CLINICAL STUDY PROTOCOL

TITLE PAGE

Protocol Title:	A Randomized, Double-blinded, Placebo-controlled, Phase 2a Study to Evaluate the Efficacy and Safety of RIST4721 in Subjects with Hidradenitis Suppurativa
Short Title:	RIST4721 in subjects with hidradenitis suppurativa
Protocol Number:	RIST4721-221
Investigational Product:	RIST4721
Study Phase:	Phase 2a
Sponsor Name:	Aristea Therapeutics, Inc.
Legal Registered Address:	[redacted]
Regulatory Agency Identifier Number(s):	IND: 160528
Version:	Original, Version 1.0
Approval Date:	11 February 2022

SPONSOR'S AUTHORIZED REPRESENTATIVE SIGNATURE PAGE

Protocol Title:	A Randomized, Double-blinded, Placebo-controlled, Phase 2a Study to Evaluate the Efficacy and Safety of RIST4721 in Subjects with Hidradenitis Suppurativa
Protocol Number:	RIST4721-221
Version and Date:	Original, Version 1.0

[redacted] _____ [redacted]

Date

Aristea Therapeutics, Inc.

Medical Monitor name and contact information will be provided separately.

INVESTIGATOR AGREEMENT

Protocol Title:	A Randomized, Double-blinded, Placebo-controlled, Phase 2a Study to Evaluate the Efficacy and Safety of RIST4721 in Subjects with Hidradenitis Suppurativa
Protocol Number:	RIST4721-221
Version and Date:	Original, Version 1.0

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Randomized, Double-blinded, Placebo-controlled, Phase 2a Study to Evaluate the Efficacy and Safety of RIST4721 in Subjects with Hidradenitis Suppurativa

Short Title: RIST4721 in subjects with hidradenitis suppurativa

Rationale

RIST4721 is a small-molecule 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 hidradenitis suppurativa (HS). HS is a chronic, inflammatory skin disease characterized by recurrent painful nodules and abscesses that rupture, leading to the formation of sinus tracts and scarring. Recruitment of neutrophils to HS lesion sites may play an essential role in the development of the painful inflammatory nodules and abscesses that characterize the disease (Narla, 2021).

CXCR2 is a G-protein coupled receptor (GPCR) expressed on the epithelium and on a variety of inflammatory cells (including neutrophils and macrophages). It 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 interleukin (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 HS (Boppana, 2014; Aarts, 2021).

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 (Nicholls, 2015). 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 evaluated in 5 Phase 1 clinical studies in healthy subjects and is also being evaluated in clinical setting for treatment of palmoplantar pustulosis (PPP) and familial Mediterranean fever (FMF). RIST4721 was generally well tolerated in completed clinical studies. The present study will evaluate the safety, tolerability, and efficacy of RIST4721 monotherapy in subjects with moderate-to-severe HS.

Objectives, Endpoints, and Estimand (Primary and Secondary)

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of RIST4721 monotherapy in subjects with moderate-to-severe HS	• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
Key Secondary	
• To assess the efficacy of RIST4721 in subjects with moderate-to-severe HS	• Proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) 50 at Week 12
Key Secondary Estimand	
Treatment regimen: RIST4721 400 mg, placebo **Target population**: Subjects with HS as defined by the inclusion and exclusion criteria (Section 5), grouped per randomization assignment **Variable of interest**: Proportion of subjects achieving HiSCR50 at Week 12 defined as at least a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to baseline. **Intercurrent events and corresponding strategy**: For subjects who discontinue study treatment prior to Week 12 due to any reason, their last observation will be used to impute response status. **Population-level summary variable**: Difference in proportions	
Secondary	
• Additional secondary efficacy endpoints	• Proportion of subjects achieving HS Clinical Response 75 (HiSCR75) at Week 12 • Proportion of subjects with flare (≥ 25% increase and ≥ 2 absolute increase in AN count relative to baseline) at Week 12. • Proportion of subjects achieving AN count of 0, 1, or 2 at Week 12 • Change from baseline in skin pain score using the numeric rating scale (NRS) at Week 12 • Change from baseline in International HS Severity Score System (IHS4) at Week 12
• To assess pharmacokinetics (PK) of RIST4721 in subjects with moderate-to-severe HS	• RIST4721 PK characterization in subjects with moderate-to-severe HS

Overall Design

This is a Phase 2a, randomized, double-blind, placebo-controlled, multicenter, 12-week study to evaluate the efficacy and safety of RIST4721 once daily (QD) in subjects with moderate-to-severe HS.

The study will consist of a screening period, a treatment period, and a follow-up period. Study schema is shown in Section 1.2. Subjects will be evaluated throughout the study as specified in the Schedule of Activities (SoA; Section 1.3).

After signing an informed consent form (ICF), subjects will be screened for study eligibility over 4 weeks.

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

- RIST4721 400 mg QD
- Placebo QD

All subjects who remain on study treatment through and including Week 12 will be asked to return for a follow-up visit, approximately 4 weeks after their last dose of study treatment, to assess safety and efficacy. Subjects who permanently discontinue study treatment will be followed as described in Section 7.1.

Treatment Groups and Number of Subjects:

Approximately 33 subjects are planned to be enrolled (~22 subjects expected in the RIST4721 group and 11 subjects in the placebo group).

Duration

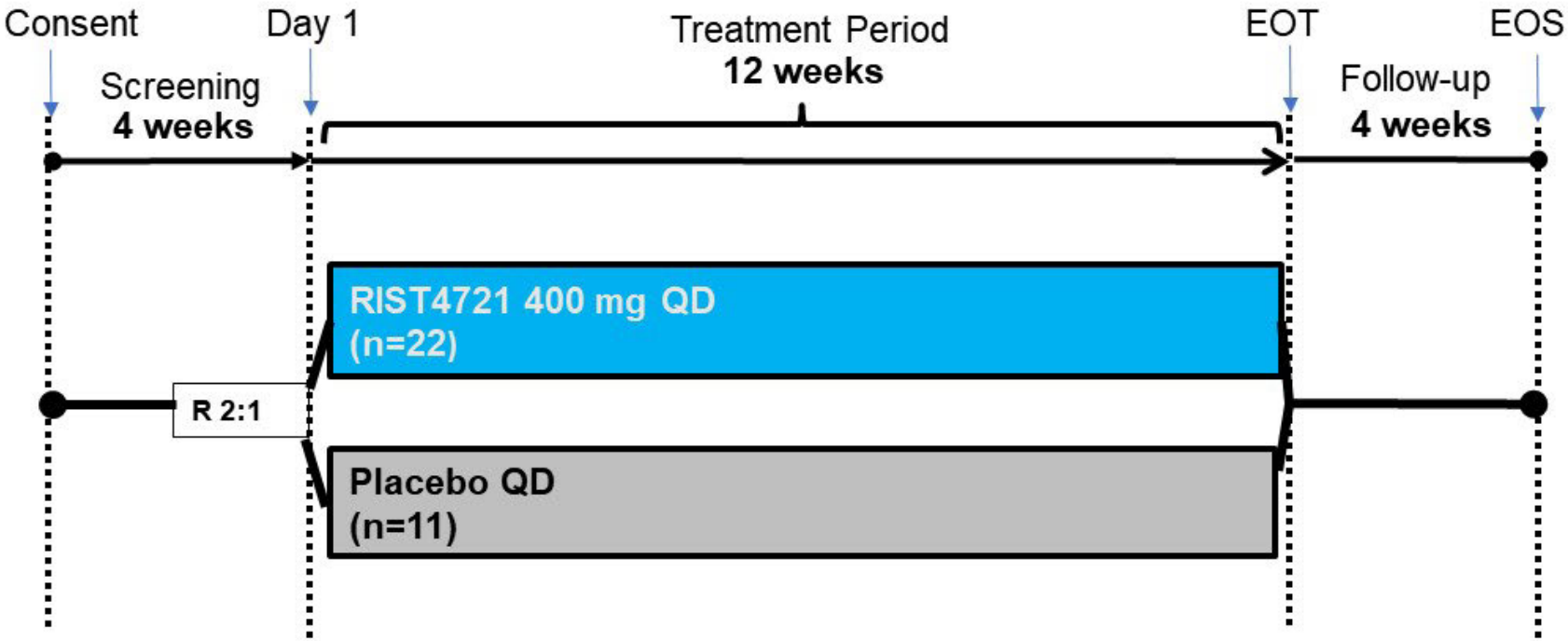
For each subject, the total study duration is expected to be approximately 20 weeks as follows:

Screening period:	4 weeks
Treatment period:	12 weeks
Follow-up period	4 weeks from last dose of study treatment

Data Review Committee: No

1.2. Study Scheme

Figure 1: Study Scheme



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

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities

Guidance to address the coronavirus disease 2019 (COVID-19) global pandemic and potential impact on the clinical study are provided in Section 10.5, Appendix 5.

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

	Screening	Treatment Period					Follow-up	Notes
Study Week	**-4 to -1**	**Baseline (Week 0)**	**2**	**4**	**8**	**12/EOT**	**+4 Weeks from EOT**	End of treatment (EOT); subjects discontinuing treatment prematurely will attend EOT visit and then continue study visits as planned.
Study Day	**-28 to -1**	**1**	**15**	**29**	**57**	**85**	**+28 days from EOT**	
Visit Window (days)			**±3**	**±3**	**±3**	**±7**	**±3**	
SARS-CoV-2 PCR test	X							Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); polymerase chain reaction (PCR).
Urine drug screen	X							Refer to Appendix 2, Section 10.2.
Pregnancy test (for WOCBP)	S	U	U	U	U	U	U	Serum (S); Urine (U); women of childbearing potential (WOCBP) If urine test is positive, confirm with serum test.
FSH (postmenopausal women only)	X							Follicle stimulating hormone (FSH)
Study Treatment Administration								
Randomization		X						
Study treatment distribution		X		X	X			
In clinic study treatment administration		X	X	X	X	X		
Study treatment accountability				X	X	X		
Safety Assessments								
Adverse events	X[a]	<========== X ==========						**a.** AEs will be collected after signing informed consent.
Concomitant medications		X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	Assessments should occur in the following order: 1. Vital signs 2. 12-lead ECG (refer to Section 8.3.3) 3. Blood draws for safety laboratories; refer to Appendix 2, Section 10.2 Note: questionnaires are recommended to be completed before any of these procedures.
Weight	X					X	X	
Physical examination	X					X		
12-lead electrocardiogram (ECG)	X	X	X	X	X	X	X	
Serum chemistry	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	
SARS-CoV-2 antigen test		X	X	X	X	X	X	If positive, will be confirmed with SARS-CoV-2 polymerase chain reaction (PCR) test.

	Screening	Treatment Period					Follow-up	Notes
Study Week	**-4 to -1**	**Baseline (Week 0)**	**2**	**4**	**8**	**12/EOT**	**+4 Weeks from EOT**	End of treatment (EOT); subjects discontinuing treatment prematurely will attend EOT visit and then continue study visits as planned.
Study Day	**-28 to -1**	**1**	**15**	**29**	**57**	**85**	**+28 days from EOT**	
Visit Window (days)			**±3**	**±3**	**±3**	**±7**	**±3**	
Efficacy/PK Assessments								
HiSCR assessment		X	X	X	X	X	X	HS Clinical Response (HiSCR). Calculated based on abscess and inflammatory nodule (AN) count
Lesion Count	X	X	X	X	X	X	X	Includes AN and draining fistula
NRS for skin pain	X	X	X	X	X	X	X	Numeric rating scale (NRS).
IHS4		X	X	X	X	X	X	International Hidradenitis Suppurativa Severity Score System (IHS4).
HS-IGA		X	X	X	X	X	X	Hidradenitis Suppurativa-Investigator's Global Assessment (HS-IGA).
HS-PGA		X	X	X	X	X	X	Physician Global Assessment (HS-PGA).
HiSQOL		X				X	X	HS Quality of Life (HiSQOL).
DLQI		X				X	X	Dermatology Life Quality Index (DLQI).
Medical photography of HS-affected areas		X				X		To be performed at select sites.
Serum sample for RIST4721 concentration		X	X	X	X	X		Blood samples for trough PK will be collected 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 experience a potentially related SAE (refer to Section 8.5.1).
Serum sample for biomarkers		X	X	X	X	X	X	To be collected and stored for future analyses.

2. INTRODUCTION

2.1. Study Rationale

RIST4721 is a small-molecule high-potency antagonist of human CXCR2 that is proposed to have potential as a novel oral treatment for neutrophil-mediated inflammatory diseases, including HS. HS is a chronic, inflammatory skin disease characterized by recurrent painful nodules and abscesses that rupture, leading to the formation of sinus tracts and scarring. Recruitment of neutrophils to HS lesion sites may play an essential role in the development of the painful inflammatory nodules and abscesses that characterize the disease (Narla, 2021).

CXCR2 is a GPCR expressed on the epithelium and on a variety of inflammatory cells (including neutrophils and macrophages). It 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 HS (Boppana, 2014; Aarts, 2021).

RIST4721 antagonism of CXCR2 was demonstrated in vitro by measuring both primary binding affinity in 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 CXCR1 and CCR2, respectively (Nicholls, 2015). 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 MSU crystal-induced inflammation. When rats were previously challenged with MSU injection, RIST4721 caused significant, dose-dependent decreases in exudate volume, total WBC count, and neutrophil infiltration at doses 30, 100, and 300 µmol/kg.

RIST4721 was evaluated in 5 Phase 1 clinical studies in healthy subjects and is also being evaluated in clinical setting for treatment of PPP and FMF. RIST4721 was generally well tolerated in completed clinical studies. The present study will evaluate the safety, tolerability, and efficacy of RIST4721 monotherapy in subjects with moderate-to-severe HS.

2.2. Background

2.2.1. Hidradenitis Suppurativa

HS is a recurrent inflammatory skin disease characterized by comedones, painful inflammatory nodules, abscesses, dermal tunnels, and scarring, with a predilection for intertriginous areas of the body (axillae, inguinal, and anogenital regions) (Wipperman, 2019; Sabat, 2020). Due to its chronic nature and frequently occurring relapses, HS has a great impact on the patient's quality of life, deeply affecting social, working, and psychological aspects (Alikhan, 2009). Prevalence estimates of HS in North America and Europe range from < 1 to 4%. HS typically occurs after

puberty, with the average age of onset in the second or third decades of life and with a female predominance (Revuz, 2008; Cosmatos, 2013; Vazquez, 2013; Deckers, 2014; Garg, 2017).

HS is a multifactorial disease in which genetic and environmental factors play a key role including smoking and obesity. The diagnosis of HS is made by lesion morphology (nodules, abscesses, tunnels, and scars), location (axillae, inframammary folds, groin, perigenital, or perineal), and lesion progression (2 recurrences within 6 months or chronic or persistent lesions for ≥3 months) (Saunte, 2017; Preda-Naumescu, 2021).

The precise pathogenesis of HS remains still unclear. The primary event in disease development is thought to be follicular occlusion, based on histopathological observations in very early lesions. The occlusion of the terminal hair follicle results in dilation and cyst formation, followed by rupture of the hair follicle. The introduction of follicular contents to the surrounding dermis induces an inflammatory response and subsequent formation of abscess, sinus tracts, fibrosis, and scars (von Laffert, 2010; Prens, 2015; Napolitano, 2017).

HS management usually consists of the combination of anti-inflammatory therapies in addition to surgical intervention and lifestyle changes such as smoking cessation and weight loss (Saunte, 2017; van Straalen, 2020). Therapeutic approaches have evolved rapidly in the last decade and include the use of topical therapies, systemic antibiotics, hormonal therapies, and a wide range of immunomodulating medications (Napolitano, 2017; Alikhan, 2019). First-line treatment options may include the use of systemic antibiotics like tetracyclines and the combination of clindamycin and rifampicin. Adalimumab, a monoclonal antibody against tumor necrosis factor (TNF)-α, is the only biologic which has been approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of moderate to severe HS (Lim, 2019).

The inflammatory response in HS has in recent years been better characterized, although there are many components that remain to be elucidated. In particular, it has been recently established that innate pro-inflammatory cytokines (eg, IL-1β, and TNF-α), mediators of activated T helper (Th)1 and Th17 cells (eg, interferon gamma [IFN-γ], and IL-17), and effector mechanisms of neutrophilic granulocytes, macrophages, and plasma cells are involved (Kelly, 2015; Moran, 2017; Vossen, 2018; Wolk, 2020; Scala, 2021). It is hypothesized that pharmacologic manipulation of the various pathways involved in the process of neutrophil recruitment and activation could allow for successful control and stabilization of HS lesions and the remission of active, severe flares (Narla, 2021).

2.2.2. Study Treatment: RIST4721

RIST4721 is a high-potency antagonist of human CXCR2 as validated in in vitro and in vivo studies. Five Phase 1 clinical studies of RIST4721 in healthy subjects and one Phase 2a study in patients with moderate-to-severe PPP have been completed. Phase 2 studies in subjects with PPP and FMF are ongoing. RIST4721 was generally well tolerated in the clinical setting.

For more detailed information on nonclinical and clinical studies with RIST4721 refer to the Investigator's Brochure (IB).

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 5 Phase 1 clinical studies in healthy subjects (155 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 once daily [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 serious adverse events (SAEs) or deaths were reported.

Table 2 summarizes identified and potential risks associated with RIST4721 as well as risk mitigation strategies.

Table 2: 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 6.5.2) • 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.

Safety Considerations of RIST4721	Summary of Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal effects	GI 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 nonclinical 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.
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

Evaluation of the serum and lesional skin from patients with HS compared to healthy volunteers suggests that HS is a condition driven by neutrophils (Navrazhina, 2021). Reduction in migration of neutrophils to the skin of patients with HS in participants randomized to the RIST4721 treatment arm may have an improvement in their HS condition. Additionally, participation in this study may help generate future benefit for larger groups of subjects with HS 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 risk to subjects in this study will be minimized by compliance with the eligibility criteria, proper study design, and close monitoring.

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 receiving treatment during 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 also 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.

It is expected that subjects treated with RIST4721 might see an improvement in their HS condition and improved quality of life. This study may inform future studies of RIST4721 in HS. All quality, pharmacology, and toxicology data, as well as 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 HS with RIST4721, and therefore to initiate this study.

Considering the potential benefits, potential risks, and risk mitigation measures that have been implemented in clinical studies with RIST4721, the Sponsor considers the benefit-risk profile of administering RIST4721 for the treatment of HS to be favorable. The overall benefit-risk associated with administration of RIST4721 will be continually reassessed with the emergence of additional data.

3. OBJECTIVES, ENDPOINTS, AND ESTIMAND

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of RIST4721 monotherapy in subjects with moderate-to-severe HS	• Incidence of TEAEs and SAEs
Key Secondary	
• To assess the efficacy of RIST4721 in subjects with moderate-to-severe HS	• Proportion of subjects achieving HiSCR50 at Week 12
Key Secondary Estimand	
Treatment regimen: RIST4721 400 mg, placebo **Target population**: Subjects with HS as defined by the inclusion and exclusion criteria (Section 5), grouped per randomization assignment. **Variable of interest**: Proportion of subjects achieving HiSCR50 at Week 12 defined as at least a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to baseline. **Intercurrent events and corresponding strategy**: For subjects who discontinue study treatment prior to Week 12 due to any reason, their last observation will be used to impute response status. **Population-level summary variable**: Difference in proportions	
Secondary	
• Additional secondary efficacy endpoints	• Proportion of subjects achieving HS Clinical Response 75 (HiSCR75) at Week 12. • Proportion of subjects with flare (≥ 25% increase and ≥ 2 absolute increase in AN count relative to baseline) at Week 12. • Proportion of subjects achieving AN count of 0, 1, or 2 at Week 12. • Change from baseline in skin pain score using the numeric rating scale (NRS) at Week 12. • Change from baseline in International HS Severity Score System (IHS4) at Week 12
• To assess pharmacokinetics (PK) of RIST4721 in subjects with moderate-to-severe HS	• RIST4721 PK characterization in subjects with moderate-to-severe HS

Objectives	Endpoints
Exploratory	
• To evaluate the effect of RIST4721 on exploratory measures of efficacy	• Proportion of subjects achieving at least 2-grade improvement on the HS-Physician Global Assessment (HS-PGA). • Proportion of subjects achieving 0 or 1 on the HS-PGA • Proportion of subjects with HS-Investigator's Global Assessment (HS-IGA) with at least 2-grade improvement relative to baseline at Week 12 • Proportion of subjects achieving 0 or 1 on the HS-IGA • Change from baseline in AN count at Week 12 • Change from baseline in: – HS Quality of Life (HiSQOL) – Dermatology Life Quality Index (DLQI) Total Score at Week 12.

4. STUDY DESIGN

4.1. Overall Study Design

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

The study will consist of a screening period, a treatment period, and a follow-up period. Study schema is shown in Section 1.2. Subjects will be evaluated throughout the study as specified in the Schedule of Activities (SoA; Section 1.3).

After signing an informed consent form (ICF), subjects will be screened for study eligibility over 4 weeks.

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

- RIST4721 400 mg QD
- Placebo QD

All subjects who remain on study treatment through and including Week 12 will be asked to return for a follow-up visit, approximately 4 weeks after their last dose of study treatment, to assess safety and efficacy. Subjects who permanently discontinue study treatment will be followed as described in Section 7.1.

4.2. Scientific Rationale for Study Design

This Phase 2a, randomized, double-blind, placebo-controlled, multicenter study is designed to assess the safety and efficacy of RIST4721 over 12 weeks in adult subjects with moderate-to-severe HS. Other therapeutic regimens for the treatment of moderate to severe HS have demonstrated treatment success in a 12-week timeframe.

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 HS.

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 (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. Blinded treatment will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

4.3. Dose Rationale

The dose of RIST4721 to be tested in this proof-of-concept Phase 2a study is 400 mg QD. RIST4721 was well tolerated in multiple Phase 1 studies in healthy volunteers at single doses up to 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.

RIST4721 dose level of 400 mg QD was selected based on safety and PK data (including absorption, half-life, and bioaccumulation after repeated doses) from previously conducted studies. The 400 mg QD dose level is expected to be clinically safe and effective. In case of treatment-related adverse events (AEs) (Section 6.5.1) or absolute neutrophil count (ANC) laboratory abnormalities (Section 6.5.2), the dose can be reduced to 200 mg QD (refer to Section 6.5); this dose is anticipated to be a potentially effective dose in subjects with HS.

Modeling was conducted using the safety data of RIST4721 by dose in PPP patients from Study RIST4721-201 coupled with data from normal healthy volunteers from 5 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).

Systemic exposure to RIST4721 tablets has been demonstrated to be modestly influenced by food with an increase of in maximum observed plasma concentration (C_{max}) of 52% and area under the curve $(AUC)_{inf}$ of 18% when administered with a high fat meal compared with fasted. It is considered that the increase of 18% in AUC_{inf} is small and would not be clinically important with respect to either safety or efficacy. The increase of C_{max} is more substantial, however, with the solution formulation (given under fasted conditions): C_{max} is approximately 25% higher compared to the tablet in fed conditions. Safety data are available for the solution formulation in healthy subjects at single doses up to 730 mg and repeated doses of up to 500 mg QD and in patients with PPP at repeated doses of 300 mg QD. C_{max} at those doses would be expected to be comparable to or greater than that from fed tablets at 400 mg QD. In addition, tablets at the 400 mg dose (fed) QD over 14 days were recently demonstrated to be well tolerated in healthy subjects (RIST4721-103). Based on the modest effect of food on AUC_{inf} and the good safety profile at C_{max} concentrations achieved with 400 mg tablets (fed), it is considered that RIST4721 can be administered without respect to food intake.

4.4. Study Duration

For each subject, the total study duration is expected to be approximately 20 weeks as follows:

Screening period:	4 weeks
Treatment period:	12 weeks
Follow-up period	4 weeks from 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 (Section 1.3).

- For subjects who permanently discontinued study treatment, the end of study will be defined as the completed Week 12 visit or the follow-up evaluation 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 SoA 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 of age at the time of consent.

Subject and Disease Characteristics

2. Diagnosis of HS based on documented clinical history for at least 1 year prior to screening (information obtained from medical chart or subject's physician, or directly from the subject).
3. HS lesions must be present in at least 2 distinct anatomic areas (eg, left and right axilla; or left axilla and left inguinal fold), one of which must be Hurley Stage II, at both the screening and baseline visits.
4. Moderate-to-severe HS defined as a total AN count (sum of abscesses and inflammatory nodules) ≥ 6 across all anatomical sites at both the screening and baseline visits.
5. Inadequate response to a course of at least 3-months of a systemic antibiotic or demonstrated intolerance to/have a contraindication to oral antibiotics for treatment of their HS, as assessed by the investigator through study participant interview and review of medical records.
6. Agree to continue use of current over-the-counter topical therapies for HS, if any, at the same strength and frequency for the duration of the study.
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 through 5 days after the last study treatment administration.
11. Male subject agrees to use contraception/barrier (a male condom) and spermicide from consent through 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.

5.2. Exclusion Criteria

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

Medical Conditions and Diagnostic Assessments

1. Presence of other skin conditions which may interfere with study assessments (eg, bacterial cellulitis, keloids, candida intertrigo, extensive condyloma, excessive scarring)
2. Draining fistula count >20 at baseline
3. Evidence of active or 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).

   Subjects with latent TB, who have been ruled out for active TB according to local country guidelines, (eg, chest X ray); have completed an appropriate course of TB prophylaxis treatment are eligible to enroll in the study.
4. Known active bacterial, viral, fungal, mycobacterial systemic infection, or other infection (including atypical mycobacterial disease) or any major episode of infection that required hospitalization or treatment with intravenous antibiotics within 4 weeks prior to screening or during screening, or oral antibiotics within 2 weeks prior to screening or during screening. Superficial fungal infection of the nail bed is allowed.
5. Any condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, compromise the well-being) of the subject or that could prevent, limit, or confound the protocol-specified assessments, including, but not limited to:
   a. Positive results for SARS-CoV-2 using antigen test **and** confirmatory polymerase chain reaction (PCR) test at screening.
   b. Primary or secondary immunodeficiency syndromes (eg, hereditary immunodeficiency syndrome, acquired immunodeficiency syndrome, drug-induced immune deficiency).
   c. History of organ transplant (except corneal transplant).
   d. Any clinically significant history of infection (except for localized herpes simplex) within 4 weeks prior to Day 1.
   e. 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).
   f. 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.

g. Diagnosis of active peptic ulcer disease as determined by endoscopy, radiography, angiography, or other appropriate means within 12 months prior to screening.
h. Coagulopathy (regardless if controlled by pharmacotherapy or not).
i. Significant central nervous system effects including vertigo and dizziness, or major neurologic event, including cerebrovascular events, within 60 days of screening.
j. 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.
k. Major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study, including planned endodontic and periodontal procedures.
l. QT corrected interval by Fridericia (QTcF) >440 msec as confirmed by triplicate electrocardiogram (ECG) measurement at screening or Day 1 assessment.
m. A positive test for drugs of abuse (amphetamines, methamphetamines, barbiturates, cocaine, phencyclidine) or use of opioids without prescription for pain management. Retest may be performed for potential false positive results with approval from the Sponsor's Medical Monitor (or designee).
n. Serious hepatic disorder (Child-Turcott-Pugh scores B or C).
o. History of clinically significant anemia or hemoglobin (Hgb) value ≤9.5 g/dL at screening.
p. Body mass index (BMI) >48 kg/m^2.
q. Confirmed chronic kidney disease (CKD) as per National Kidney Foundation stages ≥3: estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m^2 based on the CKD-Epidemiology Collaboration (EPI) equation.
r. Concurrent uncontrolled diabetes.
s. Significant cardiovascular disease including poor peripheral circulation and venous stasis.
t. Peripheral capillary oxygen saturation (SpO_2) ≤94%.
u. Uncontrolled hyperlipidemia.
v. Uncontrolled other rheumatological, dermatological, and autoimmune disease. Any other clinically significant medical condition or ECG, physical examination, laboratory, or vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results (eg, celiac disease, streptococcal infection, allergy/delayed type hypersensitivity to tobacco and products within which tobacco is contained).

6. Confirmed alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin values ≥2 times the upper limit of normal (ULN), or other clinical evidence of significant hepatic impairment (eg, ascites, peri-umbilical veins, esophageal varices) at screening. Note: A confirmed result means there have been 2 consecutive assessments showing a consistent clinically relevant abnormal result.

Prior Therapy and Prior/Concurrent Clinical Study Experience

7. Received any systemic non-biologic therapies for HS including oral antibiotics within 30 days prior to the baseline visit.
8. Received prescription topical therapies for the treatment of HS within 14 days prior to the baseline visit.
9. Use of any biologic agents (eg, adalimumab, ustekinumab, secukinumab) regardless of indication, within 5 half-lives (if known) or 12 weeks prior to screening, whichever is longer, or during screening. Refer to Section 6.7.5 for additional list of medications.
10. Received any live or live-attenuated vaccines ≤ 4 weeks prior to baseline.
11. Received any investigational drug within a minimum of 30 days or 5 half-lives of the drug prior to the baseline visit, whichever is longer, or during screening.
12. 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).

Other Exclusion Criteria

13. Pregnant or breastfeeding or intends to become pregnant during the duration of the study.
14. Consumption of any food or drinks 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. Prior participation in RIST4721 studies.
17. Close affiliation with the investigator (eg, a close relative), including any study staff of the sites or persons working at the contract research organization CRO or subject is an employee of Sponsor.
18. 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 3: Study Treatment Description

Study Treatment Name	Active: RIST4721	Control: Placebo
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	4 tablets QD
Route of Administration and Instructions	Oral. On Day 1, the clinical study team will instruct the subject how to administer the study treatment. Study treatment (RIST4721 or placebo) 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 bottles containing 70 tablets.	
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

6.3.2. All subjects will be centrally randomized 2:1 to RIST4721 400 mg QD or placebo QD using interactive response technology (IRT).

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

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

6.3.4. Assignment of Study Treatment Kit Number

Study treatment will be dispensed at the study visits as summarized in the SoA. 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.

6.3.5. Blinding and Unblinding of an Individual Subject

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

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

The 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 end of treatment (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. 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 laboratory, 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).

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

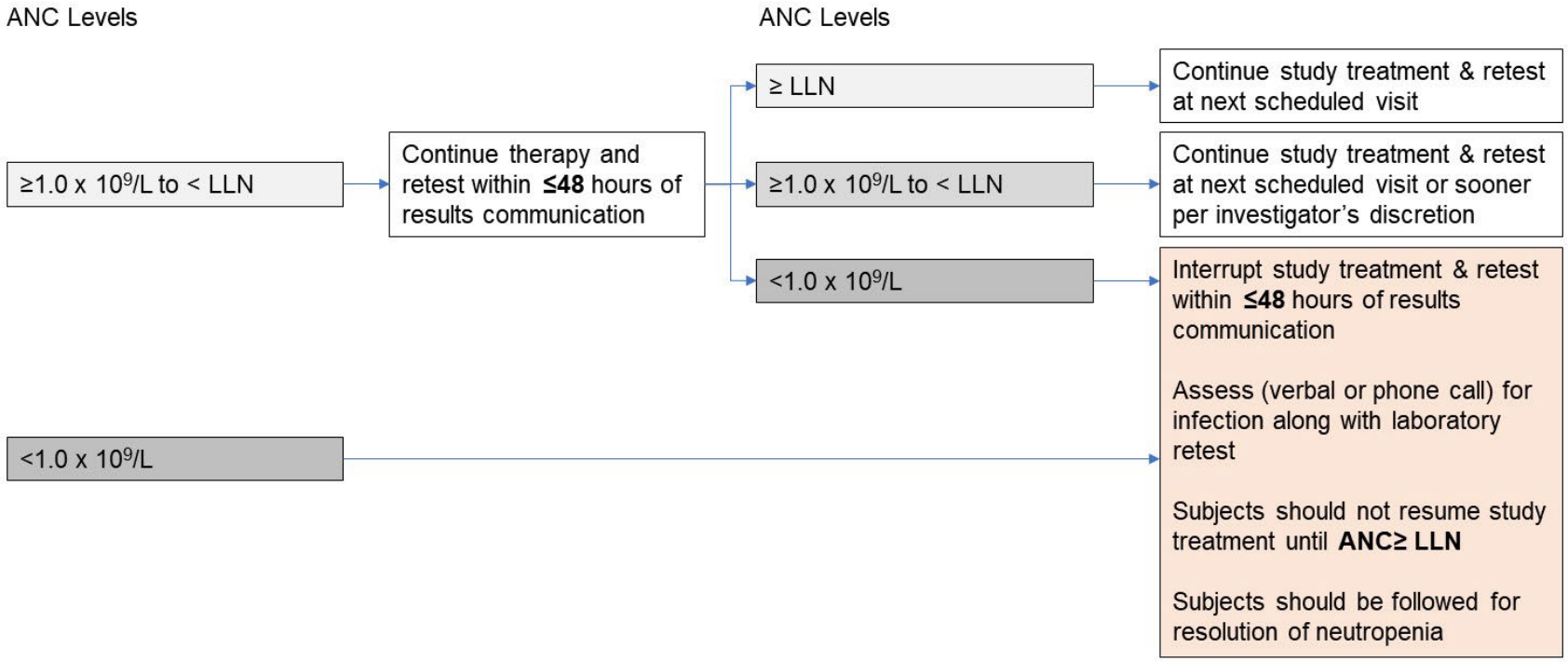
Absolute and relative neutrophil and WBC count results will only be disclosed to the respective investigators if ANC < LLN in which case immediate actions will be taken, as described in Figure 2. Retest results will be communicated to investigators who will follow up on neutrophil count and the incidence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

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

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

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

Figure 2: Steps for Addressing Neutrophil Counts



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

6.6. 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 (refer to Section 10.3.1), 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.

6.7. 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 6.7.5) 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.

6.7.1. Antiseptic Therapy

Subjects are required to agree to continue use of current over-the-counter topical therapies, if any, for the duration of the study.

6.7.2. Analgesia

Subjects may remain on any type of analgesia (oral, topical, and opioid) provided that they are on a stable dose within 4 weeks prior to baseline visit.

6.7.3. Wound Care

Concomitant use of wound care dressings on HS wounds is allowed.

6.7.4. Lesion Intervention

In the event that an acutely painful lesion occurs that requires an immediate intervention, physicians will have the option to perform protocol-allowed interventions.

Only 2 types of lesion interventions are allowed:

1. Injection with intralesional triamcinolone acetonide suspension (up to a strength of 10 mg/mL and no more than 1 mL).
2. Incision and drainage.

No more than 2 lesions may receive either intervention through the course of the study.

The specific treated lesion will be excluded from lesion count efficacy assessment for the reminder of the study.

New systemic and topical therapies following incision and drainage (including antibiotics) are prohibited. Concomitant use of wound care dressings is allowed.

6.7.5. Prohibited Medications

Medications specifically prohibited in the exclusion criteria are not allowed during the ongoing study (Section 5.2).

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).

The following treatments are prohibited for all subjects **during the study**:

- Phototherapy (PUVA and/or UVB)
- All biologic therapy with a potential therapeutic impact on the disease being studied, including but not limited to the following: anakinra (Kineret®), abatacept (Orencia®), adalimumab (Humira®), natalizumab (Tysabri®), ustekinumab (Stelara®), etanercept (Enbrel®), infliximab (Remicade®), rituximab (Rituxan®), tocilizumab (Actemra®), efalizumab (Raptiva®), golimumab (Simponi®), certolizumab (Cimzia®), belimumab (Benlysta®), secukinumab (Cosentyx®)
- Any investigational agents

- Any oral antibiotic treatment for HS or other systemic non-biologic therapies with potential therapeutic impact on HS, including but not limited to antibiotics, methotrexate, cyclosporine, retinoids, corticosteroids, and fumaric acid esters
- Live or live-attenuated vaccines (during the study and for 28 days after the last dose of study treatment)
- New use of oral, topical, and opioid analgesics for HS
- Prescription topical therapies for the treatment of HS, including topical steroids, calcineurin inhibitors, and phosphodiesterase inhibitors
- New use of over-the-counter topical antiseptic washes, creams, soaps, ointments, gels, and liquids containing antibacterial agents to treat HS not listed in Section 6.7.1
- Surgical, intense pulsed light and laser intervention for an HS lesion except as outlined in Section 6.7.4
- Strong CYP3A inhibitors including 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
- Strong CYP3A inducers including by not limited to: apalutamide carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort

6.7.6. 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 inhibitors (eg, amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil)
- Breast cancer resistance protein (BCRP) inhibitors (eg, curcumin, cyclosporine A, eltrombopag)
- Moderate inhibitors of CYP3A, including but not limited to aprepitant, crizotinib, diltiazem, erythromycin, fluconazole, verapamil

- Moderate inducers of CYP3A including but not limited to bosentan, efavirenz, etravirine, phenobarbital, primidone
- 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 the study, and the subject will be encouraged to remain in the study, complete the EOT visit at the time of study treatment discontinuation, and then continue to complete remaining study visits as per the SoA (Section 1.3). 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 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 SoA (Section 1.3). 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) for additional details.

See the SoA (Section 1.3) for data to be collected at the Week 12/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 SoA (Section 1.3). 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 (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility 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 (Section 1.3).
- Clinical evaluations of HS 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. Hurley Stage

The Hurley severity stage (Hurley, 1996) is based on 3 clinical stages:

- Stage 1 – abscess formation, single or multiple, without sinus tracts and cicatrization
- Stage 2 – single or multiple, widely separated, recurrent abscesses with tract formation and cicatrization
- Stage 3 – diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

A subject's overall Hurley Stage should be determined by the worst Hurley stage across all affected anatomic regions.

8.2. Efficacy Assessments

8.2.1. Hidradenitis Suppurativa Clinical Response (HiSCR)

The HiSCR is used to assess the inflammatory signs and symptoms of HS (Kimball, 2014). The score is determined by counting the number of inflammatory nodules, abscesses, and draining fistulas before and after an intervention (see below).

- HiSCR50 is defined as a 50% or greater reduction in total AN count and no increase in abscesses or draining fistulas compared with baseline.
- HiSCR75 is defined as at least a 75% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count.

AN count will be done at timepoints specified in the SoA. AN count is correlated with disease severity and is used in HiSCR to evaluate HS. Abscess (fluctuant, with or without drainage, tender or painful), inflammatory nodules (tender, erythematous, pyogenic granuloma lesion), draining fistulas, sinus tracts with communications to skin surface, draining purulent fluid, and other lesions (noninflammatory nodules, non-draining fistulas) will all be individually counted on the entire body at each visit. The AN count will be calculated based on the sum of the abscesses and inflammatory nodules. Draining fistulas should also be counted.

8.2.2. International Hidradenitis Suppurativa Severity Score System (IHS4)

IHS4 is a validated tool to dynamically assess HS severity and can be used both in real-life and the clinical studies setting (Zouboulis, 2017; Napolitano, 2020). IHS4 score is arrived at by the number of nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4). A total score of 3 or less signifies mild, 4-10 signifies moderate, and 11 or higher signifies severe disease.

8.2.3. Numeric Rating Scale for Skin Pain

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

8.2.4. Hidradenitis Suppurativa-Investigator's Global Assessment (HS-IGA)

The HS-IGA score is based on the maximum count of abscesses, fistulas (draining and non-draining), and nodules (inflammatory and non-inflammatory) in either the upper or lower body region. The region used at baseline may not be the same region used at a given post-baseline visit. Response is defined as a 2-point improvement (reduction) in IGA score relative to baseline. (Table 4).

Table 4: Hidradenitis Suppurativa-Investigator's Global Assessment (HS-IGA) Score

HS-IGA Score	Maximum Lower Body OR Upper Body Count
0	**0-1**
1	**2-5**
2	**6-10**
3	**11-15**
4	**16-20**
5	**>20**

8.2.5. Hidradenitis Suppurativa -Physician Global Assessment (HS-PGA)

The HS-PGA categorizes HS into 6 degrees of progressive severity based on number of nodules, abscesses, and fistulas, as shown in Table 5 (Kimball, 2012).

Table 5: Hidradenitis Suppurativa -Physician Global Assessment (HS-PGA)

Severity	Description
Clear	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and 0 noninflammatory nodules
Minimal	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and presence of noninflammatory nodules
Mild	0 abscesses, 0 draining fistulas, and 1–4 inflammatory nodules or 1 abscess or draining fistula and 0 inflammatory nodules
Moderate	0 abscesses, 0 draining fistulae, and ≥5 inflammatory nodules or 1 abscess or draining fistula and ≥1 inflammatory nodules or 2–5 abscesses or draining fistulas and <10 inflammatory nodules
Severe	2–5 abscesses or draining fistulas and ≥10 inflammatory nodules
Very severe	>5 abscesses or draining fistulas

8.2.6. Hidradenitis Suppurativa Quality of Life (HiSQOL)

HiSQOL scale was developed and validated for clinical trial measurement of HS-specific health-related quality of life. It is a 17-item instrument separated into 3 sub-scales

(symptom, psychosocial, and functional concepts) with a 7-day recall period (Kirby, 2020; Kirby, 2021).

8.2.7. Dermatology Life Quality Index (DLQI)

The DLQI is a simple 10-question validated questionnaire that has been used in more than 40 different skin conditions. It is the most frequently used instrument in studies of randomized controlled studies in dermatology. The DLQI includes questions concerning symptoms and feelings, daily activities, leisure, work, and school, 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).

8.2.8. Medical Photography

Medical photographs of HS-affected areas will be performed on subjects at participating select sites.

Photographs will be 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 (Section 1.3). Study procedures should be completed within the windows provided in the 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 HS)
- 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 HS)

- 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. Pulse oximetry will be measured at screening only.
- 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 on Week 12/EOT and Follow-up.

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 at timepoints specified in the SoA (Section 1.3) 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 approximately 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 (eg, 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 at the visits designated in the SoA (Section 1.3). 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 and SAEs will be collected from consent until the follow-up visit (4 weeks from last dose of study treatment). 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 (eg, 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 (eg, spontaneous abortion, 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 trough measurement of plasma concentrations of RIST4721 and its metabolites, if applicable, as specified in Table 6. Subjects will be requested to hold their dose on clinic visits until after PK samples are obtained. The 24-hour clock actual time and calendar 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 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.

Table 6: Pharmacokinetic Collection Schedule

Timepoint	Dose	Time	PK Collection Time Window
Day 1/baseline Weeks 2, 4, and 8	morning	predose	within 1 hour prior to dosing
Week 12/EOT	morning	predose, if applicable	within 1 hour prior to dosing
Unscheduled visit any time after baseline visit (in case of SAEs or AE leading to study treatment discontinuation)	none	anytime	

Abbreviations: AE, adverse event; EOT, end of treatment; PK, pharmacokinetic; SAE, serious adverse event.

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, ie, placebo subjects will not have their samples analyzed. For RIST4721-treated subjects, the baseline (ie, 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. Biomarkers and Pharmacodynamics

Serum biomarkers will be collected as specified in the SoA (Table 1) and stored for future analyses.

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

8.5.3. 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

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

9.2. Populations for Analyses

The following analysis populations are planned:

Analysis Set	Definition
Full Analysis Set	All subjects who are randomized. Subjects will be classified according to the treatment assigned at randomization. The Full Analysis Set will be the primary population for evaluating all efficacy endpoints and subject characteristics.
Per-protocol Analysis Set	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	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	All treated subjects who have at least 1 concentration above the limit of quantitation of the study treatment in RIST4721 arm only.

9.3. Statistical Analyses

9.3.1. General Considerations

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

Continuous data will be summarized using an 8-point descriptive summary (n, mean, standard deviation [SD], median, IQR [25% quartile, 75% quartile], minimum, and maximum) or 7 point descriptive summary (n, mean, SD, coefficient of variation [CV], median, minimum, and maximum) unless otherwise specified.

Categorical data will be summarized using the frequency of events and percentage of total events.

Data will be presented by treatment group. Changes in primary, secondary, and exploratory endpoints will be analyzed over time, with change from baseline summarized for each post baseline time point measured.

9.3.2. Baseline Descriptive Statistics

Demographics and baseline characteristics (including age, sex, race, ethnicity, height, weight, and body mass index) will be summarized for the Full Analysis Set.

Baseline clinical characteristics and history will be summarized.

9.3.3. Efficacy Analysis

The key secondary endpoint, proportion of subjects achieving HiSCR50 at Week 12, will be analyzed using Fisher's exact test. Proportions and difference in proportions between treatment groups, and their associated 95% confidence intervals (CIs) will be reported. For subjects who discontinue study treatment prior to Week 12 due to any reason, their last observation will be used to impute response status.

Fisher's exact test will also be used to analyze additional secondary endpoints which are dichotomized in nature, eg, proportion of subjects achieving HiSCR75 at Week 12, proportion of subjects with flare by Week 12, and other proportion endpoints.

Change from baseline in NRS skin pain score, change from baseline in IHS4, and other continuous endpoints will be summarized using descriptive statistics. Change from baseline of these continuous endpoints will also be analyzed by a Mixed-effects model for repeated measures (MMRM). MMRM will include baseline as a covariate, treatment and visit as factors, and treatment-by-visit and baseline-by-visit interactions in the model.

9.3.4. Safety Analyses

The Safety Analysis Set will be used for all safety analyses. All safety data will be presented in listings. Summary tables will be provided for concomitant medications, AE, hematology and chemistry laboratory results, vital signs, and ECG findings. Safety data will be summarized by treatment group using frequency of event or descriptive statistics, as appropriate.

9.3.4.1. Extent of Exposure

Dosing information for individual subjects will be listed. Using dosing data, estimates of exposure to study treatment will be summarized. Dose discontinuations and reasons for study treatment discontinuation will be listed and summarized.

9.3.4.2. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). TEAE summaries will be presented by SOC, Preferred Term, severity, and frequency and percentage of subjects reporting each observed event.

AEs that occur before the first dose of study treatment will be distinguished from TEAEs. All AEs and TEAEs will be listed by subject. The frequency of subjects who experience TEAEs will be summarized. TEAEs will also be summarized by relationship to study treatment and severity. 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.

Listings will be provided for subjects who experience an SAE or discontinue study treatment/withdraw from the study because of an AE.

9.3.4.3. Clinical Laboratory

Clinical laboratory (eg, 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 (eg, 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.

9.3.4.4. 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.

9.3.4.5. Electrocardiograms

QT intervals will be corrected for heart rate (QTc) using standard correction factors (eg, 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.

9.3.5. Pharmacokinetics Analyses

A descriptive summary of observed plasma concentrations of RIST4721will be displayed by time and by treatment group. Full details of the PK analysis will be provided in the SAP.

9.4. Planned Interim Analyses

No interim analysis is planned for this study.

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 (eg, 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 (eg, 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.

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 (eg, 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 (eg, 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 (eg, 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 listed in Table 7 will be performed by the central laboratory, unless otherwise noted, at the visits designated in the SoA (Section 1.3). Details for collection, processing, and shipping of samples to the central laboratory are provided in a separate Laboratory Manual.
- 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 (nonfasting), creatinine (enzymatic), GGT, glucose random, hs-CRP, LDH, potassium, sodium, total bilirubin, triglycerides, BUN, uric acid
Urinalysis	Dipstick and microscopic analysis
Urine pregnancy test	For WOCBP (at each visit, except screening)
Virology	• SARS-CoV-2 antigen test at each visit (except screening); if positive, will be confirmed by PCR test
Laboratory tests required at screening only	• FSH levels for females who have had a cessation of menses for at least 12 months without an alternative medical cause • β-hCG (serum pregnancy test) 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 test
Laboratory tests required at screening and baseline only	• Urine drugs of abuse: amphetamines, methamphetamines, barbiturates, cocaine, phencyclidine

Abbreviations: ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; β-hCG, β-human chorionic gonadotropin; BUN, blood urea nitrogen; FSH, follicle-stimulating hormone; GGT, gamma-glutamyl-transferase; HBsAg, hepatitis B surface antigens; HBV, hepatitis B virus; HCT, hematocrit; HCV, hepatitis C virus; Hgb, hemoglobin; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; INR, international normalized

ratio; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PCR, polychain reaction; PLT, platelets; PPD, purified protein derivative; PT, prothrombin time; RBC, red blood cell; WBC, white blood cell; 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 (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, 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 (eg, 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 (eg, 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 (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

An SAE is defined as any untoward medical occurrence that, at any dose:
• **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 (eg, 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. • 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.
- 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.**

Assessment of Causality
• 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 (eg, 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 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]
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 (eg, 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, (eg, 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

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 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 WOCBP. 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: 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 (eg, 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 (eg, 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, eg, 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 (eg, 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 reassessed 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 (eg, 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.

10.6. Appendix 6: List of Abbreviations

Abbreviation Term	Description
AE	adverse event
AN	abscess and inflammatory nodule
ANC	absolute neutrophil count
AUC	area under the curve
BCRP	breast cancer resistance protein
BMI	body mass index
CCR2	C-C motif chemokine receptor 2
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
C_{max}	maximum observed plasma concentration
CRO	contract research organization
CXCR1	CXC chemokine receptor type 1
CXCR2	CXC chemokine receptor type 2
CYP	cytochrome P450
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
FMF	familial Mediterranean fever
FMF	familial Mediterranean fever
GCP	Good Clinical Practice
GPCR	G-protein coupled receptor
HEK293	human embryo kidney 293
HiSCR	Hidradenitis Suppurativa Clinical Response
HiSQOL	Hidradenitis Suppurativa Quality of Life
HS	hidradenitis suppurativa
HS-IGA	Hidradenitis Suppurativa-Investigator's Global Assessment
HS-PGA	Hidradenitis Suppurativa -Physician Global Assessment
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IHS4	International Hidradenitis Suppurativa Severity Score System
IL	interleukin
IRB	institutional review board

Abbreviation Term	Description
IRT	interactive response technologies
LLN	lower limit of normal
MMRM	mixed-effects model for repeated measures
MSU	monosodium urate
NRS	numeric rating scale
PCR	polymerase chain reaction
PK	pharmacokinetics
PPD	purified protein derivative
PPP	palmoplantar pustulosis
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
SoA	Schedule of Activities
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
Th	T helper
ULN	upper limit of normal
WBC	white blood cell
WOCBP	women of childbearing potential

11. REFERENCES

Aarts, P., Dudink, K., Vossen, A., van Straalen, K. R., Ardon, C. B., Prens, E. P., et al. (2021). "Clinical Implementation of Biologics and Small Molecules in the Treatment of Hidradenitis Suppurativa." Drugs 81(12): 1397-1410.

Alikhan, A., Lynch, P. J. and Eisen, D. B. (2009). "Hidradenitis suppurativa: a comprehensive review." J Am Acad Dermatol 60(4): 539-561; quiz 562-533.

Alikhan, A., Sayed, C., Alavi, A., Alhusayen, R., Brassard, A., Burkhart, C., et al. (2019). "North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part I: Diagnosis, evaluation, and the use of complementary and procedural management." J Am Acad Dermatol 81(1): 76-90.

Australian Government (April 9, 2020). COVID-19: Guidance on clinical trials for institutions, HRECs, researchers and sponsors. Department of Health and National Health and Medical Research Council. from https://www1.health.gov.au/internet/main/publishing.nsf/Content/Clinical-Trials.

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

Boppana, N. B., Devarajan, A., Gopal, K., Barathan, M., Bakar, S. A., Shankar, E. M., et al. (2014). "Blockade of CXCR2 signalling: a potential therapeutic target for preventing neutrophil-mediated inflammatory diseases." Exp Biol Med (Maywood) 239(5): 509-518.

Cosmatos, I., Matcho, A., Weinstein, R., Montgomery, M. O. and Stang, P. (2013). "Analysis of patient claims data to determine the prevalence of hidradenitis suppurativa in the United States." J Am Acad Dermatol 68(3): 412-419.

Deckers, I. E., van der Zee, H. H. and Prens, E. P. (2014). "Epidemiology of Hidradenitis Suppurativa: Prevalence, Pathogenesis, and Factors Associated with the Development of HS." Current Dermatology Reports 3(1): 54-60.

Dyer, D. P., Pallas, K., Ruiz, L. M., Schuette, F., Wilson, G. J. and Graham, G. J. (2017). "CXCR2 deficient mice display macrophage-dependent exaggerated acute inflammatory responses." Sci Rep 7: 42681.

Eash, K. J., Greenbaum, A. M., Gopalan, P. K. and Link, D. C. (2010). "CXCR2 and CXCR4 antagonistically regulate neutrophil trafficking from murine bone marrow." J Clin Invest 120(7): 2423-2431.

EMA (April 2020). Guidance on the management of clinical trials during the COVID-19 (Coronavirus) pandemic, version 4, released February 04, 2021. Agency, E. M., from https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf.

FDA (March 2020). FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency – Guidance for Industry, Investigators and Institutional Review Boards. Updated August 30, 2021. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). from https://www.fda.gov/media/136238/download.

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

Garg, A., Kirby, J. S., Lavian, J., Lin, G. and Strunk, A. (2017). "Sex- and Age-Adjusted Population Analysis of Prevalence Estimates for Hidradenitis Suppurativa in the United States." JAMA Dermatol 153(8): 760-764.

Health Canada (April 7, 2020). Management of clinical trials during the COVID-19 pandemic: Notice to clinical trial sponsors. Updated May 6, 2021. from https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/management-clinical-trials-during-covid-19-pandemic.html.

Hurley, H. (1996). " Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa and familial benign pemphigus. Surgical approach In Roenigk R, Roenigk HJ, eds. Dermatologic Surgery: Principles and Practice, 2nd edn, Marcel Dekker, New York. ." 623–645.

Jamieson, T., Clarke, M., Steele, C. W., Samuel, M. S., Neumann, J., Jung, A., et al. (2012). "Inhibition of CXCR2 profoundly suppresses inflammation-driven and spontaneous tumorigenesis." J Clin Invest 122(9): 3127-3144.

Kelly, G., Hughes, R., McGarry, T., van den Born, M., Adamzik, K., Fitzgerald, R., et al. (2015). "Dysregulated cytokine expression in lesional and nonlesional skin in hidradenitis suppurativa." Br J Dermatol 173(6): 1431-1439.

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

Kimball, A. B., Kerdel, F., Adams, D., Mrowietz, U., Gelfand, J. M., Gniadecki, R., et al. (2012). "Adalimumab for the treatment of moderate to severe Hidradenitis suppurativa: a parallel randomized trial." Ann Intern Med 157(12): 846-855.

Kirby, J. S., Hereford, B., Thorlacius, L., Villumsen, B., Ingram, J. R., Garg, A., et al. (2021). "Validation of global item for assessing impact on quality of life of patients with hidradenitis suppurativa*." British Journal of Dermatology 184(4): 681-687.

Kirby, J. S., Thorlacius, L., Villumsen, B., Ingram, J. R., Garg, A., Christensen, K. B., et al. (2020). "The Hidradenitis Suppurativa Quality of Life (HiSQOL) score: development and validation of a measure for clinical trials." British Journal of Dermatology 183(2): 340-348.

Lim, S. Y. D. and Oon, H. H. (2019). "Systematic review of immunomodulatory therapies for hidradenitis suppurativa." Biologics 13: 53-78.

MHRA (March 19, 2020). Guidance: Managing clinical trials during Coronavirus (COVID-19). Last updated November 16, 2021. from https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19.

Moran, B., Sweeney, C. M., Hughes, R., Malara, A., Kirthi, S., Tobin, A. M., et al. (2017). "Hidradenitis Suppurativa Is Characterized by Dysregulation of the Th17:Treg Cell Axis, Which Is Corrected by Anti-TNF Therapy." J Invest Dermatol 137(11): 2389-2395.

Napolitano, M., Mastroeni, S., Fusari, R., Mazzanti, C., Ciccone, D., Pallotta, S., et al. (2020). "The International Hidradenitis Suppurativa Severity Score System (IHS4) is a valuable tool to assess gender-associated differences." Eur J Dermatol.

Napolitano, M., Megna, M., Timoshchuk, E. A., Patruno, C., Balato, N., Fabbrocini, G., et al. (2017). "Hidradenitis suppurativa: from pathogenesis to diagnosis and treatment." Clin Cosmet Investig Dermatol 10: 105-115.

Narla, S., Azzam, M., Townsend, S., Vellaichamy, G., Marzano, A. V., Alavi, A., et al. (2021). "Identifying key components and therapeutic targets of the immune system in hidradenitis suppurativa with an emphasis on neutrophils." Br J Dermatol 184(6): 1004-1013.

Navrazhina, K., Garcet, S., Gonzalez, J., Grand, D., Frew, J. W. and Krueger, J. G. (2021). "In-Depth Analysis of the Hidradenitis Suppurativa Serum Proteome Identifies Distinct Inflammatory Subtypes." J Invest Dermatol 141(9): 2197-2207.

Nicholls, D. J., Wiley, K., Dainty, I., MacIntosh, F., Phillips, C., Gaw, A., et al. (2015). "Pharmacological characterization of AZD5069, a slowly reversible CXC chemokine receptor 2 antagonist." J Pharmacol Exp Ther 353(2): 340-350.

Preda-Naumescu, A., Ahmed, H. N., Mayo, T. T. and Yusuf, N. (2021). "Hidradenitis suppurativa: pathogenesis, clinical presentation, epidemiology, and comorbid associations." Int J Dermatol.

Prens, E. and Deckers, I. (2015). "Pathophysiology of hidradenitis suppurativa: An update." J Am Acad Dermatol 73(5 Suppl 1): S8-11.

Revuz, J. E., Canoui-Poitrine, F., Wolkenstein, P., Viallette, C., Gabison, G., Pouget, F., et al. (2008). "Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies." J Am Acad Dermatol 59(4): 596-601.

Sabat, R., Jemec, G. B. E., Matusiak, Ł., Kimball, A. B., Prens, E. and Wolk, K. (2020). "Hidradenitis suppurativa." Nature Reviews Disease Primers 6(1): 18.

Saunte, D. M. L. and Jemec, G. B. E. (2017). "Hidradenitis Suppurativa: Advances in Diagnosis and Treatment." Jama 318(20): 2019-2032.

Scala, E., Cacciapuoti, S., Garzorz-Stark, N., Megna, M., Marasca, C., Seiringer, P., et al. (2021). "Hidradenitis Suppurativa: Where We Are and Where We Are Going." Cells 10(8).

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

van Straalen, K. R., Schneider-Burrus, S. and Prens, E. P. (2020). "Current and future treatment of hidradenitis suppurativa." Br J Dermatol 183(6): e178-e187.

Vazquez, B. G., Alikhan, A., Weaver, A. L., Wetter, D. A. and Davis, M. D. (2013). "Incidence of hidradenitis suppurativa and associated factors: a population-based study of Olmsted County, Minnesota." J Invest Dermatol 133(1): 97-103.

von Laffert, M., Helmbold, P., Wohlrab, J., Fiedler, E., Stadie, V. and Marsch, W. C. (2010). "Hidradenitis suppurativa (acne inversa): early inflammatory events at terminal follicles and at interfollicular epidermis." Exp Dermatol 19(6): 533-537.

Vossen, A., van der Zee, H. H. and Prens, E. P. (2018). "Hidradenitis Suppurativa: A Systematic Review Integrating Inflammatory Pathways Into a Cohesive Pathogenic Model." Front Immunol 9: 2965.

Wipperman, J., Bragg, D. A. and Litzner, B. (2019). "Hidradenitis Suppurativa: Rapid Evidence Review." Am Fam Physician 100(9): 562-569.

Wolk, K., Join-Lambert, O. and Sabat, R. (2020). "Aetiology and pathogenesis of hidradenitis suppurativa." Br J Dermatol 183(6): 999-1010.

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