CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	A Randomized, Double-blind, Placebo-controlled, Dose Ranging Phase 2 Study to Evaluate the Efficacy and Safety of RIST4721 in Subjects with Palmoplantar Pustulosis
Short Title:	RIST4721 in Subjects with Palmoplantar Pustulosis
Protocol Number:	RIST4721-202
Study Treatment:	RIST4721
Study Phase:	Phase 2
Sponsor Name:	Aristea Therapeutics, Inc.
Legal Registered Address:	[redacted]
Regulatory Agency Identifier Number(s):	IND: 142756 EudraCT: 2021-003029-31
Version:	5.0, Amendment 4.0
Approval Date:	05 April 2022

SPONSOR'S AUTHORIZED REPRESENTATIVE SIGNATURE PAGE

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

Aristea Therapeutics, Inc.

Medical Monitor name and contact information will be provided separately.

INVESTIGATOR AGREEMENT

Protocol Title:	A Randomized, Double-blind, Placebo-controlled, Dose Ranging Phase 2 Study to Evaluate the Efficacy and Safety of RIST4721 in Subjects with Palmoplantar Pustulosis
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I have read this protocol and agree to conduct this study in accordance with ethical principles as outlined in the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice, any applicable laws and requirements and any additional conditions mandated by a regulatory authority and/or Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

I acknowledge that I am responsible for the overall study conduct and I agree to personally conduct or supervise the described clinical study.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Aristea Therapeutics, Inc.

_____

Signature

_____ _____

Name of Investigator Date

DOCUMENT HISTORY

DOCUMENT HISTORY	
Document	**Date**
Protocol Amendment 4.0	05 April 2022
Protocol Amendment 3.0	10 November 2021
Protocol Amendment 2.0	08 September 2021
Protocol Amendment 1.0	09 August 2021
Original Protocol	24 May 2021

Amendment 4.0; 05 April 2022

Overall Rationale for the Amendment:

Summary of Changes (in order of appearance)

Section Number and Name	Description of Change	Rationale for Change
1.1 Synopsis 1.2 Study Scheme 1.3.1 Table 2, Schedule of Activities – Part B (OLE) 2.1 Study Rationale 3 Objectives, Endpoints and Estimand 4 Study Design 5.1.1 Part B Inclusion Criteria 6 Study Treatment and Concomitant Therapy 7 Discontinuation of Study Treatment 8 Study Assessments and Procedures 9 Statistical Considerations 10 Appendices	• Incorporate open-label extension	• To allow long-term evaluation of RIST4721 as part of this protocol
2.3.1 Risk Assessments	• Update number of completed Phase 1 studies	• To include the most up-to date information from clinical studies
5.1 Inclusion Criteria	• Minor clarification to inclusion criteria	• For clarity
5.2 Exclusion Criteria 6.8 Concomitant Medications and Therapies	• Minor updates to exclusion criteria including list of prohibited medications (with indication that the list is not exhaustive)	• To align within the protocol and across other protocols

Section Number and Name	Description of Change	Rationale for Change
6.6 Continued Access to Study Treatment after the End of the Study	• Add section	• For clarity
8.5 PK, Biomarkers and PD	• Re-arrange section	• For clarity
10.4 Appendix 4 Contraceptive Guidance	• Update language on contraception	• For clarity
General	• Minor administrative changes and clarifications made throughout the protocol • Eliminate redundancy • Correct typographical errors, hyperlinks/cross-references, style, and formatting (not tracked) • Align across protocol sections • Update list of abbreviation (not tracked) • Update header	• For consistency and clarity • Alignment within protocol and across documents

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

Short Title: RIST4721 in Subjects with Palmoplantar Pustulosis

Rationale

RIST4721 is a small-molecule a high-potency antagonist of human CXC chemokine receptor type 2 (CXCR2) that is proposed to have potential as a novel oral treatment for neutrophil-mediated inflammatory diseases, including palmoplantar pustulosis (PPP).

PPP is a rare, recurrent, auto-immune, chronic inflammatory skin condition typically confined to the palms and soles. While several factors have been shown to induce PPP, such as infections, trauma, stress, and various therapeutic agents, the disease pathophysiology remains poorly understood (Benjegerdes, 2016). Recent studies have begun to highlight the importance of the innate immune system and cytokines in the development of PPP (Benjegerdes, 2016). 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 (Bissonnette, 2017). In addition, high levels of neutrophil-recruiting chemokines, including interleukin (IL)-1 and IL-8, were measured in PPP lesions (Kim, 2013; Bissonnette, 2016).

CXCR2 plays important roles in various acute and chronic inflammatory processes (Jamieson, 2012; Dyer, 2017). 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 (Eash, 2010; Boppana, 2014). 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 (Boppana, 2014). The utility of antagonizing the CXCR2 receptor was formerly investigated with the use of neutralizing antibodies targeting IL-8, one of several CXCR2 ligands (Skov, 2008; Veenstra, 2012). This study revealed that inhibition of the IL-8/CXCR2 axis causes clinically relevant reductions in disease activity in PPP subjects (Skov, 2008).

RIST4721 antagonism of CXCR2 was demonstrated 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 in vitro pharmacology studies covering a number of related receptors and targets inhibited by structurally similar molecules, RIST4721 demonstrated a CXCR2 selectivity of 134-fold and 47-fold relative to its potency at the human CXC motif chemokine receptor 1 (CXCR1) and C-C motif chemokine receptor 2 (CCR2), respectively (RIST4721 Investigator's Brochure [IB]). 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 inflammation. When rats were previously challenged with MSU injection, RIST4721 caused significant, dose-dependent decreases in exudate volume, total white blood cell (WBC) count, and neutrophil infiltration at doses 30, 100, and 300 µmol/kg.

RIST4721 was also evaluated in clinical setting including a Phase 2a, randomized, double-blind, placebo-controlled study in subjects with moderate to severe PPP. The primary endpoints of this study were related to pustule count assessments as these were hypothesized to be an early indicator of efficacy. The primary efficacy endpoints of relative change from baseline in fresh and total pustule count at Day 28 did not show statistically significant differences between the RIST4721 and placebo groups. The proportion of subjects who achieved a 50% reduction in the Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI-50) was numerically higher in the RIST4721 group (40.0%) compared to the placebo group (26.3%) at Day 28 (p=0.475). No other statistically significant differences were observed between treatment groups. A post-hoc subgroup analysis of subjects with an increase in total pustule count between screening and baseline was performed (n=20; 13 subjects randomized to placebo and 7 subjects randomized to RIST4721); the proportion of subjects with a PPPASI-50 at Day 28 was significantly higher for subjects treated with RIST4721 (5 of 7 subjects [71%]) as compared to placebo (2 of 13 subjects [15%]; p=0.0223 using Fisher's exact test).

The present study will further evaluate the efficacy and safety of RIST4721 at multiple doses over 12 weeks (Part A, randomized, double-blind, placebo-controlled) and at 400 mg once daily (QD) over 72 weeks (Part B, open-label extension [OLE]) in subjects with moderate to severe PPP.

Objectives, Endpoints, and Estimand (Primary and Secondary)

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

Objectives	Endpoints
	Global Assessment (PPPGA) of 0 or 1 at Week 12 • Proportion of subjects achieving 75% reduction in PPPASI score at Week 12
Secondary	
• Additional secondary efficacy endpoints	• Absolute change from baseline in PPPGA at Week 12 • Absolute change from baseline in PPPASI at Week 12
Safety	
• To assess the safety of RIST4721 in this population	• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) • Change from Baseline in clinical laboratory parameters, electrocardiogram (ECG) parameters, and vital signs

Overall Design

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

- Part A is a Phase 2, randomized, double-blind, placebo-controlled, multicenter, 12-week study evaluating the efficacy and safety of 2 doses of RIST4721.
- Part B is an open-label extension, 72 weeks evaluating the safety, tolerability and efficacy of RIST4721 400 mg once daily (QD).

The study will consist of a screening period, a treatment period (12 weeks in Part A and 72 weeks in Part B), and a follow-up period. All subjects will attend a follow-up visit at the clinic 4 weeks after last dose of study treatment. Subjects who permanently discontinue study treatment will be followed as described in Section 7.1.

Study schema is shown in Section 1.2.

Part A: Double-Blind

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

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

- RIST4721 400 mg

- RIST4721 200 mg
- Placebo

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

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

All subjects who remain on study treatment through and including Week 12 will be eligible to enter Part B (OLE) as specified below.

Part B: OLE

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

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

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

Treatment Groups and Number of Subjects:

The study will randomize approximately 156 evaluable subjects, with 52 subjects per treatment group (RIST4721 400 mg, RIST4721 200 mg, and placebo).

Duration

For each subject, the total study duration is expected to be as follows:

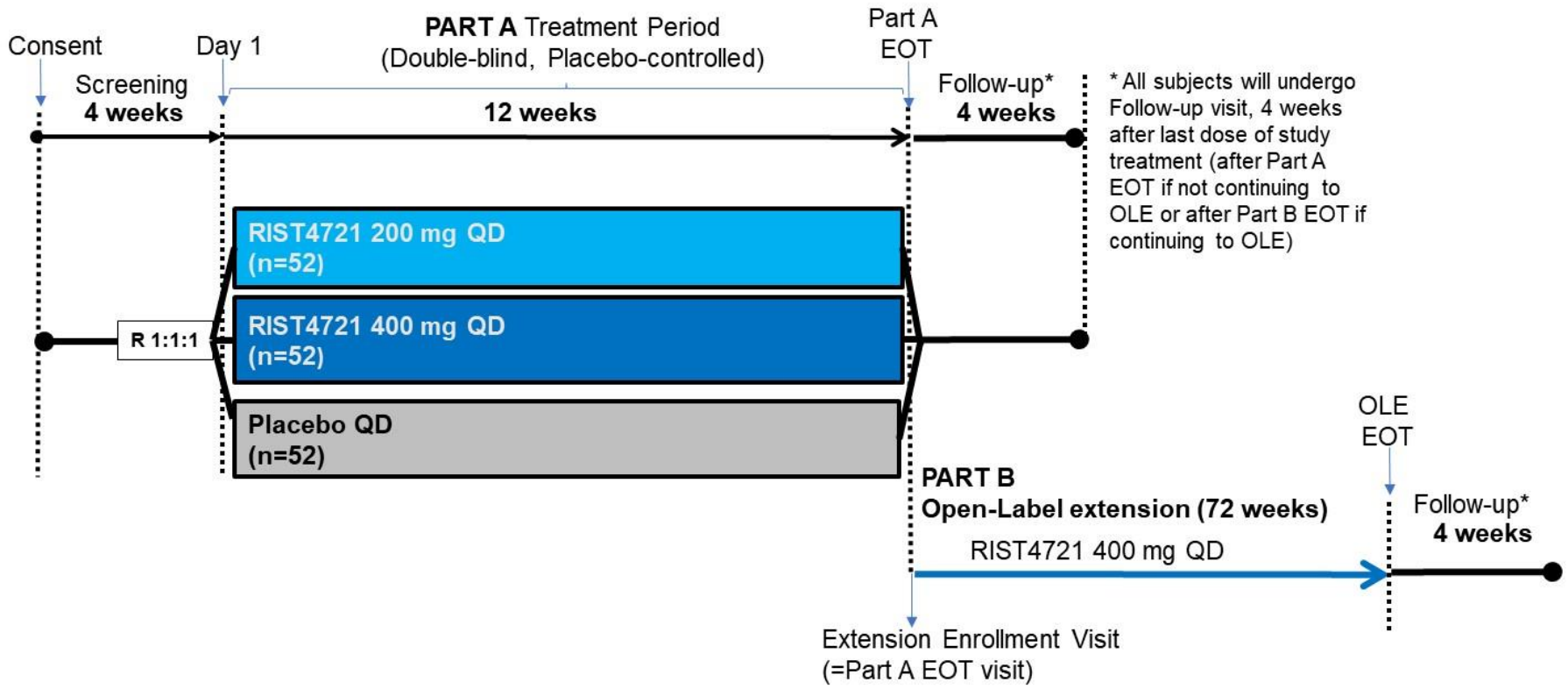
Study Period	**Part A**	**Part B**
Screening/observation period:	4 weeks	Not applicable
Treatment period:	12 weeks	72 weeks
Follow-up period	4 weeks after last dose of study treatment	

Data Review Committee

A non-independent, internal Data Review Committee (DRC) comprised of Sponsor representatives not directly involved in the conduct of the study, and/or external expert physician(s), will regularly monitor overall safety and emerging efficacy results on an unblinded basis, as well as general aspects of study conduct, to ensure that the benefits and risks of study participation remain acceptable (refer to Section 9.6.1).

1.2. Study Scheme

Figure 1: Study Scheme



Abbreviations: EOT, end of treatment; OLE, open-label extension; QD, once daily, R, randomization.

1.3. Schedule of Activities (SoA)

Guidance to address the coronavirus disease 2019 (COVID-19) global pandemic and potential impact on the clinical study are provided in Section 10.6, Appendix 6.

Table 1: Schedule of Activities – Part A (Double-blind)

Part A	**Screening**	**Double-Blind Treatment Period**					**Follow-up[2]**	**Notes**
Study Week	**-4 to -1**	**Baseline (Week 0)**	**2**	**4[1]**	**8[1]**	**12/EOT**	**+ 4 weeks from Week 12/EOT**	End of treatment (EOT) **1.** The total time between Weeks 4 and 8 and Weeks 8 and 12 should not exceed 5 weeks. **2.** Follow-up visit is not applicable for subjects continuing to Part B (Open-label extension [OLE])
Study Day	**-28 to -1**	**1**	**15**	**29**	**57**	**85**		
Visit Window (days)			**±3**	**±7**	**±7**	**±7**	**±7**	
Screening/Administrative								
Informed consent	X					X[a]		**a.** Consent for Part B (OLE)
Demographics	X							
Smoking status	X	X	X	X	X	X	X	
Eligibility criteria	X	X						
PASI	X							Psoriasis Area Severity Index (PASI)
Medical and medication history	X							
Height	X							
Serology	X[b]							**b.** If a subject has a positive test, confirmatory serology will be performed Refer to Section 10.2 (Appendix 2)
QuantiFERON-TB Gold test	X							Tuberculosis (TB) Refer to Section 10.2 (Appendix 2) If done within 6 months and negative result is available for documentation, test is not required at screening.
SARS-CoV-2 antibody test		X						Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Urine drug of abuse test	X							Refer to Section 10.2 (Appendix 2)

Part A	**Screening**	**Double-Blind Treatment Period**					**Follow-up[2]**	**Notes**
Study Week	**-4 to -1**	**Baseline (Week 0)**	**2**	**4[1]**	**8[1]**	**12/EOT**	**+ 4 weeks from Week 12/EOT**	End of treatment (EOT) **1.** The total time between Weeks 4 and 8 and Weeks 8 and 12 should not exceed 5 weeks. **2.** Follow-up visit is not applicable for subjects continuing to Part B (Open-label extension [OLE])
Study Day	**-28 to -1**	**1**	**15**	**29**	**57**	**85**		
Visit Window (days)			**±3**	**±7**	**±7**	**±7**	**±7**	
Pregnancy test (for WOCBP)	S	U	U	U	U	U	U	Serum (S); Urine (U); women of childbearing potential (WOCBP) If urine test is positive, confirm with serum test.
Study Treatment Administration								
Randomization		X						
Study treatment distribution		X		X	X			
Study treatment accountability				X	X	X		
Safety Assessments								
Adverse event	<========== X ==========						==========>	
Concomitant medications		X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	Assessments should occur in the following order: 1. Vital signs 2. 12-lead ECG 3. Blood draws for safety laboratories; refer to Section 10.2 (Appendix 2) Note: questionnaires are recommended to be completed before any of these procedures.
Weight	X					X	X	
Physical examination	X					X		
Supine 12-lead electrocardiogram (ECG)	X	X	X	X	X	X	X	
Serum chemistry	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	
SARS-CoV-2 antigen test	X	X	X	X	X	X	X	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); if positive, will be confirmed with SARS-CoV-2 polymerase chain reaction (PCR) test
Efficacy Assessments								
Medical photography of PPP skin areas	X	X		X	X	X	X	Palmoplantar pustulosis (PPP)

Part A	**Screening**	**Double-Blind Treatment Period**					**Follow-up[2]**	**Notes**
Study Week	**-4 to -1**	**Baseline (Week 0)**	**2**	**4[1]**	**8[1]**	**12/EOT**	**+ 4 weeks from Week 12/EOT**	End of treatment (EOT) **1.** The total time between Weeks 4 and 8 and Weeks 8 and 12 should not exceed 5 weeks. **2.** Follow-up visit is not applicable for subjects continuing to Part B (Open-label extension [OLE])
Study Day	**-28 to -1**	**1**	**15**	**29**	**57**	**85**		
Visit Window (days)			**±3**	±7	±7	±7	±7	
PPPASI	X	X		X	X	X	X	Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI)
PPPGA	X	X		X	X	X	X	Palmoplantar Pustulosis Physician Global Assessment (PPPGA)
PtGA	X	X		X	X	X	X	Patient Global Assessment (PtGA)
NRS for Pain, Pruritus, and Burning	X	X		X	X	X	X	Numeric rating scale (NRS)
DLQI		X		X		X	X	Dermatology Life Quality Index (DLQI)
SF-36		X		X	X	X	X	36-Item Short Form Survey (SF-36)
PPQLI		X		X		X	X	Palmoplantar Quality of Life (PPQLI)
Pharmacokinetics (PK) and Biomarkers								
Serum sample for RIST4721 concentration		X	X	X	X	X		Blood samples for trough PK will be collected predose; subjects will be requested to hold their dose on clinic visits until after PK samples are obtained; a PK sample will also be collected if a subject experiences a potentially related SAE (refer to Section 8.5.1).
Serum sample for biomarkers		X (predose)	X	X	X	X	X	Refer to Section 8.5.2
Skin tape strip for transcriptomic profiling		X (predose)				X	X	To be conducted at select sites in the US and Canada (refer to Section 8.5.3).

Table 2: Schedule of Activities - Part B (OLE)

Part B Study Assessments	Extension Enrollment Visit [1]	Open-label Extension Treatment Period					Follow-up	Notes
Study Week	E0	E2[2]	E4[2]	E8, E12, E20, E28, E36	E48, E60	E72/OLE EOT	+4 weeks from Week E72/ OLE EOT	Extension (E); End of treatment (EOT) **1.** If the assessment was performed as part of Part A EOT visit and within 7 days prior to the extension enrollment visit, assessment does not need to be repeated. **2.** The total time between Weeks E2 and E4 visits should not exceed 17 days
Visit Window (days)		±3	±3	+3/-7	+3/-7	+3/-7	±7	
Administrative								
Informed consent for OLE	X							
Part B eligibility criteria	X							Confirm eligibility prior to administering treatment. Refer to Section 5.1.1
PASI	X							Psoriasis Area Severity Index (PASI)
Study Treatment Administration								
Study treatment distribution	X	X	X	X	X			
Study treatment accountability			X	X	X	X		
Safety Assessments								
Adverse event	X	<========== X ==========>						
Concomitant medications	X		X	X	X	X	X	
Vital signs	X		X	X	X	X	X	Assessments should occur in the following order: 1. Vital signs 2. 12-lead ECG 3. Blood draws for safety laboratories (hematology and serum chemistry); refer to Section 10.2 (Appendix 2) Note: study questionnaires are recommended to be completed before any of these procedures.
Weight	X					X	X	
Physical examination	X					X		
Supine 12-lead electrocardiogram (ECG)	X		X	X	X	X	X	
Safety laboratories	X	X	X	X	X	X	X	
Pregnancy test (WOCBP)	U	U	U	U	U	U	U	Serum (S); Urine (U); women of childbearing potential (WOCBP) If urine test is positive, confirm with serum test.
				Every 4 weeks with a provided at-home urine pregnancy test				
Urinalysis	X		X	X	X	X	X	

Part B Study Assessments	Extension Enrollment Visit [1]	Open-label Extension Treatment Period					Follow-up	Notes
Study Week	E0	E2[2]	E4[2]	E8, E12, E20, E28, E36	E48, E60	E72/OLE EOT	+4 weeks from Week E72/ OLE EOT	Extension (E); End of treatment (EOT) **1.** If the assessment was performed as part of Part A EOT visit and within 7 days prior to the extension enrollment visit, assessment does not need to be repeated. **2.** The total time between Weeks E2 and E4 visits should not exceed 17 days
Visit Window (days)		±3	±3	+3/-7	+3/-7	+3/-7	±7	
SARS-CoV-2 antigen test	X	X	X	X	X	X	X	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); if positive, will be confirmed with SARS-CoV-2 polymerase chain reaction (PCR) test
Efficacy Assessments								
Medical photography of PPP skin areas	X		X	X	X	X	X	Palmoplantar pustulosis (PPP)
PPPASI	X		X	X	X	X	X	Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI)
PPPGA	X		X	X	X	X	X	Palmoplantar Pustulosis Physician Global Assessment (PPPGA)
PtGA	X		X	X	X	X	X	Patient Global Assessment (PtGA)
NRS for Pain, Pruritus, and Burning	X		X	X	X	X	X	Numeric rating scale (NRS)
DLQI	X		X	E12, E28	E48	X	X	Dermatology Life Quality Index (DLQI)
SF-36	X			E8, E12		X	X	36-Item Short Form Survey (SF-36)
PPQLI	X			E8, E12		X	X	Palmoplantar Quality of Life (PPQLI)
Biomarkers								
Serum sample for biomarkers	X		X	X	X	X	X	

2. INTRODUCTION

RIST4721 is a small-molecule a high-potency antagonist of human CXC chemokine receptor type 2 (CXCR2) that is proposed to have potential as a novel oral treatment for neutrophil mediated inflammatory diseases, including palmoplantar pustulosis (PPP). PPP is a rare, recurrent, auto-immune, chronic inflammatory skin condition typically confined to the palms and soles.

2.1. Study Rationale

While several factors have been shown to induce PPP, such as infections, trauma, stress, and various therapeutic agents, the disease pathophysiology remains poorly understood (Benjegerdes, 2016). Recent studies have begun to highlight the importance of the innate immune system and cytokines in the development of PPP (Benjegerdes, 2016). 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 (Bissonnette, 2017). In addition, high levels of neutrophil-recruiting chemokines, including interleukin (IL)-1 and IL-8, were measured in PPP lesions (Kim, 2013; Bissonnette, 2016).

The CXCR2 plays important roles in various acute and chronic inflammatory processes (Jamieson, 2012; Dyer, 2017). 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 (Eash, 2010; Boppana, 2014). 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 (Boppana, 2014). The utility of antagonizing the CXCR2 receptor was formerly investigated with the use of neutralizing antibodies targeting IL-8, one of several CXCR2 ligands (Skov, 2008; Veenstra, 2012). This study revealed that inhibition of the IL-8/CXCR2 axis causes clinically relevant reductions in disease activity in PPP subjects (Skov, 2008).

RIST4721 antagonism of CXCR2 was demonstrated 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 in vitro pharmacology studies covering a number of related receptors and targets inhibited by structurally similar molecules, RIST4721 demonstrated a CXCR2 selectivity of 134-fold and 47-fold relative to its potency at the human CXC motif chemokine receptor 1 (CXCR1) and C-C motif chemokine receptor 2 (CCR2), respectively (RIST4721 Investigator's Brochure [IB]). 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 inflammation. When rats were previously challenged with MSU injection, RIST4721 caused significant, dose-dependent decreases in exudate volume, total white blood cell (WBC) count, and neutrophil infiltration at doses 30, 100, and 300 µmol/kg.

RIST4721 was also evaluated in clinical setting including a Phase 2a, randomized, double-blind, placebo-controlled study in subjects with moderate to severe PPP. The primary endpoints of this study were related to pustule count assessments as these were hypothesized to be an early indicator of efficacy. The primary efficacy endpoints of relative change from baseline in fresh

and total pustule count at Day 28 did not show statistically significant differences between the RIST4721 and placebo groups. The proportion of subjects who achieved at 50% reduction in the Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI-50) was numerically higher in the RIST4721 group (40.0%) compared to the placebo group (26.3%) at Day 28 (p=0.475). No other statistically significant differences were observed between treatment groups. A post-hoc subgroup analysis of subjects with an increase in total pustule count between screening and baseline was performed (n=20; 13 subjects randomized to placebo and 7 subjects randomized to RIST4721); the proportion of subjects with a PPPASI-50 at Day 28 was significantly higher for subjects treated with RIST4721 (5 of 7 subjects [71%]) as compared to placebo (2 of 13 subjects [15%]; p=0.0223 using Fisher's exact test).

The present study will further evaluate the efficacy and safety of RIST4721 at multiple doses over 12 weeks (Part A, randomized, double-blind, placebo-controlled) and at 400 mg once daily (QD) over 72 weeks (Part B, open-label extension [OLE]) in subjects with moderate to severe PPP.

2.2. Background

2.2.1. Palmoplantar Pustulosis

PPP is a chronic inflammatory skin condition characterized by sterile pustules with erythema, hyperkeratosis, and scaling on the palms and soles (Benjegerdes, 2016; Dermatologists, 2018). It is considered a rare disease with an estimated prevalence of 0.01 to 0.05% (Lomholt, 1964; Hellgren, 1971; Mrowietz, 2011; Brunasso, 2013) and reported as high as 0.12% in a Japanese study, suggesting higher rate in Japan (Kubota, 2015). PPP is more commonly diagnosed in females (estimated prevalence range of 65.3% to 94%) than males, and in smokers (Michaëlsson, 2007; Kubota, 2015; Wilsmann-Theis, 2017). The mean age at disease onset ranges from 40 to 58 (Eriksson, 1998; Adişen, 2009; Brunasso, 2013; Wilsmann-Theis, 2017; Misiak-Galazka, 2018). Triggering factors include smoking, infections and stress, metal allergy, certain drugs, and co-morbid diseases such as thyroid disease, metabolic syndrome, atopy, arthritis, and celiac disease (Misiak-Galazka, 2020). There is a high prevalence of thyroid dysfunction in patients with PPP, often times underdiagnosed (Benjegerdes, 2016; Bissonnette, 2016; Wilsmann-Theis, 2017).

A number of reports suggest that PPP represents a distinct entity because of its unique genetic and molecular features (Benjegerdes, 2016; Bissonnette, 2016; Wilsmann-Theis, 2017). 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 (Benjegerdes, 2016). Erythema develops at the periphery of the lesions. Itching may be present. 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 (Stanford, 2014).

Off-label topical therapy typically consists of corticosteroid treatment with or without occlusion. Other topical agents used for the treatment of PPP include calcipotriene, photochemotherapy (i.e., psoralen and long-wave ultraviolet radiation [PUVA]), and tacrolimus (Benjegerdes, 2016). Topical agents are generally known to have limited efficacy in PPP, in part due to the lower relative absorptive capacity of the palms and soles compared to other body areas (Greaves, 1989; Kumar, 2004).

Off-label systemic treatments, including methotrexate and cyclosporin, have been used to treat PPP, although little controlled data exist on administration of these drugs to PPP patients (Thomsen, 1971; Reitamo, 1993; Erkko, 1998; Jin, 2019). Retinoids, such as acitretin, have been shown to be effective in some PPP cases. However, significant safety concerns, such as extensive dryness of mouth and lips, sicca symptoms of the eyes, hair loss, and increased blood lipid values, were associated with the use of these agents (Lassus, 1988). Side effects associated with the use of cyclosporin and methotrexate can include headache, nausea, mouth ulcers, hypertension, frequent urination, gastrointestinal reactions, inflammation of the liver or lung, hypertrichosis, and increased creatinine laboratory values (Reitamo, 1993; Erkko, 1998; Jin, 2019; AOCD, 2021) . Additional off-label systemic treatments that have been investigated include colchicine, dapsone, and biologic agents, such as tumor necrosis factor alpha (TNF-α) inhibitors (e.g., etanercept, infliximab, adalimumab) or IL inhibitors (e.g., guselkumab, ustekinumab, secukinumab, spesolimab) (Bissonnette, 2008; Bissonnette, 2011; Mrowietz, 2019; Terui, 2019; Mrowietz, 2021). These treatments have modest efficacy at best in PPP and can be associated with side effects, such as higher rates of infections, in addition to nasopharyngitis, headache, urticaria, and cellulitis (Bissonnette, 2011; Terui, 2018). More serious adverse events (SAEs) included infusion reactions and hepatitis (Bissonnette, 2011; Sanchez, 2017).

In a German cohort of 172 PPP patients, the most common systemic agents used were corticosteroids (40.1%), acitretin (37.8%), and methotrexate (27.9%). Despite treatment with these therapies, patients continued to experience a high burden of disease defined by PPPASI scores and there was no improvement in quality of life measured by the Dermatology Life Quality Index (DLQI) (Wilsmann-Theis, 2017).

The lack of targeted systemic treatments for PPP warrants development of a more effective and well-tolerated option.

2.3. Benefit/Risk Assessment

More detailed information about the known and potential benefits and potential risks of RIST4721 may be found in the IB.

2.3.1. Risk Assessments

The safety of RIST4721 has been assessed in 6 Phase 1 clinical studies in healthy subjects (161 subjects received single or multiple doses of RIST4721 ranging from 19 to 730 mg) and 1 Phase 2a study in subjects with moderate to severe PPP (15 subjects with moderate to severe PPP received RIST4721 300 mg QD for 28 days in the Phase 2a study RIST4721-201). RIST4721 was generally well tolerated. In the Phase 2a study, RIST4721-201 more subjects in the RIST4721 group (87%) compared to the placebo group (37%) experienced treatment-emergent adverse events (TEAEs). Most TEAEs were mild in severity, belonged to the system organ class (SOC) Gastrointestinal Disorders (diarrhea, abnormal feces, and nausea) or Musculoskeletal and Connective Tissue Disorders, and were resolved at the time of study completion. Two subjects in the RIST4721 group experienced mild, transient, and asymptomatic neutropenia during the study, which did not lead to treatment discontinuation. Neutrophil concentrations in both subjects returned to within the reference range by the time of the study follow-up visit. No SAEs or deaths were reported.

Table 3 summarizes identified and potential risks associated with RIST4721 as well as risk mitigation strategies. Further information related to nonclinical and clinical studies as well as other potential risks are available in the IB.

Table 3: RIST4721 Potential Risks and Risk Mitigation Strategy

Safety Considerations of RIST4721	Summary of Data/Rationale for Risk	Mitigation Strategy
Safety Consideration Based on Clinical Data		
Neutropenia	In both the SAD and MAD studies with RIST4721, dose-dependent reductions in neutrophils were observed. These reductions were rapidly reversible following discontinuation of RIST4721. Values resolved within 6 days following dosing. Similar reductions in neutrophils and leukocytes were observed in patients with PPP during treatment with RIST4721 300 mg QD for 28 days. Values returned to within the normal range by 14 days following completion of dosing.	• Relative and absolute neutrophil counts will be measured and monitored during the study. • Monitor AEs associated with neutropenia. • Stopping rules based on blood neutrophil count (refer to Section 7.1). • Based on studies with other CXCR2 inhibitors, the reduction in blood neutrophils associated with this CXCR2 inhibitor may be rapidly reversed by administration of G-CSF. • Address baseline neutrophil counts in clinical study inclusion criteria.
Gastrointestinal effects	Gastrointestinal effects are potential risks with RIST4721. In the conscious rat, single doses of RIST4721 at 2 mg/kg increased gastric emptying, whereas it was decreased at 100 mg/kg and above. In clinical studies, AEs in the Gastrointestinal Disorders SOC were frequently reported. Events included diarrhea, abnormal feces, nausea, abdominal pain, constipation, flatulence, dyspepsia.	• Monitor AEs associated with GI tract.
Safety Considerations Based on Theoretical Concern (not observed in clinical or nonclinical studies)		
Immune Suppression	No specific risk of infection has been identified from the non-clinical data or human data with RIST4721. However, the CXCR2 antagonist activity of RIST4721 could potentially interfere with mechanisms important in normal host defenses against infection.	• Monitor immune-mediated AEs. • Monitor incidence of AEs associated with infections. • Complete blood counts with differentials will be monitored frequently at the protocol-specified frequency.

Safety Considerations of RIST4721	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential Drug Interactions	In vitro assays suggest that RIST4721 is primarily metabolized by CYP3A4/5. RIST4721 was determined to be a P-gp/MDR1 and BCRP efflux transporter substrate in vitro. RIST4721 induced CYP3A4 and inhibited the efflux transporter BCRP and the uptake transporters OAT1, OAT3, OATP1B1, and OATP1B3 in vitro. Data from a clinical drug-drug interaction study, however, suggested that there does not appear to be a clinically relevant effect of RIST4721 on CYP3A4 or these transporters. No clinical drug-drug interaction studies have been conducted to examine the effect of other drugs on RIST4721.	• Caution should be used when co-administering RIST4721 with known inhibitors of P-gp or BCRP; or with moderate inhibitors or inducers of CYP3A4/5 (strong inhibitors/inducers are prohibited).

Abbreviations: AE, adverse event; BCRP, breast cancer resistance protein; CXCR2, CXC chemokine receptor-2; CYP, cytochrome P450; G-CSF, granulocyte colony-stimulating factor; GI, gastrointestinal; MAD, multiple ascending dose; MDR1, multidrug resistance protein 1; OAT, organic anion transporter; OATP, organic anion-transporting polypeptide; P-gp, P-glycoprotein; QD, once daily; SAD, single ascending dose; SOC, system organ class.

2.3.1.1. Risks of Study Participation

There are some risks to participation in any clinical study. The risks associated with this clinical study include the potential risks or discomforts from venipuncture such as temporary discomfort from the needle stick, bruising, bleeding, and rarely may cause infection or fainting. Additionally given the known risk and potential for transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there is a potential for increased risk of contracting SARS-CoV-2 infection as a result of study participation. The risks associated with RIST4721 and co-administration of vaccines for SARS-CoV-2 are not known.

2.3.2. Benefit Assessment

It is anticipated that subjects randomized to the RIST4721 will have an improvement in their PPP condition, specifically with respect to the PPPASI score, as over a shorter timeframe there were trends in favor of RIST4721 on a number of efficacy endpoints (refer to Section 2.1). Specifically, potential benefits may include fewer pustules, less pain, decreased redness and desquamation, smaller involved surface areas, and less functional impairment.

A longer duration of therapy than the 4 weeks of therapy in the initial Phase 2a study (RIST4721-201) with RIST4721 in subjects with PPP is expected to demonstrate a larger treatment effect in this challenging disease.

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.

Please refer to RIST4721 IB for additional details.

2.3.3. Overall Benefit: Risk Conclusion

While there are potential risks associated with the study treatment and the study procedures for this Phase 2 clinical study, the risk is expected to be minimal. The risks associated with RIST4721 and co-administration of vaccines for SARS-CoV-2 are not known, therefore the SARS-CoV-2 vaccine is listed as a restricted medication while a subject is participating in this study. If a subject requests or requires new or additional vaccination for SARS-CoV-2, the investigator should consider and discuss the potential risks and benefits with the subject. Once a determination has been made, the investigator will notify the medical monitor. Regardless of their vaccination status, subjects will be tested at each study visit as part of the routine safety assessments for SARS-CoV- 2 to determine if a new infection has taken place. Additionally, all adverse events (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 2.

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. This dose ranging study may inform future pivotal studies of RIST4721 in PPP, with the ultimate goal of providing much needed treatment to patients who 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 study will be minimized by compliance with the eligibility criteria, proper study design, and close monitoring.

Given the potential for efficacy in combination with the tolerated safety profile of RIST4721, the benefits of study participation outweigh the risks of participation in the study.

3. OBJECTIVES, ENDPOINTS, AND ESTIMAND

Objectives	Endpoints
Primary	
• To assess the efficacy of RIST4721 in the treatment of subjects with moderate to severe PPP	• Proportion of subjects achieving a 50% reduction in PPPASI score at Week 12
Primary Estimand	
For the primary objective, the primary estimand is as follows: **Treatment regimen:** RIST4721 400 mg, RIST4721 200 mg, and placebo **Target population:** Subjects with moderate to severe PPP as defined by the inclusion and exclusion criteria (Section 5), grouped per randomization assignment **Variable of interest:** responders who achieve a 50% reduction in PPPASI score at Week 12 **Intercurrent events and corresponding strategy:** Subjects who withdraw from the study prior to Week 12 due to any reason will be imputed as non-responders. Subjects who permanently discontinue study treatment but continue in the study will have their response statuses derived based on their observed data. **Population-level summary variable:** Difference in proportions of responders	
Key Secondary	
• Key efficacy secondary endpoints	• Proportion of subjects achieving Palmoplantar Pustulosis Physician Global Assessment (PPPGA) of 0 or 1 at Week 12 • Proportion of subjects achieving 75% reduction in PPPASI score at Week 12
Secondary	
• Additional secondary efficacy endpoints	• Absolute change from baseline in PPPGA at Week 12 • Absolute change from baseline in PPPASI at Week 12
Safety	
• To assess the safety of RIST4721 in this population	• Incidence of TEAEs and SAEs • Change from Baseline in clinical laboratory parameters, electrocardiogram (ECG) parameters, and vital signs

Objectives	Endpoints
Exploratory	
• To assess the impact of treatment with RIST4721 on the health-related quality of life (QoL)	• Absolute change from baseline in PPPASI at each visit • Achieving a 50% or 75% reduction from baseline in PPPASI score at each visit and during the study • Absolute and relative change from baseline in DLQI at each visit • Proportion of subjects achieving a score of 0 or 1 on each of the component (pustules, erythema, and scaling) in the Patient Global Assessment (PtGA) • Change from baseline at each visit in: – Pain Numerical Rating Scale (NRS) – Pruritus NRS – Burning NRS – Palmoplantar Quality of Life (PPQLI) – 36-Item Short Form Survey (SF-36)
• To evaluate the relationship between efficacy and pharmacokinetics (PK) exposure to RIST4721 at different doses	• Plasma PK concentrations of RIST4721 and its metabolites, if appropriate
• To evaluate the pharmacodynamics (PD) of RIST4721 in this population	• Changes from baseline in biomarkers and cytokines measured in blood samples
• To evaluate translational biomarkers in the skin and blood of participants treated with RIST4721	• Change from baseline in the expression of select biomarkers in skin (adhesive strips) and peripheral blood.

4. STUDY DESIGN

4.1. Overall Study Design

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

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

A non-independent, internal Data Review Committee (DRC), comprised of Sponsor representatives not directly involved in the conduct of the study, and/or external expert physician(s), will regularly monitor overall safety and emerging efficacy results on an unblinded basis, as well as general aspects of study conduct, to ensure that the benefits and risks of study participation remain acceptable (refer to Section 9.6.1).

The study will consist of a screening period, a treatment period (12 weeks in Part A and 72 weeks in Part B), and a follow-up period. All subjects will attend a Follow-up visit at the clinic 4 weeks after last dose of study treatment. Subjects who permanently discontinue study treatment will be followed as described in Section 7.1.

Study schema is shown in Section 1.2.

4.1.1. Part A – Double-Blind

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

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

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

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

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

All subjects who remain on study treatment through and including Week 12 will be eligible to enter Part B (OLE) as specified in Section 4.1.2. .

4.1.2. Part B – OLE

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

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

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

4.2. Scientific Rationale for Study Design

This Phase 2, randomized, placebo-controlled, multicenter study is designed to assess the efficacy and safety of RIST4721 in adult subjects with PPP. This is the second study with RIST4721 administration in subjects with PPP. The overall design of the study, including dose levels, was selected based on the data from a Phase 2 proof-of-concept study (RIST4721-201) and a relative bioavailability study conducted with a tablet formulation of RIST4721 (RIST4721-101).

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active treatment. A placebo control is considered appropriate as opposed to a comparator control because there is no common standard of care for PPP in any of the countries that this study will be conducted. Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups (refer to Section 6.3.1). Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

The OLE portion of the study is designed to assess the long-term safety, tolerability, and efficacy of RIST4721 in adult subjects with PPP.

4.3. Dose Rationale

Based on data from previous clinical studies with RIST4721, a dose of approximately 200 mg/day is anticipated to be a minimally effective dose in patients with PPP.

RIST4721 was well tolerated in multiple Phase 1 studies in healthy volunteers at single doses as high as 730 mg and multiple doses up to 500 mg/day for 10 days. In addition, one Phase 2a study in patients with PPP evaluated a dose of 300 mg QD for 4 weeks.

Study RIST4721-102 was a Phase 1, randomized, single-blind, placebo-controlled, crossover study that investigated the effect of multiple doses of 150 mg or 300 mg RIST4721 on the inflammatory response in healthy male subjects using a standardized blister model. The primary endpoint of inflammatory response was evaluated by measuring absolute neutrophil count

(ANC) in the blister exudate at various timepoints. In the assessment of the primary endpoint, ANC values demonstrated significant variability across both placebo and RIST4721 treatments at both doses and there was no discernible RIST4721 dose-related effect in this study. However, CXCR2-related cytokine (e.g., CXCL1, CXCL2, CXCL5, IL-8) levels were significantly higher in the blister exudate for RIST4721 300 mg compared to placebo at the 24-hour post-blister application timepoint, consistent with the mechanism of RIST4721. Less of an effect was observed at the 150 mg dose and differences between groups did not reach statistical significance for any parameter. Based upon these data and clinical effects observed with the 300 mg dose in RIST4721-201, it appears that the minimally efficacious dose of RIST4721 is likely to be a QD dose between 150 mg and 300 mg RIST4721. Consequently, a daily dose of 200 mg has been selected as the lower dose for investigation in the Phase 2 study RIST4721-202.

The higher dose level of 400 mg/day of RIST4721 was selected based on safety and PK data (including absorption, half-life, and bioaccumulation after repeated doses) from previously conducted studies. Modeling was conducted using the safety data of RIST4721 by dose in patients from Study RIST4721-201 coupled with data from normal healthy volunteers from completed Phase 1 studies with respect to the potential to develop an ANC of $<1.0 \times 10^9$/L. The modeling results indicate that doses of 400 mg or higher provide greater estimated probabilities of reducing ANC to levels needed for maximal activity and doses of 400 mg or lower yield estimated probabilities of meeting the safety threshold at or below 5% if the mean baseline ANC is 3.0×10^9 cells/L or higher. These results suggest that a 400 mg dose of RIST4721 may be utilized for further clinical evaluation in populations with ANC $\geq 3.0 \times 10^9$ cells/L at study entry (refer to inclusion criterion number 7).

4.4. Study Duration

For each subject, the total study duration is expected to be as follows:

Study Period	Part A	Part B
Screening/observation period:	4 weeks	Not applicable
Treatment period:	12 weeks	72 weeks
Follow-up period	4 weeks after last dose of study treatment	

4.5. 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 SoA (Table 1 – Part A; Table 2 – Part B).

For subjects who permanently discontinued treatment, the end of study will be defined if they completed the EOT visit and follow-up visit 4 weeks after the last dose of study treatment.

The end of the study is defined as completion of the last visit or procedure shown in the corresponding SoA (Table 1 – Part A; Table 2 – Part B) for the last enrolled subject in the study globally for all sites.

5. STUDY POPULATION

5.1. Inclusion Criteria

To be eligible for participation in this study, subjects must meet all the following:

Age and Sex

1. Male or female subject aged ≥18 years and <75 years of age at the time of consent.

Type of Subject and Disease Characteristics

2. A confirmed diagnosis of PPP (sterile, macroscopically visible pustules on the palms and/or soles) for at least 6 months prior to screening based on documented clinical history (information obtained from medical chart or subject's physician, or directly from the subject), with presence of active pustulation and without evidence of infection on palms and/or soles at screening.
3. Moderate or severe PPP, as defined by PPPASI ≥12 and PPPGA ≥3 at screening and confirmed by central photographic assessment of PPGA at screening. Subjects must have an area involvement of at least 30% on 2 palmoplantar surfaces or at least 60% on one palmoplantar surface.
4. At randomization visit, all of the following must be met:
   - PPPASI score must be ≥ 90% of the score at screening and PPPASI score of ≥12;
   - PPPGA score must be ≥3 and ≥ the score at screening;
   - PPPASI subscore of pustules/vesicles on at least one palm or sole ≥2.
5. Candidate for systemic therapy, defined as having PPP inadequately controlled by topical treatment, phototherapy, and/or previous systemic therapy. Eligible subjects shall demonstrate a lack of response or tolerability to local standard of care therapy for PPP **or** be contraindicated to such therapies.
6. 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/baseline and throughout the study. Note: On the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time. For more information on concomitant therapies, please refer to Section 6.8.
7. At screening, the results of the ANC performed at the central laboratory must be ≥3.0 x 10^9 cells/L.
8. Subject has been previously vaccinated for SARS-CoV-2 or has chosen not to be vaccinated at the start of participation (screening) in the clinical study.

Contraception

Contraception use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Refer to Section 10.4 for more details.

9. Women of childbearing potential (WOCBP) must have a negative serum pregnancy test at screening and negative urine pregnancy test at baseline, prior to randomization.

10. Female subject agrees to use a contraceptive method that is highly effective from consent until at least 5 days after the last study treatment administration
11. Male subject agrees to use condom and spermicide from consent until at least 5 days after the last study treatment administration.

Informed Consent

12. Evidence of a personally signed and dated ICF indicating that the subject has been informed of all pertinent aspects of the study prior to initiation of any subject-mandated procedures.
13. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

5.1.1. Part B Inclusion Criteria

In addition, to be eligible for participation in Part B, subjects must meet all the following at the extension enrollment visit:

Subject and Disease Characteristics

14. Must have completed Part A, been compliant with study procedures, and currently receiving study treatment (RIST4721 or placebo).
15. Subject does not have any new or existing condition that, in the opinion of the investigator, would make participation not be in the best interest (e.g., compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments.

Informed Consent

16. Evidence of a personally signed and dated ICF indicating that the subject has been informed of all pertinent aspects of the study prior to initiation of any subject-mandated procedures.
17. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

5.2. Exclusion Criteria (Part A only)

A subject must be excluded from participating in the study if he/she meets any of the following**:**

Medical Conditions and Diagnostic Assessments

1. Current diagnosis of superinfected hand dermatitis as a variant of contact or atopic hand dermatitis.
2. Any condition that, in the opinion of the investigator, would make participation not be in the best interest (e.g., compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments, including, but not limited to:
    a. Evidence of erythrodermic, generalized pustular psoriasis, predominantly guttate psoriasis, or drug-induced psoriasis.

b. Concomitant active systemic autoimmune or chronic inflammatory disease, including but not limited to: inflammatory bowel disease (Crohn's disease or ulcerative colitis), rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, or multiple sclerosis.
c. A history of synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO syndrome) or pustulotic arthro-osteitis (PAO syndrome).
d. 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.
e. Moderate to severe psoriasis, as defined by plaque psoriasis covering ≥10% of total body surface area (BSA) at Day 1.
f. Pompholyx dermatitis.
g. Known immune deficiency or is immunocompromised.
h. 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 localized carcinoma in situ of the cervix are not to be excluded.
i. Major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study, including planned dental procedures.
j. Any clinically significant history of infection (except for localized controlled herpes simplex) within 4 weeks prior to Day 1.
k. Uncontrolled thyroid disease (unless the subject is taking a stable dose of thyroid hormone or antithyroid medications [hyperthyroidism] for at least 12 weeks), which in the opinion of the investigator should exclude the subject from the study.
l. Diagnosis of active peptic ulcer disease as determined by endoscopy, radiography, angiography, or other appropriate means within 12 months prior to screening.
m. Primary coagulopathy excluding expected coagulation abnormalities due to concomitant pharmacotherapy.
n. Significant central nervous system (CNS) effects including vertigo and dizziness, or major neurologic event, including cerebrovascular events, within 60 days of screening.
o. QT corrected interval by Fridericia (QTcF) >440 msec as confirmed by triplicate ECG measurement at screening or Day 1 assessment.
p. A positive test for drugs of abuse (amphetamines, methamphetamines, barbiturates, cocaine, phencyclidine [PCP], methadone, and opioids [narcotics]). Retest may be performed for potential false positive results with approval from the Sponsor's Medical Monitor (or designee).
q. 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 (e.g., ascites, peri-umbilical veins, esophageal varices) at screening.
r. Serious hepatic disorder (Child-Turcott-Pugh scores B or C).
s. History of clinically significant anemia or hemoglobin (Hgb) value ≤10 g/dL at screening.

t. Chronic kidney disease as per National Kidney Foundation stages >2: estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2.
u. Positive results for hepatitis B surface antigens (HbsAg), antibodies to anti-core hepatitis B (HBc), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at screening (refer to Appendix 2, Section 10.2).
v. Positive result indicating active SARS-CoV-2 infection.
w. History of malabsorption including bariatric surgery (gastric bypass).
x. Any other 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 (e.g., celiac disease, streptococcal infection, allergy/delayed type hypersensitivity to tobacco and products within which tobacco is contained).

3. Evidence of latent tuberculosis (TB) infection (either purified protein derivative [PPD] ≥5 mm of induration or positive QuantiFERON-TB Gold test, irrespective of bacille Calmette-Guérin vaccination status).

   Note: 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 with documented completed treatment for latent TB will be allowed to participate in the study without retesting.

4. Breastfeeding, pregnant, or planning to become pregnant during the study.

Prior Therapy and Prior/Concurrent Clinical Study Experience

5. Any topical medication (exception of emollients [see Section 6.8]) to treat PPP, including corticosteroids, dapsone, retinoids, vitamin D analogs (such as calcipotriol), or tar within 2 weeks prior to Day 1.
6. Any systemic treatment that affects PPP, including, but not limited to, corticosteroids, oral retinoids, immunosuppressive medication, methotrexate, cyclosporine, dapsone, 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 agrees to maintain the same dose for the duration of the study. Eye drops containing corticosteroids are allowed.
7. Any ultraviolet (UV)-B phototherapy (including tanning beds) or excimer laser within 4 weeks prior to Day 1.
8. PUVA treatment within 4 weeks prior to Day 1.
9. Use of any marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to screening.
10. Currently receiving a nonbiological investigational product or investigational device or has received one within 4 weeks prior to Day 1.
11. Received strong cytochrome P450 (CYP)3A inhibitors and/or CYP3A inducers within 4 weeks prior to Day 1
    Examples of strong CYP3A inhibitors include but not limited to: cobicistat, boceprevir, ritonavir, indinavir, telaprevir, nelfinavir, danoprevir, dasabuvir, elvitegravir, lopinavir,

ombitasvir, paritaprevir, saquinavir, tipranavir, itraconazole, ketoconazole, posaconazole, voriconazole, troleandomycin, clarithromycin, idelalisib, conivaptan, nefazodone. Examples of strong CYP3A inducers include by not limited to: apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort.

12. Received RIST4721 in prior study.

Other Exclusion Criteria

13. 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 permitted when exposure cannot be avoided.
14. Consumption of any food or beverages containing cranberry, pomegranate, starfruit, grapefruit, pomelos, exotic citrus fruits, or Seville oranges (including marmalade and juices made from these fruits) within 7 days before baseline and unwillingness to avoid these during the study.
15. Known or suspected allergy to RIST4721 or any component of the study treatment.
16. Close affiliation with the investigator (e.g., a close relative), including any study staff of the sites, persons working at the contract research organization (CRO), or subject is an employee of Sponsor.
17. Institutionalized because of legal or regulatory order.

5.3. Lifestyle Considerations

Subjects will be instructed to avoid food or beverages containing cranberry, pomegranate, starfruit, grapefruit, pomelos, exotic citrus fruits, or Seville oranges (including marmalade and juices made from these fruits) during the study.

5.4. Screen Failure

Screen failures are defined as individuals who consent to participate in the clinical study 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.

Retesting of abnormal laboratory parameters can be done during the initial screening period at the discretion of the investigator in consultation with the Sponsor's Medical Monitor (or designee).

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

6. STUDY TREATMENT AND CONCOMITANT THERAPY

6.1. Study Treatment Administered

Table 4: Study Treatment Description

Study Treatment Name	Active: RIST4721 (Part A and Part B)	Control: Placebo (Part A only)
Dose Formulation	Blue, oval, biconvex film-coated tablets	Matching tablets containing placebo
Unit Dose Strength(s)	100 mg per tablet	placebo tablet
Dose Regimen	**400 mg**: 4 tablets QD (Part A and Part B)	4 tablets QD
	200 mg: 2 active tablets QD + 2 placebo tablets (Part A only)	
Route of Administration and Instructions	Oral. On Day 1, the clinical study team will instruct the subject how to administer the study treatment. RIST4721 should be taken QD with or without food.	
Sourcing	Study treatment will be provided to the site centrally by the Sponsor or designated representative.	
Packaging	RIST4721 and placebo tablets will be centrally sourced by the Sponsor in blister packages or bottles.	
Labeling	Label text will at a minimum include the protocol number, lot number, storage conditions, and Sponsor name and address. Labels will comply with local regulatory requirements for study treatments.	

6.2. Shipping/Handling/Storage/Accountability

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

All study treatment accountability forms and treatment logs must be retained in the investigator's study files. Study treatment inventory and accountability records will be maintained as per International Council for Harmonisation (ICH) Good Clinical Practice (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 treatment are provided in the study manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Randomization and Stratification

In Part A, Day 1, all subjects will be centrally randomized 1:1:1 to RIST4721 400 mg QD, 200 mg QD, or placebo QD using interactive response technology (IRT).

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

Before the study is initiated, appropriate IRT training, log-in information, and instructions will be provided to each site.

6.3.2. Assignment of Subject Number

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 (e.g., 02-010 for the 10th subject screened at Site #02).

6.3.3. Assignment of Study Treatment Kit Number

Study treatment will be dispensed at the study visits as summarized in the corresponding SoA (Table 1 – Part A; Table 2 – Part B). The study treatment kit number(s) will be assigned by the IRT system upon obtaining the subject's randomized treatment group.

For subsequent visits when study treatment is dispensed, the IRT system will assign study treatment kits based on the subject's randomized treatment group.

6.3.4. Blinding and Unblinding of an Individual Subject

The first 12 weeks of the study (Part A) will be double-blinded. Subjects, investigators, other site personnel, and Sponsor (and/or designee) personnel (except as described below) who are directly involved in the conduct of the study, collection of the data, and analysis of the data will remain blinded to treatment assignments until after a formal Part A unblinding has been performed (database lock).

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

A non-independent, internal DRC will periodically convene to review unblinded overall safety and emerging efficacy results (refer to Section 9.6.1).

The IRT system will be programmed with blind-breaking instructions. Blinding codes should only be broken in emergency situations for reasons of subject safety. If the blind is broken, the investigator should immediately inform (within 24 hours) the Sponsor's Medical Monitor (or designee). The date, reason why the blind was broken, and the names of the personnel involved must be recorded in the source documentation. The date and reason why the blind was broken will also be collected in the electronic case report form (eCRF). The subject for whom the blind

has been broken will be discontinued from the study and undergo the EOT procedures as specified in SoA.

Appropriate personnel at the Sponsor will unblind suspected unexpected serious adverse reactions (SUSARs) for the purpose of regulatory reporting. The Sponsor will submit SUSARs to regulatory agencies in blinded or unblinded fashion according to local law. The Sponsor will submit SUSARs to investigators in a blinded fashion.

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

Absolute and relative neutrophil and WBC count results will only be disclosed to the respective investigators if the ANC reach values below the reference range of the lower limit of normal (LLN) for the central, in which case immediate actions will be taken, as described in Figure 2 (Section 6.5.2).

6.4. Study Treatment Compliance

Study treatment compliance will be assessed, as appropriate, by direct questioning, and by maintaining adequate study treatment dispensing and return records. Deviation(s) from the prescribed dosage regimen will be evaluated. Subjects who demonstrate poor study treatment compliance (compliance under 80%) should be reeducated on the importance of taking their study treatment as prescribed.

Subjects who are significantly noncompliant with study treatment (subject has missed 7 consecutive days of dosing) 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 treatment, as judged by the investigator.

For all clinic visits, study treatment will be administered at the clinic to allow collection of blood samples for trough PK sampling predose. Date and time of the 2 doses prior to each PK sample will be recorded.

Guidance for Missed Dose(s)

If a dose is missed, subjects should be instructed to skip the missed dose if there are less than 12 hours before the time of the next dose, and resume dosing at their next scheduled dosing time ±2 hour.

6.5. Stopping Rules and Dose Modifications

Dose modification, as described below, may be considered for treatment-related AEs (Section 6.5.1) and ANC laboratory abnormalities (Section 6.5.2).

Dose reduction will be performed via the IRT system.

6.5.1. Treatment-related AEs

Dose modification of study treatment may be undertaken only after consultation and approval from the Sponsor's Medical Monitor (or designee) for moderate or severe AEs assessed by the

investigator as treatment-related, such as tolerability-related AEs. Subjects may be requested to attend an unscheduled visit after dose reduction to collect blood samples for safety and PK, if possible.

6.5.2. Neutrophil Count Laboratory Abnormality

There will be blinded evaluation of the neutrophil counts performed by an independent Medical Monitor in order to reduce the risk of breaking the blind in Part A.

During Part A, investigators, the study staff, the CRO, and the Sponsor's study team will not receive absolute and relative neutrophil or WBC count results. Absolute and relative neutrophil and WBC count results will only be disclosed to the respective investigators if ANC < LLN in which case immediate actions will be taken, as described in Figure 2. Retest results will be communicated to investigators who will follow up on neutrophil count and the incidence of infections in subjects having ANC results <1.0 x 10^9/L. Neutrophil count will be followed until resolution.

Dose interruption of study treatment ***must*** be undertaken for confirmed ANC results <1.0 x 10^9/L. Once the ANC result is above the LLN, subjects will re-initiate study treatment by reducing the study treatment dose as follows with approval from the Sponsor's Medical Monitor (or designee).

Part A; subject will receive blinded therapy as follows:

- For subjects who are on placebo (4 tablets), they will receive placebo (4 tablets).
- For subjects who are on RIST4721 400 mg (4 tablets), they will receive RIST4721 200 mg dose (2 tablets of RIST4721 100 mg plus 2 tablets of placebo; total of 4 tablets to maintain the blind).
- For subjects who are on RIST4721 200 mg (2 tablets of RIST4721 100 mg plus 2 tablets of placebo), they will receive 100 mg dose (1 tablet of RIST4721 100 mg plus 3 tablets of placebo; total of 4 tablets to maintain the blind).

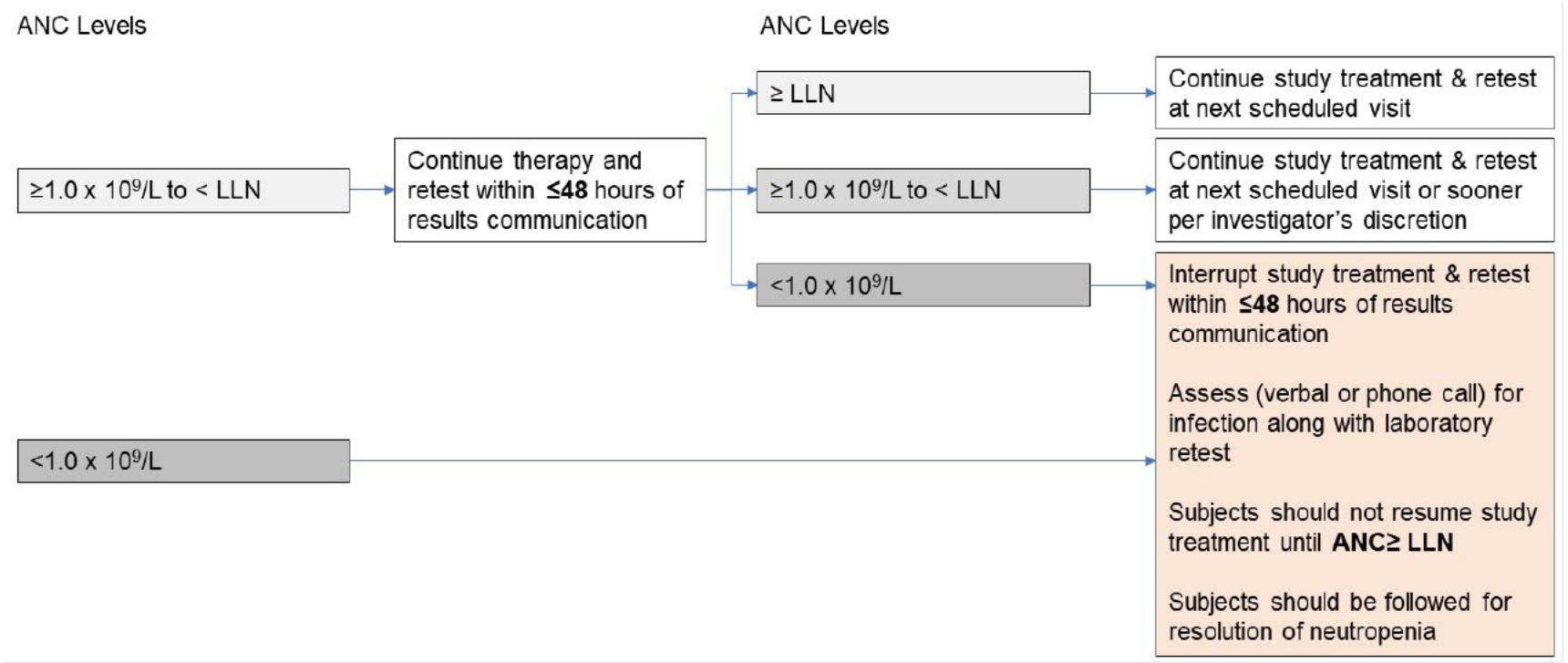
Part B (all subjects will be receiving RIST4721 400 mg QD prior to dose reduction):

- Subjects will receive RIST4721 200 mg QD (2 tablets of RIST4721 100 mg)

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

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

Figure 2: Steps for Addressing Neutrophil Counts



Abbreviations: ANC, absolute neutrophile count, LLN, lower limit of normal (central laboratory), PI, principal investigator

6.6. Continued Access to Study Treatment After the End of the Study

No additional intervention is planned beyond the end of Part B.

6.7. Treatment of Overdose

Study treatment overdose is defined as any accidental or intentional use of study treatment in an amount higher than the dose indicated per protocol for a given subject. Study treatment compliance (see Section 6.4) should be reviewed to detect potential instances of overdose (intentional or accidental).

There is no specific treatment recommended to treat an overdose of study treatment, and the subject should receive treatment directed toward any symptoms manifested.

In the event of an overdose, the investigator should:

- Contact the Medical Monitor (or designee) as soon as possible.
- Closely monitor the subject for any AEs/SAEs and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor (or designee) based on clinical evaluation of the subject.

All AEs associated with an overdose should be entered on the AE eCRF. 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 AE eCRF.

6.8. Concomitant Medications and Therapies

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- Name of medication/therapy (generic name)
- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Concomitant medications necessary for the health and well-being of the subject that do not interfere with study assessments and are not prohibited by protocol (see Section 6.8.2) are permitted during the study at the investigator's discretion. This includes the use of appropriate medications for the treatment of AEs and/or concurrent illnesses under the direction of the investigator. All medications must be recorded in the source and on the appropriate eCRFs.

The Sponsor's Medical Monitor (or designee) should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Permitted Dermatologic Therapies

- Emollients: Subjects can apply an emollient of their choice (except those containing any active ingredients) 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 Day1/baseline and throughout the study. However, on the day of scheduled visits, subjects cannot apply emollient before their scheduled visit time.
- 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.

6.8.2. Prohibited Medications

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study. Table 5 lists prohibited medications that are not to be used from the defined washout periods from 4 weeks prior to Day 1 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 doubt, investigators are advised to discuss medications with the Sponsor's Medical Monitor (or designee).

Table 5: Prohibited Therapies or Procedures

Prohibited medications, products, and procedures	Washout period
Any marketed or investigational biological agent	12 weeks or 5 half-lives (whichever is longer) prior to screening
Nonbiological investigational product or device	4 weeks prior to Day 1
Systemic treatment to treat PPP, including corticosteroids, oral retinoids, immunosuppressive medication, methotrexate, cyclosporine, dapsone, colchicine, or apremilast	4 weeks prior to Day 1
PUVA treatment, UV-B phototherapy (including tanning beds), excimer laser, excessive sun exposure, or has used tanning booths	4 weeks prior to Day 1
Topical medication to treat PPP (exception of emollients [see Section 6.8]), including corticosteroids, dapsone retinoids, vitamin D analogs (calcipotriol), and tar	2 weeks prior to Day 1
Strong CYP3A inhibitors and/or CYP3A inducers Examples of strong CYP3A inhibitors include but not limited to: cobicistat, boceprevir, ritonavir, indinavir, telaprevir, nelfinavir, danoprevir, dasabuvir, elvitegravir, lopinavir, ombitasvir, paritaprevir, saquinavir, tipranavir, itraconazole, ketoconazole, posaconazole, voriconazole, troleandomycin, clarithromycin, idelalisib, conivaptan, nefazodone Examples of strong CYP3A inducers include but not limited to: apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	4 weeks prior to Day 1

Abbreviations: CYP, cytochrome P450; PPP, palmoplantar pustulosis; PUVA, psoralen and ultraviolet A; UV-B, ultraviolet B.
Notes: The list of medications is not exhaustive. Consult with Medical Monitor when in doubt.

6.8.3. Restricted Medications

Restricted medications are defined as medications that **should be avoided**, if possible; however, they are not necessarily prohibited during this study. If such medications are required, consider switching to another medication in the class that is not restricted. If a restricted medication is required, the restricted medication should be used with caution per approved product label and Sponsor's Medical Monitor (or designee) should be notified.

The list of medications below is not exhaustive. If there are any questions regarding a medication, the investigator can consult with the Sponsor's Medical Monitor (or designee).

- P-glycoprotein (P-gp) inhibitors (e.g., amiodarone, carvedilol, dronedarone, lapatinib, propafenone, quinidine, ranolazine, and verapamil)
- Breast cancer resistance protein (BCRP) inhibitors (e.g., curcumin, cyclosporine A, eltrombopag)

- Moderate inhibitors of CYP3A, include but not limited to aprepitant, crizotinib, diltiazem, erythromycin, fluconazole, verapamil
- Moderate inducers of CYP3A, including but not limited to bosentan, efavirenz, etravirine, phenobarbital, primodone
- SARS-CoV-2 vaccines including those approved for emergency use or fully approved

7. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT WITHDRAWAL FROM STUDY

7.1. Discontinuation of Study Treatment and Withdrawal from the Study

In some instances, it may be necessary for a subject to permanently discontinue study treatment.

Dosing of study treatment must be interrupted for any SAEs assessed by the investigator as related to study treatment. Restart of dosing may be considered upon discussion with and approval by the Sponsor's Medical Monitor (or designee) after resolution of study treatment-related events to baseline.

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

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

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the institution. The reason for subject withdrawal from the study will be recorded in the eCRF. At the time of withdrawal from the study, an EOT visit should be conducted per the corresponding SoA (Table 1 – Part A; Table 2 – Part B). If a subject 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.

A subject may discontinue study treatment or withdraw from the study for the following reasons:

- Adverse event
- Death
- Lost to follow-up
- Non-compliance with study treatment
- Physician decision

- Pregnancy
- Progressive disease
- Protocol deviation
- Withdrawal by subject
- Study terminated by Sponsor

The reason for subject discontinuation from study treatment or withdrawal from the study will be recorded in the eCRF.

For neutrophil counts below 1.0 x 10^9/L, refer to Section 6.5.2 for more details regarding procedures to address neutrophil count and dose modification guidelines.

Pregnancy is a mandatory criterion for permanent discontinuation of study treatment (see Section 7.1.2).

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

7.1.1. Premature Termination of the Study

The Sponsor may terminate this study prematurely for any reasonable cause. The Institutional Review Boards (IRB)/ Independent Ethics Committees (IEC) and regulatory authorities should be informed promptly.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study, or potential study subjects
- A decision on the part of the Sponsor to suspend or discontinue development of study treatment

If the study is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the study subjects and ensure appropriate follow-up is provided for the subjects.

7.1.2. Pregnancy

A subject must permanently discontinue study treatment if she becomes pregnant. See Appendix 4 (Section 10.4.3) and Section 8.4.5 for additional details.

See the SoA (Table 1) for data to be collected at the EOT visit.

7.2. Lost to Follow-up

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

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

- Study procedures and their timing are summarized in the corresponding SoA (Table 1 – Part A; Table 2 – Part B). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness of occurrence to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA (Table 1 – Part A; Table 2 – Part B), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria and randomization entry criteria. The investigator will maintain a log to record details of all subjects screened (including demographic data) and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management and obtained before signing the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- 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. Key Screening Assessment(s)

8.1.1. Psoriasis Area Severity Index (PASI)

PASI quantifies the severity of a subject's psoriasis based on both lesion severity and the percentage of BSA affected (Fredriksson, 1978; Marks, 1989). 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.

8.2. Efficacy Assessments

8.2.1. Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI)

The PPPASI is a scale from 0 to 72 that is used to evaluate the severity of PPP on palms and soles (Bhushan, 2001). Refer to Section 10.5 (Appendix 5) for a complete description of this scale.

8.2.2. Palmoplantar Pustulosis Physician Global Assessment (PPPGA)

The PPPGA is a 5-point scale that evaluates the severity of PPP (Trust, 2017; Cornelius, 2018). A detailed description of PPPGA score calculation is provided in Table 6.

Table 6: PPPGA (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)
Abbreviations: PPP, palmoplantar pustulosis; PPPGA, Palmoplantar Pustulosis Physician Global Assessment		

8.2.3. Patient Global Assessment (PtGA)

The PtGA is a commonly used patient reported outcome for measuring disease severity. The PtGA is modified from the Physician Global Assessment used for PPP (Benzian-Olsson, 2020) and includes the following disease manifestations, pustules, erythema, and scaling, each rated on a 5-point scale (range 0 to 4), with a score of zero (clear), 1 (almost clear), 2 (mild), 3 (moderate), and 4 (severe).

8.2.4. Numeric Rating Scale (NRS)

NRS, a self-assessed patient reported outcome, will be used to assess pain, pruritus, and burning. NRS is an 11-point scale (zero to 10), with score of zero denoting no symptom (pain, pruritus, or burning) and a score of 10 denotes worst possible symptom. NRS has been used across different indications, including skin disorders and was shown to be valid (Barrett, 2019; Silverberg, 2021).

8.2.5. Health-related Quality of Life

Health-related Quality of Life will be evaluated as described below. The questionnaires are recommended to be completed before any of these procedures.

- The DLQI 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 studies in dermatology. It includes questions concerning symptoms and feelings; about daily activities, leisure, work, and school; and about personal relationships and treatment.

All questions relate "to the last week", and the score ranges from 0 (no impairment of life quality) to 30 (maximum impairment) (Finlay, 1994).

- The SF-36 health survey is a validated questionnaire that includes 36 questions covering eight domains of health.
- The PPQLI assesses relevant dimensions affected by palmoplantar psoriasis (pain/discomfort, functionality, and social/activity limitations) on a 1-5 scale (Farley, 2009).

The questionnaires should be completed by the subjects at the scheduled visits before any other clinical assessments. The subjects should be given sufficient space and time to complete the questionnaires. The study coordinator should check the questionnaires for completeness and encourage the subjects to complete any missing responses. The questionnaires will be completed on an electronic device, e.g. tablet.

Completed questionnaires will be reviewed and examined by the investigator for responses that may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires, but also any unsolicited comments written by the subjects. If AEs or SAEs are confirmed, the investigator must record the events as per instructions given in Section 8.4. Investigators should not encourage the subjects to change the responses reported in the questionnaires.

8.2.6. Medical Photography

Medical photographs of PPP areas will be performed on all subjects to confirm eligibility related to PPPASI and PPPGA for the study via central reading. In addition, photographs will be taken, labeled, and stored as instructed in the study reference manual.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1 – Part A; Table 2 – Part B). Study procedures should be completed within the windows provided in the corresponding SoA and as specified in this section.

8.3.1. Physical Examinations

A complete physical examination will be performed and will include, at a minimum, assessments of:

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

- Lymphatic system

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

- General appearance
- Dermatological system (except PPP)
- Musculoskeletal system
- Respiratory system
- Cardiovascular system
- Abdominal region

Information for all physical examinations must be included in the source documents. 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.

8.3.2. Vital Signs

- Vital signs (heart rate, respiratory rate, body temperature, and blood pressure) will be measured after the subject in a seated position after at least 5 minutes rest and prior to ECG measurements.
- Blood pressure and heart rate measurements will be assessed with the subject in a sitting position using a completely automated device. Manual techniques will be used only if an automated device is not available.
- Weight and height will be collected at screening, and weight will be measured as specified in the SoA (Table 1 – Part A; Table 2 – Part B).

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.

8.3.3. Electrocardiograms

Single 12-lead ECGs will be obtained and evaluated locally using an ECG machine that automatically calculates heart rate and measure PR, QRS, QT, and QTc intervals.

In all cases in which an ECG has a potentially clinically significant finding, it will be repeated in triplicate within about 30 minutes and reviewed by the investigator or designee prior to subsequent dosing or study disposition decisions that do not constitute a subject emergency.

Clinically significant findings in the ECG obtained at screening should exclude a subject from study participation (as deemed appropriate by the investigator). Any clinically significant change will be reported as an AE.

Subjects should be in the supine position after the subject has rested for at least 10 minutes with minimal movement and minimal exposure to noise and other environmental stimuli (e.g., TV, loud radio, interactions with other subjects, etc.). In the event of possible ECG findings, additional ECG reads could be added at follow-up visit(s). Clinically significant ECG abnormalities will be recorded on the eCRF and in source documents.

Original paper tracings and tracing copies of the ECGs, including the interpretation, should be stored in the source documents. If ECG is thermal paper, it should be photocopied and then signed and dated since it fades over time.

8.3.4. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed. Details for collection, processing, and shipping of samples to the central laboratory are provided in a separate Laboratory Manual.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The signed laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered abnormal and clinically significant during participation in the study should be repeated per standard practices until the values return to normal or baseline or are no longer considered clinically relevant by the investigator or Sponsor's Medical Monitor (or designee).
  Note: If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.
- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator, then the events must be recorded in the eCRF and retained in source documents.
- 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.

8.4. Adverse Events and Serious Adverse Events

The definitions of an AE and SAE can be found in Appendix 3 (Section 10.3).

AEs will be reported to the investigator by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of AE and SAE.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from consent until the end of study follow-up. SAEs will be collected beginning at the time of consent until the end of study follow-up. All medical occurrences, with the exception of SAEs, that begin after obtaining ICF and before the first dose of study treatment will be recorded on the Medical History/Current Medical Conditions section of the eCRF and not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee immediately upon the site learning of an event, and under no circumstance should the initial notification exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs that start after conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a subject has been withdrawn from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care is to be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire whether AEs occurred.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.2). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the investigator to the Sponsor is essential so that the Sponsor's legal obligations and ethical responsibilities toward the safety of subjects and the safety of study treatment under clinical investigation can be met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific

regulatory requirements relating to safety reporting to regulatory authorities, IRB/ IEC, and investigators.

- Investigator safety reports must be prepared for SUSARs (defined in Section 10.3.3) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

8.4.5. Pregnancy

- Details of all pregnancies will be collected as outlined in Appendix 4 (Section 10.4).
- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, elective termination of a pregnancy, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4.6. Death Events

Timelines for reporting of death events are identical to the requirements for SAE reporting. (Appendix 3, Section 10.3).

8.5. Pharmacokinetics, Biomarkers, and Pharmacodynamics

8.5.1. Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of RIST4721 and its metabolites, if applicable, as specified in the SoA (Table 1 – Part A). On clinic visits, subjects will be requested to hold their study treatment dose until after PK samples are obtained. The actual time and date of each sample collection will be recorded in eCRF. The actual time and date of the completion of dosing on the PK days and the dates and approximate times of the last 2 doses before the PK days will be recorded in eCRF. A more detailed description of plasma sample preparation will be provided in the Laboratory Manual.

In case of the occurrence of a potentially related SAE, an unscheduled plasma sample for determination of RIST4721 plasma concentration should be collected as soon as possible. The approximate time of administration of the dose of study treatment prior to obtaining the sample should be recorded.

PK samples will be analyzed with a validated method; for metabolites, the samples may be analyzed with a fit-for-purpose method(s). The samples may be used for metabolite profiling or bioanalytical method development and validation. PK samples will only be analyzed for subjects who received active treatment with RIST4721, i.e., placebo subjects

will not have their samples analyzed. For RIST4721 treated subjects, the baseline (i.e., blank) sample taken prior to initiating therapy will not be analyzed unless necessary to investigate any unusual findings with the on-treatment samples.

8.5.2. Serum Biomarkers

Serum biomarkers will be collected as specified in the SoA (Table 1 – Part A; Table 2 – Part B) and stored for analysis.

Details about the collection, processing, handling, storage, and shipping of biomarker samples will be provided in the Laboratory Manual.

8.5.3. Biomarkers from Skin Tape Strips (Part A only)

Skin tape discs will be collected from all subjects, at selected sites, for whole RNA transcript analysis at the timepoints outlined in the SoA (Table 1 – Part A). The purpose of these analyses will be to retrospectively evaluate biomarkers predictive of subject response at baseline, before study treatment administration, as well as to potentially identify additional correlative and pharmacodynamic biomarkers.

Samples are to be collected from the active periphery of the target palm or sole after a photograph of the target lesion has been taken. The areas where samples were collected will be documented in the subject's medical record at each subsequent visit.

All samples collected must be from the same location; the skin tape disc sample will continue to be collected from that original target palm or sole.

8.5.4. Storage and Handling of Blood Samples

Blood samples may be stored according to local regulations for a maximum of 15 years at a facility selected by the Sponsor or destroyed at the end of the study.

9. STATISTICAL CONSIDERATIONS

Statistical considerations are summarized here. A detailed description of statistical methods will be provided in the Statistical Analysis Plan (SAP).

9.1. Sample Size Determination

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

9.2. Population for Analyses

The following populations are defined:

Study Population	Definitions
Full Analysis Set	The Full Analysis Set will include all subjects who are randomized. Subjects will be classified according to the treatment and stratum assigned at randomization. The Full Analysis Set will be the primary population for evaluating all efficacy endpoints and subject characteristics.
Per-protocol Analysis Set	The Per-protocol Analysis Set is a subset of the Full Analysis Set and will include subjects who receive at least 1 dose of study treatment and do not have major protocol deviations expected to impact the primary objective of the study. Major protocol deviations will be pre-specified in the SAP. The Per-protocol Analysis Set will be used for sensitivity analyses for the primary efficacy endpoint.
Safety Analysis Set	The Safety Analysis Set will include all subjects who receive at least 1 dose of study treatment. Subjects will be classified according to the treatment assigned at randomization unless the incorrect treatment(s) are received throughout the dosing period in which case subjects will be classified according to the first treatment received. The Safety Analysis Set will be the primary population for evaluating treatment administration/compliance and safety.
PK Analysis Set	The PK Analysis Set will include all treated subjects who have at least 1 concentration above the below limit of quantitation (BLQ) of the study treatment in RIST4721 arms only.

9.3. Statistical Analyses

9.3.1. Study Reporting

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

9.3.2. General Considerations

All individual data will be listed as measured. All statistical summaries and analyses will be performed using SAS software [redacted].

Unless specified otherwise, all statistical analyses will be performed using a 2-sided hypothesis test at the 5% level of significance. Continuous data will be presented using descriptive statistics: number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum. Descriptive statistics on continuous efficacy measures will also include the standard error (SE) or 95% confidence interval (CI) when needed. Categorical data will be summarized by the number and percent of subjects. Time-to-event data will be summarized using the median (if estimable) and the 25^{th} and 75^{th} percentiles. CIs will be 95% and two-sided, unless otherwise stated. All efficacy and safety data will be summarized by treatment group and study part (Part A or Part B). For Part B reporting, treatment groups based on study randomization and overall (all three treatment groups combined) will be included.

For Part A, baseline will be defined as the last observed values prior to randomization. For Part B, baseline of efficacy endpoints will be RIST4721 baseline (before start of active treatment), and baseline of safety endpoints (e.g., lab parameters) will be defined as the last observed values on or prior to the Extension Enrollment visit.

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

9.3.3. Efficacy Analysis

9.3.3.1. Analysis of Primary Endpoint

Primary efficacy endpoint analyses will be performed using the estimand framework defined in Section 3.

The primary endpoint, proportion of subjects achieving a 50% reduction in PPPASI score at Week 12, will be analyzed using a logistic regression model. The model will include stratification (current smoker vs. former or non-smoker) and treatment (all 3 arms) as explanatory variables.

The null hypothesis for the study is to test if treatment effect of RIST4721 400 mg is equal to placebo control. Logistic regression parameter for the difference between RIST4721 400 mg and placebo will be tested by a Wald Chi-Square test at 2-sided alpha=0.05. Odds ratio of the two arms will also be presented.

A stepdown procedure will be used to control the type I error. If 400 mg is significantly different from placebo, logistic regression parameter for the difference between RIST4721 200 mg and placebo will then also be tested by a Wald Chi-Square test at 2-sided alpha=0.05. Odds ratio of the two arms will also be presented.

Subjects who withdraw from the study prior to Week 12 due to any reason (AE, death, lack of efficacy, withdrawal informed consent, and others) will be imputed as non-responders for the primary analyses. Subjects who permanently discontinue study treatment but continue in the study will have their response statuses derived based on their observed data.

Logistic regression model without stratification will be conducted as a sensitivity analysis.

9.3.3.2. Analyses of Key Secondary Endpoints

Subjects achieving PPPGA of 0 or 1 at Week 12 will be analyzed using the same logistic regression model as in the analyses of the primary endpoint.

Subjects achieving a 75% reduction in PPPASI score at Week 12 will be analyzed using the same logistic regression model as in the analyses of the primary endpoint.

9.3.3.3. Type I Error Control for Primary and Key Secondary Endpoints

Type I error for the primary endpoint analyses will be controlled by a stepdown procedure. Only when the primary comparison between 400 mg and placebo is statistically significant at 2-sided alpha=0.05, comparison between 200 mg and placebo will then be conducted.

When both of the above comparisons are significant, treatment comparisons on subjects achieving PPPGA of 0 or 1 at Week 12 will be conducted, starting with 400 mg vs placebo, then 200 mg vs placebo.

9.3.3.4. Analyses of Other Efficacy Endpoints

Absolute change from baseline of PPPGA and PPPASI score will be analyzed using mixed-effects model for repeated measures (MMRM). The MMRM model will include stratification, visit, and treatment as fixed effects, baseline score as a covariate, interaction between visit and treatment, and interaction between visit and baseline score.

Other secondary efficacy endpoints will be analyzed using the same logistic regression model if it is a dichotomous endpoint and MMRM model if it is a continuous endpoint.

Descriptive summary statistics (e.g., n, mean, SD, median, minimum, and maximum for continuous variables; n [%] for categorical variables) will be provided for the exploratory endpoints.

9.3.4. Safety Analyses

9.3.4.1. Adverse Events

AEs verbatim descriptions will be coded using a current version of the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE will be defined as an AE that

is new or worsening after the subject has received the first dose of study treatment and with onset within 30 days after the last dose of study treatment.

An overall summary of subjects with AEs, TEAEs, and SAEs will be tabulated with numbers and percentages of subjects and repeated for severity and relationship to study treatment per treatment group. A subject will be counted only once by the highest severity grade within an SOC and preferred term, even if the subject experienced more than 1 TEAE within a specific SOC and preferred term. The number of TEAEs leading to withdrawal and SAEs leading to death will also be summarized.

The incidence of TEAEs and SAEs will be summarized by body system and treatment group. All AEs and SAEs will be listed by subjects.

9.3.5. Clinical Laboratory Tests

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

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

9.3.6. Electrocardiograms

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

12-lead ECG data will be listed by subject and visit.

9.3.7. Vital Signs

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

Vital signs data will be listed by subject and visit.

9.3.8. Treatment Exposure and Disposition

Exposure to treatment will be summarized descriptively, and compliance on treatments for both active and placebo will be evaluated.

Summary tables for subject disposition and population assignment will be provided.

9.4. Plasma Concentration Analyses

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

9.5. Pharmacodynamic Analyses

Biomarker analysis from serum and skin tap strips will be summarized using a MMRM with change from baseline as the response variable. The model will include fixed covariates for treatment group, week, and baseline biomarker, and a random effect for subject.

9.6. Planned Interim Analyses

No interim analysis is planned for this study.

9.6.1. Data Review Committee

A non-independent, internal DRC comprised of Sponsor representatives not directly involved in the conduct of the study, and/or external expert physician(s), will regularly monitor overall safety and emerging efficacy results on an unblinded basis, as well as general aspects of study conduct, to ensure that the benefits and risks of study participation remain acceptable.

Based on these regular reviews of emerging results, the DRC will recommend continuation, modification, or termination of the study. The DRC charter will include potential reasons for modifications and/or termination of the study.

Composition of the DRC, meeting structure, schedule, and procedures, the content and format of DRC reports, and other relevant details will be determined in consultation with DRC members and detailed in a separate DRC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations (Site Responsibilities)

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable ICH GCP Guidelines (E6 R2).
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant subject-facing documents (e.g., surveys, instructions for use, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of title 21 Code of Federal Regulations (CFR) (or equivalent as applicable), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Informed Consent Process

Prior to enrolling in the study, and before performance of any procedures, potential subjects will attend a screening session at which time they will be provided with full information concerning details of the study assessments and procedures. The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, ICH guidelines, local regulations, and data privacy laws (e.g., The General Data Protection Regulation (EU) 2016/679 [GDPR] and Health

Insurance Portability and Accountability Act [HIPAA]) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the subject entered the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

Subjects entering Part B will sign an OLE-specific ICF.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

10.1.3. Data Protection

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law(s). The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.4. Dissemination of Clinical Study Data

A clinical study report will be developed by the Sponsor at completion of data analysis. This report will be an integrated clinical and statistical report prepared according to the ICH E3 guidelines.

Sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

10.1.5. Data Quality Assurance

All subject data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain attributable, legible, contemporaneous, original, and accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Details describing monitoring strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of

noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study including quality review of the data.

The Sponsor maintains ultimate responsibility for the quality and integrity of study data, even if study-related duties and functions are transferred to other individuals or organizations (e.g., contractors or contract research organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are attributable, legible, contemporaneous, original, and accurate from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator per ICH GCP and local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.6. Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents should be generated utilizing good documentation practices and are filed at the investigator's site.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.7. Study and Site Closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at its sole discretion. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study treatment development.

10.1.8. Publication Policy

The publication policy is located within the Clinical Study Agreement with the investigator and/or Institution.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the central laboratory, unless otherwise noted.
- Protocol-specific requirements for inclusion or exclusion of subjects, including those based on selected laboratory test results, are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report in subject's source records.

Table 7: Protocol-Required Safety Laboratory Assessments

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])
Serum chemistry	Albumin, alkaline phosphatase, ALT, AST, chloride, cholesterol (non-fasting), creatinine (enzymatic), GGT, glucose random, hs-CRP, LDH, potassium, sodium, total bilirubin, triglycerides, urea (BUN), uric acid
Urinalysis	Dipstick and microscopic analysis
Urine pregnancy test	For WOCBP (at each visit, except screening) Note: In Part B, at Week E12, WOCBP will be provided with at-home urine pregnancy tests to be conducted every 4 weeks at home (at non-study visits).
Virology	SARS-CoV-2 antigen test at each visit; if positive, will be confirmed by PCR test
Laboratory tests required at screening only	β-hCG for WOCBP (screening only) Tuberculosis test (PPD or QuantiFERON-TB Gold) If done within 6 months and negative result is available for documentation, test is not required at screening Serology (HBV [HBsAg, anti-HBc], HCV, HIV, SARS-CoV-2 antibody) at screening. If anti-HBc is positive, HBV DNA test will be tested; If anti-HBc and/or HBsAg are positive and the HBV DNA test is negative, HBV DNA quantitation should be monitored at least every 3 months. If HCV antibody is positive, HCV RNA will be tested. Urine drugs of abuse test (amphetamines, methamphetamines, cocaine, and phencyclidine)
Laboratory texts at baseline	SARS-CoV-2 antibody test

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; GGT, gamma-glutamyl-transferase; HBc, core hepatitis B antibody; HBsAg, hepatitis B surface antigens; HBV, hepatitis B virus; HCT, hematocrit; HCV, hepatitis C virus; Hgb, hemoglobin; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; INR, international normalized ratio; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PCR, polymerase chain reaction; PLT, platelets; PPD, purified protein derivative; PT, prothrombin time; RBC, red blood cell (count); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WBC, white blood cell (count); WOCBP, women of childbearing potential

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a subject or clinical study subject, whether or not considered related to the study treatment. NOTE: An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease in any subject in a clinical study (including those in an untreated control group), whether or not considered related to the study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition other than the disease under study including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless

judged by the investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

Results in death

- **Is life-threatening**

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, which hypothetically might have caused death, if it were more severe.

- **Requires inpatient hospitalization or prolongation of existing hospitalization**

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- **Results in persistent disability/incapacity**

The term disability means a substantial disruption of a person's ability to conduct normal life functions.
This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

An SAE is defined as any untoward medical occurrence that, at any dose:
• **Is a congenital anomaly/birth defect**
• **Other situations:** Medical or scientific judgment should be exercised in deciding whether SAE 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 medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, 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.

10.3.3. Definition of Suspected and Unsuspected Adverse Reaction

Suspected adverse reactions are defined as:
• Any AE for which there is a reasonable possibility that the study treatment caused the AE. For the purposes of Sponsor regulatory safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the study treatment and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by study treatment(s).
Unexpected Adverse events are defined as:
• AE that is not listed in the IB or approved label of the study treatment or is not listed at the specificity or severity that has been observed

10.3.4. Recording and Follow-Up of Adverse Events and Serious Adverse Events

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the AE/SAE eCRF page.

AE and SAE Recording

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will assess intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.

- ***Related*** – The AE is known to occur with the study treatment, there is a reasonable possibility that the study treatment caused the AE, or there is a temporal relationship between the study treatment and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study treatment and the AE.
- ***Not Related*** – There is not a reasonable possibility that the administration of the study treatment caused the event, there is no temporal relationship between the study treatment and event onset, or an alternate etiology has been established.
- The investigator will use clinical judgment to determine the relationship.

Assessment of Causality

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the investigator always assesses causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology, if available.
- New or updated information will be recorded in the originally completed eCRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5. Reporting of SAEs

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

All SAEs should be reported as soon as possible and no later than 24 hours after the site is notified of the event.

- The mechanism for reporting an SAE to the Sponsor will be the electronic data (eCRF) capture system.
- The site will enter the SAE data into the electronic system as soon as it becomes available and within 24 hours of learning of the event.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If the eCRF capture system is down or no longer active, the site should submit any reports of a new or updated SAE by submitting the paper SAE form to the contact below within 24 hours. The site should also notify the Medical Monitor (or designee) in these circumstances.

Contacts for SAE reporting are:

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

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterilized (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

There is no known drug interaction between RIST4721 and hormonal contraception.

Male Subjects:

Male subjects are eligible to participate if they agree to the following from informed consent through 5 days after the last dose of study treatment：

- Be abstinent and agree to remain abstinent

OR

- Must agree to use contraception/barrier (a male condom) and spermicide

  OR

- Be surgically sterile

Female Subjects:

- A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)

OR

  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency (see table below), from consent through 5 days after the last dose of study treatment, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
  - A WOCBP must have negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) at screening and a negative urine pregnancy test before first administration of study treatment. On-treatment urine pregnancy tests will be done routinely as specified in the SoA. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required and results must be negative.

Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

Highly Effective Methods[a] That Have Low User Dependency
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD) (hormonal and non-hormonal)
• Surgical sterilization
• Bilateral tubal occlusion or ligation
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[a] That Are User-Dependent
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*

[a] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
[b] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction).

10.4.3. Collection of Pregnancy Information

Male subjects with partners who become pregnant:

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study.
- After obtaining the necessary signed ICF from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The Sponsor will attempt to follow the female partner to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. The Sponsor will follow the female partner until birth or termination of pregnancy when possible. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female subjects who become pregnant

Any female subject who becomes pregnant while participating in the study will discontinue study treatment(s). Additionally:

- The investigator will collect pregnancy information, which will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy.
- The subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate and the information will be forwarded to the Sponsor. The subject will be followed until birth or termination of pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post study pregnancy related SAE considered reasonably related to the study treatment by the investigator will be reported to the Sponsor as described in Section 10.3.5. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

10.5. Appendix 5: Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) Scoring

Left palm, right palm, left foot, and right foot are assessed based on 3 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 foot, and right foot) 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.

10.6. Appendix 6: Guidance to Address the COVID-19 Pandemic and Potential Impact on the Clinical Study

In the occurrence of a global health emergency affecting the conduct of the ongoing study, such as the COVID-19 pandemic, study conduct may be adjusted due to subjects being in self-isolation/quarantine, limited access to public places (including hospitals) due to the risk of spreading infections, and health care professionals being committed to critical tasks.

Adjustments to this protocol may be made as described below, in line with global regulatory authorities' guidance in order to ensure the safety of study subjects, maintain compliance with GCP, and minimize the risks to study integrity during the COVID-19 pandemic (Health Canada, April 7, 2020; Australian Government, April 9, 2020; EMA, April 2020; MHRA, March 19, 2020; FDA, March 2020). Other countries may issue their own guidance requiring country-specific recommendations to be followed.

Informed Consent

- If written consent by the study subject is not possible (e.g., because of physical isolation due to COVID-19 or other global health emergencies), consent could be given orally by the study subject and documented according to regulatory guidance.
- Study subjects and the person obtaining consent could sign and date separate ICFs.
- In case written informed consent cannot be obtained at the clinical site, electronic informed consent can be obtained remotely. Alternatively, the consent form may be sent to the subject or the subject's legally authorized representative by facsimile or e-mail, and the consent interview may then be conducted by telephone/teleconference when the subject or subject's legally authorized representative can read the consent form during the discussion; the subject or subject's legally authorized representative will be requested to sign and date a blank piece of paper with a written statement affirming that they agree to participate in the study and documented according to regulatory guidance.
- If re-consent is necessary for the implementation of **new urgent changes in study conduct** (mainly expected for reasons related to global health emergencies or important safety issues for other studies), alternative ways of obtaining consent may include contacting the study subject via phone or video-calls and obtaining verbal consent, to be documented in the study subjects' medical records, supplemented with e-mail confirmation.
- The informed consent procedure is to remain compliant with the study protocol as well as local regulatory requirements. All relevant records should be archived in the investigator's site master file. A correctly signed and dated ICF should be obtained from the study subjects later, as soon as possible.

Study Visits and Procedures

- COVID-19 screening procedures that may be mandated by the health care system in which a clinical study is being conducted do not need to be reported as an amendment to the protocol even if done during clinical study visits. The investigator in consultation with the Sponsor will decide if it is in the best interest of COVID-19-positive subjects to remain in the study.
- In the case of missed visits due to global health emergencies (or other pandemic-related reasons):
  - The site should make every effort to contact the study subject to confirm and document the reason for the missed visit and at minimum, evaluate AEs/SAEs, and concomitant medications to assess subject safety.
- In order to maintain the integrity of the study, alternative methods of collecting study procedures may be considered where possible:
  - In cases where global health emergencies-related circumstances preclude a visit to the investigative site, remote visits (e.g., by telemedicine or phone contact) will be allowed for relevant study procedures.
  - In certain situations, with Sponsor approval, and according to site business continuity plans, home visits may be used, e.g., to collect laboratory samples and assessments as required by the protocol.
  - Study assessments will only be conducted in a remote manner if they can be done without affecting the well-being of the subject during the study and with the same level of scientific integrity as assessments conducted in a physical study center.
  - Remote study assessments can be completed via online technology. The subject may interact with study personnel using online communication tools that incorporate telemedicine.
  - In certain situations, with Sponsor approval, a local laboratory may be used to collect laboratory samples as required by the protocol. Local analysis can be used for safety decisions.
  - Urine pregnancy tests can be performed if serum pregnancy cannot be performed.

Supply of Study Treatment

- Alternative methods of supplying study treatment to enrolled study subjects (e.g., direct-to-patient shipment from site) may be considered where possible.
- Additional study treatment will not be released to the subject without an evaluation of subject safety, including protocol-required laboratory results (at a minimum hematology, clinical chemistry, and pregnancy for WOCBP), and clearance communicated to the subject. Subjects must also consent for study treatment shipment.

Monitoring and Audits

- Certain Sponsor oversight responsibilities, such as monitoring and quality assurance activities, may need to be re-assessed and temporary, alternative proportionate mechanisms of oversight may be required. On-site audits will be avoided or postponed, and if permitted under local regulations, social distancing restrictions should apply.
- Canceling or postponing on-site monitoring visits and extending the period between monitoring visits will be allowed.
- To the extent on-site monitoring remains feasible, it should take into account national, local, and/or organizational social distancing restrictions.
- Centralized monitoring can be considered for data acquired by electronic data capture systems (e.g., eCRFs, central laboratory or ECG data, electronic patient reported outcomes) that are in place or could be put in place, providing additional monitoring capabilities that can supplement and temporarily replace on-site monitoring through remote evaluation of ongoing and/or cumulative data collected from study sites, in a timely manner.
- Off-site monitoring can be conducted and will include phone calls, video visits, e-mail, or other online tools in order to discuss the study with the investigator and site staff. Remote monitoring should be focused on review of critical study site documentation and source data. These activities could be used to get information on the clinical study progress, to exchange information on the resolution of problems, review of procedures, study subject status, as well as to facilitate remote site selection and investigator training for critical study procedures.

Risk Mitigation

- The Sponsor will continually assess whether the limitations imposed by the COVID-19 public health emergency on protocol implementation pose new safety risks to study subjects, and whether it is feasible to mitigate these risks by amending study processes and/or procedures.

10.7. Appendix 7: List of Abbreviations

Abbreviation Term	Description
AE	adverse event
ANC	absolute neutrophil count
BSA	body surface area
CCR2	chemokine motif receptor 2
CI	confidence interval
CRO	contract research organization
CXCR1	CXC chemokine receptor type 1
CXCR2	CXC chemokine receptor type 2
CYP	cytochrome P450
DLQI	Dermatology Life Quality Index
DRC	Data Review Committee
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
GCP	Good Clinical Practice
HEK293	human embryo kidney 293
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
IRB	institutional review board
IRT	interactive response technologies
LLN	lower limit of normal
MMRM	Mixed-effects model for repeated measures
MSU	monosodium urate
NRS	numeric rating scale
OLE	open-label extension
PCR	polymerase chain reaction
PD	pharmacodynamics

Abbreviation Term	Description
PGA	Physician Global Assessment
P-gp	p-glycoprotein
PK	pharmacokinetics
PPD	purified protein derivative
PPP	palmoplantar pustulosis
PPPASI	Palmoplantar Pustulosis Psoriasis Area and Severity Index
PPPASI-50	50% reduction in PPPASI
PPPGA	Palmoplantar Pustulosis Physician Global Assessment
PtGA	Patient Global Assessment
PUVA	psoralen and ultraviolet A
QD	once daily
QTcF	QT interval corrected by Fridericia
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SF-36	36-Item Short Form Survey
SoA	Schedule of Activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WOCBP	women of childbearing potential

10.8. Appendix 8: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC). Prior amendments are provided in this section in chronological order.

Prior Amendments

Amendment 1.0; 09 August 2021

Summary of Changes (in order of appearance)

Section Number and Name	Description of Change	Rationale for Change
1.1 Synopsis 3 Objectives, Endpoints and Estimand 9.3.2.1 Analysis of Primary Endpoint	• Add primary estimand	• To satisfy updated regulatory guidelines
1.3 Schedule of Activities 10.2 Appendix 2 Clinical Laboratory Tests	• Change from PCR to antigen test (with confirmatory PCR if positive) for routine COVID testing	• To allow results to be available during clinic visit.
1.3 Schedule of Activities 8.5 Pharmacokinetics	• Clarify PK samples will also be collected in case of potentially related SAEs • Clarify PK samples will be only analyzed in subjects receiving active treatment (e.g. RIST4721)	• To better assess safety • For clarity
2.3.1 Risk Assessment	• Update potential risk relating to drug interaction	• Based on emerging data from recently completed RIST4721-103 drug interaction study
5.1 Inclusion Criteria 6.7.2 Prohibited Medications	• Removal of SARs-CoV-2 vaccination requirement (inclusion criterion no. 8) • Add SARs-CoV-2 vaccine to prohibited medications list	• Based upon up to date information regarding vaccination status and potential immune protection from emerging variants • Based upon lack of data with RIST4721 and vaccines
5.2 Exclusion Criteria 6.7.2 Prohibited Medications (Table 4)	• Clarify Exclusion criterion no. 2u regarding SARS-CoV-2 infection determination • Update duration of exclusion topical medication to 2 weeks (exclusion criterion no. 5) • Clarify exclusion criterion 12 for subjects receiving RIST4721	• To align with SoA • To align with standard of care in the countries where study is being conducted • For clarity
10.1.2 Informed Consent Process	• Clarify requirements for ICF	• To comply with international regulations

Section Number and Name	Description of Change	Rationale for Change
10.4 Appendix 4 Contraceptive Guidance	• Require double barrier for male subjects (e.g. condom and spermicide)	• For safety and consistency
General	• Minor administrative changes and clarifications made throughout the protocol • Correct typographical errors, hyperlinks/cross-references, style, and formatting (not tracked). • Align across protocol sections. • Update glossary (not tracked). • Update header	• For consistency and clarity • Alignment across documents

Amendment 2.0; 08 September 2021

Summary of Changes (in order of appearance)

Section Number and Name	Description of Change	Rationale for Change
2.3.1 Risk Assessments	• Update number of completed Phase 1 studies and number of healthy subjects exposed to RIST4721	• Based on recently completed Phase 1 study
2.3.3 Overall Benefit: Risk Conclusion	• Clarify that SARS-CoV-2 vaccines are a prohibited medication	• For consistency with Section 5.2 and Section 6.7.2
5.2 Exclusion Criteria	• Clarify exclusion criterion 5 that topical medications must be discontinued 2 weeks prior to Day 1	• For clarity
5.2 Exclusion Criteria	• Clarify exclusion criterion 14 that subjects unwilling to avoid the foods or beverages specified are excluded	• For clarity

Amendment 3.0; 10 November 2021

Overall Rationale for the Amendment:

Summary of Changes (in order of appearance)

Section Number and Name	Description of Change	Rationale for Change
2.3.3 Overall Benefit: Risk Conclusion 6.7.2 Prohibited Medications	• Reclassified SARS-CoV-2 vaccine as Restricted Medication (vs. Prohibited Medication) • In the case that a subject requests or requires new or additional vaccination for SARS-CoV-2, guidance was added	• To allow flexibility for subjects to receive SARS-CoV-2 vaccine during the study • To add clarification about the benefit : risk discussion

Section Number and Name	Description of Change	Rationale for Change
6.7.3 Restricted Medications	for the Investigator to discuss the potential risks and benefits with the subject prior to making a determination	between the investigator and the subject
5.1 Inclusion Criteria	• Added IC #8: Subject has been previously vaccinated for SARS-CoV-2 or has chosen not to be vaccinated at the start of participation (screening) in the clinical study.	• To clarify entry criteria regarding vaccination status
10.3.5 Reporting of SAEs	• Amended contact in the case of an SAE/Pregnancy if the electronic system is unavailable	• To add clarification regarding SAE reporting process
General	• Minor administrative changes and clarifications made throughout the protocol • Correct typographical errors, hyperlinks/cross-references, style, and formatting (not tracked). • Align across protocol sections. • Update glossary (not tracked). • Update header	• For consistency and clarity • Alignment across documents

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