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Statistical Analysis Plan

A Randomized, Double-blind, Placebo-controlled, Dose Ranging Phase 2 Study to Evaluate the Efficacy and Safety of RIST4721 in Subjects with Palmoplantar Pustulosis

Sponsor	Aristea Therapeutics, Inc.
Product/Compound/Device	RIST4721
Phase of the study	Phase 2
EudraCT number	2021-003029-31

[redacted]

SIGNATURES

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1. Abbreviations

AE	Adverse Event
AIC	Akaike's Information Criterion
ANC	Absolute Neutrophil Count
AR(1)	Autoregression (variance-covariance matrix structure)
ATC	Anatomical Therapeutic Chemical
BIC	Bayesian Information Criterion
eCRF	electronic Case Report Form
ePRO	electronic Patient Reported Outcome
CI	Confidence Interval
CS	Compound Symmetry (variance-covariance matrix structure)
CSP	Clinical Study Protocol
CSR	Clinical Study Report
DLQI	Dermatology Life Quality Index
DRC	Data Review Committee
EOT	End of treatment
FAS	Full Analysis Set
IL	Interleukin
IMP	Investigational Medicinal Product
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Model for Repeated Measures
NRS	Numerical Rating Scale
OLE	Open-Label Extension
PASI	Psoriasis Area Severity Index
PD	Pharmacodynamics
PK	Pharmacokinetics
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
PPQLI	Palmoplantar Quality-of-Life
PPS	Per Protocol Set

PT	Preferred Term
PtGA	Patient Global Assessment
QD	Once Daily
QoL	Quality of life
Q1	First Quartile
Q3	Third Quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
SD	Standard Deviation
SF-36	36-Item Short Form Survey
SoA	Schedule of Activities
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TOEP	TOEP (variance-covariance matrix structure)
UN	Unstructured (variance-covariance matrix structure)
WBC	White Blood Cells
WHO	World Health Organization

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2. Document Version History

Version Number	Version date	Section(s) Updated	Change since previous version (with reason)
1.0	17-Feb-2023	Not applicable	Original document

3. Introduction

This Statistical Analysis Plan (SAP) is based on Clinical Study Protocol (CSP) Version 5.0, Amendment 4.0, dated April 5, 2022.

Biomarker / pharmacodynamics (PD) analyses are not described in this document.

Due to safety reason, the study sponsor, Aristea, reached a decision to terminate the study and an abbreviated clinical study report (CSR) focusing on safety analyses will be produced in lieu of the full CSR. At the time the decision was made, the current SAP had been written and reviewed. Rather than eliminating the unneeded analyses for the abbreviated CSR, a table of content for the selected tables, figures, and listings (TFLs) are provided in Appendix 1 included in this document. The analysis method for the selected TFLs for the abbreviated CSR will follow what is stated in this SAP.

4. Study Objectives and Endpoints

The primary efficacy endpoint and key efficacy secondary endpoints will only be analyzed for Part A of the study

Objective	***Endpoint***
Primary	
To assess the efficacy of RIST4721 in the treatment of subjects with moderate to severe palmoplantar pustulosis (PPP)	Proportion of subjects achieving a 50% reduction in Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) score at Week 12
Primary estimand	
For the primary objective the Primary Estimand is as follows: **Treatment regimen:** RIST4721 400 mg, RIST4721 200 mg, and placebo **Target population:** Subjects with moderate to severe PPP as defined by the inclusion and exclusion criteria (Section 5 of the study protocol), grouped per randomization assignment **Variable of interest:** responders who achieve a 50% reduction in PPPASI score at Week 12 **Intercurrent events and corresponding strategy:** Subjects who withdraw from the study prior to Week 12 due to any reason will be imputed as non-responders. Subjects who permanently discontinue study treatment but continue in the study will have their response statuses derived based on their observed data. **Population-level summary variable:** Difference in proportions of responders	
Secondary	
Efficacy	
Key efficacy secondary endpoints	• Proportion of subjects achieving Palmoplantar Pustulosis Physician Global Assessment (PPPGA) of 0 or 1 at Week 12 • Proportion of subjects achieving 75% reduction in PPPASI score at Week 12

Objective	*Endpoint*
Additional secondary efficacy endpoints	• Absolute change from baseline in PPPGA at Week 12 • Absolute change from baseline in PPPASI at Week 12
Safety	
To assess the safety of RIST4721 in this population	• Incidence of Treatment-Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAEs) • Change from Baseline in clinical laboratory parameters, electrocardiogram (ECG) parameters, and vital signs
Exploratory	
To assess the impact of treatment with RIST4721 on the health-related quality of life (QoL)	• Absolute change from baseline in PPPASI at each visit • Achieving a 50% or 75% reduction from baseline in PPPASI score at each visit and during the study • Absolute and relative change from baseline in DLQI at each visit • Proportion of subjects achieving a score of 0 or 1 on each of the component (pustules, erythema, and scaling) in the Patient Global Assessment (PtGA) • Change from baseline at each visit in: o Pain Numerical Rating Scale (NRS) o Pruritus NRS o Burning NRS o Palmoplantar Quality-of-Life (PPQLI) o 36-Item Short Form Survey (SF-36)
To evaluate the relationship between efficacy and pharmacokinetics exposure to RIST4721 at different doses	Plasma PK concentrations of RIST4721 and its metabolites, if appropriate
To evaluate the pharmacodynamics (PD) of RIST4721 in this population	Changes from baseline in biomarkers and cytokines measured in blood samples
To evaluate translational biomarkers in the skin and blood of participants treated with RIST4721	Change from baseline in the expression of select biomarkers in skin (adhesive strips) and peripheral blood

5. Overall Study Design

This is a 2-part Phase 2 study in subjects with moderate to severe PPP (defined by a PPPASI ≥12 and a PPPGA ≥3 at screening).

- Part A is a Phase 2, randomized, double-blind, placebo-controlled, multicenter, 12-week study evaluating the efficacy and safety of 2 doses of RIST4721. Approximately 156 subjects are planned to be enrolled into Part A (approximately 52 per treatment group).
- Part B is an open-label extension (OLE), 72 weeks evaluating the safety, tolerability and efficacy of RIST4721 400 mg QD.

The study will consist of a screening period, a treatment period (12 weeks in Part A and 72 weeks in Part B), and a follow-up period. Study schema is shown in Section 1.2 of the study protocol.

5.1 Part A – Double blind

After signing an informed consent form, subjects will be screened for study eligibility over 4 weeks. PPPASI assessments will be performed and recorded to determine eligibility for the study. Additionally, medical photographs of the palms of hands and soles of feet from all subjects will be collected and centrally read to confirm eligibility for the study. Subjects will be required to discontinue any topical medications (with the exception of emollients) used to treat PPP at 4 weeks prior to first dose of study treatment (at screening).

In Part A, Day 1 (baseline visit) eligible subjects will be randomized in 1:1:1 ratio to receive study treatment orally QD for 12 weeks:

- RIST4721 400 mg QD
- RIST4721 200 mg QD
- Placebo QD

Randomization will be stratified by smoking status (current smoker vs. former or non-smoker).

After initiation of study treatment on Day 1, subjects will return to the clinic and be evaluated as specified in the Schedule of Activities (SoA); Table 1 of the study protocol – Part A).

All subjects who remain on study treatment through and including Week 12 will be eligible to enter Part B (OLE) as specified below. . Permanent discontinuation of study treatment does not mean withdrawal from Part A of the study, and the subject will be encouraged to remain in the study, complete the end of treatment (EOT) visit at the time of study treatment discontinuation, and then continue to complete remaining study visits as per the SoA (Table 1 of the study protocol). At subsequent visits, all study procedures will be completed per the SoA except for dispensation/return and accountability of study treatment. If a subject permanently discontinues study treatment prior to or at the Week 8 visit and remains in the study through the Week 12 visit, the subject will not need to return for the follow-up visit. If a subject permanently discontinues study treatment after the Week 8 visit, the subject will attend an EOT visit and then will attend the follow-up visit 4 weeks after last dose of study treatment. Subjects who withdraw from the study, regardless of the reason, will be requested to return to the clinic to complete the EOT visit.

5.2 Part B -OLE

Subject may participate in Part B if they have completed Part A, have been compliant with study procedures, and are currently receiving study treatment (RIST4721 or placebo), and meet eligibility criteria for Part B (refer to Section 5.1.1 of the study protocol).

Subjects who consent to participate in this portion of the study will commence with the extension enrollment visit, which will occur on the same day as Part A End of Treatment (EOT) visit; these subjects will not complete Part A follow-up visit. Subjects must enroll into Part B portion of the study within 7 days of Part A EOT visit.

After signing Part B informed consent, eligible subjects will receive RIST4721 400 mg QD for 72 weeks of treatment. Subjects who received lower doses of RIST4721 or placebo, will be switched to RIST4721 400 mg QD. Throughout the study, subjects will be evaluated as specified in the SoA (Table 2 of the study protocol – Part B).

Subjects who permanently discontinue RIST4721 during Part B will be withdrawn from the study, complete an EOT visit, and will be asked to return for the follow-up visit per the SoA (Table 2 of the study protocol– Part B).

6. Determination of Sample Size

Assuming proportion of subjects achieving a 50% reduction in PPPASI score at Week 12 for RIST4721 400 mg arm and placebo arm are 60% and 25% respectively, 47 subjects per arm will have 90% power to detect the difference at 2-sided alpha=0.05 based on a Chi-square test. Adjusting for 10% drop-out, 52 subjects per arm will be randomized for the study.

7. Data Sets to be Analyzed

The following analysis sets will be used for the statistical analysis and presentation of data:

Part A:

- The Full Analysis Set (FAS) will include all subjects who are randomized. Subjects will be classified according to the treatment and stratum assigned at randomization. The Full Analysis Set will be the primary population for evaluating all efficacy endpoints and subject characteristics, i.e., tables for baseline and demographic data.
- The Per-protocol Analysis Set (PPS) is a subset of the Full Analysis Set and will include subjects who receive at least 1 dose of study treatment and do not have major protocol deviations expected to impact the primary objective of the study. The Per-protocol Analysis Set will be used for sensitivity analyses for the primary efficacy endpoint.

The final criteria for the PPS, regarding which protocol deviations that warrant exclusion, will be determined during the pre-analysis review for the database lock when all data on protocol deviations are available and before breaking the blind. This review is described in section 8.3.

- The Safety Analysis Set will include all subjects who receive at least 1 dose of study treatment. Subjects will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) are received throughout the dosing period in which case subjects will be classified according to the first treatment received. The Safety Analysis Set will be the primary population for evaluating treatment administration/compliance and safety.

Part B:

- The Full Analysis Set (FAS) will include all subjects who are randomized in Part A and participate in Part B after signing Part B informed consent. Subjects will be classified according to the treatment and stratum assigned at randomization in Part A. The Full Analysis Set will be the primary population for evaluating all efficacy endpoints and subject characteristics, i.e., tables for baseline and demographic data.

- The Safety Analysis Set will include all subjects who receive at least 1 dose of study treatment in Part B. Subjects will be classified according to the treatment assigned at randomization in Part A unless the incorrect treatment(s) are received throughout the dosing period in Part A in which case subjects will be classified according to the first treatment received. The Safety Analysis Set will be the primary population for evaluating treatment administration/compliance and safety.

As stated above, the FAS is considered as the primary analysis dataset and will be used for all primary and secondary efficacy analyses. The primary efficacy analyses will be repeated using the PPS (Part A only).

FAS will be analyzed according to randomized (planned) treatment in Part A. Safety Analysis Set and PPS (Part A only) will be analyzed on actual treatment received in Part A. This rule will apply for both parts, Part A and Part B. As Part B reporting will be based on treatment groups at study randomization.

8. Statistical and Analytical Plans

8.1 Changes in the Planned Analyses

New exploratory analyses not included in the CSP will be performed and are described in detail in section 8.4.6.3. These endpoints are the following:

- Time to first PPPASI-50 reduction
- Duration of PPPASI-50
- Proportion of subjects achieving PPPASI-50 at any time point

The following sensitivity analysis has been included in the SAP apart from the ones included in the CSP:

- A complete case analysis for the primary efficacy endpoint will be performed. This analysis will consist of a subset of PPS including subjects who completed the treatment with no interruptions/dose changes and no missing data in the primary efficacy endpoint.

8.2 Study Reporting

There will be two reporting events for this study, one reporting for Part A data and another reporting for Part B data. For Part A reporting, when all subjects complete Part A, data from Part A will be cleaned and locked at the subject level. The study will be unblinded for Part A reporting purposes. For Part B reporting, when all subjects complete Part B, data from Part B will be cleaned and the database will be locked.

Part A is the double blinded portion of the study. Part B is open label. For Part B reporting, only safety data from Part B will be summarized, i.e., incremental safety reporting without Part A's safety data. Part A's efficacy data from subjects who participate in Part B will be present in Part B's efficacy descriptive summary tables for ease of efficacy result comparison. Reporting for 'Demography and Background Characteristics' that will be provided for Part B will be the same as for Part A only for subjects who participate in Part B. If there is any difference it is specified how it will be reported in the corresponding section of this document.

In general terms, all the Tables, Figures and Listings (TFLs) included in this document will apply for both parts of the study unless it is specified '(Part A only)'.

TFLs will indicate the reporting event in the title (Part A or Part B). In addition, the TFLs numbering will include the letter A or letter B. For example, 14.1.1.A or 14.1.1.B.

8.3 Pre-Analysis Review

The Pre-Analysis Review is an evaluation that will be made before each study reporting. The Pre-Analysis Review for Part A will be performed on blinded data.

The review will focus on the definitions of the datasets to be analyzed as defined in section 7.

The decisions taken in this review and possible changes to the planned analyses decided will be documented in the Pre-Analysis Review report. In case that any stated in this SAP changes after this review, a new version of the SAP will be created and signed before the blind is broken.

8.4 Hypothesis and Statistical Methods

8.4.1 Definitions

Baseline	Part A: A baseline measurement will refer to the last non-missing assessment made before the first administration of study treatment, i.e., measurements collected at baseline (Week 0) (last observed values prior to randomization). If any measurement is done at the screening visit, but not in Week 0, then the baseline measurement will be that from the screening visit. Part B: Baseline of efficacy endpoints will be RIST4721 baseline (before start of active treatment), and baseline of safety endpoints (e.g., lab parameters) will be defined as the last observed values on or prior to the Extension Enrollment visit.
Study day	The Study Day of an event is derived as: Study day =(Start date – (Randomization date) + 1 For events occurring or starting before the randomization date, the Study Day is derived as: Study day = (Start date) - (Randomization date) In this way, there will be no Day 0. Day 1 is the same day as the randomization date, and Day -1 is the day before. Study day will only be calculated if the dates are complete.
Date format	All dates in analysis datasets and tables, listings and figures will be in the format YYYY-MM-DD
Time since PPP diagnosis (months)	Signed date of Informed Consent and PPP diagnosis date will be used for the calculus. This variable will be computed with a SAS function that calculates the precise time in months considering the days per month.
Absolute Change from Baseline	Absolute Change from Baseline at Visit X will be calculated as: Absolute change from Baseline = Visit X - Baseline
Relative Change from Baseline (Percent Change from Baseline)	Relative Change from Baseline at Visit X will be calculated as: Relative Change from Baseline (%) = ([Visit X - Baseline]/Baseline) *100 In case of Visit X = Baseline, relative change to Baseline will be 0%

Treatment duration (weeks)	Treatment duration (weeks) = ((Date of the last dose of study treatment - Date of the first dose of study treatment) +1)/7
Study Treatment Compliance (per tablets taken)	Study Treatment Compliance (per tablets taken) = Compliance of tablets administered (%)= ((Exposure days[(1)]-Total of tablets returned) / Exposure days[(1)])*100 [(1)]Exposure days=((Date of the last dose of study treatment - Date of the first dose of study treatment) +1)*4 (tablets per day)
Duration of PPPASI-50 response in weeks	Duration of PPPASI-50 response in weeks will be calculated as follows: Duration of PPPASI-50 response (weeks) = Date until PPPASI does not have a reduction of at least 50% - Date of first PPPASI-50 Response This variable will be computed with a SAS function that calculates the precise time in weeks.
TEAE	A TEAE will be defined as an AE that is new or worsens either in severity, seriousness or frequency after the subject has received the first dose of study treatment and with onset within the part A or part B follow-up periods, after the last dose of study treatment, i.e., start date AE ≥ Day 1. If no clear assignment is possible due to incomplete or missing start dates, the AE will be accounted as TEAE. TEAEs will be allocated to the corresponding part, i.e., Part A or Part B in the same manner, i.e., starting during Part A (Weeks 0-12) or Part B (after starting OLE first dose or on-going with worsening after OLE). In case there is any incomplete date the rules detailed in section 8.10 will apply.

8.4.2 Summary Statistics

All statistical summaries and analyses will be performed using SAS software (SAS Institute Inc, Cary, North Carolina, USA).

Summary statistics will be presented by treatment group and visit, as applicable.

Unless specified otherwise, all statistical analyses will be performed using a 2-sided hypothesis test at the 5% level of significance.

Continuous data will be presented using descriptive statistics: number of subjects (n), number of missing values, mean, standard deviation (SD), minimum, first quartile (Q1), median, third quartile (Q3), maximum and mean 95% confidence interval (CI).

Categorical data will be summarized by the number and percent of subjects.

Time-to-event data will be summarized using the number of events, censored observations, the median (if estimable) and the 25th and 75th percentiles based on Kaplan-Meier (KM). The corresponding 95% confidence intervals will be included.

All efficacy and safety data will be summarized by treatment group and study part (Part A or Part B).

For Part A, reporting will be based on study randomization, as follows: RIST4721 400 mg, RIST4721 200 mg, Placebo and Total. For Part B reporting, treatment groups will be based on study randomization and overall (all three treatment groups combined) will be included. The following headers will be used for the tables: RIST 4721 400 mg/400 mg, RIST 4721 200 mg/400 mg, Placebo/RIST 4721 400 mg, and Total.

For Part A reporting, statistical modeling and testing as described in the next section, will apply to Part A efficacy data analyses. For Part B reporting, only descriptive summary statistics will be used.

All individual data will be listed as collected.

8.4.3 Statistical models for Part A analyses

The general statistical model to be used for dichotomous endpoint will be the logistic regression. The model will include stratification (current smoker vs. former or non-smoker) and treatment (all 3 arms) as explanatory variables.

Logistic regression parameter for the difference between RIST4721 400 mg and placebo will be tested by a Wald Chi-Square test at 2-sided alpha=0.05. Odds ratio of the two arms will also be presented together with corresponding two-sided 95%CI. The model will be fitted using SAS proc GENMOD.

For continuous endpoints, the general statistical model to be used will be the MMRM (Mixed-Model for Repeated Measures). This model will include stratification, visit, and treatment as fixed effects, baseline score as a covariate, interaction between visit and treatment, and interaction between visit and baseline score. Estimation of parameters will be done by means of Restricted Maximum Likelihood method. The Unstructured (UN) variance-covariance structure will be initially used to explore the variance-covariance matrix across visits. If the algorithm doesn't converge, a heterogeneous Toeplitz (TOEPH) as the covariance matrix will be tried first, and then autoregression (AR(1)) to achieve convergence. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

Least Square Means and the corresponding 95% CI for the difference between RIST4721 groups and placebo will be presented together with the p-value. This model will be performed using SAS proc mixed.

8.4.4 Subject Data Listings

Data collected in the electronic Case Report Form (eCRF) will be listed in Appendix 16.2 (see Section 9), eCRF check questions (e.g., reminders) will not be listed.

Listings will be sorted by subject id, part (Part A or Part B) and visit.

For AEs and medications, the study day and duration will be included in the listings. Study days will only be calculated for records with complete dates.

8.4.5 Demographic and Other Baseline Characteristics

The following summaries will be presented by treatment group:

- Study disposition, discontinuation and reasons for withdrawal will be presented in two different tables for each part as follows:
- Part A:
    - Screened, randomized subjects, subjects in the study populations, subjects completing Part A, subjects discontinuing after Part A reasons for not completing Part A of the study (Table 14.1.1.A)
    - Subjects who complete the treatment period up until Week 12 (Yes / No), subjects who continued to complete remaining study Visits through Week 12, subjects not participating in Part B who did not complete the Follow-Up period (Yes / No) and reasons for early treatment discontinuation (Table 14.1.2.A)
- Part B:

- Subjects completing Part A participating in Part B, subjects participating in Part B, subjects who complete the treatment period up until Week 72 (Yes / No), subjects completing the treatment period until Week 72 but did not complete the Follow-up period and reasons for not completing the study (Table 14.1.1.B)
- Subjects who did not complete the treatment period up until Week 72, subjects who continued to complete remaining study Visits through Week 72 , reasons for early treatment discontinuation (Table 14.1.2.B)

- Subject disposition in populations for analyses and reasons for exclusion
- Demography (Age, sex, ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown), race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Unknown, Other) and subject of childbearing potential (Yes / No)
- Smoking status (current smoker, former or non-smoker) and description of products being used currently
- Palmoplantar Pustulosis history: Time since PPP diagnosis, prior treatment for Palmoplantar Pustulosis will be described per subject and presence/absence of psoriasis.
- Medical history. All medical diseases collected in the 'Medical history' form will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system and will be tabulated by System Organ Class (SOC) and Preferred Term. (PT)
- Psoriasis Area Severity Index (PASI). The PASI will only be collected at screening and will be evaluated excluding lesions on palms and soles

For parameters where assessments are made at baseline and at other visits, baseline data will be presented together with the rest of the data in by-visit displays.

These summaries will be based on the FAS population.

8.4.6 Primary Analysis (Part A only)

8.4.6.1 Primary efficacy analysis (Part A only)

The primary objective of this phase 2 study is to assess the efficacy of RIST4721 in the treatment of subjects with moderate to severe PPP. The primary efficacy endpoint is 'Proportion of subjects achieving a 50% reduction in PPPASI score at Week 12'. This objective will only be evaluated for Part A of the study.

The primary endpoint and several secondary endpoints will be based on the absolute PPPASI score. The PPPASI is a scale from 0 (absence of disease) to 72 (most severe disease) that is used to evaluate the severity of PPP on palms and soles (Bhushan, 2001). The PPPASI score will be derived automatically in the eCRF. The partial scores from evaluations of erythema, desquamation (scaling), and pustules for each subject and visit will be listed.

The primary endpoint is defined as the PPPASI-50 response at Week 12. It will be derived as a dichotomous endpoint (Yes / No), defined as a subject reaching a 50% or higher reduction in PPPASI score compared to baseline vs reaching less than a 50% reduction or an increase in PPPASI score relative to baseline.

The primary endpoint will be analyzed using a logistic regression model as explained in section 8.4.3.

The observed PPPASI – 50 responses will be summarized descriptively (number of subjects and percentages) by treatment group and visit. In addition, the observed proportions reaching PPPASI -50

will be plotted by treatment group and visit. The absolute change from baseline in PPPASI will also be plotted by treatment and visit.

Primary efficacy endpoint analyses will be performed using the estimand framework as defined in Section 4. According to the definition, when an intercurrent event occurs, i.e., subjects who withdraw from the study prior to Week 12 due to any reason (AE, death, lack of efficacy, withdrawal informed consent, and others) will be imputed as non-responders. Subjects who permanently discontinue study treatment but continue in the study will have their response statuses derived based on their observed data.

Hypothesis:

The null hypothesis for the study is to test if treatment effect of RIST4721 400 mg is equal to placebo control.

H0: P1-P0 = 0

H1: P1-P0 ≠ 0

where:

P_1 is defined as proportion of subjects reaching a 50% or higher reduction in PPPASI score in RIST4721 400 mg treatment group.

P_0 is defined as proportion of subjects reaching a 50% or higher reduction in PPPASI score in placebo treatment arm.

The null hypothesis H_0 will be rejected if the p-value for the comparison of RIST47 400 mg vs placebo from the primary analysis is lower than 0.05.

In order to control type-1 error for the primary endpoint analysis, the analysis will be conducted using a stepdown procedure in a hierarchical manner so the level of significance (α) will be fixed at the standard 0.05 for all tests performed. Only when the primary comparison between 400 mg and placebo is statistically significant at 2-sided alpha=0.05, comparison between 200 mg and placebo will then be conducted. This method is described in more detail in section 8.6.

The primary analysis will be based on the FAS population.

Sensitivity analyses:

Three sensitivity analyses will be performed to confirm the results of primary efficacy endpoint analysis obtained:

- The Per-protocol Analysis Set will be analyzed using the same analysis used for the primary efficacy endpoint
- Logistic regression model without stratification will be conducted as a sensitivity analysis on the FAS population
- A complete case analysis for the primary efficacy endpoint will be performed. This analysis will consist of a subset of PPS including subjects who completed the treatment with no interruptions/dose changes and no missing data in the primary efficacy endpoint.

8.4.6.2 Secondary efficacy analyses

8.4.6.2.1 Key secondary efficacy analyses (Part A only)

The following key secondary efficacy endpoints will be analyzed for Part A by hierarchical order:

- **Subjects achieving a 75% reduction in PPPASI score at Week 12 (PPPASI-75).**

  This endpoint is defined as a subject reaching a 75% or higher reduction in PPPASI score compared to baseline vs reaching less than a 75% reduction or an increase in PPPASI score relative to baseline.

- **Subjects achieving PPPGA of 0 or 1 at Week 12.**

  The PPPGA is a 5-point scale from 0 (Clear) to 4 (Severe) that evaluates the severity of PPP (Trust, 2017; Cornelius, 2018). A detailed description of PPPGA score calculation is provided in Table 5 in the study protocol.

Key secondary efficacy endpoints will be tested by hierarchical order through a stepdown method, i.e., when both primary comparisons for the primary efficacy endpoint (400 mg vs placebo and 200 mg vs placebo) are significant:
First, the first key secondary efficacy endpoint (PPPASI-75) will be tested using the same logistic regression model as the primary efficacy analysis starting with 400 mg vs placebo, then 200 mg vs placebo.
Then, if both comparisons are statistically significant the second key secondary efficacy endpoint will be tested (PPPGA of 0 or 1) using a logistic regression model starting with 400 mg vs placebo and then 200 mg vs placebo.
In the case the primary comparison for the primary efficacy endpoint is not rejected, p-values from these analyses will be considered as descriptive only.

In addition, the observed proportions reaching PPPGA of 0 or 1 and PPPASI-75 will be plotted by treatment group and visit.

The key secondary efficacy analyses will be based on the FAS population.

8.4.6.2.2 Other secondary efficacy analyses

Absolute change from baseline of PPPGA and PPPASI score will be analyzed using MMRM model. The MMRM model will be defined as in section 8.4.3. (Part A only)

8.4.6.3 Exploratory analyses

Descriptive summary statistics will be provided for the exploratory endpoints.

The following exploratory endpoints will be analyzed:

Absolute and relative change from baseline in DLQI at Week 12

The DLQI is a simple 10-question validated questionnaire. All questions relate "to the last week", and the score ranges from 0 (no impairment of life quality) to 30 (maximum impairment) (Finlay, 1994).

The DLQI total score is calculated by summing the score of each question, the higher the score, the more quality of life is impaired.

Absolute change from baseline in PPPASI at each visit

Absolute change from baseline in PPPASI will be presented by summary statistics by treatment group and visit.

Proportion of subjects achieving a 50% or 75% reduction from baseline in PPPASI score at each visit and during the study

The observed PPPASI-50 response and the observed PPPASI-75 response will be summarized descriptively (number of subjects and percentages) by treatment group and visit.

Absolute and relative change from baseline in DLQI at each visit

Absolute and relative change in DLQI from baseline will be presented by summary statistics by treatment group and visit.

Proportion of subjects achieving a score of 0 or 1 on each of the component (pustules, erythema, and scaling) in the PtGA

The PtGA is a commonly used patient reported outcome for measuring disease severity. It includes the following disease manifestations, pustules, erythema, and scaling, each rated on a 5-point scale (range 0 to 4), with a score of zero (clear), 1(almost clear), 2(mild), 3(moderate), and 4(severe).

The proportion of subjects achieving a score of 0 or 1 on each of the component (pustules, erythema, and scaling) will be summarized as a category endpoint (Yes / No) by treatment group and visit.

The following endpoints will be summarized as absolute and change from baseline values by treatment group and visit.

Change from baseline at each visit in:

- Pain Numerical Rating Scale (NRS). This scale will be assessed by subjects on a scale of 0 to 10, with 0 being 'no pain and 10 being the 'worst pain imaginable'.
- Pruritus NRS. Pruritus will be assessed by subjects on a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable'.
- Burning NRS. This scale will be assessed by subjects on a scale of 0 to 10, with 0 being 'no burning' and 10 being the 'worst burning imaginable'.
- Palmoplantar Quality-of-Life (PPQLI). The aim of this questionnaire is to measure how much the skin problem has affected subject's life over the last week through 10 questions.
- 36-Item Short Form Survey (SF-36). Change from baseline per visit will be summarized for the eight dimensions (physical function, physical role, body pain, general health, vitality, social function, emotional role and mental health) and the total score.

Proportion of subjects achieving PPPASI-50 at any time point

The proportion of subjects achieving PPPASI-50 at any time point during the study period will be summarized as a category endpoint (Yes / No) by treatment group.

Time to first PPPASI-50 reduction.

Time to first PPPASI-50 in weeks will be defined as time from randomization date until date of PPPASI-50 reduction for Part A. For Part B this variable will be defined as time from randomization (subjects who received active treatment in Part A) or time from start of active treatment in Part B (for subjects that received Placebo in Part A). Subjects that never reach PPPASI-50 will be censored at date of last assessment of PPPASI collected. Time to first PPPASI-50 will be displayed using KM. If estimable, the quartile (25, 50, 75 percentiles) estimates will be tabulated including CI 95% for each treatment group.

Duration of PPPASI-50 Response

Duration of PPPASI-50 response in weeks will be calculated from time of first PPPASI-50 until PPPASI does not have a reduction of at least 50%, as defined in section 8.4.1. It will be summarized by treatment group for the subset of subjects who reach a PPPASI-50 reduction during the study period.

Pharmacokinetics (Part A only)

Blood samples will be collected for measurement of plasma concentrations of RIST4721 and its metabolites, if applicable, as specified in the SoA (Table 1 of the study protocol – Part A). PK samples will only be analyzed for subjects who received active treatment with RIST4721.

Summary statistics for plasma concentration values for each post-baseline visit will be performed. These descriptive summaries will be presented by treatment group and visit.

8.4.7 Exposure to Treatment

Treatment duration and study treatment compliance will be calculated as defined in section 8.4.1.

Compliance will be summarized categorically (compliance higher or equal to 80% vs compliance under 80%) by treatment group.

Subjects who missed 7 consecutive days of dosing will be listed.

The number of dosing cards or bottles returned, tablets returned, if any dose adjustment or a temporal suspension is reported, and the reasons will be described by treatment group.
All data will be summarized by treatment group for the Safety analysis set.

8.4.8 Concomitant Medications and Concomitant Procedures / Therapies during study

Part A

All concomitant medications/ concomitant procedures or therapies will be classified according to Anatomical Therapeutic Chemical (ATC) level 3 group text and World Health Organization (WHO) Drug Dictionary preferred name. The medications will be classified into categories Prior, Concomitant and Post study treatment based on start date and end date in relation to study treatment exposure.

- Prior medications are those were end dates of the medication/therapy are strictly before date of first administration of study treatment.
- Concomitant medications are those for which the period between their start dates and end dates coincide with exposure to study treatment and can be further classified into:
    - Concomitant medications starting prior to first exposure of IMP having start dates strictly before first exposure of IMP and end dates on same date or after date of first administration of study treatment or are ongoing.
    - Concomitant medications starting on the date of first administration of study treatment or after but before or on the date of last administration of study treatment
    - Post medications are those for which the start dates are strictly after date of last administration of study treatment

For medication and therapies with partial dates, the rules detailed in section 8.10 will apply.

- If start date is completely missing, it will be assumed that the medication started before date of first administration of study treatment.
- If end date is completely missing and ongoing is not ticked, it will be assumed that the medication ended before date of first administration of study treatment.

Study day will not be calculated for medications with incomplete dates.

The concomitant medications will be presented in a summary table broken down on timing in relation to study treatment administration (i.e., Prior, Concomitant and Post). Each subject will only be counted once for each medication and timing category, on a preferred name level in each period.

Part B

The reporting of concomitant medication for this part will be the same including only the subjects who participate in Part B.

In addition, concomitant medication for this part will include any on-going medication from part A and medications that start in OLE period.

One list for each period will be presented for the Safety analysis set.

8.4.9 Adverse Events

AEs will be coded according to MedDRA system and will be tabulated by SOC and PT.

Only TEAEs (as defined in section 8.4.1) will be included in summary tables and non-TEAEs will be listed separately.

An overall summary table will give:

- number of events
- number of unique events (counted once within each subject at the preferred term level)
- number of subjects with at least one event

for:

- AEs
- AEs leading to discontinuation of study treatment
- AEs leading to withdrawal from study
- AEs leading to death:

The overall summary presentation will be repeated for:

- Severity (i.e., mild, moderate, and severe)
- Related AEs (Unless an AE was classified as Not Related or Not Related—COVID-19 vaccination related, it will be regarded as Related)
- SAEs

The total number and percentage of subjects with at least one AE and the total number of AEs will be presented by SOC and PT in a table. This presentation will be repeated for SAEs and related AEs.

AEs listings will include the study day in relation to date and time of first administration of study treatment and duration of AEs. For AEs with incomplete dates no study day or duration will be calculated.

8.5 Other Safety Assessments

These safety analyses will be based on the Safety analysis set.

Vital Signs

Descriptive summary statistics for vital sign parameters (systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature) and changes from baseline will be presented by treatment group and visit.

Vital signs data will be listed by subject and visit.

Clinical Laboratory Measurements

Clinical laboratory (e.g., hematology, clinical chemistry, coagulation, and urinalysis) values will be evaluated for each laboratory parameter as appropriate. Abnormal laboratory values will be flagged and identified as outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be provided.

Descriptive summary statistics (e.g., n, mean, SD, median, minimum, and maximum for continuous variables; n (%) for categorical variables) for laboratory parameters and their changes from baseline will be calculated. Laboratory values will be summarized by treatment group and visit.

Shift tables showing the number of subjects who shifted to low, normal or high from baseline at each post-baseline time of assessment will be presented.

Absolute Neutrophil Count (ANC) and White Blood Cell (WBC) count analyses

Apart from the analyses for all the laboratory parameters, ANC and WBC count will be analyzed separately as follows by treatment group and visit:

- ANC
  - Absolute values and relative change from baseline by treatment group and visit
  - Proportion of subjects with ANC <1.0 x 10^9 and <LLN
  - Correlation between ANC and PPPASI scores (absolute values and relative change from baseline)
  - Correlation between ANC and PPPGA
- WBC
  - Absolute values and relative change from baseline by treatment group and visit
  - Correlation between WBC and PPPASI scores
  - Correlation between WBC and PPPGA

Notes: If laboratory values are below the limit of quantification, the value corresponding to the limit of quantification will be used when summarizing data (e.g., if the result is <x.x, then the value x.x will be used in the statistical analysis).

For urinalysis, the number of positive and clinically significant observations will be tabulated by treatment group and visit, and shift tables will be given if applicable.

Electrocardiograms

QT intervals will be corrected for heart rate (QTc) using standard correction factors (e.g., QTcF). Data will be summarized for QT, HR, RR, PR, QRS, and QTc. A categorical QTc analysis will also be performed by treatment group as follows:

The maximum post-dose values will be summarized by treatment according to the following categories:

- ≤450 ms
- >450 ms (all instances flagged in the listing)
- >480 ms (all instances flagged in the listing)
- >500 ms (all instances flagged in the listing)

The maximum increases from baseline will be summarized by treatment according to the following categories:

- ≤30 ms
- >30 ms (all instances flagged in the listing)
- >60 ms (all instances flagged in the listing)

If applicable, shift tables showing the number of subjects who shifted from normal, abnormal not clinically significant or abnormal clinically significant at baseline to normal, abnormal not clinically significant or abnormal clinically significant at each post-baseline time of assessment will be presented.

SARS-CoV-2 Antigen test

Results for SARS-CoV-2 Antigen test will be described by treatment group and visit. PCR tests performed will also be described.

8.6 Level of Significance, Multiple Comparisons and Multiplicity (Part A only)

In order to control for inflation of type-1 error rate, the efficacy analyses will be conducted using a stepdown procedure in a hierarchical manner so the level of significance (α) will be fixed at the standard 0.05 for all tests performed.

As it has been described in sections 8.4.6.1 and 8.4.6.2.1 and as a summary, the following analyses will be hierarchically ordered in a sequence at level α until first non-rejection:

Primary efficacy endpoint:

1) Proportion of subjects achieving a 50% reduction in PPPASI score at Week 12 of RIST4721 400 mg vs Placebo (p1).

In case p1 ≤ α, reject $H1$ and continue:

2) Proportion of subjects achieving a 50% reduction in PPPASI score at Week 12 of RIST4721 200 mg vs Placebo.

When both above comparisons are significant, treatment comparisons will be performed in the key secondary endpoints in a hierarchical manner as follows:

First key secondary endpoint:

1) Proportion of subjects achieving a 75% reduction in PPPASI score at Week 12 of RIST4721 400 mg vs Placebo.

In case this comparison is rejected the next one will be tested:

2) Proportion of subjects achieving a 75% reduction in PPPASI score at Week 12 of RIST4721 200 mg vs Placebo.

When both above comparisons are significant the second key secondary efficacy endpoint will be tested as follows:

Second key secondary endpoint:

1) Proportion of subjects achieving PPPGA of 0 or 1 at Week 12 of RIST4721 400 mg vs Placebo.

In case this comparison is rejected the next one will be tested:

2) Proportion of subjects achieving PPPGA of 0 or 1 at Week 12 of RIST4721 200 mg vs Placebo.

All tests will be 2-sided at the 5% significance level.

8.7 Multicenter Studies

No adjustment for site effect or country effect will be done.

8.8 Adjustment for Covariates (Part A only)

Smoking status (current smoker vs. former or non-smoker) that were used to stratify the randomization, will be accounted for MMRM as a factor analysis for logistic regression as described in section 8.4.3.

The MMRM that will be used for continuous efficacy endpoints will be adjusted for the baseline value as a covariate for the variable being assessed.

8.9 Examination of Subgroups (Part A only)

Exploratory subgroup analyses will be conducted for the primary efficacy endpoint (PPPASI-50) and for the key secondary endpoints (PPPGA of 0 or 1 and PPPASI -75) by the following subgroups for the FAS:

- Smoking status at baseline (A table will not be necessary for this subgroup as it will be summarized and analyzed in the Logistic Regression Models applied in the efficacy analyses section)
- PPPASI >20 vs <20 at baseline

8.10 Handling of Dropouts and Missing Data

Missing data for primary efficacy endpoint and key secondary efficacy endpoints will be handled using the estimand framework as defined in Section 4.

No missing imputation methods will be used for MMRM models. MMRM assume missing at random.

In case there is any incomplete date that is necessary for the analysis, the following rules will apply:

- if date is completely missing: no imputation will be performed,
- if only the year is available: Day “01” and month of “July” will be imputed,
- if the month and year are available: Day “15” will be imputed.

8.11 Interim Analysis

No interim analysis is planned for this study.

8.12 Data Monitoring

The data from the study will be reviewed regularly during the study by a Data Review Committee (DRC), the procedures for these reviews are included in the DRC Charter of the study.

8.13 References

Bhushan, M., Burden, A. D., McElhone, K., James, R., Vanhoutte, F. P. and Griffiths, C.E. (2001). "Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study." Br J Dermatol 145(4): 546-553.

Finlay, A. Y. and Khan, G. K. (1994). "Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use." Clin Exp Dermatol 19(3): 210-216.

9. Tables, Listings and Figures Overview

Data from subjects screened but not included in the study will not be presented in any listings or tables.

As described in section 8.2, TFLs will indicate the reporting event in the title (Part A or Part B). In addition, the numbering will include the letter A or letter B. For example, 14.1.1.A or 14.1.1.B.
For this document only the section for the TFLs has been inserted.
All the TFLs will apply for both parts of the study unless it is specified '(Part A only)'.

9.1 Tables to be produced for the Clinical Study Report (Section 14 according to ICH E3)

14.1 Demography and Background Characteristics

Table
Study Disposition / Discontinuation and Reasons for not Completing the Study (Full Analysis Set)
Study Discontinuation and Reasons for Early Treatment Discontinuation (Full Analysis Set)
Subject Disposition in Per Protocol Set and Reasons for Exclusion (Per Protocol Set) (Part A only)
Number of Subjects by Visit (Full Analysis Set)
Demography (Full Analysis Set)
Smoking Status at Baseline Visit (Full Analysis Set)
PPP history and PASI (FAS)
PPPASI and PPPGA at Baseline Visit (Full Analysis Set)
Prior Treatments for PPP (Full Analysis Set)
Medical History (Full Analysis Set)
Disease Characteristics (Full Analysis Set)

14.2 EFFICACY DATA

14.2.1 Primary Efficacy Analysis (Part A only)

Table
Primary Efficacy Analysis. Proportion of Subjects Achieving a 50% Reduction in PPPASI Score at Week 12. Logistic Regression Model (Full Analysis Set)

14.2.2 Sensitivity analyses (Part A only)

Table

Proportion of Subjects Achieving a 50% Reduction in PPPASI Score at Week 12. Logistic Regression Model (Per Protocol Set)
Proportion of Subjects Achieving a 50% Reduction in PPPASI Score at Week 12. Logistic Regression Model without Stratification (Full Analysis Set)
Proportion of Subjects Achieving a 50% Reduction in PPPASI Score at Week 12. Logistic Regression Model (Complete Case Analysis)

14.2.3 Key Secondary Efficacy Analysis (Part A only)

Table
Proportion of Subjects Achieving PPPGA of 0 or 1 at Week 12. Logistic Regression Model (Full Analysis Set)
Proportion of Subjects Achieving a 75% Reduction in PPPASI Score at Week 12. Logistic Regression Model (Full Analysis Set)

14.2.4 Other Secondary Efficacy Analyses

Table
Change from Baseline of PPPASI. MMRM Model (Full Analysis Set) (Part A only)
Change from Baseline of PPPASI by Visit (Full Analysis Set)
Change from Baseline of PPPASI by Visit (Figure) (Full Analysis Set)
Change from Baseline of PPPGA. MMRM Model (Full Analysis Set) (Part A only)
Change from Baseline of PPPGA by Visit (Full Analysis Set)
Change from Baseline of PPPGA by Visit (Figure) (Full Analysis Set)

14.2.5 Exploratory Analyses

Table
Proportion of Subjects Achieving a 50% Reduction from Baseline in PPPASI Score by Visit (Full Analysis Set)
Proportion of Subjects Achieving a 50% Reduction from Baseline in PPPASI Score by Visit (Figure)
Proportion of Subjects Achieving a 75 % Reduction from Baseline in PPPASI Score by Visit (Full Analysis Set)
Proportion of Subjects Achieving a 75% Reduction from Baseline in PPPASI Score by Visit (Figure) (Full Analysis Set)
Absolute and Relative Change from Baseline in DLQI by Visit (Full Analysis Set)
Absolute and Relative Change from Baseline in DLQI by Visit (Figure) (Full Analysis Set)
Proportion of Subjects Achieving a Score of 0 or 1 on Each of the Component (Pustules, Erythema, and Scaling) in the Patient Global Assessment (PtGA) (Full Analysis Set)

Absolute Change from Baseline of NRS by Visit (Full Analysis Set)
Absolute Change from Baseline of NRS by Visit (Figure) (Full Analysis Set)
Absolute Change from Baseline of Pruritus NRS by Visit (Full Analysis Set)
Absolute Change from Baseline of Pruritus NRS by Visit (Figure) (Full Analysis Set)
Absolute Change from Baseline of Burning NRS by Visit (Full Analysis Set)
Absolute Change from Baseline of Burning NRS by Visit (Figure) (Full Analysis Set)
Absolute Change from Baseline of PPQLI by Visit (Full Analysis Set)
Absolute Change from Baseline of PPQLI by Visit (Figure) (Full Analysis Set)
Absolute Change from Baseline of SF-36 by Visit (Full Analysis Set)
Absolute Change from Baseline of SF-36 by Visit (Figure) (Full Analysis Set)
Proportion of Subjects Achieving PPPASI-50 At any Time Point (Full Analysis Set)
Time to First PPPASI-50 Reduction (Table) (Full Analysis Set)
Time to First PPPASI-50 Reduction (Figure-Kaplan-Meier) (Full Analysis Set)
Duration of PPPASI-50 (Full Analysis Set)
Pharmacokinetics (Part A only)

14.2.6. Subgroup Analyses (Part A only)

Proportion of Subjects Achieving a 50% Reduction in PPPASI Score at Week 12 by PPPASI >20 vs <20 at Baseline (Full Analysis Set)
Proportion of Subjects Achieving PPPGA of 0 or 1 at Week 12 by PPPASI >20 vs <20 at Baseline (Full Analysis Set)
Proportion of Subjects Achieving a 75% Reduction in PPPASI Score at Week 12 by PPPASI >20 vs <20 at Baseline (Full Analysis Set)

14.3 SAFETY DATA

14.3.1 Display of Adverse Events

Table
Summary of TEAEs (Safety Analysis Set)
TEAEs by System Organ Class and Preferred Term (Safety Analysis Set)
TESAEs by System Organ Class and Preferred Term (Safety Analysis Set)
Related TEAEs by System Organ Class and Preferred Term (Safety Analysis Set)
TESAEs by System Organ Class and Preferred Term by Severity (Safety Analysis Set)

14.3.2 Listings of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Listing
TEAEs Leading to Death (Safety Analysis Set)

14.3.3 Section reserved for narratives

14.3.4 Laboratory Assessments

Table
Summary of Absolute Values and Changes from Baseline of Hematology by Visit (Safety Analysis Set)
Shift table for Hematology by Visit (Safety Analysis Set)
Summary of Absolute Values and Changes from Baseline of Chemistry by Visit (Safety Analysis Set)
Shift table for Chemistry by Visit (Safety Analysis Set)
Summary of Absolute Values and Changes from Baseline of Urinalysis by Visit (Safety Analysis Set)
Shift table for Urinalysis by Visit (Safety Analysis Set)
Summary of Absolute Values and Changes from Baseline of ANC by Visit (Safety Analysis Set)
Absolute Change from Baseline of ANC by Visit (Figure) (Safety Analysis Set)
Proportion of Subjects with ANC <1.0 x 10^9 and <LLN by Visit (Safety Analysis Set)
Correlation between ANC and PPPASI Scores (Safety Analysis Set)
Correlation between ANC and PPPGA (Safety Analysis Set)
Summary of Absolute Values and Changes from Baseline of WBC by Visit (Safety Analysis Set)
Absolute Change from Baseline of WBC by Visit (Figure) (Safety Analysis Set)
Correlation between WBC and PPPASI Scores (Safety Analysis Set)
Correlation between WBC and PPPGA (Safety Analysis Set)

14.3.5 Extent of Exposure

Table
Exposure to Study Treatment (Treatment Duration, Study Treatment Compliance, No. of Dosing Cards or Bottles Returned, No. of Tablets Returned, Dose Adjustments and Reasons) (Safety Analysis Set)
Subjects who Missed 7 Consecutive Days of Dosing (Listing) (Safety Analysis Set)

14.3.6 Vital Signs

Table

Summary of Absolute Values and Changes from Baseline of Vital Signs by Visit (Safety Analysis Set)
Shift Table for Vital Signs (Safety Analysis Set)

14.3.7 Electrocardiograms (12– Lead ECG)

Table
Summary of Absolute Values and Absolute Changes from Baseline of 12– Lead ECG by Visit (Safety Analysis Set)
Shift table for 12– Lead ECG (Safety Analysis Set)
Categorical QTc by Visit (Safety Analysis Set)

14.3.8. Concomitant Medication and Therapy

Table
Prior Medications (Safety Analysis Set)
Concomitant Medications (Safety Analysis Set)
Post Medications (Safety Analysis Set)
Concomitant Procedures / Therapies (Safety Analysis Set)

14.3.9 Other Safety Assessments

14.3.9.1 SARS-CoV-2 Antigen test

Table
Summary of SARS-CoV-2 Antigen Test Results by Visit (Safety Analysis Set)

Listings of Individual Subject Data and Other Information to be produced for the Clinical Study Report

(Listing numbers refer to the relevant appendix number in ICH E3. CRF check questions/reminders will not be listed.)

16.1.7 Randomization Scheme

Listing
Randomization Scheme (All)

16.2.1 Discontinued Subjects, Reason for Discontinuation

Listing
Study Discontinuation, Reasons for not Completing the Study (All)
Treatment Discontinuation and Reasons for Early Withdrawal (Safety Analysis Set)

Study Visits (Safety Analysis Set)

16.2.2 Protocol Deviations

Listing
Major Protocol Deviations (All)

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing
Subject Disposition in Analysis Data Sets and Reasons for Exclusion (All)

16.2.4 Demographics and Other Background Characteristics

Listing
Demographics data (FAS and SAF)
PPP History (Full Analysis Set and Safety Analysis Set)
Medical History (Full Analysis Set and Safety Analysis Set)
Prior Medication (Safety Analysis Set)

16.2.5 Compliance and/or Drug Concentration Data

Listing
Exposure to Study Treatment, Study Treatment Compliance and Dose Adjustments (Safety Analysis Set)

16.2.6 Individual Efficacy Response Data

Listing
Primary Efficacy Endpoint: PPPASI Values and PPPASI-50 (Full Analysis Set)
Key Secondary Efficacy Endpoints: PPPASI Values, PPPASI-75 and PPPGA (Full Analysis Set)
Exploratory Endpoints: DLQI (Full Analysis Set)
Exploratory Endpoints: PtGA (Full Analysis Set)
Exploratory Endpoints: NRS, Pruritus NRS and Burning NRS (Full Analysis Set)
Exploratory Endpoints: PPQLI (Full Analysis Set)
Exploratory Endpoints: SF-36 (Full Analysis Set)

16.2.7 Adverse Events by Treatment, Subject, Study Day or Week.

Listing
Adverse Events by Subject, Study Day (Safety Analysis Set)
Adverse Events by SOC, PT and Subject (Safety Analysis Set)
Serious Adverse Events by Subject, Study Day (Safety Analysis Set)

Note: TEAEs will be flagged in the listings.

16.2.8 Laboratory parameters

Listing
Hematology (Safety Analysis Set)
Biochemistry (Safety Analysis Set)
Urinalysis (Safety Analysis Set)

16.2.9 Vital Signs

Listing
Vital Signs (Safety Analysis Set)

16.2.10 12-Lead Electrocardiogram

Listing
12-Lead Electrocardiogram (Safety Analysis Set)

16.2.11 SARS-CoV-2 Antigen test

Listing
SARS-CoV-2 Antigen test (Safety Analysis Set)

16.2.12 Concomitant Medication and Therapy

Listing
Concomitant Medication and Therapy (Safety Analysis Set)
Concomitant Procedures / Therapies During Study (Safety Analysis Set)

9.2 US Archival Listings (Appendix 16.4 in ICH E3)

Not applicable

10. Appendices

10.1 Appendix 1. Index of Tables, Listings and Figures for the abbreviated CSR

14.1 Demography and Background Characteristics

Table	Part A	Part B
Study Disposition / Discontinuation and Reasons for not Completing the Study (Full Analysis Set)	X	X
Study Discontinuation and Reasons for Early Treatment Discontinuation (Full Analysis Set)	X	X
Number of Subjects by Visit (Full Analysis Set)	X	X
Demography (Full Analysis Set)	X	
Smoking Status at Baseline Visit (Full Analysis Set)	X	
PPP history and PASI (FAS)	X	
PPPASI and PPPGA at Baseline Visit (Full Analysis Set)	X	
Prior Treatments for PPP (Full Analysis Set)	X	
Disease Characteristics (Full Analysis Set)	X	

14.2 EFFICACY DATA

14.2.1 Primary Efficacy Analysis (Part A only)

Table	Part A	Part B
Proportion of Subjects Achieving a 50% Reduction (Full Analysis Set)	X	

14.2.4 Other Secondary Efficacy Analyses

Table	Part A	Part B
Change from Baseline of PPPASI by Visit (Full Analysis Set)	X	
Change from Baseline of PPPGA by Visit (Full Analysis Set)	X	

14.3 SAFETY DATA

14.3.1 Display of Adverse Events

Table	Part A	Part B
Summary of TEAEs (Safety Analysis Set)	X	X
TEAEs by System Organ Class and Preferred Term (Safety Analysis Set)	X	X

TESAEs by System Organ Class and Preferred Term (Safety Analysis Set)	X	X
Related TEAEs by System Organ Class and Preferred Term (Safety Analysis Set)	X	X
TEAEs by System Organ Class and Preferred Term by Severity (Safety Analysis Set)	X	X

14.3.2 Listings of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Listing	Part A	Part B
TEAEs Leading to Death (Safety Analysis Set)	X	X

14.3.4 Laboratory Assessments

Table	Part A	Part B
Summary of Absolute Values and Changes from Baseline of Hematology by Visit (Safety Analysis Set)	X	X
Shift table for Hematology by Visit (Safety Analysis Set)	X	X
Summary of Absolute Values and Changes from Baseline of Chemistry by Visit (Safety Analysis Set)	X	X
Shift table for Chemistry by Visit (Safety Analysis Set)	X	X
Summary of Absolute Values and Changes from Baseline of Urinalysis by Visit (Safety Analysis Set)	X	X
Shift table for Urinalysis by Visit (Safety Analysis Set)	X	X
Summary of Absolute Values and Changes from Baseline of ANC by Visit (Safety Analysis Set)	X	X
Absolute Change from Baseline of ANC by Visit (Figure) (Safety Analysis Set)	X	X
Proportion of Subjects with ANC <1.0 x 10^9 and <LLN by Visit (Safety Analysis Set)	X	X
Summary of Absolute Values and Changes from Baseline of WBC by Visit (Safety Analysis Set)	X	X
Absolute Change from Baseline of WBC by Visit (Figure) (Safety Analysis Set)	X	X
Subjects with AST/ALT >3xULN	X	X
Subjects with AST/ALT >3xULN and Total bilirubin >2xULN	X	X
Subjects with creatinine change of >0.3 mg /dl from baseline	X	X

Subjects with dose reductions due to ANC protocol or AE	X	X

14.3.5 Extent of Exposure

Table	Part A	Part B
Exposure to Study Treatment (Treatment Duration, Study Treatment Compliance, No. of Dosing Cards or Bottles Returned, No. of Tablets Returned, Dose Adjustments and Reasons) (Safety Analysis Set)	X	X
Subjects who Missed 7 Consecutive Days of Dosing (Listing) (Safety Analysis Set)	X	X

Listings of Individual Subject Data and Other Information to be produced for the abbreviated CSR

(Listing numbers refer to the relevant appendix number in ICH E3. CRF check questions/reminders will not be listed.)

16.1.7 Randomization Scheme

Listing	Part A	Part B
Randomization Scheme (All)	X	

16.2.1 Discontinued Subjects, Reason for Discontinuation

Listing	Part A	Part B
Study Discontinuation, Reasons for not Completing the Study (All)	X	X
Treatment Discontinuation and Reasons for Early Withdrawal (Safety Analysis Set)	X	X
Study Visits (Safety Analysis Set)	X	X

16.2.2 Protocol Deviations

Listing	Part A	Part B
Major Protocol Deviations (All)	X	X

16.2.3 Subjects Excluded from the Efficacy Analysis

Listing	Part A	Part B
Subject Disposition in Analysis Data Sets and Reasons for Exclusion (All)	X	X

16.2.4 Demographics and Other Background Characteristics

Listing	Part A	Part B
Demographics data (FAS and SAF)	X	
PPP History (Full Analysis Set and Safety Analysis Set)	X	
Medical History (Full Analysis Set and Safety Analysis Set)	X	
Prior Medication (Safety Analysis Set)	X	

16.2.5 Compliance and/or Drug Concentration Data

Listing	Part A	Part B
Exposure to Study Treatment, Study Treatment Compliance and Dose Adjustments (Safety Analysis Set)	X	X

16.2.6 Individual Efficacy Response Data

Listing	Part A	Part B
Primary Efficacy Endpoint: PPPASI Values and PPPASI-50 (Full Analysis Set)	X	
Key Secondary Efficacy Endpoints: PPPASI Values, PPPASI-75 and PPPGA (Full Analysis Set)	X	

16.2.7 Adverse Events by Treatment, Subject, Study Day or Week.

Listing	Part A	Part B
Adverse Events by Subject, Study Day (Safety Analysis Set)	X	X
Adverse Events by SOC, PT and Subject (Safety Analysis Set)	X	X
Serious Adverse Events by Subject, Study Day (Safety Analysis Set)	X	X

Note: TEAEs will be flagged in the listings.

16.2.8 Laboratory parameters

Listing	Part A	Part B
Hematology (Safety Analysis Set)	X	X
Biochemistry (Safety Analysis Set)	X	X
Urinalysis (Safety Analysis Set)	X	X

16.2.9 Vital Signs

Listing	Part A	Part B

Vital Signs (Safety Analysis Set)	X	X

16.2.11 12-Lead Electrocardiogram

Listing	Part A	Part B
12-Lead Electrocardiogram (Safety Analysis Set)	X	X

16.2.12 SARS-CoV-2 Antigen test

Listing	Part A	Part B
SARS-CoV-2 Antigen test (Safety Analysis Set)	X	X

16.2.12 Concomitant Medication and Therapy

Listing	Part A	Part B
Concomitant Medication and Therapy (Safety Analysis Set)	X	X
Concomitant Procedures / Therapies During Study (Safety Analysis Set)	X	X