[redacted]

# Statistical Analysis Plan

| | |
|---|---|
| **Study Title:** | **A Randomized, Double-blinded, Placebo-Controlled, Phase 2a Study to Evaluate the Efficacy and Safety of RIST4721 in Subjects with Hidradenitis Suppurativa** |
| **Protocol Number and Version:** | **RIST4721-221 V1.0 USA, dated 11-Feb-2022**<br>**RIST4721-221 V1.1 Canada, dated 08-Apr-2022** |
| **Product:** | **RIST4721** |
| **Sponsor:** | **Aristea Therapeutics**<br>[redacted] |
| **Date:** | **21-Feb-2023** |
| **Version:** | **Final, V1.0** |
| **Prepared by:** | [redacted] |

| **STATISTICAL ANALYSIS PLAN REVISION SUMMARY** | | | |
|---|---|---|---|
| **Version** | **Version Date** | **Author** | **Summary of Changes** |
| Final V1.0 | 21-Feb-2023 | [redacted] | Initial version |

# SIGNATURE PAGE

**AUTHOR:**

| Name | Title | Signature | Date (DD-MMM-YYYY) |
|---|---|---|---|
| [redacted] | [redacted] | [redacted] | |

**APPROVALS:**

| Name | Title | Signature | Date (DD-MMM-YYYY) |
|---|---|---|---|
| [redacted] | [redacted] | [redacted] | |
| [redacted] | [redacted] | [redacted] | |

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 |
| AICC | Akaike's information criteria corrected |
| ALT | alanine aminotransferase |
| AN | abscess and inflammatory nodule |
| ANC | absolute neutrophils count |
| ANTE(1) | first-order ante dependence |
| aPTT | activated partial thromboplastin time |
| ARH(1) | heterogenous first-order autoregressive |
| AST | aspartate aminotransferase |
| ATC | anatomical therapeutic chemical |
| β-hCG | β-human chorionic gonadotropin |
| BLQ | below the limit of quantification |
| BMI | body mass index |
| BUN | blood urea nitrogen |
| CI | confidence interval |
| CRO | contract research organization |
| CSR | clinical study report |
| CV | coefficient of variation |
| DBP | diastolic blood pressure |
| DLQI | dermatology life quality index |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| EOT | end of treatment |
| FAS | full analysis set |
| FSH | follicle stimulating hormone |
| GGT | gamma-glutamyl-transferase |
| HBsAG | hepatitis B surface antigens |
| HBc | anti-core hepatitis B |
| HCT | hematocrit |
| HCV | hepatitis C virus |
| Hgb | hemoglobin |
| HiSCR50 | hidradenitis suppurativa clinical response 50 |
| HiSCR75 | hidradenitis suppurativa clinical response 75 |
| HiSQOL | hidradenitis suppurativa quality of life |
| HIV | human immunodeficiency virus |
| HR | heart rate |
| HRQOL | health-related quality of life |
| HS | hidradenitis suppurativa |
| hs-CRP | high-sensitivity C-reactive protein |
| HS-IGA | hidradenitis suppurativa-Investigator's global assessment |
| HS-PGA | hidradenitis suppurativa-physician global assessment |
| ICF | informed consent form |

| | |
|---|---|
| INR | international normalized ratio |
| IHS4 | hidradenitis suppurativa severity score system |
| IWRS | interactive web response system |
| LDH | lactate dehydrogenase |
| LLN | lower limit of normal |
| LOCF | last observation carried forward |
| MCH | mean corpuscular hemoglobin |
| MCHC | mean corpuscular hemoglobin concentration |
| MCV | mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | mixed model for repeated measurements |
| MPV | mean platelet volume |
| msec | millisecond |
| NRI | non-responder imputation |
| NRS | numerical rating scale |
| PCR | polymerase chain reaction |
| PD | protocol deviation |
| PDMP | protocol deviation management plan |
| PLT | platelets |
| PP | per-protocol (population) |
| PPD | purified protein derivative |
| PK | pharmacokinetic |
| PT | preferred term |
| Q1 | 25% percentile |
| Q3 | 75% percentile |
| QD | once a day |
| QTcF | Fridericia's correction formula for QT interval |
| RBC | red blood cell |
| S | serum |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SARS-CoV-2 | severe acute respiratory syndrome coronavirus 2 |
| SAS | statistical analysis system® |
| SBP | systolic blood pressure |
| SD | standard deviation |
| SE | standard error |
| SI | international system of units, universally abbreviated as SI (from the French 'système international') |
| SoA | schedule of activities |
| SOC | system organ class |
| SUSAR | suspected unexpected serious adverse reactions |
| TB | tuberculosis |
| TEAE | treatment emergent adverse event |
| TLF | tables, listings, and figures |

| | |
|---|---|
| TOEPH | heterogenous Toeplitz |
| U | urine |
| USA | United States of America |
| WBC | white blood cell |
| WHO-DD | World Health Organization Drug Dictionary |
| WOCBP | women of childbearing potential |

# 1 INTRODUCTION

This statistical analysis plan (SAP) describes the analyses that were planned to be performed and reported for Aristea Therapeutics clinical protocol RIST4721-221 United States of America (USA) version 1.0, dated 11-Feb-2022, and Canada version 1.1, dated 08-Apr-2022. Due to safety reasons, the study Sponsor, Aristea Therapeutics, has reached the decision of terminating the study. In consequence, an abbreviated clinical study report (CSR) will be produced in lieu of a 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 selected tables, listings, and figures (TLFs) are provided in Appendix 1. The analysis method of the selected TLFs for the abbreviated CSR will follow what is stated in this SAP.

This SAP was developed prior to database lock, study unblinding, and final analyses. All final analyses will be performed after the signature of this SAP. data are entered into the database, any discrepancies in the data are resolved, database is locked, and study is unblinded. The approval of this SAP will also stand for the approval of the inclusion/exclusion of each subject into each analysis population (refer to Section 4) since all outputs that will be produced for the abbreviated CSR are based on an analysis population including only objective criteria in their definition.

Analyses related to biomarker data are not covered in this SAP and will be described in a separate document.

# 2 STUDY OBJECTIVES, ENDPOINTS, AND ESTIMAND

| OBJECTIVE | ENDPOINT AND ESTIMAND (when applicable) |
|---|---|
| **Primary** | Primary endpoint: |
| To assess the safety and tolerability of RIST4721 monotherapy in subjects with moderate to severe hidradenitis suppurativa (HS) | • Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) |

| OBJECTIVE | ENDPOINT AND ESTIMAND (when applicable) |
|---|---|
| **Secondary** | Secondary endpoint: |
| To assess the efficacy of RIST4721 in subjects with moderate to severe HS | **Key secondary efficacy endpoint and estimand:**<br>**Treatment regimen**: RIST4721 400 mg and placebo<br>**Target population**: Subjects with HS as defined by the inclusion and exclusion criteria (refer to protocol Section 5), grouped per randomized treatment<br>**Variable of interest (endpoint)**: Proportion of subjects achieving hidradenitis suppurativa clinical response 50 (HiSCR50) at Week 12 defined as at least 50% reduction in the total abscesses and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to baseline<br>**Intercurrent events and corresponding strategy**: For subjects who discontinue study treatment prior to Week 12 due to any reason, their last observation will be used to impute response status<br>**Population-level summary variable**: Difference in proportions<br>**Other secondary efficacy endpoints**:<br>• Proportion of subjects achieving hidradenitis suppurativa clinical response 75 (HiSCR75) at Week 12<br>• Proportion of subjects with flare (≥ 25% increase and ≥ 2 absolute increase in AN count relative to baseline) at Week 12<br>• Proportion of subjects achieving AN count of 0, 1, or 2 at Week 12<br>• Change from baseline in skin pain score using the numeric rating scale (NRS) at Week 12<br>• Change from baseline in international HS severity score system (IHS4) at Week 12 |
| To assess PK of RIST4721 in subjects with moderate to severe HS | • RIST4721 PK characterization in subjects with moderate to severe HS |

| OBJECTIVE | ENDPOINT AND ESTIMAND (when applicable) |
|---|---|
| **Exploratory** | |
| To assess the effect of RIS4721 on exploratory measures of efficacy in subjects with moderate to severe HS | • Proportion of subjects achieving at least 2-grade improvement on the HS-physician global assessment (HS-PGA) relative to baseline<br>• Proportion of subjects achieving 0 or 1 on the HS-PGA<br>• Proportion of subjects with HS-Investigator's global assessment (HS-IGA) with at least 2-grade improvement relative to baseline at Week 12<br>• Proportion of subjects achieving 0 or 1 on the HS-IGA<br>• Change from baseline in AN count at Week 12<br>• Change from baseline in HS quality of life (HiSQOL) total and subscale scores<br>• Change from baseline in dermatology life quality index (DLQI) total score at Week 12 |

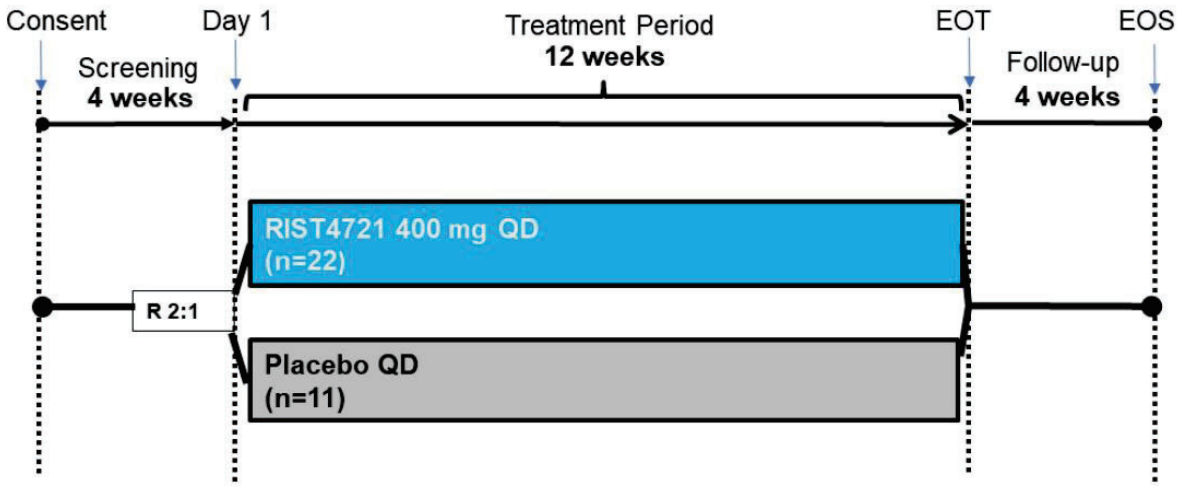
# 3 STUDY DESIGN

## 3.1 Overall Design

This is a Phase 2a, randomized, double-blind, placebo-controlled, multicenter, 12-week study to evaluate the efficacy and safety of RIST4721 once a day (QD) in subjects with moderate to severe HS. Approximately 33 subjects are planned to be enrolled (approximately 22 subjects expected in the RIST4721 group and 11 subjects in the placebo group).

The study will consist of a 4-week screening period, a 12-week treatment period, and a 4-week follow-up period. Study scheme is shown in Figure 1.

**Figure 1**: **Study Scheme**




Abbreviations: EOT, end of treatment; EOS, end of study; QD, once daily, R, randomization

After signing the informed consent form (ICF), subjects will be screened for eligibility over 4 weeks. At each study site, each screened subject will be assigned a subject identifier number during screening that will be used on all subject documentation. The subject identifier number, which will contain the stie number and the subject number, will be assigned in numerical order at the screening visit based on chronological order of screening dates (eg, 02-010 for the 10$^{th}$ subject screened at Site #02).

Subjects who are not enrolled into the study can be rescreened for inclusion in the study one additional time. These subjects will be assigned a new screening number; such subjects will be determined a permanent screen failure after the second screening determines the subject is ineligible.

On Day 1 (baseline visit), eligible subjects will be randomized in 2:1 ratio to receive oral study treatment for 12 weeks:

- RIST4721 400 mg QD
- Placebo QD

All subjects who remain on study treatment through and including Week 12 will be asked to return for a follow-up visit, approximately 4 weeks after their last dose of study treatment, to assess safety and efficacy. Permanent discontinuation of study treatment will not mean withdrawal from 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 schedule of activities (SoA; refer to Table 1). 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 the EOT visit and then will attend the Follow-up visit 4 weeks after last dose of study treatment.

## 3.2 Schedule of Activities

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

**Table 1: Schedule of Activities**

| | Screening | Treatment Period | | | | | Follow-up | Notes |
|---|---|---|---|---|---|---|---|---|
| **Study Week** | **-4 to -1** | **Baseline (Week 0)** | **2** | **4** | **8** | **12/EOT** | **+4 Weeks from EOT** | End of treatment (EOT); subjects discontinuing treatment prematurely will attend EOT visit and then continue study visits as planned. |
| **Study Day** | **-28 to -1** | **1** | **15** | **29** | **57** | **85** | **+28 days from EOT** | |
| **Visit Window (days)** | | | **±3** | **±3** | **±3** | **±7** | **±3** | |
| **Screening/Administrative** | | | | | | | | |
| Informed consent | X | | | | | | | |
| Demographics, social, and family history | X | | | | | | | |
| Eligibility criteria | X | X | | | | | | |
| Medical and medication history | X | | | | | | | Including general medical history, hidradenitis suppurativa medical history, and prior therapies. |
| Height | X | | | | | | | |
| Pulse oximetry | X | | | | | | | |
| Hurley Stage Classification | X | X | | | | | | |
| Serology (HBV [HBsAg, anti-HBc], HCV, HIV) | X | | | | | | | If a subject has a positive test, confirmatory serology will be performed. Refer to protocol Appendix 2, Section 10.2.<br>Hepatitis B surface antigens (HBsAg), antibodies to anti-core hepatitis B (HBc), hepatitis C virus (HCV), human immunodeficiency virus (HIV). |
| PPD or QuantiFERON-TB Gold test | X | | | | | | | Purified protein derivative (PPD); tuberculosis (TB)<br>Refer to protocol Appendix 2, Section 10.2<br>If done within 6 months and negative result is available for documentation, test is not required at screening. |

| Study Week | Screening | Treatment Period | | | | | Follow-up | Notes |
|---|---|---|---|---|---|---|---|---|
| | -4 to -1 | Baseline (Week 0) | 2 | 4 | 8 | 12/EOT | +4 Weeks from EOT | End of treatment (EOT); subjects discontinuing treatment prematurely will attend EOT visit and then continue study visits as planned. |
| **Study Day** | -28 to -1 | 1 | 15 | 29 | 57 | 85 | +28 days from EOT | |
| **Visit Window (days)** | | | ±3 | ±3 | ±3 | ±7 | ±3 | |
| SARS-CoV-2 PCR test | X | | | | | | | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); polymerase chain reaction (PCR). |
| Urine drug screen | X | | | | | | | Refer to protocol Appendix 2, Section 10.2. |
| Pregnancy test (for WOCBP) | S | U | U | U | U | U | U | Serum (S); Urine (U); women of childbearing potential (WOCBP)<br>If urine test is positive, confirm with serum test. |
| FSH (postmenopausal women only) | X | | | | | | | Follicle stimulating hormone (FSH) |
| **Study Treatment Administration** | | | | | | | | |
| Randomization | | X | | | | | | |
| Study treatment distribution | | X | | X | X | | | |
| In clinic study treatment administration | | X | X | X | X | X | | |
| Study treatment accountability | | | | X | X | X | | |

| Study Week | Screening | Treatment Period | | | | | Follow-up | Notes |
|---|---|---|---|---|---|---|---|---|
| | -4 to -1 | Baseline (Week 0) | 2 | 4 | 8 | 12/EOT | +4 Weeks from EOT | End of treatment (EOT); subjects discontinuing treatment prematurely will attend EOT visit and then continue study visits as planned. |
| **Study Day** | -28 to -1 | 1 | 15 | 29 | 57 | 85 | +28 days from EOT | |
| **Visit Window (days)** | | | ±3 | ±3 | ±3 | ±7 | ±3 | |
| **Safety Assessments** | | | | | | | | |
| Adverse events | X[a] | <========== X ==========> | | | | | | **a.** AEs will be collected after signing informed consent. |
| Concomitant medications | | X | X | X | X | X | X | |
| Vital signs | X | X | X | X | X | X | X | Assessments should occur in the following order:<br>1. Vital signs<br>2. 12-lead ECG (refer to protocol Section 8.3.3)<br>3. Blood draws for safety laboratories; refer to protocol Appendix 2, Section 10.2<br>Note: questionnaires are recommended to be completed before any of these procedures. |
| Weight | X | | | | | X | X | |
| Physical examination | X | | | | | X | | |
| 12-lead electrocardiogram (ECG) | X | X | X | X | X | X | X | |
| Serum chemistry | X | X | X | X | X | X | X | |
| Hematology | X | X | X | X | X | X | X | |
| Urinalysis | X | X | X | X | X | X | X | |
| SARS-CoV-2 antigen test | | X | X | X | X | X | X | If positive, will be confirmed with SARS-CoV-2 PCR test. |
| **Efficacy/PK Assessments** | | | | | | | | |
| HiSCR assessment | | X | X | X | X | X | X | HS Clinical Response (HiSCR). Calculated based on abscess and inflammatory nodule (AN) count |
| Lesion Count | X | X | X | X | X | X | X | Includes AN and draining fistula |
| NRS for skin pain | X | X | X | X | X | X | X | Numeric rating scale (NRS). |
| IHS4 | | X | X | X | X | X | X | International Hidradenitis Suppurativa Severity Score System (IHS4). |

| Study Week | Screening -4 to -1 | Treatment Period Baseline (Week 0) | 2 | 4 | 8 | 12/EOT | Follow-up +4 Weeks from EOT | Notes |
|---|---|---|---|---|---|---|---|---|
| **Study Day** | **-28 to -1** | **1** | **15** | **29** | **57** | **85** | **+28 days from EOT** | End of treatment (EOT); subjects discontinuing treatment prematurely will attend EOT visit and then continue study visits as planned. |
| **Visit Window (days)** | | | **±3** | **±3** | **±3** | **±7** | **±3** | |
| HS-IGA | | X | X | X | X | X | X | Hidradenitis Suppurativa-Investigator's Global Assessment (HS-IGA). |
| HS-PGA | | X | X | X | X | X | X | Physician Global Assessment (HS-PGA). |
| HiSQOL | | X | | | | X | X | HS Quality of Life (HiSQOL). |
| DLQI | | X | | | | X | X | Dermatology Life Quality Index (DLQI). |
| Medical photography of HS-affected areas | | X | | | | X | | To be performed at select sites. |
| Serum sample for RIST4721 concentration | | X | X | X | X | X | | Blood samples for trough PK will be collected pre-dose; subjects will be requested to hold their dose on clinic visits until after PK samples are obtained; a PK sample will also be collected if a subject experience a potentially related SAE (refer to protocol Section 8.5.1). |
| Serum sample for biomarkers | | X | X | X | X | X | X | To be collected and stored for future analyses. |

## 3.3 Treatment

The treatment groups are:

- RIST4721 400 mg QD (ie, 4 tablets of 100 mg each QD)
- Placebo QD (ie, 4 tablets QD)

## 3.4 Randomization, Replacement, and Unblinding Procedures

On Day 1 (baseline visit), eligible subjects will be centrally randomized in 2:1 ratio to receive oral study treatment for 12 weeks using interactive web response system (IWRS):

- RIST4721 400 mg QD
- Placebo QD

Subjects who withdrew from the study or discontinue study treatment after randomization will not be replaced.

This study will be double-blinded. Subjects, investigators, other site personnel, and Sponsor (and/or designee) personnel (except as described below) who are directly involved in the conduct of the study, collection of the data, and analysis of the final safety and efficacy results will remain blinded to treatment assignments until after the completion of the study and the database has been locked.

Sponsor (or designee) personnel will have access to unblinded individual subject treatment assignments for the purposes of study-required activities, including management of study treatment inventory, and performance of bioanalytical analysis of PK. These personnel will not be directly involved in the conduct of the study.

The IWRS system will be programmed with blind-breaking instructions. Blinding codes should only be broken in emergency situations for reasons of subject safety. If the blind is broken, the investigator should immediately inform (within 24 hours) the Sponsor's Medical Monitor (or designee). The date, reason why the blind was broken, and the names of the personnel involved must be recorded in the source documentation. The date and reason why the blind was broken will also be collected in the electronic case report form (eCRF). The subject for whom the blind has been broken will be discontinued from the study and undergo the EOT procedures as specified in the SoA (refer to Table 1).

Appropriate personnel at the Sponsor will unblind suspected unexpected serious adverse reactions (SUSARs) for the purpose of regulatory reporting. The Sponsor will submit SUSARs to regulatory

agencies in blinded or unblinded fashion according to local law. The Sponsor will submit SUSARs to investigators in a blinded fashion.

In order to reduce risk of breaking the blind, starting on Day 1 (baseline), investigators, the study staff, the contract research organization (CRO) personnel, and the Sponsor's study team will not receive absolute or relative neutrophils and white blood cell (WBC) count results. A Medical Monitor will review the blinded data and ensure that the safety of all enrolled subjects is preserved.

Absolute and relative neutrophil and WBC count results will only be disclosed to the respective investigators if the absolute neutrophil count (ANC) reach values below the reference range of the lower limit of normal (LLN) for the central laboratory, in which case immediate actions will be taken, as described in Section 3.5.

Refer to the study Biostatistics Unblinding Plan for additional information on study blinding and unblinding procedures.

## 3.5 Absolute Neutrophil Count Laboratory Abnormality

There will be evaluation of the neutrophil counts and WBC performed by an independent Medical Monitor in order to reduce the risk of breaking the blind. Investigators, the study staff, the CRO, and the Sponsor's study team will not receive absolute and relative neutrophil or WBC count results.

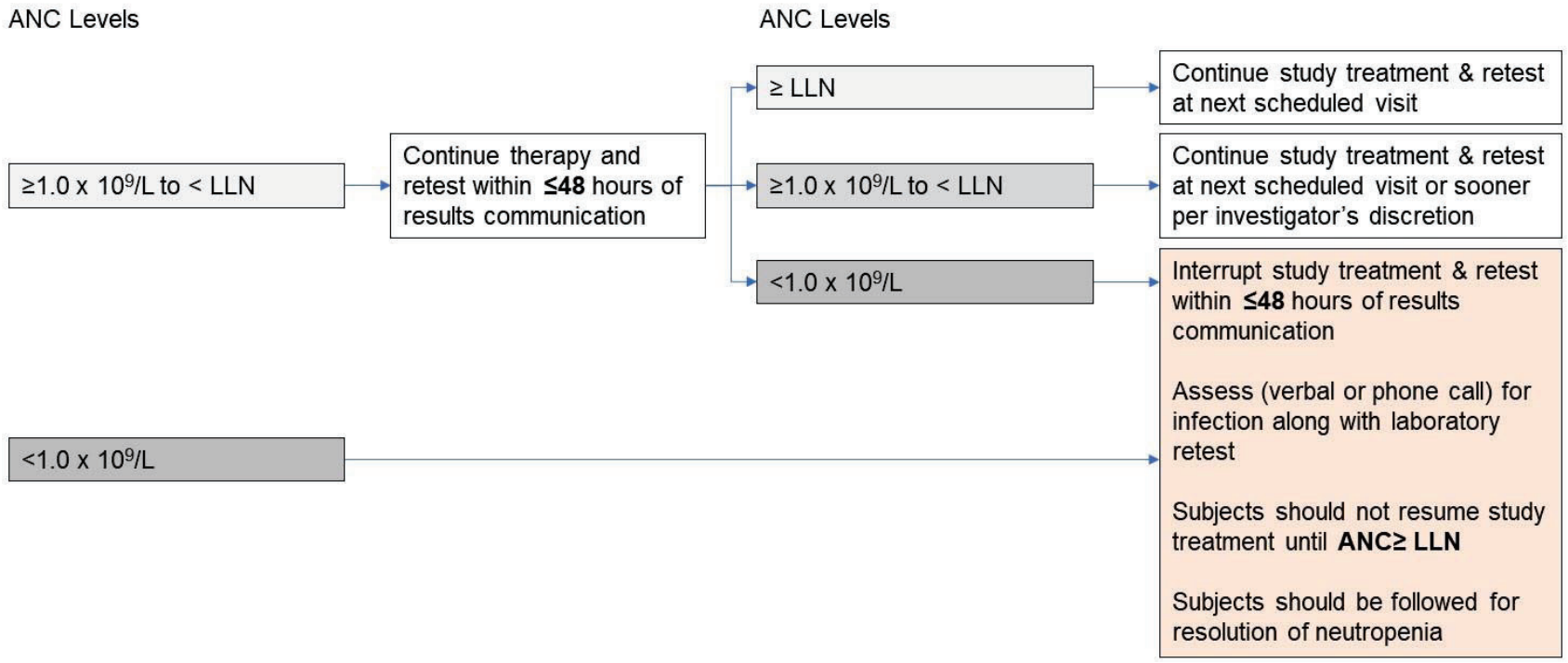
Absolute and relative neutrophils and WBC count results will only be disclosed to the respective investigators if ANC < LLN in which case immediate actions will be taken, as described in Figure 2. Retest results will be communicated to investigators who will follow up on neutrophil count and the incidence of infections in subjects having ANC results $<1.0 \times 10^9$/L. Neutrophil count will be followed until resolution.

Dose interruption of study treatment ***must*** be undertaken for confirmed ANC results $<1.0 \times 10^9$/L. The investigator must notify the Sponsor's Medical Monitor (or designee) within 48 hours of dose interruption. Once the ANC result is above the LLN, subjects may re-initiate blinded study treatment by reducing the study treatment dose to 2 tablets QD (regardless of treatment group) with approval from the Sponsor's Medical Monitor (or designee).

Subjects may be requested to attend an unscheduled visit after dose reduction to collect blood samples for safety and plasma concentrations, if possible.

For subjects who have already experienced a dose reduction: If a subject experiences another case of ANC results <1.0 x $10^9$/L, they must permanently discontinue study treatment (refer to protocol Section 7.1).

**Figure 2: Steps for Addressing Absolute Neutrophil Counts**




Abbreviations: ANC, absolute neutrophil count; LLN, lower limit of normal (central laboratory).

## 3.6 Changes to the Analysis from the Protocol

**Table 2: Summary of Changes to the Protocol**

| Description of the change | Rationale for change |
|---|---|
| Exploratory efficacy endpoint (refer to protocol Section 3)<br><br>"Proportion of subjects achieving at least 2-grade improvement on the HS-physician global assessment (HS-PGA)"<br><br>was updated to (refer to Section 2)<br><br>"Proportion of subjects achieving at least 2-grade improvement on the HS-physician global assessment (HS-PGA) *relative to baseline*" | To clarify period of improvement that needs to be considered |
| Exploratory efficacy endpoint (refer to protocol Section 3)<br><br>"Change from baseline in HS quality of life (HiSQOL)"<br><br>was updated to (refer to Section 2)<br><br>"Change from baseline in HS quality of life (HiSQOL) *total and subscale scores*" | To clarify that both the HiSQOL total score and HiSQOL subscale scores will be analyzed |

| **Description of the change** | **Rationale for change** |
|---|---|
| Per protocol analysis set definition (refer to protocol Section 9.2)<br><br>"Randomized subjects who received 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."<br><br>was updated to (refer to Section 4.3)<br><br>"Randomized subjects who received at least 1 dose of study treatment and do not have major protocol deviations expected to impact the *key secondary efficacy endpoint* of the study. The Per protocol analysis set will be used for sensitivity analyses for the *key secondary* efficacy endpoint." | The per protocol analysis set should be used to perform sensitivity analysis for the key secondary efficacy endpoint, corresponding to one of the secondary objectives of the study, not to performed sensitivity analysis for the incidence of TEAEs and SAEs, corresponding to the primary objective of the study |

| Description of the change | Rationale for change |
|---|---|
| Summarization of continuous data (refer to protocol Section 9.3.1)<br><br>"Continuous data will be summarized using an 8-point descriptive summary (n, mean, standard deviation [SD], median, IQR [25% quartile, 75% quartile], minimum, and maximum) or 7-point descriptive summary (n, mean, SD, coefficient of variation [CV], median, minimum, and maximum) unless otherwise specified"<br><br>was updated to (refer to Section 6.2)<br><br>"Continuous variables will be summarized using descriptive statistics (number of subjects with available data [n], mean, standard deviation [SD], median, IQR (25% quartile, 75% quartile), minimum, and maximum). For, PK concentration data, the *geometric mean*, coefficient of variation (CV), and *geometric CV* will also be provided." | To clarify that CV will only be used to summarize the PK concentration data. |

| Description of the change | Rationale for change |
|---|---|
| Exclusion of lesion that required an intervention from lesion count efficacy assessment (refer to protocol Section 6.7.4)<br><br>"The specific treated lesion will be excluded from lesion count efficacy assessment for the remainder of the study."<br><br>was updated to (refer to Sections 12.2.1, 12.3.1 and 12.4.1):<br><br>"Of note, lesions that required an intervention will be *included* in the lesion count efficacy assessment for the remainder of the study." | Lesions that required an intervention will be included rather than excluded from the lesion count for the remainder of the study for all efficacy assessments in order to avoid artificially increase the percentage of reduction in lesion counts, which, in turn, would artificially increase the number of subjects reaching the key secondary efficacy endpoint (refer to Section 12.2.1) and the other secondary/exploratory efficacy endpoints that are based on the lesion counts (refer to Sections 12.3.1 and 12.4.1). |

# 4 POPULATIONS FOR ANALYSIS

Prior to the database lock, each subject inclusion/exclusion from each analysis set will be reviewed and finalized by the Sponsor and CRO in a blinded fashion.

## 4.1 All Screened Subjects Analysis Set

The all screened subject analysis set include all subjects who signed the ICF.

This analysis set will be used to summarize subject disposition.

## 4.2 Full Analysis Set

The full analysis set (FAS) will include all randomized subjects who received at least 1 dose of study treatment. All subjects will be analyzed according to the treatment group to which they were randomized.

The FAS will be the primary population for evaluating all efficacy endpoints and subject characteristics.

### 4.3 Per-Protocol Analysis Set

The per-protocol (PP) analysis set will include a subset of the FAS ie, randomized subjects who received at least 1 dose of study treatment and do not have major protocol deviations (PDs) expected to impact the key secondary efficacy endpoint of the study (refer to Section 7.2). All subjects will be analyzed according to the treatment group to which they were randomized.

The PP analysis set will be used for a supportive analysis to the main analysis of the key secondary efficacy endpoint.

### 4.4 Safety Analysis Set

The safety analysis set will include all subjects who received at least 1 dose of study treatment. All subjects will be analyzed according to the treatment group to which they were randomized unless the incorrect treatment is received throughout the dosing period, in which case subjects will be analyzed according to the first treatment received.

The safety analysis set will be the primary population for evaluating treatment administration/ compliance and safety endpoint.

### 4.5 Pharmacokinetic Analysis Set

The PK analysis set will include all subjects who have at least 1 concentration above the limit of quantification of the study treatment in RIST4721 arm only.

The PK analysis set will be the primary population for evaluating the PK concentrations.

## 5 General Considerations

Formats and layouts of TLFs will be provided in a separate document (output general layout is described in Appendix 2).

### 5.1 Reference Start Date and Study Day

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

Study day = (assessment/event date – study treatment first dose date) + 1 if the assessment/event date is on or after the study treatment first dose date

or

(assessment/event date – study treatment first dose date) if the assessment/event date is before the study treatment first dose date

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

## 5.2 Baseline

Unless otherwise specified, baseline value will be defined as the last non-missing assessment prior to the first dose of study treatment (including unscheduled assessments). If the last non-missing assessment is performed on the same date as the first dose of study treatment and time is not available, the assessment will be considered as baseline, except for adverse events (AEs) not associated with a pre-dose assessment and medications starting on the same date as the first dose of study treatment which will be considered post-baseline. For partially or completely missing AEs and medication start date, refer to Appendix 3.

## 5.3 On-Treatment

A subject is considered on-treatment from the date of his/her first dose of study treatment up to the date of the Week 12/EOT visit (refer to Table 1), inclusively.

## 5.4 Change and Percent from Baseline

Change from baseline will be computed as follows:

Change from baseline = Post-baseline visit value – Baseline value

Percent change from baseline will be computed as follows:

$$\text{Percent change from baseline (\%)} = \frac{\text{Change from baseline value}}{\text{Baseline value}} \text{ x } 100$$

## 5.5 Handling of Retests Data

When retests measurements are done for a specific visit, the retests measurements will be considered for that visit summary analysis.

All data (original and retest) will be listed.

## 5.6 Windowing Conventions

Visits will be summarized and analyzed as scheduled. Data from unscheduled and EOT visits will only be included if data from a scheduled visit are not available, and the unscheduled/EOT visit falls within the analysis visit windows. Of note, only subjects who permanently discontinued study

treatment will complete an EOT visit (refer to Section 3.1) and, unless other specified in the efficacy, safety and PK analysis sections (refer to Sections 12, 13, and 14), data collected after the EOT visit will not be used in the by-visit summaries and analyses.

If there is more than one unscheduled/EOT visit with available data for a given analysis visit when data from the scheduled visit are not available, data from the unscheduled/EOT visit closest to the analysis visit target day will be considered for the analysis.

The following analysis visit windows will be used:

| Analysis Visit | Target Day | Lower Limit | Upper Limit |
|---|---|---|---|
| Baseline | 1 | Refer to Section 5.2 | |
| Week 2 | 15 | 2 | 22 |
| Week 4 | 29 | 23 | 43 |
| Week 8 | 57 | 44 | 71 |
| Week 12 | 85 | 72 | 99 |
| Follow-up | 113 | 100 | N/A |

Abbreviation: N/A, not applicable.

All data from scheduled, unscheduled, EOT, and Follow-up visits will be listed, including data collected after an EOT visit for subjects who remain in the study after the EOT visit.

# 6 STATISTICAL CONSIDERATIONS

## 6.1 Sample Size

Group sample sizes were chosen empirically for this initial Phase 2 study to determine the safety and tolerability of RIST4721.

## 6.2 Descriptive Statistics

Unless otherwise indicated, continuous variables will be summarized using descriptive statistics (number of subjects with available data [n], mean, standard deviation [SD], median, 25% percentile [Q1], 75% percentile [Q3], minimum, and maximum). For, PK concentration data, the geometric mean, coefficient of variation (CV), and geometric CV will also be provided.

Categorical variables will be summarized using frequencies and percentages.

Summary tables will be presented by treatment group and visit, when applicable.

## 6.3 Handling of Dropouts or Missing data

Exception of missing data mentioned in the following sub-sections, no missing will be imputed.

### 6.3.1 Efficacy Endpoints

#### *6.3.1.1 LOCF*

For the main analysis of the key secondary efficacy endpoint (refer to Section 12.2.3) and other secondary efficacy endpoints that are dichotomous in nature (refer to Section 12.3.2), the last observation carried forward (LOCF) method will be used to impute missing post-baseline response status. Following the LOCF method, if a value is missing for a given post-baseline assessment, this value is imputed with the last non-missing post-baseline assessment (including unscheduled assessments) collected while subject was on-treatment (refer to Section 5.3) but prior to the missing assessment. That is, should post-baseline data be captured after the EOT visit for subjects who discontinued early from study treatment, these data will not be considered for this LOCF imputation.

#### *6.3.1.2 Non-Responder Imputation*

As a sensitivity analysis to the missing data imputation assumption used for the main analysis of the key secondary endpoint (refer to Sections 6.3.1.1 and 12.2.4), missing data will also be imputed as per the non-responder imputation (NRI) method . Following this method, if a value is missing for a given post-baseline assessment, this value is imputed to 'No' (ie, not achieving the endpoint criteria).

#### *6.3.1.3 Modified LOCF*

As sensitivity analysis to the missing data imputation assumption used for the main analysis of the key secondary endpoint (refer to Section 12.2.4), missing data will also be imputed using a modified version of the LOCF method (refer to Section 6.3.1.1) in which all non-missing post-baseline data (including unscheduled assessments) collected prior to the missing assessment will be considered, regardless of if they were collected while subject was on-treatment (refer to Section 5.3) or after as long as data have been collected prior to the missing assessment.

#### *6.3.1.4 MMRM*

For the main analysis of other secondary efficacy endpoints that are continuous in nature (refer to Section 12.3.2), missing post-baseline data will not be imputed before being analyzed using a Mixed-Model for Repeated Measurements (MMRM) model since, under a MMRM model, the missing data are predicted by the observed data via the model of conditional mean.

### 6.3.2 Safety Endpoints

With the following exception, missing safety data will not be imputed. The exception is that partially or completely missing AEs and medication start and stop dates which will be imputed as per the algorithm described in Appendix 3. This imputation will be performed only to classify an AE as treatment-emergent or not (refer to Section 13.1) and a medication as concomitant or not (refer to Section 10). That is, imputed AE and medication dates will not be used for the derivation of any other variables (eg, AE start study day, AE duration, medication start study day, etc.) and will not be presented in the subject data listing.

## 6.4 Multicenter Studies

Data from all study sites will be pooled for the summary and analysis of the study data.

## 6.5 Adjustments for Covariates

For continuous efficacy endpoints, baseline values and baseline-by-visit interaction will be included in the MMRM model as covariates.

## 6.6 Statistical Tests

Unless otherwise specified, all statistical tests will be two-sided and performed with a significant level of 0.05. Confidence intervals (CIs) will be two-sided with 95% coverage.

## 6.7 Interim Analysis and Data Monitoring

No interim analysis (safety or efficacy/futility) is planned for this study.

## 6.8 Multiple Comparisons/Multiplicity

Given the exploratory nature of this study (eg, no formal sample size calculation was performed), no adjustments for multiple comparison will be made for this study. That is, all p-values will be nominal.

### 6.9 Examination of Subgroups

The following subgroups will be examined for the key secondary efficacy endpoint (refer to Section 12.2.1) and other secondary efficacy endpoints (refer to Section 12.3.1):

- Hurley stage (Stage I, Stage II, and Stage III) at baseline (refer to Section 5.2).

Details for these analyses are described in Section 12.6.

### 6.10 Software Version

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

## 7 STUDY SUBJECTS

### 7.1 Disposition of Subjects

All subjects who provide informed consent will be accounted for in this study. The number of subjects screened and rescreened will be presented. The number and percentage of subjects with screen failure will be presented based on the 'all screened subjects' analysis set. Screen failure will be further broken down by reason for screen failure based on the number of subjects with screen failure. First screen failure and reason for screen failure of rescreened subjects who did not fail the second screening (refer to Section 3.1) will not be reported in the summary table but will be included in the subject data listing.

The number of subjects randomized will be presented overall and by treatment group.

Number and percentage of randomized subjects who discontinued early from the study before receiving any study treatment (if any), completed study treatment, and discontinued early from study treatment will be presented overall and by treatment group based on the FAS. Early discontinuation from study treatment will be further broken down by reason for early discontinuation based on the number of FAS subjects who discontinued early from study treatment.

Number and percentage of subjects who completed or discontinued early from study will be presented overall and by treatment group based on the FAS. Early discontinuation from study will be further broken down by reason for early discontinuation based on the number of FAS subjects who discontinued early from study.

Number and percentage of subjects included in and excluded from each analysis set will be summarized overall and by treatment group based on the FAS population along with the reason(s) for exclusion from each analysis set (when applicable).

Number of days in the study will be calculated as follows and summarized using descriptive statistics overall and by treatment group:

Number of days in study (days) = (Date of study completion/ discontinuation – Date of first dose of study treatment) +1

A listing of subject's disposition will 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. A listing of subject's randomization information and a listing of subjects included in and excluded from each of the analysis sets will also be provided, including reason(s) for exclusion.

## 7.2 Protocol Deviations

A data review will be conducted before database lock by the Medical Monitor and Sponsor to classify each PD as major or minor (refer to the PD management plan [PDMP] for more details, including definition of major and minor PDs). Major PDs expected to impact the key secondary objective of the study (refer to Section 2) will also be identified during this data review and will result in the exclusion of the concerned subject from the PP analysis set (refer to Section 4.3). Major PDs expected to impact the key secondary objective of the study include, but are not limited to:

- Violation of key inclusion/exclusion criteria
- Randomized to RIST4721 but received Placebo at any time during the study, and vice-versa
- Received clinically significant amount of prohibited concomitant medications/treatments during the study (refer to protocol Section 6.7.5)
- Compliance with study treatment (refer to Section 11) < 80%
- Other

The number and percentage of subjects with at least one major PD and number of major PDs will be summarized overall and by treatment group based on the safety analysis set and will be broken down further by PD category and sub-category. The subset of major PDs expected to impact the

key secondary efficacy endpoint and subset of PDs associated with COVID-19 will be summarized similarly.

A listing of all PDs will also be provided. PDs associated with COVID-19 and major PDs will be flagged.

# 8 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The list of demographics and baseline characteristics to be summarized include:

- Age (years) – calculated relative to date of consent
- Sex
- Ethnicity
- Race
- Baseline height (cm)
- Baseline weight (kg)
- Baseline body mass index (BMI; $kg/m^2$)
- Time since diagnosis of HS (years), defined as the date of screening visit minus the date of diagnosis of HS divided by 365.25 days
- Baseline overall Hurley stage
- Baseline total AN count (refer to Section 12.2.1)
- Baseline total abscess count
- Baseline total inflammatory nodule count
- Baseline total draining fistula count
- Baseline total non-inflammatory nodule count
- Baseline total non-draining fistula count
- Baseline NRS for skin pain (refer to Section 12.3.1)
- Baseline IHS4 count (refer to Section 12.3.1)

- Baseline HS-IGA score (refer to Section 12.4.1)
- Baseline HS-PGA score (refer to Section 12.4.1)
- Baseline HiSQOL total and subscale scores (refer to Section 12.4.1)
- Baseline DLQI total score (refer to Section 12.4.1)

Continuous endpoints will be summarized using descriptive statistics overall and by treatment group based on the FAS while categorical endpoints will be similarly summarized using frequencies and percentages.

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

# 9 SURGICAL AND MEDICAL HISTORY

Surgical and medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 25.0.

The number and percentage of subjects reporting at least one surgical and/or medical event will be summarized overall and by treatment group based on the FAS and further broken down by system organ class (SOC) and preferred term (PT) based on the FAS. A subject who experienced the same event multiple times within the same SOC will be counted only once for the corresponding SOC. Similarly, if a subject experienced multiple events within the same PT, the subject will be counted only once for that PT. Surgical and medical history events will be sorted alphabetically by SOC and within each SOC, the PT will be presented by decreasing order of total frequencies.

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) B3, March 2022.

Prior medications are defined as any medication started and discontinued prior to the first dose of study treatment. Concomitant medications are defined as any medication taken on or after the first dose of study treatment, including those who started prior to the date of the first dose of study treatment and continued past that date. See Appendix 3 for handling of completely or partially missing dates for prior and concomitant medications.

Number and percentage of subjects with at least one prior medication will be summarized overall and by treatment group based on the FAS and further broken down by anatomical therapeutic chemical (ATC) level 3 term and preferred drug name. A subject with the same medication taken multiple times within the same preferred drug name 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 3 term, then the subject will be counted only once for that ATC level 3 term. Concomitant medications will be sorted alphabetically by ATC level 3 term and within each ATC level 3 term, the preferred drug name will be presented by decreasing order of total frequencies. Concomitant medications will be summarized similarly.

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

# 11 EXPOSURE TO AND COMPLIANCE WITH STUDY TREATMENT

Total exposure to study treatment, in days, will be computed as follows and summarized using descriptive statistics by treatment group based on the safety analysis set.

Total exposure (days) = (Date of last dose of study treatment – Date of first dose of study treatment) + 1

Number and percentage of subjects with at least one dose interruption (no dose) will be presented by treatment group based on the safety analysis set and further broken down by reason for dose interruption. Dose reduction and reason for dose reduction will be summarized similarly.

Total number of doses missed and total exposure to reduced dose, in days, will be summarized using descriptive statistics by treatment group based on the safety analysis set, where total exposure to a reduced dose will be computed as follows:

$$\text{Total exposure to reduced dose (days)} = \sum_{i=1}^{m}(\text{Date of last dose of dose reduction i} - \text{Date of first dose of dose reduciton i}) + 1$$

where:

m is the subject's total number of dose reduction periods during the study.

Compliance with study treatment, in percentage, will be computed as follows and summarized using descriptive statistics by treatment group based on the safety analysis set

$$\text{Compliance (\%)} = \frac{\text{Total number of doses administered}}{\text{Total number of expected doses to be administered}} \text{ x } 100$$

where:

Total number of expected doses = (exposure to a reduced dose x 2) + [(total exposure – exposure to a reduced dose) x 4]

Total number of doses administered = Total number of expected doses – Total number of doses missed

# 12 EFFICACY ANALYSIS

Unless otherwise indicated, all efficacy summaries and analyses will be performed based on the FAS (refer to Section 4.2).

## 12.1 Primary Efficacy Analysis

Not applicable.

## 12.2 Key Secondary Efficacy Analysis

### 12.2.1 Definition and Estimand of Key Secondary Efficacy Endpoint

**Treatment groups**: RIST4721 400 mg and placebo

**Target population**: Subjects with HS as defined by the inclusion and exclusion criteria (refer to protocol Section 5), grouped per randomization assignment

**Endpoint**: Proportion of subjects achieving HiSCR50 at Week 12

**Intercurrent events and corresponding strategy**: For subjects who discontinue study treatment prior to Week 12 due to any reason, their last observation will be used to impute response status

**Population-level summary variable**: Difference in proportions between treatment groups

The HiSCR is used to assess the inflammatory signs and symptoms of HS (Kimball, 2014).

To determine if a subject achieves HiSCR50 (yes vs. no) at an analysis visit (refer to Section 5.6), the number of abscesses, inflammatory nodules, and draining fistulas on the entire body at that analysis visit will first be counted separately. Of note, abscesses, inflammatory nodules, and draining fistulas that required an intervention during the course of the study will be included in the concerned count of lesions for the remainder of the study. That is, if, for example, an abscess that

was present at the Week 2 analysis visit required an intervention between the Week 4 and Week 8 analysis visits, this lesion will be included in the count of abscesses for the Week 2, Week 4, Week 8, Week 12, and Follow-up analysis visits.

Subject's achievement of HiSCR50 (yes vs. no) at each post-baseline analysis visit, which is defined as follows, will then be determined.

- Achieving a 50% or greater reduction in total AN count and no increase in abscess or draining fistula counts at the concerned post-baseline analysis visit compared with baseline

where:

- Total AN count is the sum of the total number of abscesses and total number of inflammatory nodules at the analysis visit
- Change from baseline in abscesses, change from baseline in draining fistula, and percent change from baseline in total AN count will be computed as calculated as defined in Section 5.4.

### 12.2.2 Hypothesis Testing

$H_0$: $P_R - P_P = 0$

versus

$H_1$: $P_R - P_P \neq 0$

where:

$P_R$ = Proportion of subjects achieving HiSCR50 at Week 12 in RIST4721 treatment group

$P_P$ = Proportion of subjects achieving HiSCR50 at Week 12 in placebo treatment group

The direction of superiority is indicated by a difference in proportions greater than 0.

### 12.2.3 Main Analysis of Key Secondary Efficacy Endpoint

For subjects who discontinued early from study treatment due to any reason, missing subject's achievement of HiSCR50 status will be imputed as per the LOCF method (refer to Section 6.3.1.1).

The number and proportion of subjects achieving or not HiSCR50 (refer to Section 12.2.1) will be presented by treatment group for each post-baseline analysis visit (refer to Section 5.6) along with

the difference in proportions between treatment groups (RIST4721 – placebo). Two-sided 95% Clopper-Pearson CI will also be presented for the proportion of subjects achieving HiSCR50 for each treatment group while two-sided 95% exact unconditional CI will also be presented for the difference in proportions between treatment groups.

The key secondary efficacy endpoint of proportion of subjects achieving HiSCR50 at Week 12 will be analyzed using a Fisher's exact test and a p-value will be provided. The proportion of subjects achieving HiSCR50 at other post-baseline analysis visits will be analyzed similarly and p-value will also be provided.

### 12.2.4 Sensitivity Analyses to Main Analysis of the Key Secondary Efficacy Endpoint

Sensitivity to missing data imputation assumptions

The imputation method used for the main analysis of the key secondary efficacy endpoint (i.e., LOCF; refer to Section 6.3.1.1) assumes that achievement of HiSCR50 status of subjects who discontinued early from study treatment would not have changed from the last observed achievement of HiSCR50 status while subject was on-treatment (refer to Section 5.3) to the end of the trial, had they stayed on the study treatment. In other words, LOCF assumes that no improvement or worsening of the lesions count would have occurred after a subject discontinued early from study treatment should a subject had stayed on the study treatment.

To assess the robustness of the imputation assumption of the method used for the main analysis of the key secondary efficacy endpoint, the following sensitivity analyses will be performed:

- The main analysis to the key secondary efficacy endpoint will be repeated but missing HiSCR50 achievement status at Week 12 will be imputed as per the NRI method (refer to Section 6.3.1.2).
- The main analysis to the key secondary efficacy endpoint will be repeated but missing HiSCR50 achievement status at Week 12 will be imputed as per a modified LOCF method (refer to Section 6.3.1.3).

Sensitivity analysis to analysis set

The main analysis of the key secondary efficacy endpoint (refer to Section 12.2.3) will be repeated based on the PP analysis set (refer to Section 4.3).

## 12.3 Other Secondary Efficacy Analyses

### 12.3.1 Definition of Other Secondary Efficacy Endpoints

The other secondary efficacy endpoints are:

- Proportion of subjects achieving HiSCR75 at Week 12
- Proportion of subjects with flare at Week 12
- Proportion of subjects achieving AN count of 0, 1, or 2 at Week 12
- Change from baseline in NRS skin pain score at Week 12
- Change from baseline in IHS4 total score at Week 12

Proportion of Subjects Achieving HiSCR75 at Week 12

Achievement of HiSCR75 (yes vs. no) at Week 12 is defined similarly to the achievement of HiSCR50 at Week 12 (refer to Section 12.2.1) but using a 75% or greater reduction in total AN count as criterion instead of a 50% or greater reduction in total AN count. The analysis visit of interest will be the Week 12 analysis visit.

Proportion of Subjects with Flare at Week 12

At each post-baseline analysis visit (refer to Section 5.6), subject's flare status (yes or no) will be determined, where a flare is defined as follows:

- Having ≥ 25% increase and ≥ 2 absolute increase in AN count at the concerned post-baseline analysis visit compared to baseline

where AN count will be calculated as defined in Section 12.2.1 and change and percent change from baseline in AN count will be computed as defined in Section 5.4. The analysis visit of interest will be the Week 12 analysis visit.

Proportion of Subjects Achieving AN Count of 0, 1 or 2 at Week 12

At each post-baseline analysis visit (refer to Section 5.6), subject's achievement (yes or no) of an AN count (refer to section 12.2.1) of 0, 1, or 2 will be determined as follows:

- Having an AN count of 0, 1, or 2 at at the concerned post-baseline analysis visit

The analysis visit of interest will be the Week 12 analysis visit.

Change from Baseline in NRS Skin Pain Score at Week 12

The NRS (Barrett, 2019; Silverberg, 2021) for skin pain is a self-assessed patient reported outcome. The NRS is an 11-point scale (0 to 10), with a score of zero denoting no pain and a score of 10 denoting worst possible pain.

Change from baseline in NRS skin pain score at each post-baseline analysis visit (refer to Section 5.6) will be computed as defined in Section 5.4. The analysis visit of interest will be the Week 12 analysis visit.

Change from baseline in IHS4 Total Score at Week 12

The IHS4 is a validated tool that dynamically assess HS severity (Zouboulis, 2017; Napolitano, 2020). For each analysis visit (refer to Section 5.6), IHS4 total score will be calculated as follows:

IHS4 total score = (Total number of nodules x 1) + (Total number of abscesses x 2) + (Total number of draining fistulas x 4)

Of note,

- Only the inflammatory nodules should be considered when calculating the IHS4 total score.
- Abscesses, inflammatory nodules, and draining fistulas that required an intervention during the course of the study will be handle using the same methodology as for the key secondary efficacy endpoint (refer to Section 12.2.1) when calculating the IHS4 total score.

An ISH4 total score of 3 or less signifies mild disease, 4 to 10 moderate disease, and 11 or higher severe disease.

Change from baseline in IHS4 total score at each post-baseline analysis visit will be computed as defined in Section 5.4. The analysis visit of interest will be the Week 12 analysis visit.

### 12.3.2 Main Analysis of Other Secondary Efficacy Endpoints

Missing other secondary efficacy endpoints that are dichotomous in nature (i.e., proportion of subjects) will be imputed as per the LOCF method (refer to Section 6.3.1.1). These endpoints will then be summarized and analyzed as for the key secondary efficacy endpoint (refer to Section 12.2.3). The analysis visit of interest will be the Week 12 analysis visit.

Missing other secondary efficacy endpoints that are continuous in nature (i.e., change from baseline) will not be imputed, but rather predicted using a MMRM model (refer to Section 6.3.1.4). Hence, the descriptive statistics that will be presented for each of these endpoints by treatment

group at baseline and each post-baseline analysis visit (refer to Section 5.6) will be based on observed data only. Data collected after a subject discontinued from study treatment, if any, will be excluded from these summaries for the Weeks 2, 4, 8, and 12 post-baseline analysis visits. Descriptive statistics will also be presented similarly for the scale (total) score at each post-baseline analysis visit.

The change from baseline will be analyzed using a MMRM model including change from baseline as the dependent variable, treatment group (RIST4721 and placebo), visit (Weeks 2, 4, 8, and 12), treatment group-by-visit interaction as fixed effects, baseline and baseline-by-visit interaction as covariates, and subjects as random effect. As for the descriptive statistics, data collected after a subject discontinued from study treatment, if any, will be excluded from the MMRM model. An unstructured covariance structure will be used to model the within-subject error and the Kenward-Roger approximation to estimate the degrees of freedom will be used for tests of fixed effects derived from the MMRM model. If this analysis fails to converge, the following covariance structure will be tested and the covariance structure converging to the best fit, as determined by the Akaike's information criteria corrected (AICC) will be used for the main analysis: heterogenous Toeplitz (TOEPH), heterogenous first-order autoregressive (ARH[1]), and first-order ante dependence (ANTE[1]).

Least square mean (LS mean) estimate (and associated standard error [SE]) will be provided by treatment group and visit. Difference in LS mean estimates between the two treatment groups (and associated SE) at each visit will also be estimated, along with its two-sided 95% and p-value. The contrast of interest will be between the RIST4721 and placebo treatment groups at Week 12.

Additionally, LS mean estimates of the mean change from baseline (+/- SE) over time will be displayed graphically by treatment group.

### 12.3.3 Sensitivity Analyses to Other Secondary Efficacy Endpoint

No sensitivity analyses will be performed for other secondary efficacy endpoints.

## 12.4 Exploratory Efficacy Analyses

### 12.4.1 Definition of Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are:

- Proportion of subjects achieving at least 2-grade improvement on the HS-PGA
- Proportion of subjects achieving 0 or 1 on the HS-PGA

- Proportion of subjects achieving at least 2-grade improvement on the HS-IGA relative to baseline at Week 12
- Proportion of subjects achieving 0 or 1 on the HS-IGA
- Change from baseline in AN count at Week 12
- Change from baseline in HiSQOL total and subscale scores
- Change from baseline in DLQI total score at Week 12

Proportion of Subjects Achieving at Least 2-grade Improvement on the HS-PGA at Week 12

The HS-PGA categorizes HS into 6 categories of progressive severity based on number of nodules, abscesses, and fistulas, as shown in Table 3. Of note, nodules, abscesses, and fistulas that required an intervention during the course of the study will be handle using the same methodology as for the key secondary efficacy endpoint (refer to Section 12.2.1) when establishing the grade/severity in HS-PGA.

**Table 3: HS-PGA**

| Grade | Severity | Description |
|---|---|---|
| 0 | Clear | 0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and 0 non-inflammatory nodules |
| 1 | Minimal | 0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and presence of non-inflammatory nodules |
| 2 | Mild | 0 abscesses, 0 draining fistulas, and 1–4 inflammatory nodules<br>or<br>1 abscess or draining fistula and 0 inflammatory nodules |
| 3 | Moderate | 0 abscesses, 0 draining fistulas, and ≥5 inflammatory nodules<br>or<br>1 abscess or draining fistula and ≥1 inflammatory nodules<br>or<br>2–5 abscesses or draining fistulas and <10 inflammatory nodules |
| 4 | Severe | 2–5 abscesses or draining fistulas and ≥10 inflammatory nodules |
| 5 | Very severe | >5 abscesses or draining fistulas |

The HS-PGA score will be established at each analysis visit (refer to Section 5.6) and change from baseline in HS-PGA grade to each post-baseline analysis visit will be computed as defined in Section 5.4. Achievement at least 2-grade improvement on the HS-PGA (yes or no) at each post-baseline analysis visit, defined as follows, will then be determined based on the change from baseline value:

- Having a change from baseline in HS-PGA grade ≥ 2

Proportion of Subjects Achieving 0 or 1 on the HS-PGA at Week 12

Achievement of 0 or 1 on the HS-PGA (yes or no) is defined as follows:

- Having a HS-PGA grade or 0 or 1

Proportion of Subjects Achieving at Least 2-grade Improvement on the HS-IGA at Week 12

The HS-IGA score is based on the maximum count of abscesses, fistulas (draining and non-draining), and nodules (inflammatory and non-inflammatory) in either the upper or lower body region as showed in Table 4. Of note,

- The region used at baseline may not be the same region used at a given post-baseline scheduled visit.
- Abscesses, fistulas, and nodules that required an intervention during the course of the study will be handle using the same methodology as for the key secondary efficacy endpoint (refer to Section 12.2.1) when establishing the HS-IGA score.

**Table 4: HS-IGA**

| Score | Maximum Lower Body or Upper Body Count |
|---|---|
| 0 | 0-1 |
| 1 | 2-5 |
| 2 | 6-10 |
| 3 | 11-15 |
| 4 | 16-20 |
| 5 | > 20 |

The HS-IGA score will be established at each analysis visit and change from baseline in HS-IGA score to each post-baseline analysis visit will be computed as defined in Section 5.4. Achievement at least 2-grade improvement on the HS-IGA score (yes or no) at each post-baseline analysis visit, defined as follows, will then be determined based on the change from baseline value:

- Having a change from baseline in HS-IGA score ≥ 2

Proportion of Subjects Achieving 0 or 1 on the HS-IGA at Week 12

Achievement of 0 or 1 on the HS-IGA is defined as follows:

- Having a HS-IGA score or 0 or 1

Change from Baseline in AN Count at Week 12

AN count is defined in Section 12.2.1.

Change from baseline in AN count to each post-baseline analysis visit (refer to Section 5.6) will be computed as defined in Section 5.4.

Change from Baseline in HiSQOL Total and Subscale Scores at Week 12

The HiSQOL scale was developed and validated for clinical trial measurement of HS-specific health-related quality of life (HRQOL). It is a 17-item instrument separated into 3 subscales (4 symptom items, 5 psychosocial items, and 8 functional concept items) with a 7-day recall period (Kirby, 2020; Kirby, 2021). Each item is rated from 0 (not at all/I do not normally do this, HS did not influence) to 4 (extremely/unable to do, due to HS).

Each subscale score is the sum of its related items. The symptom subscale scores range from 0 to 16, the psychosocial subscale from 0 to 20, and the functional concept subscale from 0 to 32, with higher scores indicating more severe impact on HRQOL. If more than 50% of a subscale related items are unanswered, the concerned subscale score will be considered as missing.

The HiSQOL total score is the sum of the and ranges from 0 to 68, with higher scores indicating more severe impact on HRQOL. If one or more subscale score is missing, the HiSQOL total score will be considered as missing.

Changes from baseline in HiSQOL total and subscale score to each post-baseline analysis visit (refer to Section 5.6) will be computed as defined in Section 5.4.

Change from Baseline in DLQI Total Score at Week 12

The DLQI is a simple 10-question validated questionnaire including questions concerning symptoms and feelings, daily activities, leisure, work/school, personal relationships, and treatment (Finlay, 1994). All questions relate "to the last week" and each question is rated from 0 (Not at all) to 3 (Very much).

The DLQI total score is the sum of all 10 questions and ranges from 0 (no impairment of life quality) to 30 (maximum impairment). If one question is unanswered, this question is allocated a score of 0 and the DLQI total score is calculated the usual way. If two or more questions are unanswered, the DLQI total score cannot be calculated and is considered as missing.

Change from baseline in DLQI total score to each post-baseline analysis visit (refer to Section 5.6) will be computed as defined in Section 5.4.

### 12.4.2 Main Analysis of Exploratory Efficacy Endpoints

Missing exploratory efficacy data will not be imputed.

For each dichotomic exploratory efficacy endpoints, the number and proportion of subjects achieving or not the endpoint criteria (refer to Section 12.4.1) will be presented by treatment group for each post-baseline scheduled visit along with the difference in proportions between treatment groups (RIST4721 – placebo). Two-sided 95% Clopper-Pearson CI will also be presented for the proportion of subjects achieving the endpoint criteria for each treatment group and a two-sided 95% exact unconditional CI will also be provided for the difference in proportions between treatment groups. No statistical inferences will be performed for the exploratory dichotomic efficacy endpoint.

For each continuous exploratory efficacy endpoint, descriptive statistics for the change from baseline in the AN count or scale total/subscale score at each post-baseline analysis visit (refer to Section 5.6) will be presented by treatment group). Descriptive statistics will also be presented by treatment group for the AN count or scale total/subscale score at each analysis visit.

### 12.4.3 Sensitivity Analyses to Exploratory Efficacy Endpoint

No sensitivity analyses will be performed for exploratory efficacy endpoints.

## 12.5 Additional Efficacy Analyses

Total number of abscesses, total number of inflammatory nodules, and total number of draining fistulas will be summarized using descriptive statistics by treatment group and analysis visit (refer

to Section 5.6). Of note, abscesses, inflammatory nodules, and draining fistulas that required an intervention during the course of the study will be handle using the same methodology as for the key secondary efficacy endpoint (refer to Section 12.2.1) when calculating the total number of concerned lesions. Change and percent from baseline in each of these total counts at each post-baseline analysis visit will also be summarized using descriptive statistics by treatment group. Additionally, percent change from baseline in total AN count (refer to Section 12.2.1) to each post-baseline analysis visit will be summarized similarly.

Number and percentage of subjects with a 50% or greater reduction in total AN count, with a 75% or greater reduction in total AN count, with no increase in abscess count, with no increase in draining fistula, with a 25% or greater increase in total AN count, and with an increase of 2 or more in total AN count, all compared to baseline, as well as numbers and percentages of subjects with an AN count of 0, of 1, of 2, and of 3 or more will be provided by treatment group and analysis visit.

Shift tables from baseline in HS-PGA grade, HS-IGA score, and IHS4 categories (mild [IHS4 total score of 3 or less], moderate [IHS4 total score of 4 to 10], and severe [IHS4 total score of 11 or higher]) to each post-baseline analysis visit will be provided by treatment group. The number of subjects with a non-missing grade/score at both the baseline and a specific post-baseline analysis visit will be used as denominator for that post-baseline analysis visit.

All efficacy data will be listed.

### 12.6 Subgroup Analyses

The main analysis of the key and other secondary efficacy endpoints (refer to Sections 12.2.3 and 12.3.2) will be repeated for the subgroups specified in Section 6.9.

No subgroup analyses will be performed for the additional efficacy endpoints.

## 13 SAFETY ANALYSIS

All safety summaries will be conducted based on the safety analysis set (refer to Section 4.4). No statistical inferences will be performed.

### 13.1 Adverse Events

AEs will be coded according to the MedDRA, Version 25.0.

A TEAE is defined as an AE that is new or worsening on or after the subject has received the first dose of study treatment and with an onset within 30 days after the last dose of study treatment. See Appendix 3 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, except for AEs associated with a pre-dose assessment which will not be classified as treatment-emergent.

An overall summary table of AEs will be provided. The number of events and the number and percentage of subjects who experienced AE, TEAE, TEAE by greatest reported relationship with study treatment (related or not related), TEAE by highest reported severity (mild, moderate, or severe), AE with an outcome of death, serious TEAE, treatment-related serious TEAE, TEAE leading to study treatment discontinuation, and TEAE leading to study withdrawal will be presented by treatment group. TEAE with an unknown relationship with study treatment will be considered as related and TEAE with an unknown severity will be considered as severe.

Frequency and percentage of subjects who experience TEAE will be summarized by SOC and PT. A subject experiencing the same TEAE multiple times within the same SOC will be counted only once for that SOC. Similarly, a subject experiencing the same TEAE multiple times within the same PT will be counted only once for that PT. TEAEs will be sorted alphabetically by SOC and within each SOC, the PT will be presented by decreasing order. Treatment-emergent SAEs, TEAEs leading to study treatment discontinuation, and TEAEs leading to study withdrawal will be summarized similarly.

Frequency and percentage of subjects who experience TEAE will also be summarized by SOC, PT, and greatest reported relationship with the study treatment. A subject experiencing the same TEAE multiple times within the same SOC will be counted only once for that SOC under the greatest reported relationship with study treatment. Similarly, a subject experiencing the same TEAE multiple times within the same PT will be counted only once for that PT under the greatest reported relationship with study treatment.

Frequency and percentage of subjects who experience TEAE will be summarized by SOC, PT, and highest reported severity. A subject experiencing the same TEAE multiple times within the same SOC will be counted only once for that SOC under the highest reported severity. Similarly, a subject experiencing the same TEAE multiple times within the same PT will be counted only once for that PT under the highest reported severity.

Listings of all AEs, all AEs with an outcome of death, all SAEs, all TEAEs leading to study treatment discontinuation, and all TEAEs leading to study withdrawal will be provided.

## 13.2 Clinical Laboratory

Laboratory data will be presented as per the international system of units, universally abbreviated as SI (from the French 'système international').

Hematology, serum chemistry, and quantitative urinalysis tests (refer to Appendix 4) will be summarized using descriptive statistics by treatment group and visit. Of note, Q1 and Q3 will not be included in the summaries for continuous laboratory tests. Change from baseline values will be summarized similarly by treatment group for each post-baseline scheduled visit (refer to Table 1). Number and percentage of subjects in each qualitative urinalysis test category will be provided by treatment group and visit.

Shift tables from baseline in each hematology, serum chemistry, and quantitative urinalysis test to each post-baseline assessment, describing shifts to abnormality (low, normal, or high), will be provided as well. The number of subjects with a non-missing result at both baseline and a specific post-baseline scheduled visit will be used as denominator for that post-baseline scheduled visit.

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

Urine pregnancy test, virology, and laboratory tests required at screening and/or baseline only will be listed.

## 13.3 Vital Signs

Vital signs (systolic blood pressure [SBP; mmHg], diastolic blood pressure [DBP, mmHg], heart rate [HR; beats per minute], respiratory rate [breaths per minute], body temperature [°C], pulse oximetry [%], weight [kg], and BMI [$kg/m^2$]) will be summarized using descriptive statistics by treatment group and visit (refer to Table 1). Change from baseline values will also be summarized similarly for each post-baseline scheduled visit.

Shift tables from baseline in SBP, DBP, heart rate, respiratory rate, and body temperature to each post-baseline assessment, describing shifts to abnormality (normal/abnormal, non-clinically significant/abnormal, clinically significant), will be provided as well by treatment group. The number of subjects with a non-missing result at both baseline and a specific post-baseline scheduled visit will be used as denominator for that post-baseline scheduled visit.

A listing of all vital sign assessments will be provided.

### 13.4 ECG

Electrocardiogram (ECG) parameters (HR [beats per minute], PR interval [msec], RR interval [msec], QRS duration [msec], QT interval [msec], and QTcF [msec]) will be summarized using descriptive statistics by treatment group and visit (refer to Table 1). Change from baseline values in each ECG test to each post-baseline scheduled visit by treatment group.

Number and percentage of subjects with a QTcF interval > 450 msec, > 480 msec, and > 500 msec as well as with a change from baseline in QTcF interval > 30 msec and > 60 msec will be provided by treatment group and visit.

Shift tables from baseline in ECG overall interpretation to each post-baseline scheduled visit, describing shifts to abnormality (normal/abnormal, non-clinically significant/abnormal, clinically significant), will be provided by treatment group. The number of subjects with a non-missing result at both baseline and a specific post-baseline scheduled visit will be used as denominator for that post-baseline scheduled visit.

A listing of all ECG assessments will be provided.

### 13.5 Physical Examination

Information for all physical examinations will be included in the source documents. Any significant change will be reported as an AE in the source document and eCRF.

## 14 PHARMACOKINETICS ANALYSIS

Observed plasma concentration data of RIST4721 will be summarized by visit for the RIST4721 treatment group based on the PK analysis set (refer to Section 4.5) using the following descriptive statistics: n, mean, SD, median, minimum, and maximum as well as the geometric mean, CV, and geometric CV. For computation of mean plasma concentrations, data that are below the limit of quantification (BLQ) will be set to zero.

Line plots of individual and mean plasma concentrations (+/- SD) over time will also be provided separately.

PK data will be listed.

# 15 REFERENCES

Barrett, A., Hahn-Pedersen, J., Kragh, N., Evans, E. and Gnanasakthy, A. (2019). "Patient-Reported Outcome Measures in Atopic Dermatitis and Chronic Hand Eczema in Adults." Patient 12(5): 445-459.

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Kimball, A. B., Jemec, G. B., Yang, M., Kageleiry, A., Signorovitch, J. E., Okun, M. M., et al. (2014). "Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment." Br J Dermatol 171(6): 1434-1442.

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Silverberg, J. I. (2021). "Validity and reliability of a novel numeric rating scale to measure skin-pain in adults with atopic dermatitis." Arch Dermatol Res.

Zouboulis, C. C., Tzellos, T., Kyrgidis, A., Jemec, G. B. E., Bechara, F. G., Giamarellos-Bourboulis, E. J., et al. (2017). "Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity." Br J Dermatol 177(5): 1401-1409.

# Appendix 1

## Abbreviated CSR - Table of Contents

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# Appendix 2

## Output Conventions

TLF*s* 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, reference listings and name of the program.

The mean, median, and quantiles will be displayed to one more decimal place than the original value; minimum and maximum will keep the same number of decimal places as the original value; standard deviation, standard error, and CI 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" while 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.

P-values from ≥ 0.001 to ≤ 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".

Listings will be ordered by treatment group, subject number, date, and visit (where applicable).

## Dates & Times Format

Date and time (when 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 400 mg QD | RIST4721 |
| Placebo QD | Placebo |

# Appendix 3

## 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 then 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 then 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 (and not flagged as "ongoing"): Impute to the last contact date.
- Missing day and month: Impute to December 31st, unless year is the same as last contact date then 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 then impute to the last contact date.

# Appendix 4

| Laboratory Testing | Tests Included |
|---|---|
| Hematology | aPTT, HCT, Hgb, INR, MCH, MCHC, MCV, MPV, PLT, prothrombin time, RBC, WBC, and differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils [relative and absolute]) |
| Serum chemistry | Albumin, alkaline phosphatase, ALT, AST, chloride, cholesterol (non-fasting), creatinine (enzymatic), GGT, glucose random, hs-CRP, LDH, potassium, sodium, total bilirubin, triglycerides, BUN, uric acid |
| Urinalysis | Dipstick and microscopic analysis |
| Urine pregnancy test | For WOCBP (at each visit, except screening) |
| Virology | • SARS-CoV-2 antigen test at each visit (except screening); if positive, will be confirmed by PCR test |
| Laboratory tests required at screening only | • FSH levels for females who have had a cessation of menses for at least 12 months without an alternative medical cause<br>• β-hCG (serum pregnancy test) for WOCBP (screening only)<br>• Tuberculosis test (PPD or QuantiFERON-TB Gold)<br>If done within 6 months and negative result is available for documentation, test is not required at screening<br>• Serology (HBV [HBsAg, anti-HBc], HCV, HIV)<br>• SARS-CoV-2 antibody test |
| Laboratory tests required at screening and baseline only | • Urine drugs of abuse: amphetamines, methamphetamines, barbiturates, cocaine, phencyclidine |

Abbreviations: ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; β-hCG, β-human chorionic gonadotropin; BUN, blood urea nitrogen; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl-transferase; HBsAg, hepatitis B surface antigens; HBV, hepatitis B virus; HCT, hematocrit; HCV, hepatitis C virus; Hgb, hemoglobin; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PCR, polymerase chain reaction; PLT, platelets; PPD, purified protein derivative; RBC, red blood cell; WBC, white blood cell; WOCBP, women of childbearing potential.