AMENDED CLINICAL TRIAL PROTOCOL 04

Protocol title:	**A randomized, double-blind, placebo-controlled, proof-of-concept study assessing the efficacy and safety of an anti-TNF-OX40L NANOBODY® molecule, SAR442970, in participants with moderate to severe hidradenitis suppurativa**
Protocol number:	**ACT16852**
Amendment number:	**04**
Compound number (INN/Trademark):	**SAR442970** **Not applicable**
Brief title:	**A study to test the efficacy and safety of SAR442970 in adults with hidradenitis suppurativa**
Acronym:	**HS OBTAIN**
Study phase:	**Phase 2**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**1 avenue Pierre Brossolette** **91380 Chilly-Mazarin, France**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	165047
NCT:	NCT05849922
WHO:	U1111-1280-6493
EUDAMED:	Not applicable
EU trial number:	2022-502370-17
Other:	Not applicable

Date: 16-Feb-2024 Total number of pages: 164

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 04	All	16-Feb-2024, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 03	All	02-Oct-2023, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 02	EU	18-Jul-2023, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 01	United States and Australia	26-May-2023, version 1 (electronic 1.0)
Original Protocol		01-Feb-2023, version 1 (electronic 2.0)

Amended protocol 04 (16-Feb-2024)

This amended protocol (amendment 04) is considered to be non-substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union because it does not significantly impact the safety or rights of the participants and/or the reliability and robustness of the data generated in the clinical trial.

Overall Rationale for the Amendment

The main rationale for the amendment is to address comments from the European Health Authorities.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
8.2.1.1 Hidradenitis Suppurativa Clinical Parameters (HS Clinical Parameters)	Removed the statement indicating that the Hidradenitis Suppurativa Clinical Parameters will be completed using an internet-enabled device.	Operational change to collection of endpoints
10.8.1 European Union	[redacted]	[redacted]

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LIST OF ABBREVIATIONS

ADA:	anti-drug antibodies
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AN:	abscess and inflammatory nodule
ANC:	absolute neutrophil count
ANCOVA:	Analysis of Covariance
AST:	aspartate aminotranferase
AUC:	area under curve
BCG:	Bacille Calmette Guerin
CFR:	Code of Federal Regulations
CIOMS:	Council for International Organizations of Medical Sciences
C_{max}:	maximum serum drug concentration
COVID-19:	coronavirus disease 2019
CRP:	C-reactive protein
CSICF:	core study informed consent form
CSR:	clinical study report
C-SSRS:	Columbia-Suicide Severity Rating Scale
CTCAE:	Common Terminology Criteria for Adverse Events
DLQI:	Dermatology Life Quality Index
DTH:	delayed-type hypersensitivity
ECG:	electrocardiogram
eCRF:	electronic case report form
ELISPOT:	enzyme-linked immunosorbent spot
EOS:	end of study, end of study
EOT:	end of treatment
[redacted]	
EU:	European Union
FIH:	first-in-human
FoxP3:	forkhead box P3
FSH:	follicle-stimulating hormone
GCP:	Good Clinical Practice
GDPR:	General Data Protection Regulation
GLP:	good laboratory practice
HBc Ab:	hepatitis B core antibody
HBs Ag:	hepatitis B surface antigen
HBV:	hepatitis B virus
HCPs:	healthcare professional
HCV:	hepatitis C virus
HiSCR:	Hidradenitis Suppurativa Clinical Response
HIV:	human immunodeficiency virus
HRT:	hormone replacement therapy

HS:	hidradenitis suppurativa
HSA:	human serum albumin
hs-CRP:	high-sensitivity C-reactive protein
HS-PGA:	Hidradenitis Suppurativa Physician's Global Assessment
[redacted]	
I&D:	incision and drainage
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Conference on Harmonization
IDMC:	Independent Data Monitoring Committee
IEC:	independent ethics committee
IFN-γ:	interferon gamma
[redacted]	
IHS4:	International Hidradenitis Suppurativa Severity Score System
IL:	interleukin
IL-1β:	interleukin-1β
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	interactive response technology
IV:	intravenous(ly)
JAK:	Janus kinase
kg:	kilogram
KLH:	keyhole limpet hemocyanin
LAR:	legally authorized representative
LLOQ:	lower limit of quantification
LPLV:	last participant last visit
MAD:	multiple ascending dose
mg:	milligrams
mL:	milliliter
mmol/L:	millimole/liter
MTX:	methotrexate
NOAEL:	no-observed-adverse-effect level
NTM:	nontuberculous mycobacteria
NYHA:	New York Health Association
OX40L:	OX40-Ligand
PBMC:	peripheral blood mononuclear cell
PD:	pharmacodynamics
PI:	principal investigator
PK:	pharmacokinetics
PML:	progressive multifocal leukoencephalopathy
PO:	per oral
[redacted]	
PRN:	as needed
PT:	preferred term
Q2W:	every 2 weeks
QoL:	quality of life

QTLs:	quality tolerance limits
RNA:	ribonucleic acid
SAA:	serum amyloid A
SAD:	single ascending dose
SAEs:	serious adverse event(s)
SAP:	statistical analysis plan
SC:	subcutaneous(ly)
SIB:	suicidal ideation and behavior
SoA:	schedule of activities
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
$t_{1/2}$:	terminal half-life
TB:	tuberculosis
TBI:	tuberculosis infection
[redacted]	
TE:	treatment-emergent
TEAEs:	treatment-emergent adverse events
Th1:	T helper 1
Th17:	T helper 17
T_{max}:	time to reach serum peak drug concentration (C_{max})
[redacted]	
TOC:	table of contents
TTx:	tetanus-toxoid
TYK:	tyrosine kinase
ULN:	upper limit of normal
US:	United States
UVA:	ultraviolet A
UVB:	ultraviolet B
V_{HH}:	variable domain of heavy chain antibodies
WOCBP:	woman of childbearing potential
WONCBP:	woman of nonchildbearing potential

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A randomized, double-blind, placebo-controlled, proof-of-concept study assessing the efficacy and safety of an anti-TNF-OX40L NANOBODY® molecule, SAR442970, in participants with moderate to severe hidradenitis suppurativa

Brief title:

A study to test the efficacy and safety of SAR442970 in adult people with hidradenitis suppurativa.

Regulatory agency identifier number(s):

IND:	165047
NCT:	NCT05849922
WHO:	U1111-1280-6493
EUDAMED:	Not applicable
EU trial number:	2022-502370-17
Other:	Not applicable

Rationale:

The purpose of this study is to demonstrate the efficacy and safety of SAR442970 in participants of 18 to 70 years of age, inclusive, with moderate to severe hidradenitis suppurativa (HS). Hidradenitis suppurativa or acne inversa is a chronic, relapsing, debilitating, inflammatory skin disease that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillary, inguinal, and anogenital regions (Dessau definition, 1st International Conference on Hidradenitis Suppurativa, 30 March to 01 April 2006, Dessau, Germany) (1, 2). Patients develop HS in anatomic areas bearing apocrine sweat glands with a high degree of mechanical friction, such as skin folds, which triggers local perifollicular cell damage leading to hyperplasia and hyperkeratosis of the infundibular epithelium of the hair, causing follicular occlusion. This results in intrafollicular stasis and propagation of resident bacteria resulting in dilatation of the hair follicle along with an accumulation of a mixed inflammatory cell infiltrate, including T and B cells, in the surrounding tissues. In later stages, the accumulation of inflammatory cells leads to follicular rupture in the form of nodules and/or abscesses. Subsequent extracellular matrix degradation by fibroblasts and neutrophil infiltration can eventually result in the formation of pus-draining tunnels. The infiltrating T cells of the adaptive immune system are a dominant source of tumor necrosis factor-alpha (further referred to herein as “TNF”) that propagate pathogenic inflammation (3). Additionally in HS skin, relative to other inflammatory skin conditions, regulatory T cells are decreased, and T cell ratios are skewed (4). OX40 stimulation may suppress forkhead box P3 (FoxP3) protein expression, a master regulator in the pathway necessary for regulatory T cell development and function (5). Targeting the OX40-OX40L (interaction between OX40 and OX40-Ligand [OX40L]) immune synapse circuit implicated in T cell survival, T and B cell interaction, and an effector T cell phenotype

with cytokine release along with TNF-inhibition is postulated to have an additive effect on decreasing the inflammation present in HS (6).

SAR442970 is a bispecific pentavalent NANOBODY®[1] molecule. NANOBODY® molecules are therapeutic proteins that are derived from the variable domain of heavy chain antibodies (V_{HH}); heavy chain only antibodies occur naturally in the Camelidae family. They have a high degree of homology (in terms of sequence and structure) to human immunoglobulin heavy chain variable region domains and can be further engineered and expressed by a variety of expression systems. SAR442970 is composed of five V_{HH}: 2 V_{HH} bind to an OX40L epitope, 2 V_{HH} bind to a TNF epitope, and 1 V_{HH} binds to an albumin epitope to extend the molecule's half-life. All domains have been humanized to reduce immunogenicity. SAR442970 binds to both TNF as well as OX40L with high affinity, and thereby is able to simultaneously inhibit the binding of OX40L and TNF to their respective receptors systems. SAR442970 is proposed to target the chronic inflammatory process that contributes to the formation and progression of lesions associated with HS through binding to TNF as well as OX40L. TNF-inhibition has already been shown to be efficacious in the treatment of HS in clinical trials (7). Additional targeting of OX40L is expected to prevent the contribution of T effector cells and B cells to the inflammation in HS thereby improving lesions and associated symptoms. The efficacy of SAR442970 will be evaluated in the primary analysis population, a subgroup of biologic and small molecule immunosuppressive-naïve participants (specific definition below and in Section 5.1 and Section 5.2) and will be evaluated in an exploratory manner in a subgroup of TNF-experienced participants (specific definition below and in Section 5.1 and Section 5.2). Safety analyses will include both biologic and small molecule immunosuppressive-naïve and TNF-experienced participants. Exploratory analysis of Hidradenitis Suppurativa Clinical Response (HiSCR) 50 in the combined biologic and small molecule immunosuppressive-naïve subgroup and TNF-experienced subgroup will be performed up to Week 28. Additional exploratory analyses for effect of SAR442970 on HiSCR50, HiSCR75, HiSCR90, International Hidradenitis Suppurativa Severity Score System (IHS4), [redacted], components of the HiSCR50, disease flares, use of rescue therapy, Hidradenitis Suppurativa-Physician's Global Assessment (HS-PGA), quality of life (QoL) measures, and pruritus will be performed up to Week 28 in the biologic and small molecule immunosuppressive-naïve and TNF-experienced subgroups.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of SAR442970 during the double-blind, placebo-controlled period in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS	• The clinical response as measured by the percentage of biologic and small molecule immunosuppressive-naïve participants achieving Hidradenitis Suppurativa Clinical Response (HiSCR50) (defined as ≥50% reduction from Baseline in the total abscess and inflammatory nodule [AN] count, with no increase from Baseline in abscess or draining tunnel count) at Week 16 (8, 9)

[1] NANOBODY is a registered trademark of Ablynx N.V.

Objectives	Endpoints
Secondary	
• To evaluate the efficacy and safety of SAR442970 in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS	• Time to onset of achieving HiSCR50 • Percentage of participants achieving HiSCR75 (defined as ≥75% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count) at Week 16 • Percentage of participants achieving HiSCR90 (defined as ≥90% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count) at Week 16 • Percentage of participants who experience improvement by at least one International Hidradenitis Suppurativa Severity Score System (IHS4) stage at Week 16 (See also Section 8.2.1.3 for definition of IHS4) • Change in absolute score from Baseline in IHS4 at Week 16 • Percentage of participants who experience a flare, defined as at least a 25% increase in AN count (with a minimum increase of 2) relative to Baseline at Week 16 (See also Section 8.2.1.4 for definition of flare) • Percentage of participants achieving IHS4-55 at Week 16 (defined as achievement of a 55% reduction in IHS4 score from Baseline) • Incidence of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) including local reactions • Incidence of potentially clinically significant abnormalities in laboratory tests, vital signs, and electrocardiograms
• To evaluate the effect of SAR442970 on pain in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS	• Percentage of participants achieving at least 30% reduction and at least 1 unit reduction from Baseline in weekly average of daily [redacted]
• To evaluate the pharmacokinetics (PK) of SAR442970 and anti-drug antibodies to SAR442970 in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS	• Serum SAR442970 concentrations throughout the study • Incidence of anti-SAR442970 antibody positive response throughout the study

Overall design synopsis:

This is a multinational, multi-center, randomized, double-blind, placebo-controlled, Phase 2a proof of concept study to evaluate the efficacy and safety of SAR442970 in adult participants with moderate to severe HS.

The intervention in the study includes investigational medicinal product (IMP) administration every 2 weeks (Q2W) to complete 28 weeks of treatment with SAR442970. The study is

composed of 3 parts: a double-blind, placebo-controlled period (Period A), followed by an open-label period (Period B), and then followed by a safety Follow-up Period (Period C).

Participants will receive SAR442970 150 milligrams (mg) or matching placebo Q2W at the Week 0 visit up to the Week 14 visit as part of Period A, the double-blind, placebo-controlled period. Beginning at the Week 16 visit, all participants will receive SAR442970 150 mg Q2W up to the visit prior to the individual participant's end of treatment (EOT) visit as part of Period B, the open-label period. Period C will be an 8-week safety Follow-up Period commencing with the End of Treatment (EOT) visit and concluding with the End of Study (EOS) visit. Participants will not be expected to receive more than 14 doses of SAR442970. [For participants in the US, response will be assessed at the Week 20 visit (see definition of response in Section 4.1). Responders at Week 20 will continue in Period B to complete the 12-week open-label period. Non-responders at Week 20 will move directly to the safety follow-up period (Period C) with the Week 20 visit serving as their EOT visit. No IMP will be administered to non-responders at their EOT visit at Week 20].

The target population of the study is participants with HS based on a history of signs and symptoms consistent with HS for at least 1 year prior to Baseline and demonstrating moderate to severe disease at Baseline as defined by HS lesions present in at least 2 distinct anatomic areas (eg, left and right axilla; or left axilla and left inguino-crural fold), one of which must be Hurley Stage II or Hurley Stage III, an abscess and inflammatory nodule (AN) count of ≥3, a draining tunnel count ≤20, and C-reactive protein (CRP) level of >3 mg/L.

Additionally, all participants must have had an inadequate response to a course of an oral (PO) antibiotic for treatment of HS; have exhibited recurrence after discontinuation of antibiotics; or have demonstrated intolerance to antibiotics or have a contraindication to oral antibiotics for treatment of HS as assessed by the Investigator through participant interview and review of medical history. Participants will be considered to have had an inadequate response or loss of response to oral antibiotics if at least 1 of the following occurs while receiving antibiotics:

- Progression of Hurley Stage (ie, the Hurley Stage of at least one affected anatomic region progressed from I→II, II→III, or I→III).
- Participant required at least one intervention (eg, incision and drainage [I&D] or intralesional injection of corticosteroid).
- Participant experienced pain interfering with activities of daily living, with unsatisfactory relief from over-the-counter analgesics (eg, ibuprofen or acetaminophen).
- Participant experienced pain requiring opioids, including tramadol.
- Participant experienced drainage interfering with activities of daily living (eg, requires multiple dressing changes and/or changes of clothes daily).
- Participant experienced an increase in the number of anatomic regions affected by HS.
- Participant experienced at least one new abscess or one new draining fistula.
- Participant experienced a flare (or worsening of disease) as determined by the Investigator while on oral antibiotics.

Participants will be considered as intolerant to oral antibiotic when oral antibiotic therapy has been discontinued as a result of a significant adverse reaction to oral antibiotic administration.

A reaction will be considered significant if the adverse reaction is at least moderate (ie, the adverse event causes discomfort or interrupts the participant's usual activities or function) as assessed by the Investigator through participant interview and review of medical history. Examples of significant adverse reactions include, but are not limited to:

- Nausea resulting in decreased oral intake.
- Dizziness/disequilibrium/lightheadedness/vertigo interfering with normal function.
- Hypersensitivity reactions including, but not limited to, rash, flushing, urticaria, dyspnea, or drug fever ≥38°C.
- Diarrhea manifesting as an increase in stool frequency of at least 4 stools per day over participant's baseline.

Approximately, 84 participants will be randomized in a 2:1 ratio to SAR442970 150 mg or matching placebo. Randomization will first be stratified by HS treatment history into 2 major subgroups:

- Biologic and small molecule immunosuppressive-naïve subgroup.
- TNF-experienced subgroup.

The biologic and small molecule immunosuppressive-naïve subgroup is composed of participants who have never received biologic therapies, such as anti-TNF therapy, anti-interleukin (IL)17, anti-IL1, anti-IL36, or anti-IL23, or small molecule immunosuppressive therapies, such as Janus kinase/tyrosine kinase (JAK/TYK) inhibitors. The recruitment target for the biologic and small molecule immunosuppressive-naïve subgroup is approximately 66 participants. Randomization will be further stratified by Hurley Stage (II or III). Within the biologic and small molecule immunosuppressive-naïve subgroup, the number of participants with Hurley Stage III is not to exceed more than 50% in order to recruit a population with the desired disease severity.

The TNF-experienced subgroup is composed of participants who experienced at least one of the following scenarios after receiving a single anti-TNF therapy (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, etc) for at least 12 weeks as assessed by the Investigator through participant interview and review of medical history:

- Participants who had a complete response to anti-TNF therapy for HS per Investigator discretion and subsequently lost response, or
- Participants who had a partial response to anti-TNF therapy for HS per Investigator discretion, or
- Participants who did not achieve a partial response to anti-TNF therapy for HS per Investigator discretion, or
- Participants who stopped using anti-TNF therapy due to reasons other than an adverse event (AE) (ie, insurance or access or other reasons) (8, 9).

For the TNF-experienced subgroup, if participants have received more than 1 anti-TNF therapy for HS, they are not eligible for participation. Participants that have experienced an AE related to anti-TNF therapy (examples include, but are not limited to, serum sickness or anaphylaxis) that would contraindicate re-administration of an anti-TNF class therapy will be excluded. The recruitment target for the TNF-experienced subgroup is approximately 18 participants.

Randomization will be further stratified by Hurley Stage (II or III). Within the TNF-experienced subgroup, the number of participants with Hurley Stage III is not to exceed more than 50% in order to recruit a population with the desired disease severity.

The primary analysis population is the biologic and small molecule immunosuppressive-naïve subgroup. Efficacy objectives and endpoints will be evaluated in an exploratory manner in the TNF-experienced subgroup.

Brief summary:

This is a multinational, multi-center, randomized, double-blind, placebo-controlled, Phase 2 study. The purpose of the present study is to measure efficacy, safety, PK, and biological effects of treatment with SAR442970 compared with placebo in adult participants with moderate to severe HS.

Study details include the following:

- The study duration will be up to 40 weeks. For US participants who are non-responders at the Week 20 assessment, the study duration will be 28 weeks.
- The treatment duration will be up to 28 weeks. Participants will receive SAR442970 150 mg or matching placebo Q2W beginning at the Week 0 visit up to the Week 14 visit as part of Period A, the double-blind, placebo-controlled period. Beginning at the Week 16 visit, all participants will receive SAR442970 150 mg Q2W up to the visit prior to the individual participant's EOT visit as part of Period B, the open-label period. For US participants, response will be assessed at the Week 20 visit. Responders at Week 20 will continue in Period B to complete the 12-week open-label period. Non-responders at Week 20 will move directly to the safety follow-up period with the Week 20 visit serving as their EOT visit.
- The number of visits will be at maximum 17.

Number of participants:

The study will include approximately 84 adult participants with moderate to severe HS stratified based on prior treatment experience (approximately 66 biologic and small molecule immunosuppressive-naïve and approximately 18 TNF-experienced).

Study interventions and duration:

Study intervention(s)

SAR442970 or matching placebo.

Investigational medicinal product(s)

SAR442970:

- Formulation: 1 milliliter (mL) extractable volume of 150 mg/mL SAR442970 filled in 2 mL glass vial.
- Route of administration: subcutaneous (SC).
- Dose regimen:

- Double-blind treatment period (Period A): 150 mg Q2W from Week 0 to Week 14 (to complete 16 weeks of treatment).
- Open-label treatment period (Period B): 150 mg Q2W from Week 16 up to Week 28 (to complete up to 12 weeks of treatment).

Placebo:

- Formulation: identical formulation to the active 150 mg/mL SAR442970 formulation without SAR442970, 1 mL extractable volume in a 2 mL glass vial.
- Route of administration: SC
- Dose regimen:
  - Double-blind treatment period: Placebo Q2W from Week 0 to Week 14.

A complete description of the IMP and its proper preparation steps and handling will be provided in the pharmacy manual available to the clinical sites.

Devices

Not applicable.

Post-trial access to study medication

No post-trial access to study medication is planned for this study.

Duration of study intervention

Each participant will have a Screening Period of up to 4 weeks to assess eligibility and treatment period (Period A and B) of up to 28 weeks beginning from the day of randomization (Baseline, Day 1). Period C will commence with an EOT visit and after 8 weeks conclude with an EOS Visit.

Statistical considerations:

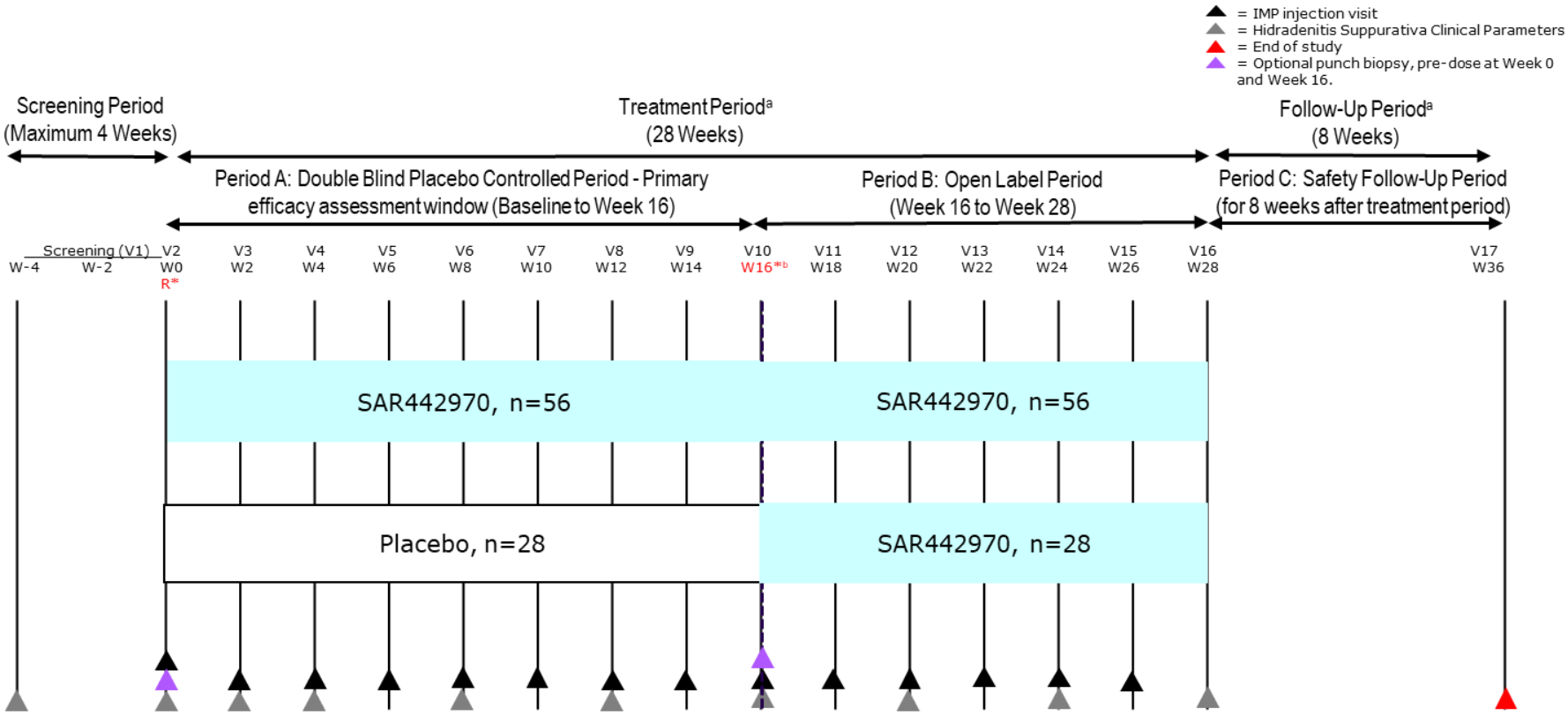
- **Primary endpoint:**
  - The primary efficacy analysis will be the comparison between SAR442970 and placebo in the percentage of participants achieving HiSCR50 at Week 16, using a Bayesian logistic regression model including treatment group and adjusted by randomization stratum (Hurley stage).
- **Main secondary endpoints:**
  - Responder main secondary endpoints in Period A will be analyzed using the Cochran-Mantel-Haenszel test including treatment group and adjusted by randomization stratum (Hurley stage). For continuous main secondary endpoints in Period A, data will be analyzed by fitting an ANCOVA model with the Baseline covariates and factors for treatment, Hurley stage.

Data Monitoring/Other committee: Yes

An external Independent Data Monitoring Committee (IDMC) has been appointed for this study. The Data Monitoring Committee (board) is a group of scientists independent from the Sponsor who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for safety reasons. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.

1.2 SCHEMA

Figure 1 - Graphical study design for All Participants (Except for Participants in the United States)[c]



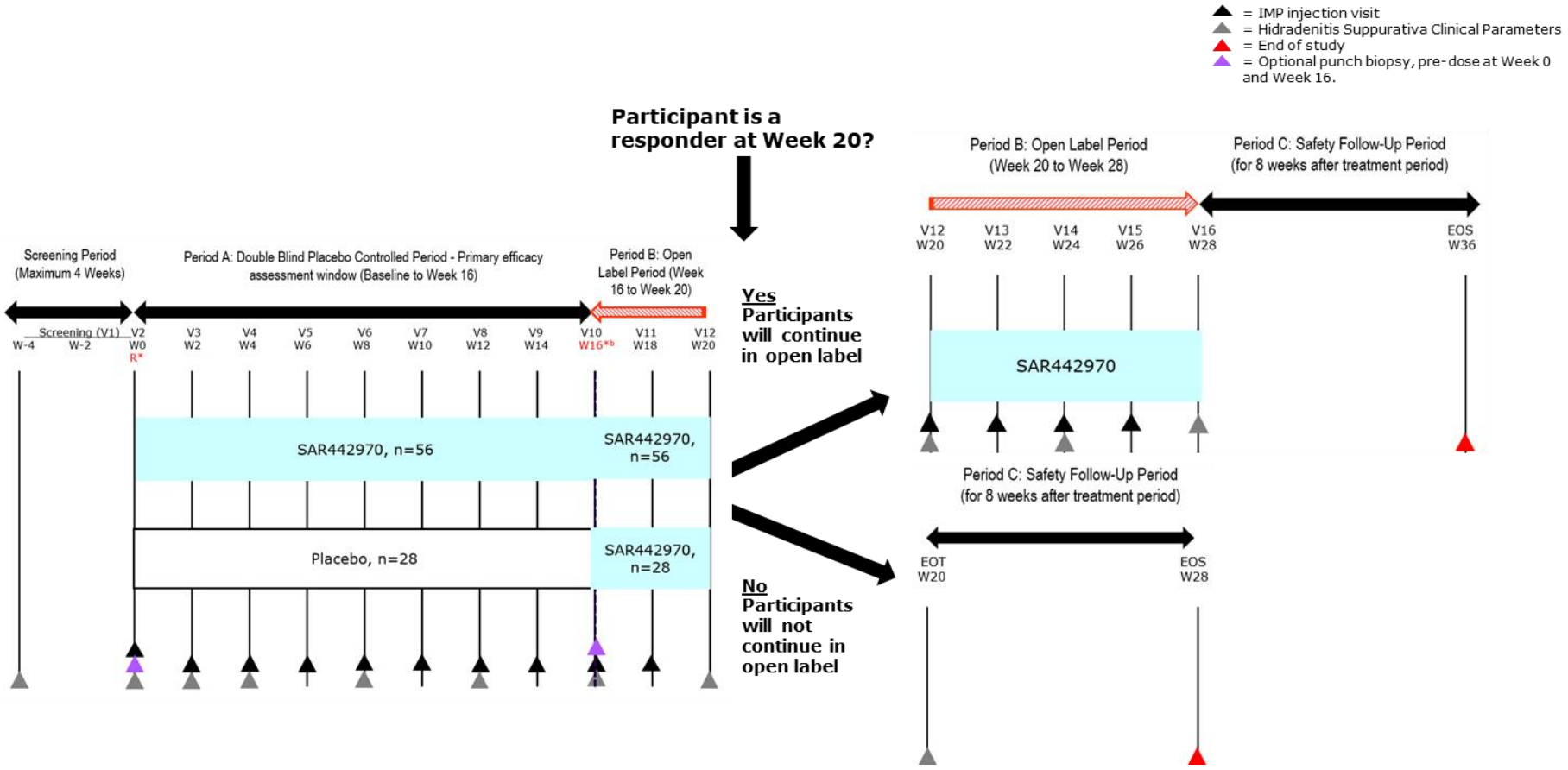
IMP=investigational medicinal product; n=number of participants; R=randomization; V=Visit; W=Week

a All participants consent to 28-week treatment period and 8-week Follow-up Period at enrollment

b Primary endpoint: Hidradenitis Suppurativa Clinical Response (HiSCR50).

c Please see Figure 2 - Graphical study design for Participants in the United States.

Figure 2 - Graphical study design for Participants in the United States



EOT=end of treatment; EOS=end of study; IMP=investigational medicinal product; n=number of participants; R=randomization; V=Visit; W=Week

a All participants consent to 28-week treatment period and 8-week follow-up period at enrollment. Clinical response will be assessed at Week 20 for all participants. Only participants who meet criteria for clinical response will continue to Period B. Response will be defined as ≥50% reduction from Baseline in the total abscess and inflammatory nodule (AN) count, with no increase from Baseline in abscess or draining tunnel count at Week 20. For non-responders, they will not continue in Period B and will immediately continue to Period C (an 8-week Safety Follow-up period) starting with an EOT visit and ending with an EOS visit.

b Primary endpoint: Hidradenitis Suppurativa Clinical Response (HiSCR50).

1.3 SCHEDULE OF ACTIVITIES (SOA)

1.3.1 Flowchart for All Participants (Except for Participants in the United States)

Procedure[a]	Screening Period (Maximum 4 weeks)[b]	Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)								End of Double-blind/ Start of Open Label	Treatment Period B: Open Label Period (12 weeks)					End of Open Label/ Start of Safety Follow-Up	Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)
Visit Number (V)[c]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15		
Visit Label	Screening	Baseline														EOT[d]	EOS[d]
Visit Weeks[e]	W-4 to W0	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18[f]	W20	W22[f]	W24	W26[f]	W28	W36
Visit Days	D-28 to D-1	D1	D15 (±3d)	D29 (±3d)	D43 (±3d)	D57 (±3d)	D71 (±3d)	D85 (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)	D141 (±3d)	D155 (±3d)	D169 (±3d)	D183 (±3d)	D197 (±3d)	D253 (±5d)
Participant Eligibility																	
Informed Consent	X																
Inclusion and Exclusion Criteria[g]	X	X[h, i]															
Demographics	X																
Medical and Surgical History (Includes Alcohol, Nicotine, and Substance Usage)	X	X[h, i]															

Procedure[a]	**Screening Period (Maximum 4 weeks)**[b]	**Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)**								**End of Double-blind/ Start of Open Label**	**Treatment Period B: Open Label Period (12 weeks)**					**End of Open Label/ Start of Safety Follow-Up**	**Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)**
Visit Number (V)[c]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**		
Visit Label	**Screening**	**Baseline**														**EOT**[d]	**EOS**[d]
Visit Weeks[e]	**W-4 to W0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**[f]	**W20**	**W22**[f]	**W24**	**W26**[f]	**W28**	**W36**
Visit Days	**D-28 to D-1**	**D1**	**D15 (±3d)**	**D29 (±3d)**	**D43 (±3d)**	**D57 (±3d)**	**D71 (±3d)**	**D85 (±3d)**	**D99 (±3d)**	**D113 (±3d)**	**D127 (±3d)**	**D141 (±3d)**	**D155 (±3d)**	**D169 (±3d)**	**D183 (±3d)**	**D197 (±3d)**	**D253 (±5d)**
Hidradenitis Suppurativa History[j]	X																
Family History of Hidradenitis Suppurativa[k]	X																
Hepatitis B and C and HIV Serology Tests[l]	X[n]																
Serum Sample for Tetanus Toxoid IgG Ab[m]	X																
TB Assessment[o]	X																
FSH[p]	X																
COVID-19 Testing[q]	X																
Screening CRP	X																

Procedure[a]	**Screening Period (Maximum 4 weeks)**[b]	**Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)**								**End of Double-blind/ Start of Open Label**	**Treatment Period B: Open Label Period (12 weeks)**					**End of Open Label/ Start of Safety Follow-Up**	**Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)**
Visit Number (V)[c]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**		
Visit Label	**Screening**	**Baseline**														**EOT**[d]	**EOS**[d]
Visit Weeks[e]	**W-4 to W0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**[f]	**W20**	**W22**[f]	**W24**	**W26**[f]	**W28**	**W36**
Visit Days	**D-28 to D-1**	**D1**	**D15 (±3d)**	**D29 (±3d)**	**D43 (±3d)**	**D57 (±3d)**	**D71 (±3d)**	**D85 (±3d)**	**D99 (±3d)**	**D113 (±3d)**	**D127 (±3d)**	**D141 (±3d)**	**D155 (±3d)**	**D169 (±3d)**	**D183 (±3d)**	**D197 (±3d)**	**D253 (±5d)**
Initiate Washout of HS and Non-HS Medications If Needed[r]	X																
Daily Diary Introduction and Training[s]	X																
Follow-Up Phone Call[u]	X																
Treatment																	
Call IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X[f]															
IMP Administration[v]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Diary for IMP Administration[t]											X		X		X		
Daily Analgesic Usage Diary[s]	←═══→																

Procedure[a]	**Screening Period (Maximum 4 weeks)**[b]	**Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)**								**End of Double-blind/ Start of Open Label**	**Treatment Period B: Open Label Period (12 weeks)**					**End of Open Label/ Start of Safety Follow-Up**	**Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)**
Visit Number (V)[c]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**		
Visit Label	**Screening**	**Baseline**														**EOT**[d]	**EOS**[d]
Visit Weeks[e]	**W-4 to W0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**[f]	**W20**	**W22**[f]	**W24**	**W26**[f]	**W28**	**W36**
Visit Days	**D-28 to D-1**	**D1**	**D15 (±3d)**	**D29 (±3d)**	**D43 (±3d)**	**D57 (±3d)**	**D71 (±3d)**	**D85 (±3d)**	**D99 (±3d)**	**D113 (±3d)**	**D127 (±3d)**	**D141 (±3d)**	**D155 (±3d)**	**D169 (±3d)**	**D183 (±3d)**	**D197 (±3d)**	**D253 (±5d)**
Prior and Concomitant Medications	X	X[h, i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Resume HS Medication if Needed[w]																X	
Safety																	
AE Reporting, Including SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X									X						X	X
Vital Signs[x]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination (including height and weight)[y]	X	X		X		X		X		X		X		X		X	X
Fasting Lipid Panel[z]	X	X		X		X				X		X				X	X

Procedure[a]	**Screening Period (Maximum 4 weeks)**[b]	**Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)**								**End of Double-blind/ Start of Open Label**	**Treatment Period B: Open Label Period (12 weeks)**					**End of Open Label/ Start of Safety Follow-Up**	**Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)**
Visit Number (V)[c]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**		
Visit Label	**Screening**	**Baseline**														**EOT**[d]	**EOS**[d]
Visit Weeks[e]	**W-4 to W0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**[f]	**W20**	**W22**[f]	**W24**	**W26**[f]	**W28**	**W36**
Visit Days	**D-28 to D-1**	**D1**	**D15 (±3d)**	**D29 (±3d)**	**D43 (±3d)**	**D57 (±3d)**	**D71 (±3d)**	**D85 (±3d)**	**D99 (±3d)**	**D113 (±3d)**	**D127 (±3d)**	**D141 (±3d)**	**D155 (±3d)**	**D169 (±3d)**	**D183 (±3d)**	**D197 (±3d)**	**D253 (±5d)**
Non-fasting Laboratory Testing[z]	X	X		X		X		X		X		X		X		X	X
Urinalysis	X	X				X				X		X				X	X
Pregnancy Test (WOCBP Only)[aa]	X	X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X			X				X		X		X		X	X
Efficacy																	
Hidradenitis Suppurativa Clinical Parameters[bb]	X	X	X	X		X		X		X		X		X		X	
[redacted]																	
Daily Diary Review[cc]		X	X	X	X	X	X	X	X	X		X		X		X	
[redacted]																	

Procedure[a]	Screening Period (Maximum 4 weeks)[b]	Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)								End of Double-blind/ Start of Open Label	Treatment Period B: Open Label Period (12 weeks)					End of Open Label/ Start of Safety Follow-Up	Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)
Visit Number (V)[c]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15		
Visit Label	Screening	Baseline														EOT[d]	EOS[d]
Visit Weeks[e]	W-4 to W0	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18[f]	W20	W22[f]	W24	W26[f]	W28	W36
Visit Days	D-28 to D-1	D1	D15 (±3d)	D29 (±3d)	D43 (±3d)	D57 (±3d)	D71 (±3d)	D85 (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)	D141 (±3d)	D155 (±3d)	D169 (±3d)	D183 (±3d)	D197 (±3d)	D253 (±5d)
[redacted]																	
PK, Immunogenicity, PD, [redacted], and Biomarkers																	
Serum PK Sampling[ee, ff]		X		X		X	X	X		X	X	X				X	X
Serum Anti-Drug Antibodies[ee, ff]		X	X	X						X						X	X
Serum PD Biomarkers[ee, ff, gg]		X		X			X			X						X	X
[redacted]																	

Procedure[a]	Screening Period (Maximum 4 weeks)[b]	Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)								End of Double-blind/ Start of Open Label	Treatment Period B: Open Label Period (12 weeks)					End of Open Label/ Start of Safety Follow-Up	Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)
Visit Number (V)[c]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15		
Visit Label	Screening	Baseline														EOT[d]	EOS[d]
Visit Weeks[e]	W-4 to W0	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18[f]	W20	W22[f]	W24	W26[f]	W28	W36
Visit Days	D-28 to D-1	D1	D15 (±3d)	D29 (±3d)	D43 (±3d)	D57 (±3d)	D71 (±3d)	D85 (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)	D141 (±3d)	D155 (±3d)	D169 (±3d)	D183 (±3d)	D197 (±3d)	D253 (±5d)
[redacted]																	
Plasma Biomarker Panel[ee, ff, ii]		X		X				X		X						X	
Serum Biomarker Panel[ee, ff, ii]		X		X				X		X						X	
[redacted]																	

Procedure[a]	Screening Period (Maximum 4 weeks)[b]	Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)								End of Double-blind/ Start of Open Label	Treatment Period B: Open Label Period (12 weeks)					End of Open Label/ Start of Safety Follow-Up	Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)
Visit Number (V)[c]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15		
Visit Label	Screening	Baseline														EOT[d]	EOS[d]
Visit Weeks[e]	W-4 to W0	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18[f]	W20	W22[f]	W24	W26[f]	W28	W36
Visit Days	D-28 to D-1	D1	D15 (±3d)	D29 (±3d)	D43 (±3d)	D57 (±3d)	D71 (±3d)	D85 (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)	D141 (±3d)	D155 (±3d)	D169 (±3d)	D183 (±3d)	D197 (±3d)	D253 (±5d)
[redacted]																	

AE=adverse event; Ab=antibody; AN=abscess and inflammatory nodule; ANC=absolute neutrophil count; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; COVID-19=coronavirus disease 2019; [redacted]; C-SSRS= Columbia-Suicide Severity Rating Scale; D=day; ECG=electrocardiogram; eCRF=electronic case report form; EOT=end of treatment; EOS=end of study; [redacted] FSH=follicle stimulating hormone; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV-Ab=hepatitis C virus antibody; HiSCR=hidradenitis suppurativa clinical response; HIV=human immunodeficiency virus; HS=hidradenitis suppurativa; [redacted] hs-CRP=high-sensitivity C-reactive protein; IgG=immunoglobulin G; IgM anti-HBc=immunoglobulin M antibody to hepatitis B core antigen; IHS4=International Hidradenitis Suppurativa Severity Score System; IMP=Investigational Medicinal Product; IRT=interactive response technology; OX40L=OX40-Ligand; PD=pharmacodynamic(s); PK=pharmacokinetic(s); [redacted]; SAA=serum amyloid A; SAE=serious adverse event; SC=subcutaneous(ly); TB=tuberculosis; [redacted] V=visit; W=week; WOCBP=women of childbearing potential.

a When several assessments take place at the same time, the following order should be respected: questionnaires, ECG, followed by vital signs, AE reporting, prior and concomitant medications, daily diary review, blood sampling, physical examination, lesion intervention if needed, HS clinical parameters, skin biopsy, and IMP administration.

b A maximum of 28 days is required depending on participants' prior and concomitant medications. Randomization of the participant must take these constraints into consideration.

c All visits are done on-site except if home nursing is arranged for visits at Week 18, 22, or 26. Participants in Denmark will not have home nursing, please refer to Section 10.8.1.2.

d Participants who discontinue IMP treatment prior to completing the 28-week treatment period and 8-week Follow-up Period will be evaluated as soon as possible at the individual participant's EOT Visit, using procedures as planned for the EOT Visit at Week 28 (Visit 16). At their EOT Visit, participants will resume their HS medications or other appropriate therapy as needed per Investigator discretion after the EOT study assessments have been performed and will enter the 8-week safety Follow-up Period, concluding with EOS Visit (Visit 17).

e The study visits occur on the planned dates (relative to the first IMP), as scheduled.

f Visits at Week 18, 22, and 26 may be performed with a home nursing service.

g To qualify for randomization all inclusion criteria and none of the exclusion criteria are met by the participant.

h Update inclusion/exclusion criteria, medical and surgical history, and prior and concomitant medications information to assure participant eligibility.

i Prior to randomization.

j Investigators must obtain a history of prior therapies used to treat HS, including antibiotics. The prior doses and reasons for discontinuation of antibiotic therapy will need to be recorded in the eCRF to verify eligibility. In the TNF-experienced population, Investigators will be asked to complete a questionnaire on the duration of anti-TNF therapy use as well as providing a description of the treatment response to anti-TNF therapy.

k Investigators will be asked to complete a questionnaire on participant's family history of HS in first-degree relatives (parents, siblings, and children) to be recorded in the eCRF.

l Clinical laboratory testing at Screening (Visit 1) will include a hepatitis screen covering HBsAg, anti-HBs, total anti-HBc, IgM anti-HBc, HCV-Ab, and HIV (anti-HIV-1 and HIV-2 antibodies). In case of results showing HBsAg negative and anti-HBc positive, HBV DNA testing will be performed prior to randomization to rule out a false positive and to clarify serological status. In case of results showing HCV Ab positive, HCV RNA testing will be performed to rule out a false positive. Please refer to Section 10.2. If a participant has a positive HBc Ab or anti-HBs followed by a negative HBV DNA PCR at screening and is subsequently randomized, they will undergo HBV DNA PCR testing every 3 months until the end of study visit. If a participant has a positive HCV Ab and followed by a negative HCV ribonucleic acid (RNA) PCR at screening and is subsequently randomized, they will undergo HCV RNA PCR testing every 3 months until the end of study visit. It is strongly recommended that participants have documented evidence of protective immunity to hepatitis B and have completed hepatitis B vaccination series per local guidelines 14 days prior to Baseline (Visit 2). This recommendation applies to any other age and gender-specific appropriate non-live vaccination series as per local guidelines as well. If live vaccines are required as per local guidelines, these must be completed 12 weeks prior to Baseline.

m It is strongly recommended that participants have documented evidence of protective immunity to tetanus and have completed tetanus vaccination series (with booster if needed) per local guidelines 14 days prior to Baseline (Visit 2). This recommendation applies to any other age and gender-specific appropriate non-live vaccination series as per local guidelines as well. If live vaccines are required as per local guidelines, these must be completed 12 weeks prior to Baseline.

n Assessments may be repeated for confirmation if deemed medically necessary.

o QuantiFERON TB gold test should be collected for all participants at the Screening (Visit 1). If the result is confirmed positive, the participant should be referred to an Infectious Disease specialist.

p FSH only if needed to confirm post-menopausal status during Screening.

q COVID-19 molecular test (if COVID-19 testing is required per local guidelines to be determined for each site). It is strongly recommended that participants have completed required COVID-19 vaccination series (with booster[s]), inactivated influenza vaccination, and pneumococcal vaccination per local guidelines 14 days prior to Baseline (Visit 2). This recommendation applies to any other age and gender-specific appropriate non-live vaccination series as per local guidelines as well. If live vaccines are required as per local guidelines, these must be completed 12 weeks prior to Baseline.

r Please refer to Table 4 – Prohibited therapy prior to Baseline for detailed description of required washout periods for various medications.

s Daily diary is used for daily recording of [redacted], participant daily analgesic use, and [redacted] from at minimum 4 days prior to Baseline (Visit 2) to Week 28 (Visit 16). It should preferably be completed at about the same time every evening. It may also be used to document IMP administration if the participant receives IMP through home nursing.

t Diary for IMP administration must be completed to document IMP administration if participant receives IMP through home nursing.

u Sites are encouraged to contact participants 10 days prior to Baseline (Visit 2) to confirm compliance with daily pain collection and daily analgesic use in the daily diary.

v All eligible participants will be treated for 28 weeks, receiving a SC administration of IMP or placebo every 2 weeks for the first 14 weeks based on randomization, and then starting at Week 16 (Visit 10) all participants will receive IMP every 2 weeks until the last dose is administered at Week 26 (Visit 15).

w Per Investigator discretion, participants may resume treatment for HS as needed (including, but not limited to oral and topical antibiotics, corticosteroids, opioid and non-opioid analgesics, spironolactone, finasteride, or metformin). Participants may also receive unlimited lesion intervention as needed per Investigator discretion.

x Vital signs, including body temperature (°C), heart rate (beats per minute), respiratory rate (breaths per minute), and systolic and diastolic blood pressure (mm Hg), will be measured at all visits detailed in the flowchart.

y Physical examination will include examination of skin, nasal cavities, eyes, ears, cardiovascular, respiratory, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. A brief symptom-directed physical examination should be performed at other visits if, in the opinion of the Investigator, it is warranted by the participant's AE status or on review of symptoms and will include, at a minimum, assessments of the skin, cardiovascular system, and abdomen (liver and spleen). Height will be measured and recorded at the Screening Visit. Weight will also be measured and recorded at the Screening, Baseline, Week 16, and EOS Visit.

z For fasting lipid panel, participant must be fasting for 8 hours prior to laboratory testing (may consume water). If unable to fast, participant may consume a light meal. Labs drawn during non-fasting laboratory testing will include hematology and clinical chemistry only. For laboratory testing please see Table 12.

aa Only for WOCBP: serum pregnancy test at Screening (Visit 1) and urine pregnancy tests at every visit from Baseline (Visit 2) to EOS (Visit 17). A negative result must be obtained at Screening (Visit 1) and at Baseline (Visit 2) prior to randomization. In case of positive urine test, the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to definitive treatment discontinuation in all cases.

bb Hidradenitis Suppurativa Clinical Parameters will be performed at each designated study visit and must address all relevant anatomical regions in each participant; the number, location, longest distance between relevant lesions, and whether the lesions are separated by normal-appearing skin will be measured in each anatomical area ; Hurley Stage is included as an assessment performed during the HS clinical parameters; Hidradenitis Suppurativa Physician's Global Assessment is included as an assessment performed during the HS clinical parameters. The site is responsible for counting lesions that received intervention as permanently present in the lesion counts from the date of the intervention. The data collected from the HS clinical parameters will be used for the derivation of the HiSCR50, HiSCR75, HiSCR90, IHS4, AN count, Hidradenitis Suppurative Physician's Global Assessment, raw counts, and disease flares. For each participant it is recommended that the HS Clinical Parameters is assessed by the same Investigator during the entire study if possible.

cc Investigator review of participant daily analgesic use diary.

dd The participant should complete the questionnaire before site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the participant's response.

ee Number of samples (tubes) and quantity of biological samples needed for each assessment can be found in the laboratory manual.

ff Up to 4 hours prior to IMP administration.

gg PD biomarkers will include serum TNF and serum OX40L.

hh Optional assessment with skin biopsies at Baseline (Visit 2) and Week 16 (Visit 10) will be performed. Participants without history of hypertrophic or keloid scarring as assessed by the Investigator through participant interview and review of medical history can choose whether they would like to participate in optional assessment. If they consent to participate, the participants will have one lesional biopsy of an inflammatory nodule and one non-lesional biopsy at Baseline (Visit 2) and Week 16 (Visit 10) (for a total of 4 biopsies). Biopsy is to be performed after HS clinical parameters, but before IMP administration at study visit. Sutures may be placed per the discretion of the Investigator. Participants will be scheduled for an additional visit 1 week after skin biopsy for suture removal if sutures are placed per the discretion of the Investigator. Sample will be processed per instructions in the laboratory manual.

ii Biomarker panel will include, but is not limited to, CRP, hs-CRP, [redacted], SAA, and ANC. Hematology sample will be drawn for neutrophils (with other values reported per laboratory manual).

jj Optional sample collected for potential retrospective safety follow-up and/or additional exploratory analysis.

1.3.2 Flowchart for Participants in the United States[a]

Procedure[b]	Screening Period (Maximum 4 weeks)[c]	Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)								End of Double-blind/ Start of Open Label	Treatment Period B: Open Label Period (12 weeks)						End of Open Label/ Start of Safety Follow-Up	Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)
											Open Label for All Participants (4 weeks)		Open Label for Responders Only (8 weeks)[a]					
Visit Number (V)[d]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Week 20 Response Assessed (Non-Responders Proceed Directly to EOT Visit)[a]	V12	V13	V14	V15		
Visit Label	Screening	Baseline															EOT[e]	EOS[e]
Visit Weeks[f]	W-4 to W0	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18[g]		W20	W22[g]	W24	W26[g]		
Visit Days	D-28 to D-1	D1	D15 (±3d)	D29 (±3d)	D43 (±3d)	D57 (±3d)	D71 (±3d)	D85 (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)		D141 (±3d)	D155 (±3d)	D169 (±3d)	D183 (±3d)	(±3d)	(±5d)
Participant Eligibility																		
Informed Consent	X																	
Inclusion and Exclusion Criteria[h]	X	X[i, j]																
Demographics	X																	
Medical and Surgical History (Includes Alcohol, Nicotine, and Substance Usage)	X	X[i, j]																
Hidradenitis Suppurativa History[k]	X																	

Procedure[b]	Screening Period (Maximum 4 weeks)[c]	Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)								End of Double-blind/ Start of Open Label	Treatment Period B: Open Label Period (12 weeks)						End of Open Label/ Start of Safety Follow-Up	Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)
											Open Label for All Participants (4 weeks)		Open Label for Responders Only (8 weeks)[a]					
Visit Number (V)[d]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Week 20 Response Assessed (Non-Responders Proceed Directly to EOT Visit)[a]**	**V12**	**V13**	**V14**	**V15**		
Visit Label	**Screening**	**Baseline**															**EOT**[e]	**EOS**[e]
Visit Weeks[f]	**W-4 to W0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**[g]		**W20**	**W22**[g]	**W24**	**W26**[g]		
Visit Days	**D-28 to D-1**	**D1**	**D15 (±3d)**	**D29 (±3d)**	**D43 (±3d)**	**D57 (±3d)**	**D71 (±3d)**	**D85 (±3d)**	**D99 (±3d)**	**D113 (±3d)**	**D127 (±3d)**		**D141 (±3d)**	**D155 (±3d)**	**D169 (±3d)**	**D183 (±3d)**	**(±3d)**	**(±5d)**
Family History of Hidradenitis Suppurativa[l]	X																	
Hepatitis B and C and HIV Serology Tests[m]	X[o]																	
Serum Sample for Tetanus Toxoid IgG Ab[n]	X																	
TB Assessment[p]	X																	
FSH[q]	X																	
COVID-19 Testing[r]	X																	
Screening CRP	X																	

Procedure[b]	Screening Period (Maximum 4 weeks)[c]	Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)								End of Double-blind/ Start of Open Label	Treatment Period B: Open Label Period (12 weeks)						End of Open Label/ Start of Safety Follow-Up	Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)
											Open Label for All Participants (4 weeks)		Open Label for Responders Only (8 weeks)[a]					
Visit Number (V)[d]	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**Week 20 Response Assessed (Non-Responders Proceed Directly to EOT Visit)[a]**	**V12**	**V13**	**V14**	**V15**		
Visit Label	**Screening**	**Baseline**															**EOT**[e]	**EOS**[e]
Visit Weeks[f]	**W-4 to W0**	**W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W14**	**W16**	**W18**[g]		**W20**	**W22**[g]	**W24**	**W26**[g]		
Visit Days	**D-28 to D-1**	**D1**	**D15 (±3d)**	**D29 (±3d)**	**D43 (±3d)**	**D57 (±3d)**	**D71 (±3d)**	**D85 (±3d)**	**D99 (±3d)**	**D113 (±3d)**	**D127 (±3d)**		**D141 (±3d)**	**D155 (±3d)**	**D169 (±3d)**	**D183 (±3d)**	**(±3d)**	**(±5d)**
Initiate Washout of HS and Non-HS Medications If Needed[s]	X																	
Daily Diary Introduction and Training[t]	X																	
Follow-Up Phone Call[v]	X																	
Treatment																		
Call IRT	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Randomization		X[h]																
IMP Administration[w]		X	X	X	X	X	X	X	X	X	X		X	X	X	X		
Diary for IMP Administration[u]											X			X		X		

Procedure[b]	Screening Period (Maximum 4 weeks)[c]	Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)								End of Double-blind/ Start of Open Label	Treatment Period B: Open Label Period (12 weeks)						End of Open Label/ Start of Safety Follow-Up	Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)
											Open Label for All Participants (4 weeks)		Open Label for Responders Only (8 weeks)[a]					
Visit Number (V)[d]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Week 20 Response Assessed (Non-Responders Proceed Directly to EOT Visit)[a]	V12	V13	V14	V15		
Visit Label	Screening	Baseline															EOT[e]	EOS[e]
Visit Weeks[f]	W-4 to W0	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18[g]		W20	W22[g]	W24	W26[g]		
Visit Days	D-28 to D-1	D1	D15 (±3d)	D29 (±3d)	D43 (±3d)	D57 (±3d)	D71 (±3d)	D85 (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)		D141 (±3d)	D155 (±3d)	D169 (±3d)	D183 (±3d)	(±3d)	(±5d)
Daily Analgesic Usage Diary[t]	←═══	═══	═══	═══	═══	═══	═══	═══	═══	═══	═══→		←═══	═══	═══	═══→		
Prior and Concomitant Medications	X	X[i, j]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Resume HS Medication if Needed[x]																	X	
Safety																		
AE Reporting, Including SAEs	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
12-Lead ECG	X									X							X	X
Vital Signs[y]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Physical Examination (including height and weight)[z]	X	X		X		X		X		X			X		X		X	X

Procedure[b]	Screening Period (Maximum 4 weeks)[c]	Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)								End of Double-blind/ Start of Open Label	Treatment Period B: Open Label Period (12 weeks)						End of Open Label/ Start of Safety Follow-Up	Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)
											Open Label for All Participants (4 weeks)		Open Label for Responders Only (8 weeks)[a]					
Visit Number (V)[d]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Week 20 Response Assessed (Non-Responders Proceed Directly to EOT Visit)[a]	V12	V13	V14	V15		
Visit Label	Screening	Baseline															EOT[e]	EOS[e]
Visit Weeks[f]	W-4 to W0	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18[g]		W20	W22[g]	W24	W26[g]		
Visit Days	D-28 to D-1	D1	D15 (±3d)	D29 (±3d)	D43 (±3d)	D57 (±3d)	D71 (±3d)	D85 (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)		D141 (±3d)	D155 (±3d)	D169 (±3d)	D183 (±3d)	(±3d)	(±5d)
Fasting Lipid Panel[aa]	X	X		X		X				X			X				X	X
Non-fasting Laboratory Testing[aa]	X	X		X		X		X		X			X		X		X	X
Urinalysis	X	X				X				X			X				X	X
Pregnancy Test (WOCBP Only)[bb]	X	X[j]	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X
C-SSRS	X	X	X			X				X			X		X		X	X
Efficacy																		
Hidradenitis Suppurativa Clinical Parameters[cc]	X	X	X	X		X		X		X			X		X		X	

Procedure[b]	Screening Period (Maximum 4 weeks)[c]	Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)								End of Double-blind/ Start of Open Label	Treatment Period B: Open Label Period (12 weeks)						End of Open Label/ Start of Safety Follow-Up	Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)
											Open Label for All Participants (4 weeks)		Open Label for Responders Only (8 weeks)[a]					
Visit Number (V)[d]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Week 20 Response Assessed (Non-Responders Proceed Directly to EOT Visit)[a]	V12	V13	V14	V15		
Visit Label	Screening	Baseline															EOT[e]	EOS[e]
Visit Weeks[f]	W-4 to W0	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18[g]		W20	W22[g]	W24	W26[g]		
Visit Days	D-28 to D-1	D1	D15 (±3d)	D29 (±3d)	D43 (±3d)	D57 (±3d)	D71 (±3d)	D85 (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)		D141 (±3d)	D155 (±3d)	D169 (±3d)	D183 (±3d)	(±3d)	(±5d)
Daily Diary Review[dd]		X	X	X	X	X	X	X	X	X			X		X		X	
[redacted]																		
PK, Immunogenicity, PD, [redacted] and Biomarkers																		
Serum PK Sampling[ff, gg]		X		X		X	X	X		X	X		X				X	X
Serum Anti-Drug Antibodies[ff, gg]		X	X	X						X							X	X

Procedure[b]	Screening Period (Maximum 4 weeks)[c]	Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)								End of Double-blind/ Start of Open Label	Treatment Period B: Open Label Period (12 weeks)						End of Open Label/ Start of Safety Follow-Up	Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)
											Open Label for All Participants (4 weeks)		Open Label for Responders Only (8 weeks)[a]					
Visit Number (V)[d]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Week 20 Response Assessed (Non-Responders Proceed Directly to EOT Visit)[a]	V12	V13	V14	V15		
Visit Label	Screening	Baseline															EOT[e]	EOS[e]
Visit Weeks[f]	W-4 to W0	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18[g]		W20	W22[g]	W24	W26[g]		
Visit Days	D-28 to D-1	D1	D15 (±3d)	D29 (±3d)	D43 (±3d)	D57 (±3d)	D71 (±3d)	D85 (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)		D141 (±3d)	D155 (±3d)	D169 (±3d)	D183 (±3d)	(±3d)	(±5d)
Serum PD Biomarkers[ff, gg, hh]		X		X			X			X							X	X
[redacted]																		
Plasma Biomarker Panel[ff, gg, jj]		X		X				X		X							X	
Serum Biomarker Panel[ff, gg, jj]		X		X				X		X							X	
[redacted]																		

Procedure[b]	Screening Period (Maximum 4 weeks)[c]	Treatment Period A: Double-blind Placebo Controlled Study – Primary Efficacy Assessment Window (16 weeks)								End of Double-blind/ Start of Open Label	Treatment Period B: Open Label Period (12 weeks)						End of Open Label/ Start of Safety Follow-Up	Follow-Up Period C: Safety Follow-Up Period (8 weeks after EOT)
											Open Label for All Participants (4 weeks)		Open Label for Responders Only (8 weeks)[a]					
Visit Number (V)[d]	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	Week 20 Response Assessed (Non-Responders Proceed Directly to EOT Visit)[a]	V12	V13	V14	V15		
Visit Label	Screening	Baseline															EOT[e]	EOS[e]
Visit Weeks[f]	W-4 to W0	W0	W2	W4	W6	W8	W10	W12	W14	W16	W18[g]		W20	W22[g]	W24	W26[g]		
Visit Days	D-28 to D-1	D1	D15 (±3d)	D29 (±3d)	D43 (±3d)	D57 (±3d)	D71 (±3d)	D85 (±3d)	D99 (±3d)	D113 (±3d)	D127 (±3d)		D141 (±3d)	D155 (±3d)	D169 (±3d)	D183 (±3d)	(±3d)	(±5d)
[redacted]																		

AE=adverse event; Ab=antibody; AN=abscess and inflammatory nodule; ANC=absolute neutrophil count; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; COVID-19=coronavirus disease 2019; CRP=C-reactive protein; C-SSRS= Columbia-Suicide Severity Rating Scale; D=day; ECG=electrocardiogram; eCRF=electronic case report form; EOT=end of treatment; EOS=end of study; [redacted] FSH=follicle stimulating hormone; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV-Ab=hepatitis C virus antibody; HiSCR=hidradenitis suppurativa clinical response; HIV=human immunodeficiency virus; HS=hidradenitis suppurativa; [redacted]; hs-CRP=high-sensitivity C-reactive protein; IgG=immunoglobulin G; IgM anti-HBc=immunoglobulin M antibody to hepatitis B core antigen; IHS4=International Hidradenitis Suppurativa Severity Score System; IMP=Investigational Medicinal Product; IRT=interactive response technology; OX40L=OX40-Ligand; PD=pharmacodynamic(s); PK=pharmacokinetic(s); [redacted]; SAA=serum amyloid A; SAE=serious adverse event; SC=subcutaneous(ly); TB=tuberculosis; [redacted] V=visit; W=week; WOCBP=women of childbearing potential.

a All participants in the US will be assessed for response at the Week 20 visit based on the HS Clinical Parameters. Response will be defined as ≥50% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count at Week 20. For non-responders, they will not continue in Period B and immediately begin procedures for the EOT visit as depicted in the SOA. For responders, they will continue in Period B and perform assessments for the Week 20 visit as depicted in the SOA.

b At the Week 20 visit, HS Clinical Parameters will be performed prior to any assessment to assess treatment response. At all other visits, when several assessments take place at the same time, the following order should be respected: questionnaires, ECG, followed by vital signs, AE reporting, prior and concomitant medications, daily diary review, blood sampling, physical examination, lesion intervention if needed, HS clinical parameters, skin biopsy, and IMP administration.

c A maximum of 28 days is required depending on participants' prior and concomitant medications. Randomization of the participant must take these constraints into consideration.

d All visits are done on-site except if home nursing is arranged for visits at Week 18, 22, or 26.

e Participants who discontinue IMP treatment prior to completing the treatment period and 8-week Follow-up Period will be evaluated as soon as possible at the individual participant's EOT Visit, using procedures as planned for the EOT Visit. At their EOT Visit, participants will resume their HS medications or other appropriate therapy as needed per Investigator discretion after the EOT study assessments have been performed and will enter the 8-week safety Follow-up Period, concluding with EOS Visit.

f The study visits occur on the planned dates (relative to the first IMP), as scheduled.

g Visits at Week 18, 22, and 26 may be performed with a home nursing service.

h To qualify for randomization all inclusion criteria and none of the exclusion criteria are met by the participant.

i Update inclusion/exclusion criteria, medical and surgical history, and prior and concomitant medications information to assure participant eligibility.

j Prior to randomization.

k Investigators must obtain a history of prior therapies used to treat HS, including antibiotics. The prior doses and reasons for discontinuation of antibiotic therapy will need to be recorded in the eCRF to verify eligibility. In the TNF-experienced population, Investigators will be asked to complete a questionnaire on the duration of anti-TNF therapy use as well as providing a description of the treatment response to anti-TNF therapy.

l Investigators will be asked to complete a questionnaire on participant's family history of HS in first-degree relatives (parents, siblings, and children) to be recorded in the eCRF.

m Clinical laboratory testing at Screening (Visit 1) will include a hepatitis screen covering HBsAg, anti-HBs, total anti-HBc, IgM anti-HBc, HCV-Ab, and HIV (anti-HIV-1 and HIV-2 antibodies). In case of results showing HBsAg negative and anti-HBc positive, HBV DNA testing will be performed prior to randomization to rule out a false positive and to clarify serological status. In case of results showing HCV Ab positive, HCV RNA testing will be performed to rule out a false positive. Please refer to Section 10.2. If a participant has a positive HBc Ab or anti-HBs followed by a negative HBV DNA PCR at screening and is subsequently randomized, they will undergo HBV DNA PCR testing every 3 months until the end of study visit. If a participant has a positive HCV Ab and followed by a negative HCV ribonucleic acid (RNA) PCR at screening and is subsequently randomized, they will undergo HCV RNA PCR testing every 3 months until the end of study visit. It is strongly recommended that participants have documented evidence of protective immunity to hepatitis B and have completed hepatitis B vaccination series per local guidelines 14 days prior to Baseline (Visit 2). This recommendation applies to any other age and gender-specific appropriate non-live vaccination series as per local guidelines as well. If live vaccines are required as per local guidelines, these must be completed 12 weeks prior to Baseline.

n It is strongly recommended that participants have documented evidence of protective immunity to tetanus and have completed tetanus vaccination series (with booster if needed) per local guidelines 14 days prior to Baseline (Visit 2). This recommendation applies to any other age and gender-specific appropriate non-live vaccination series as per local guidelines as well. If live vaccines are required as per local guidelines, these must be completed 12 weeks prior to Baseline.

o Assessments may be repeated for confirmation if deemed medically necessary.

p QuantiFERON TB gold test should be collected for all participants at the Screening (Visit 1). If the result is confirmed positive, the participant should be referred to an Infectious Disease specialist.

q FSH only if needed to confirm post-menopausal status during Screening.

r COVID-19 molecular test (if COVID-19 testing is required per local guidelines to be determined for each site). It is strongly recommended that participants have completed required COVID-19 vaccination series (with booster[s]), inactivated influenza vaccination, and pneumococcal vaccination per local guidelines 14 days prior to Baseline (Visit 2). This recommendation applies to any other age and gender-specific appropriate non-live vaccination series as per local guidelines as well. If live vaccines are required as per local guidelines, these must be completed 12 weeks prior to Baseline.

s Please refer to Table 4 – Prohibited therapy prior to Baseline for detailed description of required washout periods for various medications.

t Daily diary is used for daily recording of [redacted], participant daily analgesic use, and [redacted] from at minimum 4 days prior to Baseline (Visit 2) up to Week 28 (Visit 16). It should preferably be completed at about the same time every evening. It may also be used to document IMP administration if the participant receives IMP through home nursing.

u Diary for IMP administration must be completed to document IMP administration if participant receives IMP through home nursing.

v Sites are encouraged to contact participants 10 days prior to Baseline (Visit 2) to confirm compliance with daily pain collection and daily analgesic use in the daily diary.

w All eligible participants will be treated for up to 28 weeks, receiving a SC administration of IMP or placebo every 2 weeks for the first 14 weeks based on randomization, and then starting at Week 16 (Visit 10) all participants will receive IMP every 2 weeks until the last dose is administered at the individual participant's EOT visit.

x Per Investigator discretion, participants may resume treatment for HS as needed (including, but not limited to oral and topical antibiotics, corticosteroids, opioid and non-opioid analgesics, spironolactone, finasteride, or metformin). Participants may also receive unlimited lesion intervention as needed per Investigator discretion.

y Vital signs, including body temperature (°C), heart rate (beats per minute), respiratory rate (breaths per minute), and systolic and diastolic blood pressure (mm Hg), will be measured at all visits detailed in the flowchart.

z Physical examination will include examination of skin, nasal cavities, eyes, ears, cardiovascular, respiratory, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. A brief symptom-directed physical examination should be performed at other visits if, in the opinion of the Investigator, it is warranted by the participant's AE status or on review of symptoms and will include, at a minimum, assessments of the skin, cardiovascular system, and abdomen (liver and spleen). Height will be measured and recorded at the Screening Visit. Weight will also be measured and recorded at the Screening, Baseline, Week 16, and EOS Visit.

aa For fasting lipid panel, participant must be fasting for 8 hours prior to laboratory testing (may consume water). If unable to fast, participant may consume a light meal. Labs drawn during non-fasting laboratory testing will include hematology and clinical chemistry only. For laboratory testing please see Table 12.

bb Only for WOCBP: serum pregnancy test at Screening (Visit 1) and urine pregnancy tests at every visit from Baseline (Visit 2) to EOS (Visit 17). A negative result must be obtained at Screening (Visit 1) and at Baseline (Visit 2) prior to randomization. In case of positive urine test, the study treatment will be withheld and a serum pregnancy test to confirm the pregnancy should be performed as soon as possible. Pregnancy will lead to definitive treatment discontinuation in all cases.

cc Hidradenitis Suppurativa Clinical Parameters will be performed at each designated study visit and must address all relevant anatomical regions in each participant; the number, location, longest distance between relevant lesions, and whether the lesions are separated by normal-appearing skin will be measured in each anatomical area; Hurley Stage is included as an assessment performed during the HS clinical parameters; Hidradenitis Suppurativa Physician's Global Assessment is included as an assessment performed during the HS clinical parameters. The site is responsible for counting lesions that received intervention as permanently present in the lesion counts from the date of the intervention. The data collected from the HS clinical parameters will be used for the derivation of the HiSCR50, HiSCR75, HiSCR90, IHS4, AN count, Hidradenitis Suppurativa Physician's Global Assessment, raw counts, and disease flares. For each participant it is recommended that the HS Clinical Parameters is assessed by the same Investigator during the entire study if possible.

dd [redacted]

ee The participant should complete the questionnaire before site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the participant's response.

ff Number of samples (tubes) and quantity of biological samples needed for each assessment can be found in the laboratory manual.

gg Up to 4 hours prior to IMP administration.

hh PD biomarkers will include serum TNF and serum OX40L.

ii Optional assessment with skin biopsies at Baseline (Visit 2) and Week 16 (Visit 10) will be performed. Participants without history of hypertrophic or keloid scarring as assessed by the Investigator through participant interview and review of medical history can choose whether they would like to participate in optional assessment. If they consent to participate, the participants will have one lesional biopsy of an inflammatory nodule and one non-lesional biopsy at Baseline (Visit 2) and Week 16 (Visit 10) (for a total of 4 biopsies). Biopsy is to be performed after HS clinical parameters, but before IMP administration at study visit. Sutures may be placed per the discretion of the Investigator. Participants will be scheduled for an additional visit 1 week after skin biopsy for suture removal if sutures are placed per the discretion of the Investigator. Sample will be processed per instructions in the laboratory manual.

jj Biomarker panel will include, but is not limited to, CRP, hs-CRP, [redacted], SAA, and ANC. Hematology sample will be drawn for neutrophils (with other values reported per laboratory manual).

kk Optional sample collected for potential retrospective safety follow-up and/or additional exploratory analysis.

2 INTRODUCTION

Hidradenitis suppurativa or acne inversa is a chronic, relapsing, debilitating, inflammatory skin disease that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillary, inguinal, and anogenital regions (Dessau definition, 1st International Conference on Hidradenitis Suppurativa, 30 March to 01 April 2006, Dessau, Germany) (1, 2). Hidradenitis suppurativa has a significant impact on health and QoL especially affecting social functioning and psychological well-being. Treatment of HS depends on the severity of disease. Topical therapies may have variable efficacy for mild disease. The standard of care for disease that does not respond to topical therapies or more severe disease is systemic treatment with oral antibiotics, retinoids, or intralesional corticosteroids. Although systemic treatments are available, many patients do not derive optimal benefit due to either incomplete treatment responses or risk of adverse reactions due to prolonged use. Adalimumab (anti-TNF), the only approved therapy for HS, has a significant proportion of patients that do not achieve response and in those who do achieve response, the discontinuation rate at 12 and 24 months of use is high (7, 10). SAR442970, an anti-TNF-OX40L bispecific NANOBODY® molecule, has therefore been developed to address the significant unmet medical need for treatment options in this patient population.

Evolving hypotheses of HS pathogenesis postulate the primary event of follicular occlusion leads to intrafollicular stasis and propagation of resident bacteria with dilatation of the hair follicle. Patients develop HS in anatomic areas bearing apocrine sweat glands with a high degree of mechanical friction, such as skin folds, which triggers local perifollicular cell damage leading to hyperplasia and hyperkeratosis of the infundibular epithelium of the hair, causing follicular occlusion. The intrafollicular content leads to activation of innate immune cells that produce TNF and IL-1β. Tumor necrosis factor and IL-1β induce the expression of various chemokines by keratinocytes and fibroblasts in the epidermis and dermis, respectively, leading to an influx of a variety of cell types into the skin, including T cells, B cells, and monocytes that differentiate into macrophages and dendritic cells in the tissue. In later stages, as inflammatory cells have accumulated, follicular rupture manifests as nodules or abscesses. Subsequent extracellular matrix degradation by fibroblasts and neutrophil infiltration can eventually result in the formation of pus-draining tunnels. Among the various T cells recruited into HS skin, the T helper 1 (Th1) and T helper 17 (Th17) subsets predominate. While much remains to be established about the pathogenesis of HS, prevailing theories seem to suggest that it is a neutrophilic dermatosis driven by IL-1β, with an anti-inflammatory component due to IL-10, a possible component of B cells, and contribution from Th1 or Th17 cells (3). In HS, relative to other inflammatory skin conditions, regulatory T cells are decreased, and T cell ratios are skewed (4). OX40 stimulation may suppress Foxp3 protein expression, a master regulator in the pathway necessary for regulatory T cell development and function (5). The established efficacy of adalimumab in HS supports this theory of pathogenesis of HS in which TNF is a key contributor to the inflammatory milieu in HS. The addition of OX40L inhibition with SAR442970 is expected to provide additive effect by targeting the B cells and T cell-B cell interaction that are present in the inflammatory cascade in HS skin (11, 12).

In epidemiologic studies of prevalence, certain trends have been observed in patients with HS. In the US, HS is more common in African Americans (0.30%) than white individuals (0.09%), and prevalence in biracial individuals is at an intermediate level (0.22%) (3). Studies in young adults between 20 and 40 years of age have reported the highest prevalence (4%), whereas the prevalence declines in those >50 years of age. HS rarely occurs before menarche. The majority of patients reported in the Western countries are women, whereas reports from Asia do not report a gender predilection (13). Certain comorbid conditions exist with HS. The likelihood of patients with HS having polycystic ovary syndrome was 2.14 (95% confidence interval 2.04-2.24) times that of patients without HS (14). Severity of HS is increased in overweight and obese populations (15). Additionally in a systematic review, HS patients have 2.12-fold increased odds for Crohn disease and 1.51-fold increased odds for ulcerative colitis (16). Family history studies have found a positive family history of HS in about 1 in 3 patients. A mutation in the gamma secretase gene has been found in a cohort of families with an atypical, severe form of HS, but has been difficult to corroborate in the general population of patients with HS (17). Approximately 70% to 90% of patients with HS are current or former smokers (18).

The most common reported symptom related to the characteristic lesions of HS is pain. In a French population with HS, the average visual analogue scale pain score was 4.2 on an 11-point numeric rating scale, in which 0 represents no pain and 10 represents the worst imaginable or extreme pain (19). The pain can be described as soreness, sharp, throbbing, and aching. The lesions of HS may be hidden by clothing, but patients may also experience malodorous discharge that stains garments. The involvement of flexural areas can make it difficult to sit for long periods of time and embarrassment related to symptoms such as discharge can make it difficult for patients to maintain work productivity. The disfigurement, scarring, and discharge associated with the disease can also impede social relationships. Patients are often affected by decreased feelings of self-worth and depressive symptoms. Compared to other dermatologic conditions, patients with HS score higher on the Dermatology Life Quality Index (DLQI) highlighting the significant morbidity associated with the disease (20). These comorbid symptoms necessitate treatment for HS with goals of therapy being reduction of formation new lesions, improvement of existing lesions, and reducing pain and impact on social well-being.

2.1 STUDY RATIONALE

The primary purpose of this study is to assess the efficacy and safety of SAR442970 in participants of 18 to 70 years of age, inclusive, with moderate to severe HS.

2.1.1 Established Treatment in HS

The treatment of HS is determined by the level of severity of the disease. However, for all patients regardless of severity, clinical focus starts with lifestyle modifications such as weight loss. However, it must be noted that although lifestyle modifications can certainly improve overall health, these measures are not supported by high-quality evidence to influence HS severity, treatment response, or disease duration. Thus, they are usually employed as adjunctive measures to medical and surgical therapy (21). For mild, localized HS, topical clindamycin can have clinical effectiveness. However, topical therapies are not effective for widespread disease.

Treatment for individual acute symptomatic lesions is based on patient preference. Options include intralesional corticosteroid injection directly into the lesion. A small study has shown benefit with steroid injection; however, side effects such as cutaneous atrophy can occur (22). Punch debridement is a minor in-office surgical treatment, availability of which is dependent on physician clinical experience. Topical resorcinol, a chemical peeling agent, might have some limited efficacy, with an expected side effect of skin desquamation (23). Incision and drainage are also options for acute lesions causing severe pain but is not advised routinely as the procedure may promote lesion recurrence. The relative efficacy of these treatments has not been established.

Medical therapy with oral antibiotics is instituted for patients presenting with moderate to severe HS or patients with mild disease who do not have an adequate response to topical therapy. Oral tetracyclines, such as doxycycline, are the preferred antibiotic used for the treatment of HS. The mechanism by which antibiotic therapy improves HS is unclear. Hypotheses suggest that antibiotic therapy may reduce the bacterial load on affected skin in HS or there may be an anti-inflammatory effect of antibiotics. Patients are typically prescribed these regimens for a couple of months and then reassessed. Randomized trial evidence for oral antibiotic use is sparse and in one small trial was not found to be better than topical therapy (24). If patients achieve control of disease on tetracycline therapy, they may stop oral therapy and resume topical therapy for maintenance of response. If disease recurs rapidly on topical therapy, they are treated for refractory HS.

Options for refractory HS include an alternate antibiotic regimen of clindamycin and rifampin or dapsone, and oral tretinoin. Response to antibiotic therapy is usually seen within 10 to 12 weeks of therapy. Efficacy of the clindamycin and rifampin regimen is extrapolated from uncontrolled studies and traditionally this combination therapy has not been provided long-term due to concern for adverse effects, although some have challenged this (25, 26, 27, 28). Dapsone may have some effect for mild to moderate HS, based on a small uncontrolled study, but requires laboratory monitoring for hematologic toxicity (29).

Adalimumab is the only approved therapy for the treatment of moderate to severe HS based on the results of two Phase 3, randomized, controlled trials, PIONEER I and PIONEER II. In PIONEER I, 42% of treated patients achieved HiSCR50 versus 26% of placebo-treated patients at Week 12. In PIONEER II, 59% of treated patients achieved HiSCR50 versus 28% of patients who received placebo. Despite notable clinical effect of systemic biologic therapy in large-scale placebo-controlled trials, it should be noted that 41% to 58% of patients did not achieve clinical response (7). In a real-world study examining the drug survival of adalimumab, the median time to discontinuation was 36 weeks suggesting that drug survival is reduced in patients with HS and highlighting the continuing need for effective, durable therapies in HS (30). Options for severe, widespread flares of HS include intravenous (IV) ertapenem or oral glucocorticoids. However, both of these rescue therapies obviously cannot be used long-term for disease control due to the risk of antibiotic resistance and glucocorticoid toxicity, respectively.

Surgical intervention has been shown to offer the highest likelihood of disease resolution (31). However, this therapy is not a viable option for patients with multiple affected areas. Even for patients who may be candidates due to having an isolated affected area, this therapy can be disfiguring and requires significant recovery time.

The objective of this ACT16852 study is to assess the efficacy and safety of SAR442970, a bispecific pentavalent NANOBODY molecule, in participants with moderate to severe HS who have never received any biologics or small molecule immunosuppressive therapies and in participants who have received only one anti-TNF therapy and have discontinued therapy due to inadequate therapeutic response or accessibility. Participants may participate in the study with or without protocol-allowed antibiotics (eg, doxycycline or minocycline).

2.1.2 Inhibition of TNF and OX40L as a promising target in HS

Anti-TNF monoclonal antibodies are approved and broadly used in a wide range of immune-mediated diseases. Preclinical studies support the expectation that targeting the OX40-OX40L interaction by blockade of OX40L will have therapeutic benefit for several autoimmune diseases, and clinical investigations with anti-OX40L monoclonal antibodies are currently ongoing in autoimmune conditions. Based on the complementary biology of TNF and OX40L blockade and evidence from nonclinical studies it is expected that targeting of OX40L in addition to TNF can increase efficacy in HS, and that the bispecific SAR442970 NANOBODY® molecule will thus be able to achieve better disease control in HS.

OX40-ligand (CD134L, CD252) functions as a T cell costimulatory molecule which binds to OX40 (CD134) expressed predominantly on activated T cells. OX40L is expressed on antigen-presenting cells such as dendritic cells, macrophages, B cells, activated CD4+ T cells, endothelial cells, and mast cells (6). Expression of both OX40 and OX40L are increased after antigen presentation occurs as well as other pro-inflammatory factors including CD28 and CD40L and interferon gamma (IFN-γ). The OX40-OX40L immune synapse circuit promotes T cell survival, an effector T cell phenotype and cytokine release, T cell memory, reduces T regulatory function, and enhances cell mobility. A rationale for targeting the OX40-OX40L axis is the presence of upregulated B and T cell immune signatures by [redacted] analysis of whole tissues samples of anti-TNF therapy non-responders compared to responders (4).

SAR442970 binds to both TNF as well as OX40L with high affinity, and thereby is able to simultaneously inhibit the binding of OX40L and TNF to their respective receptors. Binding to human serum albumin (HSA) with high affinity extends the in vivo terminal half-life ($t_{1/2}$) of SAR442970. It was demonstrated that SAR442970 does not bind to other cytokines related to TNF or OX40L, indicating highly specific binding to TNF and OX40L. By combining the proven benefit of TNF blockade in HS with OX40L blockade that more specifically targets adaptive immune responses such as T cell and antigen-presenting cells including B cells, it is posited that the clinical response will be augmented, and the durability of response maybe prolonged in patients with HS.

2.2 BACKGROUND

2.2.1 Overview of SAR442970

SAR442970 is a bispecific pentavalent NANOBODY® molecule. NANOBODY® molecules are therapeutic proteins that are derived from the V_{HH}; heavy chain only antibodies occur naturally in the Camelidae family. They have a high degree of homology (in terms of sequence and structure)

to human immunoglobulin heavy chain variable region domains and can be further engineered and expressed by a variety of expression systems. SAR442970 is composed of five V_{HH}: 2 V_{HH} bind to an OX40L epitope, 2 V_{HH} bind to a TNF epitope, and 1 V_{HH} binds to an albumin epitope to extend the molecule's half-life. All domains have been humanized to reduce immunogenicity. SAR442970 binds to both TNF as well as OX40L with high affinity, and thereby is able to simultaneously inhibit the binding of OX40L and TNF to their respective receptors.

2.2.1.1 Nonclinical Data

2.2.1.1.1 In Vitro Characterization

SAR442970 suppressed human TNF signaling through its receptors in an in vitro cell-based TNF reporter assay measuring nuclear factor kappa B activity (Study Number IMMVT0100). Similarly, in a complex in vitro human whole blood assay, SAR442970 inhibited the phytohemagglutinin induced, TNF-dependent release of the inflammatory cytokine IL-8 in human whole blood (Study Number IMMVT0111). SAR442970 suppressed the biological activity of OX40L in a cellular assay measuring IL-2 secretion upon co-culture of human or cynomolgus OX40L overexpressing Chinese hamster ovary K1 cells with phytohemagglutinin-activated human peripheral blood mononuclear cells (PBMCs) (Study Number IMMVT0100). Furthermore, in an allogeneic mixed lymphocyte reaction assay using mature dendritic cells from different human donors in combination with peripheral blood mononuclear cells from other human donors (Study Number IMMVT0104), treatment with SAR442970 led to a strong inhibition of granulocyte-macrophage colony-stimulating factor release.

2.2.1.1.2 In Vivo Characterization

In a PK/pharmacodynamics (PD)/safety study (Study Number DIV1942) in female cynomolgus monkeys, to assess the PD effects of SAR442970 on immune system functionalities, the humoral response was evaluated through a T-Cell-Dependent Antibody Response (TDAR) assay after keyhole limpet hemocyanin (KLH) immunization. The cellular immune response was evaluated through the in vivo delayed-type hypersensitivity (DTH) test in skin and the enzyme-linked immunosorbent spot (ELISPOT) ex vivo PBMC assays, both in response to immunization with KLH as well as with tetanus-toxoid (TTx). All investigated immune system functionalities that were stimulated by the immunization with KLH or TTx, including humoral and cellular responses, were found to be downregulated by SAR442970 administration, thereby demonstrating in vivo efficacy for SAR442970, and highlighting the additive benefit of simultaneous TNF and OX40L blockade.

2.2.1.1.3 Pharmacokinetics and Nonclinical Safety

The SAR442970 nonclinical safety profile was evaluated in cynomolgus monkeys in a 2-week exploratory study with 2 administrations, a 4-Week PK/PD/safety study with 5 weekly administrations at 3, 10, 30, and 100 mg/kilogram (kg)/week followed by a 4-week evaluation period with necropsy 4 weeks after the last dose and in repeat dose good laboratory practice (GLP) cynomolgus monkey studies, namely a 3-month GLP study with 13 weekly administrations at 3, 10, and 30 mg/kg/week followed by a 12-week recovery period and a 6-month study with

26 weekly administrations at 10, 25, and 50 mg/kg/week followed by a 18-week recovery period. SAR442970 was systemically and locally well-tolerated in cynomolgus monkeys at all dose levels tested. The no-observed-adverse-effect level (NOAEL) in the GLP repeated dose studies was the highest dose tested in the 6-month study, 50 mg/kg/week.

SAR442970 was well-tolerated in cynomolgus monkeys. Minor and non-adverse reversible SAR442970-related microscopic findings were observed after weekly dosing for 4 weeks up to 100 mg/kg/week, 3 months up to 30 mg/kg/week, or 6 months up to 50 mg/kg/week. These consisted of a [redacted]. In the 3-month toxicology study a [redacted] was observed in theses tissues at the end of the 12-week recovery period. In addition, [redacted] A slight non-adverse increase in CRP concentrations at 3 and 30 mg/kg/week in the 3-month toxicology study was not considered to be of toxicological significance, because it was observed in the absence of any clinical signs or changes in body temperature and was present transiently on Day 2 but not on Day 7 or at later time. Effects on CRP were not observed in the 6-month study. Evaluation of humoral and cellular immune response was included in the 4-week PK/PD/safety study and the 6-month toxicology study. Responses in both studies were strongly inhibited at all dose levels,[redacted]. They were not considered adverse and reflected the pharmacological immunomodulation of SAR442970.

[redacted] Furthermore, no adverse SAR442970-related findings were observed in cynomolgus monkeys in subcutaneous repeat dose toxicology studies, including a 3-month and a 6-month GLP-compliant toxicology study and no risks were identified up to the maximum dose level tested (50 mg/kg/week).

2.2.1.2 Clinical Data

SAR442970 has been administered to healthy volunteers in one study with two parts: TDU16649 as the single ascending dose (SAD) and TDR16650 as the multiple ascending dose (MAD). This study is summarized below; further information can be found in the Investigator's Brochure (IB).

2.2.1.2.1 TDU16649/TDR16650

Study TDU16649/TDR16650 was the first-in-human (FIH) study of SAR442970 that explored the safety and tolerability of single dose and repeat doses of SAR442970 in healthy volunteers.

This study was conducted at a single investigative site, in line with a typical FIH dose escalation design.

A total of 39 healthy volunteers were enrolled in the TDU16649 SAD study: 5 cohorts were treated with 10, 30, 75, 150, or 300 mg of SAR442970 (or placebo), respectively.

Overall, a single SC dose of SAR442970 of up to 300 mg was safe and well-tolerated. There was no obvious dose relationship in the incidence of TEAEs. No concerning trends in vital signs, ECGs or laboratory values were identified. Only 1 participant in the placebo group had an AE of injection site reaction.

No participants experienced any TEAEs leading to death, treatment-emergent SAEs or TEAEs leading to permanent study discontinuation during the study.

Following single subcutaneous doses of SAR442970 ranging from 10 to 300 mg, median time to peak drug concentration (T_{max}) of SAR442970 occurred between approximately 108- and 144-hours post-dose followed by a monophasic decline in serum concentrations. Terminal half-life increased with increasing dose level, with a mean value of 139 hours at the 10 mg dose level and 251 hours at the 300 mg dose level. In general, exposure based on area under the curve (AUC) and maximum serum concentration (C_{max}) increased in an approximately dose proportional manner.

Anti-drug antibodies (ADA) were detected in ≥80% of the participants in all dose cohorts but the onset of ADAs was delayed at doses ≥150 mg, and ADA titers decreased with increase in dose.

The total target analysis of TNF showed a concentration increase over a few weeks for which magnitude and duration appeared dose related. As expected, all samples analyzed had OX40L concentrations below the lower limit of quantitation (LLOQ) of 200 pg/mL.

A total of 32 healthy volunteers were randomized and treated in the TDR16650 MAD study: 3 cohorts were treated with 30, 75, or 150 mg of SAR442970 (or placebo), respectively.

Repeated SC doses of SAR442970 of up to 150 mg Q2W were safe and well-tolerated. There was no obvious dose relationship in the incidence of TEAE(s) and no SAE(s) were reported.

No concerning trends in vital signs, ECGs or laboratory values were identified.

Following repeated SC administration, SAR442970 median T_{max} occurred at approximately 72 hours (3 days) post-dose; however, the next sampling time-point was at 168 hours so potentially the true T_{max} was in that range. The T_{max} was followed by a monophasic decline in serum concentrations, with a $t_{1/2}$ ranging from 170 to 212 hours (7 to 9 days). Exposure based on $AUC_{0\text{-}336h}$ and C_{max} increased in an approximately dose-proportional manner over the range of 30 to 150 mg after both the first and last dose. Accumulation ratios for C_{max} and $AUC_{0\text{-}336h}$ pooled across doses were 1.86 and 1.81, respectively, but steady state was not achieved after 3 doses administered Q2W.

Treatment-induced and/or treatment-boosted ADAs were detected in less participants in the 150 mg cohort (57.1%) compared to the 30 mg and 75 mg cohorts (100% and 87.5%). In general, there was a trend for a lower ADA incidence with increasing SAR442970 doses.

Total TNF showed a similar concentration increase over a few weeks following SAR442970 administration in all cohorts, reflecting target occupancy. At 150 mg Q2W the increase lasted longer, and higher concentrations were reached. All but one sample analyzed had OX40 concentrations below the LLOQ of 200 pg/mL.

Overall, this study identified no meaningful safety or tolerability concerns and provided PK and PD data to support the dose selection for the Phase 2 ACT16852 study.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected AEs of SAR442970 may be found in the IB and participant information leaflet.

2.3.1 Risk assessment

SAR442970 specific risks, including any associated with SC administration, have not been identified to date from the nonclinical or clinical program. Potential risks include hypersensitivity and/or anaphylactic reactions, serious and opportunistic infections, decreased antibody response to neoantigens and/or new vaccinations, injection site reactions, malignancy, hepatitis B reactivation, demyelinating disease, cytopenia/pancytopenia, heart failure, and lupus-like syndrome (discussed further in the IB). These potential risks are derived from experience with other medications in the same pharmacologic class and there is no evidence to date to suggest these will be amplified in the specific case of combined TNF and OX40L blockade.

In the SAD study, TEAEs were reported in 14/29 (48.3%) participants in the SAR442970 groups (1/6 [16.7%] in the 10 mg cohort, 2/6 [33.3%] in the 30 mg cohort, 4/6 [66.7%] in the 75 mg cohort, 4/5 [80.0%] in the 150 mg cohort, 3/6 [50.0%] in the 300 mg cohort), and 9/10 (90.0%) participants in the placebo group. No serious events were recorded and no TEAEs led to study discontinuation.

There was 1 severe TEAE [redacted] in 1 participant treated with 75 mg SAR442970. The participant had a [redacted] millimole/liter (mmol/L) on Day 15 which was considered clinically significant by the Investigator. The participant had already slightly increased values at 2.50 mmol/L on Day -1 (upper limit of normal (ULN) range 1.69 mmol/L) and at the measurement 9 days after the increase (Day 24) the value was back to normal with 1.42 mmol/L. The event was assessed as not related to the IMP.

There were 5 adverse events of special interest (AESI)s reported during the TE period. These include 1 case of bronchitis which required treatment and 4 cases of coronavirus disease 2019 (COVID-19), 3 in the SAR442970 groups and 2 in the placebo group. One COVID-19 infection was of Grade 1 severity and all other AESIs were of Grade 2 severity. All AESIs were assessed as not related to the IMP.

The most frequent TEAE by preferred term (PT) were headache (4/29 [13.8%] in the SAR442970 groups and 4/10 [40.0%] in the placebo group) and COVID-19 (3/29 [10.3%] in the SAR442970 groups and 1/10 [10.0%] in the placebo group).

One participant had a TEAE of injection site reaction in the placebo group (hematoma, Grade 1). No TEAEs were reported in the SAR442970 groups.

In the MAD study, the most frequent TEAEs by system organ class (SOC) were nervous system disorders (6/29 [20.7%] in the SAR442970 groups and 4/10 [40.0%] placebo group) and infections and infestations (5/29 [17.2%] in the SAR442970 groups and 3/10 [30.0%] in the placebo group). TEAEs were reported in 24/32 (75%) of the participants, in 3/6 (50%) in the placebo group, 10/11 (90.09%) in the 30 mg dose group, 6/8 (75.0%) in the 75 mg dose group, and 5/7 (71.4%) in the 150 mg dose group. In total 15 events that were considered related to the IMP were reported in 3/6 (50%) participants in the placebo group, 2/11 (18.2%) in the 30 mg dose group, 2/8 (25%) in the 75 mg dose group and 1/7 (14.3%) in the 150 mg dose group. No SAEs were recorded and only one TEAE led to study discontinuation (30 mg cohort, sprained ankle).

There was one severe TEAE (≥Grade 3) in one participant treated with 150 mg which was considered not related. The participant had a triglyceride value of 8.8 mmol/L on Day 43. On Day 57 the triglyceride value was down to 2.5 mmol/L again. But on Day 64 his value went up to 14.6 mmol/L and decreased again to 3.9 mmol/L on Day 72. The participant had already an increased value at screening with 4.3 mmol/L (upper reference 1.69 mmol/L). This event qualified to be Grade 4 according to the common terminology criteria for adverse events (CTCAE) classification because of the triglyceride value of 14.6 mmol/L, but as the participant had no symptoms and required no treatment the Principal Investigator (PI) rated it as Grade 3. Increased triglyceride values were not known before for this participant, and as he had in addition increased cholesterol values, he was referred to his general practitioner.

There were 3 AESIs reported. These include two cases of COVID-19, both in the 30 mg cohort and both were of mild severity. The third AESI was a pregnancy which was reported in the 150 mg cohort on the EOT visit. All AESIs were assessed as not related.

The most frequent TEAEs by SOC were gastrointestinal disorders [2/6 (33.3%) placebo group and 8/26 (30.8%) in the treatment groups] and infections and infestations [2/6 (33.3%) in the placebo group and 9/26 (34.6%) in the treatment groups].

The most frequent TEAEs by PT were headache [2/6 (33.3%) in the placebo group and 4/26 (15.4%) in the treatment groups], vomiting [2/6 (33.3%) in the placebo group and 1/26 (3.8%) in the treatment groups] and upper respiratory tract infection [1/6 (16.7%) in the placebo group and 3/26 (11.5%) in the treatment groups].

There were 3 cases of a TEAE leading to permanent study intervention discontinuation. One subject was discontinued because of a COVID-19 infection, one because of a sprained ankle and the third one had a series of adverse events. The third participant presented herself on Day 14 with a rash which was limited to the legs and consisted of small red papules, spreading over both legs, not considered related by the Investigator at that time, but this assessment was changed afterwards. She was dosed the second time on Day 15 and then developed sore throat (Day 16), dysphagia (Day 17), and flaky lips (Day 16). These events were all of mild or moderate severity but were considered related and thus the IMP was discontinued. Her leukocyte count increased on Day 18 but was still below the upper reference value. She tested negative for COVID-19 and other viruses (nose swab) and a pharynx swab was negative for yeast/mold.

There were no TEAEs of injection site reactions. Some mild reactions were reported for all dosing groups.

Further details can be found in the IB.

Table 1 - Risk assessment

Potential Risk	Mitigation
Serious and opportunistic infections	Evaluate clinical trial participants for infection, TB, history of opportunistic infections prior to treatment with the IMP, and strict eligibility criteria. Stop IMP if infection develops.
Malignancies	Evaluate for malignancies prior to initiating treatment with the IMP, strict eligibility criteria with previous or ongoing malignancy will be implemented. Monitoring for emerging malignancy through routine assessment of any new clinical signs and symptoms. Stop IMP if malignancy develops.
Anaphylaxis or serious allergic reactions including hypersensitivity reactions	Evaluate for allergic reactions prior to initiating treatment with the IMP. Stop IMP if reaction develops. See Appendix 6 (Section 10.6) (Liver and other safety. Suggested actions and follow-up assessments) for definition of anaphylaxis.
Hepatitis B virus reactivation	Evaluate for hepatitis prior to initiating treatment with the IMP. Stop IMP if symptoms suggestive of hepatitis reactivation develop. Strongly recommend documentation of hepatitis B protective immunity prior to IMP administration and completion of hepatitis B vaccination if needed per local regulations at least 14 days prior to IMP administration.
Demyelinating disease	Evaluate for demyelinating disease prior to initiating treatment with the IMP. Stop IMP if symptoms suggestive of demyelinating disease develop.
Cytopenia, pancytopenia	Evaluate for cytopenia/pancytopenia via hematology laboratory test prior to initiating treatment with the IMP. Stop IMP if cytopenia/pancytopenia occur.
Heart failure	Evaluate for history and signs of heart failure prior to initiating treatment with the IMP. Stop IMP if symptom develops.
Lupus-like syndrome	Evaluate for history of Lupus-like syndrome prior to initiating treatment with IMP. Stop IMP if syndrome develops.
Reduced antibody response to vaccination	Exclude participants who received live vaccine 12 weeks prior to first administration or non-live vaccine 14 days prior to the first administration, no vaccination during the whole study and for 6 months after last IMP administration.

Abbreviations: IMP=investigational medicinal product; TB=tuberculosis

2.3.2 Benefit assessment

Currently, there is one approved biologic therapy for the treatment of moderate to severe HS, adalimumab. But a substantial proportion of patients do not achieve clinical response with this therapy, and those who do often lose clinical response in a matter of a couple of years when they may require long-term treatment for this chronic disease. Existing options are limited including topical antibiotics, oral antibiotics, oral retinoids, and glucocorticoids. All these drugs are repurposed drugs with limited evidence supporting their efficacy and with considerable side-effects. There is a high unmet medical need in patients with moderate to severe HS.

Through combined TNF and OX40L inhibition, SAR442970 is expected to inhibit the recruitment of inflammatory cells such as neutrophils, B cells, and T cells, and downregulate effector mechanisms of T cells such as cytokine production observed in HS. Based on the mechanism of action, the potential benefits would be:

- Achievement of HiSCR50.
- Reduction in pain.
- Reduction in HS flares.
- Improvement in QoL.

2.3.3 Overall benefit/risk conclusion

The clinical development program for SAR442970 is supported by the available nonclinical and clinical data and the potential benefit in the treatment of subjects with immune-mediated diseases. Hidradenitis suppurativa is characterized by a complex disease biology. Limited existing options for the treatment of HS include topical antibiotics, oral antibiotics, oral retinoids, and glucocorticoids. Blockade of several pathways in parallel through combined TNF and OX40L inhibition may confer greater benefit in terms of reduction of HS characteristic skin nodules and abscesses that lead to pain than any monotherapy.

SAR442970 was safe and well-tolerated in nonclinical toxicology studies and in clinical studies of healthy volunteers up to 300 mg given as a single dose and up to 150 mg given Q2W for 3 doses. Mitigation of the theoretical risks is possible through selection of appropriate study populations and monitoring in clinical trials.

Risk management procedures and specific safety monitoring will be implemented (Section 2.3.1). The design of the present study including selection criteria of the study population, risk mitigation strategy, and monitoring of safety variables, should maintain the positive balance regarding the expected risk/benefit ratio for SAR442970 in the treatment of participants with HS.

SAR442970 is still in clinical development and risks are not completely understood; however, based on the acceptable safety profile summarized above and the potential for considerable benefits on HS disease activity, on both acute episodes and on long-term sequelae, the potential benefits outweigh the risks in the proposed study population.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of SAR442970 during the double-blind, placebo-controlled period in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS	• The clinical response as measured by the percentage of biologic and small molecule immunosuppressive-naïve participants achieving Hidradenitis Suppurativa Clinical Response (HiSCR50) (defined as ≥50% reduction from Baseline in the total abscess and inflammatory nodule [AN] count, with no increase from Baseline in abscess or draining tunnel count) at Week 16 (8, 9)
Secondary	
• To evaluate the efficacy and safety of SAR442970 in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS	• Time to onset of achieving HiSCR50 • Percentage of participants achieving HiSCR75 (defined as ≥75% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count) at Week 16 • Percentage of participants achieving HiSCR90 (defined as ≥90% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count) at Week 16 • Percentage of participants who experience improvement by at least one International Hidradenitis Suppurativa Severity Score System (IHS4) stage at Week 16 (See also Section 8.2.1.3 for definition of IHS4) • Change in absolute score from Baseline in IHS4 at Week 16 • Percentage of participants who experience a flare, defined as at least a 25% increase in AN count (with a minimum increase of 2) relative to Baseline at Week 16 (See also Section 8.2.1.4 for definition of flare) • Percentage of participants achieving IHS4-55 at Week 16 (defined as achievement of a 55% reduction in IHS4 score from Baseline) • Incidence of treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) including local reactions • Incidence of potentially clinically significant abnormalities in laboratory tests, vital signs, and electrocardiograms
• To evaluate the effect of SAR442970 on pain in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS	• Percentage of participants achieving at least 30% reduction and at least 1 unit reduction from Baseline in weekly average of daily [redacted]
• To evaluate the pharmacokinetics (PK) of SAR442970 and anti-drug antibodies to SAR442970 in the biologic and small molecule immunosuppressive-naïve subgroup of participants with HS	• Serum SAR442970 concentrations throughout the study • Incidence of anti-SAR442970 antibody positive response throughout the study

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	DLQI [redacted] DLQI ≥4
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Primary estimand defined for primary efficacy endpoint is summarized in Table 3. More details are provided in Section 9.2.

For all these estimands, the comparison of interest will be the comparison of SAR442970 vs placebo.

Table 3 - Summary of primary estimands for the primary endpoint

Endpoint Category	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: To evaluate the efficacy of SAR442970 during the double-blind, placebo-controlled period in the primary analysis population of the biologic and small molecule immunosuppressive-naïve subgroup participants with moderate to severe HS				
Primary endpoint	Percentage of participants achieving HiSCR50 at Week 16	Biologic and small molecule immunosuppressive-naïve population	The following intercurrent events will be handled with the composite strategy; participants will be considered as non-responders after such IE. • Starting or increase in dose of oral antibiotic therapy during the treatment period. • Starting selected prohibited medications. Please refer to Section 6.9.1. Further details of selection will be specified in the SAP. • Discontinuation of study intervention due to lack of efficacy. The following IEs will be handled with the treatment policy strategy (without IEs that need to be handled with composite strategy). Data collected after starting such IE will be included. • Starting other prohibited medications. • Discontinuation of study intervention due to reasons other than lack of efficacy.	Bayesian logistic regression model including treatment group and adjusted by randomization stratum (Hurley Stage). The statistical analysis will be conducted following a Bayesian approach using an informative prior on the placebo response rate based on the historical studies available. Missing data will be imputed as non-responder.

Abbreviations: HiSCR50=hidradenitis suppurativa clinical response; IE=intercurrent event; SAP=statistical analysis plan.

3.1 APPROPRIATENESS OF MEASUREMENTS

All efficacy measurements in this study are standard for assessing disease activity in participants with HS. The HiSCR50 and IHS4 have been validated in HS and extensively used. The HiSCR50 is widely accepted by health authorities as the basis supporting marketing authorization of adalimumab for patients with HS. The HiSCR75, HiSCR90, and flare rate are also routinely assessed in HS clinical studies because efficacy of SAR442970 may have an impact on these

derivations of the data used to calculate the HiSCR50. Pain is a common comorbid symptom in patients with HS and will be assessed by the [redacted]. Occurrence of TEAEs, SAEs, AESI, and PCSAs for vital signs, ECGs, and clinical laboratory assessments are standard measures to characterize safety and tolerability of therapeutic agents in clinical trials. Serum SAR442970 concentrations are the appropriate measures to quantify the PK profile of SAR442970 and support exposure-response analyses. Because SAR442970 is a large protein it may induce the formation of ADA, which may have the potential to impact efficacy or safety.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a multinational, multi-center, randomized, double-blind, placebo-controlled, Phase 2a proof-of-concept study to evaluate the efficacy and safety of SAR442970 in adult participants with moderate to severe HS.

The intervention in the study includes up to 14 total doses of IMP administration Q2W to complete up to 28 weeks of treatment with SAR442970.

The target population of the study is participants with HS based on a history of signs and symptoms consistent with HS for at least 1 year prior to Baseline and demonstrating moderate to severe disease at Baseline as defined by HS lesions present in at least 2 distinct anatomic areas (eg, left and right axilla; or left axilla and left inguino-crural fold), one of which must be Hurley Stage II or Hurley Stage III, an abscess and inflammatory nodule (AN) count of ≥3, a draining tunnel count ≤20, and CRP level of >3 mg/L.

Additionally, all participants must have had an inadequate response to a course of an oral antibiotic for treatment of HS or exhibited recurrence after discontinuation of antibiotics or demonstrated intolerance to antibiotics or have a contraindication to oral antibiotics for treatment of their HS as assessed by the Investigator through participant interview and review of medical history. Participants will be considered to have had an inadequate response or loss of response to oral antibiotics if at least 1 of the following occurs while receiving antibiotics:

- Progression of Hurley Stage (ie, the Hurley Stage of at least one affected anatomic region progressed from I→II, II→III, or I→III).
- Participant required at least one intervention (eg, I&D or intralesional injection of corticosteroid).
- Participant experienced pain interfering with activities of daily living, with unsatisfactory relief from over-the-counter analgesics (eg, ibuprofen or acetaminophen).
- Participant experienced pain requiring opioids, including tramadol.
- Participant experienced drainage interfering with activities of daily living (eg, requires multiple dressing changes and/or changes of clothes daily).
- Participant experienced an increase in the number of anatomic regions affected by HS.
- Participant experienced at least one new abscess or one new draining fistula.
- Participant experienced a flare (or worsening of disease) as determined by the Investigator while on oral antibiotics.

Participants will be considered as intolerant to oral antibiotic when oral antibiotic therapy has been discontinued as a result of a significant adverse reaction to oral antibiotic administration. A reaction will be considered significant if the adverse reaction is at least moderate (ie, the adverse event causes the subject discomfort or interrupts the participant's usual activities or function) as assessed by the Investigator through participant interview and review of medical history.

Examples of significant adverse reactions include, but are not limited to:

- Nausea resulting in decreased oral intake.
- Dizziness/disequilibrium/lightheadedness/vertigo interfering with normal function.
- Hypersensitivity reactions including, but not limited to, rash, flushing, urticaria, dyspnea, or drug fever ≥38°C.
- Diarrhea manifesting as an increase in stool frequency of at least 4 stools per day over participant's baseline.

Approximately 84 participants will be randomized in a 2:1 ratio to SAR442970 150 mg or matching placebo. Randomization will first be stratified by HS treatment history into 2 major subgroups:

- Biologic and small molecule immunosuppressive-naïve subgroup.
- TNF-experienced subgroup.

The biologic and small molecule immunosuppressive-naïve subgroup is composed of participants who have never received biologic therapies, such as anti-TNF therapy, anti-IL17, anti-IL1, anti-IL36, or anti-IL23, or small molecule immunosuppressive therapies, such as JAK/TYK inhibitors. The recruitment target for the biologic and small molecule immunosuppressive-naïve subgroup is approximately 66 participants. Randomization will be further stratified by Hurley Stage (II or III). Within the biologic and small molecule immunosuppressive-naïve subgroup, the number of participants with Hurley Stage III is not to exceed more than 50% in order to recruit a population with the desired disease severity.

The TNF-experienced subgroup is composed of participants who experienced at least one of the following scenarios after receiving a single anti-TNF therapy (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, etc) for at least 12 weeks as assessed by the Investigator through participant interview and review of medical history:

- Participants who had a complete response to anti-TNF therapy for HS per Investigator discretion and subsequently lost response, or
- Participants who had a partial response to anti-TNF therapy for HS per Investigator discretion, or
- Participants who did not achieve a partial response to anti-TNF therapy for HS per Investigator discretion, or
- Participants who stopped using anti-TNF therapy due to reasons other than an AE (ie, insurance or access or reasons) (8, 9).

For the TNF-experienced subgroup, if participants have received more than 1 anti-TNF therapy for HS, they are not eligible for participation. Participants that have experienced an AE related to anti-TNF therapy (examples include, but are not limited to, serum sickness or anaphylaxis) that would contraindicate re-administration of an anti-TNF class therapy will be excluded. The recruitment target for the TNF-experienced subgroup is approximately 18 participants. Randomization will be further stratified by Hurley Stage (II or III). Within the TNF-experienced subgroup, the number of participants with Hurley Stage III is not to exceed more than 50%.

The primary analysis population is the biologic and small molecule immunosuppressive-naïve subgroup. Efficacy objectives and endpoints will be evaluated in an exploratory manner in the TNF-experienced subgroup.

All participants will have a Screening Period of up to 4 weeks to assess eligibility, a treatment period of up to 28 weeks, and an 8-week safety Follow-up Period. Period A is a 16-week double-blind, placebo-controlled period. Period B is an open-label period that may last up to 12 weeks depending on the individual participant. Period C will commence with an EOT visit and conclude with an EOS Visit. All participants from Period A will proceed to Period B and will be receiving SAR442970 150 mg. After completion of Period A and Period B, all participants will proceed to Period C, an 8-week safety Follow-up Period (For participants in the US, response will be assessed at the Week 20 visit. Response will be defined as ≥50% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count at Week 20. Responders at Week 20 will continue in Period B to complete the 12-week open-label period. Non-responders at Week 20 will move directly to the safety follow-up period with the Week 20 visit serving as their EOT visit).

During the Screening Period, upon confirmation of eligibility based on inclusion and exclusion criteria, a washout of prohibited medications should be performed if necessary.

During the 28-week Treatment Period (Period A and Period B), on-site visits will be performed every 2 weeks. During the 8-week safety Follow-up Period (Period C), one on-site visit will be performed at the EOS visit. For all visits, participants will undergo all assessments specified in the schedule of activities (SoA), such as physical and/or clinical laboratory examinations, disease specific QoL measurements, and HS clinical parameters.

The primary objective of the study is to evaluate the efficacy of SAR442970 compared to matching placebo in biologic and small molecule immunosuppressive-naïve participants based on the percentage of participants who achieve clinical response at Week 16 by the HiSCR50 (defined as ≥50% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count). The secondary endpoints include HiSCR75, HiSCR90, International Hidradenitis Suppurativa Severity Score (IHS4), safety and tolerability, Hidradenitis Suppurativa Skin Pain Numeric Rating Scale, PK, and formation of ADA. The key objective of Period B is to evaluate the maintenance of response in Week 16 HiSCR50 responders at Week 28, the depth of response based on achievement of HiSCR75 and HiSCR90 during Period B, and breadth of response based on the rate of conversion of partial responders (defined as ≥25% reduction from Baseline in the total abscess and inflammatory nodule count, with no increase from Baseline in abscess or draining tunnel count) at Week 16 to HiSCR50 responders at Week 28 in biologic and small molecule immunosuppressive-naïve participants in an exploratory manner. Period C is a safety Follow-up Period. Efficacy objectives and endpoints will be evaluated in an exploratory manner in TNF-experienced participants. Safety, PK, PD, and immunogenicity assessments will be evaluated in both biologic and small molecule immunosuppressive-naïve and TNF-experienced participants.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The purpose of the present study to evaluate the efficacy, safety, PK, and biological effects of treatment with SAR442970 for SC injection compared with placebo in male and female participants of 18 to 70 years of age with moderate to severe HS.

The study design, including the washout period and the use of placebo, is in line with other clinical studies in moderate to severe HS. The study is designed to assess SAR442970 in participants with limited treatment options; therefore, all participants must have had an inadequate response to oral antibiotics. A placebo-control arm is appropriate and necessary to establish the efficacy of SAR442970 in participants with HS and to adequately characterize the potential benefits and potential risks of the IMP. The 2:1 randomization ratio is chosen to minimize the number of participants in the placebo group considering the significant impact of HS on health and quality of life. The primary efficacy assessment window is the placebo-controlled period from Baseline to Week 16. Two subgroups will be included in the study, a biologic and small molecule immunosuppressive-naïve subgroup consisting of approximately 66 participants and a TNF-experienced subgroup consisting of approximately 18 participants. The primary analysis population is the biologic and small molecule immunosuppressive-naïve subgroup. The rationale for including the TNF-experienced population is that multiple factors such as body mass index, Hurley stage, presence of draining tunnels, and time to initiation of adalimumab have been theorized to be associated with treatment efficacy with adalimumab. Inclusion of participants who have are TNF-experienced is theorized to allow for evaluation of SAR442970 in a population that may have the aforementioned characteristics.

Hidradenitis suppurativa is a chronic disease and an additional goal of therapy aside after achievement of initial efficacy is sustained efficacy. Patients on adalimumab, the only approved biologic therapy for HS, have been shown to lose clinical response in a couple of years when they may require long-term treatment for this chronic disease. However, a placebo-controlled study greater than 16 weeks is not possible in HS participants due to concerns of withholding active treatment from placebo participants for longer than 16 weeks. Thus, a 12-week open-label period was included to obtain an indirect understanding of the efficacy and safety of SAR442970 after 28 weeks of administration. Participants randomized to SAR442970 at Baseline will continue to receive SAR442970 from Week 16 to Week 26 to complete 28 weeks of treatment with SAR442970 in total. Participants randomized to placebo at Baseline will begin to receive SAR442970 at the Week 16 visit and will continue until Week 26 to complete 16 weeks of treatment with placebo and 12 weeks of treatment with SAR442970 in total. An 8-week post-treatment Follow-up Period was included to assess for safety outcomes. For participants in the US, response will be assessed at the Week 20 visit (see definition of response in Section 4.1). Responders at Week 20 will continue in Period B to complete the 12-week open-label period. Non-responders at Week 20 will move directly to the safety follow-up period so that they may complete the study and receive access to other treatments for their disease per Investigator discretion.

4.2.1 Participant input into design

In order to evaluate the attractivity and barriers related to a HS clinical trial, two patient advisory panels were conducted, in which 4 and 3 individuals living with HS in the Netherlands and United

Kingdom, respectively, participated. The Sponsor provided an overview of the proposed clinical study design, and the following points were shared: eligibility criteria, study visits and assessments, and open-label extension. Biopsy was not seen as a problem, because most of the participants had already experienced this sampling. The placebo-control arm for 16 weeks was perceived as too long if no rescue treatment is possible. The feedback from the advisory panel has been factored into the current clinical study design.

4.3 JUSTIFICATION FOR DOSE

SAR442970 is a bispecific pentavalent NANOBODY® molecule. The molecule is able to bind both targets simultaneously with picomolar binding affinities.

SAR442970 has completed the FIH study where doses ranging from 10 mg to 300 mg single dose and 30 mg to 150 mg repeated doses every 2 weeks for a total of 3 doses were generally well-tolerated and did not raise any safety concerns in healthy volunteers.

The proposed doses (SC) for this study are supported by available clinical PK and ADA data, clinical safety data in healthy volunteers, and long-term preclinical safety studies.

Toxicology studies with up to 6 months duration in monkeys at dose levels up to 50 mg/kg/week did not raise any significant safety concerns and NOAEL in the chronic toxicology studies in monkeys was defined at 50 mg/kg/week.

SAR442970 was well-tolerated after single SC doses up to 300 mg and at multiple biweekly doses up to 150 mg in healthy subjects. Of note, a maximal tolerated dose was not established in either of these clinical studies of healthy volunteers.

The human pharmacokinetic behavior was consistent with predictions based on preclinical cynomolgus monkey data. SAR442970 plasma concentrations increased roughly dose-proportionally in the first-in-human studies. Anti-drug-antibodies were observed in the FIH study (27/28 participants had treatment emerging ADAs in the SAD part). At the higher SAD doses (150 and 300 mg cohorts) the onset of ADAs was delayed (mainly on Day 50 in contrast to Day 15 in the other cohorts). After multiple dosing, ADA were generally observed to a lower degree than after single dosing and occurrence of ADA was dose-dependent with lowest ADA formation observed at the 150 mg Q2W dose.

For biological cytokine inhibitors, the free target levels after target inhibition are usually considered to be correlated to efficacy but these free target levels are too low to be directly determined bioanalytically. The suppression of ADA is considered a marker for OX40L engagement of SAR442970, and the dose-dependent ADA decrease indicates increased OX40L engagement up to 150 mg Q2W.

Inhibiting TNF is the mechanism of action of the only approved drug, adalimumab, in severe hidradenitis suppurativa participants and the dose of the TNF inhibitor adalimumab is twice as high in the treatment of hidradenitis suppurativa compared to rheumatoid arthritis. Based on model-based approaches taking into account affinity, human PK characteristics of SAR442970 and total TNF concentrations, 150 mg Q2W is considered to reduce the free TNF levels equivalent or superior to that of adalimumab in HS patients.

Currently no validated biomarkers from healthy volunteers to predict clinical efficacy in the treatment of HS are available to further guide dose selection. Therefore, for the current study, as the initial proof-of-concept study targeting HS patients, a 150 mg dose of SAR442970 administered Q2W for 28 weeks is proposed as 150 mg Q2W was shown in FIH studies to be safe and well-tolerated and showed reduced ADA frequency compared to lower doses which likely reduces immunogenicity related safety risks in the Phase 2 study. Reducing ADA formation will also improve the predictability and stability of exposure in the Phase 2 study, ensuring participants are exposed sufficiently to expect efficacy.

A Q2W regimen is selected as evaluated in FIH study to optimize drug plasma concentrations and reduce PK fluctuation during the entire dosing interval and thus to maintain maximum levels of inhibition of both targets.

Exposure for a 150 mg dose administered biweekly provides an exposure margin of about 36 in terms of C_{max} and about 20 in terms of AUC as compared to the exposure reached at the NOAEL in a 6-month monkey study.

A detailed description of the NANOBODY® molecule, toxicology, pharmacology, and safety of SAR442970 is provided in the IB.

4.4 END-OF-STUDY DEFINITION

The end-of-study visit is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities for the last participant in the study globally.

A participant is considered to have completed the study if the participant has completed all periods of the study including the last visit or the last scheduled procedure shown in the SoA.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be 18 to 70 years of age inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics (Please also refer to Section 10.11.9)

I 02. Participants with a history of signs and symptoms consistent with HS for at least 1 year prior to Baseline.

I 03. Participants must have HS lesions present in at least 2 distinct anatomic areas (eg, left and right axilla; or left axilla and left inguino-crural fold), one of which must be Hurley Stage II or Hurley Stage III.

I 04. Participant must have had an inadequate response to a trial of an oral antibiotic for treatment of HS or exhibited recurrence after discontinuation of antibiotics or demonstrated intolerance to antibiotics or has a contraindication to oral antibiotics for treatment of their HS as assessed by the Investigator through participant interview and review of medical history.

I 05. For the biologic and small molecule immunosuppressive-naïve subgroup, participants must not have received any prior treatment with any anti-TNF therapy for HS. For the TNF-experienced subgroup, participants must have received only one anti-TNF therapy for at least 12 weeks and either (1) achieved complete response per Investigator discretion then subsequently lost response, or (2) had a partial response per Investigator discretion, or (3) did not achieve partial response per Investigator discretion, or (4) stopped using anti-TNF therapy due to reasons other than an AE (ie, insurance or access or reasons). For the TNF-experienced subgroup, if participant has received more than one anti-TNF therapy for HS, they are not eligible for participation. For both subgroups, participants must not have received any other prior treatment with another biologic therapy (aside from anti-TNF therapy in the TNF-experienced subgroup) or small molecule immunosuppressive therapies, such as a JAK inhibitor, TYK inhibitor or any other IMP for the treatment of HS.

I 06. Participant must have a total AN count of ≥3 at the Baseline Visit.

I 07. Participant must have a draining tunnel count of ≤20 at the Baseline Visit.

I 08. Participant must have a CRP >3 mg/L at the Screening Visit.

I 09. Participant who is a candidate for systemic treatment per Investigator's judgment.

I 10. Participant must demonstrate understanding and appropriate use of the daily diary and participant questionnaires, including collection of [redacted] and [redacted] on each of the 7 days prior to Baseline. For participants who have not entered at least 4 daily pain numerical rating scale and analgesic use records during the 7 days immediately preceding the planned randomization date, randomization should be postponed until this requirement is met, but without exceeding the 28-day maximum duration for screening. If participants still do not complete the required number of diary entries after trial of postponement, they will still be randomized.

Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding

I 11. All contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants:

Male participants are eligible to participate if they agree to the following during the study Treatment Period and for at least 5 months after the last administration of study intervention:

- Refrain from donating or cryopreserving sperm

PLUS, either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below:
  - A male condom; the participant should also be advised of the benefit for a female partner to use a highly effective method of contraception as described in Appendix 4 Contraceptive and Barrier Guidance (Section 10.4.2) as a condom may break or leak when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

b) Female participants:

- A female participant is eligible to participate if she is incapable of becoming pregnant, not pregnant or breastfeeding, and one of the following conditions applies:
  - Is a woman of non-child bearing potential (WONCBP) as defined in Appendix 4 Contraceptive and Barrier Guidance (Section 10.4.1)

OR

- Is a WOCBP and agrees to use a contraceptive method that is highly effective, with a failure rate of <1% per year, preferably with low user dependency, as defined in Appendix 4 Contraceptive and Barrier Guidance (Section 10.4.2) during the study Treatment Period (to be effective before starting the intervention) and for at least 5 months after the last administration of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (serum as required by local regulations) within 28 days before the first administration of study intervention, see Section 8.3.5 Pregnancy testing.

Informed Consent

I 12. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.3) of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years, a specific ICF must also be signed by the participant's legally authorized representative (LAR).

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Any other active skin disease or condition (eg, bacterial, fungal, or viral infection) that may interfere with assessment of HS.

E 02. History of recurrent or recent serious infection (eg, pneumonia, septicemia) within 4 weeks of screening, or infection(s) requiring hospitalization or treatment with IV anti-infectives (antibiotics, antivirals, antifungals, antihelminthics) within 30 days prior to Baseline, or infections(s) requiring oral anti-infectives (antibiotics, antivirals, antifungals, antihelminthics) within 14 days prior to Baseline, except as required as part of an anti-tuberculosis (anti-TB) regimen or as part of permitted concomitant oral antibiotic therapy for HS.

E 03. Known history of or suspected significant current immunosuppression, including history of invasive opportunistic or helminthic infections despite infection resolution or otherwise recurrent infections of abnormal frequency or prolonged duration.

E 04. History of solid organ transplant.

E 05. History of splenectomy.

E 06. History of moderate to severe congestive heart failure (New York Health Association [NYHA] Class III or IV), or recent cerebrovascular accident, or any other condition which, in the opinion of the Investigator, would put the participant at risk by participation in the protocol.

E 07. History of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.

E 08. Participants with a history of malignancy or lymphoproliferative disease other than adequately treated or nonmetastatic squamous cell carcinoma, or nonmetastatic basal cell carcinoma of the skin that was excised and completely cured.

E 09. Participants with a diagnosis of inflammatory conditions other than HS (including but not limited to systemic lupus erythematosus, systemic sclerosis, myositis, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, multiple sclerosis, Behcet's disease, sarcoidosis, etc).

E 10. History of human immunodeficiency virus (HIV) infection or positive HIV serology at Screening.

E 11. Participants with any of the following result at Screening:

- Positive (or indeterminate) hepatitis B surface antigen (HBs Ag) with or without positive hepatitis B virus (HBV) deoxyribonucleic acid (DNA) polymerase chain reaction (PCR) test or,
- Positive total hepatitis B core antibody (HBc Ab) confirmed by positive hepatitis B virus (HBV) DNA or,
- Positive antibody to hepatitis B surface antigen (anti-HBs) with positive HBV DNA PCR test or,
- Positive hepatitis C virus (HCV) antibody.

If a participant has a positive HBc Ab or anti-HBs followed by a negative HBV DNA PCR at screening and is subsequently randomized, they will undergo HBV DNA PCR testing every 3 months until the end of study visit.

If a participant has a positive HCV Ab and followed by a negative HCV ribonucleic acid (RNA) PCR at screening and is subsequently randomized, they will undergo HCV RNA PCR testing every 3 months until the end of study visit.

E 12. Elective surgery within 4 weeks prior to the Screening Visit or with planned surgery during the Treatment Period, or in the period up to 3 months following the last dose of IMP.

E 13. Positive COVID-19 molecular test, suspected of having COVID-19 infection, or known exposure to COVID-19 during the Screening Period.

E 14. History of COVID-19 infection within 4 weeks prior to Screening; history of mechanical ventilation or extracorporeal membrane oxygenation due to COVID-19 infection within 3 months prior to Screening or with residual significant complications from COVID-19 making it unsafe for the participant to enter this study.

E 15. Presence of active suicidal ideation, or positive suicide behavior, or participant has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or participant has had suicidal ideation in the past 6 months as indicated

by a positive response ("Yes") using the Screening or Baseline version of the Columbia-Suicide Severity Rating Scale (C-SSRS) or as assessed by the Investigator through participant interview and review of medical history.

Prior/concomitant therapy (Please also refer to Section 10.11.9)

E 16. Participant received any oral or IV antibiotic treatment for HS within 28 days prior to the Baseline Visit except if participant plans to stay on stable dose of doxycycline up to 100 mg PO BID or minocycline up to 100 mg BID for 28 days prior to Baseline and throughout the 28-week Treatment Period.

E 17. Participant received prescription topical therapies for the treatment of HS within 14 days prior to the Baseline Visit.

E 18. Participant received systemic non-biologic therapies with potential therapeutic impact for HS <4 weeks prior to Baseline Visit.

E 19. Participant is using concomitant oral analgesics for HS-related or non-HS-related pain at study entry:
- Opioid analgesics within 14 days prior to the Baseline Visit.
- Non-opioid analgesics for HS-related pain within 14 days prior the Baseline Visit. Exception: (1) ibuprofen (at a dose of up to 800 mg PO every 6 hours) not to exceed 3.2 gm/24 hours; and/or acetaminophen (at a dose of up to 1000 mg PO every 6 hours not to exceed 4.0 gm/24 hours or a lower maximum dose as per local regulations) at a stable dose for at least 10 days prior to the Baseline Visit (as needed [PRN] use is not considered a stable dose) for HS-related or non-HS-related pain. If ibuprofen or acetaminophen is not at a stable dose 10 days prior to baseline, participants must undergo washout period of 10 days prior to Baseline Visit; (2) non-opioid analgesic that is at a stable dose for at least 14 days prior to Baseline (PRN use is not considered a stable dose) for non-HS-related pain.

E 20. Prior exposure to biologics that have a potential or known association with progressive multifocal leukoencephalopathy (PML) or receipt of any B-cell or T-cell depleting therapies (ie, rituximab [Rituxan®]).

E 21. For the biologic and small molecule immunosuppressive-naïve subgroup - exposure to another biologic therapy at any time prior to Baseline. For the TNF-experienced subgroup – exposure to another biologic therapy (except for anti-TNF therapy) at any time prior to Baseline. For anti-TNF therapy for HS in the TNF-experienced subgroup within the period specified as follows: an interval of less than 4 months or <5 PK half-lives for monoclonal antibodies prior to Baseline, whichever is longer.

E 22. Exposure to a small molecule immunosuppressive therapy at any time prior to Baseline for both the biologic and small molecule immunosuppressive-naïve and TNF-experienced subgroup.

E 23. A history of an AE to anti-TNF therapy (examples include, but are not limited, to serum sickness or anaphylaxis) for an HS or non-HS indication that would contraindicate re-administration of an anti-TNF class therapy.

E 24. Treatment with a live (attenuated) immunization within 12 weeks prior to Baseline; treatment with a non-live immunization 2 weeks prior to Baseline; completion of COVID-19 vaccine within 14 days prior to Baseline. It is strongly recommended that participants have documented evidence of protective immunity and/or have completed age and gender-specific appropriate non-live vaccination series as per local guidelines 14 days prior to Baseline. If live vaccines are required as per local guidelines, these must be completed 12 weeks prior to Baseline.

Table 4 - Exclusionary therapy prior to Baseline

Therapy	Time frame
Topical treatments	
Topical antibiotics or topical retinoids	Within 14 days
Systemic treatments	
Oral or IV antibiotic treatment for HS indication except if participant plans to stay on stable dose of doxycycline up to 100 mg PO BID or minocycline up to 100 mg BID for 28 days prior to Baseline and throughout the 28-week Treatment Period.	Within 28 days
IV anti-infectives (antibiotics, antivirals, antifungals, anthelminthics) for non-HS indication	Within 30 days
Oral anti-infectives (antibiotics, antivirals, antifungals, anthelminthics) for non-HS indication	Within 14 days
Anti-TNF therapy such as adalimumab, certolizumab pegol, etanercept, golimumab, infliximab	At any time for the biologic-naïve subgroup Within 5 half-lives or the limit of PD effects or 4 months when the $t_{1/2}$ is not known for the TNF-experienced subgroup
Biologic therapies such as anakinra, canakinumab, bermekimab, lutikizumab, risankizumab, guselkumab, ustekinumab, secukinumab, bimekizumab, etc.	At any time
JAK or TYK inhibitors such as abrocitinib, baricitinib, ruxolitinib, tofacitinib, upadacitinib, etc.	At any time
Prior exposure to biologics that have a potential or know association with PML or receipt of depleting agents/therapies such as rituximab or ofatumumab or other long-acting biologics	At any time
Systemic non-biologic therapies for HS such as oral corticosteroids, MTX, dapsone, spironolactone, or metformin	4 weeks
Oral retinoids such as isotretinoin and acitretin	4 weeks
Phototherapy or laser therapy (carbon dioxide laser or laser hair removal)	4 weeks
Herbal medications for HS	4 weeks
Prior use of any anti-OX40 or anti-OX40L monoclonal antibody	At any time
Investigational therapy for the treatment of HS	At any time
Investigational therapy for the treatment of other conditions	At any time
All opioid analgesics	Within 14 days

Therapy	Time frame
Non-opioid analgesics for non-HS-related pain that is not at a stable dose (except for ibuprofen and acetaminophen for which specific requirements apply)	Within 14 days
Ibuprofen that is not at a stable dose up to 800 mg PO every 6 hours, not to exceed 3.2 gm/24 hours and/or acetaminophen that is not at a stable dose of up to 1000 mg PO every 6 hours, not to exceed 4.0 gm/24 hours or a lower maximum dose as per local regulations	Within 10 days
Live (attenuated) vaccine	12 weeks
Non-live vaccine	2 weeks

Abbreviations: BID=twice a day; HS=hidradenitis suppurativa; IV=intravenous(ly); JAK=Janus kinase; MTX=methotrexate; OX40L=OX40-Ligand; PD=pharmacodynamics; PO=oral; PML=progressive multifocal leukoencephalopathy; TNF=tumor necrosis factor; TYK=tyrosine kinase; $t_{1/2}$=terminal half-life.

Prior/concurrent clinical study experience

E 25. Prior or current participation in another clinical study involving the administration of an investigative drug for the treatment of HS. Exception: Participant in a clinical study involving the administration of an anti-TNF therapy for a participant in the TNF-experienced subgroup.

E 26. Participation in another clinical study for a non-HS indication 60 days before Baseline Visit.

Diagnostic assessments

E 27. Exclusion related to TB or nontuberculous mycobacteria (NTM) infection:

- Active or latent TB or NTM infection or a history of incompletely treated TB or NTM infection regardless of screening QuantiFERON TB gold test result.
- Participants with QuantiFERON TB gold test positive or 1 indeterminate test result (no active disease) are excluded from the study unless all of the following conditions are met:
    - Participants with a history of prior documented completed chemoprophylaxis for latent tuberculosis infection (TBI) (eg, acceptable treatments would be 9 months of isoniazid 300 mg PO daily or equivalent proven regimen per local guidelines) or treatment of active TBI who has obtained consultation with a specialist to rule out active TBI or treat active TBI.
    - Participants have written documentation for approval for participation in the present study approved by a TB specialist who ruled out latent or active TB infection or other mycobacterial infection in the participant.
- Clinically significant abnormality consistent with prior/active TB or NTM infection based upon chest radiograph with at least posterior-anterior view (radiograph must be taken within 12 weeks prior to Screening Visit or during the Screening Period). Additional lateral view is recommended but not required.
- Suspected extrapulmonary TB or NTM infection regardless of screening QuantiFERON TB gold test result.

- Participants at high risk of contracting TB, such as close contact with individuals with active or latent TB.
- Participant who received Bacille Calmette Guerin (BCG) vaccination within 12 months prior to Screening.

E 28. Any of the following laboratory abnormalities at the Screening Visit:

- Hemoglobin <10 g/dL.
- Absolute neutrophil count (ANC) <1500 /mm^3 (or <1000 /mm^3 for participants of African descent).
- Platelet count <100 000 /mm^3.
- Creatinine clearance <60 mL/min using Cockcroft-Gault equation.
- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or alkaline phosphatase (ALP) >2 × ULN.
- Total Bilirubin >2 × ULN; unless the participant has been diagnosed with Gilbert disease documented by genetic testing.
- For participants in the EU: Fasting triglyceride level ≥500 mg/dL.
- Retest can be done to reassess the eligibility during Screening Period as per Investigator's judgement that observed abnormality is not clinically significant and not consistent with participant's medical history.

Other exclusion criteria

E 29. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 30. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 31. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with section 1.61 of the International Conference on Harmonization [ICH]-GCP Ordinance E6).

E 32. Participants dependent on the Sponsor or Investigator (in conjunction with section 1.61 of the ICH-GCP Ordinance E6).

E 33. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

E 34. Any country-related specific regulation that would prevent the participant from entering the study - see Appendix 8 of the protocol (Section 10.8) (country-specific requirements).

E 35. Female participants who are breastfeeding or considering becoming pregnant during the study.

E 36. History (within last 2 years prior to Baseline) of prescription drug or substance abuse, including alcohol, considered significant by the Investigator. Any specific situation during study implementation/course that may raise ethics considerations.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

No restrictions are required.

5.3.2 Caffeine, alcohol, and tobacco

- The protocol does not impose any restrictions on caffeine or tobacco use.
- Participants will be excluded from the study if there is a history of chronic alcohol abuse within 2 years prior to the first study drug administration. Prior to each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.

5.3.3 Activity

Not applicable.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once only. Participants who are rescreened are required to sign a new informed consent form, and should be assigned a new study participant number, and all the screening procedures should be repeated and entered in the Screening Visit pages. In case the participant is a temporary screen failure, there is no need to have participant reconsent (ie, new ICF signed) if the participant finally participates in the trial. However, if the reason for temporary screen failure is a reason that might have altered the initial given agreement of the participant to participate, the Investigator should ensure the willingness of the participant to continue or redo some screening procedures and his/her participation to the trial. This oral agreement should be documented in the participant’s chart. All the tests out of protocol window should be repeated and entered in the additional pages.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT/RANDOMIZATION/ADMINISTRATION OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 9: (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency) should be considered for screening, enrollment, randomization, and administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified, investigational, and non-investigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 STUDY INTERVENTION(S) ADMINISTERED

For a description of study interventions administered see Table 5.

Table 5 - Study intervention(s) administered

Intervention label	SAR442970	SAR442970 matching placebo
Intervention name	SAR442970	Placebo
Type	Drug	Other
Dose formulation	1 mL extractable volume of 150 mg/mL SAR442970 filled in 2 mL glass vial	1 mL extractable volume of placebo filled in 2 mL glass vial
Unit dose strength(s)	150 mg	0 mg
Dosage level(s)	150 mg every 2 weeks	0 mg every 2 weeks
Route of administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Experimental
IMP	IMP	IMP
Packaging and labeling	One vial in a kit box. Both the box and the vial will be labeled as required per country requirement.	One vial in a kit box. Both the box and the vial will be labeled as required per country requirement.
Current/former name(s) or alias(es)	NANOBODY® VHH anti-TNFa/OX40L	Not applicable

Abbreviations: IMP=investigational medicinal product

Table 6 - Study arm(s)

Arm title	SAR442970 150 mg	Placebo
Arm type	Experimental	Placebo
Arm description	Participants will receive 150 mg of SAR442970 Q2W to complete 14 total doses (or 28 weeks of treatment with SAR442970).	Participants will receive placebo Q2W to complete 8 total doses of placebo (or 16 weeks of treatment with placebo), then 150 mg of SAR442970 Q2W to complete 6 total doses (or 12 weeks of treatment with SAR442970).

Abbreviations: Q2W=once every 2 weeks

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, or administer study intervention.
3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
4. The Investigator and authorized site staff are responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.4.9).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

IMP is provided in vials, which are to be used to fill a syringe for the subcutaneous injection. Instructions on IMP handling, storage, and preparation are provided in the Pharmacy Manual.

Participants should be instructed to avoid missing any dose of medication during the study. Any participant who misses one dose should be reminded to be diligent, to avoid further missing doses thereafter. In case of missed dose(s), no loading dose of 2 injections will be administered when restarting the treatment, whatever the number of missed doses. The participant should continue their scheduled IMP treatment and visits if ≤2 consecutive doses were missed. Missing >2 doses of schedule IMP is criterion for permanent discontinuation.

6.3 ASSIGNMENT TO STUDY INTERVENTION

During the double-blind Treatment Period, up to Week 16, Investigators and participants will be blinded to the allocation of active or placebo treatment arms. SAR442970 and placebo will be provided in open-label kits with vials that will be distinguishable between SAR442970 and placebo. An unblinded pharmacist will use the vial to fill a syringe to be administered by the site staff that will remain blinded. The syringe will be covered with a transparent orange label by the unblinded site pharmacist to ensure that the Investigator and the nurse administering the IMP will remain blinded.

During the open-label period, from Week 16 to Week 28, participants will receive active treatment. Either a nurse or pharmacist will use the vial to fill a syringe to be administered by the site staff that is no longer blinded to the IMP administered at the visit. The use of the transparent orange label will not be necessary during this period.

Detailed information on IMP preparation is available in the Pharmacy Manual.

All participants will be centrally assigned to randomized study intervention using an interactive response technology (IRT). Before the study is initiated, log in information and directions for the IRT will be provided to each site. Study intervention will be dispensed at the study visits summarized in the SoA. Details of the IRT procedure will be provided in the IRT Site Manual.

The randomization and intervention allocation are performed centrally by the IRT which generates participant number and allocates the corresponding intervention kits to the participants according to the randomization arm.

Participant's randomization list will be stratified by treatment history (biologic and small molecule immunosuppressive-naïve or TNF-experienced) and Hurley stage (II or III).

A randomized participant is defined as a participant from the screened population who has been allocated to a randomized intervention regardless of whether the intervention was received or not.

Time of randomization for a participant is defined as the time recorded by the IRT.

A participant cannot be randomized more than once in the study. Randomization will occur at Week 0 (Visit 2).

Due to the study duration, several intervention kits number will be allocated to participants by the IRT across visits in the same arm assigned at the randomization visit. That is, in these cases, the intervention/kit number varies but the arm assignment at randomization does not change.

6.4 BLINDING

In accordance with the double-blind design, Investigators will remain blinded to study treatment and will not have access to the randomization (treatment) codes except under exceptional medical circumstances.

The blind may be broken if, in the opinion of the Investigator, it is in the participant's best interest for the Investigator to know the study treatment assignment. The Sponsor must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition. In this case, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

Code breaking can be performed at any time by using the proper module of the IRT and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken,

the Investigator should document the date, time of day, and reason for code breaking. If the code is broken by the Investigator, the participant must withdraw from IMP administration.

Randomization code breaking will also be performed during the analysis of the PK serum concentration samples and ADA samples in order to enable the laboratory to sort the samples (SAR442970 group, placebo) and start analyzing the samples (SAR442970 group only) while the study is still ongoing. Only the project manager and lead scientist at the Bioanalytical Laboratory will have access to the randomization code to allow for the sorting of the SAR442970 blood samples. The Bioanalytical Laboratory and responsible personnel will follow the standard procedures to ensure the protection of the blind within the Sponsor's clinical team. The randomization code or the individual analytical results will not be disclosed to any team personnel prior to the database lock.

Randomization code breaking may also be performed to initiate the population PK analysis before the final database lock. Only the PK programmers will have access to the randomization code to allow dataset creation. The PK programmers will follow the standard procedures to ensure the protection of the blind within the Sponsor's clinical team and modeling team. The randomization code will not be disclosed to any clinical or modeling team personnel prior to the database lock.

Reports of analyses for IDMC review will be performed by statistician(s) and programmer(s) independent from the study team members. Two types of Independent Data Monitoring Committee (IDMC) reports will be generated: an open meeting report which does not present results by treatment arm and a closed meeting report which presents results by treatment arm. The open meeting report(s) will be accessible to both the study team members and the IDMC; however, the closed meeting reports will only be accessible to the IDMC until after the database is locked and treatment codes released for the final efficacy analysis by the Sponsor.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report (see Section 8.4.4) be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy. Sponsor staff involved in the conduct of the study will remain blinded to the participant intervention assignment.

Methods of blinding

SAR442970 and placebo will be provided in 2 mL vial. Each treatment kit of 2 mL (SAR442970/placebo) vials will be distinguishable and labeled with a treatment kit number. The IMP will be provided in open-label vials. An unblinded pharmacist will use the vial to fill a syringe to be administered by the site staff that will remain blinded. The syringe will be covered with a transparent orange label by the unblinded site pharmacist to ensure that the Investigator and the nurse administering the IMP will remain blinded. Detailed information on IMP preparation is available in the Pharmacy Manual.

These methods for blinding will be necessary during Period A up until Visit 9 (Week 14). Beginning at Week 16 (Visit 10), site staff will no longer be blinded to the IMP administered at the visit.

Measures to protect the blinding of the study will be applied for IDMC review, PK, and antibody analysis at laboratory level.

In case of an interim analysis, procedure to maintain blinding for study team members will be applied.

At the time of the early analysis when all participants will have completed Week 16 visit, the blind will be broken for study team member to conduct statistical analysis but will not be disseminated to sites and at local level until the end of the study.

6.5 STUDY INTERVENTION COMPLIANCE

Participants will receive study intervention directly from the Investigator or designee at the site, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When IMP is administered, local skin reactions around the site of injection will be assessed by the Investigator or other appropriately trained site personnel 30 minutes after the injection.

Light pressure will be applied at the injection site and any pain, itchiness, tenderness, erythema, and induration will be recorded in the eCRF. Pain and tenderness will be assessed according to the following scale:

Definitions of pain and tenderness:

- None: nothing.
- Mild: easily tolerated.
- Moderate: interferes with daily activities.
- Severe: prevents normal everyday activities or sleep.

Erythema and induration will be measured using a ruler, or a template supplied by the Sponsor.

A record of the quantity of IMP dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

6.6 DOSE MODIFICATION

No participant level dose modifications are planned.

6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Not applicable.

6.8 TREATMENT OF OVERDOSE

An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose within the planned intervals (2 weeks ±3 days).

Sponsor does not recommend specific treatment for an overdose other than supportive care.

In the event of an overdose, the Investigator should:

- Closely monitor the participant for any AE/SAE and laboratory abnormalities until the next study visit or for up to 75 days if IMP has been permanently discontinued.
- Evaluate the participant to determine, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Obtain a plasma sample for PK analysis as soon as possible and 120 hours after ingestion.
- Document appropriately in the CRF.
- Contact the Sponsor as soon as possible.

6.9 PRIOR AND CONCOMITANT THERAPY

Any treatment (including nutritional supplements) or procedure administered from the time of consent to the EOS Visit is considered concomitant. This includes permitted medications ongoing at the time of consent. Concomitant medications and procedures are allowed, with the exception of those listed in Section 6.9.1.

Prior medications will not be recorded in the eCRF, with the exception of prior use of anti-TNF therapy, other biologics and small molecule immunosuppressive therapies, antibiotics (oral, IV, or topical), systemic corticosteroids, methotrexate (MTX), hormonal therapy, metformin, and opioid and non-opioid analgesic therapies for HS or non-HS conditions. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until

completion of the Follow-up Visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

6.9.1 Prohibited Medications

The following treatments are prohibited for all participants during the Treatment Period:

- Any biologic or small molecule immunosuppressive therapy that would have potential therapeutic impact on the disease being studied, including but not limited to anti-TNF (eg, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, etc), anti-IL1 (eg, anakinra, canakinumab, bermekimab), anti-IL12/23 (eg, ustekinumab), other anti-IL23 (eg, guselkumab), anti-IL-17 (eg, secukinumab, bimekizumab), JAK inhibitors, or TYK inhibitors.
- Any other systemic therapy that can also be used to treat HS, including but not limited to apremilast, corticosteroids, methotrexate, cyclosporine, retinoids, acitretin/etretinate, hormonal therapy (except for contraception), zinc gluconate, intramuscular gamma-globulin, colchicine, metformin (except for continuous treatment of pre-existing diabetes), and fumaric acid esters.
- Any antibiotic therapy (topical and/or systemic [oral or IV]) for HS-related infection. Exception:
    - Participants who have been on a stable dose and frequency of a permitted oral antibiotic therapy (doxycycline up to 100 mg PO BID or minocycline up to 100 mg PO BID) for at least 4 consecutive weeks (28 days) prior to Baseline and throughout the duration of the 28-week Treatment Period of the trial. Additionally, systemic and/or topical antibiotic use is allowed for the treatment of acute, non-HS-related infections.
    - Participants who receive antibiotic therapy for HS-related infections will not be randomized if they start oral antibiotic therapy or increase dose of concomitant oral antibiotic therapy within 28 days of Baseline and will be counted as a non-responder and meet criteria for permanent discontinuation if they start oral antibiotic therapy or increase the dose of concomitant oral antibiotic therapy during the Treatment Period. Participants who stop oral antibiotic therapy or decrease the dose of concomitant oral antibiotic therapy during the Screening Period will still be randomized and will continue to receive IMP if they stop oral antibiotic therapy or decrease dose of concomitant oral antibiotic therapy during the Treatment Period (refer to Table 7).

Table 7 - Antibiotic therapy

Antibiotic	Indication	Study Period	Increase Dose or Frequency of Antibiotic	Decrease Dose or Frequency of Antibiotic	Stop Antibiotic
Permitted oral antibiotic*	HS	Screening Period (after enrollment)	See exclusion criteria.	If this occurs, the Baseline Visit must be scheduled at least 2 weeks from date that change in medication administration was implemented by participant.	
		Treatment Period (after Baseline Visit)	Prohibited.	Permitted.	
		Follow-up Period (after EOT visit)	Permitted without any dose restriction per Investigator discretion.		
Systemic (oral or IV) or topical antibiotic	Non-HS (eg, urinary tract infection)	Screening Period (after enrollment)	Permitted without any dose restriction per Investigator discretion. However, the Baseline Visit must be scheduled 14 days after the last dose of oral antibiotic was taken by the participant and 30 days after the last dose of IV antibiotic was taken by the participant (ie, participant may need to be re-screened).		
		Treatment Period (after Baseline Visit)	Permitted without any dose restriction per Investigator discretion.		
		Follow-up Period (after EOT Visit)	Permitted without any dose restriction per Investigator discretion.		

Abbreviations: EOT=end of treatment; HS=hidradenitis suppurativa; IV=intravenous; mg=milligram(s); PO=oral
*Permitted oral antibiotics are stable doses of doxycycline up to 100 mg PO BID or minocycline up to 100 mg PO BID.

- Use of any treatments for HS-related pain including but not limited to antiepileptics (eg, gabapentin), tricyclics (eg, nortriptyline), or selective serotonin norepinephrine reuptake inhibitors (eg, duloxetine, venlafaxine). Use of any opioid is prohibited, regardless of the indication. Exception:
  - Ibuprofen (at a dose of up to 800 mg PO every 6 hours not to exceed 3.2 gm/24 hours) and/or acetaminophen (at a dose of up to 1000 mg PO every 6 hours not to exceed 4.0 gm/24 hours or a lower maximum dose as per local regulations) provided the dose is stable (PRN is not considered stable) 10 days before Baseline and continued until Week 28 for HS-related or HS-unrelated pain,
  - Ibuprofen (at a dose of up to 800 mg PO every 6 hours not to exceed 3.2 gm/24 hours) and/or acetaminophen (at a dose of up to 1000 mg PO every 6 hours not to exceed 4.0 gm/24 hours or a lower maximum dose as per local regulations) can be taken after Baseline Visit for HS-related or HS-unrelated pain,
  - Participants in Australia may receive tramadol (at a dose of up to 100 mg PO every 4 hours, not to exceed 400 mg/24 hours) as a rescue therapy after Baseline for HS-related pain that is refractory to treatment with ibuprofen or acetaminophen per Investigator discretion,

- Local anesthetic administered in the setting of rescue treatment with intralesional triamcinolone acetonide injection after Week 16 (Visit 10) provided the number of protocol-allowed interventions is not exceeded (Note: For participants in Australia, 2 lesion interventions are allowed during Period A prior to Week 16 [Visit 10]) (See Section 6.9.2),
- Local anesthetic administered in the setting of rescue treatment with local I&D after Week 16 (Visit 10) provided the number of protocol-allowed interventions is not exceeded (Note: For participants in Australia, 2 lesion interventions are allowed during Period A prior to Week 16 [Visit 10]) (See Section 6.9.2),
- Local anesthetic administered in the setting of [redacted]
- Non-opioid analgesics for HS-unrelated pain provided dose is stable for 14 days prior to Baseline and is continued until Week 28 for HS-unrelated pain.
  - Participants who receive prohibited analgesic therapy for HS-related pain or non-HS-related pain will continue to receive IMP (refer to Table 8).

Table 8 - Analgesic therapy

Analgesic	Indication	Study Period	Increase Dose or Frequency of Analgesic	Decrease Dose or Frequency of Analgesic	Stop Analgesic
Opioid Analgesics	HS or non-HS	Screening Period (after enrollment)	See exclusion criteria.		
		Treatment Period (after Baseline Visit)	Prohibited for all participants except for participants in Australia.¥		
		Follow-up Period (after EOT Visit)	Permitted per Investigator discretion.		
Non-opioid Analgesics (eg, gabapentin) Excluding Ibuprofen and Acetaminophen	Non-HS	Screening Period (after enrollment)	Stable doses of non-opioid analgesics are permitted.		
		Treatment Period (after Baseline Visit)	Prohibited. Dose must remain stable.		
		Follow-up Period (after EOT Visit)	Permitted per Investigator discretion.		
Non-opioid Analgesics (eg, gabapentin) Excluding Ibuprofen and Acetaminophen	HS	Screening Period (after enrollment)	Non-opioid analgesics are prohibited.		
		Treatment Period (after Baseline Visit)			
		Follow-up Period (after EOT Visit)	Permitted per Investigator discretion.		
Ibuprofen	HS or non-HS	Screening Period (after enrollment)	Stable doses of ibuprofen are permitted.		
		Treatment Period (after Baseline Visit)	If medically necessary, permitted per Investigator discretion provided dose does not exceed maximum limit.*		
		Follow-up Period (after EOT Visit)	Permitted without any dose restriction per Investigator discretion.		

Analgesic	Indication	Study Period	Increase Dose or Frequency of Analgesic	Decrease Dose or Frequency of Analgesic	Stop Analgesic
Acetaminophen	HS or non-HS	Screening Period (after enrollment)	Stable doses of acetaminophen are permitted.		
		Treatment Period (after Baseline Visit)	If medically necessary, permitted per Investigator discretion provided dose does not exceed maximum limit.**		
		Follow-up Period (after EOT Visit)	Permitted without any dose restriction per Investigator discretion.		
Local Anesthetic	Prior to [redacted] for biomarker assessment	Screening Period (after enrollment)	Permitted without any dose restriction per Investigator discretion.		
		Treatment Period (after Baseline Visit)			
		Follow-up Period (after EOT Visit)			
Local Anesthetic	Prior to intralesional triamcinolone injection or in-office I&D	Screening Period (after enrollment)	See exclusion criteria.		
		Treatment Period (after Baseline Visit)	Prohibited until after completion of Week 16 (Visit 10). After Week 16, permitted, provided that participant maximally has two interventions every 4 weeks.§		
		Follow-up Period (after EOT Visit)	Permitted without any dose restriction per Investigator discretion.		

Abbreviations: EOT=end of treatment; HS=hidradenitis suppurativa; I&D=incision and drainage
¥ Participants in Australia may receive tramadol (at a dose of up to 100 mg PO every 4 hours, not to exceed 400 mg/24 hours) as a rescue therapy after Baseline for HS-related pain that is refractory to treatment with ibuprofen or acetaminophen per Investigator discretion.
§ For participants in Australia, 2 lesion interventions are allowed during Period A. An intervention can occur on two different lesions at the same visit or on the same lesion at two different study visits (See Section 6.9.2).
* Maximum limit for ibuprofen is up to 800 mg PO every 6 hours not to exceed 3.2 gm/24 hours.
** Maximum limit for acetaminophen is up to 1000 mg PO every 6 hours not to exceed 4.0 gm/24 hours or a lower maximum dose as per local regulations.

- Injectable corticosteroids. Exception: rescue treatment (intralesional triamcinolone acetonide via intradermal injection) after Week 16 (Visit 10).
- Deroofing or skin-tissue-saving excision with electrosurgical peeling, laser therapy, intense pulse light, local/wide/radical excision, incision and/or draining of lesions is prohibited. Exception: Rescue treatment (local I&D).
- Phototherapy treatment (ultraviolet B [UVB] or ultraviolet A [UVA] phototherapy, including psoralen and ultraviolet A), tanning booth, or extended sun exposure.
- Non-antibiotic topical therapies or changes in the concentration/frequency of such treatments that may be used to treat HS (eg, zinc pyrithione, resorcinol, dapsone, and delgocitinib). Other non-antibiotic topical treatments (eg, corticosteroids, antifungals, etc) are permitted, provided these are not being used in anatomic regions where HS lesions are located.
- Over-the-counter topical antiseptic washes, creams, ointments, gels, and liquids containing antibacterial agents to treat HS, other than those allowed as per concomitant therapy section.

- Live vaccines (during the study and for 6 months after the last dose of study drug). Examples of live attenuated vaccine include, but are not limited to, BCG vaccine, live zoster vaccine (Zostavax®), measles-mumps-rubella or measles-mumps-rubella-varicella vaccine, monovalent live attenuated influenza A (intranasal) vaccine, oral polio vaccine, rotavirus vaccine, seasonal trivalent live attenuated influenza (intranasal) vaccine, smallpox vaccine, oral typhoid vaccine, varicella (chicken pox) vaccine, yellow fever vaccine, or dengue fever vaccine (Dengvaxia®).
- Natalizumab (Tysabri®).
- Rituximab.
- Any investigational agents.
- Medicinal and recreational cannabis or cannabinoid use.
- Herbal medications for HS or non-HS indications.

The Investigator should contact the Medical Monitor if there are any questions regarding concomitant or prior therapy.

In addition, any medications listed in exclusion criteria (from E 16 to E 24) should not be initiated during the study except what is specifically mentioned in the concomitant-medication section.

During Period C, the safety Follow-up Period, these medications may be resumed per the discretion of the Investigator.

6.9.2 Concomitant Medications

Other than the prohibited medications listed in Section 6.9.1, treatment with the following medications as outlined in this section is permitted during the study.

During Period C, the safety Follow-up Period, all concomitant medications may be continued without the restrictions mentioned below per the discretion of the Investigator.

Oral Antibiotic Therapy

Participants may use oral antibiotic therapy for the treatment of HS provided the dosing regimen (dose and frequency) has been stable for at least 4 consecutive weeks (28 days) prior to Baseline and throughout the duration of the 28-week Treatment Period of the trial. Antibiotics taken on a PRN basis are not considered a stable dose. Permitted oral concomitant antibiotics are the following: oral doxycycline (at a dose of up to 100 mg PO BID) or minocycline (at a dose of up to 100 mg PO BID). If oral antibiotic therapy is used concomitantly, the dose should remain stable and constant.

Analgesic Therapy for HS-Related Pain and Non-HS-Related Pain

Most participants will be required to washout all analgesics prior to Baseline. For more guidance, refer to Table 4. This includes analgesics for HS-related and non-HS-related pain. However, if a participant is on a stable dose of ibuprofen or acetaminophen (PRN is not considered stable) for HS-related pain, the participant may continue the analgesic, provided the dose is stable for

10 days prior to Baseline and is anticipated to remain stable through Week 28. Additionally, if a participant is on a stable dose of non-opioid analgesic (other than ibuprofen or acetaminophen) for non-HS-related pain (eg, gabapentin for osteoarthritis), the participant may continue the analgesic, provided the dose is stable for 14 days prior to Baseline and is anticipated to remain stable through Week 28.

If a participant experiences HS-related or non-HS-related pain after Baseline, they may initiate analgesic treatment. Analgesic therapy is limited to ibuprofen (at a dose of up to 800 mg PO every 6 hours not to exceed 3.2 gm/24 hours) and/or acetaminophen (at a dose of up to 1000 mg PO every 6 hours not to exceed 4.0 gm/24 hours or a lower maximum dose as per local regulations). Participants in Australia may receive tramadol (at a dose of up to 100 mg PO every 4 hours, not to exceed 400 mg/24 hours) as a rescue therapy after Baseline for HS-related pain that is refractory to treatment with ibuprofen or acetaminophen per Investigator discretion. Participants will complete a daily diary of their analgesic use. Participants will be required to record their analgesic use daily through Week 28. Any changes in dosing and/or frequency need to be reported in the daily diary; documentation of only PRN use is not permitted. Dose adjustments of ibuprofen or acetaminophen up to the maximum permitted dose and frequency are allowed during the study.

Lesion Intervention

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

Only 2 types of interventions are allowed: injection with intralesional triamcinolone acetonide suspension (at a concentration of up to 10 mg/mL, up to 1 mL) and I&D.

For participants in Chile, intralesional betamethasone (at a maximum dose of up to 1.5 mg, diluted in sterile normal saline per Investigator discretion) may be substituted for intralesional triamcinolone.

New systemic and topical therapies following I&D (including antibiotics), are prohibited.

Participants should continue using any ongoing oral and topical therapies (with the constraints as described in Section 6.9.1) during the study. Concomitant medications associated with the lesion intervention(s) must be captured in the source and on the appropriate eCRF.

Protocol-allowed interventions are prohibited during Period A for all participants except those in Australia. For participants in Australia, 2 lesion interventions are allowed during Period A. An intervention can occur on two different lesions at the same visit or on the same lesion at two different study visits.

During Period B, maximally two interventions every 4 weeks are permitted. An intervention can occur on two different lesions at the same visit or on the same lesion at two different study visits.

All study visit assessments must occur before any interventions are performed. The site will be required to count any lesion that undergoes an intervention as permanently present from the date of the intervention and must account for it in the source document(s) and on the appropriate eCRF.

Antiseptic Therapy

Participants may use 1 of the following over-the-counter topical antiseptics on their HS lesions: chlorhexidine gluconate, triclosan, benzoyl peroxide, dilute bleach in bathwater, or zinc pyrithione shampoo as body wash. However, they must use it 2 weeks prior to Baseline Visit and throughout the duration of the 28-week Treatment Period of the trial.

Wound Care

Concomitant use of wound care dressings on HS wounds is allowed; however, options are limited to alginates, hydrocolloids, and hydrogels.

Local Anesthetic

Local anesthetic (with lidocaine or lidocaine with epinephrine, dose per Investigator discretion) is permitted in the setting of (1) rescue treatment with intralesional triamcinolone acetonide via intradermal injection, (2) rescue treatment with local I&D, and (3) [redacted] assessment.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1).

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant should, if at all possible, remain in the study to be evaluated for all assessments indicated in the SoA. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Under the following circumstances IMP should be permanently discontinued:

- At participant's own request or at the request of their LAR (ie, an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the participant's well-being.
- At the specific request of the Sponsor.
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor.
- Severe allergic or hypersensitivity reaction (See Section 10.6).
- Confirmed diagnosis of malignancy.
- Major surgery or elective surgical procedure.
- Severe intercurrent illness.
- Pregnancy (See Section 8.4.5).
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (See Section 10.6).
- Severe laboratory abnormalities:
  - Neutrophil count <1 500/mm³ (See Section 10.6).
  - Platelet count <100 000/mm³ (See Section 10.6).
  - ALT >5 ULN or ALT >3 ULN with concomitant total bilirubin >2 ULN (unless participant with documented Gilbert's syndrome) (See Section 10.6).
  - Increase in serum creatinine as per algorithm in Section 10.6.
- Any clinically significant abnormal laboratory value will be immediately rechecked for confirmation after 24 hours before making a decision of permanent discontinuation of the IMP for the concerned participant. If the laboratory abnormality is considered causally related to the IMP, the IMP will be permanently discontinued. In cases where a causal

relationship to the IMP can be reasonably excluded (ie, an alternative cause is evident), the IMP will be discontinued but it may be resumed when the laboratory abnormality is sufficiently normalized. A decision to resume the IMP will be made jointly by the Investigator and Medical Monitor (Medical Monitor's written approval is required).

- Occurrence of AEs, that, in the opinion of Investigator/Sponsor, may jeopardize participant's safety or data integrity.
- Initiation of systemic immunosuppressive or immunomodulating drugs such as those described in Section 6.9.1.
- Receipt of a live (attenuated) immunization.
- Treatment with any prohibited systemic concomitant medication or procedure (See Section 6.9.1).
- Treatment with any prohibited rescue medication or procedure (See Section 6.9.1).
- Missing >2 doses of scheduled IMP administration.

See the SoA (Section 1.3) for data to be collected at the time of definitive intervention discontinuation and follow-up and for any further evaluations that need to be completed. Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation after 24 hours before making a decision of permanent discontinuation of the IMP for the concerned participant.

Handling of participants after permanent intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a pharmacokinetics sample, if appropriate.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in Section 10.6 or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study are not allowed.

7.1.3 QTc stopping criteria

Administration of study drug should be interrupted if a participant meets either bulleted criterion:

- QTc >500 msec confirmed by repeat measurement or manual over-read.
- QTc increase from Baseline >60 msec.

If a clinically significant finding is identified (including, but not limited to changes from Baseline in QT interval corrected using formula (QTcF) after enrollment, the Investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed). This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.4 Temporary discontinuation

Temporary intervention discontinuation decided by the Investigator corresponds to ≤2 doses not administered to the participant.

Dosing of IMP should be temporarily interrupted for the following reasons:

- Clinically important laboratory abnormalities, such as:
  - Absolute neutrophil count ≤1.0 × 10^9/L but >0.5 × 10^9/L,
  - Platelet count ≤100 × 10^9/L but >50 × 10^9/L,
  - Creatine phosphokinase >10 × ULN.
- Other intercurrent illness.
- An infection requiring systemic treatment with antibiotic, antifungal, antiviral, antiparasitic or antiprotozoal agents, or requiring oral treatment with such agents for more than 2 weeks.
- Where elective surgery is required, this must be communicated in writing with the Medical Monitor regarding temporary discontinuation of IMP prior to any planned surgical intervention. IMP **must not** be re-started without communication with the Medical Monitor.

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9 [Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency]). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF or eCRF.

7.1.5 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned adverse event

was unlikely and if the selection criteria for the study are still met (refer to Section 5.1 and Section 5.2).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an EOT Visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent from the study, the Sponsor will retain and continue to use any data collected before such a withdrawal of consent, as per applicable clinical regulation(s).
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study and to complete the safety follow-up.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for Follow-up Visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized/reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count, urine tests) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local Health Authority/ethics requirements (see Appendix 9 [Section 10.9]).
- Safety/laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

8.1 ADMINISTRATIVE AND SCREENING/BASELINE PROCEDURES

8.1.1 Inclusion and Exclusion Criteria

Participants will be evaluated to ensure they meet all inclusion criteria and none of the exclusion criteria at the Screening and Baseline Visits.

8.1.2 Informed Consent

An Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approved, study-specific informed consent will be reviewed, signed and dated by the participant before any study procedures are undertaken, or before any medications are withheld from the participant in order to participate in this study.

8.1.3 Informed Consent for [redacted]

[redacted]

8.1.4 Informed Consent fo [redacted]

[redacted]

8.1.5 Demographics

Demographic information will be collected at the Screening Visit as follows:

- Age.
- Gender.
- Ethnicity.

8.1.6 Medical and Surgical History (Includes Alcohol, Nicotine, and Substance Usage)

At the Screening Visit, the Investigator will record significant medical or surgical events (including tonsillectomy) and be responsible for review of the medical history (including history of hypertension and/or diabetes) of participants to ensure that they meet the criteria for eligibility for the study. This will include a review of the study inclusion and exclusion criteria, which will be repeated at the Baseline Visit.

History of current prescription drug or substance abuse, including alcohol, considered significant by the Investigator is an exclusion criterion for this study (see Section 5.2). Drug abuse is a patterned use of a substance in which the participant uses amounts or methods that are harmful to themselves or others during the study period. If the medical history suggests such abuse, then the Investigator should consider whether the participant meets the exclusion criteria. Drugs of abuse screening, including breath test, may be performed at the Investigator's discretion. Tobacco use (duration of current or past use and quantity used) will also be documented but is not an exclusion criterion.

8.1.7 Hidradenitis Suppurativa and Other Dermatologic History

Detailed information of each participant's HS and other dermatologic history will be collected at the Screening Visit and will include, but will not be limited to, the following:

- The date of initial onset of HS.
- The date, onset, and duration of past treatments for HS.
- The date of any prior surgeries for HS.

- The presence of comorbid atopic dermatitis and psoriasis in HS participants as assessed by the Investigator through participant interview and review of medical history.

8.1.8 Family History of Hidradenitis Suppurativa

Detailed information of each participant's family history of HS will be collected at the Screening Visit and will include whether the participant's first-degree relatives (ie, parent, sibling, or child of the participant) carry a physician-diagnosis of HS or experienced signs and symptoms consistent with a diagnosis of HS currently or in the past.

8.2 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA.

8.2.1 Clinician Reported Outcome Measures

8.2.1.1 Hidradenitis Suppurativa Clinical Parameters (HS Clinical Parameters)

The HS Clinical Parameters are defined as a broad assessment of affected anatomic areas, lesions count in the respective areas, and characterization of intervening skin in the respective areas in HS participants. The HS Clinical Parameters must address all relevant anatomical regions in each participant. The parameters will include the following:

- Affected area (ie, left and right axilla, left and right sub/inframammary area, intermammary area, left and right buttock, left and right inguino-crural fold, perianal area, perineal area, or other area, as described in guidance provided to the Investigator.
- Lesion counts in each affected area. Types of lesions counted will be:
  - Abscess: a circumscribed collection of purulent exudate frequently associated with swelling and other signs of inflammation, such as fluctuance, tenderness and pain.
  - Non-inflammatory nodule: nontender or minimally tender, nonerythematous nodule.
  - Inflammatory nodule: a tender, erythematous, well-defined nodule; the lesion has no evidence of fluctuance. A pyogenic granuloma is considered an inflammatory nodule; a papule or pustule is not considered an inflammatory nodule.
  - Nondraining tunnel: a tunnel is a pathologic passageway connecting to the skin surface from dermis or subcutaneous tissue. A nondraining tunnel is a nontender or minimally tender, non-erythematous tunnel.
  - Draining tunnel: a tunnel that drains serous or purulent fluid, either spontaneously or by gentle palpation.
  - Hypertrophic scar: enlargement or overgrowth of a scar so that it extends above the surrounding skin surface.
- Hurley Stage assessment (see Section 8.2.1.5).

The HS Clinical Parameters will be assessed at the designated study visits according to the SoA (see Section 1.3). Appendix 11 (Section 10.11.1) provides a representative example of the HS Clinical Parameters that will be used in this study.

8.2.1.2 Hidradenitis Suppurativa Clinical Response

The Hidradenitis Suppurativa Clinical Response (HiSCR50) is a valid and meaningful endpoint for assessing HS treatment effectiveness in controlling inflammatory manifestations in this population (8). The HiSCR50 is defined as at least a 50% reduction from Baseline in the total abscess and inflammatory nodule count, with no increase from Baseline in abscess or draining tunnel count.

The HiSCR75 is defined as at least a 75% reduction from Baseline in the total abscess and inflammatory nodule count, with no increase from Baseline in abscess or draining tunnel count. The HiSCR90 is defined as at least a 90% reduction from Baseline in the total abscess and inflammatory nodule count, with no increase from Baseline in abscess or draining tunnel count.

The HiSCR50, HiSCR75, and HiSCR90 will be assessed at each of the prespecified times when the HS Clinical Parameters are scheduled to be assessed, at the designated study visits according to the SoA (see Section 1.3). The score will be calculated using data recorded for HS Clinical Parameters in the eCRF (see Section 8.2.1.1).

8.2.1.3 International Hidradenitis Suppurativa Severity Score System (IHS4)

The IHS4 is a validated tool to assess HS severity (32). The determination of IHS4 requires counting inflammatory nodules, abscesses and draining tunnels and multiplying each by a specific coefficient making it straightforward to apply in both research and clinical practice and easy to use in conjunction with the HiSCR50. A continuous IHS4 score can be derived based on this weighted score. A categorial IHS4 score can also be derived from the weighted score: a total score of 3 or less signifies mild, 4-10 signifies moderate, and 11 or higher signifies severe disease. A dichotomous score can also be derived, known as IHS4-55, which is defined as a 55% reduction in IHS4 score from Baseline (33).

The IHS4 will be assessed at each of the prespecified times when the HS Clinical Parameters are scheduled to be assessed, at the designated study visits according to the Schedule of Activities Section 1.3. The score will be calculated using data recorded for HS Clinical Parameters in the eCRF (see Section 8.2.1.1).

8.2.1.4 Abscess and Inflammatory Nodule (AN) Count

The AN count is the sum of the abscess count and inflammatory nodule count at any given clinical assessment. It is derived from the lesion counts count obtained as part of the HS Clinical Parameters (see Section 8.2). It can be used to determine whether a participant is experiencing an HS disease flare, defined as at least 25% increase in AN count (with a minimum increase of 2) relative to Baseline.

8.2.1.5 Hurley Stage

The Hurley Stage is a severity classification for HS that was developed in 1989 and is widely used for the determination of the severity of HS. The Hurley Stage is defined by the following criteria:

- Stage I: Abscess formation (single or multiple) without sinus tracts and cicatrization.
- Stage II: Recurrent abscesses with tract formation and cicatrization; single or multiple, widely separated lesions.
- Stage III: Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area (34).

The Investigator will determine the Hurley Stage in each affected anatomical region at the designated study visits according to the SoA (see Section 1.3). Appendix 11 (Section 10.11.1) provides a representative example of the HS Clinical Parameters that will be used in this study in which the Hurley Stage is also included.

8.2.1.6 Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA)

The HS-PGA is a validated 6-point scale that is used to measure improvement in inflammatory nodules, abscesses, and draining fistulas (35). The HS-PGA scale is defined by the following:

- Clear: 0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and 0 non-inflammatory nodules.
- Minimal: 0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and presence of non-inflammatory 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 fistulas, and ≥5 inflammatory nodules OR 1 abscess or draining fistula and ≥1 inflammatory nodule 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.

The HS-PGA will be assessed at the prespecified times when the HS Clinical Parameters are scheduled to be assessed, at the designated study visits according to the SoA (see Section 1.3). The score will be calculated using data recorded for HS Clinical Parameters in the eCRF (see Section 8.2.1.1).

8.2.1.7 [redacted]

[redacted]s

[redacted]

8.2.2 Patient Reported Outcome Measures

8.2.2.1 [redacted]

[redacted]

8.2.2.2 Analgesic Diary

Participants will be asked to complete an analgesic diary of their daily analgesic use. They will provide the name or type of medication taken, whether the medication was taken for HS-related pain, the dose and unit of each pill (eg, 325 mg), and the number of pills taken (eg, 2 pills).

8.2.2.3 [redacted]

[redacted]

8.2.2.4 [redacted]

[redacted]

[redacted]

8.2.2.5 [redacted]

[redacted]

8.3 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.4.

Planned timepoints for all safety assessments are provided in the SoA (see Section 1.3).

8.3.1 Physical examinations

- Physical examination will include examination of skin, nasal cavities, eyes, ears, respiratory, cardiovascular, respiratory, gastrointestinal, neurological, lymphatic, and musculoskeletal systems. Height will be measured and recorded at the Screening Visit. Weight will also be measured and recorded at the screening, Baseline, Week 16, and EOS Visit.
- A brief symptom-directed physical examination should be performed at other visits if, in the opinion of the Investigator, it is warranted by the participant's AE status or on review of symptoms and will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital signs

- Oral/forehead/temporal artery temperature, heart rate, respiratory rate, and blood pressure will be recorded (before blood collection for laboratory tests).
- Blood pressure and pulse measurements will be assessed in a semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

8.3.3 Electrocardiograms

- Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.3 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

8.3.4 Clinical safety laboratory tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents. See Appendix 3 (Section 10.3) for abnormal laboratory results reporting. All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 75 days after the last dose of study intervention should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant 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.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.3.5 Pregnancy testing

Refer to Section 5.1 for pregnancy testing criteria; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Pregnancy testing (urine or serum as required by local regulations) should be conducted at study visits according to the SoA (Section 1.3) prior to IMP administration.
- Pregnancy testing (urine or serum as required by local regulations) must be conducted corresponding with the time frame for female participant contraception in Section 5.1 Inclusion Criteria.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6 Suicidal ideation and behavior risk monitoring

Participants with HS may occasionally develop suicidal ideation or behavior.

Participants being treated with SAR442970 should be monitored appropriately and observed closely for suicidal ideation and behavior (SIB) or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of SIB, should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study intervention.

When informed consent or assent has been given, families and caregivers of participants being treated with SAR442970 should be alerted about the need to monitor participants for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study Investigator.

Suicidal ideation and behavior/intervention emergent suicidal ideation and behavior will be monitored during the study using the C-SSRS according to the SoA (Section 1.3). The C-SSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior (39, 40). Participants respond to standardized clinical questions that are presented in a uniform fashion. The C-SSRS defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The C-SSRS takes approximately 3 to 10 minutes to complete and will be administered by the Investigator.

8.4 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.4.7.

The definitions of unsolicited and solicited adverse events can be found in Appendix 3 (Section 10.3).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) that meet the definition of an AE or SAE and remain responsible for following up all AEs OR AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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).

8.4.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious) will be collected from the signing of the ICF until the EOS Visit at the timepoints specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3).

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs and AEs of special interest (as defined in Section 8.4.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.4.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators. In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.
- Serious adverse events that are considered expected will be specified in the reference safety information (ie, the IB).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) 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, SUSAR or any 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. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.4.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 5 months after the last dose of IMP.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate, and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former participant/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.4.6 Cardiovascular and death events

Cardiovascular and death events should be reported to the Sponsor and/or health authority per reporting rules for AEs or SAEs if seriousness criteria met.

8.4.7 Adverse events of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified, or removed during a study by protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP.
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP must be discontinued.

  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Section 8.4.5).
- Symptomatic overdose (serious or nonserious) with IMP (see definition of an overdose in Section 6.8).
- Increase in ALT: If increase in ALT >3 × ULN, see the "Increase in ALT" flow chart in Appendix 6 (Section 10.6).
- Other project specific AESI(s)
  - Any severe or opportunistic viral, bacterial, fungal, or helminthic infection whose nature or course may suggest an immunocompromised status and/or any uncommon, unanticipated, or persistent infection (viral, parasitic, bacterial, or fungal; for example, but not limited to tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystis, aspergillosis).
  - Diagnosis of a malignancy during the study.
  - Systemic or localized allergic reactions that require immediate treatment (in the event that a participant has a systemic allergic reaction that requires immediate treatment, blood samples should be withdrawn as soon as feasible [not to interfere with treatment of the reaction] for the analysis of ADA, serum tryptase, C1q, C1 inhibitor, C3 and C4, and repeated at 4 hours and 24 hours).
  - Reactivation of hepatitis B.
  - Demyelinating disorders or progressive multifocal leukoencephalopathy.
  - Congestive heart failure.
  - Myocardial infarction.
  - Lupus-like reaction or systemic lupus erythematosus.

8.4.8 Overdose, medication errors, misuses, or abuses of medicinal product

All reports of overdose, medication error, misuse, or abuse in relation to the IMP with or without an AE must be recorded on the corresponding page(s) of the CRF and transmitted to the Sponsor's representative following standard processes. The Investigator will assess whether or not the overdose, medication error, misuse or abuse event has to be reported together with an AE or SAE.

An overdose definition is given in Section 6.8.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

An abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects, ie, intentional

non-therapeutic use of a medicinal product by a participant for a perceived reward or desired non-therapeutic effect including, but not limited to, “getting high” (euphoria).

This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not. Of note, if a medication error or misuse meets the protocol definition of an overdose, it will be recorded in the overdose page of the CRF.

8.4.9 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.5 PHARMACOKINETICS

- Blood samples will be collected for measurement of serum concentrations of SAR442970 as specified in the SoA (see Section 1.3).
- Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate document. The actual date and time of each sample will be recorded. Pharmacokinetic samples will be tested by the Sponsor or Sponsor's designee.
- Samples collected for analyses of SAR442970 serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Pharmacokinetic samples could be used for testing analytical method performance such as comparability and incurred sample reproducibility and for possible exploratory analysis of drug metabolites. The exploratory data will not be included in the study report but will be kept on file.

The pharmacokinetic parameters will be calculated using non-compartmental methods from serum SAR442970 concentrations obtained after SAR442970 administration. The full list to be reported in the Clinical Study Report (CSR) will be mentioned in the SAP.

Population PK approaches will be used for SAR442970.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6 PHARMACODYNAMICS

Blood samples will be collected for [redacted] specified in the SoA (see Section 1.3).

Samples collected for analyses of pharmacodynamic markers may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

8.7 [redacted]

[redacted]

8.8 BIOMARKERS

Blood samples will be collected to characterize the effect of SAR442970 on soluble blood biomarkers. Samples will be collected pre-dose according to the schedule described in the SoA (see Section 1.3) and as detailed in the laboratory manual provided separately to sites.

Exploratory analysis of soluble blood biomarkers will be performed for markers associated with HS and/or SAR442970 activity, including:

- Serum and/or plasma biomarkers which may include but not limited to, CRP, high-sensitivity C-reactive protein (hs-CRP), [redacted] ([redacted]), serum amyloid A (SAA), and ANC.
- Exploratory blood samples for additional and/or future biomarker and safety assessments.

The analysis may also seek to identify additional and/or novel soluble markers that are associated with a clinical response (or lack of clinical response) to SAR442970 and therefore identify potentially predictive and response associated protein biomarkers, and/or to examine correlations with clinical response and/or clinical features.

[redacted]

8.9 IMMUNOGENICITY ASSESSMENTS

Antibodies to SAR442970 will be evaluated in serum samples collected from all participants according to the SoA (see Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

Instructions for the collection and handling of these samples will be provided by the Sponsor in a separate document. These samples will be tested by the Sponsor or Sponsor's designee using a qualified assay method.

Samples for immunogenicity analyses and their derivatives may be stored for up to 25 years after LPLV for potential re-analyses.

A 3-tiered approach will be employed to assess the immunogenicity of SAR442970 when applicable: Samples will be screened and then confirmed for antibodies binding to SAR442970 and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of SAR442970.

All samples collected for detection of antibodies to study intervention may also be evaluated for SAR442970 serum concentration to enable interpretation of the antibody data.

8.10 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Medical resource utilization and health economics parameters are not evaluated in this study.

8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease and the development of new medicines. Reuse of coded data and biological samples (leftover and additional) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing, or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study drug to the Sponsor or which is co-developing the study drug with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.3) and, when applicable, further information on the future research has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

Data protection – Processing of coded clinical data

The study participant will be provided will all mandatory details of the data processing in Section 2 of the core ICF.

The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Use of leftover samples and additional samples for future research

Remaining leftover samples will be used only after the study ends, ie, end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given time-point (eg, at randomization visit) as defined in the study protocol.

The study participant will be provided with all mandatory details of the use of the human biological samples (leftover and additional) in Section 2 of the Core ICF.

Relating data will be stored for up to 25 years for regulatory purposes and future research. Biological samples for future use will be stored for up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

9 STATISTICAL CONSIDERATIONS

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined. The biologic and small molecule immunosuppressive-naïve, TNF-experienced, safety and PK populations will be defined separately for Periods A and B. The primary population of the efficacy endpoints will be the biologic and small molecule immunosuppressive-naïve population.

Table 9 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized	All participants from the screened population who have been allocated to a randomized intervention by IRT regardless of whether the intervention was received.
Biologic and small molecule immunosuppressive-naïve	All randomized participants in the biologic and small molecule immunosuppressive-naïve subgroup (please see Section 1.1 for definition of biologic and small molecule immunosuppressive-naïve subgroup) who have taken at least 1 dose of study intervention. Participants will be analyzed according to the intervention allocated by randomization. Randomized participants for whom it is unclear whether they took the study medication will be included.
TNF-experienced	All randomized participants in the TNF-experienced subgroup (please see Section 1.1 for definition of TNF-experienced subgroup) who have taken at least 1 dose of study intervention. Participants will be analyzed according to the intervention allocated by randomization. Randomized participants for whom it is unclear whether they took the study medication will be included.
Safety	All randomized participants who have taken at least one dose of study intervention, regardless of the amount of intervention administered. Participants will be analyzed according to the intervention they actually received.
PK	All participants from the safety population with at least one post-Baseline PK result. Participants will be analyzed according to the intervention they actually received.
ADA	All participants from the safety population treated with SAR442970 with at least one post-Baseline ADA result (positive, negative, or inconclusive). Participants will be analyzed according to the intervention they actually received.

Abbreviations: ADA=anti-drug antibody; ICF=informed consent form; IRT= interactive response technology; PK=pharmacokinetic(s); TNF=tumor necrosis factor.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant randomized more than once, only the data associated with the first randomization will be used in any analysis population (except if the first randomization is done by error). The safety experience associated with any later randomization will be reported separately.

9.2 STATISTICAL ANALYSES

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.2.1 General considerations

The Baseline value is defined as the last available value before the first dose of double-blind IMP. For participants randomized but not treated, the Baseline value is defined as the last available value before randomization.

Unless otherwise specified, analyses will be performed by intervention group, and overall for Baseline and demographics characteristics.

Interventions groups will be presented as follows:

- Period A (up to Week 16): SAR442970 and Placebo.
- Period B (from Week 16 to Week 28) and Period C (from Week 28 to Week 36): SAR442970/SAR442970 and Placebo/SAR442970.

The observation period will be divided into 4 segments:

- The **pretreatment** period is defined as the period up to first IMP administration.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration to the last IMP administration + 75 days. The TE period includes the following 2 periods:
  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP + 14 days.
  - The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the TE period.
- The **post-treatment period** is defined as the period from the end of the TE period.

9.2.2 Primary endpoint(s) analyses

9.2.2.1 Definition of endpoint(s)

The primary endpoint is the percentage of biologic and small molecule immunosuppressive-naïve participants achieving HiSCR50 (defined as ≥50% reduction from Baseline in the total abscess and inflammatory nodule [AN] count, with no increase from Baseline in abscess or draining tunnel count) at Week 16. All the efficacy assessments collected during the study will be used, including those obtained after IMP discontinuation or introduction of rescue therapy. Intercurrent events defined in Table 3 will be taken into account to determined endpoints status.

9.2.2.2 Main analytical approach

The primary endpoint will be analyzed with the primary estimand defined according to the following attributes:

- Endpoint: Percentage of participants achieving HiSCR50 at Week 16.
- Treatment condition: SAR442970 will be compared to placebo.
- Analysis population: Biologic and small molecule immunosuppressive-naïve population.
- Intercurrent events:
  - Starting or increase in dose of oral antibiotic therapy during the Treatment Period: Participant will be considered as non-responder (composite strategy).
  - Starting selected prohibited medications: Participant will be considered as non-responder. Details of selection will be specified in the SAP (composite strategy).
  - Starting other prohibited medications: Data collected after use will be used to determine the responder/non-responder status (treatment policy strategy).
  - Discontinuation of study intervention due to lack of efficacy: Participant will be considered as non-responder (composite strategy).
  - Discontinuation of study intervention (due to reasons other than lack of efficacy): All data collected after treatment discontinuation will be used to determine the responder/non-responder status (treatment policy strategy).
- Population-level summary: The primary efficacy analysis will be the comparison between SAR442970 and placebo in the percentage of participants achieving HiSCR50 at Week 16, using a Bayesian logistic regression model including treatment group and adjusted by randomization stratum (Hurley stage). The statistical analysis will be conducted following a Bayesian approach using an informative prior on the placebo response rate based on the historical studies available.

Missing data will be imputed to non-responders when HiSCR50 is missing.

Data will be presented graphically, where applicable, and with summary statistics by visit and by treatment regimen. Difference of response rate, and the 80% and 90% credibility intervals, will be provided.

9.2.2.3 Supplementary/Sensitivity analysis

Supplementary/sensitivity analyses to assess the robustness of the conclusion of the primary analysis might be performed. To assess the consistency of treatment effects across different subgroup levels, subgroup analyses will be performed for the primary efficacy endpoints, such as age, gender, etc. Further details will be specified in SAP.

9.2.3 Secondary endpoint(s) analyses

Responder main secondary endpoints in Period A will be analyzed using the Cochran-Mantel-Haenszel test including treatment group and adjusted by randomization stratum (Hurley stage).

For continuous main secondary endpoints in Period A, data will be analyzed by fitting an Analysis of Covariance (ANCOVA) model with the Baseline covariates and factors for treatment, Hurley stage. Data collected after start or increase in dose of oral antibiotic therapy; or use of selected prohibited concomitant medication, or treatment discontinuation due to lack of efficacy will be set to missing. For participants who early discontinue the treatment due to reasons other than lack of efficacy, all data collected after early treatment discontinuation will be included in the analysis.

Further details on missing data handling will be specified in SAP.

Other secondary endpoints analyses will be defined in Section 9.2.6.1 (AE, SAE), Section 9.2.6.2 (laboratory abnormalities), Section 9.2.7 (PK, immunogenicity).

9.2.4 Exploratory endpoint(s) analyses

Exploratory endpoints analysis will be descriptive. [redacted] Further details will be provided in SAP.

9.2.5 Multiplicity adjustment

No multiplicity adjustment will be applied in this study.

9.2.6 Safety analyses

The summary of safety results will be presented by treatment group. All safety analyses (includes reported TEAEs and other safety parameters as clinical laboratory evaluations, vital signs, and 12-lead ECG results) will be performed on the safety population.

Safety parameters will be analyzed according to following analysis periods:

- Period A (up to Week 16).
- Period B and C.

9.2.6.1 Adverse events

General common rules for adverse events

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened, or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened, or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened, or became serious during the post-treatment period.

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

Analysis of all adverse events

Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment-emergent AESI (defined with a PT or a prespecified grouping), all treatment-emergent SAEs and all TEAEs leading to permanent treatment discontinuation. AEs will be summarized separately for Period A, B, and C.

The AE summaries will be generated with number (%) of participants experiencing at least one event.

Deaths will also be analyzed.

9.2.6.2 Laboratory variables, vital signs, and electrocardiograms (ECGs)

Quantitative analyses

When relevant, for laboratory variables, vital signs and ECG variables, descriptive statistics for results and changes from Baseline will be provided for each planned visit during the on-treatment period. These analyses will be performed using central measurements only for laboratory variables.

Analyses according to PCSA

PCSA analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements, either scheduled, nonscheduled or repeated.

For laboratory variables, vital signs and ECG variables, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the Baseline level and according to the following Baseline status categories:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the Baseline level and according to the following Baseline status categories:

- Normal/missing.
- Abnormal.

9.2.6.3 Product complaints

Product complaints will be summarized in the safety population.

9.2.7 Other analyses

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

9.3 INTERIM ANALYSES

An interim analysis may be performed when 50% to 80% of the participants have completed Period A. The purpose of the interim analysis would be to provide early information which will be used by the Sponsor to plan for future development. The results of the interim analysis will not impact the conduct of the study, and, in the case of an interim analysis, the study team will remain blinded to the data. Measures will be taken to maintain the integrity of the study. If performed, the details including timing of the interim analysis will be provided in the SAP.

9.4 TIMING OF STATISTICAL ANALYSES

A primary database lock and an early analysis will be performed when the last participant (biologic and small molecule immunosuppressive-naïve and TNF-experienced) completes 16 weeks treatment duration (ie, complete study primary endpoint assessment). The analysis of the primary endpoint performed during the early analysis will be the final analysis of the primary endpoint.

Final analysis will be performed when all participants will have reached EOS Visit.

The SAP will describe the planned early analysis in greater detail.

9.5 SAMPLE SIZE DETERMINATION

Data from historical studies which have similar target population and study design will be used as prior information supplementing the placebo arm, using a Bayesian approach. A prior distribution of the percentage of participants that achieved HiSCR50 at Week 16 of the placebo arm was determined based on the data observed in the historical studies (41).

For the biologic and small molecule immunosuppressive-naïve population, an informative prior distribution for the placebo group HiSCR50 rate has been chosen as a beta distribution with parameter ([redacted]). This prior distribution contributes an approximate effective sample size of [redacted] participants for the placebo treatment group. Sample size calculations were performed to ensure reasonable accuracy for the estimation of the response rate. [redacted]

[redacted] Table 10 (42).

Table 10 - Accuracy of the 80% credible interval in the biologic and small molecule immunosuppressive-naïve population

SAR442970 incidence rate (n)	Placebo rate (n)	Lower limit	Upper limit	Half-width
[redacted]				

A sample size of 66 participants randomized in a [redacted] ratio to SAR442970 versus placebo will provide a half-width for the 80% credible interval of less than 0.145 which is deemed sufficient.

For TNF-experienced population, an informative prior distribution for the placebo group HiSCR50 rate has been chosen as a beta distribution with parameter ([redacted]). This prior distribution contributes an approximate effective sample size of 2 participants for the placebo treatment group. Sample size calculations were performed to ensure reasonable accuracy for the estimation of the response rate. [redacted]

Table 11 - Accuracy of the 80% credible interval in the TNF-experienced population

SAR442970 incidence rate (n)	Placebo rate (n)	Lower limit	Upper limit	Half-width
[redacted]				

A sample size of 18 participants randomized in a [redacted] ratio to SAR442970 versus placebo will provide a half-width for the 80% credible interval of less than [redacted] which is deemed sufficient.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

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 the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
  - Applicable ICH Good Clinical Practice (GCP) guidelines:
    - The Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use, as applicable.
    - The General Data Protection Regulation (GDPR) and any other applicable data protection laws.
    - Any other applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, 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 participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - 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), ICH guidelines, the IRB/IEC, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being

performed). The following should be considered when determining the return of an incidental finding:

- The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
- The finding reveals a substantial risk of a serious health condition or has concerned reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

As applicable, according to requirements of the Regulation No536/2014 of the European Parliament and the Council of the European Union, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as “substantial” (ie*,* changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EEA countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The Sponsor shall ensure that all parties involved in the conduct of the clinical trial promptly report any events that might meet the definition of a serious breach.

Therefore, Investigators shall within 48h after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal Investigator must have a process in place to ensure that the site staff or service providers engaged by the principal Investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The ICF will be provided to the study participant in paper version. When feasible, an eConsent process may be used at global level and/or locally if permitted by country regulations.
- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants or their LAR, and answer all questions regarding the study, including what happens to the participants when their participation ends (strategy for the study).
- Potential participants must be informed that their participation is voluntary. They or their LAR will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the GDPR and of the French law, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be reconsented to the most current version of the ICF(s). Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not reconsent or be informed of the amendment (eg, if the processing of personal data are modified, if the Sponsor changes, etc.).
- A copy of the ICF(s) must be provided to the participant or their LAR, where applicable.
- Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that address the use for future research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking checkboxes in CSICF Part 3, each checkbox corresponding to a specific use: consent for the performance of an optional exploratory research; consent for storage and use of coded data for future research; consent for use of leftover samples and associated coded data for future research; consent for collection of additional biological samples for storage and use for future research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including trial participants, Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant personal data

Data collected must be adequate, relevant, and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they are required by regulatory agencies, except in country where it is not allowed per local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- Participants must be informed that their 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.
- The contract between Sponsor, Investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the Investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, Sponsor's personnel, study participants or their relatives, healthcare professionals, etc.), the approximate number of subjects concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or Investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or Investigator will record all information

relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.

- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of personal data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative, and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred toward entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers toward our partners and service providers.
  - Sanofi's Binding Corporate Rules for intragroup transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.

- Personal data of professionals will be retained by Sanofi for up to thirty (30) years unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry) Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by e-mail, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

10.1.5.1 Independent Data Monitoring Committee

- An external Independent Data Monitoring Committee (IDMC) with members independent from the Sponsor and the Investigators will be implemented to make appropriate recommendations on the conduct of the clinical trial to ensure the protection and the safety of the enrolled participants on the study. The IDMC reviews and analyses, on a regular basis, blinded safety and, if requested by the IDMC, efficacy data throughout the study (and unblinded if deemed necessary by the IDMC).
- The primary responsibility of the IDMC will be to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress and make recommendations concerning the continuation, modification, or termination of the trial due to safety. IDMC membership will include clinicians and biostatisticians with collective experience in management of participants with HS, general internal medicine, pharmacovigilance, conduct of clinical trials, and biostatistics. Details regarding membership, scope, and logistics (including meeting intervals) of the IDMC are addressed in the IDMC charter.

10.1.6 Dissemination of clinical study data and results

Study participants

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use “coded” data of all the study participants to independently verify the study’s results.

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These

websites include ClinicalTrials.gov, euclinicaltrials.eu, and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual anonymized participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF 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.
- Guidance on completion of CRFs will be provided in CRF completion guidelines.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (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 separate study documents.
- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. 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.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or 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.
- Definition of what constitutes source data can be found in study manuals and monitoring guidelines.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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 all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. 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 study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio.
  - Discontinuation of further study intervention development.
- For site termination:
  - 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 or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
  - Total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multi-center studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 12 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 the protocol.

  Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 12 - Protocol-required laboratory tests

Laboratory tests	Parameters
Hematology	Platelet count Red blood cell (RBC) count RBC indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Hemoglobin Hematocrit
Clinical chemistry[a]	Blood urea nitrogen (BUN) Potassium Creatinine Fasting glucose Sodium Calcium Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT) Alkaline phosphatase[b] Total and direct bilirubin Total protein Albumin Creatine phosphokinase
Fasting lipid panel	Fasting total cholesterol Fasting triglycerides Fasting high-density lipoprotein cholesterol Fasting low-density lipoprotein cholesterol Fasting very low-density lipoprotein cholesterol
Routine urinalysis	Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal)
Pregnancy testing	Serum or highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)
Other screening tests	Follicle-stimulating hormone and estradiol (as needed in women of non-child bearing potential only) Serology covering hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), total hepatitis B surface antibody (anti-HBc), IgM anti-HBc, hepatitis C virus antibody (HCV Ab), and human immunodeficiency virus (HIV) screen (anti-HIV-1 and HIV-2 antibodies). In case of results showing HBsAg negative and anti-HBc positive, hepatitis B virus DNA testing will be performed prior to randomization to rule out a false positive and to clarify serological status. In case of results showing hepatitis C virus antibody positive, HCV RNA testing will be performed to rule out a false positive. COVID-19 molecular test (if COVID-19 testing is required per local guidelines to be determined for each site) QuantiFERON® -Tuberculosis (TB) Gold blood test All study-required laboratory tests will be performed by a central laboratory, with the exception of urine pregnancy testing.

NOTES:

a Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 Liver Chemistry Stopping Criteria and Appendix 6 (Section 10.6) (Liver and other safety. Suggested actions and follow-up assessments).

b If alkaline phosphatase is elevated, consider fractionating.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: 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 clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant/participant's LAR(s) who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a health care provider). The participants/ participant's LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/participant's LAR(s) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/participant's LAR(s) will be collected during an interview with the participant/participant's LAR(s) and by review of available medical records at the next visit.
- Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned, and which are noted by the participants in their diary.

Events <u>meeting</u> 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, or more severe than expected for the participant's condition), eg:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or

  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention 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 intervention or a concomitant medication.
- Signs, symptoms, or the clinical sequelae of any medication errors, misuse, and abuse with the IMP.
- 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 fulfil the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfil the definition of an AE or SAE. Lack of efficacy or failure of expected pharmacological action also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any 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 participant'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 participant'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

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a) **Results in death**

b) **Is life-threatening**

The term *life-threatening* in the definition of *serious* refers to an event in which the participant 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.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (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.

d) Results in persistent or significant 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.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator 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 participant 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.
- The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm.
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc).
    - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
  - Development of drug dependence or drug abuse.
  - ALT >3 × ULN + total bilirubin >2 × ULN or asymptomatic ALT increase >10 × ULN.
  - Suicide attempt or any event suggestive of suicidality.

- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Bullous cutaneous eruptions.
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

10.3.3 Recording and follow-up of AE and/or SAE

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.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- 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 make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. 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's representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor's representative**.
- 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's representative 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 participant dies during participation in the study or during a recognized Follow-up Period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken

offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.

- Contacts for SAE reporting can be found in the Investigator Site File.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in the Investigator Site File.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range should be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- 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.

Permanent sterilization methods include:

- 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, gonadal dysgenesis), Investigator discretion should be applied to determining study entry eligibility.

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

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

Women in the following categories are considered WONCBP:

1. Any female with permanent infertility due to one 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, gonadal dysgenesis), Investigator discretion should be applied to determining study entry.
2. Postmenopausal female

   A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
   - A high FSH level in the postmenopausal range should be used to confirm a postmenopausal state in women not using hormonal contraception or HRT.
   - Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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

10.4.2 Contraception guidance

- Participants should be given advice about donation and cryopreservation of germ cells prior to the start of the study intervention, in line with the fact that study intervention may affect ova up to 5 months and sperm up to 5 months (see inclusion criteria).
- If locally required, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)

  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

  Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - 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 intervention. 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 participant.

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

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c Male condoms must be used in addition to hormonal contraception

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 from friction).

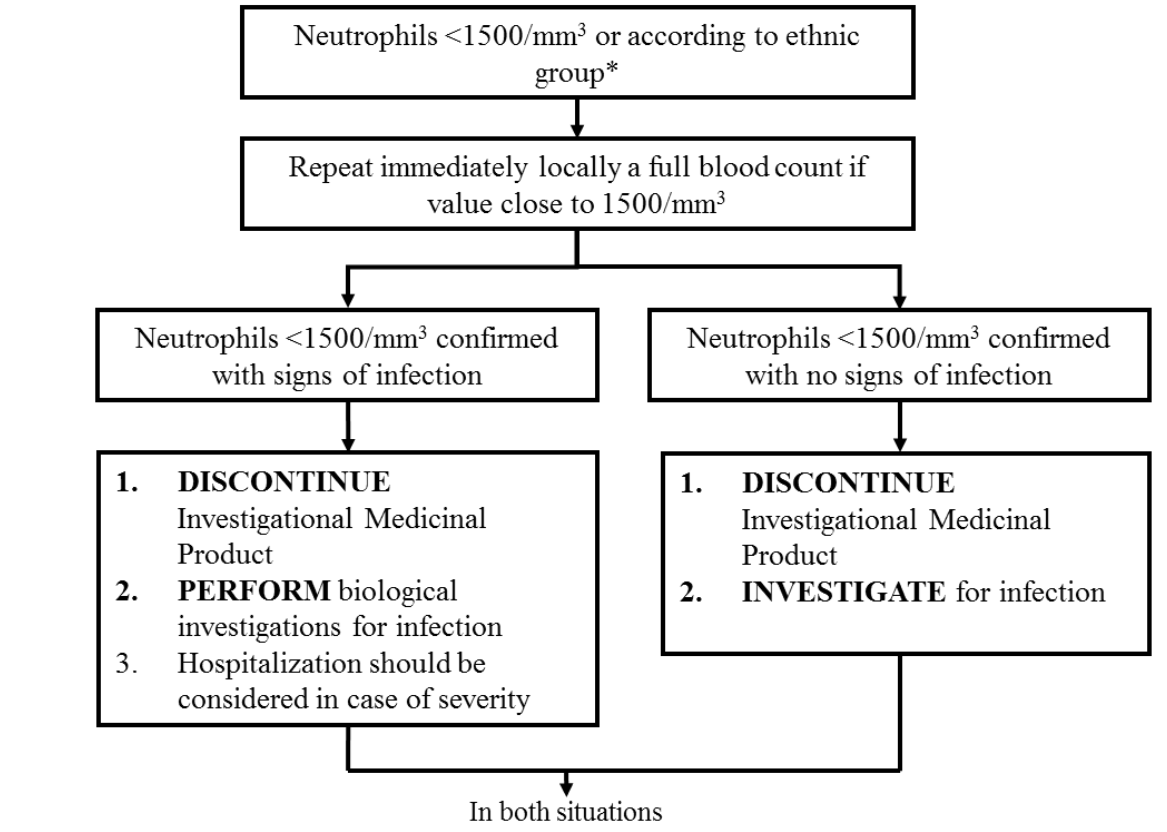
10.5 APPENDIX 5: [redacted]

[redacted]

[redacted]

10.6 APPENDIX 6: LIVER AND OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

NEUTROPENIA



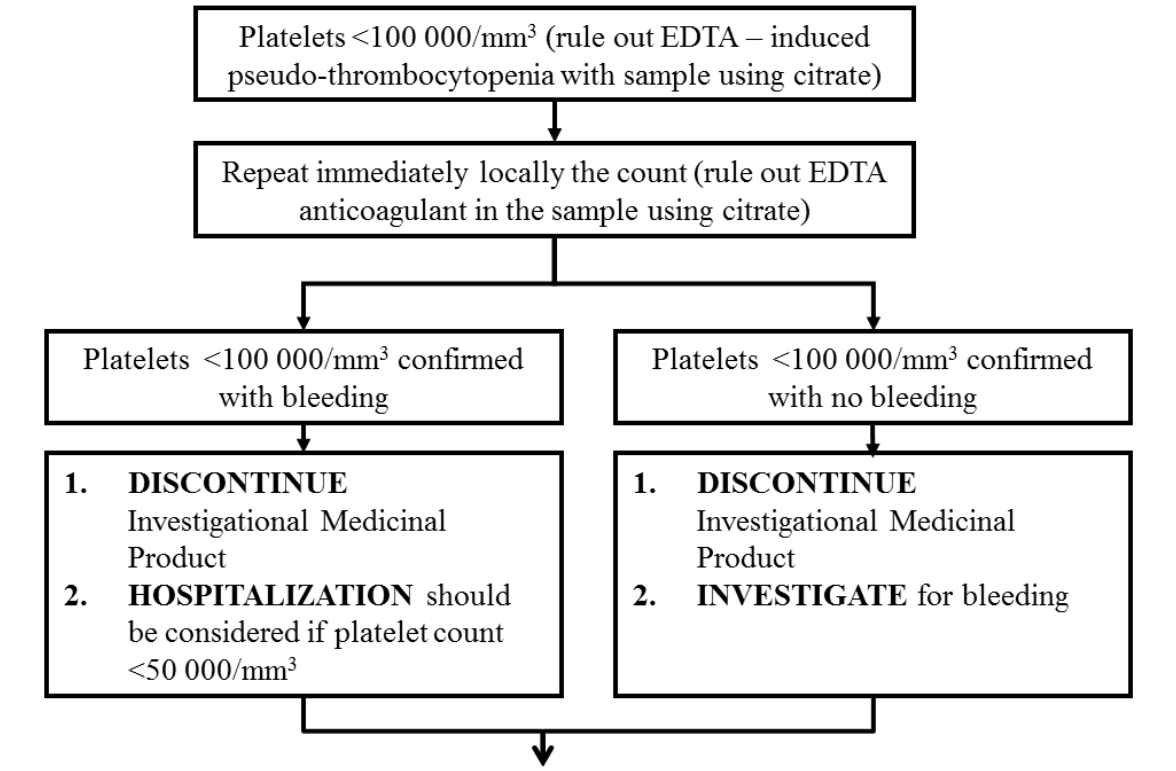
3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
   - Infectious serologies to be performed locally, according to clinical symptoms / medical history
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)**
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

***** For individuals of African descent, the relevant value of concern is <1000/mm³

PK=pharmacokinetic(s); RBC=red blood cell.

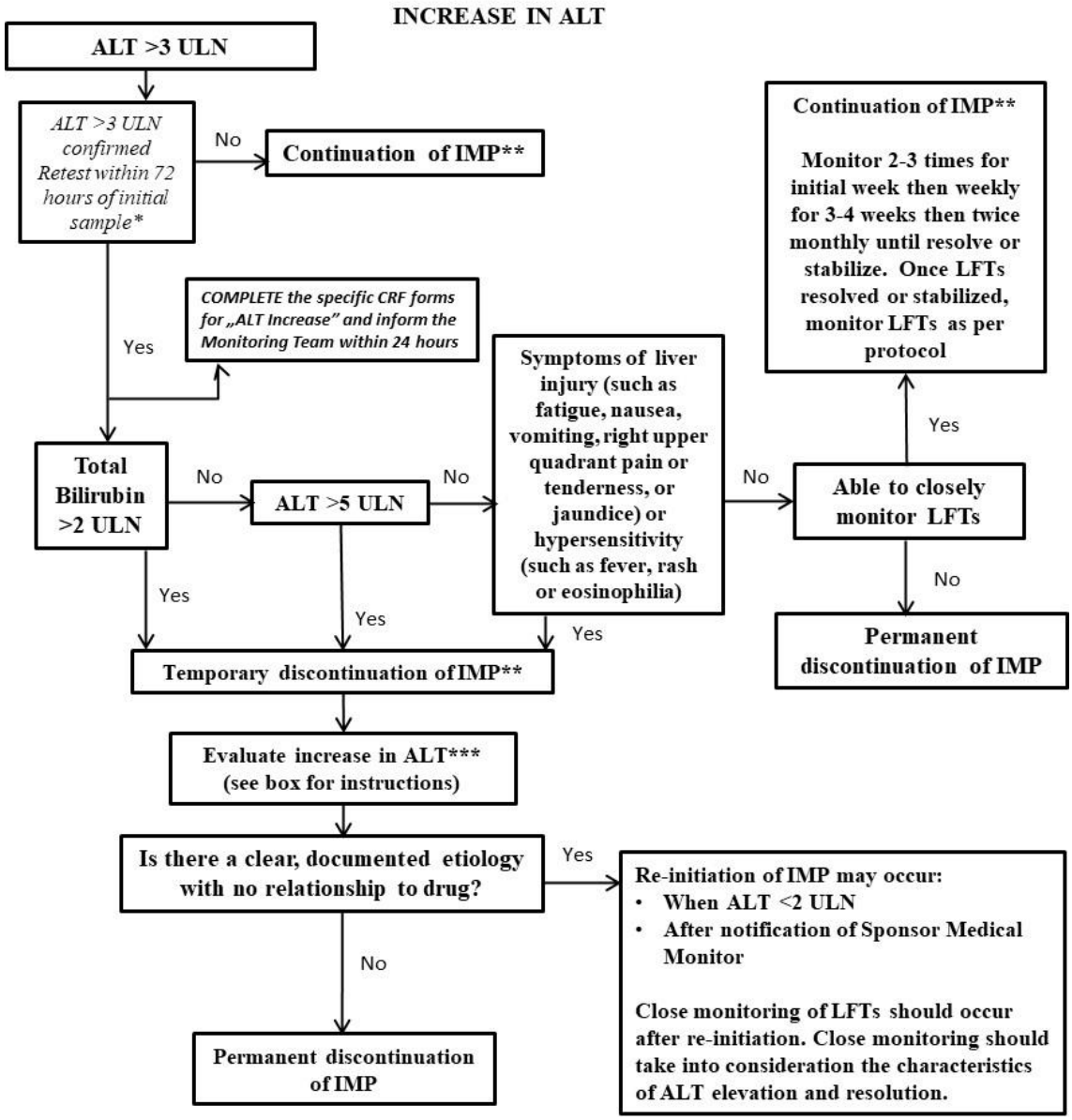
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.

THROMBOCYTOPENIA



aPTT=activated partial thromboplastin time; EDTA= Ethylenediaminetetraacetic acid; INR=international normalized ratio; PK=pharmacokinetic(s); PT=prothrombin time

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.



ALT=alanine aminotransferase; CRF=case report form; IMP=investigational medicinal product; LFTs=liver function tests; ULN=upper limit of normal

* If unable to retest in 72 hours, use original laboratory results to decide on further reporting/monitoring/discontinuation.

** Unless a protocol-defined criterion for permanent discontinuation is met

*** See box below

Note:

- "Baseline" refers to ALT sampled at Baseline Visit; or if Baseline value unavailable, to the latest ALT sampled before the Baseline Visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 10.3 for guidance on safety reporting.

Evaluate Increase in ALT***

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
3. **INVESTIGATE** if any recent alcohol use or travel
4. **INVESTIGATE** if any use of non-prescription medications including herbal or dietary supplements
5. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, GGT, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM, (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
4. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
5. **CONSIDER** iron, ferritin and transferrin
6. **CONSIDER** biomarkers for alcohol use (eg, urine ethyl glucuronide (EtG)]
7. **CONSIDER** consulting with hepatologist
8. **CONSIDER** patient hospitalization if INR>2 (or PT<50%) and/or central nervous system disturbances suggesting hepatic encephalopathy
9. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to ≤ULN, baseline value (if baseline >ULN) or clinical resolution.
10. **FREEZE** serum sample (5ml x 2)
11. **In case of suspicion of GILBERT Syndrome**, a DNA diagnostic test should be done

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CMV= cytomegalovirus; CPK=creatine phosphokinase; DNA=deoxyribonucleic acid; EBV=Epstein–Barr virus; HAV=hepatitis A virus; HBc=hepatitis B core; HBV=hepatitis B virus; HCV=hepatitis C virus; HEV=hepatitis E virus; IgM= Immunoglobulin G; LFTs=liver function tests; LKM= liver-kidney microsomal; GGT=gamma-glutamyl transferase; INR=international normalized ratio; IMP=investigational medicinal product; PT=prothrombin time; RNA=ribonucleic acid; ULN=upper limit of normal.

* If unable to retest in 72 hours, use original laboratory results to decide on further reporting/monitoring/discontinuation.

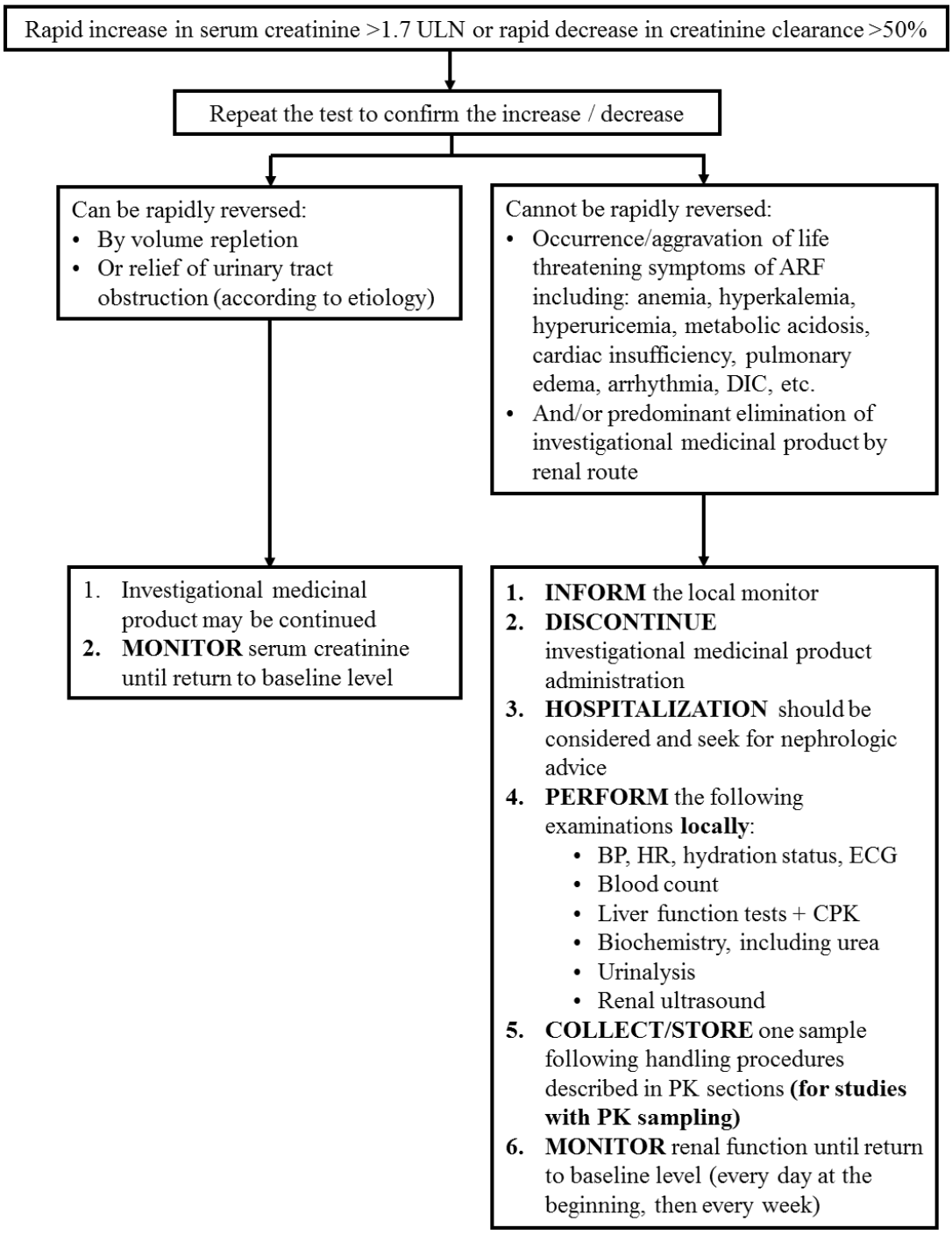
** Unless a protocol-defined criterion for permanent discontinuation is met.

*** See box below

Note:

- "Baseline" refers to ALT sampled at Baseline Visit; or if Baseline value unavailable, to the latest ALT sampled before the Baseline Visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 10.3 for guidance on safety reporting.

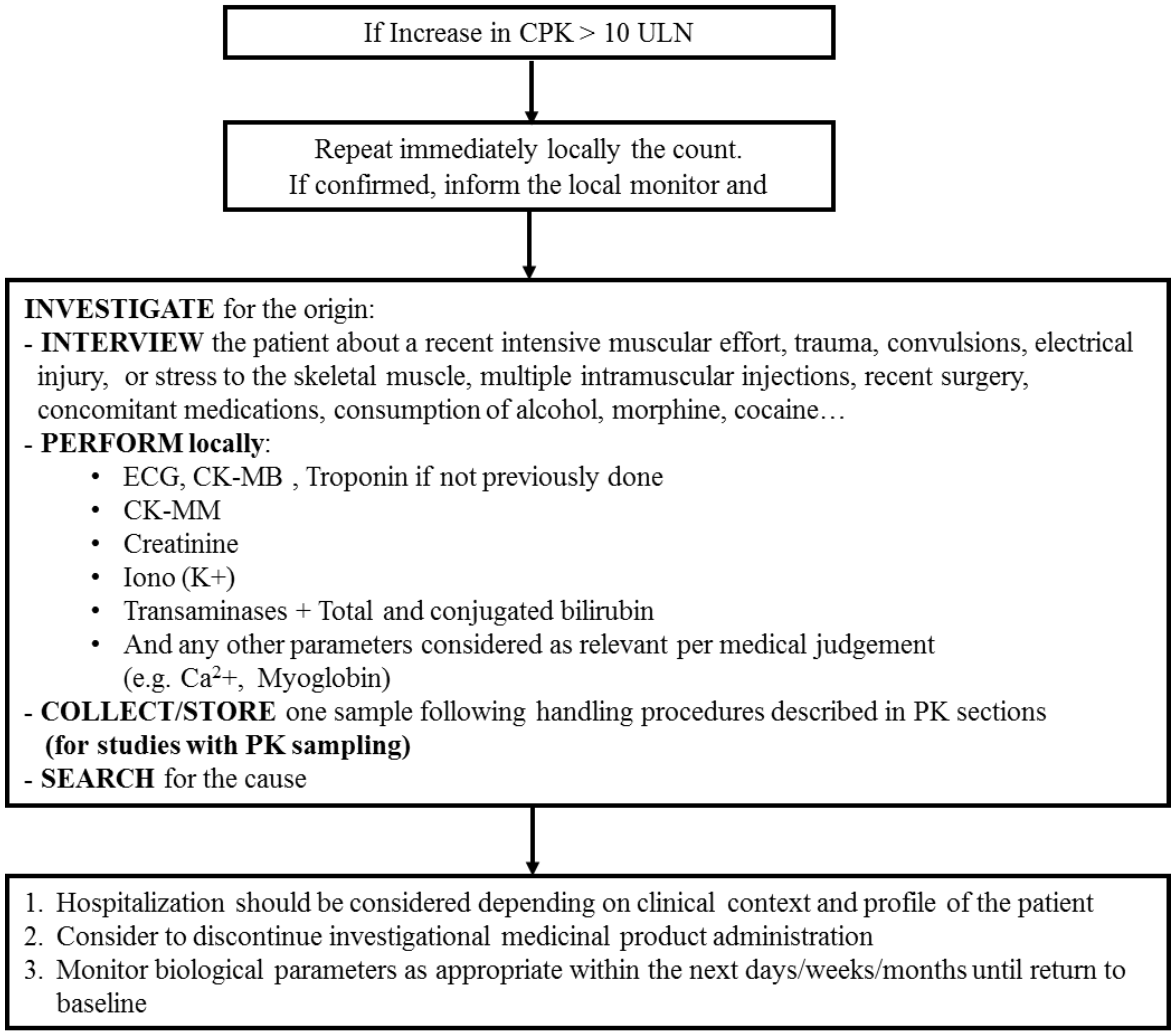
INCREASE IN SERUM CREATININE in patients with normal baseline (creatininemia between 45 µmol/L and 84 µmol/L)



ARF=acute renal failure; BP=blood pressure; CPK=creatine phosphokinase; DIC=disseminated intravascular coagulation; ECG=electrocardiogram; HR=heart rate; PK=pharmacokinetic(s); ULN=upper limit of normal.

Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Section 10.3 is met.

INCREASE IN CPK OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



CK-MB=creatine kinase, heart; CK-MM=creatine kinase, muscle; ECG=electrocardiogram; PK=pharmacokinetic(s); ULN=upper limit of normal.

Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting adverse events in events in Section 10.3 is met.

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
    a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure *to known allergen for that patient* (minutes to several hours):
    a. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure

List of opportunistic infections
Aspergillosis
Blastomyces dermatitidis (endemic in the south-eastern and south-central states US, along the Mississippi and Ohio Rivers)
Candidiasis - only systemic, extensive mucosal or cutaneous candidiasis.
Coccidioides immitis (endemic south-western US and Central and South America)
Cryptococcus
Cytomegalovirus
Herpes simplex (severe/disseminated)
Herpes zoster
Histoplasmosis (pulmonary or disseminated; most common tropical areas
Tennessee-Ohio-Mississippi river basins)
Listeriosis
Mycobacterium avium
Nontuberculous mycobacteria
Pneumocystis pneumonia (PCP)
Tuberculosis (TB)
*This list is indicative and not exhaustive

10.7 APPENDIX 7: MEDICAL DEVICES AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS

10.8.1 European Union

[redacted]

[redacted]

10.8.1.1 Germany

Informed consent process: All references to "legally authorized representative" are not applicable in Germany; only participants who can give written consent themselves are included in the study. References to "legally authorized representative" are found in Section 5.1, Section 8.4, Section 10.1.3, and Section 10.3.1.

[redacted]

10.8.1.2 Denmark

Participants in Denmark will not have home nursing.

10.8.1.3 France

[redacted]

10.8.1.4 Poland

[redacted]

10.8.1.5 Spain

[redacted]

10.8.2 United States (US)

At the Week 20 visit, all participants in the US will be assessed for response defined as ≥50% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count. Participants who meet the definition of response will continue in the open-label period to receive SAR442970 150 mg Q2W up to the Week 26 visit. Thereafter, responders will move to Period C which will commence with an end of treatment visit (approximately 2 weeks after the last IMP administration) and after 8 weeks conclude with an EOS Visit. Participants who do not meet the definition of response at the Week 20 visit will immediately begin Period C. The Week 20 visit will be the EOT visit for non-responders (SAR442970 will not be administered at this visit), and the EOS visit will be scheduled approximately 8 weeks after the EOT visit.

All participants in the US who complete the Week 4, Week 8, Week 12, Week 20, and Week 24 visit will have a complete physical examination at these visits. All participants in the US who complete the Week 4, Week 12, Week 20, and Week 24 visit will have laboratory testing at these visits. For details, please refer to Section 1.3.2.

10.8.3 Australia

Participants in Australia may receive tramadol (at a dose of up to 100 mg PO every 4 hours, not to exceed 400 mg/24 hours) as a rescue therapy after Baseline for HS-related pain that is refractory to treatment with ibuprofen or acetaminophen per Investigator discretion.

Participants in Australia are permitted two lesion interventions during Period A. An intervention can occur on maximally two different lesions at the same visit or on the same lesion at two different study visits. The same lesion cannot be treated two times at the same visit. Please refer to Section 6.9.2.

10.8.4 Chile

For participants in Chile, intralesional betamethasone (at a maximum dose of up to 1.5 mg, diluted in sterile normal saline per Investigator discretion) may be substituted for intralesional triamcinolone.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with GCP in Conduct of Clinical Trials Guidance.

The following contingencies may be implemented for the duration of the emergency (after Sponsor agreement is obtained). Contingencies implemented due to emergency will be documented.

Informed consent

In exceptional circumstances, such as a regional or national emergency declared by a governmental agency, consent may be collected through a remote solution if allowed through country and site regulations and following approval by the IEC/IRB. Implementation must have prior approval from the Sponsor (or its designee). Contingency procedures may be implemented for the duration of the emergency.

The participant or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg, study visit delays/treatment extension).

Study drug administration

During the initial part of the study (up to and including Week 8), study drug must be administered in accordance with Section 6. At all other times, consideration may be given to administration of study drug at home if all conditions in the Pharmacy manual are adhered to and prior Sponsor agreement is obtained.

Temporary IMP discontinuation may apply in exceptional cases, under regional or national emergencies (eg, natural disaster, epidemic diseases, terrorist attack) due to which a visit at the clinical study site is no longer feasible.

In the case of an exceptional temporary treatment discontinuation, the discontinuation should be approved by the Sponsor. The Sponsor should also be notified to determine if treatment should be resumed. If deemed safe, the treatment can be resumed at the next scheduled or unscheduled visit. During the discontinuation period, remote checks (eg, telephone/video calls) will take the place of on-site visits per the Schedule of Assessments (Section 1.3).

Study assessments and procedures

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by a government-declared regional or national emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Use of local clinic or laboratory locations may be allowed when central laboratory tests analyses cannot be performed due to a government-declared regional or national emergency. These local laboratory results will only be performed to ensure participant safety and will not be used for the purpose of statistical analyses.

If on-site visits are not possible the implementation of remote visits (eg, phone call, virtual consultation, televisit, etc.) or home visits (eg, home nurses, etc) may be planned for the collection of possible safety and/or efficacy data.

A Televisit is defined as a videoconference, video call or telephone call.

The following conditions must be met at a site level before such visits can be authorised.

- The visit must be performed by appropriately delegated study site staff or a home healthcare service.
- The correct equipment necessary to perform the required assessments must be taken to the visits.
- Home visits or televisits must be permitted by the site, local regulations, relevant ethics committee, relevant regulatory authority.
- The participant must have given consent via informed consent.
- Prior to implementing remote study visits for participants, notification to the Sponsor (or its designee) must be provided. The notification should include justification and expected participants and visits that may be impacted.

Visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely. Possibility of visit extension and duration of such extension must be discussed on a case-by-case basis with the Sponsor considering first of all participants' safety and best interests.

If the above emergency scenario occurs during the Follow-up Period, one or more Follow-up Visits can be performed remotely (eg, via telephone calls or video calls), but at least one Follow-up Visit should be performed on site (EOS Visit), even if the visit window needs to be extended. Remote follow-up should be conducted according to local regulations and approved by the Sponsor.

If the above emergency scenario leads to site closure or complete regional or national lock down, the study may be suspended for the affected sites.

For European countries contingency measures are currently only applicable for the COVID-19 pandemic.

10.10 APPENDIX 10: COLLECTION, STORAGE AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES

10.10.1 Compliance with Member State applicable rules for the collection, storage, and future use of human biological samples (Article 7.1h)

This appendix is provided separately.

10.10.2 Compliance with Member State applicable rules for the collection, storage, and future use of (personal) data (article 7 (1 d) of EU Regulation 536/2014)

This appendix is provided separately.

10.11 APPENDIX 11: ADDITIONAL APPENDICES

10.11.1 [redacted]

10.11.2 Hurley Stage

Stage I	Abscess formation (single or multiple) without sinus tracts and cicatrization.
Stage II	Recurrent abscesses with tract formation and cicatrization; single or multiple, widely separated lesions.
Stage III	Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

10.11.3 Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA)

Clear	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and 0 non-inflammatory nodules.
Minimal	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and presence of non-inflammatory 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 fistulas, and ≥5 inflammatory nodules OR 1 abscess or draining fistula and ≥1 inflammatory nodule 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.

10.11.4 [redacted]

[redacted]

10.11.5 Participant Daily Analgesic Use Diary Example

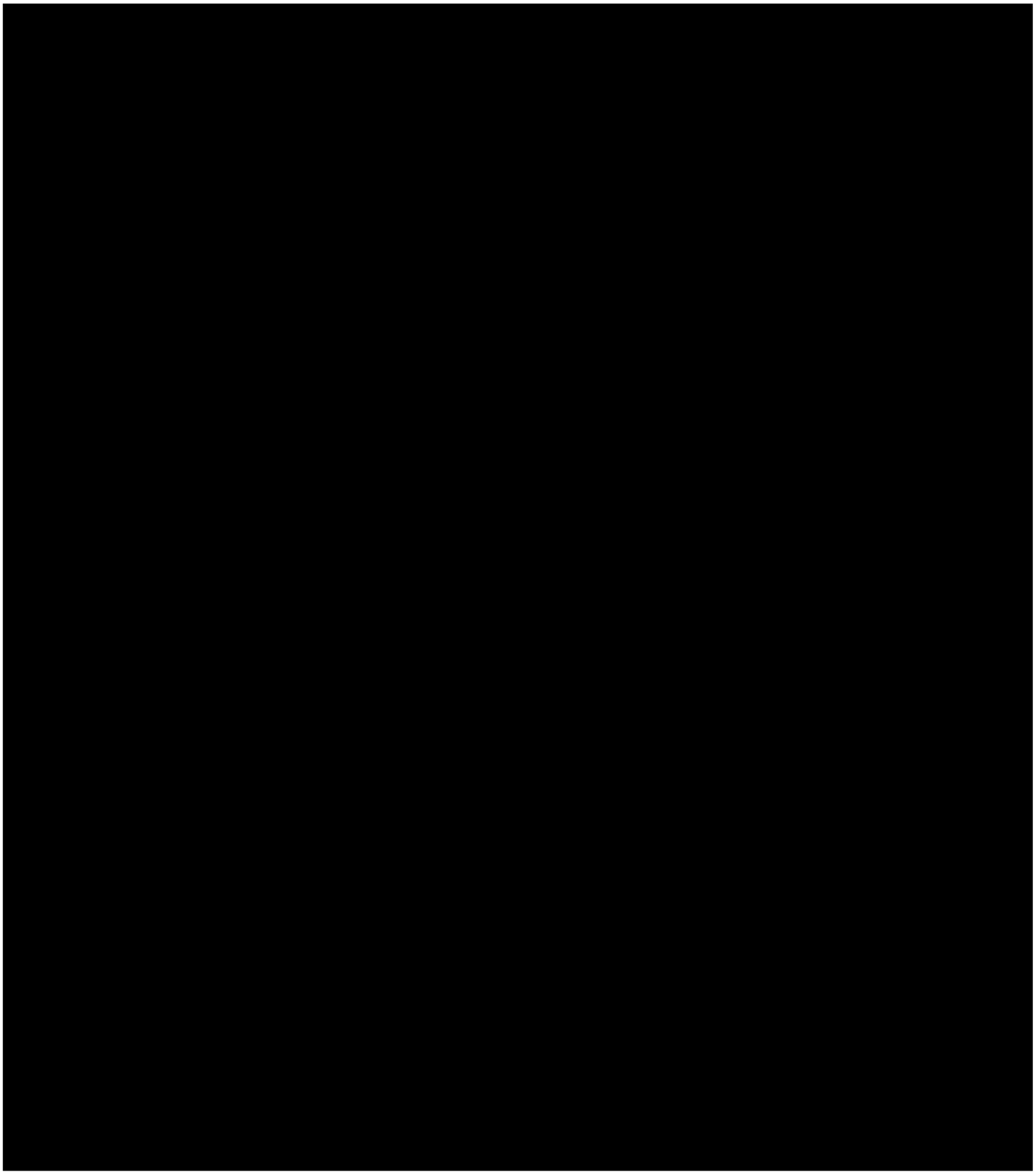
Participant Daily Analgesic Use Diary

Please answer the questions below each night before you go to bed. Provide your response for each day based on the past 24 hours of that day.

	Monday		Tuesday		Wednesday		Thursday		Friday		Saturday		Sunday	
	Did you take any **Pain** medication the past 24 hours?		Did you take any **Pain** medication the past 24 hours?		Did you take any **Pain** medication the past 24 hours?		Did you take any **Pain** medication the past 24 hours?		Did you take any **Pain** medication the past 24 hours?		Did you take any **Pain** medication the past 24 hours?		Did you take any **Pain** medication the past 24 hours?	
	☐ Yes*	☐ No	☐ Yes*	☐ No	☐ Yes*	☐ No	☐ Yes*	☐ No	☐ Yes*	☐ No	☐ Yes*	☐ No	☐ Yes*	☐ No
Pain Medication	*Total **dose** mg*	Was the pain medication **specifically for HS**?	*Total **dose** mg*	Was the pain medication **specifically for HS**?	*Total **dose** mg*	Was the pain medication **specifically for HS**?	*Total **dose** mg*	Was the pain medication **specifically for HS**?	*Total **dose** mg*	Was the pain medication **specifically for HS**?	*Total **dose** mg*	Was the pain medication **specifically for HS**?	*Total **dose** mg*	Was the pain medication **specifically for HS**?
Ibuprofen	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No
Acetaminophen / Paracetamol	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No
TBC Australia: Opoid	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No
Other Pain medication: _____	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No
Other Pain medication: _____	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No	_____ *mg*	☐ Yes ☐ No

** If Yes, fill in the chart the information about the **Pain** medication you took. If "Other" write in the name of Pain medication you took.*

10.11.6 [redacted]



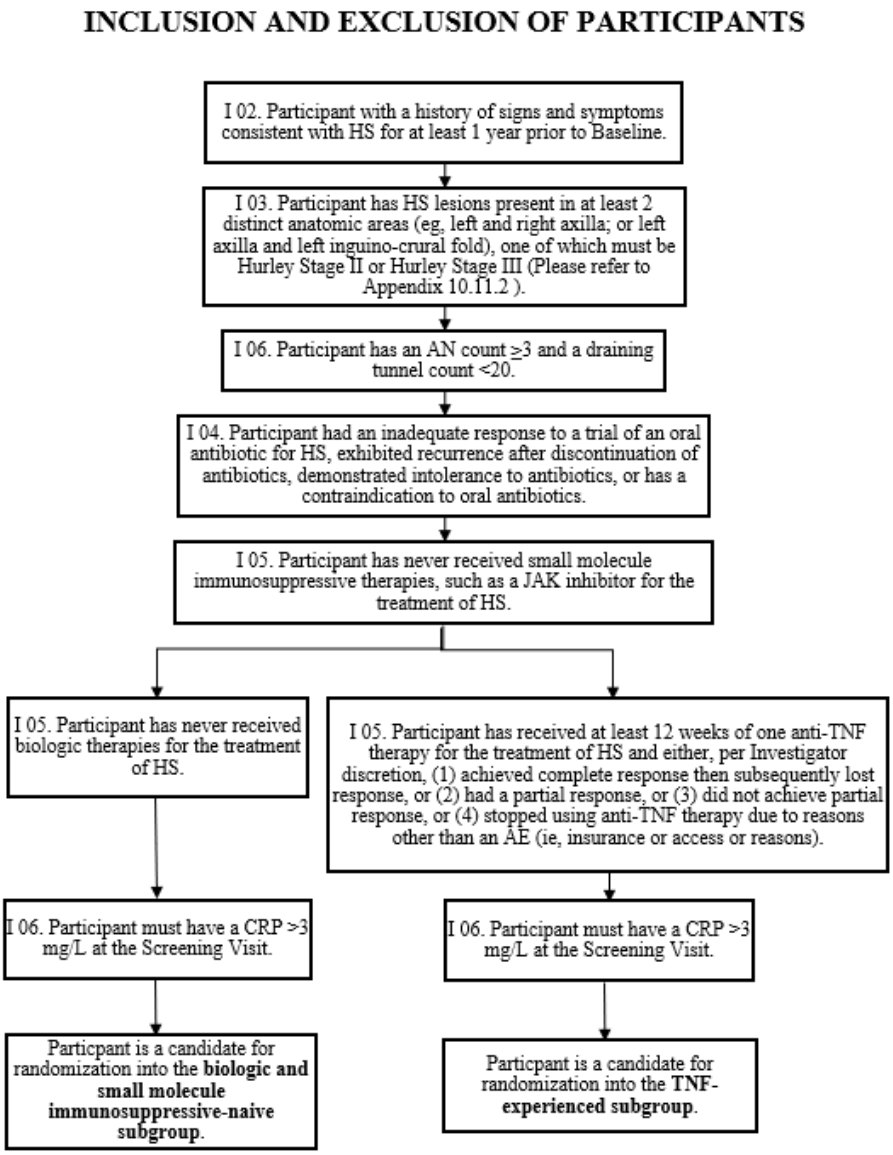
Please check you have answered EVERY question. Thank you.

10.11.7 [redacted]

[redacted]

10.11.8 [redacted]

10.11.9 Decision Tree for Inclusion and Exclusion of Participants



10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

10.12.1 Amended protocol 01 (26-May-2023)

This amended protocol (amendment 01) is considered to be non-substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The main rationale of the amendment pertaining to the United States (US) is to provide a plan for non-responders after the Week 16 assessment and to provide additional safety monitoring during double-blind placebo-controlled period and the open-label period recommended by the US Food and Drug Administration.

The main rationale of the amendment pertaining to Australia is to provide participants additional treatment options for HS-related pain after the Baseline visit recommended by the Australian Ethics Committee.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Updated paragraph #2 and #3 in "Overall design synopsis" section, "Brief summary" section, and "Study interventions and duration" section to provide description of updated study design for US participants for responders versus non-responders at Week 20.	To incorporate plan for excluding non-responders after the Week 20 assessment for participants in the US.
1.2 Schema	Provided schema for participants in the US.	To incorporate plan for excluding non-responders after the Week 20 assessment for participants in the US.
1.3.1 Flowchart for All Participants (Except for Participants in the United States)	Added line for visit label and deleted visit number for end of treatment and end of study visit.	To match formatting to schedule of activities for participants in the US.
1.3.2 Flowchart for Participants in the United States	Created a new flowchart for participants in the US.	To incorporate plan for excluding non-responders after the Week 20 assessment and to incorporate additional safety monitoring during the double-blind, placebo-controlled period, and open-label period for participants in the US.

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design	Updated paragraph #2 and #12 to provide description of updated study design for US participants for responders versus non-responders at Week 20.	To incorporate plan for excluding non-responders after the Week 20 assessment for participants in the US.
4.2 Scientific Rationale for Study Design	Updated paragraph #3 to provide description of updated study design for US participants for responders versus non-responders at Week 20.	To incorporate plan for excluding non-responders after the Week 20 assessment for participants in the US.
6.9.1 Prohibited Medications	Provided exceptions for participants in Australia for HS-related pain. Updated sub-list under major bullet #4 and Table 8 - Analgesic therapy.	To provide participants in Australia additional treatment options for HS-related pain after the Baseline visit.
6.9.2 Concomitant Medications	Provided rescue treatment options for HS-related pain for participants in Australia in paragraph #2 in “Analgesic Therapy for HS-Related Pain and Non-HS-Related Pain” sub-section and paragraph #5 in “Lesion Intervention” sub-section.	To provide participants in Australia additional treatment options for HS-related pain after the Baseline visit.
10.8.2 United States (US)	Described change in study design to incorporate plan for non-responders after Week 20 assessment for response and increased safety monitoring during the double-blind, placebo-controlled period and open-label period.	To incorporate plan for excluding non-responders after the Week 20 assessment and to incorporate additional safety monitoring during the double-blind, placebo-controlled period, and open-label period for participants in the US.
10.8.3 Australia	Provided rescue treatment options for HS-related pain for participants in Australia.	To provide participants in Australia additional treatment options for HS-related pain after the Baseline visit.
10.12 Appendix 12: Protocol Amendment History	Section updated to state that the Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.	Aligned with Sanofi procedures.

Abbreviations: HS: hidradenitis suppurativa

10.12.2 Amended protocol 02 (18-Jul-2023)

This amended protocol (amendment 02) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The main rationale of the amendment is a result of the European Union (EU) consideration to incorporate the recommendation to have an external Data Monitoring Committee, describe how

ACT16852 separates from standard treatment for HS, rename the biologic-naïve subgroup to the biologic and small molecule immunosuppressive-naïve subgroup throughout the Protocol, incorporate recommendations for increased safety monitoring, clarify the objective of [redacted] and to specify that participants from the EU will be excluded from genetic testing.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Changed label of biologic-naïve subgroup to biologic and small molecule immunosuppressive-naïve subgroup.	To incorporate recommendation to rename subgroup.
1.1 Synopsis	Changed Independent Data Monitoring Committee from internal to external.	To incorporate recommendation to have an external Independent Data Monitoring Committee as per Guideline EMEA/CHMP/EWP/5872/03 Corr; July 27, 2005.
1.3.1 Flowchart for All Participants (Except for Participants in the United States)	Added that participants in Denmark will not have home nursing to footnote c.	To clarify that Denmark will not have home nursing.
1.3.1 Flowchart for All Participants (Except for Participants in the United States)	Added recommendation regarding vaccination prior to study drug administration to footnotes *l*, *m*, and *q*.	To incorporate recommendation to carry out vaccination prior to study drug administration.
1.3.1 Flowchart for All Participants (Except for Participants in the United States)	For footnote *l*, added additional criteria for safety monitoring if participants that are serologically positive but have undetectable levels of viruses present are randomized.	To incorporate recommendation for additional safety monitoring related to hepatitis B and C.
[redacted]	[redacted]	[redacted]
1.3.2 Flowchart for Participants in the United States	Added recommendation regarding vaccination prior to study drug administration to footnotes *m*, *n*, and *r*.	To incorporate recommendation to carry out vaccination prior to study drug administration.
1.3.2 Flowchart for Participants in the United States	For footnote *m*, added additional criteria for safety monitoring if participants that are serologically positive but have undetectable levels of viruses present are randomized.	To incorporate recommendation for additional safety monitoring related to hepatitis B and C.
[redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
2.1.1 Established Treatment in HS	Added description of how ACT16852 separates from standard treatment for HS.	To incorporate recommendation for how ACT16852 separates from standard treatment.
4.1 Overall Design	Changed label of biologic-naïve subgroup to biologic and small molecule immunosuppressive-naïve subgroup.	To incorporate recommendation to rename subgroup.
4.2 Scientific Rationale for Study Design	Added the below sentence: The 2:1 randomization ratio is chosen to minimize the number of participants in the placebo group considering the significant impact of HS on health and quality of life.	To clarify the rationale of the 2:1 randomization ratio.
4.2 Scientific Rationale for Study Design	Changed label of biologic-naïve subgroup to biologic and small molecule immunosuppressive-naïve subgroup.	To incorporate recommendation to rename subgroup.
5.1 Inclusion Criteria	Added reference to Section 10.11.9 Decision Tree for Inclusion and Exclusion of Participants in the Type of participant and disease characteristics sub-section.	To incorporate recommendation to create standard operating procedure for inclusion and exclusion criteria.
5.2 Exclusion Criteria	Removed exception for localized carcinoma in situ of the cervix for Exclusion Criterion #8.	To incorporate recommendation for exclusion of participants with risk of reactivation of latent human papillomavirus infection from study.
5.2 Exclusion Criteria	Changed Exclusion Criterion #11 to additional exclusion criteria for hepatitis B or C positivity and additional criteria for safety monitoring if participants that are serologically positive but have undetectable levels of viruses present are randomized.	To incorporate recommendation for additional safety monitoring related to hepatitis B and C.
5.2 Exclusion Criteria	Changed label of biologic-naïve subgroup to biologic and small molecule immunosuppressive-naïve subgroup.	To incorporate recommendation to rename subgroup.
5.2 Exclusion Criteria	Added recommendation regarding vaccination prior to study drug administration to Exclusion Criterion #24.	To incorporate recommendation to carry out vaccination prior to study drug administration.
5.2 Exclusion Criteria	Added reference to Section 10.11.9 Decision Tree for Inclusion and Exclusion of Participants in the Prior/concomitant therapy sub-section.	To incorporate recommendation to create standard operating procedure for inclusion and exclusion criteria.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	For Exclusion Criterion #27, added "or latent" to first bullet point. Changed second bullet point to only allow 1 indeterminate test result. Change second bullet point to delineate that participant must meet "all of the following criteria" listed under second bullet point. Removed second sub-paragraph under second bullet point saying that participants on 1 month of treatment for TB may participate in study. Add second sub-paragraph under second bullet point to say that participants that are QuantiFERON TB gold test positive or have 1 indeterminate test result must have written documentation of approval to participate in study.	To incorporate recommendation for exclusion of participants with risk of progression of active tuberculosis (TB) or reactivation of latent TB.
[redacted]	[redacted]	[redacted]
6.3 Assignment to Study Intervention	Changed label of biologic-naïve subgroup to biologic and small molecule immunosuppressive-naïve subgroup.	To incorporate recommendation to rename subgroup.
6.4 Blinding	Align with rest of Protocol regarding external Independent Data Monitoring Committee.	To incorporate recommendation to have an external Independent Data Monitoring Committee as per Guideline EMEA/CHMP/EWP/5872/03 Corr; July 27, 2005.
[redacted]	New section created under Clinical Reported Outcome Measures for description of [redacted] Description of [redacted] moved to this section and deleted from previous Section 8.2.2.6 under Patient Reported Outcome Measures. Added statement about intention to use [redacted] in an exploratory manner to objectively document improvement in primary endpoint.	To clarify objective of [redacted]
[redacted]	New section created under Clinical Reported Outcome Measures for [redacted] Description of [redacted] deleted from previous section in 8.2.2.6 under Patient Reported Outcome Measures and moved to newly created Section 8.2.1.1 under Clinical Reported Outcome Measures.	To clarify objective of [redacted]

Section # and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
9.1 Populations for Analyses	Changed label of biologic-naïve subgroup to biologic and small molecule immunosuppressive-naïve subgroup.	To incorporate recommendation to rename subgroup.
9.1 Populations for Analyses – Table 9 – Population for analyses	Changed label of biologic-naïve subgroup to biologic and small molecule immunosuppressive-naïve subgroup.	To incorporate recommendation to rename subgroup.
9.2.2.2 Main Analytical Approach	Changed label of biologic-naïve subgroup to biologic and small molecule immunosuppressive-naïve subgroup.	To incorporate recommendation to rename subgroup.
9.3 Interim Analyses	The below sentences are removed: An interim analysis may be performed before the final database lock for this study. The details will be provided in the SAP. The following paragraph is added: An interim analysis may be performed when 50% to 80% of the participants have completed Period A. The purpose of the interim analysis would be to provide early information which will be used by the Sponsor to plan for future development. The results of the interim analysis will not impact the conduct of the study, and, in the case of an interim analysis, the study team will remain blinded to the data. Measures will be taken to maintain the integrity of the study. If performed, the details including timing of the interim analysis will be provided in the SAP.	To clarify the timing and purpose of the optional interim analysis.
9.4 Timing of Statistical Analyses	Changed label of biologic-naïve subgroup to biologic and small molecule immunosuppressive-naïve subgroup.	To incorporate recommendation to rename subgroup.
9.5 Sample Size Determination	Changed label of biologic-naïve subgroup to biologic and small molecule immunosuppressive-naïve subgroup.	To incorporate recommendation to rename subgroup.

Section # and Name	Description of Change	Brief Rationale
10.1.5.1 Independent Data Monitoring Committee	Changed Independent Data Monitoring Committee from internal to external.	To incorporate recommendation to have an external Independent Data Monitoring Committee as per Guideline EMEA/CHMP/EWP/5872/03 Corr; July 27, 2005.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
10.8 Appendix 8: Country-Specific/Region requirements	Added a section for Denmark. Participants will not have home nursing.	To clarify that Denmark will not have home nursing.
[redacted]	[redacted]	[redacted]
10.8 Appendix 8: Country-Specific/Region Requirements	Moved section on informed consent to be sub-section under section for EU.	To align formatting.
10.11.9 Decision Tree for Inclusion and Exclusion of Participants	Added section with decision tree for inclusion and exclusion of participants.	To incorporate recommendation to create standard operating procedure for inclusion and exclusion criteria.

In addition, other minor editorial changes were implemented throughout the protocol.
Abbreviations: EU: European Union; HS: hidradenitis suppurativa; SAP: statistical analysis plan; TB: tuberculosis.

10.12.3 Amended protocol 03 (02-Oct-2023)

This amended protocol (amendment 03) is considered to be substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The main rationale for the amendment is to align safety monitoring globally, modify the study sample size, [redacted] globally specify that it is preferred that the same Investigator performs efficacy assessments throughout the study for each participant, implement operational changes related to collection of endpoints, and correct typographical errors that do not affect content.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Sample size changed from 114 to 84 [redacted]	Estimate of the primary endpoint in the primary analysis population changed from 90% credible interval to 80% credible interval which will provide half widths that are sufficiently narrow under the new sample size.
1.3 Schedule of Activities	Phrase “E-Diary” removed from multiple instances in Protocol and replaced with “diary” only.	Participants will complete certain secondary and exploratory assessments on a combination of electronic diary and paper diary formats or entirely on paper diary format.
1.3.1 Flowchart for All Participants (Except for Participants in the United States)	Visit label for end of study visit change to EOS instead of EOT.	To fix typographical error with no impact on content.
1.3.1 Flowchart for All Participants (Except for Participants in the United States)	Added physical examination at Week 4, 8, 12, 20, and 24. Added non-fasting laboratory testing at Week 4, 12, 20, and 24. Added urinalysis at Week 20.	To align safety monitoring globally.
1.3.1 Flowchart for All Participants (Except for Participants in the United States)	For footnote bb, added that HS Physician’s Global Assessment will be derived and that for each participant it is recommended that the HS Clinical Parameters is assessed by the same Investigator during the entire study if possible.	To reduce variability in assessment of primary endpoint and due to operational change to collection of endpoints.
1.3.2 Flowchart for Participants in the United States	For footnote cc, added that HS Physician’s Global Assessment will be derived and that for each participant it is recommended that the HS Clinical Parameters is assessed by the same Investigator during the entire study if possible.	To reduce variability in assessment of primary endpoint.
2.2.1.1.3 Pharmacokinetics and Nonclinical Safety	Remove the word “study” in the phrase “study studies” in the third paragraph.	To fix typographical error with no impact on content.
4.1 Overall Design	Sample size changed from 114 to 84 [redacted]	Estimate of the primary endpoint in the primary analysis population changed from 90% credible interval to 80% credible interval which will provide half widths that are sufficiently narrow under the new sample size.
4.2 Scientific Rationale for Study Design	Sample size changed from 114 to 84 [redacted]	Estimate of the primary endpoint in the primary analysis population changed from 90% credible interval to 80% credible interval which will provide half widths that are sufficiently narrow under the new sample size.

Section # and Name	Description of Change	Brief Rationale
4.3 Justification for dose	Changed oral to subcutaneous (SC) in the fifth paragraph.	To fix typographical error with no impact on content.
6.9.2 Concomitant Medications	Under section for Lesion Intervention added that intralesional betamethasone may substituted for intralesional triamcinolone in Chile.	Betamethasone is available and used locally in Chile rather than triamcinolone.
8.2.1.1 Hidradenitis Suppurativa Clinical Parameters (HS Clinical Parameters)	Removed parameters related to Modified Sartorius score as this will not be assessed. Removed parameter related to HS Physician's Global Assessment as this will be derived rather than assessed. Deleted sentence related to device as parameters will be assessed on paper.	Operational change to collection of endpoints.
8.2.1.5 Hurley Stage	Deleted sentence related to device as parameters will be assessed on paper.	Operational change to collection of endpoints.
8.2.1.6 Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA)	Removed parameter related to HS Physician's Global Assessment as this will be derived rather than assessed.	Operational change to collection of endpoints.
8.3.2 Vital signs	Section modified to state that blood pressure and pulse measurements will only be taken once in a semi-supine position instead of a seated and supine position.	Guidelines for the management of hypertension do not give preference to a particular patient position and consider positions interchangeable. No added benefit to measure blood pressure 3 times and take average.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
8.8 Biomarkers	Removed the phrase "In the EU."	To fix typographical error with no impact on content.
9.2.2 Primary endpoint(s) analyses 9.5 Sample Size Determination	80% and 90% credible intervals will be provided in addition to 90% credible interval for the primary endpoint. Sample size changed from 114 to 84 [redacted] Prior distributions of the primary endpoint in the placebo group updated. Tables 10 and 11 updated to show	Estimate of the primary endpoint in the primary analysis population changed from 90% credible interval to 80% credible interval which will provide half widths that are sufficiently narrow under the new sample size.

Section # and Name	Description of Change	Brief Rationale
	accuracy of the 80% credible interval under the new sample size.	
[redacted]	[redacted]	[redacted]
10.8.1.1 Germany	[redacted]	
10.8.1.3 France		
10.8.1.4 Poland		
10.8.1.5 Spain		
10.8.4 Chile	Described change that intralesional betamethasone may substituted for intralesional triamcinolone in Chile.	Betamethasone is available and used locally in Chile rather than triamcinolone.
10.11.1 Hidradenitis Suppurativa Clinical Parameters Example	Removed parameters related to Modified Sartorius score as this will not be assessed. Remove parameter related to HS Physician's Global Assessment as this will be derived rather than assessed.	Operational change to collection of endpoints.

In addition, other minor editorial changes were implemented throughout the protocol.
Abbreviations: EOS: end of study; EOT: end of treatment; EU: European Union; HS: hidradenitis suppurativa; RNA: ribonucleic acid; SC: subcutaneous.

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