Statistical Analysis Plan

Study Title:	**A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Evaluate the Efficacy and Safety of RIST4721 in Subjects with Palmoplantar Pustulosis**
Protocol Number and Version:	**RIST4721-201 v3.0, dated 22 March 2019**
Product:	**RIST4721 Solution**
Sponsor:	**Aristea Therapeutics, Inc.** [redacted]
Date:	**20-Dec-2019**
Version:	**Final v1.0**
Prepared by:	[redacted]

	STATISTICAL ANALYSIS PLAN, Version Final v1.0
Protocol Number: RIST4721-201	Sponsor: Aristea Therapeutics, Inc.

STATISTICAL ANALYSIS PLAN REVISION SUMMARY			
Version	**Version Date**	**Author**	**Summary of Changes**
Final v1.0	20-Dec-2019	[redacted]	Initial version

SIGNATURE PAGE

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This statistical analysis plan will be reviewed and revised as needed. The most recent version will replace the previous version in place.

TABLE OF CONTENT

ABBREVIATIONS

AE	adverse event
ATC	anatomical therapeutic chemical
BSA	body surface area
CI	confidence interval
CRO	contract research organization
CV	coefficient of variation
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
IQR	interquartile range
IWRS	Interactive Web Response System
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
n	number of subjects with non-missing data
PASI	Psoriasis Area Severity Index
PD	pharmacodynamic
PGA	Physician Global Assessment
PPP	palmoplantar pustulosis
PPPASI	Palmoplantar Pustulosis Psoriasis Area and Severity Index
PPPASI-50	50% reduction in PPPASI
PPPASI-75	75% reduction in PPPASI
PPPGA	Palmoplantar Pustulosis Physician Global Assessment
PPSI	Palmoplantar Pustulosis Severity Index
PPSI-50	50% reduction in PPSI
PPSI-75	75% reduction in PPSI
PT	preferred term
QT	QT interval
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System®
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse event
TLF	tables, listings, and figures
VAS	visual analog scale
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis and reporting for Aristea Therapeutics clinical protocol RIST4721-201. The analyses described in the SAP are based upon the protocol version 3.0 dated 22-Mar-2019 (version available in Canada and Germany).

This SAP has been developed prior to database lock, final unblinding, and final analyses. All final analyses will be performed after the clinical trial data are entered into the database, any discrepancies in the data are resolved, the lock of the database, and following the signature of the SAP.

Analyses related to pharmacodynamic assessments (i.e. skin biomarkers) and plasma concentrations of RIST4721 are not covered in this SAP and will be described in separate documents.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary

- To assess the efficacy of RIST4721 versus placebo in adult subjects with moderate to severe palmoplantar pustulosis (PPP) using a range of efficacy endpoints

Secondary

- To assess the safety of RIST4721 versus placebo in adult subjects with moderate to severe PPP

Exploratory

- To evaluate the effects of RIST4721 on skin biomarkers in adult subjects with moderate to severe PPP
- To evaluate the plasma concentration of RIST4721 in adult subjects with moderate to severe PPP

2.2 Endpoints

Primary Efficacy Endpoints

- Relative change from baseline in fresh pustule count at Day 28
- Relative change from baseline in total pustule count at Day 28

Secondary Efficacy Endpoints

- Absolute change from baseline in fresh pustule count at Day 28
- Absolute change from baseline in total pustule count at Day 28
- Proportion of subjects achieving at least a 50% reduction in fresh pustule count at Day 28
- Proportion of subjects achieving at least a 50% reduction in total pustule count at Day 28

Secondary Safety Endpoints

- Incidence of treatment-emergent adverse events (TEAEs)
- Changes in vital signs, electrocardiogram (ECG), and laboratory tests

Exploratory Endpoints

- Absolute change from baseline in fresh pustule count at Day 7, Day 14, and Day 21
- Relative change from baseline in fresh pustule count at Day 7, Day 14, and Day 21
- Absolute change from baseline in total pustule count at Day 7, Day 14, and Day 21
- Relative change from baseline in total pustule count at Day 7, Day 14, and Day 21
- Proportion of subjects achieving a 50% reduction in fresh pustule count at Day 7, Day 14, and Day 21
- Proportion of subjects achieving a 75% reduction in fresh pustule count at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a 50% reduction in total pustule count at Day 7, Day 14, and Day 21
- Proportion of subjects achieving a 75% reduction in total pustule count at Day 7, Day 14, Day 21, and Day 28
- Absolute change from baseline in Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) at Day 7, Day 14, Day 21, and Day 28
- Relative change from baseline in PPPASI at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a 50% reduction in PPPASI (PPPASI-50) at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a 75% reduction in PPPASI (PPPASI-75) at Day 7, Day 14, Day 21, and Day 28

- Absolute change from baseline in Palmoplantar Pustulosis Physician Global Assessment (PPPGA) at Day 7, Day 14, Day 21, and Day 28
- Relative change from baseline in PPPGA at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a PPPGA of clear (0) or almost clear (1) with a 2-point decrease at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving at least a 2-point decrease in PPPGA at Day 7, Day 14, Day 21, and Day 28
- Absolute change from baseline in palmoplantar pustulosis severity index (PPSI) at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a 50% reduction in PPSI (PPSI-50) at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a 75% reduction in PPSI (PPSI-75) at Day 7, Day 14, Day 21, and Day 28
- Relative change from baseline in PPSI at Day 7, Day 14, Day 21, and Day 28
- Absolute change from baseline in pain visual analog scale (VAS) at Day 7, Day 14, Day 21, and Day 28
- Relative change from baseline in pain VAS at Day 7, Day 14, Day 21, and Day 28
- Absolute change from baseline in Dermatology Life Quality Index (DLQI) at Day 7, Day 14, Day 21, and Day 28
- Relative change from baseline in DLQI at Day 7, Day 14, Day 21, and Day 28
- Absolute change from baseline in body surface area (BSA) at Day 7, Day 14, Day 21, and Day 28
- Relative change from baseline in BSA at Day 7, Day 14, Day 21, and Day 28
- Absolute change from baseline in Psoriasis Area Severity Index (PASI) at Day 7, Day 14, Day 21, and Day 28
- Relative change from baseline in PASI at Day 7, Day 14, Day 21, and Day 28
- Absolute change from baseline in Physician Global Assessment (PGA) at Day 7, Day 14, Day 21, and Day 28
- Relative change from baseline in PGA at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a PGA of clear (0) or almost clear (1) at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving at least a 2-point decrease in PGA at Day 7, Day 14, Day 21, and Day 28
- Changes in skin biomarker levels
- Plasma concentration of RIST4721

3 STUDY DESIGN

3.1 Overall Design

Approximately 30 subjects with moderate to severe PPP, as defined by a PPPASI ≥8, a PPPGA ≥3, and a minimum of 8 fresh pustules (fresh pustule count on both right/left palms and soles) at screening and 20 fresh pustules (fresh pustule count on both right/left palms and soles) at Day –1, will be included in this 4-week, multicenter, randomized, double-blind, placebo controlled, Phase2a study to evaluate the efficacy and safety of RIST4721.

All subjects will sign an informed consent and undergo screening for study eligibility. After a screening period of no more than 30 days, subjects will be randomized (1:1) at Day -1 to receive oral RIST4721 300 mg solution or placebo, once daily for 28 days. Subjects will come to the study site at 7 occasions: screening; baseline (Day -1); and Days 7, 14, 21, 28, and 42 (follow-up) or early termination (ET) visit. Study drug will be dispensed weekly to subjects.

Efficacy will be evaluated using fresh pustule count, total pustule count, PPPASI, PPPGA, PPSI, and pain VAS. BSA affected with psoriasis (excluding PPP lesions on palms and soles) will be evaluated to assess eligibility. BSA, PGA and PASI will also be evaluated to assess impact on body psoriasis (only for subjects who have psoriasis elsewhere on the body at Day -1). Quality of life will be evaluated using the DLQI. Safety will be assessed with physical examinations, vital signs, ECG, and clinical laboratory tests (hematology, biochemistry, and urinalysis), and by collecting adverse events (AEs).

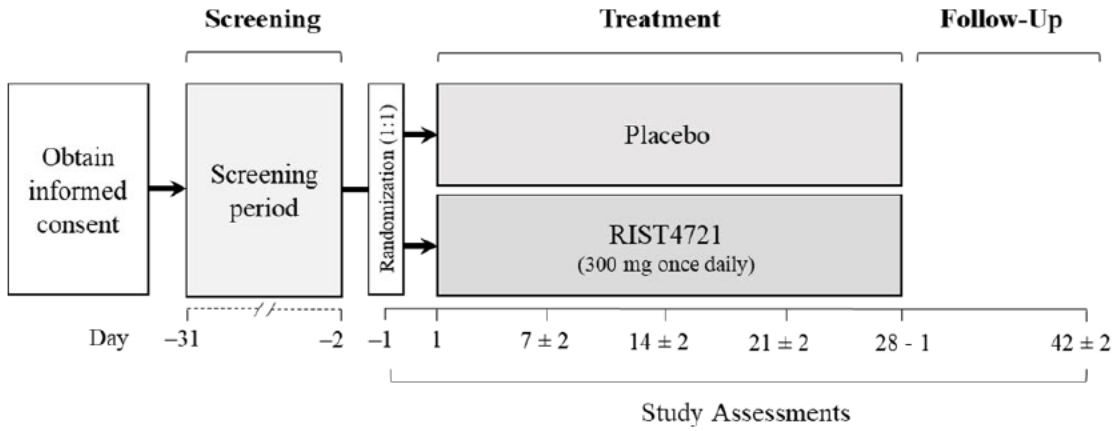
A total of 6 blood samples will be collected from a subgroup of up to 20 subjects who consent to the procedure for plasma concentration analyses. Samples will be collected within 1 hour prior to dosing (pre-dose) and 1 hour ±10 minutes and 2 hours ±10 minutes post-dose on Days 7 and 21.

A total of three 4.5-mm skin biopsies will be collected from a subgroup of approximately 20 subjects who consent to the procedure for reverse transcription polymerase chain reaction (RT-PCR), transcriptome profiling, and immunohistochemistry (IHC). Two skin biopsies will be taken at Day -1 (1 from lesional skin and 1 from adjacent nonlesional skin, either from palm or sole), and one biopsy will be taken at Day 28 from lesional skin, preferably from the same anatomical region as for biopsies collected on Day –1.

Medical photographs of PPP areas will be taken at Day -1, Days 28, and 42 from a subgroup of approximately 15 subjects who consent to the procedure at selected sites to illustrate the outcome of the trial.

Figure 1 provides an overview of the study.

Figure 1: Study Diagram



3.2 Schedule of Events

Table 1 provides a description of the procedures planned at each visit.

Table 1: Schedule of Events

	Screening[a]	Treatment Period						Follow-Up
Study Visits		**Day –1**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 42 or ET**
Window (days)	-31 to -2			±2	±2	±2	-1	±2
Informed consent	X							
Demographics	X							
Medical and surgical history	X	X						
Smoking status (never, former, or current)[b]	X	X		X	X	X	X	X
Inclusion-exclusion criteria	X	X						
Pregnancy test[c]	X	X		X	X	X	X	X
Clinical laboratory test (biochemistry, hematology, urinalysis), FSH[d]	X	X		X	X	X	X	X
Serology (HIV, HBV, HCV)	X							
Tuberculosis evaluation[e]	X							

		Treatment Period						Follow-Up
Study Visits	**Screening[a]**	**Day –1**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 42 or ET**
Window (days)	-31 to -2			±2	±2	±2	-1	±2
Physical examination[f]	X	X			X		X	X
Vital signs[g]	X	X		X	X	X	X	X
Electrocardiogram	X	X					X	X
PPPASI	X	X		X	X	X	X	X
PPSI	X	X		X	X	X	X	X
PPPGA	X	X		X	X	X	X	X
Fresh pustule count	X	X		X	X	X	X	X
Total pustule count	X	X		X	X	X	X	X
PGA, excluding PPP lesions[h]	X	X		X	X	X	X	X
PASI, excluding PPP lesions[h]	X	X		X	X	X	X	X
BSA, excluding PPP lesions[h]	X	X		X	X	X	X	X
Pain VAS	X	X		X	X	X	X	X
DLQI		X		X	X	X	X	X
Randomization		X						
Study drug distribution		X		X	X	X		
Study drug collection				X	X	X	X	X[i]
Demonstration of study drug administration		X						
Study drug administration daily			Day 1 X				Day 28 X	
Daily subject diary			Day 1 X				Day 28 X	
Phone call with subject[j]			X					
Subject dosing diary distribution/collection/review		X		X	X	X	X	X[i]
Medical photography[k]		X					X	X
Skin biopsy collection[l]		X					X	
Blood sampling for RIST4721 concentration[m]				X		X		
Suture removal, if applicable[n]					X			X
Concomitant medication	X	X		X	X	X	X	X

		Treatment Period						Follow-Up
Study Visits	**Screening[a]**	**Day –1**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 42 or ET**
Window (days)	-31 to -2			±2	±2	±2	-1	±2
Adverse events evaluation	X	X		X	X	X	X	X

Abbreviations: BSA, body surface area; DLQI, Dermatology Life Quality Index; ET, early termination; FSH, follicular-stimulating hormone; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment PPPASI, Palmoplantar Pustulosis Psoriasis Area and Severity Index; PPPGA, Palmoplantar Pustulosis Physician Global Assessment; PPSI, Palmoplantar Pustulosis Severity Index; VAS, visual analog scale.

[a] All screening results will be seen and analyzed by the treating investigator prior to randomization and first study drug administration.
[b] For current smokers, the daily consumption of cigarettes, cigars, and other products will be recorded.
[c] Females of childbearing potential only. Serum pregnancy test at screening, and urine pregnancy test at other visits.
[d] FSH at screening only, for females of nonchildbearing potential who had a cessation of menses for at least 12 months without an alternative medical cause.
[e] If PPD is used, a second visit will be necessary for PPD reading only.
[f] Complete physical examination will be performed at screening, Day –1, Day 28, and Day 42 (follow-up) or ET, and brief physical examinations will be performed at Day 14. A symptom-oriented physical examination may be performed during the study, if judged necessary by the investigator.
[g] Including height measured at screening, and weight measured at screening and at Day 42 (follow-up) or ET.
[h] Only performed on subjects with psoriasis.
[i] Applicable to ET visit only.
[j] Study team will follow up with the subject to address any concern and ensure that dosing at Day 1 did not pose a problem.
[k] Performed on a subgroup of approximately 15 subjects at selected sites.
[l] Performed on a subgroup of approximately 20 subjects consenting to the procedure. Biopsies will be collected on Day -1 and Day 28 (after all other assessments).
[m] Performed on a subgroup of approximately 20 subjects consenting to the procedure. Blood samples will be collected within 1 hour prior to dosing (pre-dose) and 1 hour ±10 minutes and 2 hours ±10 minutes post-dose on Days 7 and 21. The time of last meal prior to dosing will be recorded on Days 7 and 21.
[n] Within 10 to 16 days after biopsies collection, if applicable.

3.3 Treatment

The treatment groups are:

- Treatment group A: RIST4721 300 mg solution once daily for 28 days
- Treatment group B: Placebo solution once daily for 28 days

3.4 Randomization, Replacement, and Unblinding Procedures

At the study site, each screened subject will be assigned a subject identifier number during screening that will be used on all subject documentation.

Approximately 30 subjects will be randomized (1:1) to receive RIST4721 or placebo. Randomization will occur prior to first dosing, at the Day –1 visit. The randomization list will be generated using a validated software. Randomization will be stratified by consent to biopsy collection. The master randomization list will be kept secured until the study blind is broken at the end of study. This list will be uploaded into an Interactive Web Response System (IWRS). The investigator or designee will be able to acquire a randomization number for eligible subjects by connecting to the IWRS.

This study will be double-blinded. At all times, treatment and randomization information will be kept confidential and will not be released to the investigator, the study staff, the contract research organization (CRO), or the sponsor's study team until after the conclusion of the study.

Blinding codes should only be broken in emergency situations for reasons of subject safety. When the blind for a subject has been broken, the reason must be fully documented in the source document and electronic case report form (eCRF). Whenever possible, the investigator should contact the sponsor or its designee before breaking the blind. If the blind is broken, the investigator should promptly inform the medical monitor. Documentation of breaking the blind should be recorded with the date/time and reason why the blind was broken, and the names of the personnel involved.

The subject for whom the blind has been broken will be discontinued from the study and undergo the ET procedures. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded.

In order to reduce risk of breaking the blind, investigators, the study staff, the CRO, and the sponsor's study team will not receive absolute and relative neutrophil and WBC count results, starting on Day 7. A medical monitor will review the blinded data and ensure that the safety of all enrolled subjects is preserved.

Subjects who discontinue will not be replaced.

3.5 Changes to the Analysis from the Protocol

The definition of the modified Intent-to-Treat (mITT) analysis set has been clarified so that only randomized subjects who received at least one dose of study drug be included in that population.

Due to emerging fresh and total pustule count data of 0, the planned MMRM analysis with the natural log ratio of the post-dose values to baseline as dependent variable has been revised to a MMRM analysis with the ratio of the post-baseline values to baseline transformed as per McCune and Grace (2002) as dependent variable. Refer to Section 12.1 for more details.

Since this is a Phase 2 study, the secondary efficacy endpoints will not be formally tested and no adjustment to the overall alpha level will be done for these endpoints. Hence, only nominal p-values will be presented for the secondary efficacy endpoints.

Due to emerging data, the following exploratory endpoints will not be summarized and analyzed:

- Proportion of subjects achieving a 75% reduction in total pustule count at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a 75% reduction in PPPASI (PPPASI-75) at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a PPPGA of clear (0) or almost clear (1) with a 2-point decrease at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving at least a 2-point decrease in PPPGA at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a 75% reduction in PPSI (PPSI-75) at Day 7, Day 14, Day 21, and Day 28
- Relative change from baseline in pain VAS at Day 7, Day 14, Day 21, and Day 28

Having said that, subjects meeting any of these criteria will be identified in the by-subject data listings. Similarly, the relative change from baseline in pain VAS will be included in the by-subject data listing.

Count and percentage for each category of the PPPGA and PGA will be provided by visit and treatment group instead of descriptive statistics for the actual score, and absolute and relative changes from baseline by visit and treatment group. Also, a chi-square test will be performed at each visit to detect any difference of distribution across the categories between the treatment group instead of a MMRM model.

4 POPULATIONS FOR ANALYSIS

4.1 All Screened Subjects Analysis Set

The all screened subjects analysis set will include all subjects who signed the informed consent. This analysis set will be used to summarize the subject disposition data.

4.2 Modified Intent-to-Treat Analysis Set

The modified intent-to-treat (mITT) analysis set will include all randomized subjects who received at least one dose of the study drug. All subjects will be analyzed according to the treatment group to which they were randomized. The mITT analysis set will be used as the primary analysis set for efficacy.

4.3 Safety Analysis Set

The safety analysis set will include all subjects who received at least one dose of the study drug. All subjects will be analyzed according to the treatment that they actually received. This analysis set will be used to summarize the major protocol deviations, demographic and other baseline characteristics, surgical and medical history events, prior and concomitant medications, exposure and compliance, and safety data.

5 GENERAL CONSIDERATIONS

Formats and layouts of tables, listings, and figures (TLFs) will be provided in a separate document (outputs general layout is described in Appendix 1).

5.1 Sample Size

This trial is a proof-of-concept trial aimed at exploring preliminary indications of efficacy and safety of RIST4721 in PPP, with the aim of informing a decision about proceeding into full development. The exploratory nature of this study necessitates a minimum number of subjects to be exposed to the drug, yet without losing the possibility of inferring meaningful conclusions.

Approximately 30 subjects with moderate to severe PPP will be randomized 1:1 to receive placebo or RIST4721. A sample size of 30 (approximately 15 per group) will ensure 85 % power to detect a statistically significant difference in the relative change from baseline in pustules counts at Day 28 with a 2-sided level of significance of 10%. This assumes a log-Normal distribution of the pustules counts, a 3-fold change (Placebo/RIST4721 at Day 28 relative to Baseline), and a

coefficient of variation (CV) in the original scale of 150%. This sample size is expected to result in approximately 90% power if the CV is 130%.

5.2 Baseline

Unless otherwise specified, baseline value will be defined as the last non-missing assessment prior to the first study treatment dose (including unscheduled assessments). If the last non-missing assessment is performed on the same date as the first study treatment and time is not available, the assessment will be considered as baseline, except for AEs and medications starting on the first study treatment dose date, which will be considered post-baseline.

5.3 Reference Start Date and Analysis Day

Analysis Day will be calculated from the first study treatment date and will be used to show start/end day of assessments or events.

If the date of the assessment or event is before the date of the first dose of study treatment, the Analysis Day will be calculated as follows:

(Date of first dose of study treatment – Date of assessment or event)

If the date of the assessment or event is on or after the date of the first dose of study treatment, the Analysis Day will be calculated as follows:

(Date of first dose of study treatment – Date of assessment or event) + 1

In the situation where the assessment/event date is partial or missing, Analysis Day will be missing.

5.4 Windowing Conventions

No statistical windowing conventions apply for this study.

5.5 Descriptive Statistics

All continuous variables will be summarized by presenting the number of subjects with non-missing data (n), mean, standard deviation (SD), median, interquartile range (IQR), minimum and maximum. Geometric mean and geometric coefficient of correlation (CV) will also be provided for the relative change from baseline in fresh and total pustule counts. Categorical variables will be presented as frequencies and percentages and will include a “Missing” category (when applicable).

Unless otherwise specified, summary tables will be presented by visit, when applicable, for each treatment.

Change from baseline will be calculated as:

Assessment value at post-baseline visit X – Baseline value.

Percent change from baseline will be calculated as:

(Assessment value at post-baseline visit X / Baseline value) * 100.

Relative change from baseline will be calculated as:

Assessment value at post-baseline visit X / Baseline value

5.6 Statistical Tests

Unless otherwise specified, all statistical tests will be two-sided and will be performed with a significance level of 0.10. Confidence intervals (CIs) will be two-sided with 90% coverage.

5.7 Handling of Retests, Repeats, Unscheduled Visits, and Early Termination Data

For the by-visit summary tables and figures, retest, repeat, and unscheduled measurements will not be considered, exception of the unscheduled measurements who might contribute to the baseline value. Early Termination visit assessments will be summarized as a separate visit in by-visit outputs.

For the outputs not presented by visit (e.g., adverse events, etc.), all data will be analyzed, including retest, repeat, unscheduled, and early discontinuation measurements.

All data from scheduled, retest, repeat, and unscheduled visits will be listed.

5.8 Software Version

All analyses will be performed using SAS® software Version 9.4 or higher.

6 STATISTICAL CONSIDERATIONS

6.1 Adjustments for Covariates

For the efficacy parameters analyzed using a mixed model for repeated measures (MMRM), the corresponding baseline value will be included as covariate in the statistical model.

6.2 Handling of Dropouts or Missing data

See Appendix 2 for handling of completely or partially missing dates for prior and concomitant medications and adverse events. Imputed AE onset and end dates/medication start and stop dates will only be used for the determination of the treatment-emergent/concomitant status. That is, they will not be used to compute any study day or duration and will not be presented in the by-patient data listings.

For the continuous efficacy endpoints (i.e. absolute and relative changes from baseline), the primary method of addressing missing data will be the MMRM method without explicit imputations for missing data because MMRM has an inherent mechanism of imputing missing data under the assumption of missing at random (MAR).

For the categorical efficacy endpoints (i.e., proportion of subjects achieving at least a 50% reduction, etc.), subjects with a missing post-baseline assessment at a specific visit will be considered as not having achieved at least a 50% reduction for that visit.

Missing safety and other data will not be imputed.

6.3 Interim Analysis and Data Monitoring

No interim analysis is planned for this study.

6.4 Multicenter Studies

Subjects from all study centers will be combined for the analyses. Center effect will not be included in the statistical analysis models due to the small sample size for each site.

6.5 Multiple Comparisons/Multiplicity

The two primary efficacy endpoints and the secondary efficacy endpoints will be tested using a Gatekeeper strategy and the Hochberg's method. The primary endpoints (i.e. relative change in fresh pustules at Day 28 and relative change in total pustules at Day 28) will first be tested at alpha of 10% (2-sided). If the larger p-value is less than 10% (2-sided), both primary endpoints will be declared statistically significant. If the larger p-value is greater than 10%, but the smaller p-value is less than 5% (2-sided), then the primary endpoint with the smaller p-value will be declared statistically significant. With Hochberg's method, the study will be considered positive in terms of efficacy, if at least one of the primary endpoints is declared statistically significant.

Secondary and exploratory endpoints will be tested at nominal alpha of 10% with no adjustment for multiplicity for exploratory purposes.

6.6 Examination of Subgroups

No subgroup analysis is planned for this study.

7 STUDY SUBJECTS

7.1 Disposition of Subjects

All subjects who provide informed consent will be accounted for in this study. The total number of subjects screened and rescreened will be presented. The total number and percentage of subjects with screen failure will be presented as well as their reason for screen failure, except for those who were rescreened and did not fail the second screening.

Moreover, the number and percentage of subjects randomized and included in each analysis set will be presented for each treatment and overall. Study completion status and the reason for study discontinuation will be presented similarly.

The percentage of subjects with screen failure will be calculated using the number of subjects screened as denominator. The percentage of screen failures by reason will be calculated using the number of screen failures as denominator. The percentage of study discontinuations by reason will be calculated using the number of subjects who did not complete study as denominator. Otherwise, the percentages will be calculated using the number of subjects randomized as denominator.

Descriptive summaries for the subjects' number of days in the study will be provided for each treatment and overall, where number of days in the study will be calculated as follows:

$$\text{Number of days in study} = \text{Date of completion/discontinuation} - 1^{st} \text{ dose date} + 1$$

A listing of subject's disposition and a listing of subject's randomization information will be provided. A listing of subjects included in and excluded from each of the analysis sets will also be provided. Information on first screening for subjects who were rescreened, including the rescreened subject identifier, will be presented under the first screening subject identifier.

7.2 Protocol Deviations

The number of events, and the number and percentage of subjects with at least one major protocol deviation will be summarized by deviation category for each treatment and overall. A listing of all protocol deviations will also be provided.

8 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized with descriptive statistics for each treatment and overall. The list of demographics and baseline characteristics to be summarized will include:

- Age (years) – calculated relative to date of consent
- Gender
- Race*
- Ethnicity
- Baseline height (cm)
- Baseline weight (kg)
- Baseline fresh pustule count (total and right/left palm/sole)
- Baseline total pustule count (total and right/left palm/sole)
- Baseline PPPASI
- Baseline PPPGA
- Baseline PPSI
- Baseline BSA, PGA and PASI (only for subjects who have psoriasis elsewhere on the body at Day -1)
- Palmoplantar pustulosis history
- Baseline smoking status.

* Subjects who reported more than one race will be summarized under the 'Multiple' race category, but all races selected will be displayed in the listing.

A listing of all demographics and baseline characteristics will be provided.

9 SURGICAL AND MEDICAL HISTORY

Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.1.

Surgical and medical history will be summarized by system organ class (SOC) and preferred term (PT) for each treatment and overall. A subject who experienced the same surgical and medical history event multiple times within the same PT will be counted only once for the that PT. Similarly, if a subject experienced multiple surgical and medical history events within the same SOC, the subject will be counted only once for that SOC. Surgical and medical history events will be sorted alphabetically by SOC and PTs will be presented by decreasing order of total frequency within each SOC.

A listing of all surgical and medical history events will be provided.

10 PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD), September 2018 B3.

Prior medications are defined as any medication started and discontinued prior to the first study treatment dose. Concomitant medications are defined as any medication taken on or after the first study treatment dose and the last study treatment dose, including those that started prior to the first study treatment date and continued past that date. See Appendix 2 for handling of completely or partially missing dates for prior and concomitant medications.

Incidence of prior and concomitant medications will be tabulated by anatomical therapeutic chemical (ATC) level 3 and preferred drug name for each treatment and overall. A subject with the same medication taken multiple times will be counted only once for the corresponding preferred drug name. Similarly, if a subject has taken more than one medication within the same ATC level, then the subject will be counted only once for that ATC. Prior and concomitant medications will be sorted alphabetically by ATC level and preferred drug name will be presented by decreasing order of total frequency within each ATC level.

A listing of all prior and concomitant medications will be provided by subjects.

11 STUDY TREATMENT EXPOSURE AND TREATMENT COMPLIANCE

A summary of exposure will be presented for each treatment and overall, where exposure to study drug will be calculated as (Date of last dose of study drug – Date of first dose of study drug) +1. Descriptive statistics for the number of missed doses will be presented similarly.

For each treatment, compliance will be calculated as follows:

$$\frac{\text{Number of doses taken}}{\text{Number of expected doses}} \times 100$$

where the number of expected doses is determined until the end of study participation.

Descriptive statistics for the compliance will be presented for each treatment and overall. Compliance will also be categorized as follows: <85%, 85% to 100%, and >100%. Frequencies and percentages will be presented for each category by treatment.

Exposure and compliance will be displayed in a listing of study treatment administration by subject. A listing of drug accountability, including kit number, dispensed and returned used and unused bottles will also be provided.

12 EFFICACY ANALYSIS

12.1 Primary Efficacy Endpoints

The relative change from baseline in fresh pustule count at Day 28 and the relative change from baseline in total pustule count at Day 28 are the primary efficacy endpoints in this study.

The number of fresh and total pustules will be counted on each palm and sole. Fresh pustules are defined as macroscopically visible pustules that are white/yellow in color with no brown color, with or without crust, and present on the glabrous skin of the palms and/or soles. The fresh/total pustule count will refer to the sum of fresh/total pustules counted on all palms and soles.

Descriptive statistics on fresh and total pustule counts will be presented for each treatment. Absolute and relative change from baseline will also be summarized for each treatment.

A MMRM model will be used for analyzing the relative change from baseline in fresh and total pustule counts. Each endpoint will be transformed as follows (McCune et al., 2002) for each treatment group and each visit separately:

1. First, the ratio (x) of the post-baseline values to baseline will be computed;
2. Then, the smallest nonzero ratio (min(x)) will be identified;
3. The following constants will be calculated:
    a. The order of magnitude of the data (c), which will be equal to the truncated value of the natural log of min(x) to the integer by dropping the digits after the decimal point i.e., the smallest integer of ln(min(x));
    b. The decimal constant (d), which will be equal to the exponential of c i.e., exp ^{c};
4. Finally, each ratio (x_{ij}) will be transformed as follows:

$$b_i = \ln(x_i + d)$$

where i represents the subjects (i = 1 to maximum number of subjects included in the analysis population for that treatment group at that visit).

The transformed ratios b_i will be used as dependent variables in the analysis. The model will include fixed effects for treatment, visit (Days 7, 14, 21, and 28) and treatment-by-visit interaction, and natural log of baseline value as covariate. Unstructured covariance will be used to model the correlation. In the case where convergence issues arise, the autoregressive (AR(1)) structure will be used. The least squares (LS) mean estimates and associated standard errors (SEs) will be provided for each treatment and for each visit. The LS mean estimates will be transformed backed to the original scale to calculate the LS mean relative change from baseline for each treatment. The SEs of the LS means will be calculated by the Delta Method. The LS mean difference between the two treatment groups along with the associated SEs, two-sided 90% CIs, and p-values will be reported for each visit. In this model, the estimates will be back-transformed to the ratio scale and presented as a relative change-from-baseline for ease of interpretation. The Delta Method will be applied to obtain the difference in the ratios between the two treatments, their SEs, and the 90% CIs. The treatment effect of interest will be the contrast between treatment groups at Day 28. Line plots of LS mean estimates with the two-sided 90% CI for the absolute and relative changes from baseline will be presented graphically by visit.

Assumptions of heteroscedasticity and normality of the residuals will be visually inspected and different transformations of the dependant variable may be used as sensitivity analysis if the assumptions do not appear valid.

All summaries and analyses will be based on the mITT analysis set.

12.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are listed below:

- absolute change from baseline in fresh pustule count at Day 28
- absolute change from baseline in total pustule count at Day 28
- proportion of subjects achieving at least a 50% reduction in fresh pustule count at Day 28
- proportion of subjects achieving at least a 50% reduction in total pustule count at Day 28

The absolute change from baseline in fresh and total pustule counts at Day 28 will be summarized and analyzed similarly to the primary efficacy endpoints (refer to section 12.1), where the absolute change from baseline will be used as dependent variable in the analysis. The absolute change from baseline will not be transformed for the analysis.

Proportion of subjects achieving at least a 50% reduction in fresh pustule count at Day 28 and the proportion of subjects achieving at least a 50% reduction in total pustule count at Day 28 will be summarized (frequencies and percentages) by treatment group. Difference in response between the treatment groups at Day 28 will be analyzed using a Fisher's exact test. A 90% CI for the treatment difference in response will also be provided (exact unconditional confidence limits). Subjects with a missing a percent change from baseline in fresh or total pustule count at Day 28 will be classified as subjects who did not achieve at least a 50% reduction.

A sensitivity analysis will also be performed based only on subjects with a non-missing percent change from baseline at Day 28 for the proportion of subjects achieving at least a 50% reduction (i.e. missing observations will not be treated as non-responders).

All summaries and analyses will be based on the mITT analysis set.

12.3 Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be summarized and analyzed.

- Absolute and relative change from baseline in fresh pustule count at Day 7, Day 14, and Day 21
- Absolute and relative change from baseline in total pustule count at Day 7, Day 14, and Day 21
- Proportion of subjects achieving a 50% reduction in fresh pustule count at Day 7, Day 14, and Day 21
- Proportion of subjects achieving a 75% reduction in fresh pustule count at Day 7, Day 14, Day 21 and Day 28
- Proportion of subjects achieving a 50% reduction in total pustule count at Day 7, Day 14, and Day 21
- Proportion of subjects achieving a 75% reduction in total pustule count at Day 7, Day 14, Day 21 and Day 28
- Absolute and relative change from baseline in PPPASI at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a PPPASI-50/PPASI-75 at Day 7, Day 14, Day 21, and Day 28
- Absolute and relative change from baseline in PPPGA at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a PPPGA of clear (0) or almost clear (1) with a 2-point decrease at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving at least a 2-point decrease in PPPGA at Day 7, Day 14, Day 21, and Day 28
- Absolute and relative change from baseline in PPSI at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a PPSI-50/PPSI-75 at Day 7, Day 14, Day 21, and Day 28
- Absolute and relative change from baseline in pain VAS at Day 7, Day 14, Day 21, and Day 28
- Absolute and relative change from baseline in DLQI at Day 7, Day 14, Day 21, and Day 28
- Absolute and relative change from baseline in BSA at Day 7, Day 14, Day 21, and Day 28
- Absolute and relative change from baseline in PASI at Day 7, Day 14, Day 21, and Day 28

- Absolute and relative change from baseline in PGA at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a PGA of clear (0) or almost clear (1) at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving at least a 2-point decrease in PGA at Day 7, Day 14, Day 21, and Day 28

12.3.1 Exploratory Efficacy Endpoint Variables

Fresh and Total pustules

As described in section 12.1, the absolute and relative change from baseline in fresh pustule count and total pustule count will be evaluated at Day 7, Day 14, and Day 21.

Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI)

The PPPASI is a scale from 0 to 72 that is used to evaluate the severity of PPP on palms and soles. Left palm, right palm, left sole, and right sole are assessed based on three target symptoms: erythema, desquamation (scaling) and pustules, as seen on the day of the examination.

The severity of each sign is assessed using a 5-point scale:

0 = not present

1 = slight

2 = moderate

3 = severe

4 = very severe

The affected area within a given anatomic site (left palm, right palm, left sole, and right sole) is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of PPP involvement as follows:

0 = no involvement

1 = < 10% involvement

2 = 10 to < 30% involvement

3 = 30 to < 50% involvement

4 = 50 to < 70% involvement

5 = 70 to < 90% involvement

6 = 90 to < 100% involvement

The PPPASI score can vary from 0 (absence of disease) to 72 (most severe disease). The PPPASI score for palms and soles is obtained by using the formula below:

$$PPPASI = 0.2\ (E + P + D)\ A_{R\ palm} + 0.2\ (E + P + D)\ A_{L\ palm} + 0.3\ (E + P + D)\ A_{R\ sole} + 0.3\ (E + P + D)\ A_{L\ sole}.$$

where E, D, P, A, L, and R denote erythema, desquamation, pustules, PPP involvement, left, and right, respectively. The score will be set to missing in case of at least one missing value.

The absolute and the relative change from baseline in PPPASI will be evaluated by visit and treatment group. Proportion of subjects who have achieved PPPASI-50, as well as those who have achieved PPPASI-75, will be evaluated by visit and treatment group.

Palmoplantar Pustulosis Physician Global Assessment (PPPGA)

The PPPGA is a 5-point scale that evaluates the severity of PPP. Description of PPPGA score calculation is provided in Table 2 below.

Table 2: Palmoplantar Pustulosis Physician Global Assessment (Averaged Over all Palmoplantar Lesions)

Score	Category	Definition
0	Clear	No signs of PPP; no scaling or crusts or pustules
1	Almost clear	Slight scaling and/or slight erythema and/or very few new (yellow) and/or old (brown) pustules
2	Mild	Scaling and/or erythema and/or new (yellow) and/or old (brown) pustules of limited number and extent
3	Moderate	Prominent scaling and/or prominent erythema; and prominent new (yellow) and/or old (brown) pustules covering most of the affected site(s)
4	Severe	Severe scaling and/or severe erythema; numerous new (yellow) and/or old (brown) pustules with/without major confluence, covering the entire affected site(s)

The absolute and relative change from baseline in PPPGA will be evaluated by visit and treatment group. The proportion of subjects achieving a rating of "Clear" (0) or "Almost clear" (1) and at least a 2-point decrease on the 5-point scale using the PPPGA will be evaluated by visit and treatment group. The proportion of subjects achieving at least a 2-point decrease from baseline will also be evaluated by visit and treatment group.

Palmoplantar Pustulosis Severity Index (PPSI)

The PPSI is a scale from 0 to 12 that is used to evaluate the severity of PPP lesions on palms and soles. The severity of PPP lesions on palms and soles is assessed based on three target symptoms; erythema, desquamation (scaling), and pustules or vesicles, as seen on the day of the examination.

The severity of each sign is assessed using a 5-point scale:

0 = not present

1 = minimal

2 = mild

3 = moderate

4 = severe

The PPSI score can vary from 0 (absence of disease) to 12 (most severe PPP possible), and is obtained by using the formula below:

$$PPSI = E + D + P$$

where E, D, and P denote erythema, desquamation (scaling), and pustules or vesicles, respectively. The score will be set to missing in case of at least one missing value.

The absolute and relative change from baseline in PPSI will be evaluated by visit and treatment group. Proportion of subjects who have achieved PPSI-50, as well as those who have achieved PPSI-75, will be determined by visit and treatment group

Pain Visual Analog Scale (VAS)

Pain intensity will be evaluated by asking subjects to place a line perpendicular to the VAS line at the point that represents their worst pain intensity over the last 24 hours. The pain VAS is a scale from 0 to 10, where 0 indicates no pain and 10 indicate the worst imaginable pain.

Dermatology Life Quality Index Questionnaire (DLQI)

The DLQI is a simple 10-question validated questionnaire that has been used in more than 40 different skin condition. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. The questionnaire is provided in Appendix 3 of the protocol. The DLQI total score is defined as the sum of the 10 item scales, ranging from 0 to 30. If missing answers or mistakes, the following rules will be followed:

1. If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30.
2. If two or more questions are left unanswered the questionnaire is not scored.
3. If question 7 is answered 'yes' this is scored 3 even if in the same question one of the other boxes is ticked.
4. If question 7 is answered 'no' or 'not relevant' but then either 'a lot' or 'a little' is ticked this is then scored 2 or 1. If it is answered 'no', but the second half is left incomplete, the score will remain 0.

Body Surface Area (BSA)

The overall BSA affected by psoriasis, excluding lesions on palms and soles, will be evaluated (from 0% to 100%). One subject's palm with the palmar aspect of all fingers represents 1% of his or her total BSA.

Psoriasis Area Severity Index (PASI)

The PASI is the Investigator's assessment of the area and severity of psoriasis on the subject's entire body, including areas that are not treated with the study drug. The PASI describes the area and severity of a subject's psoriasis at a point in time.

The body is divided into 4 sections: head/neck (H) (10% of total BSA); upper extremities (U) (20% of total BSA); trunk (T) (30% of total BSA); and lower extremities (40% of total BSA). Within each area, the severities of psoriatic plaques are determined for 3 signs of psoriasis: erythema (E), induration/infiltration (I), and desquamation (D) on each body region on a 5-point scale of 0 to 4, from no sign to very marked. The area covered by psoriasis (A) on each body region is evaluated on a score from 0 to 6, i.e., 0=0%; 1=>0–9%; 2=10–29%; 3=30–49%; 4=50–69%; 5=70–89% and 6=90–100%.

The results of these evaluations are used to calculate the PASI for each subject at each assessment using the following algorithm:

$$PASI = 0.1*(E_H+I_H+D_H)*A_H+0.2*(E_U+I_U+D_U)*A_U+0.3*(E_T+I_T+D_T)*A_T+0.4*(E_L+I_L+D_L)*A_L$$

Where E, I, D, and A denote erythema, induration, desquamation, and area, respectively, and H, U, T, and L denote head, upper extremities, trunk, and lower extremities, respectively.

The PASI ranges between a minimum of 0 and a maximum of 72. The score will be set to missing in case of at least one missing value.

Physician Global Assessment (PGA)

The PGA is a 5-point scale (clear to severe) used to evaluate the degree of psoriasis severity, excluding lesions on palms and soles. Description of PGA score calculation is provided in Table .

Table 3: Physician Global Assessment

Score	Category	Definition
0	Clear	No signs of psoriasis; postinflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

The proportion of subjects achieving a rating of "Clear" (0) or "Almost clear" (1) using the PGA will be evaluated by visit and treatment group. The proportion of subjects achieving at least a 2-point decrease from baseline will also be evaluated.

12.3.2 Exploratory Efficacy Endpoints Analyses

Due to emerging data, the following exploratory endpoints will not be summarized and analyzed:

- Proportion of subjects achieving a 75% reduction in total pustule count at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a 75% reduction in PPPASI (PPPASI-75) at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a PPPGA of clear (0) or almost clear (1) with a 2-point decrease at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving at least a 2-point decrease in PPPGA at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving a 75% reduction in PPSI (PPSI-75) at Day 7, Day 14, Day 21, and Day 28
- Relative change from baseline in pain VAS at Day 7, Day 14, Day 21, and Day 28

Having said that, subjects meeting any of these criteria will be identified in the by-subject data listings. Similarly, the relative change from baseline in pain VAS will be included in the by-subject data listing.

For all other exploratory endpoints, descriptive statistics on continuous parameters will be presented by visit and treatment group. Change and relative change from baseline will also be summarized descriptively by visit and treatment group. Categorical variables will be presented as frequencies and percentages by visit and treatment group.

A MMRM model will be used for analyzing the absolute and relative changes from baseline in fresh and total pustule count, PPPASI, PPSI, pain VAS, DLQI, BSA, and PASI. The same models as described in sections 12.1 and 12.2 will be used. The treatment effect will be the contrast between treatment groups at specified visit(s) (e.g., Day 7, Day 14, Day 21 and Day 28).

For the PPPGA and PGA, a Chi-square test will be used to compare the distribution each treatment group across the PPPGA/PGA categories at each visit. Missing data will not be imputed for these endpoints.

For each post-dose study visit, a Fisher's exact test will be used to compare the proportion of subjects with a 50% reduction in fresh and total pustule count, the proportion of subjects with a 75% reduction in fresh pustule count, and the proportion of subjects achieving PPPASI-50, PPSI-50, at Day 7, Day 14, Day 21 and Day 28 (if applicable) between the treatment groups. Ninety (90) percent CI for the treatment difference in response will also be provided (exact unconditional confidence limits). Subjects without an absolute change from baseline at a specific visit will be classified as subjects who did not achieve at least a 50%/75% reduction for that visit.

Sensitivity analysis will also be performed for each post-dose study visit based only on subjects with a non-missing relative change from baseline for the proportion of subjects achieving at least a 50%/75% reduction (i.e. missing observations will not be treated as non-responders).

Similar analyses will be performed on the proportion of subjects achieving a PGA of clear (0) or almost clear (1) and the proportion of subjects achieving at least a 2-point decrease in PGA.

All the analyses will be based on the mITT analysis set.

12.4 Additional Exploratory Endpoint

Additional analyses will be performed for the absolute change from baseline to Day 42 and relative change from baseline to Day 42 in fresh and total pustule counts as well as each concerned secondary and exploratory efficacy endpoint. An analysis of covariance (ANCOVA) will be performed on the absolute change from baseline to Day 42 for each efficacy endpoint. The ANCOVA model will include treatment as fixed effect and baseline as covariate. The treatment effect will be the contrast between treatment groups estimated through LS means. The LS mean estimates, associated two-sided 90% CIs, and p-values will be reported. The analyses will be based on the mITT analysis set. Similar analyses will be performed for the relative change from baseline to Day 42 for each efficacy endpoint, with the exception that the transformed ratios b_i will be used as dependent variable in the analysis (refer to Section 12.1 for additional details on the transformed ratios b_i).

The proportion of subjects with a 50% reduction in fresh and total pustule count, 75% reduction in fresh pustule count, achieving PPPASI-50, achieving PPSI-50, achieving a PGA of clear (0) or almost clear (1) and achieving at least a 2-point decrease in PGA will also be analyzed at Day 42 using the same analysis described in Section 12.3.2.

Moreover, the fresh and total pustule counts on treatment will be analyzed through area under the curve (AUC) type approach. A MMRM model will be performed with the fresh (or total) pustule counts as dependent variable. The model will include fixed effects for treatment, visit (including baseline, Day 7, Day 14, Day 21 and Day 28) and treatment-by-visit interaction. Unstructured covariance will be used to model the correlation. In the case where convergence issues arise, the autoregressive (AR(1)) structure will be used. A linear contrast in PROC MIXED of SAS such as:

> ESTIMATE “Pustule MEAN in treatment 1” intercept 1 treatment 1 0 treatment*visit 0.2 0.2 0.2 0.2 0.2 0 0 0 0 0;

will be used to estimate the average pustule counts over 4 weeks per treatment. The LS mean estimates, associated two-sided 90% CIs, and p-values will be reported.

13 SAFETY ANALYSIS

All safety analyses will be conducted using the safety analysis set.

13.1 Adverse Events

Adverse events (AEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 21.1.

Treatment-emergent adverse event (TEAEs) are defined as any condition that was not present prior to treatment with the study product but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated). See Appendix 2 for handling of completely or partially missing dates for AEs. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified as treatment-emergent.

An overall summary table of adverse events will be provided. The number of events and the number and percentage of subjects who experienced AE, TEAE, TEAE by greatest reported relationship, TEAE by highest reported severity, related TEAE by highest reported severity, serious TEAE, related serious TEAE, TEAE leading to study drug discontinuation, TEAE leading to discontinuation from study, and TEAE leading to death will be presented.

Unless otherwise specified, a subject experiencing the same TEAE multiple times will be counted only once for the corresponding PT. Similarly, if a subject experienced multiple TEAEs within the same SOC, the subject will be counted only once for that SOC. TEAEs will be sorted alphabetically by SOC and PT will be presented by decreasing order of total frequency within each SOC.

Frequency and percentage of subjects who experienced TEAE will be summarized by SOC and PT within SOC.

Frequency and percentage of subjects who experienced TEAE will be summarized by SOC, PT and relationship. A treatment-related AE is defined as any TEAE that is assessed by the Investigator as related to study treatment. TEAE that is assessed as not related will be defined as not treatment related. If a subject experienced more than one TEAE within different relationship categories within the same SOC/PT, only the worst case (greatest reported relationship) will be reported. TEAE with an unknown relationship will be considered as treatment related.

Frequency and percentage of subjects who experienced TEAE will be summarized by SOC, PT and severity (mild/moderate/severe). If a subject experienced more than one TEAE within different

severity categories within the same SOC/PT, only the worst case (worst reported severity) will be reported. TEAE with an unknown severity will be considered as severe.

Frequency and percentage of subjects who experienced TEAE will be summarized by SOC, PT, relationship and severity (mild/moderate/severe). Each subject will be counted only once within a SOC or PT by using 1) the greatest reported relationship followed by 2) the highest reported severity.

Frequency and percentage of subjects who experience serious TEAE will be summarized by SOC and PT within SOC.

Frequency and percentage of subjects who experience serious TEAE will be summarized by SOC, PT and relationship (related/not-related). If a subject experienced more than one serious TEAE within different relationship categories within the same SOC/PT, only the worst case (greatest reported relationship) will be reported. Serious TEAE with an unknown relationship will be considered as treatment-related.

Listings of all AEs, all AEs leading to death, all serious AEs, all TEAEs leading to study drug discontinuation, and all TEAES leading to discontinuation from study will be provided. Information pertaining to AEs noted during the study will be listed by subject, detailing verbatim, SOC, PT, start date, stop date, intensity, outcome, and relationship to study drug. The AE onset will also be shown relative (in number of days) to the first day of study drug administration.

13.2 Clinical Laboratory

Descriptive statistics will be presented for data related to biochemistry, hematology and quantitative urinalysis by visit and treatment group. Change from baseline values will be presented for each post-baseline assessment and tabulated by visit and treatment group. Frequencies and percentages for each result will be provided for qualitative urinalysis data by visit and treatment group.

Shift tables from baseline to the worst post-baseline assessment describing shifts to abnormality will be provided for data related to biochemistry and hematology as well. Only subjects with a baseline result and a result at least one post-dose result for the parameter will be considered. For parameters for which a worst post-baseline result could be identified for each directionality (lower and upper), shift tables from baseline to the worst post-baseline assessment for each directionality will be provided.

Separate listings of all data for biochemistry, hematology, urinalysis and pregnancy tests will be provided.

In addition, separate listings of data for biochemistry, hematology, and urinalysis will be provided for each parameter where a subject had at least one abnormal result.

13.3 Vital Signs

Descriptive statistics will be presented for data related to vital signs (systolic blood pressure diastolic blood pressure, pulse rate, respiratory rate and body temperature) by visit and treatment group. Change from baseline values will be presented for each post-baseline assessment by visit and treatment group.

Shift tables from baseline to the worst result/abnormality will be provided as well. Only subjects with a baseline result and at least one post-dose result for the parameter will be considered.

A listing of all vital sign assessments by subject will be provided.

13.4 Electrocardiogram (ECG)

Descriptive statistics will be presented for data related to ECGs (heart rate, PR interval, QRS interval, QT interval, QTc interval, and QTc interval by Fredericia [QTcF]) by visit and treatment group. The QTcF interval will be derived as follows:

$$\text{QTcF} = \frac{\text{QT inverval}}{\sqrt[3]{\text{RR interval}}}$$

where RR interval = (60 / heart rate).

Change from baseline values will be presented for each post-baseline assessment by visit and treatment group.

Shift tables from baseline to the worst result/abnormality will be provided as well for overall interpretation. Only subjects with a baseline result and at least one post-dose result will be considered.

A listing of all ECG assessments by subject will be provided.

14 REFERENCE

McCune B, Grace JB, and Urban DL. Analysis of Ecological Communities. MjM Software Design, 2002, 300 pages. ISBN 0972129006, 9780972129008

15 APPENDICES

Appendix 1

Output Conventions

Tables, listings, and figures (TLFs) will be generated using SAS® and will be displayed on letter size paper with landscape orientation, 1 inch margins and 9 pt Courier New font.

The header section will comprise the Sponsor's name, protocol number, delivery description, data cut-off date (if applicable), TLF number, TLF title, analysis set, and page number (Page X of Y). The footer section will include the TLF footnotes, CRO's name, date and time of the execution of the program, and name of the program.

P-values ≥ 0.001 and ≤ 0.999 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as ">0.999".

Means, medians and interquartile ranges will be displayed to one more decimal place than the original value; minimums and maximums will keep the same number of decimal places as the original value; standard deviations (SDs), standard errors (SEs), and confidence intervals (CIs) will be displayed to two more decimal places than the original value. If derived parameters are to be summarized, the number of decimals of the derived values is to be chosen on a case-by-case basis, but the rule above applies.

For categorical summary tables, percentages will be reported to one decimal place. Percentages between 0 and 0.1 (both exclusive) will be displayed as "<0.1". Percentages between 99.9 and 100 (both exclusive) will be displayed as ">99.9". The denominator for each percentage will be the number of subjects within the population per treatment group unless otherwise specified.

Listings will be ordered by treatment group, subject number, date, and visit (where applicable). Imputed dates will not be presented in the listings.

Dates & Times Format

Date and time (if available) will be presented in the format yyyy-mm-dd/hh:mm.

Presentation of Treatment Groups

When applicable, study treatments will be represented as follows in the different outputs:

Study Treatment Full Names	Study Treatment Output Names
RIST4721 300 mg Solution	RIST4721
Placebo Solution	Placebo

Appendix 2

Algorithm for Imputation of Start/End Date of Adverse Events and Prior/Concomitant Medications

Event Start Date Imputation

- Imputation of event end date should be done before imputation of event start date;
- Completely missing: Impute to the first study treatment date;
- Missing day and month: Impute to January 1st, unless year is the same as year of first study treatment dose; if so, impute to the first study treatment date;
- Missing day: Impute to the 1st of the month, unless month and year are the same as month and year of first study treatment dose; if so, impute to the first study treatment date;
- If imputed event start date is after event end date (imputed or not), set the event start date to the imputed event end date.

Event End Date Imputation

- Completely Missing: Impute to the last contact date;
- Missing day and month: Impute to December 31st, unless year is the same as last contact date; if so, impute to the last contact date;
- Missing day: Impute to the last day of the month, unless year and month are the same as year and month of last contact date; if so, impute to the last contact date.