Sponsor	*Arcutis, Inc.*
Protocol Title:	*A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.3% Administered QD in Subjects with Chronic Plaque Psoriasis*
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Role	Signatures	Date (dd-Mmm-yyyy)
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Document History

Not applicable.

Table of Contents

List of Tables

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Arcutis, Inc. protocol number ARQ-151-301 (*A Phase 3, 8-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.3% Administered QD in Subjects with Chronic Plaque Psoriasis*), final version dated 31-Oct-2019. 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[3] and the Royal Statistical Society[1], 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-151-301.

2. Study Objectives and Endpoints

2.1. Study Objectives

Psoriasis is a chronic inflammatory skin disease characterized by raised, well-demarcated, erythematous oval plaques with adherent silvery scales.

The advent of biological therapies has caused a transformation in the systemic treatment of moderate to severe psoriasis. However, for patients with milder forms of disease, the therapeutic landscape has not significantly changed in several decades. Lower potency topical steroids are not effective and the higher potency steroids can cause local skin atrophy and the potential for hypothalamic-pituitary axis suppression. Another typical therapy, vitamin D, is irritating and is not suitable for use on the face or intertriginous areas. There is substantial medical need for additional topical approaches in the treatment of mild to moderate psoriasis. The Phase 2 results suggest that ARQ-151 may be a highly efficacious and well-tolerated topical treatment for psoriasis.

2.1.1. Primary Objective

The primary objective is to assess the safety and efficacy of ARQ-151 cream 0.3% vs. vehicle administered QD for 8 weeks to individuals with 2-20% BSA of chronic plaque psoriasis.

2.2. Study Endpoints

2.2.1. Safety Endpoints

The safety endpoints of this study include the following:

- adverse events
- local tolerance assessments
- Patient Health Questionnaire depression scale (PHQ-8) and Modified PHQ-9 for Adolescents (PHQ-A)
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- clinical laboratory results
- vital signs

2.2.2. Efficacy Endpoints

2.2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is success in Investigator Global Assessment (IGA) of disease severity, defined as an IGA of 'Clear' or 'Almost Clear' plus a 2-grade improvement from Baseline at Week 8.

2.2.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study include the following:

- Achievement of Psoriasis Area Severity Index-75 (PASI-75; subjects who achieve a 75% reduction in PASI from Baseline) at week 8.
- For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (intertriginous IGA (I-IGA) ≥2) at Baseline, achievement of 'I-IGA' score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at week 8.
- In subjects with Worst Itch – Numeric Rating Score (WI-NRS) pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 8 as compared to Baseline.
- In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 4 as compared to Baseline.
- In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 2 as compared to Baseline.
- Change from Baseline in total Psoriasis Symptoms Diary (PSD) score at week 8.
- Change from Baseline in total PSD score at week 4.
- Time to achieving Psoriasis Area Severity Index-50 (PASI-50; subjects who achieve a 50% reduction in PASI from Baseline)
- For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (I-IGA ≥2) at Baseline, achievement of 'I-IGA' score of 'clear' at week 8.
- Achievement of PASI-90 (subjects who achieve a 90% reduction in PASI from Baseline) at week 8.

3. Overall Study Design and Plan

3.1. Overall Design

3.2. Sample Size and Power

A sample size of approximately 400 subjects are planned for the study.

Approximately 267 subjects will receive ARQ-151 cream 0.3% QD; approximately 133 subjects will receive vehicle cream QD. The randomization scheme will be 2:1 (ARQ-151 cream 0.3% QD: matching vehicle QD).

This sample size provides >99% power to detect a 22.4% difference between treatment groups on IGA success at α=0.05 using a 2-sided Chi-squared test. The results from a recent phase 2b study (ARQ 151 201) of ARQ-151 compared to vehicle treatment were used to estimate the treatment difference. Specifically, in this trial 32.2% of subjects reported IGA success in the ARQ-151 0.3% group and 9.8% of subjects reported IGA success in the vehicle group.

The number of subjects to be enrolled will also provide sufficient power for the first 5 secondary endpoints. Additionally, the larger study size is included in order to provide additional/sufficient numbers of subjects on ARQ-151 treatment for a safety database.

3.3. Study Population

Males and females ages 12 years and older with a clinical diagnosis of psoriasis vulgaris on the face, extremities, trunk, and/or intertriginous areas involving 2% to 20% BSA (excluding the scalp, palms and soles) of at least 6 months duration that has been stable for the past 4 weeks, with an Investigator's Global Assessment of disease severity (IGA) of at least Mild ('2') and a PASI score of at least 2 (excluding the scalp, palms and soles) at Baseline.

3.4. Treatments Administered

Subjects will be randomized to one of the two following treatment groups in a 2:1 ratio (active:vehicle):

- ARQ-151 cream 0.3% QD
- vehicle cream QD.

3.5. Method of Assigning Subjects to Treatment Groups

Subjects will be randomized and assigned to active drug or vehicle in a 2:1 ratio (active:vehicle) according to a computer-generated randomization list. The randomization schedule will be stratified by study site, baseline IGA (IGA=2 vs. IGA≥3), and intertriginous involvement at baseline (I-IGA>2, yes vs no).

3.6. Blinding and Unblinding

This study is double-blind. In the event of a serious safety concern where the situation requires emergency unblinding this will be done by investigator using the study IWRS system after discussion with Medial Monitor and the Sponsor's CMO.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 1: Schedule of Events

Study Procedure	Screen	Baseline Day 1	Wk 2 Day 15	Wk 4 Day 29	Wk 6 Day 43	Wk 8[r] Day 57	Wk 9 Day 64
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Window	**-35 days**		**+/- 3 days**	**+/- 5 days**	**+/- 5 days**	**+/- 7 days**	**+/- 7 days**
Informed consent/assent	X						
Medical history	X						
Physical examination[a]	X	X				X	
I/E criteria	X	X					
Hematology, Serum Chemistries, and Urine Analysis[b]	X	X		X		X	
Vital signs, height, weight[c]	X	X	X	X	X	X	X
IGA[d], BSA[d], PASI/mPASI[d]	X	X	X	X	X	X	X
Intertriginous area IGA (I-IGA)[e]		X	X	X	X	X	X
WI-NRS[f]	X	X	X	X	X	X	
DLQI/CDLQI[g]	X	X	X	X		X	
Local Tolerability Assessments[h]		X		X		X	
C-SSRS, PHQ-8 / modified PHQ-A	X	X		X		X	
PSD	X	X	X	X	X	X	
Photography[i]		X	X	X	X	X	
Serum pregnancy test	X						
Urine pregnancy test[j]		X		X		X	
PK draws[k]		X		X		X	
IP application in clinic[l]		X	X	X	X	X	
Assign investigational product kit[m]		X					
Dispense/review diary		X	X	X	X	X	
Weigh investigational product tubes[n]		X	X	X	X	X	
Compliance calculation[n]		X	X	X	X	X	
Adverse event assessment[o]	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Study Exit[p]							X

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

[b] To be collected at Screening, Baseline, Week 4 and Week 8. If Baseline is within 14 days of Screening, the Screening results may be utilized.

[c] Height will be collected at Baseline only. Weight will be collected at every visit. Subject to void prior to weight being taken. Remove any jackets, outerwear and shoes. Remove any objects of significant weight (i.e. cell phones, wallet, key chains). A 5% unintentional weight loss should be reported to the medical monitor on Page 1.

[d] IGA (based on whole body involvement) will be a 5-point scale ranging from clear (0) to severe (4). **IGA should be completed prior to other physician assessments.** Total BSA affected by psoriasis will be determined. PASI/mPASI will be determined by standard methods. PASI-75, PASI-90, and PASI-100, and mPASI-75, mPASI-90, and mPASI-100 responses will be determined.

[e] For subjects with intertriginous area involvement of at least 'mild' severity by IGA (IGA≥2) at Baseline (using the IGA scale but evaluating intertriginous areas ONLY and NOT whole body involvement), an IGA for the intertriginous region alone (I-IGA) will be recorded at weeks 2, 4, 6, 8, and 9. **This 'intertriginous area IGA' should be done AFTER the 'standard whole body IGA' (primary endpoint) in subjects who qualify.**

[f] Subjects will complete WI-NRS pruritus assessment.

[g] Subjects ≥17 years will complete DLQI. For subjects 12-16 years of age, CDLQI will be completed.

[h] Tolerability assessments should be recorded prior to investigational product application for Investigator assessment (Berger and Bowman skin irritation score) and 10-15 minutes post-investigational product application for subject '0-3' burning/stinging assessment.

[i] Photography will be performed using Canfield equipment on all subjects at all sites. All efforts will be made to de-identify the subjects.

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

[k] PK draws will be collected from all subjects at Days 1, 29 and 57. The draws will be pre-dose investigational product application in the clinic (i.e., trough levels). The tube weight will be collected prior to the application and after the application. Ensure investigational product is not applied in the area where PK will be drawn.

[l] Subjects to apply assigned IP in clinic at every visit. The time of application will be documented.

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

[n.] Each tube should be weighed and recorded at every visit. See IP Handling Manual for details.

[o] 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.

[p] Subjects who enroll into the open label extension study (ARQ-151-306) will complete the study at Week 8; subjects that do not enroll into ARQ-151-306 will return at Week 9 to complete the study.

[r] Or early termination visit.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will be performed primarily using SAS (release 9.4 or higher). If the use of other software is warranted, the final clinical study report will detail what software was used for what purposes.

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 group, 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, unless otherwise specified.

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 where appropriate.

A *p*-value of ≤ 0.10 but > 0.05 will be considered evidence of a trend.

4.2. Interim Analysis and Data Monitoring

No interim analyses or data safety monitoring are planned.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population (SAF):** The Safety Population includes all subjects who are enrolled and received at least one confirmed dose of investigational product. This population will be used for all safety analyses.
- **Intent-To-Treat Population (ITT):** The ITT population includes all randomized subjects. This population will be the primary analysis population for the analysis of efficacy endpoints.
- **I-IGA Population (I-IGA):** The I-IGA population is a subset of the ITT population and includes subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least ‘mild’ (intertriginous IGA (I-IGA) ≥2) at Baseline. This population will be used for the analysis of I-IGA endpoints.

- **Pruritis Population (PRU):** The PRU population is a subset of the ITT population and includes subjects with WI-NRS pruritus score ≥ 4 at Baseline. This population will be used for the analysis of achievement of a 4-point reduction in WI-NRS pruritus score as compared to Baseline.
- **Pharmacokinetic Population (PK):** The PK Population includes all subjects receiving the active drug with sufficient plasma concentrations of roflumilast to define a profile, as determined by the pharmacokineticist. This population will be used for analyses of PK parameters.

6. General Issues for Statistical Analysis

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

The last observation recorded prior to the first dose of investigational product being administered will be used as the baseline observation for all calculations of change from baseline.

6.1.2. Adjustments for Covariates

If there is a statistical difference among treatment groups with respect to baseline characteristics, that variable may be added to the statistical models as a blocking factor or covariate to determine the effect on treatment.

6.1.3. Multiple Comparisons

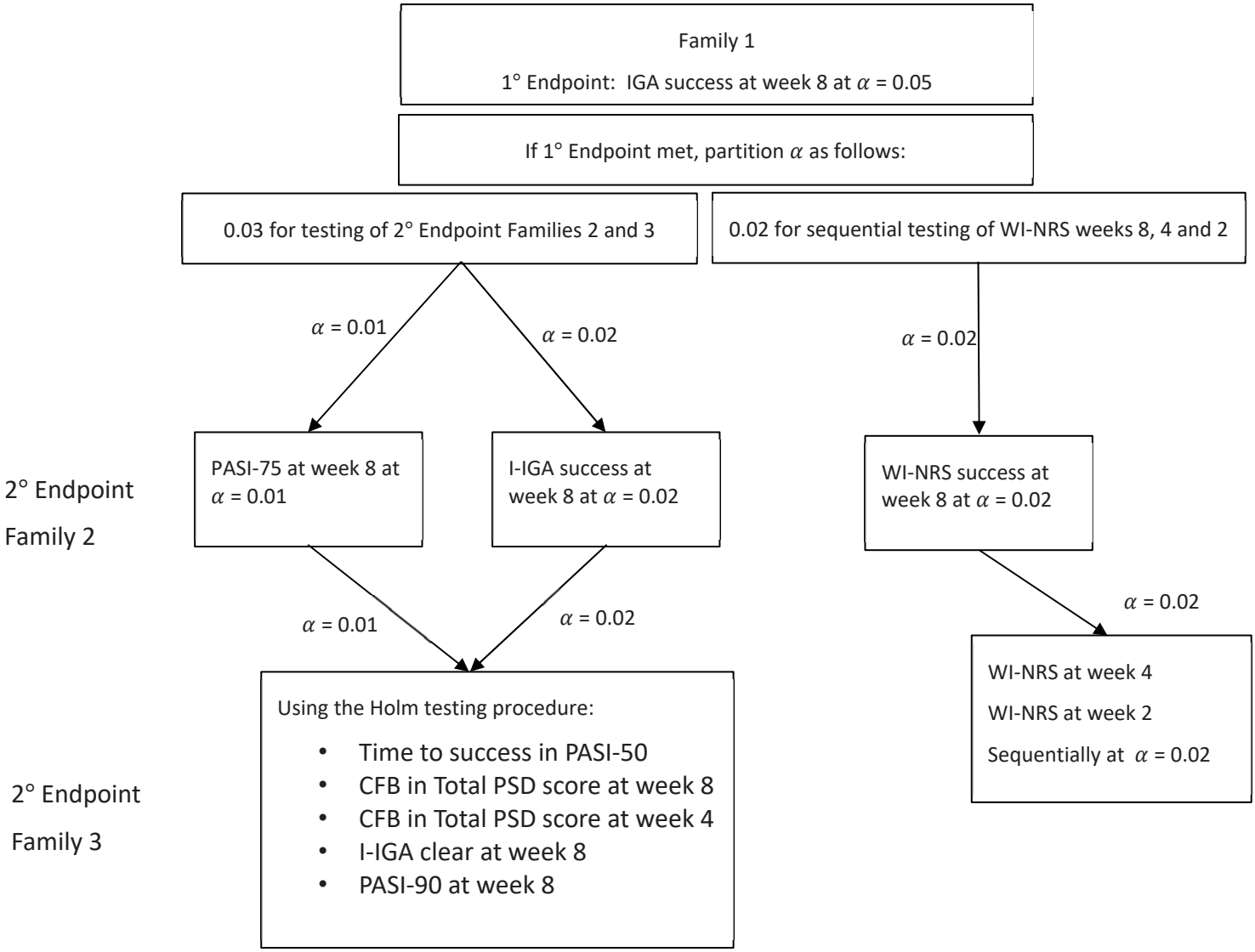
The type I error rate of $\alpha = 0.05$ will be maintained for all secondary efficacy endpoints included in the hierarchical testing strategy by assigning the endpoints into families and only proceeding to the next family in accordance with the rules of the pre-specified sequential testing strategy.

Secondary endpoints will only be tested statistically if the primary endpoint is considered statistically significant. To control for multiple comparisons among the secondary endpoints, the following multiplicity procedure will be used:

Upon successful testing of the primary endpoint (Family 1) the alpha will be partitioned to test secondary endpoint Families 2 and 3 (Partition 1) and to test WI-NRS timepoints (Partition 2).

Partition 1 of alpha = 0.03 will be allocated to test Family 2 and Family 3. The endpoints in Family 2 will be tested independently using a Bonferroni split of the alpha; the next 5 secondary endpoints (Family 3) will be tested using the alpha available after testing endpoint Family 2. The Holm procedure will be used to control for multiple comparisons in endpoint Family 3.

Partition 2 of alpha = 0.02 will be allocated to sequentially test WI-NRS success at week 8, then week 4 and finally week 2.



No adjustments will be made for multiple comparisons for other endpoints.

6.1.4. Handling of Dropouts or Missing Data

Any subject who prematurely withdraws from the study will have their last available data assigned to an analysis window as described in Section 6.1.5.

For the primary efficacy endpoint of IGA score, the primary analysis will impute missing values using a regression-based multiple imputation model. For subjects with complete data up to a particular visit, a multiple regression model will be fit that includes the outcome at that visit as

the dependent variable and as independent variables, IGA score outcomes at previous visits, baseline IGA score, treatment group, investigational site, and intertriginous involvement at baseline. Separate models will be similarly constructed for each visit. Using these regression models, a missing value for a subject at a particular visit will be imputed as a draw from the predictive distribution given the outcomes at previous visits (some possibly imputed), treatment group, investigational site, baseline IGA score, and intertriginous involvement at baseline. This process will be repeated up to 10 times, resulting in 10 complete analysis data sets. The Cochran-Mantel-Haenszel (CMH) analysis will be performed separately for each of the 10 complete analysis data sets, and the results will be combined into one multiple imputation inference (estimated treatment effect and associated confidence interval and *p*-value).

This strategy is appropriate for data sets that have a monotone missing pattern. If the data set does not precisely have this pattern (i.e. there are existing values for baseline and week 8 visits, but missing values for the week 2, 4, or 6 visits), the monotone data augmentation method using Markov-Chain Monte-Carlo (MCMC) described below will be used to impute the small amount of missing data that may be missing at the intermediate visits that is required to make the missing data pattern monotone before applying the multiple imputation algorithm described above. This method uses a non-informative Jeffreys prior to derive the posterior mode from the expectation-maximization (EM) algorithm as the starting values for the MCMC method.

The most reliable method of multiple imputation for categorical variables is logistic regression which relies on the input dataset having monotone missingness. The number of imputed monotone datasets will be determined based on the amount of missing data that is required to be imputed to make the original dataset monotone per the below:

Non-monotone Missing Data	Number of Imputed Datasets
≤ 2%	1
> 2% to ≤ 5%	3
> 5%	10

These imputed monotone missing pattern datasets will be used to impute the remaining missing data based the logistic regression method for categorical variables with monotone data. Using these logistic regression models, a missing IGA score for a subject at a particular visit will be imputed as a draw from the predictive distribution given the outcomes at previous visits (some possibly imputed), baseline IGA score, treatment group, site, and baseline intertriginous involvement. This process will be repeated 25 times, using seed 461903, resulting in a total of 25 to 250 complete analysis datasets, depending on the number of imputed monotone datasets that are required. The seed may be changed after unblinding in case of any issues with the imputation process, and it will be documented in the CSR if any change is required.

This approach to imputation should be superior to other strategies such as carrying forward the last available observation, which may yield unrealistic imputed values. Also, the use of multiple

imputation avoids the problem of artificially increasing power through data imputation associated with single-imputation methods because it accounts for the uncertainty associated with the imputation.

All other missing data for all other analyses and summaries will remain missing and will not be imputed. Only observed data will be summarized using descriptive statistics.

6.1.5. Analysis Visit Windows

Subjects who prematurely withdraw from the study within 7 days of their next scheduled visit will have their efficacy data collected at the withdrawal visit assigned to the next scheduled visit, if that data was scheduled to have been collected at that visit. If they withdraw outside that window, their efficacy data will be considered missing for the visit. All safety data collected at the withdrawal visit will be assigned to the Week 8 visit. Data that is otherwise missing will be left as missing for all analyses.

6.1.6. Pooling of Sites

Sites will be pooled for statistical analysis as follows. For analysis, sites should have a minimum of 12 randomized subjects. The smallest sites will be grouped sequentially in order of smallest to largest, restricting to those sites that did not meet the minimum enrollment of 12, until each pooled site has a minimum of 12 subjects with at least one subject in each treatment group.

6.1.7. Derived Variables

- Investigator Global Assessment (IGA) success = IGA of 'Clear' or 'Almost Clear' plus a 2-grade improvement from Baseline.

- Worst Itch – Numeric Rating Score (WI-NRS) success = achievement of a 4-point reduction in WI-NRS pruritus score at week 8 compared to baseline, calculated only for subjects with a pruritus score of ≥ 4 at baseline.

- PASI = $0.1 (E_h + T_h + S_h) A_h + 0.2 (E_a + T_a + S_a) A_a + 0.3 (E_t + T_t + S_t) A_t + 0.4 (E_l + T_l + S_l) A_l$ where E, T, and S are erythema, thickness, and scaling, respectively, scored on a scale of 0 to 4, A is estimated area of skin involved, graded on a scale of 0 to 6, and h, e, t, and l are head, arms, trunk, and legs, respectively (range for total score 0 to 72).

- mPASI = same as PASI above, except that for subjects with < 10% of any particular involved anatomic area, the mPASI will be calculated using the actual percentage of the anatomical area involved rather than the 0 to 6 estimated area score (e.g. 0.1 for 1%, 0.2 for 2%, 0.3 for 3%, … 0.9 for 9%).

- PASI-50(mPASI-50) = achievement of a 50% reduction in PASI(mPASI) from Baseline.

- Time to PASI-50 Success (days) = date of PASI-50 acheivement – Day 1 date + 1.

- PASI-75(mPASI-75) = achievement of a 75% reduction in PASI(mPASI) from Baseline.

- PASI-90(mPASI-90) = achievement of a 90% reduction in PASI(mPASI) from Baseline.

- PASI-100(mPASI-100) = achievement of a 100% reduction in PASI(mPASI) from Baseline.

- PSD Total Score = sum of the 16 questions (individual questions scored 0 to 10; range for total score 0 to 160). If 1 or more items are missing, the score is not calculated.

- DLQI Score = sum of the 10 questions (individual questions scored as Very much=3, A lot=2, A little=1, Not at all=0, Not relevant=0, Question 7: Yes=3; range for score 0 to 30). If 1 item is missing, it is scored as 0 for that item. If 2 or more items are missing, the score should not be calculated.

- CDLQI Score = sum of the 10 questions (individual questions scored as Very much=3, A lot=2, A little=1, Not at all=0, Not relevant=0, Question 7: Yes=3; range for score 0 to 30). If 1 item is missing, it is scored as 0 for that item. If 2 or more items are missing, the score should not be calculated.

- PHQ-8 = sum of the 8 questions (individual questions scored as Not at all=0, Several days=1, More than half the days=2, and Nearly every day=3, (range for score 0 to 24). If more than 1 item is missing the score should not be calculated. If 1 item is missing the score is calculated as (sum of answered items*8)/number of answered items.

- PHQ-A = sum of the 9 questions (individual questions scored as Not at all=0, Several days=1, More than half the days=2, and Nearly every day=3, (range for score 0 to 27). If 3 or more items are missing the score should not be calculated. If 1-2 items are missing the score is calculated as (sum of answered items*9)/number of answered items.

- Change from baseline = value at current time point – value at Baseline.

- TEAE = any adverse event with an onset date/time after the first application of investigational product.

- C-SSRS Suicidal ideation = A “yes” answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5: Wish to be Dead, Non-specific Active Suicidal Thoughts, Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act, Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active Suicidal Ideation with Specific Plan and Intent).

- C-SSRS Suicidal behavior = A “yes” answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-10: Preparatory Acts or Behavior, Aborted Attempt, Interrupted Attempt, Actual Attempt (non-fatal), Completed Suicide).

- C-SSRS Suicidal ideation or behavior = A “yes” answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-10) on the C-SSRS.

6.1.8. Data Adjustments/Handling/Conventions

All collected data will be presented in listings or CDISC datasets. 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 or CDISC datasets.

All *P* values will be displayed in four 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 analyses that include the stratification factors (site, baseline IGA, and baseline intertriginous involvement) will use the data as collected in the IVR system. If the overall number of discrepancies between the IVR and the eCRF database exceeds 10%, a sensitivity analysis will be conducted in which the stratification will be based on the stratification values as collected in the eCRF database.

Adverse events will be coded using the MedDRA version 22.1 thesaurus.

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

If partial dates occur, the convention for replacing missing dates for the purpose of statistical analysis is as follows: 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 either the first day of the month or the first dose date, whichever is later.

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

These conventions will be applied only to adverse event onset dates and times with the following precaution: if the missing date and time reflect the date and time of onset of an adverse event, the modified date and time will be constructed to match the first documented date/time post drug administration while preserving the order in which the AE was reported in the CRF.

7. Study Patients/Subjects and Demographics

7.1. Disposition of Patients/Subjects and Withdrawals

Disposition will include tabulations of the number of subjects randomized into each treatment group, the number of subjects who received treatment, tabulated reasons for discontinuation from the study, and number of subjects in each analysis population.

7.2. Protocol Violations and Deviations

Protocol deviations will be listed.

7.3. Demographics and Other Baseline Characteristics

Summary statistics for age, gender, race, ethnicity, height, weight, total BSA, percent BSA covered with plaque psoriasis, and BMI will be presented by treatment group.

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 ITT, I-IGA, PRU, and Safety populations.

The number and percent of subjects reporting various medical histories, grouped by MedDRA system organ class and preferred term (coded using MedDRA v. 22.1), will be tabulated by treatment group. This analysis will be conducted for the Safety Population.

7.4. Exposure and Compliance

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

The amount of investigational product used by each subject based on tube weight will be summarized descriptively by treatment using continuous methods.

A subject will be considered compliant with the dosing regimen if the subject applies at least 80% of the expected applications during the investigational product 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 investigational product applications for each subject. Compliance will be summarized descriptively by treatment group using the following categories:

$> 100\%$

$\geq 80\% - \leq 100\%$

$< 80\%$.

8. Efficacy Analysis

All efficacy analyses that include the stratification factors (site, baseline IGA, and baseline intertriginous involvement) will use the data as collected in the IVR system. If the overall number of discrepancies between the IVR and the eCRF database exceeds 10%, a sensitivity analysis will be conducted in which the stratification will be based on the stratification values as collected in the eCRF database.

8.1. Primary Efficacy Analysis

For this study, the primary estimand is the ratio of the odds of achieving IGA success after 8 weeks of using ARQ-151, relative to the odds of success after 8 weeks of using a matching vehicle cream. In the course of the 8-week randomized treatment period, subjects may be exposed to possible known or unknown inter-current events that could possibly impact the estimand, such as treatment discontinuation due to a specific adverse effect or perhaps a lack of effect. The "Treatment Policy Strategy" has been adopted for handling all known or unknown inter-current events in this study. To this end, the intent-to-treat (ITT) principle will serve as the analytical basis for interpreting the estimand. In other words, the odds ratio of achieving IGA success for ARQ-151 relative to vehicle after 8 weeks will be evaluated regardless of the occurrence of any such inter-current event. This estimand shall be estimated using the CMH approach. This approach produces an estimate which is the combined odds ratio resulting from adjusting for the possible confounding effects of three classification factors – investigative site, baseline IGA and baseline intertriginous involvement.

The primary efficacy endpoint is success in IGA of disease severity, defined as an IGA of 'Clear' or 'Almost Clear' plus a 2-grade improvement from Baseline at Week 8.

The primary endpoint will be analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by site, baseline IGA, and baseline intertriginous involvement. Statistical significance will be concluded at the 5% significance level (2-sided).

For the primary analysis, missing IGA scores will be imputed using multiple imputation as described in Section 6.1.4. These imputations will result in a minimum of 25 to a maximum of 250 complete analysis datasets, depending on the number of imputed monotone datasets that are required.

The CMH analyses will be performed separately for each of the complete analysis data sets, and the results will be combined into one multiple imputation inference (estimated treatment effect and associated confidence interval and p-value).

Sensitivity analyses of the primary endpoint will also be performed using the original (non-imputed) dataset. These will include a repeated measures logistic regression model (GEE) with IGA success as the dependent variable and treatment, site, and visit as the independent variables, as well as the above described CMH test using last observation carried forward (LOCF) techniques.

All other missing data for all other analyses and summaries will remain missing and will not be imputed. Only observed data will be included in the summaries showing descriptive statistics.

The primary efficacy analysis and the sensitivity analyses will be based on the ITT population.

8.2. Secondary Efficacy Analysis

The secondary endpoints are:

- Achievement of Psoriasis Area Severity Index-75 (PASI-75; subjects who achieve a 75% reduction in PASI from Baseline) at week 8.
- For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (intertriginous IGA (I-IGA) ≥2) at Baseline, achievement of 'I-IGA' score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at week 8.
- In subjects with Worst Itch – Numeric Rating Score (WI-NRS) pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 8 as compared to Baseline.
- In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 4 as compared to Baseline.
- In subjects with WI-NRS pruritus score ≥ 4 at baseline, achievement of a 4-point reduction in WI-NRS pruritus score at week 2 as compared to Baseline.
- Change from Baseline in total Psoriasis Symptoms Diary (PSD) score at week 8.
- Change from Baseline in total PSD score at week 4.
- Time to achieving Psoriasis Area Severity Index-50 (PASI-50; subjects who achieve a 50% reduction in PASI from Baseline)
- For subjects with intertriginous area involvement, and with severity of the intertriginous lesions at least 'mild' (I-IGA ≥2) at Baseline, achievement of 'I-IGA' score of 'clear' at week 8.
- Achievement of PASI-90 (subjects who achieve a 90% reduction in PASI from Baseline) at week 8.

For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, median and maximum will be tabulated by treatment group and visit and similarly, categorical variables will have the counts and proportions of each value will be tabulated by treatment group and visit.

Each of the binary endpoints - achievement of PASI-50 at week 8, achievement of PASI-90 at week 8, achievement of 'I-IGA' score of 'clear' or 'almost clear' PLUS a 2-grade improvement from Baseline at week 8 in the I-IGA population, achievement of a 4-point reduction in WI-NRS pruritus score from baseline to weeks 8, 4, and 2 in the Pruritis population, and achievement of 'I-IGA' score of 'clear' at week 8 in the I-IGA population - will be analyzed using CMH tests stratified by site, baseline IGA, and baseline intertriginous involvement similar to the primary analysis above, with the exception that missing data will not be replaced. Analyses of variables mentioned above with no population specified will be performed on the ITT population. Only observed data will be included in the descriptive statistics.

The continuous endpoints change from baseline in total PSD score at week 4 and at week 8 will be analyzed using a repeated measures analysis of covariance with the factors treatment, site, baseline IGA, baseline intertriginous involvement, and visit as independent variables. Statistical comparisons between the treatment groups will be obtained using contrasts. The LS Means,

standard errors, 95% confidence intervals, and p-values will be presented. These analyses will be performed on the ITT population.

The secondary endpoint time to achieving PASI-50 will be summarized using Kaplan-Meier methods and the difference between treatment groups evaluated using the log-rank statistic and 95% confidence intervals of the median for each treatment group will be presented. In addition, a Cox proportional hazards model that includes the stratification factors will be run and the hazard ratio and associated 95% confidence interval will be presented. These analyses will be performed on the ITT population.

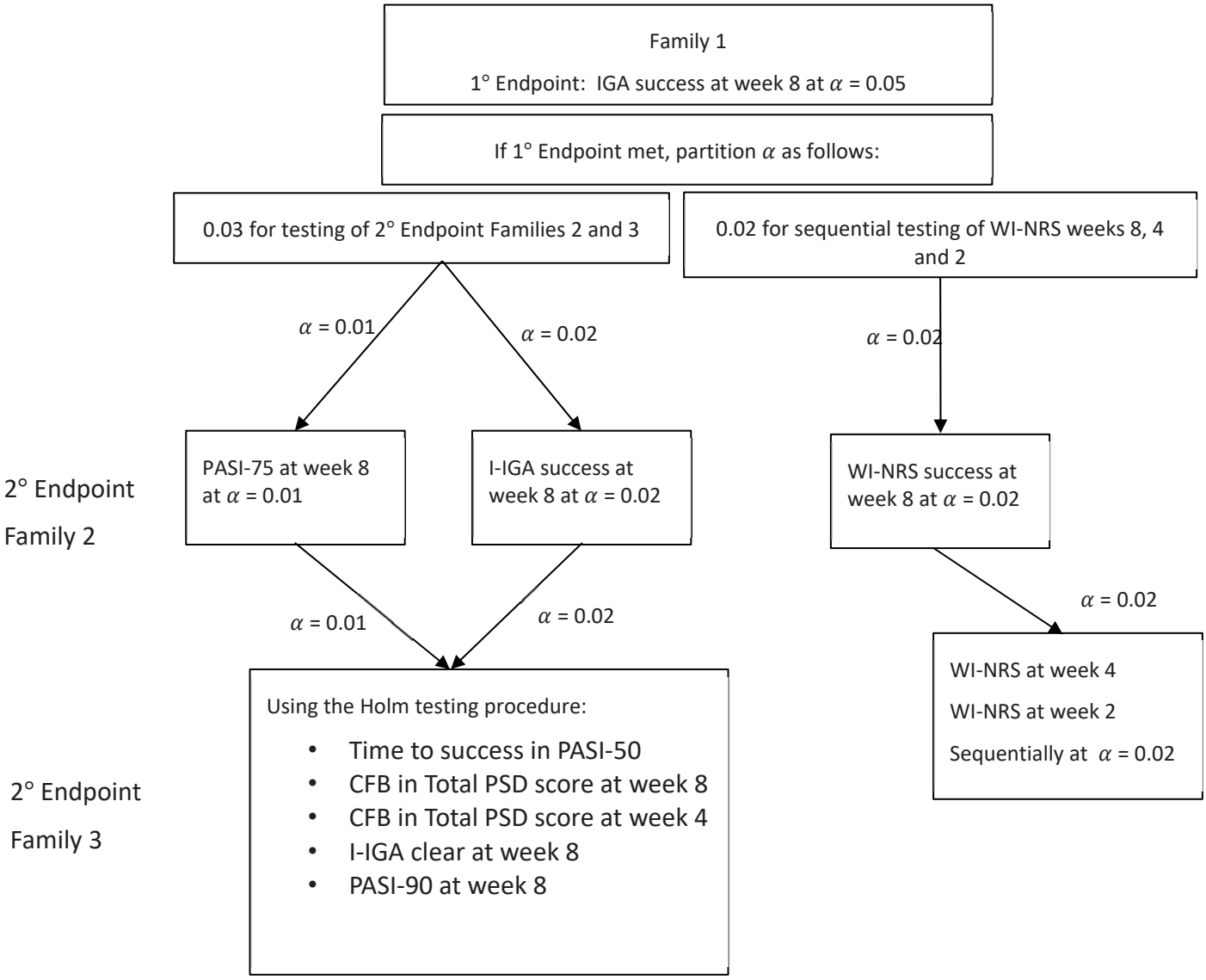
Secondary endpoints will only be tested statistically if the primary endpoint is considered statistically significant. To control for multiple comparisons among the secondary endpoints, the following multiplicity procedure will be used:

Upon successful testing of the primary endpoint (Family 1) the alpha will be partitioned to test secondary endpoint Families 2 and 3 (Partition 1) and to test WI-NRS timepoints (Partition 2).

Partition 1 of alpha = 0.03 will be allocated to test Family 2 and Family 3. The endpoints in Family 2 will be tested independently using a Bonferroni split of the alpha; the next 5 secondary endpoints (Family 3) will be tested using the alpha available after testing endpoint Family 2. The Holm procedure will be used to control for multiple comparisons in endpoint Family 3.

Partition 2 of alpha = 0.02 will be allocated to sequentially test WI-NRS success at week 8, then week 4 and finally week 2.

A figure summarizing the endpoint testing is presentedbelow.



Failure to successfully pass any testing gate in the hierarchy of testing families at any stage in the sequence implies automatic failure at subsequent stages. The p-value for each comparison will be reported in the summaries for informational purposes regardless of whether the previous comparison reaches significance.

8.3. Other Efficacy Analysis

The binary variables at weeks other than the primary/secondary endpoints – IGA success, WI-NRS success, IGA score of "clear', PASI-50, PASI-75, PASI-90, and PASI-100 – as well as mPASI-50, mPASI-75, mPASI-90, and mPASI-100 at all weeks, will be analyzed using the same CMH model described above on the ITT population.

IGA success at weeks 2, 4, and 6 will also be analyzed using the same CMH methodology on the I-IGA population.

Continuous endpoints including percent change from baseline in PASI, change from baseline in affected percent BSA, and percent change from baseline in mPASI will be analyzed using a repeated measures analysis of covariance with the factors treatment, site, baseline IGA, baseline intertriginous involvement, and visit as independent variables. Statistical comparisons between the treatment groups will be obtained using contrasts. The LS Means, standard errors, 95% confidence intervals, and p-values will be presented. These analyses will be performed on the ITT population.

All analyses of these endpoints will be performed on the observed data with no imputation.

8.4. Patient Reported Outcomes

The continuous endpoints change from baseline in WI-NRS, change from baseline in PSD, change from baseline in total DLQI score, and change from baseline in total CDLQI will be analyzed using a repeated measures analysis of covariance with the factors treatment, site, baseline IGA, baseline intertriginous involvement, and visit as independent variables. Statistical comparisons between the treatment groups will be obtained using contrasts. The LS Means, standard errors, 95% confidence intervals, and p-values will be presented. These analyses will be performed on the ITT population.

Observed and change from baseline scores in WI-NRS itch severity, the individual PDS items, and the individual DLQI and CDLQI items will be summarized descriptively by treatment group and time point using both continuous and categorical summary statistics. These summaries will be presented for both the ITT and Pruritis populations.

All analyses will be performed on the observed data with no imputation.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, local tolerability assessments, changes in clinical laboratory values, changes in vital signs, C-SSRS, and PHQ-8/PHQ-A results.

All safety analyses will be performed on the Safety population.

9.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA dictionary v. 22.1.

An overall summary of TEAEs will be provided; this will present number and percent of subjects who reported at least 1: TEAE (including all TEAEs, TEAEs by maximum severity, and TEAEs by greatest relationship), SAE, discontinued the study due to a TEAE, or had a TEAE resulting in death.

The number and percent of subjects reporting treatment emergent AEs, grouped by MedDRA system organ class and preferred term, will be tabulated by severity or greatest releationship to study IP and treatment group. In the case of multiple occurrences of the same TEAE within the same subject, each subject will only be counted once for each preferred term.

In the summaries showing severity and relationship to study medication the event with the maximum severity (mild < moderate < severe) or strongest relationship (not related < unlikely < possibly < probably < likely) will be reported. If a particular event is missing the severity and/or relationship, then the strongest possible severity or relationship will be assumed for analysis (severity = severe, relationship = likely).

In the AE data listings, all AEs will be displayed. AEs that are not treatment-emergent will be flagged.

9.1.1. Adverse Events Leading to Withdrawal

A summary of incidence rates (frequencies and percentages) of TEAEs leading to withdrawal of study drug, by treatment group, SOC, and preferred term will be prepared for the Safety Population. No inferential statistical tests will be performed.

A data listing of AEs leading to withdrawal 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

Any deaths that occur during the study will be listed.

Serious adverse events will be listed and also tabulated by system organ class and preferred term and presented by treatment.

9.1.3. Adverse Events of Special Interest (AESIs)

AESIs may be identified and multiple MedDRA preferred terms may be grouped together to calculate the subject incidence of adverse events of interest.

Serious adverse events will be listed and also tabulated by system organ class and preferred term and presented by treatment.

9.2. Local Tolerance Assessments

The investigator's assessment of the application site reaction will be summarized by visit using both categorical methods (number and percentage of subject with each score) as well as continuous methods (e.g., mean, standard deviation, etc.). No inferential statistical tests will be performed.

The subject's assessment of the application site reaction will be summarized similarly.

9.3. Clinical Laboratory Evaluations

Laboratory test results will be summarized descriptively by treatment and time point as both observed values and changes from baseline.

The number of subjects with clinical laboratory values below, within, or above the normal range by time point and in relation to baseline will be tabulated for each clinical laboratory analyte by treatment group (shift table).

9.4. Vital Signs

Descriptive summaries of observed values and changes from baseline will be calculated for body weight, systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, and oral body temperature by treatment group and time point.

Shift tables by treatment group will summarize the number of subjects who gain or lose >5% of their baseline body weight during the course of the study, as well as subjects who gain or lose >10% of their baseline body weight over the course of the study.

9.5. PHQ and Modified PHQ-A

Data for PHQ-8 and Modified PHQ-A will be classified using each subject's total score at a time point into a category based on the following scoring system:

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

The number and percentage of subjects in each category will be summarized by treatment and time point. Additionally, shift tables showing the category of severity at each time point by treatment group will be presented.

9.6. C-SSRS

Baseline is defined as the most severe ideation and behavior reported in the past 6 months prior to the first dose of study drug. Tables will include results from the Suicidal Ideation and Suicidal Behavior sections of the C-SSRS. Frequencies and percentages of subjects with a response of "Yes" at any point as well as by study visit on the Suicidal Ideation and Suicidal Behavior items will be summarized by treatment received.

Additionally, shifts of whether subjects experienced suicidal ideation, behavior, or both from pre-treatment to post-treatment will be summarized in a shift table. An additional shift table of maximum ideation from pre-treatment to post-treatment will also be provided.

All C-SSRS data will be listed.

9.7. Concomitant Medication

Prior and concomitant medications will be summarized descriptively by treatment using counts and percentages.

Prior medications will be presented separately from concomitant medications. Medications that started prior to the first application of study drug will be considered prior medications whether or not they were stopped prior to the first application of study drug. Any medications continuing or starting post the first application of study drug will be considered to be concomitant. If a medication starts prior to the first application of study drug and continues after the first application of study drug it will be considered both prior and concomitant.

Medications will be coded using WhoDrug Global B3, vSep2019.

10. Changes from Planned Analysis

No changes from the protocol planned analysis.

11. Other Planned Analysis

11.1. Pharmacokinetic Analysis

Pharmacokinetic results will be summarized descriptively by time point.

12. References

1. 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.
2. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2016. http://www.amstat.org/about/ethicalguidelines.cfm
3. RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. http://www.rss.org.uk/Images/PDF/join-us/RSS-Code-of-Conduct-2014.pdf.

13. Tables, Listings, and Figures

All listings, tables, and graphs 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 Descriptions

The following are planned summary tables for protocol number ARQ-151-301. The table numbers and page numbers are place holders only and will be determined when the tables are produced.

Table 2: Demographic Data Summary Tables and Figures

Table Number	Population	Table Title/Summary
13.1 Demographic Data Summary Tables and Figures		

13.2. Efficacy Data

Table 3: Efficacy Data

Table Number	Population	Table Title / Summary

13.3. Safety Data

Table 4: Safety Data

Table Number	Population	Table Title / Summary
14.3.1 Displays of Adverse Events		
14.3.2 Summary of Deaths, Other Serious and Significant Adverse Events		

Table Number	Population	Table Title / Summary
		14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events
		14.3.4 Abnormal Laboratory Value **14.3.5 Laboratory Data Summary Tables**
		14.3.6 Other Safety Data Summary Tables

13.4. Pharmacokinetic/Pharmacodynamic Data

Table 5: Pharmacokinetic/Pharmcodynamic Data

Table Number	Population	Table Title / Summary
14.4 Pharmacokinetic and Pharmacodynamic Data Summary Tables		

13.5. Other Data Summary Tables

Table 6: Other Data Summary Tables

Table Number	Population	Table Title / Summary

13.6. Planned Listing Descriptions

The following are planned data and patient/subject data listings for protocol number ARQ-151-301.

In general, one listing will be produced per CRF domain. All listings will be sorted by treatment, site, 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 one subject will be kept on one page if at all possible, rather than splitting a subject's information across pages.

Table 7: Planned Listings

Data Listing Number	Population	Data Listing Title / Summary
16.2 Patient/Subject Data Listings		
16.2.1 Patient/Subject Discontinuations/Completions		
16.2.2 Protocol Deviations		
16.2.3 Patients/Subjects Excluded from the Efficacy Analyses		
16.2.4 Demographic Data and Other Baseline Characteristics		
16.2.5 Compliance and/or Drug Concentration Data		
16.2.6 Individual Efficacy Response Data		
16.2.7 Adverse Event Listings (by Patient/Subject)		
16.2.8 Laboratory Values (by Patient/Subject)		
16.2.9 Other Clinical Observations and Measurements (by Patient/Subject)		
16.2.10 Other Study Measurements or Assessments (by Patient/Subject)		

13.7. Planned Figure Descriptions

The following are planned summary figures for protocol number ARQ-151-301. The figure numbers and page numbers are place holders only and will be determined when the figures are produced.

Table 8: Planned Figures

Figure Number	Population	Figure Title/Summary	
14.x.x			16.2.x.x

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
CIP	clinical investigational plan
CM	clinical manager

Abbreviation	Definition
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
DIA	drug information association
DIS	data integration specification
DLT	dose limiting toxicity
DM	data management

Abbreviation	Definition
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
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

Abbreviation	Definition
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
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

Abbreviation	Definition
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
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

Abbreviation	Definition
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
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

Abbreviation	Definition
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
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

Abbreviation	Definition
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
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

Abbreviation	Definition
WHO	world health organization
WHO-DD	world health organization drug dictionary