A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2A STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RIST4721 IN SUBJECTS WITH PALMOPLANTAR PUSTULOSIS

PROTOCOL RIST4721-201
EudraCT Number - 2018-004176-35

FINAL

VERSION 3.0_DE
22 March 2019

Sponsor:	Aristea Therapeutics, Inc. [redacted]
Sponsor Medical Expert:	[redacted]
Sponsor Signatory:	[redacted]
Medical Monitor:	[redacted]
Clinical Research Organization:	[redacted]

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PROTOCOL VERSION HISTORY

Version	Rationale for amendment	Main changes to the protocol
1.0 / 10 December 2018	Initial version	N/A
2.0 / 26 February 2019	[redacted]	• Synopsis and Section 5.1 (inclusion criterion 11)–The inclusion criterion 11 was updated to clarify that subjects must be capable of giving written informed consent, which must be personally signed and dated by the subject and obtained prior to any trial-related activities. • Synopsis and Section 5.2–An exclusion criterion was added to the list to clarify that subjects should be excluded from the study if, in the opinion of the investigator performing the initial examination, a subject should not participate in the trial (eg, due to probable noncompliance or inability to understand the nature, meaning, and consequences of the trial, and give adequately informed consent). • Section 1.2 (Table 1)–The superscript "h" in the last columns of Table 1 (Schedule of Events) was intended to clarify that the activities "Study drug collection" and "Subject dosing diary collection" are applicable to the early termination visit only, and should instead read "i". • Section 2.2.1–To substantiate the potential risks of RIST4721 and other risks that may emerge due to study-specific procedures. • Section 2.2.2–To detail that potential benefits of participating in the study may include fewer pustules, less pain, decreased redness and desquamation, smaller involved surface areas, and less functional impairment. • Section 2.2.3–To detail and discuss the potential risks and benefits of participation in study RIST4721-201.

	[redacted]	• Section 10.1–A reference to the German Drug Law (AMG) §40 and §41 was added to provide an example of the "applicable laws" referred to in Section 10.1. • Section 10.3–To provide clarification regarding the informed consent process and for alignment with the exclusion criterion 2 added to this amended version of the protocol. • Synopsis, Sections 1.2 (Table 1), and 4.1– To specify that subjects who consent to either biopsy or plasma concentration procedures must consent to both. • Synopsis and Section 4.1–To clarify that blood sample collection for plasma concentration analyses will be performed on approximately 20 subjects. These changes were applied to align with the footnote of Table 1 and with the number of subjects who will have biopsy sample collection. • Section 2.2.1–To specify that the Reference Safety Information for RIST4721 can be found in Section 6.1 of the Investigator Brochure.
3.0 / 22 March 2019	[redacted]	• Synopsis and Section 5.2—To exclude from the study subjects who have used strong systemic cytochrome P450 3A4/5 inhibitors or inducers within 4 weeks or 5 half-lives, whichever is longer, prior to baseline (Day –1). However, subjects who have used topical cytochrome P450 3A4/5 inducers or inhibitors with known limited systemic availability may be permitted. • Section 8.1.8 and Section 11—To add missing information to the description of psoriasis of Moderate severity, as per supportive reference. The citation of the corresponding reference was also updated in the reference list for alignment.

	[redacted]	• Section 5.3—To specify that subjects will be instructed to avoid food or beverages containing grapefruit within 7 days prior to Day –1 and during the study.

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with the protocol, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and applicable local regulations. The principal investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the institutional review board (IRB)/research ethics board (REB)/ethics committee (EC), except where necessary to eliminate an immediate hazard(s) to the trial subjects. All personnel involved in the conduct of this study have completed ICH GCP training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB/REB/EC for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/REB/EC before the changes are implemented to the study. All changes to the consent form will be IRB/REB/EC approved.

SIGNATURE PAGE

The signatures below constitute the approval of this protocol and the attachments and provide the necessary assurances that this trial will be conducted according to this protocol, applicable local regulations, the Declaration of Helsinki, and ICH GCP guidelines.

Sponsor:

[redacted]

[redacted]

Scientific Affairs:

Study Statistician:

[redacted]

PRINCIPAL/QUALIFIED INVESTIGATOR SIGNATURE PAGE

Investigator Name: _____

Signature: _____ **Date:** _____
(DD-MMM-YYYY)

Institution Name: _____

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is compliant with the protocol, informed consent, IRB/REB/EC independent ethics committee procedures, instructions from sponsor's representatives, the Declaration of Helsinki, ICH GCP guidelines, and applicable local regulations governing the conduct of clinical studies.

LIST OF ABBREVIATIONS

AE	adverse event
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
BSA	body surface area
BUN	blood urea nitrogen
CCR2b	chemokine motif receptor 2b
CONSORT	Consolidated Standards of Reporting Trials
CRO	contract research organization
CV	coefficient of variation
CXCR1	CXC chemokine receptor type 1
CXCR2	CXC chemokine receptor type 2
DLQI	Dermatology Life Quality Index
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ET	early termination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, throat
HEK293	human embryo kidney 293
Hgb	hemoglobin
HIV	human immunodeficiency virus
hs-CRP	high-sensitivity C-reactive protein
ICH	International Council for Harmonisation
IHC	immunohistochemistry
INR	international normalized ratio
IQR	interquartile range
IL	interleukin
IRB	institutional review board
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LMW	low molecular weight
LS	least squares
MAD	Multiple Ascending Dose

[redacted]	[redacted]
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMRM	mixed model repeated measures
MPV	mean platelet volume
MSU	monosodium urate
MTD	maximum tolerated dose
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamics
PLT	platelets
PASI	Psoriasis Area Severity Index
PGA	Physician Global Assessment
PPD	purified protein derivative
PPP	palmoplantar pustulosis
PPPASI	Palmoplantar Pustulosis Psoriasis Area and Severity Index
PPPASI-50	50% reduction in PPPASI
PPPASI-75	75% reduction in PPPASI
PPPGA	Palmoplantar Pustulosis Physician Global Assessment
PPSI	Palmoplantar Pustulosis Severity Index
PPSI-50	50% reduction in PPSI
PPSI-75	75% reduction in PPSI
PT	prothrombin time
PUVA	psoralen and ultraviolet A
QC	quality control
QD	once daily
QTcF	QT interval by Fredericia
RBC	red blood cell (count)
REB	research ethics board
RT-PCR	reverse transcription polymerase chain reaction
SAD	Single Ascending Dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UV-B	ultraviolet B
VAS	visual analog scale
WBC	white blood cell (count)
WHO-DD	World Health Organization-Drug Dictionary
WOCBP	women of childbearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Name of Sponsor/Company: Aristea Therapeutics, Inc.	**Name of Investigational Product:** RIST4721	**Name of Active Ingredient:** RIST4721

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Evaluate the Efficacy and Safety of RIST4721 in Subjects with Palmoplantar Pustulosis

Phase of Development:

Phase 2a

Study Center(s):

Approximately 10–16 study centers located in Canada and Germany will participate in this study.

Number of Subjects (planned):

Approximately 30 subjects will be included in this study.

Duration of Study:

The maximum study duration per subject is approximately 73 days, including up to 30 days for the screening period, one day for eligibility confirmation and randomization (Day –1), 28 days for the treatment phase, and 14 days for the follow-up period.

Study Drugs, Dosage, and Mode of Administration:

Subjects will be randomized to a 1:1 ratio at baseline (Day –1) to receive oral RIST4721 300 mg solution or placebo, once daily for 28 days.

Objectives:

Primary:

The primary objective is:

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

Secondary:

The secondary objective is:

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

Name of Sponsor/Company: Aristea Therapeutics, Inc.	**Name of Investigational Product:** RIST4721	**Name of Active Ingredient:** RIST4721

Exploratory:

The exploratory objectives are:

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

Endpoints:

Primary Efficacy Endpoints:

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

Secondary Efficacy Endpoints:

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

Secondary Safety Endpoints:

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

Exploratory Endpoints:

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

Name of Sponsor/Company: Aristea Therapeutics, Inc.	**Name of Investigational Product:** RIST4721	**Name of Active Ingredient:** RIST4721

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

Name of Sponsor/Company: Aristea Therapeutics, Inc.	**Name of Investigational Product:** RIST4721	**Name of Active Ingredient:** RIST4721

- Proportion of subjects achieving at least a 2-point decrease in PGA at Day 7, Day 14, Day 21, and Day 28
- Changes in skin biomarker levels
- Plasma concentration of RIST4721

Study Design:

Approximately 30 subjects with moderate to severe PPP, as defined by a PPPASI ≥8, a PPPGA ≥3, and a minimum of 8 fresh pustules (fresh pustule count on both right/left palms and soles) at screening and 20 fresh pustules (fresh pustule count on both right/left palms and soles) at Day –1, will be included in this 4-week, multicenter, randomized, double-blind, placebo controlled, Phase 2a study to evaluate the efficacy and safety of RIST4721.

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

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

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

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

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

Inclusion/Exclusion Criteria:

Inclusion criteria:

In order to be eligible to participate in this study, a subject must meet all of the following criteria at the screening and Day –1 visits, unless specified otherwise:

1. Male or female subject, aged 18–70 years at the time of consent.
2. Subject has at least a 6-month history of PPP as defined by the presence of pustules on palms and/or soles, but without evidence of infection on palms and soles (information obtained from medical chart or subject's physician, or directly from the subject).
3. Subject has moderate or severe PPP, as defined by PPPASI ≥8 and PPPGA ≥3 at Day –1, and a minimum of 8 fresh pustules at screening (fresh pustule count on both right/left palms and soles) and 20 fresh pustules at Day –1 (fresh pustule count on both right/left palms and soles).
4. Subject who wants to use an emollient should agree to use the same emollient, at the same frequency of application for 7 days before Day –1 and throughout the study. Note: However, on the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.
5. For female subject of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method, from at least 4 weeks before Day –1 until at least 4 weeks after the last study drug administration. Highly effective contraceptive methods include hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, male partner(s) vasectomy, tubal ligation, or a double-barrier method of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, and contraceptive sponge) in conjunction with spermicide.

   Note: Subjects who are on a hormonal contraceptive must have been on a stable dose for at least 4 weeks before Day –1.

   Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day –1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

   Note: For countries where double-barrier methods are not accepted as highly effective contraception, then this option must not be considered.

   Note: A female of nonchildbearing potential is defined as follows:

   - Female who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).
   - Female who has had a cessation of menses for at least 12 months without an alternative medical cause, and a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).
6. Female subject of childbearing potential has a negative serum pregnancy test at screening and negative urine pregnancy test at Day –1.
7. Female subject agrees to not have egg retrieval during the study and for 1 month after the last study drug administration.
8. Male subject agrees to use condom and spermicide from Day –1 until at least 3 months after the last study drug administration.

Name of Sponsor/Company: Aristea Therapeutics, Inc.	**Name of Investigational Product:** RIST4721	**Name of Active Ingredient:** RIST4721

9. Male subject agrees not to donate sperm during the study and for 3 months after the last study drug administration.
10. Subject has negative tuberculosis (TB) infection test. Subject will be evaluated for latent TB infection with a purified protein derivative (PPD) test or a QuantiFERON-TB Gold test, if one has not been performed in the last 6 months. Subjects who demonstrate evidence of latent TB infection (either PPD ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status) will not be allowed to participate in the study. Subjects with documented completed treatment for latent TB will be allowed to participate in the study without retesting.
11. Subject must be capable of giving written informed consent, which must be personally signed and dated by the subject and obtained prior to any trial-related activities.
12. Subject must be willing to comply with all study procedures and must be available for the duration of the study.

Exclusion criteria:

A subject who meets any of the following criteria at the screening and Day –1 visits, unless specified otherwise, will be excluded from participation in this study:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. In the opinion of the investigator performing the initial examination, the subject should not participate in the trial (eg, due to probable noncompliance or inability to understand the nature, meaning, and consequences of the trial, and give adequately informed consent).
3. Subject has evidence of erythrodermic, generalized pustular psoriasis, predominantly guttate psoriasis, or drug-induced psoriasis.
4. Subject has a history of skin disease or presence of skin condition (except psoriasis) that, in the opinion of the investigator, would interfere with the study assessments.
5. Subject has moderate to severe psoriasis, as defined by plaque psoriasis covering ≥10% of his/her total BSA at Day –1.
6. Subject is known to have immune deficiency or is immunocompromised.
7. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day –1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or successfully treated localized carcinoma in situ of the cervix are not to be excluded.
8. Subject had a major surgery within 8 weeks prior to Day –1 or has a major surgery planned during the study.
9. Subject has any clinically significant medical condition or ECG/physical/laboratory/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
10. Subject has positive results for hepatitis B surface antigens (HBsAg), antibodies to hepatitis B core antigens (anti-HBc), hepatitis C virus (HCV), or human immunodeficiency virus (HIV).

Name of Sponsor/Company: Aristea Therapeutics, Inc.	**Name of Investigational Product:** RIST4721	**Name of Active Ingredient:** RIST4721

11. Any clinically significant history of infection (except for localized herpes simplex) within 4 weeks prior to Day –1.
12. Subject has absolute neutrophil count <1.8 x 10^9/L at screening.
13. Subject has alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin values ≥2 times the upper limit of normal (ULN), or other clinical evidence of significant hepatic impairment (eg, ascites, peri-umbilical veins, oesophageal varices) at screening.
14. Subject has a history of clinically significant anemia or hemoglobin (Hgb) value ≤10 g/dL at screening.
15. Subject has a creatinine clearance ≤60 ml/min at screening (calculated with Modification of Diet in Renal Disease [MDRD] formula).
16. Subject has used any topical medication to treat PPP, including corticosteroids, retinoids, vitamin D analogues (such as calcipotriol), or tar, within 2 weeks prior to Day –1.
17. Subject has used topical dapsone within 2 weeks prior to Day –1.
18. Subject has used any systemic treatment for PPP, including corticosteroids, oral retinoids, biotin, immunosuppressive medication, methotrexate, cyclosporine, colchicine or apremilast, within 4 weeks prior to Day –1. Note: Intranasal corticosteroids and inhaled corticosteroids for stable medical conditions are allowed if subject has been on a stable dose for at least 4 weeks prior to Day –1 and will agree to maintain the same dose for the duration of the study. Eye drops containing corticosteroids are allowed.
19. Subject has used strong systemic cytochrome P450 3A4/5 inhibitors or inducers within 4 weeks or 5 half-lives, whichever is longer, prior to baseline (Day –1). Topical cytochrome P450 3A4/5 inducers or inhibitors with known limited systemic availability may be permitted.
20. Subject has received any ultraviolet B (UV-B) phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day –1.
21. Subject has had psoralen and ultraviolet A (PUVA) treatment within 4 weeks prior to Day –1.
22. Subject has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day –1.
23. Subject is currently receiving a nonbiological investigational product or investigational device or has received one within 4 weeks prior to Day –1.
24. Subject had excessive sun exposure or has used tanning booths within 4 weeks prior to Day –1, or subject is planning a trip where excessive sun exposure is expected or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided.
25. Subject has a known or suspected allergy to RIST4721 or any component of the study drug.
26. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day –1.
27. Close affiliation with the investigator (eg, a close relative), including any study staff of the sites or persons working at the CRO or subject is an employee of sponsor.

Name of Sponsor/Company: Aristea Therapeutics, Inc.	**Name of Investigational Product:** RIST4721	**Name of Active Ingredient:** RIST4721

28. Subject is institutionalized because of legal or regulatory order.
29. <u>For subjects consenting to biopsies only:</u>
    a. Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
    b. Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.
    c. Subject has taken anticoagulant medication, such as heparin, low molecular weight (LMW) heparin, warfarin, antiplatelets (except low-dose aspirin, which will be allowed), within 2 weeks prior to Day –1, or has a contraindication to skin biopsies. Nonsteroidal anti-inflammatory drugs (NSAIDs) will not be considered antiplatelets and will be allowed.

Statistical methods:

Continuous variables will be summarized in tables and will include the number of subjects, mean, standard deviation (SD), median, interquartile range (IQR), minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages. A statistical analysis plan (SAP) will provide additional details on the approach to the analysis and data displays.

Efficacy Analyses:

Efficacy analyses will be performed in all subjects who receive at least one dose of study drug, also referred to as the modified intent-to-treat (mITT) analysis set. All subjects will be analyzed according to the treatment group to which they were randomized.

Mixed model repeated measures (MMRM) analysis will be used for analyzing the relative change from baseline in continuous endpoints that are collected in a longitudinal fashion (fresh and total pustule count, PPPASI, PPPGA, PPSI, pain VAS, and DLQI). The natural log ratio of the post-dose values to baseline will be used as dependent variables in the analysis. The model will include fixed effects for treatment, visit and treatment-by-visit interaction, and natural log of baseline value as covariate. Unstructured covariance will be used to model the correlation. The treatment effect will be the contrast between treatment groups at specified visit(s) (eg, at Day 28) estimated through LS means. The LS mean estimates, associated two-sided 90% confidence intervals, and p-values will be reported. In this model, the estimates will be back-transformed to the ratio scale and presented as a percent change-from-baseline for ease of interpretation.

An analogous MMRM analysis will be used to analyze the absolute change from baseline. The response variable will be the absolute change from baseline at scheduled post-baseline visits and the baseline value as covariate.

For each post-dose study visit, a Fisher's exact test will be used to compare the proportion of subjects with a 50% or 75% reduction in fresh and total pustule count and the proportion of subjects achieving PPPASI-50 and PPPASI-75, for subjects treated with RIST4721 and subjects treated with placebo.

Statistical testing of the primary and secondary efficacy endpoints will be performed following a Gatekeeper strategy over endpoint families and Hochberg procedure within endpoint families. The endpoint families are comprised of the primary endpoints (relative change in fresh pustules and relative change in total pustules) and the secondary efficacy endpoints (absolute change from baseline in fresh pustules, absolute change in total pustules, achieving at least a 50% reduction in fresh pustules, and

Name of Sponsor/Company: Aristea Therapeutics, Inc.	**Name of Investigational Product:** RIST4721	**Name of Active Ingredient:** RIST4721

achieving at least a 50% reduction in total pustules). This procedure is expected to control the type 1 error rate at 2-sided $\alpha = 10\%$.

Safety Analyses:

The safety analysis set will be defined as all subjects who received at least one dose of study drug. Analysis will be done according to the actual treatment they received. Safety data will be summarized and presented descriptively by treatment group. Safety data, including AEs and serious adverse events (SAEs), laboratory assessments, vital signs, and ECGs will be presented and tabulated.

Plasma Concentration Analyses:

The plasma concentration analysis set will include all subjects who received at least one dose of study drug and have plasma concentration data. Plasma concentration data will be summarized based on nominal timepoints using descriptive statistics, such as mean, SD, median, IQR, minimum and maximum.

Pharmacodynamic Analyses:

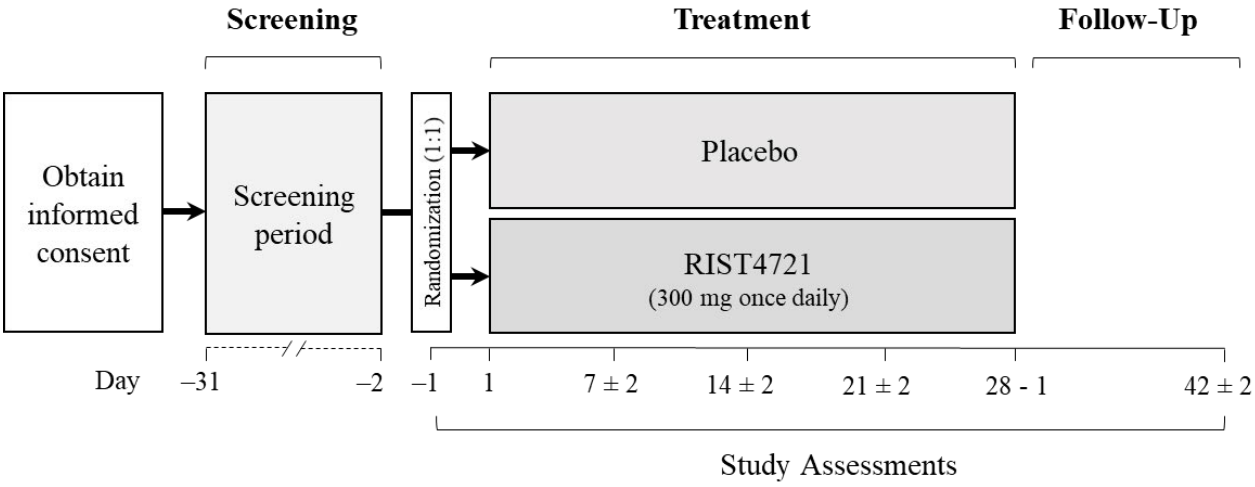
The pharmacodynamic (PD) analysis set will include all subjects who have at least one dose of study drug and who have an assessment of PD parameters. Expression levels in lesional and nonlesional PPP skin will be compared using RT-PCR, transcriptome profiling, and IHC data. A PD analysis plan will be prepared to detail the PD analyses. Results will be presented in a separate report.

Sample Size Consideration:

Approximately 30 subjects with moderate to severe PPP will be randomized 1:1 to receive placebo or RIST4721. A sample size of 30 (approximately 15 per group) will ensure 85% power to detect a statistically significant difference in the relative change from baseline in pustules counts at Day 28 with a 2-sided level of significance of 10%. This assumes a log-Normal distribution of the pustules counts, a 3-fold change (Placebo/RIST4721 at Day 28 relative to Baseline), and a coefficient of variation (CV) in the original scale of 150%. This sample size is expected to result in approximately 90% power if the CV is 130%.

1.2 Study Diagram

Figure 1: Study Diagram



1.3 Schedule of Events

The screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the informed consent form. No treatment or trial-related procedures will be initiated before the informed consent is signed. The Day –1 visit must be performed, at the latest, 30 days after the screening visit.

The screening evaluation will be performed according to the inclusion and exclusion criteria. If the subject fulfills all inclusion criteria and no exclusion criteria, he or she may be included in the study.

Table 1 provides a description of the procedures to be performed at each visit.

If assessments are scheduled for the same nominal time, then the assessments should occur in the following order:

- Vital signs
- 12-lead ECG
- Blood draws for plasma concentration analysis (time window vs administration is detailed in the footer of Table 1)

Table 1: Schedule of Events

		Treatment Period						Follow-Up
Study Visits	**Screening[a]**	**Day –1**	**Day 1**	**Day 7**	**Day 14**	**Day 21**	**Day 28**	**Day 42 or ET**
Window (days)	-31 to -2			±2	±2	±2	-1	±2
Informed consent	X							
Demographics	X							
Medical and surgical history	X	X						
Smoking status (never, former, or current)[b]	X	X		X	X	X	X	X
Inclusion-exclusion criteria	X	X						
Pregnancy test[c]	X	X		X	X	X	X	X
Clinical laboratory test (biochemistry, hematology, urinalysis), FSH[d]	X	X		X	X	X	X	X
Serology (HIV, HBV, HCV)	X							
Tuberculosis evaluation[e]	X							
Physical examination[f]	X	X			X		X	X
Vital signs[g]	X	X		X	X	X	X	X
Electrocardiogram	X	X					X	X
PPPASI	X	X		X	X	X	X	X
PPSI	X	X		X	X	X	X	X
PPPGA	X	X		X	X	X	X	X
Fresh pustule count	X	X		X	X	X	X	X
Total pustule count	X	X		X	X	X	X	X
PGA, excluding PPP lesions[h]	X	X		X	X	X	X	X
PASI, excluding PPP lesions[h]	X	X		X	X	X	X	X
BSA, excluding PPP lesions[h]	X	X		X	X	X	X	X
Pain VAS	X	X		X	X	X	X	X
DLQI		X		X	X	X	X	X
Randomization		X						
Study drug distribution		X		X	X	X		
Study drug collection				X	X	X	X	X[i]
Demonstration of study drug administration		X						

Study Visits	Screening[a]	Treatment Period						Follow-Up
		Day –1	Day 1	Day 7	Day 14	Day 21	Day 28	Day 42 or ET
Window (days)	-31 to -2			±2	±2	±2	-1	±2
Study drug administration daily			Day 1 X				Day 28 X	
Daily subject diary			Day 1 X				Day 28 X	
Phone call with subject[j]			X					
Subject dosing diary distribution/collection/review		X		X	X	X	X	X[i]
Medical photography[k]		X					X	X
Skin biopsy collection[l]		X					X	
Blood sampling for RIST4721 concentration[m]				X		X		
Suture removal, if applicable[n]					X			X
Concomitant medication	X	X		X	X	X	X	X
Adverse events evaluation	X	X		X	X	X	X	X

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

[a]All screening results will be seen and analyzed by the treating investigator prior to randomization and first study drug administration.

[b]For current smokers, the daily consumption of cigarettes, cigars, and other products will be recorded.

[c]Females of childbearing potential only. Serum pregnancy test at screening, and urine pregnancy test at other visits.

[d]FSH at screening only, for females of nonchildbearing potential who had a cessation of menses for at least 12 months without an alternative medical cause.

[e]If PPD is used, a second visit will be necessary for PPD reading only.

[f]Complete physical examination will be performed at screening, Day –1, Day 28, and Day 42 (follow-up) or ET, and brief physical examinations will be performed at Day 14. A symptom-oriented physical examination may be performed during the study, if judged necessary by the investigator.

[g]Including height measured at screening, and weight measured at screening and at Day 42 (follow-up) or ET.

[h]Only performed on subjects with psoriasis.

[i]Applicable to ET visit only.

[j]Study team will follow up with the subject to address any concern and ensure that dosing at Day 1 did not pose a problem.

[k]Performed on a subgroup of approximately 15 subjects at selected sites.

[l]Performed on a subgroup of approximately 20 subjects consenting to the procedure. These subjects must also consent to blood draws for plasma concentration analyses. Biopsies will be collected on Day -1 and Day 28 (after all other assessments).

[m]Performed on a subgroup of approximately 20 subjects consenting to the procedure. These subjects must also consent to skin biopsy collection. Blood samples will be collected within 1 hour prior to dosing (pre-dose) and 1 hour ±10 minutes and 2 hours ±10 minutes post-dose on Days 7 and 21. The time of last meal prior to dosing will be recorded on Days 7 and 21.

[n]Within 10 to 16 days after biopsies collection, if applicable.

2 INTRODUCTION

2.1 Background

2.1.1 Palmoplantar Pustulosis

Palmoplantar pustulosis (PPP) is a chronic inflammatory skin condition characterized by sterile pustules with erythema, hyperkeratosis, and scaling on the palms and soles.[1,2] A number of reports suggest that PPP represents a distinct entity because of its unique genetic and molecular features.[2-4] While few studies have investigated the characteristics, disease burden, and risk factors associated with PPP, results indicate that PPP has a mean age at disease onset of 41.6 years and is more commonly diagnosed in females than males.[4] Reports also indicate that the disease tends to affect more frequently the thenar, hypothenar, and central areas of the palms, as well as the corresponding areas of the soles, although pustular lesions may also extend to the subject's wrists and heels.[2] The clinical manifestations of PPP make it a debilitating condition that puts the afflicted subjects at risk of social stigmatism and reduced quality of life.[5]

While several factors have been shown to induce PPP, such as infections, trauma, stress, and various therapeutic agents, the disease pathophysiology remains poorly understood.[2] Recent studies have begun to highlight the importance of the innate immune system and cytokines in the development of PPP.[2] In support of these hypotheses, neutrophils were found in high numbers in the epidermis of subjects with PPP, with focal accumulations observed at the level of pustules.[6] In addition, high levels of neutrophil-recruiting chemokines, including interleukins 1 (IL-1) and 8 (IL-8), were measured in PPP lesions.[3,7]

The CXC chemokine receptor type 2 (CXCR2) plays important roles in various acute and chronic inflammatory processes.[8,9] CXCR2 serves as a receptor for a number of cytokines, including IL-8 and is required for neutrophil egress from the bone marrow and recruitment to distant inflammatory sites.[10,11] Given the role of neutrophils in inflammation, the blockade of CXCR2 may represent a novel therapeutic approach for the treatment of neutrophil-mediated inflammatory disorders, such as PPP.[11]

2.1.2 RIST4721

RIST4721 is a small-molecule CXCR2 antagonist that is proposed to have potential as a novel oral treatment for inflammatory diseases, including PPP. RIST4721 is a high-potency antagonist of human CXCR2, as validated in vitro by measuring both primary binding affinity in human embryo kidney 293 (HEK293) cells transfected with recombinant CXCR2 (whole cells and membranes) and functional end points in isolated peripheral polymorphonuclear cells and human blood neutrophils. In test systems evaluating RIST4721 selectivity to a number of related receptors, RIST4721 demonstrated a 150- and 90-fold greater selectivity for CXCR2 than CXC chemokine receptor type 1 (CXCR1) and chemokine motif receptor 2b (CCR2b), respectively.[12]

The in vitro evaluation of RIST4721 as a high potency CXCR2 antagonist translated well in vivo in 4 studies with a rat air pouch model of monosodium urate (MSU) crystal-induced arthropathy.

When the rats were challenged with MSU injection, significant, dose-dependent decreases in exudate volume, total white blood cell (WBC) count, and neutrophil infiltration were seen with RIST4721 at doses 30, 100, and 300 μmol/kg.

Taken together, the data from both in vitro (cell line) and in vivo animal studies with RIST4721 provide a rationale for its evaluation for the treatment of neutrophil-mediated inflammatory disorders, such as PPP.

2.1.3 Study Rationale

There are currently no treatments approved for PPP.[4] Off-label topical therapy typically involves corticosteroids with or without occlusion. Other topical agents used for the treatment of PPP include calcipotriene, PUVA, and tacrolimus.[2] However, topical agents often have limited efficacy in PPP, in part due to the lower relative absorptive capacity of the palms and soles compared to other body areas.[13,14]

Off-label systemic treatment options for PPP may involve the use of acitretin, cyclosporine, colchicine, and biologic agents, such tumor necrosis factor alpha, IL-23, and IL-17 antagonists.[2] These treatments have limited efficacy and can be associated with significant side effects. The lack of approved targeted treatments for PPP warrant development of a more efficacious option.

RIST4721 is an investigational small molecule targeting CXCR2. CXCR2 plays important roles in neutrophil recruitment to inflammatory sites and represents a promising therapeutic target for the treatment of neutrophil-mediated inflammatory diseases. The utility of antagonizing CXCR2 was formerly investigated with the use of neutralizing antibodies targeting IL-8, one of several CXCR2 ligands.[15,16] This study revealed that inhibition of the IL-8/CXCR2 axis causes clinically relevant reductions in disease activity in PPP subjects.[15]

In the present study, the efficacy and safety of RIST4721 will be evaluated in subjects with moderate to severe PPP.

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

The safety of RIST4721 was assessed in a 2-part, Phase 1 study. The first part was a single-blind, placebo-controlled, single-ascending dose study with 38 healthy male subjects. Dose escalation continued through all planned doses (19 mg, 50 mg, 150 mg, 350 mg, and 730 mg). The second part was an open-label, randomized, 2-way crossover relative bioavailability study comparing a single 500 mg dose of orally-administered RIST4721 in suspension to a single 500 mg dose of orally-administered RIST4721 in solution, conducted in 6 healthy male subjects. The results revealed that RIST4721 is generally well tolerated in single ascending doses, up to 730 mg. No safety or tolerability concerns were identified. All AEs resolved, and most were considered to be mild. There were no clinically significant abnormal clinical laboratory or vital signs results, other than the expected reduction in blood neutrophils. Digital ECG and telemetry data revealed no

abnormal variations in QT interval by Fredericia (QTcF) values and no trends in mean heart rate, QRS, QTcF, or PR intervals in the RIST4721 or placebo groups. No concomitant medication use or abnormal physical examination findings were reported.[12]

The safety of RIST4721 was also assessed in a multiple ascending dose study conducted in 27 healthy male subjects. RIST4721 was safe and well tolerated in multiple ascending doses (75 mg, 225 mg and 500 mg once daily [QD]) for 10 days. Nine of the eighteen subjects dosed with RIST4721 reported ≥1 AE, with the most commonly reported AEs being headache and urine odor abnormal (n=3 each). No deaths, SAEs, or discontinuation of the study drug were reported, and no safety concerns were identified. Treatment with RIST4721 did not lead to clinically significant abnormal laboratory results, vital signs, or 12-lead ECG measurements, other than the expected reduction in blood neutrophils.[12]

Reductions in blood neutrophil counts have been seen in humans on treatment with other CXCR2 antagonists, including SCH527123 and SB656933.[17,18] These reductions had a rapid onset, but resolved within a few days of treatment discontinuation, suggesting redistribution rather than destruction or failure of production of neutrophils. Consistently, in two Phase 1 studies investigating the safety and tolerability of RIST4721 in healthy subjects, CXCR2 antagonism reduced absolute neutrophil counts. In both studies, this effect resolved in the off-drug follow-up period.[12]

No allergic reactions were seen in human clinical studies conducted with RIST4721; however, as with any medication, there may still be risks or side effects that are unforeseeable and not known at this time. Symptoms of an allergic reaction includes hives, or swelling of the face, lips, tongue and/or throat, which may cause difficulty in breathing or swallowing. This could become life-threatening if it is not treated promptly. Allergic reactions may also be associated with local skin anesthesia utilized in the optional biopsy procedure.

As the potential risks of RIST4721 to an unborn fetus are currently unknown, women of childbearing potential must agree to use appropriate contraceptive methods as outlined in Section 5.1 Inclusion Criteria.

There are several potential risks to participating in study-related procedures. Serious side effects from a skin biopsy are rare but may include scarring, infection, tenosynovitis, or nerve damage. Plasma concentration blood draws may induce discomfort, bruising, swelling and, in rare instances, infection at the site of the needle. In rare cases, a nerve may be hit, which may cause pain and temporary tingling in the arm or very rarely permanent nerve damage. Although rare, skin irritation is possible after an ECG from the electrodes or gel. Tuberculosis screens may result in tenderness, swelling or a rash at the site of the injections.

Further information related to nonclinical and clinical studies is available in the Investigator Brochure. The Reference Safety Information for RIST4721 can be found in Section 6.1 of the Investigator Brochure.

2.2.2 Known Potential Benefits

It is anticipated that subjects randomized to the active study drug will see an improvement in their PPP condition as a result of participating in this Phase 2a study. Specifically, potential benefits may include fewer pustules, less pain, decreased redness and desquamation, smaller involved surface areas, and less functional impairment.

It is also anticipated that transcriptional profiling analyses performed on RIST4721- and placebo-treated PPP lesions may help deepen our knowledge of the disease and expand our understanding of RIST4721-mediated effects on PPP.

Participation in this study may help generate future benefit for larger groups of subjects with PPP if RIST4721 proves to be successful in treating this condition.

2.2.3 Assessment of Risks and Benefits

While there are potential risks associated with the study drug and the study procedures for this Phase 2 clinical study, the risk is expected to be minimal. All AEs from previous clinical studies were reported as mild or moderate in severity and there were no reported SAEs. The main safety consideration for the current study is the expected, mechanism of action-mediated reduction in peripheral blood neutrophils, which is to be closely monitored via the procedure outlined in Figure 3.

Against these minimal risks stands the benefit of information on the safety and efficacy of a promising new substance, which is intended to be used in the treatment of PPP. Despite these potential risks, it is expected that subjects randomized to RIST4721 might see an improvement in their PPP condition, such as fewer pustules, less pain, decreased redness and desquamation, smaller involved surface areas, and less functional impairment. As there are currently no approved therapies for PPP, RIST4721 has the potential to improve subjects' quality of life and daily functional mobility. Due to the range of exploratory endpoints, participation in this study will also provide useful information about the PPP disease course and correlated quality of life for subjects. This may inform future studies of RIST4721 in PPP, with the ultimate goal of providing much needed treatment to patients that today do not have effective alternative treatment options.

All quality, pharmacology and toxicology data, and satisfactory safety and tolerability results demonstrated in clinical and nonclinical studies are considered sufficient to expect a positive benefit/risk ratio for the treatment of PPP with RIST4721, and therefore to initiate this study.

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, proper study design, and close monitoring.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives

Primary:

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

Secondary:

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

Exploratory:

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

3.2 Endpoints

Primary Efficacy Endpoints:

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

Secondary Efficacy Endpoints:

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

Secondary Safety Endpoints:

- Incidence of TEAEs
- Changes in vital signs, ECG, and laboratory tests

Exploratory Endpoints:

- Absolute change from baseline in fresh pustule count at Day 7, Day 14, and Day 21
- Relative change from baseline in fresh pustule count at Day 7, Day 14, and Day 21
- Absolute change from baseline in total pustule count at Day 7, Day 14, and Day 21
- Relative change from baseline in total pustule count at Day 7, Day 14, and Day 21

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

- Proportion of subjects achieving a PGA of clear (0) or almost clear (1) at Day 7, Day 14, Day 21, and Day 28
- Proportion of subjects achieving at least a 2-point decrease in PGA at Day 7, Day 14, Day 21, and Day 28
- Changes in skin biomarker levels
- Plasma concentration of RIST4721

4 STUDY DESIGN

4.1 Overall Design

Approximately 30 subjects with moderate to severe PPP, as defined by a PPPASI ≥8, a PPPGA ≥3, and a minimum of 8 fresh pustules (fresh pustule count on both right/left palms and soles) at screening and 20 fresh pustules (fresh pustule count on both right/left palms and soles) at Day –1, will be included in this 4-week, multicenter, randomized, double-blind, placebo-controlled, Phase 2a study to evaluate the efficacy and safety of RIST4721.

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

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

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

A total of three 4.5-mm skin biopsies will be collected from a subgroup of approximately 20 subjects who consent to the procedure for RT-PCR, transcriptome profiling, and IHC. Two skin biopsies will be taken at Day –1 (1 from lesional skin and 1 from adjacent nonlesional skin, either from palm or sole), and one biopsy will be taken at Day 28 from lesional skin, preferably from the same anatomical region as for biopsies collected on Day –1. Skin biopsy samples will be obtained from the same subjects who consent to blood sample collection for plasma concentration analyses.

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

4.2 Scientific Rationale for Study Design

The proposed design is considered appropriate for assessing the efficacy, safety, and plasma concentration of RIST4721 compared to placebo in subjects with moderate to severe PPP.

This Phase 2a study is an intervention-based study. To provide the highest possible evidence of causation, this study will have a randomized, double-blind, placebo-controlled study design, the gold standard approach for intervention-based trials. The study will be randomized and double blind to ensure a random allocation of subjects to each treatment arm and minimize bias introduced by known and unknown confounding factors. In addition, the study will be placebo controlled to establish a cause-effect relationship between treatment and outcome, and differentiate any uncovered relationship from the act of treating the condition.[19]

4.3 Justification for Dose

RIST4721 has been tested in Phase 1 Single Ascending Dose (SAD) and Multiple Ascending Dose (MAD) studies and has been shown to have an acceptable safety and tolerability profile. To date, RIST4721 has not been tested in PPP patients. As this is a proof-of-concept study designed to assess the safety and efficacy of RIST4721 in adult subjects with moderate to severe PPP, the goal is to maximize potential efficacy by testing the highest dose that is expected to be safe and tolerable in humans based on existing animal toxicology and human safety and tolerability data.

RIST4721 has been tested and yielded an acceptable toxicological profile in animal toxicology studies of up to 28 days duration, which supports the 28-day dosing regimen for this clinical study. There are, however, no validated animal models of PPP. The anti-inflammatory potency of RIST4721 has been evaluated in 4 studies in a rat air pouch MSU crystal-induced arthropathy with significant, dose-dependent decreases in exudate volume, total WBC count, and neutrophil infiltration being observed, which provides support for the evaluation of RIST4721 in inflammatory conditions. It is, however, challenging to extrapolate the doses used in these animal studies to PPP disease and patients.

The results of the two Phase 1 clinical studies investigating the safety and tolerability of RIST4721 in 64 healthy human male subjects show that RIST4721 was generally safe and well tolerated in single ascending doses, up to 730 mg and multiple ascending doses, up to 500 mg for 10 days.

In the first study, where subjects received a single dose of RIST4721 between 19 and 730 mg, no safety or tolerability concerns were identified. A similar proportion of subjects reported AEs across all RIST4721 dose groups and placebo. The AEs were mostly considered to be mild and all the AEs resolved by the end of the study. No deaths, SAEs or AEs that led to subjects discontinuing from the study were reported. A number of subjects who received RIST4721 showed temporary reductions of peripheral blood neutrophils, as expected, based on the mechanism of action. All

neutrophil reductions returned to normal by the end of the study and no serious infections were noted.

In the second study, where subjects received 10 daily doses of RIST4721 at either 75 mg, 225 mg or 500 mg, no safety or tolerability concerns were identified. A similar proportion of subjects reported AEs across all RIST4721 dose groups and placebo. The AEs were mostly considered to be mild and all but 2 of the AEs resolved by the end of the study. No deaths, SAEs or AEs that led to subjects discontinuing from the study were reported. RIST4721 dosed QD for 10 days reduced absolute peripheral blood neutrophil counts, as expected, based on mechanism of action, with the largest effect observed at the 500 mg dose level. Seven subjects had mild reductions in neutrophil counts at the end of the study, but these all resolved in the off-drug, follow-up period. None of these reductions were reported as AEs and no serious infections were noted.

The main safety consideration for the current study is the expected, mechanism of action-mediated reduction in peripheral blood neutrophils. Modelling of the data from the SAD and MAD studies suggests that, within a 95% confidence interval, patients dosed QD with RIST4721 at 300 mg are not expected to experience peripheral blood neutrophil counts of $<1.0 \times 10^9$/L.

In summary, based on the existing animal toxicology data and human experience from Phase 1 SAD and MAD studies, a 300-mg once-daily dose of RIST4721 is expected to be safe, tolerable, and unlikely to result in clinically significant neutropenia whilst providing the best opportunity to establish the efficacy of RIST4721 in PPP patients.

4.4 End of Study Definition

A subject is considered to have completed the study if he or she has completed all phases of the study, including the last visit or the last scheduled procedure shown in the Schedule of Events, Table 1. For subjects undergoing the early termination visit, their study participation is considered completed when the early termination assessments are completed and they are no longer being examined.

The end of the study is defined as completion of the last visit or procedure shown in the schedule of events for the last enrolled subject in the trial globally for all sites.

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria at the screening and Day –1 visits, unless specified otherwise:

1. Male or female subject, aged 18–70 years at the time of consent.
2. Subject has at least a 6-month history of PPP as defined by the presence of pustules on palms and/or soles, but without evidence of infection on palms and soles (information obtained from medical chart or subject's physician, or directly from the subject).

3. Subject has moderate or severe PPP, as defined by PPPASI ≥8 and PPPGA ≥3 at Day –1, and a minimum of 8 fresh pustules at screening (fresh pustule count on both right/left palms and soles) and 20 fresh pustules at Day –1 (fresh pustule count on both right/left palms and soles).
4. Subject who wants to use an emollient should agree to use the same emollient, at the same frequency of application for 7 days before Day –1 and throughout the study. Note: However, on the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.
5. For female subject of childbearing potential involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method, from at least 4 weeks before Day –1 until at least 4 weeks after the last study drug administration. Highly effective contraceptive methods include hormonal contraceptives (combined oral contraceptive, patch, vaginal ring, injectable, or implant), intrauterine devices or intrauterine systems, male partner(s) vasectomy, tubal ligation, or a double-barrier method of contraception (barrier methods include male condom, female condom, cervical cap, diaphragm, and contraceptive sponge) in conjunction with spermicide.

   Note: Subjects who are on hormonal contraceptive must have been on a stable dose for at least 4 weeks before Day –1.

   Note: The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day –1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.

   Note: For countries where double-barrier methods are not accepted as highly effective contraception, then this option must not be considered.

   Note: A female of nonchildbearing potential is defined as follows:

   - Female who has had surgical sterilization (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy).
   - Female who has had a cessation of menses for at least 12 months without an alternative medical cause, and a FSH test confirming nonchildbearing potential (refer to laboratory reference ranges for confirmatory levels).
6. Female subject of childbearing potential has a negative serum pregnancy test at screening and negative urine pregnancy test at Day –1.
7. Female subject agrees to not have egg retrieval during the study and for 1 month after the last study drug administration.
8. Male subject agrees to use condom and spermicide from Day –1 until at least 3 months after the last study drug administration.
9. Male subject agrees not to donate sperm during the study and for 3 months after the last study drug administration.

10. Subject has negative TB infection test. Subject will be evaluated for latent TB infection with a PPD test or a QuantiFERON-TB Gold test, if one has not been performed in the last 6 months. Subjects who demonstrate evidence of latent TB infection (either PPD ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status) will not be allowed to participate in the study. Subjects with documented completed treatment for latent TB will be allowed to participate in the study without retesting.
11. Subject must be capable of giving written informed consent, which must be personally signed and dated by the subject and obtained prior to any trial-related activities.
12. Subject must be willing to comply with all study procedures and must be available for the duration of the study.

5.2 Exclusion Criteria

A subject who meets any of the following criteria at the screening and Day –1 visits, unless specified otherwise, will be excluded from participation in this study:

1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. In the opinion of the investigator performing the initial examination, the subject should not participate in the trial (eg, due to probable noncompliance or inability to understand nature, meaning, and consequences of the trial, and give adequately informed consent).
3. Subject has evidence of erythrodermic, generalized pustular psoriasis, predominantly guttate psoriasis, or drug-induced psoriasis.
4. Subject has a history of skin disease or presence of skin condition (except psoriasis) that, in the opinion of the investigator, would interfere with the study assessments.
5. Subject has moderate to severe psoriasis, as defined by plaque psoriasis covering ≥10% of his/her total BSA at Day –1.
6. Subject is known to have immune deficiency or is immunocompromised.
7. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day –1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or successfully treated localized carcinoma in situ of the cervix are not to be excluded.
8. Subject had a major surgery within 8 weeks prior to Day –1 or has a major surgery planned during the study.
9. Subject has any clinically significant medical condition or ECG/physical/laboratory/vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
10. Subject has positive results for HBsAg, antibodies to anti-HBc, HCV, or HIV.
11. Any clinically significant history of infection (except for localized herpes simplex) within 4 weeks prior to Day –1.

12. Subject has absolute neutrophil count <1.8 x 10^9/L at screening.
13. Subject has ALT, AST or total bilirubin values ≥2 times the ULN, or other clinical evidence of significant hepatic impairment (eg, ascites, peri-umbilical veins, oesophageal varices) at screening.
14. Subject has a history of clinically significant anemia or Hgb value ≤10 g/dL at screening.
15. Subject has a creatinine clearance ≤60 ml/min at screening (calculated with MDRD formula).
16. Subject has used any topical medication to treat PPP, including corticosteroids, retinoids, vitamin D analogues (such as calcipotriol), or tar within 2 weeks prior to Day –1.
17. Subject has used topical dapsone within 2 weeks prior to Day –1.
18. Subject has used any systemic treatment for PPP, including corticosteroids, oral retinoids, biotin, immunosuppressive medication, methotrexate, cyclosporine, colchicine or apremilast, within 4 weeks prior to Day –1. Note: Intranasal corticosteroids and inhaled corticosteroids for stable medical conditions are allowed if subject has been on a stable dose for at least 4 weeks prior to Day –1 and will agree to maintain the same dose for the duration of the study. Eye drops containing corticosteroids are allowed.
19. Subject has used strong systemic cytochrome P450 3A4/5 inhibitors or inducers within 4 weeks or 5 half-lives, whichever is longer, prior to baseline (Day –1) (topical cytochrome P450 3A4/5 inducers or inhibitors with known limited systemic availability may be permitted). Examples of strong systemic cytochrome P450 3A4/5 inhibitors or inducers are provided in Table 3.
20. Subject has received any UV-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day –1.
21. Subject has had PUVA treatment within 4 weeks prior to Day –1.
22. Subject has received any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day –1.
23. Subject is currently receiving a nonbiological investigational product or investigational device or has received one within 4 weeks prior to Day –1.
24. Subject had excessive sun exposure or has used tanning booths within 4 weeks prior to Day –1, or subject is planning a trip where excessive sun exposure is expected, or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products and protective apparel are recommended when exposure cannot be avoided.
25. Subject has a known or suspected allergy to RIST4721 or any component of the study drug.
26. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day –1.
27. Close affiliation with the investigator (eg, a close relative), including any study staff of the sites or persons working at the CRO or subject is an employee of sponsor.
28. Subject is institutionalized because of legal or regulatory order.

29. For subjects consenting to biopsies only:
    - Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
    - Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.
    - Subject has taken anticoagulant medication, such as heparin, LMW heparin, warfarin, antiplatelets (except low-dose aspirin, which will be allowed), within 2 weeks prior to Day –1, or has a contraindication to skin biopsies. NSAIDs will not be considered antiplatelets and will be allowed.

5.3 Lifestyle Considerations

Subjects will be instructed to avoid food or beverages containing grapefruit within 7 days prior to Day –1 and during the study.

5.4 Screen Failures

Screen failures are defined as individuals who consent to participate in the clinical trial but are not subsequently randomly assigned to the study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any AEs and SAEs.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened, if deemed acceptable by the investigator. Rescreened subjects should be assigned a different subject number than the initial screening. All procedures planned at the screening visit, including signature of a new consent form, will be performed.

6 TREATMENT

6.1 Study Treatment Administered

This study involves a comparison of RIST4721 300 mg solution administered orally, once daily with placebo. All study drugs will be provided by the sponsor.

On Day –1, the clinical study team will instruct the subject how to administer the study drug. On all other study days between Days 1 and 28, subjects will be instructed to self-administer the study drug daily at home at approximately the same time. Study staff will call the subjects on Day 1 to make sure that the first study drug administration occurred as planned. On Day 7 and Day 21, the study drug product will be taken at the site only for subjects who will undergo blood sample collection for plasma concentration analyses. The date and time of drug administration will be collected via a diary provided to the subject or by the study staff on days of plasma concentration sample collection.

Further details regarding the study drugs can be found in Table 2.

Table 2: Study Treatments

	Study Treatments	
Product name	RIST4721	Placebo
Dosage form	Solution	Solution
Unit dose strength(s)/Dosage level(s)	300 mg	N/A
Route of Administration	Oral	Oral
Dosing instructions	Once daily	Once daily
Physical description	Glass vial	Glass vial
Source of procurement	Aristea Therapeutics, Inc.	Aristea Therapeutics, Inc.

Abbreviation: N/A, not applicable.

The contents of the label will be in accordance with all applicable regulatory requirements.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Preparation/Storage/Handling

All study drugs must be stored in a secure environmentally-controlled and monitored area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff. The study drugs may only be supplied by authorized site staff and may only be given to subjects enrolled into the study.

Study drugs will be dispensed by the study site to the subject at the visits specified in Table 1. Subjects are to return all study drugs (used and unused) to the study site. The vials will be counted prior to dispensing and upon return, and the counts will be recorded in the source documents and electronic case report form (eCRF). Each subject will be instructed on the importance of returning study drug at the next study visit and on taking the product as prescribed. If a subject does not return study drug, he or she will be instructed to return it as soon as possible.

More details on the administration methods are described in the study manual.

6.2.2 Accountability

The investigator is responsible for maintaining accurate records of the study drug received initially and of the study drug dispensed/used. At the conclusion of the study, all used and unused investigational products and all medication containers will be returned to the sponsor unless other arrangements have been approved. Any study drug accidentally or deliberately destroyed or returned to the sponsor or designee will be accounted for. Any discrepancies between amounts dispensed and returned will be explained.

All study drug accountability forms and treatment logs must be retained in the investigator's study files. Product inventory and accountability records will be maintained as per ICH GCP. These records must be available for inspection at any time by the sponsor, its designees, or by regulatory agencies.

Further guidance and information for final disposition of study drug are provided in the study manual.

6.3 Randomization

At the 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 will contain the site number and the subject number and will be assigned in numerical order at the screening visit based on chronological order of screening dates (eg, 02-010 for the 10th subject screened at Site #02).

Approximately 30 subjects will be randomized (1:1) to receive RIST4721 or placebo.

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

Further guidance and information can be obtained in the study manual.

6.3.1 Blinding

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

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

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

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

Absolute and relative neutrophil and WBC count results will be disclosed to the respective investigators if absolute neutrophil counts reach values $<1.8 \times 10^9$/L, in which case immediate actions will be taken, as described in Figure 3. Retest results will be communicated to the investigators who will follow up on neutropenia and the incidence of infections with patients having absolute neutrophil count results $<1.0 \times 10^9$/L. Neutropenia will be followed up through resolution. Absolute and relative neutrophil and WBC count results will also be disclosed if the values are higher than the ULN.

6.3.2 Study Treatment Compliance

Study treatment compliance will be monitored at each visit. Adherence to treatment will be assessed by direct questioning, review of the subject's dosing diary, and by maintaining adequate study drug dispensing and return records. Any deviation from the prescribed dosage regimen will be recorded in the source document and eCRF.

Subjects who are significantly noncompliant with treatment will be counseled and could be discontinued from the study, at the discretion of the investigator, following consultation with the sponsor. A subject will also be considered significantly noncompliant if he or she intentionally or repeatedly takes more or less than the prescribed amount of study drug, as judged by the investigator.

6.4 Concomitant Therapy

All medications, including over-the-counter drugs, vitamins, herbal/natural products, and antacids taken within 4 weeks prior to screening and throughout the study must be recorded. In addition, the use of any prohibited medications within the prespecified timeframe described in the exclusion criteria should be documented.

Medication entries may be captured as generic or trade names. Trade names should be used for combination drugs. Entries should include as much as possible of the following information: the dose, unit, frequency of administration, route of administration, start date, end date, and indication. If the medication is stopped or the dosage is changed, these details must be recorded.

6.4.1 Permitted Therapies

6.4.1.1 Emollients

Subjects can apply an emollient of their choice (except those containing salicylic acid) on their skin, **including PPP lesions**. Subjects who want to use an emollient should use the same emollient, at the same frequency of application for 7 days before baseline and throughout the study. However, on the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.

6.4.1.2 Other Permitted Therapies

The following therapies are permitted:

- Intranasal corticosteroids and inhaled corticosteroids for stable medical conditions are allowed. Eye drops containing corticosteroids are allowed.
- Hydrocortisone and desonide are allowed for psoriasis located on the face, genitals, groin, and inframammary areas as long as they are applied with gloves.
- Shampoos containing tar, salicylic acid, or zinc pyrithione are also allowed, but they must be applied with gloves.
- Use of sunscreen products and protective apparel are permitted when sun exposure cannot be avoided.

6.4.2 Prohibited Therapies or Procedures

Table 3 lists prohibited medications that are not to be used from the defined washout periods before the baseline visit at Day –1 visit through the last study visit.

Subjects who start prohibited medications or therapies as a treatment for PPP or other reasons during the study may be withdrawn from study treatment. If in any doubt, investigators are advised to discuss medications with the medical monitor.

Table 3: Prohibited Therapies or Procedures

Prohibited medications, products, and procedures	Washout period prior to baseline (Day –1)
Any marketed or investigational biological agent	12 weeks or 5 half-lives (whichever is longer)

Prohibited medications, products, and procedures	Washout period prior to baseline (Day –1)
Strong systemic cytochrome P450 3A4/5 inhibitors or inducers, including but not limited to voriconazole, conivaptan, itroconazole, posaconazole, ketoconazole, carbamazepine, rifampin, phenytoin, and St. John's Wort	4 weeks or 5 half-lives (whichever is longer)
Nonbiological investigational product or device	4 weeks
Systemic treatment to treat PPP, including corticosteroids, oral retinoids, biotin, immunosuppressive medication, methotrexate, cyclosporine, colchicine or apremilast	4 weeks
PUVA treatment, UV-B phototherapy (including tanning beds) or excimer laser, excessive sun exposure or has used tanning booths	4 weeks
Topical medication to treat PPP, including corticosteroids, retinoids, vitamin D analogues (calcipotriol), and tar	2 weeks
Topical dapsone	2 weeks

Abbreviations: PPP, palmoplantar pustulosis; PUVA, psoralen and ultraviolet A; UV-B, ultraviolet B.

Subjects who have used anticoagulant medication, such as heparin, LMW heparin, warfarin, antiplatelets (except low-dose aspirin and NSAIDs) within the specified time period, as per exclusion criteria, will not participate in biopsy collection.

7 DISCONTINUATION AND LOST TO FOLLOW-UP

Subjects have the right to withdraw from the study at any time for any reason without penalty.

Should a subject decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible, particularly the examinations outlined in the ET visit.

The investigator or one of his or her staff members should contact the subject to determine as accurately as possible the primary reason for the withdrawal.

A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.1 Discontinuation

Subjects who discontinue the study after the first dose will be asked, if they agree, to come for a last assessment (ET visit). Subjects who are discontinued for safety reasons may be asked to come for additional follow-up visits, at the investigator's discretion, after the ET visit to ensure appropriate medical care and AEs follow-up.

Subjects who discontinue will not be replaced.

Reasons for discontinuation include the following:

- The investigator decides that the subject should be withdrawn. If this decision is made because of a SAE, the study drug is to be discontinued in that subject immediately and appropriate measures are to be taken. The investigator will notify the sponsor immediately.
- The attending physician requests that the subject be withdrawn from the study.
- The subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs immediately upon introduction of the new agent.
- The subject is lost to follow-up. In this case, a reasonable attempt to contact the subject and ascertain his or her status must be made, and these attempts must be documented.
- The subject becomes pregnant at any time during the study.
- The subject has neutrophil counts below 1.0 x 10^9/L. Refer to Figure 3 for more details.
- The subject may withdraw from the study for any other reason, including withdrawal of consent.
- The sponsor or regulatory authorities, for any reason, stop the study. In this case, all subjects will be discontinued from the study. The investigator will immediately, on discontinuance of the study by the sponsor, in its entirety or at a clinical trial site, inform both the subjects and the IRB/REB/EC of the discontinuance, provide them with the reasons for the discontinuance and advise them in writing of any potential risks to the health of subjects or other persons.

7.2 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit. The site will then counsel the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.

- If all attempts to contact the subject fail, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Efficacy Assessments

Clinical evaluations of PPP will be performed by an experienced and qualified dermatologist (board certified or eligible) or other suitably qualified and experienced designee. To assure consistency and reduce variability, the same assessor should perform all assessments on a given subject whenever possible.

8.1.1 Fresh and Total Pustule Count

The number of fresh and total pustules will be counted on each palm and sole at the visits specified in Table 1. Fresh pustules are defined as macroscopically visible pustules that are white/yellow in color with no brown color, with or without crust, and present on the glabrous skin of the palms and/or soles. The pustule count will refer to the sum of pustules counted on all palms and soles. To be eligible to enroll in this study, subjects should have a minimum of 8 fresh pustules (fresh pustule count on both right/left palms and soles) at screening and 20 fresh pustules (fresh pustule count on both right/left palms and soles) at Day –1.

8.1.2 Palmoplantar Pustulosis Psoriasis Area Severity Index

The PPPASI will be evaluated at the visits specified in Table 1. The PPPASI is a scale from 0 to 72 that is used to evaluate the severity of PPP on palms and soles.[20]

Refer to APPENDIX A for a complete description of this scale. To be eligible to enroll in this study, subjects must have a PPPASI score ≥8 at Day –1.

8.1.3 Palmoplantar Pustulosis Physician Global Assessment

The PPPGA will be assessed at the visits specified in Table 1. The PPPGA is a 5-point scale that evaluates the severity of PPP.[21,22] A detailed description of PPPGA score calculation is provided in Table 4. To be eligible to enroll in this study, subjects must have a PPPGA score ≥3 at Day –1.

Table 4: Palmoplantar Pustulosis Physician Global Assessment (Averaged Over all Palmoplantar Lesions)

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

8.1.4 Palmoplantar Pustulosis Severity Index

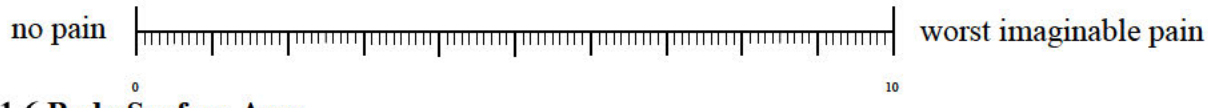
The PPSI will be evaluated at the visits specified in Table 1. The PPSI is a scale from 0 to 12 that is used to evaluate the severity of PPP lesions on palms and soles.[23]

Refer to APPENDIX B for a complete description of this scale.

8.1.5 Pain Visual Analog Scale

Pain intensity will be recorded at the visits specified in Table 1 using a pain VAS. Pain intensity will be evaluated by asking subjects to place a line perpendicular to the VAS line at the point that represents their worst pain intensity over the last 24 hours.[24] The pain VAS, represented in Figure 2, is a scale from 0 to 10, where 0 indicates no pain and 10 indicate the worst imaginable pain.[24]

Figure 2: Pain Visual Analog Scale



8.1.6 Body Surface Area

The overall BSA affected by psoriasis, excluding lesions on palms and soles, will be evaluated (from 0% to 100%) at the visits specified in Table 1. One subject's palm with the palmar aspect of all fingers represents 1% of his or her total BSA.[25] The BSA covered with psoriasis will be used to assess eligibility. Subject with moderate to severe psoriasis elsewhere on the body (excluding palms and soles), as defined by plaque psoriasis covering ≥10% of his total BSA at Day –1, will be excluded from the study.

8.1.7 Psoriasis Area Severity Index

The PASI will be evaluated at the visits specified in Table 1. This index quantifies the severity of a subject's psoriasis based on both lesion severity and the percentage of BSA affected [26,27]. The PASI is a composite score ranging from 0 to 72 that that takes into account the degree of erythema, induration/infiltration, and desquamation (each scored from 0 to 4 separately) for each of four body regions, with adjustments for the percentage of BSA involved for each body region and for the proportion of the body region to the whole body. The PASI will be evaluated excluding lesions on palms and soles. Refer to APPENDIX C for a complete description of this scale.

8.1.8 Physician Global Assessment

The PGA of disease severity will be evaluated at the visits specified in Table 1. The PGA is a 5-point scale (clear to severe) used to evaluate the degree of psoriasis severity, excluding lesions on palms and soles.[28] A detailed description of PGA score calculation is provided in Table 5.

Table 5: Physician Global Assessment

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

8.2 Quality-of-Life Assessments

8.2.1 Dermatology Life Quality Index Questionnaire

The Dermatology Life Quality Index (DLQI) will be assessed at the visits specified in Table 1. It is a simple 10-question validated questionnaire that has been used in more than 40 different skin conditions. Its use has been described in more than 1000 publications, including many multinational studies. The DLQI is the most frequently used instrument in studies of randomized controlled trials in dermatology. The questionnaire is provided in APPENDIX D.[29]

8.3 Safety and Other Assessments

8.3.1 Vital Signs

The following vital signs will be recorded at the visits specified in Table 1 with the subject in a seated position, after having sat calmly for at least 5 minutes: systolic and diastolic blood pressure (mmHg), pulse (bpm), body temperature (°C), and respiratory rate (breaths/min).

Weight (kg) and height (cm) will be collected at screening, and weight measured on Day 42 (follow-up) or ET.

If deemed appropriate by the investigator, clinically significant findings in the vital signs will exclude a subject from study participation. Any abnormal finding related to vital signs that the investigator considers to be clinically significant must be recorded as an AE.

8.3.2 Physical Examination

The following sites/systems will at least be included in the physical examination, which will be performed at the visits specified in Table 1:

- General appearance
- Dermatological (except PPP)
- Head, eyes, ears, nose, throat (HEENT)
- Respiratory
- Cardiovascular
- Abdominal
- Neurological
- Musculoskeletal
- Lymphatic

Information for all physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a subject from study participation. Any significant change will be reported as an AE in the source document and eCRF.

A symptom-oriented physical examination may be performed during the study, if deemed necessary by the investigator.

8.3.3 Brief Physical Examination

The following sites/systems will at least be included in the brief physical examination that will be performed on Day 14, as specified in Table 1:

- General appearance

- Dermatological (except PPP)
- Respiratory
- Cardiovascular
- Abdominal

Information for all physical examinations must be included in the source document. If deemed appropriate by the investigator, clinically significant findings in the physical examination will exclude a subject from study participation. Any significant change will be reported as an AE in the source document and eCRF.

If deemed appropriate by the investigator based on the subject's condition, a complete physical examination, as described in Section 8.3.2 can be performed instead of a brief/symptom-oriented examination.

8.3.4 Clinical Laboratory Tests

Laboratory tests will be performed at the visits specified in Table 1. The tests will include urinalysis, hematology with differential and coagulation testing, a standard biochemistry panel (including liver function tests and cholesterol), and serum pregnancy test (screening) for women of childbearing potential (WOCBP). At the visit specified in Table 1, a urine pregnancy test will be performed for WOCBP (conducted at the investigator site). The specific tests in these panels are listed in Table 6.

Table 6: Clinical Laboratory Testing

Laboratory Testing	Tests Included
Hematology	aPTT, HCT, Hgb, INR, MCH, MCHC, MCV, MPV, PLT, PT, RBC, WBC, and differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils relative and absolute)
Biochemistry	Albumin, alkaline phosphatase, ALT, AST, chloride, cholesterol (nonfasting), creatinine (enzymatic), GGT, glucose random, hs-CRP, LDH, potassium, sodium, total bilirubin, triglycerides, urea (BUN), uric acid
Urinalysis	Dipstick and microscopic analysis (only if required)
Urine pregnancy test	For WOCBP (at each visit, except screening)
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 β-hCG for WOCBP (screening only) Tuberculosis test (PPD or QuantiFERON-TB Gold) Serology (HBV [HBsAg, anti-HBc], HCV, HIV)

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; PLT, platelets; PPD, purified protein derivative; PT, prothrombin time; RBC, red blood cell (count); WBC, white blood cell (count); WOCBP, women of childbearing potential.

In case of a screening laboratory value abnormality, the test can be repeated within the original screening time window, if the investigator believes there is a reasonable possibility that the subject would be eligible if re-tested.

If deemed appropriate by the investigator, clinically significant findings in clinical laboratory testing will exclude a subject from study participation. Any clinically significant change will be reported as an AE.

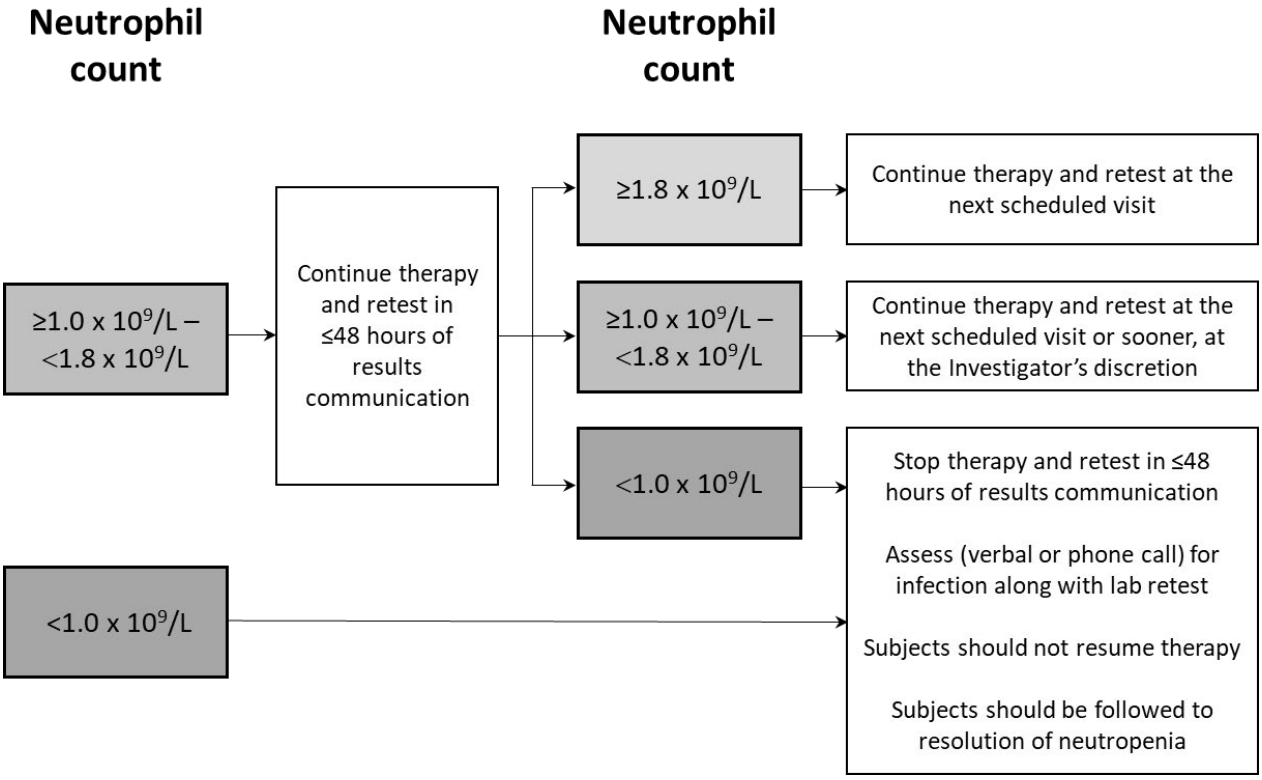
8.3.4.1 Procedure for Addressing Neutrophil Counts

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

Absolute and relative neutrophil and WBC count results will be disclosed to the respective investigators if absolute neutrophil counts reach values $<1.8 \times 10^9$/L, in which case immediate actions will be taken, as described in Figure 3. Retest results will be communicated to the investigators who will follow up on neutropenia and the incidence of infections with patients

having absolute neutrophil count results <1.0 x 10^9/L. Neutropenia will be followed up through resolution. Absolute and relative neutrophil and WBC count results will also be disclosed if the values are higher than the ULN.

Figure 3: Diagram for Addressing Neutrophil Counts



8.3.5 Electrocardiogram

Twelve-lead ECGs will be performed as a safety assessment at the visits specified in Table 1. Clinically significant findings in the ECG should exclude a subject from study participation (as deemed appropriate by the investigator). Any clinically significant change will be reported as an AE.

8.3.6 Plasma Concentration Assessment in Blood

Blood samples will be collected for analysis of RIST4721 plasma concentration on visits and time points indicated in the schedule of events in Table 1.

The actual date and time of each blood sample collection, as well as the time of last meal prior to dosing will be recorded.

Details about the collection, processing, handling, storage and shipping of blood samples will be provided in the laboratory manual.

8.3.7 Pharmacodynamic Assessments in Skin Biopsies

Approximately 20 subjects who consent to biopsy collection will have three 4.5-mm skin biopsies at the visits specified in Table 1: two biopsies will be taken at Day –1 (1 from lesional skin and 1 from adjacent nonlesional skin, either from palm or sole) and one biopsy will be taken at Day 28 from lesional skin, preferably from the same anatomical region as for biopsies collected on Day -1. For comparison of expression levels of lesional and nonlesional PPP skin, RT-PCR, transcriptome profiling, and IHC data will be performed.

The skin will be cleaned, disinfected, and anesthetized before skin biopsies are performed. Sterile gauze will be used to absorb any bleeding. The biopsy sites will be sutured, if necessary.

Details about the collection, processing, handling, storage and shipping of biopsy samples will be provided in the laboratory manual.

Pharmacodynamic results will be presented in a separate report.

8.3.8 Medical Photography

Medical photographs of PPP areas will be performed on a subgroup of approximately 15 subjects at the visits specified in Table 1. Care will be taken to use the same camera, the same magnification, and the same settings for each photograph at each visit in order to obtain comparable pictures. Medical photographs will be taken using a blue background.

Photographs will be identified and stored as instructed in the study reference manual.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the study drug.

8.4.2 Definition of Treatment-Emergent Adverse Event

A TEAE is any condition that was not present prior to treatment with the study product but appeared following treatment, was present at treatment initiation but worsened during treatment, or was present at treatment initiation but resolved and then reappeared while the individual was on treatment (regardless of the intensity of the AE when the treatment was initiated).

8.4.3 Definition of Serious Adverse Event

A SAE or reaction is any untoward medical occurrence that, at any dose has any of the following consequences:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.4.4 Classification of an Adverse Event

8.4.4.1 Relationship to Study Treatment

The investigator will establish causality of the AE to the study drug. The investigator should consider the subject's history, most recent physical examination findings, and concomitant medications.

The following definitions will be used to determine causality of an AE:

- Not related: Temporal relationship of the onset of the AE, relative to the study drug, is not reasonable, or another cause can explain the occurrence of the AE.
- Related: Temporal relationship of the onset of the AE, relative to the study drug, is reasonable, follows a known response pattern to the treatment, and an alternative cause is unlikely.

8.4.4.2 Adverse Event Severity

The intensity of an AE is an estimate of the relative severity of the event made by the investigator based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- Mild: The symptom is barely noticeable to the subject and does not influence performance of daily activities. Treatment is not ordinarily indicated.
- Moderate: The symptom is sufficiently severe to make the subject uncomfortable, and performance of daily activities is influenced. Treatment may be necessary.
- Severe: The symptom causes severe discomfort, and daily activities are significantly impaired or prevented. Treatment may be necessary.

8.4.4.3 Expectedness

[redacted] in consultation with the medical monitor, if need be, will assess the expectedness of each SAE in relation to the study drug.

8.4.5 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs, including local and systemic reactions, will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, relationship to study drug (assessed only by those with the training and authority to make

a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship.

Before subject enrollment, study site personnel will note the occurrence and nature of each subject's medical condition(s) in the appropriate section of the source document and eCRF. During the study, site personnel will note any change in the condition(s) and the occurrence and nature of any AE.

Any medical condition that is present prior to informed consent signature will be considered as part of medical history and not reported as an AE. However, if the study subject's condition deteriorates after the consent signature, it will be recorded as an AE.

If a subject experiences an AE at any time after the informed consent signature until the end of participation in the study, the event will be recorded as an AE in the source document and eCRF. Any SAE related to the study participation will be recorded in the source document and eCRF from the time a subject consents to participate in the study until the end of participation in the study.

The investigator is responsible for appropriate medical care of subjects during the study. The investigator also remains responsible for following through with an appropriate health care option for all AEs that are ongoing at the end of the study. The subject should be followed until the event is resolved or stable. If an AE is ongoing at the end of study, the follow-up duration is left to the discretion of the investigator, except for subjects with neutropenia who will be followed until resolution. Follow-up frequency will be performed at the discretion of the investigator.

Whenever possible, clinically significant abnormal laboratory results are to be reported using the diagnosis that resulted in the clinically significant abnormal laboratory results and not the actual abnormal test.

8.4.6 Adverse Event Reporting

Investigators are responsible for monitoring the safety of subjects who are participating in this study and for alerting the sponsor (via the medical monitor) to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

8.4.7 Serious Adverse Event Reporting

[redacted] will be the pharmacovigilance unit responsible for the overall pharmacovigilance process for this study. All SAEs, related to the study drug or not, occurring during the course of the study must be reported on an SAE form to the pharmacovigilance unit (see below contact information) within 24 hours of the knowledge of the occurrence. The SAE reporting period ends at the end of the follow-up period or if the subject begins an alternative therapy, except for subjects with neutropenia who will be followed until resolution.

Reporting should be done by sending the completed SAE form to the following email address (faxing can also be done as a second option in case e-mailing is not possible).

Safety Contact Information: [redacted]
E-mail [redacted]
Fax: [redacted]

The pharmacovigilance unit will inform the medical monitor, the sponsor, and CRO within 1 business day of awareness of a new SAE. The pharmacovigilance unit will process and the medical monitor will evaluate all SAEs as soon as the reports are received. For each SAE received, the pharmacovigilance unit, in consultation with the medical monitor, if needed, will determine whether the criteria for expedited reporting to relevant regulatory authorities have been met. The pharmacovigilance unit will manage the expedited reporting of relevant safety information, in accordance with local laws and regulations. SAEs will be reported to the REB/IRB/EC as per local REB/IRB/EC requirements.

8.4.8 Suspected Unexpected Serious Adverse Reactions Reporting

The sponsor will ensure that all relevant information about suspected unexpected serious adverse reactions (SUSAR) that are fatal or life-threatening is recorded and reported as soon as possible to the competent authorities in all the member states concerned, to the IRB/REB/EC as per local REB/IRB/EC requirements, and to all investigators in any case no later than seven days after knowledge by the sponsor of such an event. Finally, any additional relevant follow-up information is subsequently communicated to the competent authorities, the IRB/REB/EC as per local REB/IRB/EC requirements, and all investigators within an additional eight days.

All other SUSARs (ie, not fatal or life-threatening) shall be reported to the competent authorities concerned, to the IRB/REB/EC as per local REB/IRB/EC requirements, and all investigators concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor.

8.4.9 Pregnancy Reporting

If a female subject or a female partner of a male subject becomes pregnant during the study, the subject should inform the study site as soon as possible. Upon confirmation of the pregnancy, the female subject will be discontinued from the study. The investigator must complete a study specific pregnancy form upon confirmation of a pregnancy and send it to the pharmacovigilance unit within 24 hours of confirmation of the pregnancy (contact information to be used is the same as for SAE reporting). The pharmacovigilance unit will report all cases of pregnancy to the medical monitor, the sponsor, and CRO in a timely manner. Post-treatment follow-up should be done to ensure the safety of the pregnant subject and her fetus. Pregnancy is not itself an AE or SAE; however, maternal/fetal complications or abnormalities will be recorded as AEs or SAEs, as appropriate. The investigator will follow the pregnancy until completion or until pregnancy termination and, in the case of a live-born offspring, to 1 month of age in that infant. The investigator will notify the pharmacovigilance unit and CRO of the outcome as a follow-up to the initial pregnancy form. All pregnancies should be reported to the sponsor and, when applicable, to the ethics committee.

8.4.10 Overdose

Study drug overdose is defined as any accidental or intentional use of study drug in an amount higher than the dose indicated per protocol for a given subject. Study drug compliance (see Section 6.3.2) should be reviewed to detect potential instances of overdose (intentional or accidental).

Any study drug overdose during the study should be recorded on the source document and eCRF. In the event of overdose, the subject should be closely monitored for any potential AEs. All AEs associated with an overdose should be entered on the Adverse Event eCRF and reported using the procedures detailed in Section 8.4.7, Serious Adverse Events Reporting, even if the events do not meet seriousness criteria. If the AE associated with an overdose does not meet seriousness criteria, it must still be reported using the SAEs reporting procedures and in an expedited manner but should be noted as non-serious on the form and the Adverse Event eCRF. The excess quantity and duration of the overdose should be recorded.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

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

Approximately 30 subjects with moderate to severe PPP will be randomized 1:1 to receive placebo or RIST4721. A sample size of 30 (approximately 15 per group) will ensure 85 % power to detect a statistically significant difference in the relative change from baseline in pustules counts at

Day 28 with a 2-sided level of significance of 10%. This assumes a log-Normal distribution of the pustules counts, a 3-fold change (Placebo/RIST4721 at Day 28 relative to Baseline), and a coefficient of variation (CV) in the original scale of 150%. This sample size is expected to result in approximately 90% power if the CV is 130%.

9.2 Populations for Analyses

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

Safety analysis set: This analysis set will include all subjects who received at least one dose of the study drug. All subjects will be analyzed according to the treatment that they actually received.

Plasma concentration analysis set: This analysis set will include all subjects who received at least one dose of study drug and have plasma concentration data.

PD analysis set: This analysis set will include all subjects who have at least one dose of study drug and who have an assessment of PD parameters.

9.3 Statistical Analyses

9.3.1 General Approach

Continuous variables will be summarized in tables and will include the number of subjects, mean, SD, median, IQR, minimum, and maximum. Categorical variables will be presented in tables as frequencies and percentages.

All details regarding the efficacy and safety variable definitions, analyses strategy, statistical justification, and techniques for handling missing values will be detailed in a separate SAP that will be prepared before the database is locked and any analyses are undertaken.

The two primary efficacy endpoints (relative change in fresh pustules and relative change in total pustules) and the secondary efficacy endpoints (absolute change from baseline in fresh pustules, absolute change in total pustules, achieving at least a 50% reduction in fresh pustules, and achieving at least a 50% reduction in total pustules) will be tested using a Gatekeeper strategy and the Hochberg's method. The primary endpoints will first be tested at alpha of 10% (2-sided). If the larger p-value is less than 10% (2-sided), both primary endpoints will be declared statistically significant. If the larger p-value is greater than 10%, but the smaller p-value is less than 5% (2-sided), then the primary endpoint with the smaller p-value will be declared statistically significant.

With Hochberg's method, the study will be considered positive in terms of efficacy, if at least one of the primary endpoints is declared statistically significant.

The secondary efficacy endpoints (absolute change from baseline in fresh pustules, absolute change in total pustules, achieving at least a 50% reduction in fresh pustules, and achieving at least a 50% reduction in total pustules) will be tested using the same approach described above using Hochberg's method, only if both primary endpoints are considered statistically significant.

Exploratory endpoints will be tested at nominal alpha = 10% with no adjustment for multiplicity for exploratory purposes.

9.3.2 Efficacy Analyses

Efficacy analyses will be based on the mITT analysis set.

A MMRM model will be used for analyzing the relative change from baseline in continuous endpoints that are collected in a longitudinal fashion (fresh and total pustule count, PPPASI, PPPGA, PPSI, pain VAS, and DLQI). The natural log ratio of the post-dose values to baseline will be used as dependent variables in the analysis. The model will include fixed effects for treatment, visit and treatment-by-visit interaction, and natural log of baseline value as covariate. Unstructured covariance will be used to model the correlation. The treatment effect will be the contrast between treatment groups at specified visit(s) (eg, at Day 28) estimated through LS means. The LS mean estimates, associated two-sided 90% confidence intervals, and p-values will be reported. In this model, the estimates will be back-transformed to the ratio scale and presented as a percent change-from-baseline for ease of interpretation.

An analogous MMRM analysis will be used to analyze the absolute change from baseline. The response variable will be the absolute change from baseline at scheduled post-baseline visits and the baseline value as covariate.

For each post-dose study visit, a Fisher's exact test will be used to compare the proportion of subjects with a 50% or 75% reduction in fresh and total pustule count and the proportion of subjects achieving PPPASI-50 and PPPASI-75, for subjects treated with RIST4721 and subjects treated with placebo.

9.3.3 Safety Analyses

Safety analyses will be based on the Safety analysis set.

AEs will be presented and tabulated according to Medical Dictionary for Regulatory Activities (MedDRA) classification. Descriptions of AEs will include the start date, the stop date (if it resolved), the severity and seriousness of the AE, the causality of the AE to study drug, and the outcome. The focus in this protocol will be the prevalence of TEAEs.

Reported TEAEs will be summarized by the number of subjects reporting the events, as well as by System Organ Class, Preferred Term, severity, seriousness, and relationship to study drug. For the summary of AEs by severity, each subject will be counted only once within a System Organ Class or a Preferred Term by using the AEs with the highest intensity within each category for each

analysis. For the summary of AEs by relationship to study drug, each subject will be counted only once within a System Organ Class or a Preferred Term by using the AEs with the greatest reported relationship within each category. For the summary of AEs by relationship to study drug and severity, each subject will be counted only once within a System Organ Class or a Preferred Term by using (1) the greatest reported relationship followed by (2) the highest reported intensity.

Information pertaining to AEs noted during the study will be listed by subject, detailing verbatim, System Organ Class, Preferred Term, start date, stop date, intensity, outcome, and relationship to study drug. The AE onset will also be shown relative (in number of days) to the first day of study drug administration. Serious adverse events will be tabulated by treatment group, relationship to the study drug, and a reference to the occurrence of the SAEs to the relative day of dosing.

Results from laboratory analyses, vital signs, and ECGs will be tabulated by treatment and visit using descriptive statistics. The value at each visit as well as the change from baseline will be presented descriptively.

Concomitant medications will be coded with the World Health Organization-Drug Dictionary (WHO-DD) and listed by subject. Summary of medication classes will also be tabulated.

No inferential statistics will be done on safety variables.

9.3.4 Plasma Concentration Analyses

RIST4721 plasma concentration data will be listed per subject and summarized descriptively.

9.3.5 Pharmacodynamic Analyses

Expression levels in lesional and nonlesional PPP skin will be compared using RT-PCR, transcriptome profiling, and IHC data. A PD analysis plan will be prepared to detail the PD analyses. Results will be presented in a separate report.

9.3.6 Other Analyses

Descriptive summaries of baseline characteristics, including demographic data, prior concomitant therapy, and subject disposition will be presented.

Protocol deviations will be summarized by treatment and category.

9.3.7 Planned Interim Analyses

No interim analysis is planned in this study.

10 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1 Local Regulations/Declaration of Helsinki

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH E6 (R2) Tripartite Guideline for GCP and the applicable laws (eg, German Drug Law [AMG] §40 and §41) and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

10.2 Ethical Review

It is the understanding of the sponsor that this protocol (and any amendments) as well as appropriate consent procedures, will be reviewed and approved by a IRB/REB/EC. This board must operate in accordance with the current federal regulations. For sites with a local ethics committee, a letter or certification of approval will be sent by the investigator to the sponsor or CRO before initiation of the study and also whenever subsequent modifications to the protocol are made.

10.3 Informed Consent Process

An Informed Consent Form describing in detail the study treatment, study procedures, and risks will be given to the subject, along with an assent form when required.

It is the responsibility of the investigator, or a person designated by the investigator (if acceptable by local regulation), to obtain written informed consent from each individual participating in this study, after adequate explanation of the aims, methods, objectives, and potential hazards of the study. Should a subject be unable to understand the trial and give informed consent adequately in the opinion of the investigator, the subject will not be included in the trial.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB/REB/EC approved, and the subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of his or her rights as a research subject. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate.

Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time for any reason, without prejudice. A copy of the signed informed consent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures.

The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

If new safety information results in significant changes in the risk/benefit assessment, or if any new information becomes available that may affect the willingness of a subject to continue to participate, the consent form should, if necessary, be reviewed and updated by the IRB/REB/EC. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form, and asked to give their consent to continue in the study.

10.4 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, investigators, the sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigators will promptly inform study subjects and the IRB/REB/EC, and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension of the study include, but are not limited to the following:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete or evaluable
- Scientific or administrative reasons

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB/REB/EC, and Health Authorities.

10.5 Confidentiality and Privacy

Subject confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

The investigator must assure that the subjects' anonymity will be maintained and that subjects' identities are protected from unauthorized parties. On case report forms or other documents submitted to the sponsor, subjects should not be identified by their names, but by an identification code. The investigator should keep a subject enrollment log relating codes with the names of subjects. The investigator should maintain in strict confidence documents not for submission to Aristea Therapeutics, Inc. (eg, subjects' written consent forms).

All research activities will be conducted in a setting as private as possible.

The study monitor, other authorized representatives of the sponsor, and representatives of the IRB/REB/EC, regulatory agencies, or pharmaceutical company supplying study drug may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the applicable legal or regulatory requirements, the reviewing IRB/REB/EC, institutional policies, or sponsor requirements.

10.6 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial subjects are protected; that the reported trial data are accurate, complete, and verifiable; and that the conduct of the trial is compliant with the currently approved protocol/amendment(s), ICH GCP guidelines, and with applicable regulatory requirement(s). Details of clinical site monitoring will be documented in a Monitoring Plan.

10.7 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system, and data QC checks, which will be run on the database, will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

During the study, the sponsor or its representative will conduct monitoring visits at regular intervals. The monitoring visits will be conducted to ensure protocol adherence, quality of data, accuracy of entries on the eCRFs, study drug accountability, compliance with regulatory requirements, and continued adequacy of the study site and its facilities.

The site may be audited, monitored, or inspected by a quality assurance officer named by the sponsor, by the IRB/REB/EC, and/or by the regulatory authorities. The investigator will be expected to cooperate with any audit and provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities.

10.8 Data Handling and Record Keeping

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be

classified into two separate categories: investigator's study files and subject clinical source documents.

The investigator must maintain source documents for each subject in the study. These source documents will consist of case and visit notes (clinical medical records) containing demographic and medical information and the results of any tests or assessments. All information on the eCRFs must be traceable to the source documents in the subject's file. Data not requiring a written or electronic record will be defined before study start and will be recorded directly on the eCRFs, which will be documented as being the source data.

The records should be retained by the investigator according to ICH guidelines, local regulations, or as specified in the Clinical Trial Agreement, whichever retention period is longer.

Subject data will be entered by site personnel using [redacted], a web-based electronic data capture (EDC) and reporting system. This application will be set up for remote entry. The EDC software has been fully validated and conforms to Title 21 of the Code of Federal Regulations, Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been fully trained. Designated investigator staff will enter the data required by the protocol into the eCRFs using this web-based application. Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the investigator staff before confirming the data. The investigator must certify that the data are complete and accurate by applying an electronic signature to the eCRFs.

The data collected will be encoded and stored electronically in a database system. Validated data may subsequently be transferred to the sponsor.

10.9 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Protocol deviations must be sent to the reviewing IRB/REB/EC per their policies. The investigator is responsible for knowing and adhering to the reviewing IRB/REB/EC requirements.

10.10 Publication Policy

The publication policy will be addressed in the Research and Financial Agreement, and all details outlined in the agreement will apply to this protocol.

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APPENDIX A: Palmoplantar Pustulosis Psoriasis Area and Severity Index

PPPASI Scoring

Left palm, right palm, left sole, and right sole are assessed based on three target symptoms; erythema, desquamation (scaling), and pustules, as seen on the day of the examination.

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

- 0 = not present
- 1 = slight
- 2 = moderate
- 3 = severe
- 4 = very severe

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

- 0 = no involvement
- 1 = < 10% involvement
- 2 = 10 to < 30% involvement
- 3 = 30 to < 50% involvement
- 4 = 50 to < 70% involvement
- 5 = 70 to < 90% involvement
- 6 = 90 to < 100% involvement

The PPPASI score can vary from 0 (absence of disease) to 72 (most severe disease).

The PPPASI score for palms and soles is obtained by using the formula below:

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

Where E, D, P, A, L, and R denote erythema, desquamation, pustules, PPP involvement, left, and right, respectively.

APPENDIX B: Palmoplantar Pustulosis Severity Index

PPSI Scoring

The severity of PPP lesions on palms and soles is assessed based on three target symptoms; erythema, desquamation (scaling), and pustules or vesicles, as seen on the day of the examination.

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

- 0 = not present
- 1 = minimal
- 2 = mild
- 3 = moderate
- 4 = severe

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

$$PPSI = E + D + P$$

Where E, D, and P denote erythema, desquamation (scaling), and pustules or vesicles, respectively.

APPENDIX C: Psoriasis Area Severity Index

PASI Scoring

Four anatomic sites – head, upper extremities, trunk and lower extremities – are assessed for erythema, induration (plaque thickness), and desquamation (scaling) as seen on the day of the examination. The severity of each sign is assessed using the 5-point scale below:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Marked
- 4 = Very marked

The area affected by psoriasis within a given anatomic site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of psoriatic involvement as follows:

- 0 = no involvement
- 1 = < 10 %
- 2 = 10 to < 30%
- 3 = 30 to < 50%
- 4 = 50 to < 70%
- 5 = 70 to < 90%
- 6 = 90 to 100 %

Assignments for the following body regions are as follows:

- Neck: include with the head
- Buttocks: include with the lower extremities
- Axillae: include with the trunk
- Genitals: include with the trunk
- The inguinal canal separates the trunk and legs anteriorly

The PASI score for each body region is obtained by using the formula

$$PASI = 0.1 (E_h + I_h + D_h) A_h + 0.2 (E_u + I_u + D_u) A_u + 0.3 (E_t + I_t + D_t) A_t + 0.4 (E_l + I_l + D_l) A_l$$

Where E, I, D, and A denote erythema, induration, desquamation, and area, respectively, and h, u, t, and l denote head, upper extremities, trunk, and lower extremities, respectively.

APPENDIX D: Dermatology Life Quality Index

Subject ID #: ___ ___ - ___ ___ ___

Visit Day: _____ Visit Date (dd-mmm-yyyy): _____

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	□ □ □ □	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	□ □ □ □	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden?**	Very much A lot A little Not at all	□ □ □ □	Not relevant □
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	□ □ □ □	Not relevant □
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	□ □	Not relevant □
	If "No," over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	□ □ □	

8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □
10	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	□ □ □ □	 Not relevant □

Please check you have answered EVERY question. Thank you.

If two or more questions are left unanswered the questionnaire is not scored. If two or more response options are ticked, the response option with the highest score should be recorded. If there is a response between two tick boxes, the lower of the two score options should be recorded.