report, provided by the pharmacokineticist.
- **Per Protocol (PP) Population:** The PP Population includes all subjects who are in the Safety Population for Cohort 2, were at least on average 80% compliant with study medication, and showed no other serious deviations from the study protocol. Analyses using the PP Population will be based on randomized treatment.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last observation recorded before the first dose of study drug in each cohort will be used as the baseline observation for all calculations of change from baseline.

6.1.2. Adjustments for Covariates

Where statistical modelling is performed, the baseline value of that assessment will be used as a covariate.

6.1.3. Multiple Comparisons

The type I error rate of $\alpha = 0.05$ will be maintained for the entirety of the primary endpoint by using the Bonferroni method to control for multiplicity, where the significance level for each of the 2 comparisons of active versus placebo is $\alpha = 0.025$.

No adjustments will be made for multiple comparisons for other endpoints; all analyses will be conducted at the $\alpha = 0.05$ level.

6.1.4. Handling of Dropouts or Missing Data

Any subject who withdraws from the study may be replaced at the discretion of the Sponsor. For AEs, if severity or relationship to study drug is missing, then it will be treated as missing. In general, missing data will not be imputed, except as described in Section 6.1.8.

6.1.5. Analysis Visit Windows

For all analyses, unscheduled and/or repeated measurements will only be included if a scheduled measurement is not available and the unscheduled/repeated measurement falls within the analysis visit windows as described below (Table 3 and Table 4). Otherwise, visits will be analyzed as scheduled.

Table 3: Visit Windows (Cohort 1)

Visit	Target Start Day	Lower Limit	Upper Limit
Screening	-14	-14	-1
Day 1	1	1	1
Day 2	2	2	2
Day 8	8	3	9

Table 4: Visit Windows (Cohort 2)

Visit	Target Start Day	Lower Limit	Upper Limit
1	-6	-6	-1
2	1	1	1
3	7	2	8
4	14	9	15
5	21	16	22
6	28	23	28
7	29	29	30
--	35	31	36

Visits should occur ±1 day of the targeted date. The lower limit for each visit after Visit 2 (Day 1) starts 1 day after the upper limit for the previous visit (+1 of the targeted date).

6.1.6. Pooling of Sites

All sites will be pooled together for analysis.

6.1.7. Derived Variables

- TPSS = sum of erythema (graded 0-4), thickness (graded 0-4), and scaling (graded 0-4) for each target plaque. The sum of TPSS scores of up to 3 target plaques within a visit will be used for analysis.

- TPA (cm^2) = the longest diameter (cm) of the target plaque multiplied by the widest perpendicular diameter (cm) (ie, perpendicular to the longest diameter of the target plaque). The sum of TPA (cm^2) of up to 3 target plaques within a visit will be used for analysis.

- TPSS x TPA = sum of TPSS x TPA of up to 3 target plaques within a visit. Note that TPSS x TPA is calculated for each target plaque before summing up the results for all plaques. If a plaque is resolved after baseline with a score of 0 for all descriptors for TPSS (ie, erythema, thickness, and scaling), TPSS x TPA will be recorded as 0.

- Cream used (g) in a tube = dispensed tube weight (g) – returned tube weight (g).

- Overall cream used (g) = sum of cream used in a tube over all tubes

- Number of doses of study drug = number of expected doses (number of days on study [including BID dosing on Days 1, 14, and 28], where number of days on study is derived as last treatment – first treatment + 1) minus total number of missed doses, as collected in the CRF. Add a 1 for each of the Day 1, 14, and 28 visits that are completed (meaning, study drug discontinuation did not occur until at least the next day; so if a subject finished the study, 3 doses would be added to the final amount).

- Percent compliance (for purposes of determining the PP Population as described in Section 5) = average of compliance as recorded in the eCRF, calculated as sum of [100% if "Was the subject compliant?" marked Yes in the eCRF or percent compliance as recorded in the eCRF comments when "Was the subject compliant?" is marked as No] / number of non-missing compliance records from the eCRF.

- Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) total score = (highest score on questions 1-4) + item 5 + (highest score on questions 6-9) + item 10 + item 11 + item 12 + item 13 + item 14 + (highest score on questions 15-16). The range for the QIDS-SR total score is 0 to 27.

- QIDS-SR severity level[4]:
    - No depression: total score ≤ 5
    - Mild depression: total score = 6 to 10
    - Moderate depression: total score = 11 to 15
    - Severe depression: total score = 16 to 20
    - Very severe depression: total score ≥ 21
- Change from baseline = value at current time point – value at baseline.
- Percent change from baseline = (change from baseline / baseline) * 100.
- TEAE = any AE with an onset date/time after first dose of study drug in each cohort.

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings. Data not subject to analysis according to this plan will not appear in any tables or graphs but will be included only in the data listings.

All p-values will be displayed in 4 decimals and rounded using standard scientific notation (eg, 0.XXXX). If a p-value less than 0.0001 occurs, it will be shown in tables as <0.0001.

All AEs and medical histories will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 thesaurus. Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary Enhanced (WHO-DDE) version September 2017.

A treatment related AE is any AE with a relationship to the study drug of possibly, probably, or likely related.

If partial dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows:

For partial AE and medication start dates:

- if just day is missing then the day assigned is the first day of the month or the date of first dose (if in the same month), whichever is later;

- if just month is missing then the month assigned is the month of the first dose, unless that results in a date prior to the first dose in which case the month after the first dose is used; and

- if both month and day are missing then the month assigned is the month of the first dose and the day assigned is the first dose day.

For partial AE and medication end dates:

- if just day is missing then the day assigned is the day of the last date on study (ie, date of last contact if subject lost to follow-up or date of completion / early termination) if month and year do match the month and year of the last date of the study, or the last day of the month otherwise;

- if just month is missing then the month assigned is the month of the last date on study, unless that results in a date after the last date on study, in which case the month before the last date on study is used; and

- if both month and day are missing then the month assigned is the month of the last date on study and the day assigned is the day of last date on study, unless that results in a date after the last date on study, in which case the first day of the month is assigned.

If partial times occur, the convention is as follows:

- if the missing time occurs on the day of the first dose and both the hour and minute are missing then the time assigned is the time of the first dose, otherwise if both the hour and minute are missing and the date is not the date of first dose the time assigned is 12:00;

- if the date is the same as the date of the first dose and

    - only hour is missing the hour assigned is 12 or the hour of first dose, whichever is later;

    - only the minute is missing the minute assigned is 30 or the minute of first dose, whichever is later;

- Otherwise if the date is not the same as the date of first dose, the hour assigned is 12 if the hour is missing and the minute assigned is 30 if the minute is missing.

The time imputation only applies to Cohort 1. If a Cohort 2 time is missing, set to 12:00; if time is incomplete, set to 12 (hour) or 00 (minute).

7. Study Subjects and Demographics

Individual subject listings will be prepared for all study subjects and demographics data.

7.1. Disposition of Subjects and Withdrawals

Disposition will include tabulations of the number of subjects enrolled (Cohort 1) and/or randomized (Cohort 2), the number of subjects rolled over from Cohort1 to Cohort 2, the number of subjects who received treatment, tabulated reasons for discontinuation from the study, and number of subjects in each analysis population by treatment within cohort.

Percentages will be based on the number of subjects in the Safety Population for each cohort.

7.2. Protocol Violations and Deviations

All protocol deviations recorded by the site (classified as major or minor) will be listed.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, gender, race, ethnicity, height, weight, and BSA will be presented by treatment within cohort.

For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median, and maximum will be tabulated.

For the categorical variables, the counts and proportions of each value will be tabulated.

These analyses will be conducted for the Safety Population for each cohort.

The number and percent of subjects reporting various medical histories, grouped by MedDRA system organ class and preferred term, will be tabulated by treatment within cohort. This analysis will be conducted for the Safety Population for each cohort.

Subjects rolling over from Cohort 1 into Cohort 2 will have demographics and baseline characteristics tabulated for both cohorts.

7.4. Exposure and Compliance

The number of doses received by each subject based on diary data will be summarized by treatment for Cohort 2 subjects only, in both a continuous manner (using summary statistics) and a categorical manner (using number and percentages), presenting the following categories: 1 to 8 doses (up to 1 week of treatment); 9 to 15 doses (1-2 weeks of treatment); 16-23 doses (2-3 weeks of treatment); and 24 to 31 doses (3-4 weeks of treatment).

Similarly, the amount of study medication applied by each subject based on tube weight will be summarized by treatment for Cohort 2 subjects only, using summary statistics.

These analyses will be conducted for the Safety Population for each cohort.

Drug application for each cohort, vehicle training application for Cohort 2, study medication dispensation and return weight, and missed doses will be presented in the listings.

8. Efficacy Analysis

Efficacy will be assessed for Cohort 2 only. Individual subject listings will be prepared for all efficacy data.

8.1. Primary Efficacy Analysis

The primary efficacy endpoint is difference in mean percent change from baseline at Week 4 in the product of TPSS x TPA between each dose concentration level of ARQ-151 cream and vehicle control. This 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 within country, treatment, study visit, and treatment-by-study visit interaction as fixed effects and baseline TPSS x TPA score as a covariate. In comparing the visit value to baseline within each treatment group, least squares (LS) mean percent change from baseline will be presented along with associated 95% confidence interval (CI). In comparing treatments (ARQ-151 minus Vehicle), LS mean differences in percent change from baseline will be presented along with associated 95% CI and pairwise treatment *P* value. An unstructured covariance structure will be used, unless the model does not converge; in that case, the appropriate covariance structure will be investigated. Possible covariance structures include autoregressive (AR [1]), compound symmetry (CS), and variance components (VC) with each model fit to find the covariance structure with the best fit. The fit statistics will be compared for all covariance structures; the structure with the smallest Akaike information criterion will be retained as the preferred model.

The Bonferroni method will be used to control for multiplicity, where the significance level for each of the 2 comparisons of active versus placebo is $\alpha = 0.025$.

Descriptive statistics for absolute and percent change from baseline at Week 4 will be presented by treatment group.

The primary efficacy analysis will be based on the mITT Population. This analysis will be repeated for the PP Population.

As a sensitivity analysis, the primary endpoint will be analyzed using an analysis of covariance (ANCOVA) with factors for center within country and treatment as fixed effects and baseline TPSS x TPA score as a covariate.

8.2. Secondary Efficacy Analysis

The secondary efficacy endpoints for Cohort 2 include the following:

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.
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.
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.

Each of the secondary efficacy endpoints will be analyzed using MMRM methods similar to the primary endpoint; however, no adjustments for multiplicity will occur, and all analyses will be conducted at the $\alpha = 0.05$ level.

Additionally, descriptive statistics for absolute and percent change from baseline to each week (ie, Weeks 1, 2, 3, and 4) will be presented by treatment group.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, application site reaction assessments, physical examinations, and changes in clinical laboratory values, vital signs, and 12-lead ECGs.

Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. No formal inferential statistics will be performed on safety assessments. Individual subject listings will be prepared for all safety data.

All safety analyses will be performed on the Safety Population for each cohort. All safety data will be presented in the listings.

9.1. Adverse Events

An event that is temporally associated with administration of study product is defined as a treatment emergent adverse event (TEAE). Events meeting this definition will be those with a start date during or after administration of the first dose of study drug through the telephone follow-up in each cohort. For AEs occurring on the date of the first dose of study drug, if the time of onset is missing, the AE will be assumed to be treatment emergent.

The causal relationship of the AE to the study drug is determined by the investigator as Unrelated, Unlikely Related, Possibly Related, Probably Related, and Likely Related. These can be mapped to Unrelated (*Unrelated* and *Unlikely Related*) and Related *(Possibly Related*, *Probably Related*, and *Likely Related*).

Adverse event severity grades are reported on a 5-point scale of Grade 1 (*Mild*), Grade 2 (*Moderate*), Grade 3 (*Severe*), Grade 4 (*Life-threatening consequences*), or Grade 5 (*Death related to AE*).

An AE summary table will be presented for the following:

- All TEAEs
- TEAEs by maximum severity
- Treatment-related TEAE
- TEAEs leading to discontinuation of study drug
- Serious AEs (SAEs)
- Deaths

Summaries of incidence rates (frequencies and percentages) of individual TEAEs by MedDRA (v20.1) system organ class (SOC) and preferred term (PT). Such summaries will be displayed for all TEAEs, TEAEs by maximum severity, and treatment-related. Analysis of TEAEs will be performed by treatment within cohort.

Each subject will be counted only once within each summation level (SOC and preferred term). If a subject experiences more than 1 TEAE within each summation level only, the TEAE with the strongest relationship or the maximum severity, as appropriate, will be included in the summaries of relationship and severity.

Incidences will be presented by descending frequency of SOC and PT within SOC, and then alphabetically within PT where the incidence is the same; this is based on overall subjects.

Missing and partially missing AE start and/or stop dates will be imputed, for the purpose of statistical analysis, according to the specifications described in Section 6.1.8.

In the AE data listings, all AEs will be displayed. AEs that are treatment emergent will be flagged.

9.1.1. Adverse Events Leading to Discontinuation

A summary of incidence rates (frequencies and percentages) of TEAEs leading to discontinuation of study drug, by treatment within cohort, SOC, and PT will be prepared for subjects in the Safety Population for each cohort. No inferential statistical tests will be performed.

A data listing of AEs leading to discontinuation of study drug will also be provided, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

Serious AEs will be listed and also tabulated by SOC and PT and presented by treatment within cohort.

Any deaths that occur during the study will be listed.

9.1.3. Other Significant Adverse Events

Not applicable.

9.2. Application Site Reaction Assessments

Application site reaction assessments will be performed on Days 1 and 2 for Cohort 1 and Baseline (Visit 2), Visit 3, Visit 4, Visit 5, and Visit 6 for Cohort 2.

Dermal response reactions are graded using a scale of 0 (*no evidence of irritation*) to 7 (*strong reaction spreading beyond application site*). Additionally, other effects on an A (*slight glazed appearance*) to F scale (*small petechial erosions and/or scabs*) will be noted (where G = *no other effects may be recorded*). 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.

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

The numeric application site reaction scores will be summarized by visit and treatment within cohort, in both a continuous manner (using summary statistics) and a categorical manner (using number and percentages). The character other effects scores will be summarized by visit and treatment within cohort using number of percentages.

9.3. Clinical Laboratory Evaluations

All summaries of laboratory values will be presented using SI units. All hematology, chemistry, urinalysis, and other results will be listed by subject and timing of collection. Abnormal results will be flagged in the listings.

Observed values and change from baseline at each time point for continuous hematology, chemistry, and urinalysis results will be summarized using descriptive statistics by visit and treatment within cohort. Categorical urinalysis results will be summarized using frequencies by visit and treatment within cohort. Shifts from baseline for clinical laboratory values below, within, or above the normal range will be provided for hematology, chemistry, and urinalysis results.

Pregnancy test results and hormonal laboratory results will be listed.

9.4. Vital Signs

Descriptive summaries of observed values and change from baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate, and body temperature by visit and treatment within cohort. Shift from baseline categories for weight (change <-5%, change between -5% and 5%, and change >5%) will be provided by visit and treatment for Cohort 2 only, as no post-baseline weight was recorded for Cohort 1.

9.5. 12-Lead Electrocardiogram

Frequencies and percentages of investigator interpretation of ECG results (normal, abnormal clinically significant, and abnormal not clinically significant) will be presented by visit and treatment within cohort.

9.6. Further Safety Evaluations

The total score of the QIDS-SR (ie, the sum of the 16 individual item scores as described in Section 6.1.7) will be summarized by visit and treatment within cohort. Additionally, the number and percentage of subjects meeting the criteria for each severity level based on total score (ie, no depression, mild, moderate, severe, and very severe) will be presented by visit and treatment within cohort. A shift from baseline in QIDS-SR categories will be presented by visit and treatment within cohort.

Physical examination findings, dermal imaging data, diary dispensation and review, and telephone follow-up data for all subjects will be presented in by-subject listings.

9.7. Prior and Concomitant Medications

Prior and concomitant medications, coded using WHO-DDE (September 2017), will be summarized descriptively by Anatomical Therapeutic Chemical (ATC) classification Level 4 and preferred term (ie, ATC classification Level 5), if applicable, and by cohort and overall subjects (prior) or treatment within cohort (concomitant) using counts and percentages.

Prior medications will be presented separately from concomitant medications. The assignment of medications as prior and/or concomitant will be done as follows:

- Subjects in either Cohort 1 or Cohort 2, but not both:
    - **Prior medications:** Medications that started before first dose of study drug in either cohort will be considered prior medications whether or not they were stopped before first dose of study drug.
    - **Concomitant medications:** Any medications continuing or starting after first dose of study drug through the follow-up visit in each cohort will be considered to be concomitant to that cohort.
- Subjects in both Cohort 1 and Cohort 2:
    - **Prior medications:** Medications that started before first dose of study drug in Cohort 1 will be considered prior medications to Cohort 1; medications that started between the Cohort 1 Day 8 follow-up call and first dose of study drug in Cohort 2 will be considered prior medications to Cohort 2. This will be the case

whether or not the medications were stopped before first dose of study drug in the respective cohort.

- **Concomitant medications:** Any medications continuing or starting after first dose of study drug through the follow-up visit in each cohort will be considered to be concomitant to that cohort. A medication could be considered concomitant to both cohorts, depending on start and stop dates.

10. Changes from Planned Analysis

Amount of study medication received by each subject based on tube weight was specified in the protocol to be summarized using both continuous and categorical measures; however, this compliance measure will only be presented using summary statistics since weight is inherently a continuous measure.

Severity categories for QIDS-SR were listed in the protocol as normal, mild, moderate, moderate to severe, and severe; however, literature suggests that no depression, mild, moderate, severe, and very severe are more appropriate categories[4].

11. Other Planned Analysis

11.1. Blood Pharmacokinetic Analysis

Blood samples for PK 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, for subjects consenting to PK draws, 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.

All PK collection information from the eCRF will be presented in a listing.

All PK analysis, including calculations of PK parameters and TLF production, will be performed by a PK vendor; those results will be presented in a separate PK report.

11.2. Tissue Pharmacokinetic Analysis

An optional 4 mm diameter punch biopsy will be collected from subjects that consented to a punch biopsy of a target plaque at the Day 28 Visit. The punch biopsy will include the epidermis, dermis, and sub-cutaneous skin layers. As with plasma PK analysis, tissue PK analysis will be performed by a PK vendor and the results will be included in a separate PK report. However, collection information will be presented in a listing.

12. References

1. ASA. (1999) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, August 7, 1999. http://www.amstat.org/about/ethicalguidelines.cfm
2. RSS. (1993) The Royal Statistical Society: Code of Conduct, April 1993. http://www.rss.org.uk/main.asp?page=1875.
3. US Federal Register. (1998) International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials. Department of Health and Human Services: Food and Drug Administration [Docket No. 97D-0174]. Federal Register Volume 63, Number 179, pages 49583-49598. September 16, 1998.
4. Brown ES, Murray M, Carmody TJ, et al. The Quick Inventory of Depressive Symptomatology–Self-report: a psychometric evaluation in patients with asthma and major depressive disorder. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*. 2008;100(5):433-438. doi:10.1016/S1081-1206(10)60467-X.

13. Tables, Listings, and Figures

All listings, tables, and figures will have a header showing the sponsor company name and protocol and a footer showing the version of SAS, the file name and path, and the source of the data (CRF page or listing number).

13.1. Planned Table and Figure Descriptions

The following are planned summary tables and figures for protocol number ARQ-151-101. The table numbers and page numbers are place holders only and will be determined when the tables and figures are produced.

13.1.1. Demographic Data

Table 5: Demographic Data Summary Tables

Number	Population	Title
Table 14.1.1	All Subjects	Summary of Subject Disposition by Treatment and Cohort
Table 14.1.2	Safety	Summary of Demographics and Baseline Characteristics by Treatment and Cohort
Table 14.1.3	Safety	Incidence of Medical Histories by SOC, PT, Treatment, and Cohort
Table 14.1.4	Safety	Summary of Prior Medications by ATC Class Level 4, PT, Treatment, and Cohort
Table 14.1.5.1	Safety	Summary of Study Drug Compliance using Doses Received by Treatment

Table 14.1.5.2	Safety	Summary of Study Drug Compliance using Tube Weight (g) by Treatment

13.1.2. Efficacy Data

Table 6: Efficacy Data Summary Tables

Number	Population	Title
Table 14.2.1.1.1	mITT	Summary of Target Plaque Severity Score (TPSS) x Target Plaque Area (TPA) (cm^2) by Study Visit and Treatment
Table 14.2.1.1.2	mITT	Percent Change from Baseline in Target Plaque Severity Score (TPSS) x Target Plaque Area (TPA) (cm^2) by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from MMRM
Table 14.2.1.2.1	PP	Summary of Target Plaque Severity Score (TPSS) x Target Plaque Area (TPA) (cm^2) by Study Visit and Treatment
Table 14.2.1.2.2	PP	Percent Change from Baseline in Target Plaque Severity Score (TPSS) x Target Plaque Area (TPA) (cm^2) by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from MMRM
Table 14.2.1.3	mITT	Percent Change from Baseline in Target Plaque Severity Score (TPSS) x Target Plaque Area (TPA) (cm^2) by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from ANCOVA
Table 14.2.2.1	mITT	Summary of Target Plaque Severity Score (TPSS) by Study Visit and Treatment
Table 14.2.2.2	mITT	Percent Change from Baseline in Target Plaque Severity Score (TPSS) by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from MMRM
Table 14.2.3.1	mITT	Summary of Target Plaque Area (TPA) (cm^2) by Study Visit and Treatment
Table 14.2.3.2	mITT	Percent Change from Baseline in Target Plaque Area (TPA) (cm^2) by Study Visit and Treatment, Tabulation of Fitted Summary Statistics from MMRM

13.1.3. Safety Data

Table 7: Safety Data Summary Tables

Number	Population	Title
14.3.1 Displays of Adverse Events		
Table 14.3.1.1	Safety	Summary of Treatment Emergent Adverse Events by Treatment and Cohort
Table 14.3.1.2	Safety	Incidence of Treatment Emergent Adverse Events by SOC, PT, Treatment, and Cohort
Table 14.3.1.3	Safety	Incidence of Treatment Emergent Adverse Events by Maximum Severity, SOC, PT, Treatment, and Cohort
Table 14.3.1.4	Safety	Incidence of Treatment Related Treatment Emergent Adverse Events by SOC, PT, Treatment, and Cohort
Table 14.3.1.5	Safety	Incidence of Treatment Emergent Adverse Events Leading to Study Drug Discontinuation by SOC, PT, Treatment, and Cohort
14.3.2 Summary of Deaths, Other Serious and Significant Adverse Events		
Table 14.3.2	Safety	Incidence of Serious Adverse Events by SOC, PT, Treatment, and Cohort
14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events		
Table 14.3.3.1	Safety	Listing of Adverse Events Leading to Study Drug Discontinuation
Table 14.3.3.2	Safety	Listing of Serious Adverse Events
Table 14.3.3.3	Safety	Listing of Deaths
14.3.4 Abnormal Laboratory Value		
NA		
14.3.5 Laboratory Data Summary Tables		
Table 14.3.5.1.1	Safety	Summary of Serum Chemistry Laboratory Results by Study Visit, Treatment, and Cohort
Table 14.3.5.1.2	Safety	Shift from Baseline in Serum Chemistry Laboratory Results by Study Visit, Treatment, and Cohort
Table 14.3.5.2.1	Safety	Summary of Hematology Laboratory Results by Study Visit, Treatment, and Cohort
Table 14.3.5.2.2	Safety	Shift from Baseline in Hematology Laboratory Results by Study Visit, Treatment, and Cohort
Table 14.3.5.3.1	Safety	Shift from Baseline in Quantitative Urinalysis Laboratory Results by Study Visit, Treatment, and Cohort

Number	Population	Title
Table 14.3.5.3.2	Safety	Shift from Baseline in Quantitative Urinalysis Laboratory Results by Study Visit, Treatment, and Cohort
Table 14.3.5.3.3	Safety	Summary of Qualitative Urinalysis Laboratory Results by Study Visit, Treatment, and Cohort
14.3.6 Other Safety Data Summary Tables		
Table 14.3.6.1.1	Safety	Summary of Quantitative Dermal Response Reaction by Study Visit, Treatment, and Cohort
Table 14.3.6.1.2	Safety	Summary of Qualitative Dermal Response Reaction by Study Visit, Treatment, and Cohort
Table 14.3.6.1.3	Safety	Summary of Application Site Reaction Other Effects by Study Visit, Treatment, and Cohort
Table 14.3.6.2.1	Safety	Summary of Vital Signs by Study Visit, Treatment, and Cohort
Table 14.3.6.2.2	Safety	Shift from Baseline in Weight by Study Visit, Treatment, and Cohort
Table 14.3.6.3	Safety	Summary of 12-Lead Electrocardiogram Interpretation by Study Visit, Treatment, and Cohort
Table 14.3.6.4.1	Safety	Summary of Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) Total Score by Study Visit, Treatment, and Cohort
Table 14.3.6.4.2	Safety	Summary of Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) Total Score Severity Levels by Study Visit, Treatment, and Cohort
Table 14.3.6.4.3	Safety	Shift from Baseline in Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) Total Score Severity Levels by Study Visit, Treatment, and Cohort
Table 14.3.6.5	Safety	Summary of Concomitant Medications by ATC Class Level 4, PT, Treatment, and Cohort

13.2. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number ARQ-151-101.

In general, 1 listing will be produced per CRF domain.

All listings will be sorted by cohort, treatment, and subject number.

All calculated variables will be included in the listings.

In all listings a blank line will be placed between each subject. Within a data listing, if an item appears line after line (eg, repetition of subject number), then only the first occurrence will be displayed.

In data listings, the information for 1 subject will be kept on 1 page if at all possible, rather than splitting a subject's information across pages.

Table 8: Planned Listings

Number	Population	Title / Summary
16.2.1 Subject Discontinuations/Completions		
Listing 16.2.1	All Subjects	Subject Disposition
16.2.2 Protocol Deviations		
Listing 16.2.2.1	All Subjects	Inclusion and Exclusion Criteria Not Met
Listing 16.2.2.2	All Subjects	Protocol Deviations
16.2.3 Subjects Excluded from the Efficacy Analyses		
Listing 16.2.3	All Subjects	Analysis Populations
16.2.4 Demographic Data and Other Baseline Characteristics		
Listing 16.2.4.1	All Subjects	Demographics and Baseline Information
Listing 16.2.4.2	All Subjects	Medical History
Listing 16.2.4.3	All Subjects	Pharmacokinetic, Skin Biopsy, and Dermal Imaging Consent
16.2.5 Compliance and/or Drug Concentration Data		
Listing 16.2.5.1.1	Cohort 1 Subjects	Drug Application
Listing 16.2.5.1.2	Cohort 2 Subjects	Vehicle Application (Subject Training/Retraining)
Listing 16.2.5.2	Cohort 2 Subjects	Study Medication Dispensation and Return Weight
Listing 16.2.5.3	Cohort 2 Subjects	Missed Doses
Listing 16.2.5.4	All Consenting Subjects with Pharmacokinetic Data Collected	Pharmacokinetic Blood Collection
Listing 16.2.5.5	Consenting Cohort 2 Subjects	Skin Biopsy Collection
16.2.6 Individual Efficacy Response Data		
Listing 16.2.6	Cohort 2 Subjects	Target Plaque Severity Score and Area
16.2.7 Adverse Event Listings (by Subject)		
Listing 16.2.7.1	All Subjects	Adverse Events
16.2.8 Laboratory Values (by Subject)		
Listing 16.2.8.1	All Subjects	Clinical Laboratory Data: Serum Chemistry
Listing 16.2.8.2	All Subjects	Clinical Laboratory Data: Hematology
Listing 16.2.8.3	All Subjects	Clinical Laboratory Data: Urinalysis

Number	Population	Title / Summary
Listing 16.2.8.4	All Subjects	Clinical Laboratory Data: Urine Drug Screen and Pregnancy Tests
16.2.9 Other Clinical Observations and Measurements (by Subject)		
Listing 16.2.9.1	All Subjects	Application Site Reaction
Listing 16.2.9.2	All Subjects	Vitals Signs
Listing 16.2.9.3	All Subjects	12-Lead Electrocardiogram (ECG)
Listing 16.2.9.4	All Subjects	Limited Physical Examination
Listing 16.2.9.5	Cohort 2 Subjects	Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR)
Listing 16.2.9.6	All Subjects	Prior and Concomitant Medications
Listing 16.2.9.7	Cohort 2 Subjects	Dermal Imaging
Listing 16.2.9.8	Cohort 2 Subjects	Diary Dispensation and Review
Listing 16.2.9.9	All Subjects	Telephone Follow-up

14. Tables, Listings, and Listing Shells

Note: Shell Tables Removed (pages 36-98)

Appendix 1: Premier Research Library of Abbreviations

Abbreviation	Definition
aCRF	annotated case report form
AD	associated documents
ADR	adverse drug reactions
AE	adverse event
AESI	adverse events special interest
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BLQ	beneath limit of quantification
BMI	body mass index
BRD	business requirements document
BSL	biostatistician lead
CCGs	CRF completion guidelines
CD	compact disc
CDISC	clinical data interchange standards consortium
CEC	central ethics committee
CFR	code of federal regulations
CI	confidence intervals
CIOMS	council for international organizations of medical sciences

Abbreviation	Definition
CIP	clinical investigational plan
CM	clinical manager
CMP	clinical monitoring plan
COV	close out visit
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CS	clinically significant
CSM	clinical supply manager
CSR	clinical study report
CTA	clinical trial administrator
CTM	clinical trial manager
CTMS	clinical trial management system
DB	database
DBL	database lock
DBP	diastolic blood pressure
DCRF	data change request form
DDE	drug dispensing error form
DEA	drug enforcement administration

Abbreviation	Definition
DIA	drug information association
DIS	data integration specification
DLT	dose limiting toxicity
DM	data management
DMB	data monitoring board
DMC	data monitoring committee
DML	data management lead
DMP	data management plan
DNA	deoxyribonucleic acid
DOB	date of birth
DS	document specialist
DSG	drug safety group
DSM	drug supply management (drug distributor)
DSMB	data safety monitoring board
DSP	data safety plan
DSUR	development safety update report
DTS	data transfer specification
DVD	digital video disk
EC	ethics committee

Abbreviation	Definition
ECD	edit check and derivation specifications
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European medicines agency
eTMF	electronic trial master file
EU	European Union
FA	full analysis
FDA	food and drug administration
FMP	file management plan
FPFV	first patient first visit
FPI	first patient in
GCP	good clinical practice
GMP	good manufacturing practices
GPV	global pharmacovigilance
HR	heart rate
IB	investigator's brochure
IC or ICF	informed consent or informed consent form
ICH	international council for harmonization

Abbreviation	Definition
ID	identification
IDM	independent drug monitoring
IEC	independent ethics committee
IM	investigator meeting
IMV	interim monitoring visit
IND	investigational new drug
INDSR	investigational new drug safety reports
IP	investigational product
IRB	institutional review board
IRF	inventory release file
IRR	infusion related reactions
IRT	interactive response technology
ISF	investigator site file
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
IxRS	interactive voice/web response system
KPI	key performance indicator
LAN	local area network

Abbreviation	Definition
LDM	lead data manager
LMS	learning management system
LLOQ	lower limit of quantification
LPI	last patient in
LPLV	last patient last visit
LPO	last patient out
MAAP	medical affairs and pharmacovigilance teams
MAH	marketing authorization holder
MedDRA	medical dictionary for regulatory activities
MHRA	medicines and healthcare products regulatory agency
MM	medical monitor
MMP	medical monitoring plan
MMRM	mixed effect model repeat measurement
MTD	maximum tolerated dose
MVR	monitoring visit report
N	number
NA	not applicable
NCS	non-clinically significant
NF	non-functional

Abbreviation	Definition
PD	protocol deviation
PDGP	protocol deviation guidance plan
PE	physical examination
PI	principal investigator
PIN	personal identification number
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PM	project manager
PMP	project management plan
PP	per-protocol
PRIMS	Premier Research information management system
PS	project specialist
PV	pharmacovigilance
PVG	pharmacovigilance group
QA	quality assurance
QARC	quality assurance, risk and compliance
QC	quality control
QOL	quality of life
ROT	record of training

Abbreviation	Definition
RR	respiratory rate or relative rate
RSM	regional site monitor
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	a software system used for data analysis
SBP	systolic blood pressure
SC	study coordinator
SCR	software change request
SD	standard deviation
SDS	study design specifications
SDTM	study data tabulation model
SDV	source data verification
SECC	self-evident correction conventions
SECP	self-evident correction plan
SF	screen failure
SFT or SFTP	secure file transfer or secure file transfer plan
SIV	site initiation visit
SLA	service level agreement
SMP	safety management plan

Abbreviation	Definition
SOC	system organ class
SOP	standard operating procedure
SOW	statement of work
SQV	site qualification visit
SUA	start-up associate
SUSAR	suspected, unexpected, serious adverse (drug) reaction
TA	trial assistant
TEAE	treatment-emergent adverse event
TMF	trial master file
TOM	task ownership matrix
UAT	user acceptance testing
USA	United States of America
UTC	universal coordinated time
WAN	wide area network
WAR	work at risk
WG	working guideline
WHO	world health organization
WHO-DD	world health organization drug dictionary