Clinical Trial Protocol

	Document Number:	**c32824792-02**
EudraCT No. **EU Trial No.**	2020-003672-40	
BI Trial No.	1368-0052	
BI Investigational Medicinal Product(s)	Spesolimab (BI 655130)	
Title	Randomized, double-blind, placebo-controlled, study of spesolimab in patients with moderate to severe hidradenitis suppurativa	
Lay Title	A study to test whether spesolimab helps people with a skin disease called hidradenitis suppurativa	
Clinical Phase	IIa	
Clinical Trial Leader	[redacted] Phone: [redacted]	
Coordinating Investigator	[redacted]	
Version and Date	**Version:** Final version 2.0	**Date:** 05 JUL 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	28 Oct 2020
Revision date	05 Jul 2021
BI trial number	1368-0052
Title of trial	Randomized, double-blind, placebo-controlled, study of spesolimab in patients with moderate to severe hidradenitis suppurativa
Coordinating Investigator	[redacted]
Trial site(s)	Multi-centre trial conducted in approximately 16 countries
Clinical phase	IIa
Trial rationale	Hidradenitis suppurativa (HS) is an inflammatory disease characterised by recurrent, painful abscesses and fistulous tracts. HS and generalized pustular psoriasis (GPP) have similarity in neutrophil infiltration and pustules, with pustules in HS being subcutaneous. IL-36 alpha, beta and gamma mRNA expression are upregulated in lesional skin in HS patients. Based on the role of IL-36 driving TH17 and TH1 responses in GPP (published and our internal data) and from animal models of atopic dermatitis (AtD), the hypothesis is that IL-36 is also a key driver of Th17 responses in skin of HS patients. Study 1368-0052 is proof-of-clinical-concept study in HS designed to assess the efficacy and safety of Spesolimab in this patient population.
Trial objective(s)	The primary objective is to estimate the effect of spesolimab compared to placebo for the mean percent change from baseline in total abscess and inflammatory nodule count at Week 12.
Trial endpoints	The primary endpoint is the percent change from baseline in total abscess and inflammatory nodule count at Week 12. Secondary endpoints are defined as described below: -Percent change from baseline in draining fistula count at Week 12 -Achievement of Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12.

	-Absolute change from baseline in International Hidradenitis Suppurativa Severity Score System (IHS4) value at Week 12 -Absolute change from baseline in HASI score at Week 12 -Achievement of PGA score of 0 or 1 at Week 12 - Achievement of at least 30% reduction from baseline in Numerical rating scale (NRS30) in Patient's Global Assessment of HS Pain at Week 12 -Occurrence of complete elimination of draining fistulas at Week 12 -Occurrence of at least one flare (defined as at least 25 % increase in AN count with a minimum increase of 2 relative to baseline) up to Week 12. -Absolute change from baseline in DLQI Score at Week 12. -Absolute change from baseline in HiS-QoL Total Score at Week 12. The following safety endpoint is also defined: -The occurrence of Treatment Emergent Adverse Events (TEAEs)
Trial design	International, multi-center, placebo-controlled, double blind, randomized trial assessing the efficacy and safety of spesolimab versus placebo in patients with moderate to severe HS over 12 weeks
Total number of patients randomized	45
Number of patients on each treatment	30 active arm 15 placebo arm
Diagnosis	Hidradenitis suppurativa
Main in- and exclusion criteria	Inclusion Criteria: • Male or female adult patients, 18 years of age or older • Have moderate to severe HS for at least 1 year prior to the baseline visit, as determined by the investigator • Have HS lesions in at least 2 distinct anatomic area • Has a total abscess and inflammatory nodule (AN) count of greater than or equal to 5. • Biologic naïve or TNFi-failure for HS • Total draining fistula count of less than or equal to 20 Exclusion criteria: • Presence of active skin lesions other than HS that interferes with the assessment of HS.
Test product 1	Spesolimab
dose	1200mg weekly at Weeks 0, 1 and 2 for a total loading dose of 3600mg
mode of administration	intravenous (i.v.)
Test product 2	Spesolimab
dose	1200 mg every 2 weeks at Weeks 4, 6, 8 and 10
mode of administration	subcutaneous (s.c.)
Comparator product(s)	Placebo

dose	Matching
mode of administration	intravenous (i.v.) at weeks 0, 1 and 2 subcutaneous (s.c.) every 2 weeks at Weeks 4, 6, 8 and 10
Duration of treatment	12 weeks
Statistical methods	The primary objective of the trial is to demonstrate proof of clinical concept activity of spesolimab on the percent change from baseline in total abscess and inflammatory nodule count using a mixed effect model for repeated measurements (MMRM). No formal statistical testing is planned. For the proof of concept, the treatment effects of spesolimab compared to placebo will be estimated. Hereby, the adjusted difference in percentage change from baseline in total abscess and inflammatory nodule count between spesolimab and placebo will be evaluated. For primary analysis of the primary endpoint, all measurements will be included but those data collected after the use of rescue therapy for the purpose of disease worsening will be censored. The stratification factor, TNFi-naive population versus TNFi-failure population will be included into the model.

FLOWCHART

Trial Periods	Screening	Treatment Period							EoT	Safety Follow-Up	
Visit	**1**	**2** Baseline	**3**	**4**	**5**	**6**	**7**	**8**	**EoT[2]**	**FUP 1**	**EoS**
Day	-28 to -1	1[1]	8	15	29	43	57	71	85	56 days after last drug admin.	112 days after last drug admin.
Weeks	-4	0	1	2	4	6	8	10	12	8 weeks after last drug admin.	16 weeks after last drug admin.
Time window for visits (days)	n.a.	none	±1	±1	±3	±3	±3	±3	±3	±7	+7
Informed consent	X										
Review of in-/exclusion criteria	X	X									
Demographics	X										
Medical history	X										
Physical examination[3]	X^c	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t	X^t
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	X
Height	X										
Weight	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X								X		X
Pregnancy test[5]	X	X	X	X	X	X	X	X	X	X	X
Safety Laboratory tests[6]	X	X	X	X	X	X	X	X	X		X
Infection Testing[7]	X								X		
Hs-CRP	X								X		X
12-lead ECG	X	X			X		X		X		X
Randomization		X									
Administer trial drugs[8]		X	X	X	X	X	X	X			
PK Sampling[9]		X	X	X	X	X	X	X	X	X	X
ADA/Nab Sampling[9]		X		X	X		X		X	X	X
Blood sample (Serum soluble protein biomarkers)		X			X		X		X		
Whole blood RNA sequencing		X			X		X		X		
DNA banking (optional)[10]		X									
Skin Biopsy: Lesional		X			X				X		
Skin Biopsy: Non-lesional		X									
Ultrasound lesion evaluation[11]		X			X				X		

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Time window for visits (days)	n.a.	none	±1	±1	±3	±3	±3	±3	±3	±7	+7
Abscess count Inflammatory nodule count. Non-inflammatory nodule count Draining Fistula count.	X	X	X	X	X	X	X	X	X		
Photography		X			X				X		
Hidradenitis Suppurativa Clinical Response (HiSCR)			X	X	X	X	X	X	X		
International Hidradenitis Suppurativa Severity Score System (IHS4)	X	X	X	X	X	X	X	X	X		
Hidradenitis Suppurativa Area Severity Index (HASI)		X	X	X	X	X	X	X	X		
Hidradentis Suppurativa Physician's Global Assessment (HS-PGA)	X	X	X	X	X	X	X	X	X		
Dermatology Life Quality Index (DLQI)		X	X		X		X		X		
Hidradenitis Suppurativa Quality of Life (HiS-QoL)		X	X		X		X		X		
FACIT-Fatigue scale		X	X		X		X		X		
Patient Global Assessment of Change (PGI-C)			X		X		X		X		
Patient Global Assessment of Severity (PGI-S)		X	X		X		X		X		
Columbia-Suicide Severity rating Scale (C-SSRS)[12]	X	X	X	X	X	X	X	X	X	X	X

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Time window for visits (days)	n.a.	none	±1	±1	±3	±3	±3	±3	±3	±7	+7
Dispense Patient's Diary[13]	X	X	X	X	X	X	X	X			
Review returned Patient's Diary[14]		X	X	X	X	X	X	X	X		
All adverse events[15]	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X
Roll over into OLE trial[16]									X		
Completion of patient participation											X

1 Day of Randomization / Day of first intake of randomized medication. If needed, some visit 2 assessments may be conducted 2 days before or after the actual visit date after consultation with the Sponsor.
2 Patients who discontinue trial treatment prematurely-should undergo the End of Treatment (EoT) visit as soon as possible. All patients not entering the OLE trial are expected to complete the EoT visit, a FUP1 visit 8 weeks after their last trial drug intake and a final EoS visit 16 weeks after their last trial drug intake. For patients entering the OLE trial at week 12, the EoT visit will be their EoS visit in trial 1368-0052. (see also footnotes #8 and #16)
3 X^c is a complete physical examination. X^t is a targeted physical examination. See section 5.2.1.
4 Measurements of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements at all dosing visits. Additional assessments of vital signs should be performed at 10 minutes post-dose for s.c administrations and 5 minutes and 1 hour post dose for i.v. administrations.
5 Women of childbearing potential only. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed at all other visits indicated in the Flowchart. In case of a positive urine pregnancy test, a serum pregnancy test will be done. Urine pregnancy testing should be done prior to administration of study drug. Study drug should only be administered in case of a negative test result. More frequent testing should be done if required by the local regulation or per investigator judgment.
6 It is preferred but patients do not have to be fasted for the blood sampling for the safety laboratory. At visits with study drug administration this should be done prior to the study drug administration. See Table 5.2.3:2 for detailed information of the tests. If needed, safety lab samples for Visit 2 can be drawn within 48 hours before the actual visit date.
7 Infection Testing: At screening and at EoT visit. See section safety laboratory parameters for complete list of testing required (see Table 5.2.3:1).
8 Patients who terminate study drug early should do the EoT visit as soon as possible. These patients will then do FUP1 and EoS visits, 8 and 16 weeks after last study drug administration respectively.
9 At study visits with study drug administration, pre-dose PK/ADA/Nab samples will be obtained approximately within 1 hour prior to start of i.v. infusion or s.c. injection.
10 Desoxyribonucleid Acid (DNA) banking sample is optional. This sampling is only possible if the patient agreed by signing a separate informed consent. For details please see Section 5.5.
11 At selected sites, where ultrasound is available, it is required to do ultrasound lesion evaluation and to guide biopsies. At sites without ultrasound capabilities, biopsies will be done without ultrasound guidance.

12 At Screening, the C-SSRS baseline/screening scale will be completed. At all subsequent visits the "Since last visit" scale will be completed.
13 At visits 4, 5, 6, 7 and 8 two weekly diaries and a buffer of one additional week to capture surplus time window of visit will be dispensed to patients. Patient Diary to capture daily NRS score, analgesic use and other interventions to manage pain.
14 Patient's Diaries returned by patients must be reviewed while the patient is in the consultation, so that any information can be clarified in an interview with the patient, if needed.
15 Local tolerability at the administration site of spesolimab will be assessed by the investigator during the study drug administration visit and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction, e.g. "swelling", "induration", "heat", "redness" should be reported as adverse event.
16 All patients completing week 12 of the study may be offered to enter the open label extension study 1368-0067. These patients are not requested to complete follow up period and will have their End of study visit at EoT visit, co-inciding with the first visit in 1368-0067.

TABLE OF CONTENTS

ABBREVIATIONS

ADA	Anti-drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AMP	Auxiliary Medicinal Products
AN count	Abscess and Inflammatory Nodule count
APC	Antigen Presenting Cell
AST	Aspartate Aminotransferase
AtD	Atopic Dermatitis
AUC	Area under the Curve
b.i.d.	bis in die (twice daily dosing)
BI	Boehringer Ingelheim
CA	Competent Authority
CI	Confidence Interval
C_{max}	Maximum Concentration
C_{min}	Minimum Plasma Concentration
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CRS	Cytokine release syndrome (CRS)
CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DC	Dendritic Cells
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee

EC	Ethics Committee
ECG	Electrocardiogram
(e)COA	(electronic) Clinical Outcome Assessment
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoS	End of Study
EoT	End of Treatment
EudraCT	European Clinical Trials Database
FACIT	Functional Assessment of Chronic Illness Therapy
FC	Flowchart
FUP	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPP	Generalized Pustular Psoriasis
HA	Health Authority
HADS	Hospital Anxiety and Depression Scale
HASI	Hidradenitis Suppurativa Area and Severity Index
HiSCR	Hidradenitis Suppurativa Clinical Response
HiS-QoL	Hidradenitis Suppurativa Quality of Life
HIV	Human Immunodeficiency Virus
HS	Hidradenitis Suppurativa
hs-CRP	High-Sensitivity C-Reactive Protein
i.v.	intravenous
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IGRA	Interferon Gamma Release Assay
IHS4	International Hidradenitis Suppurativa Severity Score System
IL-36	Interleukin 36
IL-36R	Interleukin 36 Receptor
INN	International Non-Proprietary Name
IRB	Institutional Review Board

IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intention To Treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
i.v.	Intravenous
kg	Kilogram
KO	Knockout
LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Milligram
MMRM	Mixed effect Model for Repeated Measurements
MoA	Mechanism of Action
MRD	Multiple Rising Dose
Nab	Neutralizing Antibody
NRI	Non Response Imputation
NRS	Numerical Rating Scale
NRS30	Reduction of 30% in Numerical Rating Scale
OLE	Open Label Extension
OPU	Operative Unit
PD	Pharmacodynamics
PGA	Physician Global Assessment
PK	Pharmacokinetics
PPD	Purified Protein Derivative
PPP	Palmoplantar Pustulosis
q.d.	quaque die (once a day)
qw	Every week
q2wk	Once every 2 weeks
RA	Regulatory Authority
RCTC	Rheumatology Common Toxicity Criteria
REML	Restricted Maximum Likelihood
REP	Residual Effect Period

SAE	Serious Adverse Event
s.c.	subcutaneous
SC	Steering Committee
s.e.	Standard error
SoC	Standard of Care
SOC	System Organ Class
SOP	Standard Operating Procedure
SRD	Single Rising Dose
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Events
TH	T helper
$t_{1/2}$	Half Life Time
t_{max}	Timepoint of Maximum Plasma Concentration
TNF	Tumor Necrosis Factor
TNFi	TNF inhibitor
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TST	Tuberculin-Skin testing
ULN	Upper Level of Normal
vs.	versus
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Hidradenitis suppurativa (HS) is an inflammatory skin disease characterised by recurrent, painful abscesses and fistulous tracts. Patients with HS objectively have one of the lowest quality of life measures of any dermatologic disease. Lesions characteristically occur in the axillary, groin, infra-mammary, and/or anogenital regions of the body. HS lesions may progress to form sinus tracts and expansive abscesses. Sequelae include significant pain, scarring, and psychological distress. The average age of onset is during the early 20s [R20-3184]. The global prevalence of HS is reported between 0.0003% and 4.1%. Underdiagnosis or improper diagnosis is common. Overall, HS prevalence varies significantly based on population studied; however, the disease appears to be more common than was previously considered [R20-3176].
Treatment often begins with topical or oral antibiotics, such as topical clindamycin and oral tetracycline, followed by the use of other antibiotics if there is no improvement.
When topical medications and oral antibiotics fail, or the disease has progressed, biologics are recommended [R20-3177]. Adalimumab is the only approved biologic, with the response rate of 42%-59% versus placebo response of 26% – 28%, with a schedule of weekly subcutaneous dosing.
When the medical management is ineffective, surgery is the only option.
Some of the most burdensome HS symptoms from patient perspective are pain, drainage and explosive openings, itch, skin tightness (scarring), odour, fatigue and flu-like symptoms. Patients reported to be unsatisfied with the level of control offered by currently available treatment options and unmet needs from the patient perspective include the need for new medical treatments with favourable efficacy and tolerability profiles. In qualitative evidence, the most important treatment goals from the patient perspective were pain, drainage (including explosive openings) and fatigue.

1.2 DRUG PROFILE

1.2.1 Mode of action

Spesolimab is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signaling. Binding of spesolimab to IL36R is anticipated to prevent the subsequent activation of IL36R by cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways with the aim to reduce epithelial cell/ fibroblast/ immune cell-mediated inflammation and interrupt the inflammatory response that drives pathogenic cytokine production in inflammatory diseases including generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP) and inflammatory bowel disease (IBD).

Spesolimab binds to human IL36R with a binding avidity of less than 1 pM.
Spesolimab inhibits IL36 ligand-stimulated NF-kB activation in HT29 and transformed epithelial cells and in primary human dermal fibroblasts or intestinal myofibroblasts with IC90 values in a consistent range of 0.7 to 3.7 nM. Spesolimab also inhibits IL8 release in

primary human intestinal myofibroblasts and IFNγ secretion in human PBMC stimulated with IL36α, IL36β, or IL36γ combined with IL12.
Mutations of two key residues (L234 and L235) to alanine were made to spesolimab to abrogate FcR binding activity and function. Direct assessment of the impact of the mutations in the IgG1 FcR binding sites on both antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity CDC effector functions revealed that the mutations abrogate both ADCC and CDC effector functions and indicate that spesolimab will be a non-depleting therapy in vivo.

Spesolimab does not bind to IL-36R from common toxicology species.
Therefore, meaningful toxicity studies of the molecule cannot be performed in any animal species with spesolimab. However, hazard identification studies of the mode-of-action (MoA) of IL-36R inhibition were performed in mice using a mouse specific anti-IL-36R monoclonal antibody (BI 674304), which is a mouse IgG2a monoclonal antibody with rat variable regions. In a 13-week intravenous toxicity study of BI 674304 in mice, no adverse effects of IL-36R antagonism were seen at a dose (50 mg/kg, twice weekly) that was 5 fold higher than the dose that was protective in an experimental mouse colonic inflammation model. In the 26-week toxicity study, male and female mice (20-30/sex/group at 0, 10 and 50 mg/kg/day) were administered BI 674304 twice weekly for 26 weeks by intravenous injection via the caudal vein. There were no BI 674304-related changes in clinical observations, body weights, food consumption, ophthalmology, clinical pathology parameters (hematology, clinical chemistry), organ weights, macroscopic or microscopic examinations. The no-observed-adverse-effect level (NOAEL) was considered to be 50 mg/kg/day.
The in vitro cytokine release and tissue cross-reactivity assays demonstrate that the risk of transient cytokine release in humans is low and that, as expected, spesolimab stains epithelium in a variety of tissues. There were no signs of local irritation after single, 1 mL injections of the subcutaneous formulation in rabbits.
These preclinical toxicology data support chronic spesolimab dosing in humans.

Spesolimab or placebo (PBO) was administered to 78 healthy volunteers at single ascending i.v. doses from 0.001 mg/kg to 10 mg/kg body weight. Safety and tolerability of all tested i.v. doses was good. There were no drug-related SAEs. AEs categorized as related to treatment were observed in 3/19 (15.8%) subjects in the placebo group and in 7/59 (11.9%) subjects treated with spesolimab. The most frequent treatment-emergent AEs were nasopharyngitis (spesolimab: 21%; PBO: 15%), headache (spesolimab: 9%; PBO: 15%), influenza like illness (spesolimab: 7%; PBO: 10%), and diarrhea (spesolimab: 3%; PBO: 10%). There were two AEs of moderate intensity (injection site haematoma, headache), all remaining AEs were of mild intensity. There was no apparent relationship between the frequency of AEs and the dose.
There were no relevant changes compared to placebo for laboratory safety, including clinical chemistry, haematology, coagulation parameters, and urinalysis. No clinically relevant changes were observed in 12-lead ECGs, vital signs, and cardio-monitoring.
PK analysis showed that exposure (AUC0-tz and Cmax) to spesolimab increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg.

The effective half-life of spesolimab is approximately 4 weeks in the linear dose range. Overall, PK data so far suggests target-mediated drug disposition (TMDD) kinetics for

spesolimab. Anti-drug antibodies (ADA) were detected in 8 patients, 3 of those had pre-existing levels. Pharmacodynamic effects in this FIH Single Rising Dose trial [c03361085] were assessed by indirect target engagement (ITE) of IL36R by spesolimab using an ex-vivo whole blood stimulation assay. Preliminary analyses indicate that ≥94% peripheral IL36R receptor occupancy is achieved with doses ≥0.05mg/kg from 30 minutes post infusion to 10 weeks.
In a multiple rising dose trial, spesolimab or placebo have been administered to healthy volunteers at multiple ascending i.v. doses of 3, 6,10 and 20 mg/kg given qw for 4 weeks (i.e. 4 administrations) or a single dose of 20mg/kg (8 subjects each, 3:1 on active or PBO). Overall, spesolimab was well tolerated. There were no dose dependent AEs, AEs considered to be dose limiting and no SAEs. In all cases the AEs were of mild or moderate intensity. Furthermore, there were no clinically relevant abnormalities on treatment with spesolimab with respect to safety laboratory, vital signs, or ECGs as assessed by a central reader. For further details and most recent results refer to the current Investigator's Brochure (IB) [c03320877-09].

Studies in Patients
Efficacy data are available from a proof of concept study in patients with generalized pustular psoriasis (GPP). In trial 1368.11, seven patients received a single intravenous dose of 10 mg/kg spesolimab, and were monitored for 20 weeks. At week 1 after dosing, Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of clear or almost clear (0 or 1) was achieved in five patients, and by Week 4 in all seven patients. Within 48 hours post dose, pustules were completely cleared in three patients, by week 1 in five patients and by week 2 in six of seven patients. A major improvement in (GPPASI) was observed in all patients with a mean (SD) percent change from baseline of 73.2% (16.2) at week 2; by week 4, this was further reduced to 82.0% and was maintained to week 20 (83.6%).

Residual Effect Period
The Residual Effect Period (REP) of spesolimab is 16 weeks. This is the period after the last dose with measurable drug levels and pharmacodynamic effects still likely to be present.

Summary
Spesolimab is an anti IL36R antibody with a high clinical activity to block IL36R signaling, as demonstrated in patients with Generalized Pustular Psoriasis, a severe inflammatory skin disease driven by uncontrolled IL36 activity. Spesolimab has been tested in healthy volunteers with multiple dosing up to four weeks of 20 mg/kg i.v. q.w. which were all safe and well tolerated. In addition, IL36R inhibition shows a favourable nonclinical safety profile. Therefore, spesolimab might be a promising drug to treat patients suffering from hidradenitis suppurativa.
For further details and most recent results refer to the current IB [c03320877-09].

1.3 RATIONALE FOR PERFORMING THE TRIAL

Adalimumab (TNFi) is the only approved biologic for HS, with the response rate of 42%-59% versus placebo response of 26% – 28%, with a schedule of weekly subcutaneous dosing.

Long-term safety concerns are pertinent in the treatment of HS, where the dosing regimen of biologics is typically more intensive compared to other inflammatory diseases, such as psoriasis. Considering the above, a more efficacious and safer molecule with better dosing regimens is a substantial need in HS patients.
Spesolimab is an IL-36R antagonist currently in development for the treatment of GPP. HS and generalized pustular psoriasis (GPP) have similarity in neutrophil infiltration and pustules, with pustules in HS being subcutaneous. IL-36 alpha, beta and gamma mRNA expression are upregulated in lesional skin in HS patients with a decrease in IL-36RN expression [R20-3047]. Internal ISH staining of HS lesions also confirms the increased expression of ligands. IL-36 is thought to be a central upstream mediator of an inflammatory loop which further activates the keratinocytes, amplifying the secretion of chemokines that lead to infiltration of immune cells to the skin. Infiltrated DCs and monocytes can be activated by IL-36 (internal data and published) to potentiate the APC function of DCs and also lead to secretion of chemokines and cytokines that can recruit more immune cells including neutrophils. IL-36 is a potent activator of neutrophil infiltration and in the context of HS, neutrophils are shown to undergo netosis leading to secretion of AMPs and type I Interferons [R20-3155]. Based on the role of IL-36 driving TH17 and TH1 responses in GPP (published and our internal data) and from animal models of atopic dermatitis (AtD), the hypothesis is that IL-36 is also a key driver of TH17 responses in skin of HS patients.
Study 1368-0052 is proof-of-clinical-concept study in HS designed to assess the efficacy and safety of spesolimab in this patient population. The results from this trial will enable the design of the further development.

1.4 BENEFIT - RISK ASSESSMENT.

1.4.1 Benefits

Preclinical profiles of spesolimab and clinical data from healthy volunteer and patient trials suggest that spesolimab is safe, tolerable and may address an unmet medical need in patients with hidradenitis suppurativa by an anti-inflammatory mechanism of action. Efficacy in HS has not been established. The data from the completed proof of concept trial 1368.11, in patients with an acute flare of GPP, demonstrate that spesolimab treatment rapidly stops the flare and clears pustules, the primary lesions in GPP, a disease closely linked to loss-of function mutations in the natural IL-36R antagonist. (See: spesolimab IB, document number c03320877-09)

No relevant animal species is available for toxicology testing of the highly human specific antibody spesolimab. However, preclinical toxicology studies with a mouse surrogate antibody have demonstrated the safety of chronic IL-36R inhibition in mice (Spesolimab IB, document number c03320877-09, section 5.1.2). A recent publication has assessed the clinical phenotype and immune function in 12 healthy individuals harboring an IL-36R knock-out polymorphism. This study demonstrated the absence of any specific diseases or conditions, in particular of recurrent, severe or opportunistic infections or malignancies, in the medical records of these subjects. Also, serological and in-vitro studies indicated normal levels of non-, tetanus- or varicella-specific immune globulins, and normal immune functions as compared to matched controls, indicating that IL-36 blockade is likely to represent a safe and well tolerated therapeutic concept.

More than 140 healthy volunteers have been exposed in phase I SRD and MRD studies to single or multiple doses of spesolimab up to dose levels of 20mg/kg given once weekly for 4 weeks. Spesolimab was safe and well tolerated in three healthy volunteers' trials at all dose groups up to the highest tested dose of 20 mg/kg body weight given once a week for up to 4 weeks (for details see spesolimab IB, document number c03320877-09). Moreover, several clinical studies are ongoing as of May 2020, exploring efficacy and safety of spesolimab in different indications as: Atopic Dermatitis, Ulcerative colitis, Crohn's Disease, Generalized Pustular Psoriasis, and Palmoplantar Pustulosis. Spesolimab has been tested in single dose (10 mg/kg i.v.) in GPP and in multiple doses up to 900 mg i.v. in PPP which were all safe and well tolerated.

In general, these studies indicate some evidence of efficacy in inflammatory skin disease.

Based on the PoC achieved in GPP and the strong preclinical rationale, there is a reasonable chance that spesolimab may alleviate signs and symptoms of HS. Participation in this study may help to generate future benefit for larger groups of patients with HS, if spesolimab proves to be successful in treating this disease.

Patients completing the 12 weeks of treatment in this trial, will be offered to roll-over to receive open label active spesolimab maintenance treatment for up to 2 years in an open label extension (OLE) study. Patients experiencing worsening of HS will have the possibility to receive rescue treatment. Patients who fail to rescue treatment or cannot receive further trial medication (ie unbearable AEs) will be discontinued and switched to available SoC at the investigator`s discretion. This will limit the duration of spesolimab exposure in patients no longer benefitting from treatment.

1.4.2 Risks

Table 1.4.2:1 lists possible risks for spesolimab as well as theoretical risks derived from general safety considerations of immunomodulatory drugs and from this trial specific procedures.
No other IL-36 receptor antagonist is currently approved, providing information on identified risks in molecules of this class.

In order to protect the patient's safety during conduct of this trial, an independent Data Monitoring Committee (DMC) has been established for the periodic review of clinical trial safety data.

Table 1.4.2:1 Overview over trial related risks

Hypothetical risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Spesolimab		
Drug-induced liver injury (DILI)	Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators.Therefore, DILI is considered as a standard risk in all BI development programs.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety. See also section 5.2.6, adverse events of special interest. Trial treatment discontinuation criteria as well as criteria for trial treatment restart are implemented for relevant cases.
Systemic Hypersensitivity reaction	After administration of any biologic agent or protein, there is a possibility of occurrence of immediate (such as anaphylaxis) or delayed (such as drug reaction with eosinophilia and systemic symptoms) adverse immune reactions	Patients with a history of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients are excluded from the trial. In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of trial medication, the investigator should consider in accordance with the severity of the reaction and local standard of care to interrupt and treat the condition. Systemic hypersensitivity reaction is defined as an adverse event of special interest (AESI). It is subject to close monitoring

		and investigators are requested to assess these conditions using the criteria discussed in the statement paper from Sampson HA [R11-4890].
Infections	Inhibition of the immune response with an immunomodulating biologic may increase the risk of infections. A recent characterization of individuals with homozygous IL-36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL-36 signaling pathway inhibition may not substantially compromise host defenses [R17-3632]. In clinical trials with spesolimab, a higher proportion of patients with mild to moderate infections was seen in the spesolimab treatment group than in the placebo treatment group. Nevertheless, there was no indication of an increased frequency of patients with severe, serious, and opportunistic infections in association with spesolimab treatment.	Screening procedures for infections will be established for this trial. Patients with any relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis or tuberculosis are excluded from the trial. Treatment of infections should be initiated promptly according to standards of care. Severe infections and opportunistic infections are considered AESIs for this trial. These conditions and serious infections are subject to close monitoring.
Malignancies	Inhibition of the immune response with an immunomodulating biologic may potentially impair immune defences and thus theoretically	Patients with a recent history of malignancy will be excluded from participation in this trial. In case of occurrence of malignant neoplasm other than appropriately treated

	decrease immune defense against malignancies. A recent characterization of individuals with homozygous IL-36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL-36 signalling pathway inhibition does not compromise host defenses. [R17-3632].	basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with spesolimab. Diagnostics and treatment have to be initiated according to local standard of care. Malignancies represent always serious adverse events and are subject to close monitoring
Trial procedures		
Blood sampling	As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of lightheadedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain.	These risks will be addressed by careful safety monitoring and risk mitigation measures such as (a) close clinical monitoring for AEs; (b) selection of experienced sites and site staff; (c) Safety recommendations provided in laboratory manual.
Skin biopsy	Can cause local bruising, inflammation, nerve damage and pain.	These risks will be addressed by careful safety monitoring and risk mitigation measures such as (a) close clinical monitoring for AEs; (b) selection of experienced sites and site staff; (c) staff training
Other risks		

Administration of Placebo	If the patient is randomized to receive a placebo, the patient´s condition could get worse during the trial.	Minimize the number of patients on the placebo group using adequate statistical model. The use of rescue medication is foreseen in this trial for patients experiencing a worsening of their HS condition.
Suicidal ideation and behavior	Increased risk of suicidal ideation and behavior is present in the population of patients with hidradenitis suppurativa	'Baseline/ screening' version of C-SSRS will be administered with the aim to exclude patients with active moderate to severe symptomatology present within a specified time prior to the screening or screening visit. 'Since last visit' version of C-SSRS will be administered with the aim to monitor patient's safety during the trial and to initiate actions for the patient's safety if such actions are deemed necessary. All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior represent SAEs and are subject to close monitoring.

These risks will be addressed by careful safety monitoring and risk mitigation measures, which will be implemented in this trial of a novel and 1st-in-class MoA: (a) exclusion of patients with history or increased risk of malignancies or infections or allergy; (b) close clinical monitoring for AEs, including definition of malignancies as always-serious adverse events, definition of opportunistic infections and mycobacterium tuberculosis infections, severe infections and systemic hypersensitivity including infusion reaction and anaphylactic reactions as adverse events of special interest (AESI); (c) selection of sites experienced in treatment of HS patients with biologics; and (d) implementation of a fully independent data-monitoring committee (DMC).

Reactions to injections/infusions: Specific safety measures will be taken during the trial. Following the injection/infusion the patients will be monitored for reactions at the site according to Instructions for Preparation and Handling of Spesolimab/Placebo in the

Investigator Site File. Subcutaneous injection has been well tolerated in a small phase I study (1368-0003; see spesolimab IB, document number c03320877-09) and will be carefully monitored for local tolerability in this study. Intravenous infusion has been well tolerated in various clinical trials and will continue to be monitored for tolerability in trial 1368-0052.

Based on the findings in the nonclinical studies conducted to date and in accordance with international regulatory guidelines, the inclusion of Women of Child Bearing Potential (WOCBP) in this study is justified. To minimize the risk of unintentional exposure of an embryo or fetus to the investigational drug, WOCBP must agree to the requirements for the pregnancy testing and contraceptive methods.

1.4.2.1 COVID-19

To date, there is no reliable evidence suggesting a link between SARS-CoV-2 infections and the IL-36 pathway. Further investigations are needed to elucidate the molecular mechanisms underlying their biological functions in COVID-19. According to the CDC there is limited information regarding risk factors for severe COVID-19 disease. Based on currently available information and clinical expertise, older adults and people of any age who have serious poorly controlled underlying medical conditions might be at higher risk for severe illness from COVID-19. Patients with evidence of a current or previous disease/medical condition that is clinically significant in the opinion of the investigator are excluded from participation in all trials with spesolimab. On the basis of the currently available evidence and considering the population included in the clinical trials, the spectrum of patient characteristics in the spesolimab program across all investigated indications does not suggest an undue risk of more severe COVID-19 infections.
Similar to other immune modulating biological treatments, spesolimab may potentially increase the risk of infections. Therefore, risk mitigation measures, such as exclusion of patients with increased risk of infections, close monitoring of adverse events, as well as guidance on handling of acute infections occurring during the trial have been included in spesolimab clinical trial protocols. As for any other acute infection a suspected or diagnosed COVID-19 infection should be treated according to the standard of care and interruption of study medication should be considered. Considering the current knowledge of COVID-19 and the implemented risk mitigation measures addressing the potential risk of infections, patients with indications in which spesolimab is investigated are not per se believed to be at higher risk of COVID-19. Protocol-defined procedures do not impose undue risk to study participants.
To address potential risks associated with operational aspects related to the participation in clinical trials in context of COVID-19 pandemic, different risk mitigation measures are considered in ongoing and planned spesolimab clinical trials based on local requirements and development of pandemic.
The benefit-risk assessment of spesolimab remains favourable in the context of the COVID-19 pandemic.
The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each patient's (continued) participation in the planned trials. BI as the sponsor, where

required, will support the investigator in their decision making. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing, and/or is in the best interest of the patient. Regarding COVID-19 vaccination in patients receiving immune-modulating drugs like spesolimab, the impact on the protective effect of COVID-19 vaccines is not known but could be lower.

1.4.3 Discussion

Due to the lack of mechanism- or compound-related safety signals of spesolimab, it is expected that patients with moderate to severe HS will not be exposed to unacceptable, undue risks and adverse events.

Considering the medical need for development of an effective and well tolerated drug for the therapy of HS, the benefit of this trial is considered to outweigh the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

This is a proof of clinical concept trial to investigate the efficacy and safety of spesolimab compared to placebo in patients with moderate to severe hidradenitis suppurativa (HS).

The primary objective is to estimate the effect of spesolimab compared to placebo for the mean percent change from baseline in total abscess and inflammatory nodule count at Week 12. Secondary objectives are the evaluation of efficacy of spesolimab on secondary endpoints versus placebo.

The comparisons of interest for each efficacy objective are those of all treated patients but excluding the effects of rescue therapy.

2.1.2 Primary endpoint(s)

The primary endpoint is the percent change from baseline in total abscess and inflammatory nodule count at Week 12.

2.1.3 Secondary endpoint(s)

Secondary endpoints are defined as described below:

- Percent change from baseline in draining fistula count at Week 12
- Achievement of Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. HiSCR is defined as at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline.
- Absolute change from baseline in International Hidradenitis Suppurativa Severity Score System (IHS4) value at Week 12
- Absolute change from baseline in HASI score at Week 12
- Achievement of PGA score of 0 or 1 at Week 12
- Achievement of at least 30% reduction from baseline in Numerical Rating Scale (NRS30) in Patient's Global Assessment of HS Pain at Week 12
- Occurrence of complete elimination of draining fistulas at Week 12
- Occurrence of at least one flare (defined as at least 25 % increase in AN count with a minimum increase of 2 relative to baseline) up to Week 12.
- Absolute change from baseline in DLQI Score at Week 12.
- Absolute change from baseline in HiS-QoL Total Score at Week 12.

The following safety endpoint is also defined:

- The occurrence of Treatment Emergent Adverse Events (TEAEs)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is an international, phase IIa multi-center, double-blind, placebo controlled trial assessing the efficacy and safety of spesolimab in patients with moderate to severe HS. Approximately 45 patients will be randomized. A sufficient number of patients will be screened to meet this randomization target.

After signing the informed consent, patients will enter the screening period for up to 28 days and if all eligibility criteria are met, patients will be randomized in a 2:1 ratio to either active group or placebo group. The randomization will be stratified for TNFi-naive population versus TNFi−failure population. Approximately 33 patients from TNFi-naive population and 12 patients from TNFi−failure population are planned to be randomized respectively. Primary failure of TNF treatment is defined as lack of efficacy after at least 3 months of treatment with an agent blocking TNF-alpha and secondary failure is defined as loss of clinical efficacy in a patient after initial response to an agent blocking TNF-alpha.

Once randomized, patients will start a treatment period of 12 weeks. The first three weeks patients will be given an initial loading dose of 3600 mg i.v. spesolimab (1200 mg i.v. every week at Wk 0, Wk 1 and Wk 2), or matching placebo. At the time of use the i.v. solutions for dosing will be prepared as detailed in the instruction in the ISF. From week 4 and until week 10 patients will receive a maintenance subcutaneous dose of 1200 mg spesolimab every 2 weeks, or matching placebo. Patients completing week 12 of the study, will roll-over to an open-label extension (OLE) study if they agree and meet the eligibility criteria of the OLE trial. These patients are not required to complete the follow up period and their EoT visit will be considered also their end of study visit, co-inciding with the first visit in the OLE trial 1368-0067.

Patients who permanently discontinue trial drug earlier than week 12, or do not qualify to enter the OLE trial for any other reason, will be invited to do the EoT visit instead of the next planned visit and will then enter a 16 weeks safety follow-up period. The first visit in the safety follow-up period will be scheduled 8 weeks after their last study drug administration and the second visit will be scheduled 16 weeks after their last study drug administration. This is the end of study visit and patients will finish their participation in the study after completing this visit.

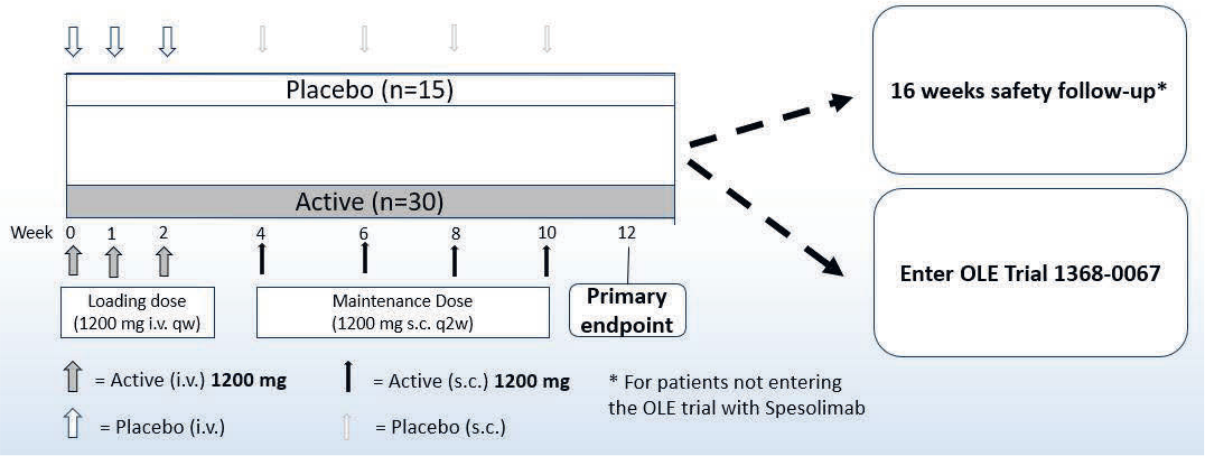

Figure 3.1:1 Trial Design

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

A parallel group, randomized, double-blind and placebo controlled trial was considered most appropriate to demonstrate PoC. The placebo control group is required to compare both efficacy and safety of spesolimab in patients with moderate-to-severe hidradenitis suppurativa who are biologic naïve or have failed previous TNFi treatments. However, a 2:1 randomization schema will help reducing the number of patients assigned to the placebo arm. Additionally, if eligible, patients will be invited to roll-over to an OLE trial with active drug.

The treatment duration of 12 weeks with spesolimab was selected to evaluate sustained efficacy over flares in these patients.

The loading dose of three i.v. administrations followed by the maintenance subcutaneous biweekly dosing was selected to optimize the exposure of spesolimab to evaluate its efficacy in HS. The intravenous loading dose is selected to maximize the treatment response, the duration of response and to reach steady state earlier. A loading dose may also allow for an earlier onset of response. This is followed by maintenance dose given subcutaneously so as to sustain the response.

Thus, this trial design is considered adequate to achieve the objectives outlined above.

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 45 patients will be randomized in this trial. A sufficient number of patients will be screened to meet this randomized goal. Patients will be recruited across multiple sites in multiple countries. The minimum planned number of patients per site is 1 – 2.

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

A pre-trial screening log collecting reasons for screen failures will be maintained in the Investigator Site File (ISF) where possible. Also, a log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF irrespective of whether they have been treated with investigational drug or not.
If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

Patients can be re-screened (see also section 6.2.1) on a case by case basis after consultation with Sponsor. These patients will need to sign a new informed consent. The re-screener will get a new unique patient number, subject numbers from screen-failed patients cannot be re-used. If a patient is re-screened and there are valid screening determinations from his/her previous participation in the trial, like for example safety labs, performed within 28 days prior to baseline (visit 2), these do not need to be repeated.

3.3.1 Main diagnosis for trial entry

Adult patients with moderate to severe Hidradenitis Suppurativa will be included in the trial if they fulfill all the inclusion criteria and do not present with any of the exclusion criteria.

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Male or female adult patients, 18 years of age or older.
2. Signed and dated written informed consent in accordance with ICH Good Clinical Practice (GCP) and local legislation prior to the start of any screening procedures.
3. Moderate to severe HS, based on IHS4 criteria, for at least 1 year prior to the baseline visit, as determined by the investigator through participant interview and/or review of the medical history. (If IHS4 scoring is not available, equivalent scoring based on scoring systems as HS-PGA or Hurley are acceptable based on documented investigator assessment)
4. HS lesions in at least 2 distinct anatomic area (right/left axillary, inguinal, inframammary, perineal)
5. Biologic naive or TNFi-failure for HS.

6. Inadequate response to an adequate course of appropriate oral antibiotics for treatment of HS in the last 1 year, as per investigator discretion. This is not applicable for TNFi-failure patients
7. Total abscess and inflammatory nodule (AN) count of greater than or equal to 5.
8. Total draining fistula count of less than or equal to 20.
9. Women of childbearing potential (WOCBP[1]) must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, for the duration of the trial and 16 weeks after last administration. A list of contraception methods meeting these criteria is provided in the patient information. (see also Section 4.2.2.7))

3.3.3 Exclusion criteria

1. Presence of active skin lesions other than HS that interfere with the assessment of HS.
2. Use of restricted medications as below. Please see section 4.2.2 for further information.
   - Topical corticosteroids over HS lesions within 1 week of Visit 2.
   - Systemic antibiotics within 4 weeks of visit 2.
   - Systemic non-biologic immunomodulatory and/or immunosuppressive agents use within 4 weeks (or 5 half lives, whichever is longer) of visit 2.
   - Biologic agents use within 12 weeks or 5 half-lives, whichever is longer, prior to visit 2.
   - Opioid analgesics within 2 weeks of visit 2.
   - Live virus vaccine within 6 weeks of visit 2.
3. Prior exposure to any immunosuppressive biologic other than TNFi for HS.
4. Prior exposure to IL-36R inhibitors including spesolimab.
5. Treatment with any investigational device or investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives of the drug, whichever is longer, prior to visit 2.
6. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Women who stop nursing before the study drug administration do not need to be excluded from participating.
7. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.
8. Patient with a transplanted organ (with exception of a corneal transplant > 12 weeks prior to screening) or who have ever received stem cell therapy (e.g., Remestemcel-L).
9. Any documented active or suspected malignancy or history of malignancy within 5 years prior to the screening visit, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
10. Active or latent TB:
    - Patients with active tuberculosis should be excluded.
    - Patients will be screened with Interferon Gamma Release Assay (IGRA) such as QuantiFERON or T-spot. Patients with positive IGRA are excluded unless they

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

have completed treatment for active or latent tuberculosis per investigator discretion, at the time of screening.

- Patients with indeterminate QuantiFERON or invalid/borderline T-spot may be retested with IGRA (once) and if inconclusive should have a PPD skin test.
- PPD skin test, also called Tuberculin- Skin testing (TST), can be performed if IGRA is not available or inconclusive. A tuberculin skin test reaction ≥10mm (≥5mm if receiving ≥15mg/d prednisone or other immunosuppressant) is considered positive. Patients with a positive TST are excluded unless they have completed treatment as above.

11. Active systemic infection within 2 weeks of visit 2. Patients can be re-screened after treatment of the acute infection, as per investigator discretion.
12. Relevant chronic infections as determined by the investigator, including human immunodeficiency virus (HIV) or viral hepatitis. In case of a positive hepatitis C antibody test, a positive reflex testing for Hepatitis C RNA PCR is considered positive.
13. Major surgery (major according to the investigator) performed within 12 weeks prior to first study drug administration or planned during the study (e.g. hip replacement, aneurysm removal, stomach ligation)
14. Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in AST or ALT or alkaline phosphatase, **or** >2-fold ULN elevation in total bilirubin. Patients with Gilbert´s syndrome can be included unless total bilirubin elevation is >5-fold ULN at screening visit and unless proportions of bilirubin fractions are inconsistent with diagnosis of Gilbert´s syndrome.
15. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse or any condition) other than HS, surgical procedure, psychiatric or social problems, medical examination finding (including vital signs and ECG), or laboratory value at the screening outside the reference range that in the opinion of the investigator is clinically significant and would compromise the safety of the patient or compromise the quality of the data, make the study participant unreliable to adhere to the protocol, comply with all study visits/procedures or to complete the trial.
16. Planned use of laser or other hair removal procedures over HS-affected areas during the trial period.
17. Any suicidal ideation of type 4 or 5 on the C-SSRS in the past 12 months (i.e. active suicidal thoughts with method and intent but without specific plan, or active suicidal thoughts with method, intent and plan).
18. Any suicidal behavior in the past 2 years (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior).
19. Previous enrolment in this trial. (exception: patients re-screened)

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the patients in the trial: if possible, on treatment, or at least to collect important trial data.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see sections 5.2.6.1 and 5.2.6.2). If the reason for discontinuation is death, this should be reported on the SAE form as well, regardless of causal relationship.

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication such as
    - immunosuppressive agents (including biologics),
    - systemic corticosteroids for HS,
    - opioid analgesics
    - systemic antibiotics for HS before week 4
    - Systemic antibiotics for HS without meeting criteria for disease worsening (as defined in Section 4.2.2.2)
    - metformin (unless on a stable dose for 12 weeks before visit 2 for a non-HS indication)
    - spironolactone (unless on a stable dose for 12 weeks before visit 2 for a non-HS indication)
    - live vaccines.
    - The patient can no longer receive trial treatment for medical reasons (such as major surgery, adverse events, other diseases, malignancies as per Section 4.2.1.3, or pregnancy). If a hepatic injury alert (as defined in Section 5.2.6.1.4) is confirmed without identification of an alternative cause in the work-up according to the "DILI checklist" the patient should not receive subsequent doses of trial treatment
- The patient develops suicidal ideation or any suicidal behavior (See Section 4.2.1.4)
- For individual stopping rules related to specific adverse events, please see section 4.2.1 other treatments and emergency procedures.

In case of a temporary reason, trial treatment should be restarted if medically justified, please see section 4.1.4.

For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the CRF. This data will be included in the trial database and reported.

If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

Even if the trial treatment is discontinued, the patients remain in the trial and, given their agreement, should undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flowchart and section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.
If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

- Failure to meet expected enrolment goals overall or at a particular trial site.
- New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see section 3.3.4.1.

Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.
Further follow up of patients affected will occur as described in section 3.3.4.1.
The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product spesolimab solution for infusion

Substance:	Spesolimab
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Anti-human IL-36 Receptor mAb
Molecular weight:	146 kDa
Unit strength:	Spesolimab 450mg/vial (60mg/mL x 7,5mL)
Route of administration:	Intravenous infusions
Posology:	**Active arm:** 1200mg weekly at Weeks 0, 1 and 2 for a total loading dose of 3600mg

Table 4.1.1: 2 Test product BI matching placebo solution for infusion

Substance:	Placebo matching to spesolimab
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Placebo to match spesolimab 450mg/vial (60mg/mL x 7,5mL)
Route of administration:	Intravenous infusions
Posology:	**Placebo arm:** Placebo weekly at Weeks 0, 1 and 2 matching a total loading dose of 3600mg spesolimab

Table 4.1.1: 3 Test product spesolimab solution for injection

Substance:	Spesolimab
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Anti-human IL-36 Receptor mAb
Molecular weight:	146 kDa
Unit strength:	Spesolimab 300mg/pre-filled syringe (150mg/mL x 2mL)
Route of administration:	Subcutaneous injections
Posology:	**Active arm:** 1200 mg every 2 weeks at Weeks 4, 6, 8 and 10

Table 4.1.1: 4 Test product BI matching placebo solution for injection

Substance:	Placebo matching to spesolimab
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Placebo to match spesolimab 300mg / Pre-filled syringe. (150mg/mL x 2mL)
Route of administration:	Subcutaneous injections
Posology:	**Placebo arm:** Placebo every two weeks at Weeks 4, 6, 8 and 10.

4.1.2 Selection of doses in the trial and dose modifications

The aim of this trial (1368-0052) is to provide proof of clinical concept that spesolimab is active in treating moderate to severe hidradenitis suppurativa when compared with placebo. It will also help understanding if this benefit is clinically relevant and sufficient to grant further clinical development of spesolimab in this indication.

Patients in the active arm will receive a loading dose of 3600mg spesolimab in 3 weekly intravenous administrations of 1200mg spesolimab each (week 0 to week 2. This is 3 infusions in total for the loading dose). Patients in the placebo arm will receive matching placebo intravenous administrations at the same planned timepoints.

From week 4 to week 10 (both included) patients will receive subcutaneous injections of 1200mg spesolimab or matching placebo every two weeks (4 injections per visit for a maximum of 4 visits)

This dose/regimen was selected to optimize the exposure of spesolimab to evaluate its efficacy in hidradenitis suppurativa. The intravenous loading dose is selected to maximize the

treatment response, the duration of response, and to reach a steady state sooner. A loading dose may also allow for an earlier onset of response prior to 12 weeks. The intravenous loading dose is followed by a subcutaneous maintenance dose given every 2 weeks. This dose is the maximum subcutaneous dose that can be conveniently given based on the injection volume and number of injections.

4.1.3 Method of assigning patients to treatment groups

An Interactive Response Technology (IRT) will be used to screen eligible patients, perform drug assignment, manage initial/re-supply ordering of drug supplies and handle emergency un-blinding. The investigator will receive all necessary instructions to access the IRT from the Sponsor. Detailed IRT functions and procedures will be documented in the user requirement specifications mutually agreed to by the sponsor and the IRT vendor.

After the assessment of all in- and exclusion criteria, each eligible patient will be randomized to receive 12 weeks of treatment with spesolimab or placebo according to a randomization plan in a 2:1 ratio at visit 2 in a blinded fashion via Interactive Response Technology (IRT). Randomization will be stratified by TNFi-naive population versus TNFi-failure population.

At randomization as well as subsequent medication administration visits, IRT will assign medication numbers. Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System). Each syringe and vial will have an individual medication number for dispensation.

4.1.4 Drug assignment and administration of doses for each patient

Patients will be treated with spesolimab or matching placebo as indicated in the Flowchart and section 3.1.
The medication will be assigned via IRT.

Patients will receive i.v. spesolimab at week 0, 1 and 2.
Detailed instructions for the preparation of the solution for infusion, the volume to be administered and the infusion rate are provided in the ISF.

Patients will receive spesolimab s.c. injections at week 4, 6, 8 and 10.
Injection site should not be close to a vein and it should avoid sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses.
Detailed instructions for use and handling of spesolimab syringes are provided in the ISF.

Patients have to be closely monitored for local or systemic hypersensitivity reactions for 1 hour following s.c. or i.v. study drug administration. Patients should be closely monitored for signs and symptoms of injection site or systemic hypersensitivity reactions following study drug administration. Study personnel should observe the injection site for signs of redness, swelling or hardness. They should also ask subjects about itching, dizziness or shortness of breath. Patients should be advised that if they experience redness, swelling or other changes

at the injection site, they should notify site personnel. They should further be advised that if they experience itching all over or a feeling of being swollen, dizzy or short of breath, they should seek emergency medical attention immediately and notify site personnel.

The administration of the trial medication on all applicable study days will be done under supervision of the investigating physician or a designee at the site. If available, a pharmacist should prepare the study medication. The so-called four eye principle (two-person rule) should be applied for preparation (e.g. choosing the correct vials with the correct medication number) and administration of trial medication.

In case of safety concerns, e.g., due to infusion reactions, it is in the discretion of the investigator or his/her designee to adapt the infusion scheme, including but not limited to slowing down the infusion rate, interrupting the infusion and - provided no further safety concern exist - restarting at a slower rate. Further, based on [redacted] medical judgment he/she will provide medications such as steroids, etc., as needed (cf. section 4.2.1 for handling of infusion reactions). Detailed instructions for handling of infusion reactions are also provided in the ISF.

Dose modifications or adjustments are not permitted. In exceptional cases of missed or delayed visits, if any of these visits has to be rescheduled, the date of subsequent visit should be calculated from baseline (visit 2). After visit 3, in case of delayed visits, IMP can be administered with a minimum interval of 7 days from the next dose, only after discussion and approval from the sponsor.

Trial treatment may be restarted after a temporary reason for treatment discontinuation on a case by case basis and after consultation with the sponsor. Reasons for temporary treatment discontinuation may include but are not limited to pandemic lockdown, temporary hospitalization, severe infections, hepatic injury if an alternative cause is identified and patient has recovered as per investigator.

During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment and trial medication may be administered at patient's home if acceptable according to local law and regulations.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients and investigators involved in the trial conduct will remain blinded with regard to the randomized treatment assignments until after database lock for the final trial analysis. The randomization code will be kept secret by Clinical Trial Support up to the final database lock.

If the trial team agrees to perform the primary analysis and the final analysis separately (see section 7.2), then a database lock for the primary analysis will be done and treatment will be unblinded to trial and project team members.

If the trial team agrees to perform the primary analysis and final analysis as one single analysis (at the time of trial completion), then patients, investigators, and sponsor personnel involved in the trial conduct will be unblinded to the randomized treatment assignments after the database lock has been performed.

The randomization codes will be provided to bioanalytics prior to last patient completed to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo patients. Bioanalytics will not disclose the randomization code or the results of their measurements until the trial is officially unblinded.

A fully external DMC will perform an un-blinded safety and efficacy assessment at specified intervals in order to ensure that patients are protected from potential harm, please refer to section 8.7 for further details.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomization code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.
For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Research Associate CRA (as provided in the list of contacts) must be contacted immediately. Refer to ISF. Trial medication must be securely stored, e.g. in a locked refrigerator at the site or at a pharmacy.
The medication may only be dispensed to trial patients according to the Clinical Trial Protocol (CTP) by authorized personnel as documented in the trial staff list.

Trial medication will be prepared for infusion just prior to infusion, for further details please see preparation instructions in the ISF.

4.1.8 Drug accountability

The investigator, pharmacist, or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator (if applicable),
- Availability of FDA Form 1572 (if applicable.).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics outside this clinical trial.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor <and/or> appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

This section provides information on restrictions regarding concomitant treatment prior to randomization and during the trial, including a definition on rescue therapy for the treatment of worsening of HS.

4.2.1 Other treatments and emergency procedures

Systemic steroids dosed intravenously or orally for less than 24 hours as treatment of infusion or anaphylactic reactions are permitted and do not lead to treatment discontinuation nor to assignment as treatment failures in the ITT analysis.

4.2.1.1 Systemic hypersensitivity including infusion reaction and anaphylactic reaction

In case of systemic hypersensitivity including infusion reaction and anaphylactic reaction emerging during or after infusion / injection(s) of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to
- Immediately interrupt the infusion (if i.v) or stop further injections (if s.c.).
- Treat with systemic anti-histamines, intravenous steroids, and in case of a severe allergic reaction (e.g., anaphylactic reaction) epinephrine
- in case of s.c. administration give epinephrine in case of signs of hypersensitivity and add further treatments, e.g. oxygen, iv fluids, antihistamines and systemic corticosteroids as needed.

Also draw a plasma sample for IgE and ADA as detailed in the Lab Manual in the ISF (Central laboratory). Consider also the evaluation of histamine, serum tryptase, and complement components.

In case of infusion reaction, based on patient's clinical course and medical judgment, the infusion may be re-initiated in case of mild or moderate infusion reactions (according to RCTC grading) at lower speed with gradual increase to complete the infusion as detailed in the Instructions for Preparation and Handling of Spesolimab/Placebo in the Investigator Site File. In any case, the total duration of infusion should not exceed 180 minutes (3 hours). If the infusion exceeds 180 minutes, it should be stopped and the infusion should be skipped. Patient should be called for the next scheduled visit as planned.

In case of systemic hypersensitivity, based on patient's clinical course and medical judgment, the injection(s) may be continued in case of mild or moderate systyemic hypersensitivity (according to RCTC grading) to complete the injections as detailed in the Instructions for Preparation and Handling of Spesolimab/Placebo in the Investigator Site File.

In case of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA (Appendix 10.13 [R11-4890]) suspected to be caused by the trial medication, the investigator should discontinue treatment permanently with spesolimab.

When a delayed hypersensitivity reaction is suspected, please draw a blood sample for laboratory assessment and evaluate for signs of extra-cutaneous organ involvement. The decision to discontinue treatment and/or restart treatment after resolution of the reaction should be based on reaction type and severity.

4.2.1.2 Severe infections (according to RCTC grading), serious infections, opportunistic or mycobacterium tuberculosis infections

Treatment of the infection should be initiated promptly according to local standard of care. No further trial medication should be administered until the active infection has resolved. Treatment with spesolimab may be restarted when the patient has recovered according to investigator's assessment.

4.2.1.3 Malignancies

In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should permanently discontinue treatment with spesolimab. Diagnostics and treatment have to be initiated according to local standard of care.

4.2.1.4 Suicidality

In case the patient develops suicidal ideation of type 4 or 5 in the C-SSRS (i.e. active suicidal thoughts with method and intent but without specific plan, or active suicidal thoughts with method, intent and plan) or any suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior), the patient should immediately be referred to a mental health professional for further work-up and permanently discontinue trial treatment.

Overall, the choice of Standard of Care treatment will be left at the discretion of the investigator. The sponsor will not provide/supply SoC treatment (s) to the sites.

Any of the above treatments in this section must be documented in the source data, including an estimate on dispensed medication, and documented in CRF (concomitant medications) and the corresponding AE if applicable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following medications/ medication classes are restricted during trial treatment and prior to visit 2 for durations as specified below. Please see section 3.3.4 for withdrawal information regarding the use of restricted medications.

Table 4.2.2.1:1 Restricted Medications.

Medication	Washout period prior to V2 (baseline)
Systemic antibiotics[1]	4 weeks
Systemic corticosteroids[2]	1 week
Biologics causing immunosuppression	12 weeks or 5 half-lives whichever is longer
Other systemic immunomodulatory and immunosupresssive agents	4 weeks or 5 half-lives whichever is longer
Live vaccines	6 weeks
Opioid analgesics	2 weeks
Spironolactone[3]	1 week
Metformin[3]	1 week
Topical cannabis oil[4]	1 week
Topical corticosteroids for HS[5]	1 week

[1] For more information on the use of systemic antibiotics please see section 4.2.2.3.
[2]Systemic corticosteroids as short courses can be used for indications other than HS.
[3] Restricted if used for HS. If used for non-HS indication, dose should be stable for at least 12 weeks prior to V2.
[4] Restricted if used over HS-affected areas. Other alternative therapies for HS are restricted, unless permitted after discussion with PI and trial team.
[5] Topical corticosteroids are allowed for indications other than HS if the areas are not affected by HS concurrently.

4.2.2.2 Rescue treatment

HS Disease worsening is defined as a 150% increase in AN count from baseline. **Rescue medication** is generally defined as the treatment for disease worsening and includes systemic antibiotics and/or immunosuppressive biologics such as TNF-inhibitors. In this trial, immunosuppressive biologics are not allowed. For more information on the use of antibiotics during the trial see section 4.2.2.3. The sponsor will not provide/supply these treatment(s) to the sites.

4.2.2.3 Antibiotic use during the trial

Non HS use:
Systemic antibiotics can be used for indications other than HS and for a duration of less than or equal to 4 weeks during the entire course of the trial (from randomization up to the last treatment administration).

HS disease worsening (as defined above in section 4.2.2.2):

At or after week 4, if the patient requires systemic antibiotics for disease worsening as per the investigator, monotherapy with either doxycycline 100mg orally twice daily or alternative as per investigator discretion, may be used for a maximum period of 2 weeks, and not more than a total of 4 weeks during the entire course of the trial.
Concomitant use of systemic antibiotic therapy for treatment of HS other than for disease worsening, or before week 4, is not allowed and will lead patient to permanent treatment discontinuation (see Section 3.3.4.1).

4.2.2.4 Analgesics use during the trial

Opiate analgesics are restricted for HS and non-HS indications.

If a subject is on a non-opioid analgesic for HS and non-HS indication (e.g. osteoarthritis), the subject may continue the analgesic, provided the dose is stable for 14 days prior to Baseline and is anticipated to remain stable throughout the study.

If a subject's pain (HS-related or non-HS-related) worsens after Baseline, they may initiate or increase the non-opioid analgesic therapy.

Use of analgesics will be documented in the Patients Diary and the CRF.

4.2.2.5 Lesion intervention

In the event that an acutely painful lesion occurs that requires immediate intervention, physicians will have the option to perform protocol-allowed interventions.
Only two types of interventions are allowed: Intra-lesional steroid and Incision and Drainage (I&D). If I&D is performed, only over the counter antiseptic wash can be used. Concomitant medications associated with the lesion intervention must be captured in the medical records.
A total of two protocol-allowed interventions are permissible. An intervention can maximally occur on two different lesions at the same time or on the same lesion at two different study visits. If the subject requires more than two interventions, then they may be discontinued from the study.

4.2.2.6 Restrictions on diet and life style

No specific restrictions on diet or life style of the patients are required.

4.2.2.7 Contraception requirements

WOCBP (for the definition please refer to section 3.3.2) must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly during the trial, and for a period of at least 16 weeks after the last study drug administration. A double barrier method of contraception is not

required. A list of contraception methods meeting these criteria is also provided in the patient information.

Female Patients
Acceptable methods of birth control for this trial are:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised sexual partner with documented absence of sperm

Or

Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

Male Patients:
Contraception of male trial participants and female partners of male trial participants are not required.

4.3 TREATMENT COMPLIANCE

Administration of the study medication will be done in the study center under the supervision of the investigator or a designee. The measured plasma concentrations will provide additional confirmation of compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

The primary, secondary and further endpoints of the study are specified in sections 2.1.2 and 2.1.3, and 2.2.2, respectively.

1. The **HiSCR (Hidradenitis Suppurativa Clinical Response)** is one of the most well-known and widely used outcome assessment in clinical trials. HiSCR is defined as at least a 50% reduction from baseline in the total abscess and inflammatory nodule count, with no increase in the abscess or draining fistula count. [R20-2976]
   HiSCR will be evaluated at the timepoints mentioned in the Flowchart and the detail is provided in Appendix 10.2
2. IHS4 – IHS4 is a valid, clinical scoring system for dynamic assessment of HS severity. Determining IHS4 requires counting nodules, abscesses and draining fistulae/sinus tracts making it straightforward to apply in clinical trials [R20-3045]. IHS4 will be evaluated at the timepoints mentioned in the Flowchart and the detail is provided in Appendix 10.3
3. HS-PGA – This documents the physician's assessment of the patient's HS at a given timepoint. It scores patient disease severity as either clear or minimal or mild or moderate to severe or very severe, based on abscesses, draining fistulae, inflammatory nodule and non-inflammatory nodule [R20-3046]. HS-PGA will be evaluated at the timepoints mentioned in the Flowchart and the detail is provided in Appendix 10.4
4. HASI - HASI is modelled after the Psoriasis Activity and Severity Index (PASI). Four classic signs of HS-related inflammation (erythema, induration, open ulcer and draining tunnels) are included. Each variable in HASI is scored on a Likert scale (0–3) for each predetermined body region. For BSA assessment, the number of palms (one palm indicated 1% of the patient's BSA) involved for each body region (head, right axilla, left axilla, anterior chest, back, anterior bathing trunk, posterior bathing trunk, other) is assessed. This is converted to a percentage of that region. An area score was assigned to each region using the PASI approach (0 = none, 1 = 1–9%, 2 = 10–29%, 3 = 30–49%, 4 = 50–69%, 5 = 70–89%, 6 = 90– 100%). To calculate the regional HASI score, the sum of the four clinical variable scores is multiplied by the area score of each involved region. This value is then multiplied by the proportion of the BSA of that region, to give a regional HASI score. Regional HASI scores are added together to give the cumulative total HASI score (range 0–72). HASI will be evaluated at the timepoints mentioned in the Flowchart and the detail is provided in Appendix 10.5
5. Pain NRS
   The HS Pain NRS is an endpoint for the assessment of HS-related pain severity for clinical trials with patients with HS. As it is a unidimensional measure of pain intensity and can be administered daily with minimal subject burden. Recall period is 24h and response is given by an 11-point scale ranging from 0 to 10. Appendix 10.6
6. DLQI
   The Dermatology Life Quality Index (DLQI) is a patient-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment [R05-2548]. The DLQI has a one-week recall period. Response categories include "not

relevant" (score of 0), "not at all" (score of 0), "a little" (score of 1), "a lot" (score of 2) and "very much" (score of 3). Question 7 is a "yes"/ "no" question where "yes" is scored as 3.

The DLQI will be analyzed under six headings as follows [R05-2548]:

Domain	Question Number	Score
Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and school	Question 7	Score maximum 3
Personal Relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

DLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30 where 0-1 = no effect on patient's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect on patient's life. The higher the score, the more the quality of life is impaired. If one question is left unanswered this is scored 0 and the total score is summed and expressed as usual out of a maximum of 30; for analysis by subscore only, the corresponding subscore is considered to be missing. If 2 or more questions are left unanswered (missing), DLQI total score is treated as missing. A 4-point change from baseline is considered a clinically important difference. Appendix 10.7

7. HiS-QoL (hidradenitis suppurativa quality of life)
   HiS-QoL is a patient-administered, 17-item instrument to measure HS-specific quality of life in clinical trials with a 7-day recall period [R20-3156]. The 17-item HiS-QoL included four symptom items, eight activity-adaptation items and five psychosocial items. The item scores are summed to create a total ranging from 0 to 68, with higher scores indicating more severe impact on HRQOL. The subscale scores range from 0 to 16 for symptoms, 0 to 20 for psychosocial and 0 to 32 for activities-adaptations. Appendix 10.8

8. FACIT-Fatigue
   The FACIT-Fatigue is a 13-item questionnaire ([R10-6433], [R07-4311], [R16-0029]) that assesses self-reported fatigue and its impact upon daily activities and function. Answers are based on a 5-point Likert scale. Responses of "not at all," "a little," "somewhat", "quite a bit," and "very much" are available for each question, and correspond to scores of 0, 1, 2, 3, and 4, respectively (total score range: 0-52). A minimal clinically important difference (MCID) of 3-4 points in change score has been reported [R16-0029]. The recall period for items is 7 days. Appendix 10.9

9. PGI-C
   The PGI-C is a 1-item tool assessing the change of HS start of taking the study medication by 5-point Likert-type scale. The tool is required for anchoring of other instruments and endpoints. Appendix 10.10

10. PGI-S
    The PGI-S is a 1-item tool assessing the severity of HS over the last week by 4-point Likert-type Scale. The tool is required for anchoring of other instruments and endpoints. Appendix 10.11

5.1.1 Patient diary

The Patient Global Assessment of HS Pain will be completed on a daily diary by subjects from Screening through Week 12.
If pain diaries are not completed for at least the seven consecutive days just prior to the Baseline visit, the subject may not be randomized.
The Patient Global Assessment of HS Pain will be used to assess the worst HS pain. Ratings will range from 0 (no HS pain) to 10 (HS pain as bad as you can imagine).
For the daily assessments being completed from Screening to Week 12, subjects should be instructed to complete the assessment before they go to bed, and respond to the items based on a recall period of the "last 24 hours".

Further instructions on diary and diary completion can be found in the ISF.

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Physical examination
- Vital signs
- Clinical laboratory values (haematology, clinical chemistry, coagulation and urinalysis)
- 12-lead ECG
- Adverse events
- Serious adverse events (SAEs)
- Intensity of adverse events will be assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (refer to ISF for details)

5.2.1 Physical examination

Physical examinations will be performed at the time points specified in the Flowchart.

A complete physical examination will be done at screening. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

For subsequent visits, targeted physical examinations will be done. These will include the evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.

Measurement of height and body weight and waist circumference will be performed at the time points specified in the Flowchart. BMI will be automatically calculated.

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flowchart, prior to blood sampling.
This includes temperature, respiratory rate, systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute). Respiratory rate, pulse rate, and blood pressure will be measured after patients have been sitting comfortably for at least five minutes. The results must be included in the source documents available at the site. Measurement of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements.
Vital signs will be measured additionally 10 min post-dose after s.c. administration and 5 and 60 min. post-dose in case of i.v. study drug administration.
Hypersensitivity reactions should be treated according to medical standards. Pre-medications for further injections might be considered and will be agreed on between investigator and the Sponsor.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3:1 and 5.2.3:2. For the sampling time points please see the Flowchart. More frequent blood sampling may be done whenever the investigator deems necessary. Unscheduled safety laboratory examinations will be reported in the CRF along with the results.

All safety laboratory analyses will be performed by a local laboratory.

It is preferred but the patients do not have to be fasted for the blood sampling for the safety laboratory.
It is the responsibility of the investigator to evaluate the laboratory results from the local laboratory.

Clinically relevant abnormal findings as judged by the investigator will be reported as baseline conditions or adverse events (please refer to section 5.2.6).
A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed and should be repeated until normalization or stabilization or until an alternative explanation has been found. Abnormal laboratory values will be also graded for intensity by using RCTC Version 2.0 criteria. [R13-3515].

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see section 5.2.6.1) and the DILI Checklist provided in the ISF eDC system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

Table 5.2.3:1 Infection testing at screening and EoT visit

Category	**Test name**
Infection Testing	Hepatitis B Surface Antigen (qualitative)[5] Hepatitis B core Antibody[5] HBV-DNA (quantitative) at screening and EoT Visit[1] Hepatitis C Antibodies (qualitative) [5] HIV-1, and HIV-2 Antibody (qualitative) [5] QuantiFERON®-TB-Gold Plus[2, 3, 4] T-spot TB test
Serum Pregnancy test (only for female patients of childbearing potential)	Human Serum Chorionic Gonadotropin

1 A HBV-DNA should be conducted if Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative. These evaluations should be conducted at screening and at the EoT visit
2 There is the trial site option to perform a PPD skin test.
3 Patients with indeterminate QuantiFERON or invalid/borderline T-spot may be retested with IGRA (once) and if inconclusive should have a PPD skin test. .
4 In subjects with a negative QuantiFERON®-TB-Gold Plus or PPD skin test, the test should be repeated at the EoT visit. Results of the PPD test should be collected in the CRF.
5 If determined as negative at screening, there's no need to retest at EoT.

Table 5.2.3:2 Safety laboratory tests

Category	Test name
Haematology	Hematocrit (Hct) Hemoglobin (Hb) Glycosylated Hbc (HbA1c) (Only at baseline) Red Blood Cell Count/ Erythrocytes Reticulocyte Count White Blood Cells / Leukocytes Platelet Count/ Thrombocytes
Diff. Automatic	Neutrophils (relative and absolute count) Eosinophils (relative and absolute count) Basophils (relative and absolute count) Monocytes (relative and absolute count) Lymphocytes (relative and absolute count)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Activated Partial Thromboplastin Time (aPTT)

	Prothrombin time (INR) Fibrinogen
Enzymes	AST (GOT) ALT (GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Amylase Lipase
Electrolytes	Calcium Sodium Potassium Chloride
Substrates	Glucose BUN (blood urea nitrogen) Uric acid Creatinine[6] eGFR (estimated by CKD-EPI formula) (only at screening) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Troponin (Reflex, in case of elevated CK) Protein, Total Albumin C-Reactive Protein (CRP and HS-CRP (high sensitivity – CRP))[5] Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol
Specific gamma-globulin quantification	IgE[1]
Urine Pregnancy test (only for female patients of childbearing potential)	Human Chorionic Gonadotropin in urine

Serum Pregnancy test (only for female patients of childbearing potential at screening. At later visits only if urine pregnancy test is positive)	
Hormones (only at screening)	TSH (free T3 and free T4 in case of abnormal TSH result)
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leukocytes Urine pH
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes
Urine (only at screening)	Albumin (quantitative)
Infections screening	HBV-DNA (quantitative) at EoT visit [2]
Interferon Gamma Release Assay	QuantiFERON®-TB or T-spot at EoT visit [3,4]

1Only in case of allergic reaction
2 HBV-DNA in case of occult HBV infection (for definition see Table 5.2.3:1 footnote 2)
3 Patients with indeterminate QuantiFERON or invalid/borderline T-spot may be retested with IGRA (once) and if inconclusive should have a PPD skin test. .
4 In subjects with a negative QuantiFERON®-TB-Gold Plus or PPD skin test, the test should be repeated at the EoT visit.
5 At screening and at EoT or EOS (as applicable) visits, a blood sample will be obtained to measure hs-CRP. This analysis will be done in the local laboratory.
6 Creatinine can be measured by any of the three serum creatinine assays listed in the table below:

Short name	Name of serum creatinine assay	Substrate	Other information
CREE	Creatinine, enzymatic	creatinine	Enzymatic
CREJIDMS	Creatinine, Jaffe, IDMS	creatinine	Jaffe reaction, IDMS standardized
CREJ	Creatinine, Jaffe, Not IDMS	creatinine	Jaffe reaction, Not IDMS standardized

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.
Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.
Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

All cases of malignancies that are detected during the trial will be reported as SAEs. Patients with a history of malignancy (except for specific cancers) will be excluded from this trial per the exclusion criteria (Section 3.3.3).

5.2.5.1 Suicidality

Suicidal thoughts and behavior will be assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS, [R08-1147]).
The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behavior and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behavior and ideation.
The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counselor, nurse, or coordinator with C-SSRS training. It has a typical duration of five minutes, and causes only a low burden on subjects. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behavior, and may be expanded to up to 17 items in case of positive responses. Free text entries are allowed for; the investigator has to directly evaluate the scale and write a report. In this trial paper forms will be used for the assessment of the C-SSRS® and results will be transcribed into the e-CRF.
The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the Screening Visit/Visit 1 (using the 'baseline/ screening' version) with the aim to exclude patients with active moderate to severe symptomatology within a specified time prior to the screening or screening visit. The lifetime and the past year history of suicidal ideation and behavior will also be recorded.
After the screening visit, the assessment 'since last visit' version will be performed at each visit. The investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated or reports may be validated by a consulting

psychiatrist or other mental health professional expert. If there is a confirmed positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the patient, and/or is to consult a mental health professional. If the positive report is confirmed, appropriate actions for the patient's safety have to be initiated.
All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior must be reported as separate SAEs by the investigator.
For 'Self-injurious behavior, without suicidal intent', standard AE / SAE reporting rules are to be applied.
For each negative report (suicidal ideation type 1, 2 or 3) after the start of the trial, the investigator is to decide based on clinical judgment whether it represents an Adverse Event (AE) as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.6.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

1. results in death,
2. is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
3. requires inpatient hospitalisation or prolongation of existing hospitalisation
4. results in persistent or significant disability or incapacity,
5. is a congenital anomaly / birth defect,

6. is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above. The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in section 5.2.6.2.
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in section 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.

The following are considered as AESIs:

Systemic hypersensitivity including infusion reaction and anaphylactic reaction
Any suspicion of severe infusion reaction systemic / hypersensitivity reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (Appendix 10.13 [R11-4890]).

Severe infections (according to RCTC grading)

Opportunistic and mycobacterium tuberculosis infections
These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, post-transplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only),

paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression [R17-2617].

Hepatic injury
A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or in samples drawn within 30 days of each other
  OR
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF.
In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.6.1.5 Intensity (severity) of AEs

The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by [redacted] [R13-3515]. Refer to the ISF for intensity/severity classification.

Intensity options are:
Grade 1 mild
Grade 2 moderate
Grade 3 severe
Grade 4 life-threatening

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.

- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.
For patients not rolling over to OLE trial, the following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of study:
  all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of study:
  the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see section 5.2.6.2.2), but not on the CRF.

For patients rolling over to OLE trial the following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent of the parent trial onwards until the first dose of trial medication in the extension trial:
  all AEs (serious and non-serious) and all AESIs.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable" , or no further information can be obtained.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.
Protocol specified exempted events should be collected on the appropriate CRF page only.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Spesolimab concentrations will be reported descriptively. No PK parameters will be calculated. PK data will be incorporated into a larger pharmacometric analysis with other trials of the spesolimab project. Also, ADAs will be measured and their impact on PK will be assessed. The relationship between PK and selected efficacy endpoints, biomarkers and

AEs may be assessed. PK and demographic data together with treatment assignments and dosing information may be made available to individuals outside of the trial team for the purpose of PK dataset generation in accordance with sponsor's standard procedures.

Refer to the Flowchart for the time points of PK and ADA/Nab sample collection. Date and exact time of drug administration and PK and ADA/Nab sampling will be recorded on CRFs. On visits with study medication dosing, PK and ADA/Nab samples should be collected prior to administration of study drug.

5.3.2 Methods of sample collection

5.3.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of spesolimab plasma concentrations, approximately 3.0 mL of blood will be taken from a forearm vein into a K_2EDTA (ethylendiaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the Flowchart under PK sampling. Handling procedures can be found in the laboratory manual in the ISF.

Samples will be stored in a freezer set at the analytical laboratory until the finalization of the clinical trial report (CTR). The plasma samples may be used for further methodological investigations, (e.g. stability testing) however, only data related to the analyte will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.3.2.2 Sampling for ADA/Nab assessment

For ADA assessment, approximately 3.0 mL of blood will be taken from a forearm vein into a K_2EDTA anticoagulant blood-drawing tube at the time points listed in the Flowchart under plasma ADA/Nab. For Nab assessment, approximately 3.0 mL of blood will be taken from a forearm vein into a serum blood drawing tube at the time points listed in the Flowchart under ADA/Nab Sampling. Handling procedures can be found in the laboratory manual in the ISF.

Samples will be stored in a freezer set at the analytical laboratory until they are analyzed. The plasma/serum samples may be used for further methodological investigations, e.g.for further investigations to characterise ADA response or to address
Health Authority questions regarding the results/methodology, however only data related to the anti-drug antibodies will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.

[redacted]

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in sections 5.1 and 5.2.
Blood samples (serum and whole blood for RNA sequencing), skin biopsies for immunohistochemistry (IHC) and RNA sequencing will be collected at time points indicated in the Flowchart for the analysis of biomarkers. After completion of the study these samples may be used for not yet specified non-genetic biomarker analyses associated with autoimmune diseases as well as method development and evaluation.

5.4.1 Biochemical and cellular biomarkers

The role of spesolimab on the IL36R pathway will be demonstrated by assessing biomarkers in skin biopsies and blood including, but not limited to IL36α and IL36γ at different time points post treatment compared to baseline. To demonstrate treatment effect of spesolimab in the peripheral compartment, pre- and at various time points post treatment, physiological response biomarkers including, but not limited to CRP, lipocalin 2, and S100 proteins will be evaluated. In addition, to understand the tissue-specific impact of spesolimab over time, skin biopsies (lesional and non-lesional) will be collected at baseline and at selected time points post treatment. The skin biopsies will be used for assessment of skin protein biomarkers using techniques such as immunohistochemistry (IHC).

5.4.2 Pharmacogenomics biomarkers

Skin biopsies and blood samples (PBMCs) will be taken at time points indicated in the Flowchart and used for RNA extraction and subsequent gene expression analysis to identify genes involved in the drug's mechanism of action or the pathology of the disease.

5.4.3 Methods of sample collection

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling timepoints refer to the Flowchart.

For the skin biopsies, one (1) punch biopsy from lesional skin (for histopathologic, immunohistopatholic and RNASeq) will be performed at baseline prior to receiving treatment (V2), on Visit 5 and on Visit EoT. A paired non-lesional skin biopsy will also be collected at baseline. At sites with ultrasound capability, ultrasound will be used to identify dermal tunnels and deep abscesses in the sites of inflammation so as to take accurate biopsies RNA and IHC samples can be taken from one biopsy sample bisected in two pieces. One (1) piece

for RNA extraction. One (1) piece for IHC. At sites without ultrasound capability, biopsies will be obtained without ultrasound guidance.
Please refer to the ISF for further instructions regarding selection, collection, handling, storing and shipment.
For the assessment of RNA expression whole blood will be collected from a forearm vein and stored according to standard procedure provided in ISF.

5.5 BIOBANKING

Participation in biobanking is voluntary and not a prerequisite for participation in the trial.
Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

Unspecified DNA Banking:
An additional blood sample for DNA banking will be collected in PAXgene Blood DNA tube at Visit 2 (see FlowChart). The DNA Banking sample, derived from the original blood sample, will be stored at Boehringer Ingelheim. The stored DNA may be retrospectively analysed.

5.6 OTHER ASSESSMENTS

Photographs
Subjects will be asked to have photographs taken of their disease response during the study. Subjects who consent will have photographs taken at the designated study visits listed in the Flowchart. The cameras for the photographs will be standardized and supplied to the site by a central photography service. Sites will submit the digital images to the centralized photography service. Training and detailed instructions will be provided by the central photography vendor.

5.7 APPROPRIATENESS OF MEASUREMENTS

All methods used are standard methods.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flowchart. Each visit date (With its window) up to EoT is to be counted from Visit 2 at Day 1 (first trial drug administration day). If any of these visits has to be rescheduled, the date of subsequent visit should be calculated from Day 1.
EoT refers to the End of Treatment visit at week 12 (or earlier if a patient terminates study drug before week 12).

For patients not rolling over to OLE trial, FUP1 refers to Follow-up visit 1 which will be scheduled 8 weeks after last study drug administration. EoS refers to the End of Study visit which will be scheduled 16 weeks after last study drug administration (after REP period).

For patients rolling over to OLE trial, EoT and EoS dates will be the same. These patients will not undergo the safety follow-up period (i.e will not do FUP1 and EoS visits) because they will be followed in the OLE trial. For these patients EoT visit of this trial and first visit of the OLE trial should occur the same day.

Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

In exceptional cases, if standard visits at the trial sites are impossible because of COVID-19 related safety risks, the investigator must assess the risk-benefit for each individual patient and may decide to perform a visit remotely if this is in the best interests of the patient and if agreed with the sponsor.
All COVID-19 related deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the relevant Flowchart and the respective protocol sections. Refer to section 5 and section 10 (Appendices) for explanations of procedures. Additional details on procedures at selected visits are provided below.
Patient Reported outcomes (PROs) should be completed by the patient on his/her own in a quiet area/room before any other visit assessments or treatments and, as much as possible, before any interaction with the investigator or other members of the study team.

Measurements of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements and be assessed pre-dose at all dosing visits.

The Baseline/screening scale of the C-SSRS will be administered for eligibility confirmation and the follow-up scale at all visits for assesment of suicidality.

Assessments/procedures to be done before study drug administration when applicable:

At visits with study drug administration safety labs and urine pregnancy test should be done prior to the study drug administration. Pre-dose PK/ADA samples will be obtained approximately within 1 hour prior to start of i.v. infusion or s.c. injections administration.

The following sequence of procedures (where applicable) is recommended and can be done within each visit window (See Flowchart):

1. PROs
2. C-SSRS
3. AE and concomitant therapy collection; smoking/tobacco/nicotine status
4. Physical examinations (including predose vital signs)
5. ECG
6. Abcess and inflammatory nodule count
7. Draining fistula count
8. HiSCR, IHS4, HS-PGA and HASI assessment
9. Photographs of skin lesions
10. Ultrasound lesion evaluation (if applicable. See section 5.4.3)
11. Skin biopsies
12. Blood and urine sampling, blood for hs-CRP, urine pregnancy testing (if applicable), PK, ADA/Nab, and biomarkers.
13. Assign (IRT call) /Administer study drug
14. Local tolerability
15. Post-dose vital signs

Due to COVID-19 pandemic restrictions, the trial conduct may need to be adjusted and remote visits performed as instructed by the Sponsor, based on each patient benefit-risk assessment.

6.2.1 Screening

Screening Period

Study requirements, including the procedure for the follow-up of prematurely withdrawn patients must be fully explained to the patient and written informed consent obtained prior to initiating any study-related evaluation. The importance of staying in the trial until completion of all study requirements will be emphasized. No trial procedures should be done unless the patient has consented to taking part in the trial.

Once consented, the patient is considered to be enrolled in the trial and has started screening. The patient should be recorded on the enrolment log and be registered in IRT as a screened patient. Patients will be assigned a patient number generated via the IRT system.

Screening (Visit 1) should normally take place no more than 28 days before Visit 2. Visit 1 procedures may be completed over multiple physical visits, if needed. The time window for Visit 1 may be extended at the discretion of the CT Manager in conjunction with the CT Leader on a case by case basis.

For the comprehensive list of the trial procedures required at the Screening Visit (Visit 1) please refer to Flowchart. Patients who have a laboratory test value that makes their participation uncertain may have the test repeated to determine eligibility; however, the result

must be available prior to Visit 2 (Day 1). Baseline conditions and medical history will be assessed during screening.

Demographics:
Informed consent date, gender, ethnicity and race (if allowed by local law) will be collected and reported in the eCRF.

Baseline Conditions
Chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, ECG, safety labs, and any condition requiring therapy will be reported on the Baseline Condition eCRF page. The smoking status and history based on the calculation of pack-years will be collected as well.

Infections screening
Infections testing will include tuberculosis, hepatitis B, hepatitis C, and HIV assessments (see section 3.3.3 and Table 5.2.3:1).

Medical History:

Medical history of HS, including the previous treatment, will be collected and reported in the eCRF.
Information on clinically significant previous and concomitant illnesses, other than HS, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the screening visits will be recorded as medical and surgical history at screening on the Baseline Condition page in the eCRF.
Patients who fail screening (i.e. does not meet the eligibility criteria) following Visit 1 assessments should be registered as a screen failure in IRT.

Re-Screening
Re-screening of a previously screen failed patient will be permitted once in a case by case basis in agreement with the Sponsor. Details of IRT procedures can be found in the IRT manual located in the Investigator Site File (ISF).
For the comprehensive list of the trial procedures required at the Screening Visit (Visit 1) please refer to the Flowchart.
Re-screened patients will need to sign a new informed consent before any re-screening procedures and will be given a new unique subject number. If a patient is re-screened and there are valid screening determinations from his/her previous participation in the trial, like for example safety labs, performed within 28 days prior to baseline (visit 2), these do not need to be repeated.

6.2.2 Treatment period(s)

When eligibility of the patient to participate in the trial is confirmed, randomization via IRT will be performed at Visit 2. The treatment period is from Day 1 to Week 12 (End of Treatment, EoT). Procedures described in the Flowchart for each visit should be performed.

Loading Period
During the first 3 weeks of the treatment period, the loading dose(s) are administered at 3 visits (Visit 2 to Visit 4) with weekly 90min iv infusions of 1200mg spesolimab. 450mg vials of 7.5mL each will be used to prepare the infusions. Please see the Flowchart and section 3.1 for further details.

Maintenance Period
From visit 5 to visit 8, maintenance doses are administered subcutaneously by pre-filled injections of 2mL containing 300mg spesolimab each. 4 injections will be used at each visit for a total dose of 1200mg every two weeks.

At visits during the treatment period, venepuncture (i.e. safety laboratories, PK, ADA, biomarkers) and skin biopsies should be the last procedures performed prior to study drug administration. Only after all blood specimens are collected, and urine pregnancy testing (if applicable) is done, will each eligible patient receive a dose of the assigned trial medication.

6.2.3 Follow-up period and trial completion

For all randomized patients termination of trial medication (EoT) and trial completion (EoS) must be recorded on the corresponding CRFs.
For patients completing the randomized trial treatment regularly at Week 12 (EoT) and not rolling-over to the OLE trial, safety follow-up visits will be performed at Week 20 (FUP1 Visit) and at Week 28 (EoS, EoS Visit).
Patients who roll-over to the OLE trial will complete their participation in the trial at week 12 (EoT visit)

Early treatment discontinuation
Patients who discontinue treatment prematurely prior to the planned EoT visit (Week 12) should be registered as withdrawn from treatment in IRT.
Patients should follow the scheduled visits as much as possible as defined in the Flowchart, this is: the EoT should be conducted either immediately or as soon as possible, followed by the FUP1 visit 8 weeks after the last trial drug administration date and the EoS visit 16 weeks after the last trial drug administration date. All efforts should be made to keep the patient in observation for at least 16 weeks after the last dose of the study drug.

Treatment completion
Treatment completion is defined as a patient having completed treatments till planned EoT visit (Week 12).

Trial completion:
Trial completion is defined as a patient having reached the EoS Visit per protocol (or rolled-over to OLE trial and therefore have completed an EoT/EoS visit).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The primary objective of the trial is to demonstrate proof of clinical concept activity of spesolimab on the percent change from baseline in total abscess and inflammatory nodule count using a mixed effect model for repeated measurements (MMRM). No formal statistical testing is planned. For the proof of concept, the treatement effects of spesolimab compared to placebo will be estimated. Hereby, the adjusted difference in percentage change from baseline in total abscess and inflammatory nodule count between spesolimab and placebo will be evaluated.

For primary analysis of the primary endpoint, all measurements will be included but those data collected after the use of rescue therapy for the purpose of disease worsening will be censored. The stratification factor, TNFi-naive population versus TNFi-failure population will be included into the model.

7.1 NULL AND ALTERNATIVE HYPOTHESES

No hypothesis testing will be performed in the confirmatory sense. All the analyses will be performed in an exploratory fashion to better understand the efficacy and safety profile of spesolimab.

7.2 PLANNED ANALYSES

The primary analysis of the trial will be performed once all randomized patients have either (1) completed the 12 weeks treatment period of the trial, or (2) have reached the 12 weeks after starting of treatment if early discontinued from the trial treatment. Final trial analysis is planned to be performed at the end of the study once all randomized patients have completed the study (including any follow-up period), if applicable. The primary analysis and final analysis may be performed as a single analysis (at the time of trial completion), if, prior to the time of the primary analysis, the trial team agrees that the expected time interval between the planned analyses is insufficient to justify the performance of separate analyses.

Details of treatment unblinding for the primary analysis and final analysis are described in section 4.1.5.1. Details of the analysis to be performed will be described in the TSAP.

7.2.1 General considerations

The following populations are planned in this trial for main efficacy and safety analyses:

Treated Set (TS)
This patient set includes all patients who were randomized and received at least one dose of study drug. It will be the main analysis set for presentation of efficacy and safety. Patients will be analyzed according to the actual treatment.

Per-Protocol Set (PPS)
This patient set includes all patients in the safety analysis set who adhered to the CTP without any Important Protocol Deviations (IPDs) potentially affecting the study outcome which lead to exclusion from the PPS. This set will be used for sensitivity analysis on the primary endpoint.

Important deviations of the protocol will include deviations of the key inclusion and exclusion criteria, incorrect medications taken, concomitant use of restricted medications and any other deviations of the protocol deemed important by the study team. All decisions concerning important protocol deviations will be made prior to un-blinding of the database for the final trial analysis.

Further analysis sets, e.g. for the biomarker assessments, will be defined in the Trial Statistical Analysis Plan (TSAP).

Standard statistical parameters (number of non-missing values, mean, standard deviation (SD), median, quartiles, minimum and maximum) or frequency tables (including patient frequencies and percentages) will be calculated where appropriate.

7.2.2 Primary endpoint analyses

The difference in percent change from baseline in total abscess and inflammatory nodule at Week 12 between spesolimab and placebo is the primary endpoint of this trial. All on-treatment data are planned to be included into analysis but any data after use of any rescue therapy will be censored in line with the primary objective to estimate the treatment effect in treated patients assuming they do not receive rescue therapy (priamry estimand). To account for the repeated nature of the data, the primary analysis is a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) comparing the adjusted relevant difference between the two arms.

The analysis will include the fixed categorical effects of treatment at each visit, stratum and the fixed continuous effect of baseline at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure to model the within-patient measurements.

The statistical model will be as follows:

$$y_{ijkm} = \beta_j S_i + \tau_{jk} + \Phi_m + e_{ij}$$

With

y_{ijkm}	response variable for patient i in stratum m at visit j receiving treatment k
S_i	baseline measurement of patient i, *i=1,2,…*
β_j	coefficient of baseline effect at visit j
τ_{jk}	effect of treatment k at visit j, *j=3,…,9 and k=1, 2*
ϕ_m	effect of stratum m, m=*1,2*
e_{ij}	random error associated with visit j of patient i.

Errors are independent between patients with $e_{ij} \sim N_Z(0, \sum)$ and $\sum$ is an unstructured covariance matrix.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Due to the exploratory character of this trial no significance test will be done. However, least-squares means (adjusted means) of each arm as well as adjusted treatment differences will be provided together with two-sided 95 %-confidence intervals for each time point.

The patients will be analysed according to the stratum to which they belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomization and is therefore consistent with regulatory guidance. Procedures to follow if the analysis fails to converge will be described in the TSAP.

Secondary analysis of the primary endpoint will include:

- A sensitivity analysis utilizing the PPS to evaluate the impact on treatment outcomes of patients who may have relevant deviations from the conduct described in the CTP;
- The effect of stratum (TNFi-naive population versus TNFi-failure population) on the primary endpoint will be descriptively displayed via subgroup assessments.

7.2.3 Secondary endpoint analyses

The continuous secondary endpoints at Week 12 will be analysed using a MMRM approach based upon the estimand concept and model specification as described for the primary endpoint.

The binary secondary endpoints will be evaluated descriptively by treatment arm via frequency tables (with 95% confidence interval) based on TS. If needed, a logistic regression model on binary endpoint at Week 12 will be applied as well. The model will include treatment and stratification factor (TNFi-naive population versus TNFi-failure population) as two categorical variables. As in the case of the primary estimand, any binary data collected after use of any rescue therapy will be censored and then imputed using the NRI method as described in section 7.3.

Further details will be provided in the TSAP.

[redacted]

7.2.5 Safety analyses

Adverse events will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard Boehringer Ingelheim's summary tables and listings will be produced.

All randomized and treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned. Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events (TEAE). To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'; the residual effect period (REP) is defined as 16 weeks after the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class (SOC) and preferred term after coding according to the current version of the MedDRA at database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The later will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Immunogenicity data will be analysed in a descriptive way.

7.2.6 Other Analyses

Biomarker analyses
The statistical analysis for biomarker assessments (cf. Section 5.4) is mainly descriptive.
Summary statistics and summary plots are produced for each assessment at each time point, and for changes from baseline when appropriate.
Correlations between biomarkers and clinical endpoints may also be examined descriptively.
For a visual assessment of this analysis scatter plots may be produced.

Changes in the gene expression profile from baseline to post-baseline will be summarized and described for selected genes. Significantly up- or down-regulated genes are reported.

Thresholds for defining significantly up- and down-regulations will be given in the statistical analysis plan.

Further details will be discussed in the statistical analysis plan.

7.2.7 Interim Analyses

No interim analysis is planned in this trial.

In order to ensure the patient's safety during the trial, a fully external DMC, independent of the trial and project teams, will review all available unblinded safety data as well as selected efficacy data at regular intervals following first-patient-in. A DMC SAP which describes the analyses required for assessment by the DMC will be produced. Further details will be provided in a DMC charter.

7.3 HANDLING OF MISSING DATA

For primary efficacy endpoint and other endpoints which are continuous in nature, the use of a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach, if feasible, will ensure that missing data are handled implicitly, via a missing at random assumption, by the statistical model.

For efficacy endpoints which are binary nature, a Non Response Imputation (NRI) approach will be applied to the missing visits up to Week 12; that is, imputing as a failure to achieve a response in the visits with missing endpoint score, however:

- If there are available data at the visits both before and after the visit with a missing outcome, then impute as a success only if both the preceding and the following measurement indicate success and no rescue medication has been given during this period.

- Otherwise, impute as a failure to achieve a response (i.e. no response imputation)

NRI is a conservative imputation scheme because it assumes that use of rescue therapy or missing data due to any other reason is related to treatment failure. In addition, for secondary binary endpoint, HiSCR at Week 12, multiple imputation based method will be applied as sensitivity analysis.

Further sensitivity analyses to assess the robustness of the results on efficacy endpoint will be described in the TSAP if necessary.

With respect to safety evaluations, it is not planned to impute missing values.

7.4 RANDOMIZATION

BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudorandom number generator so that the resulting treatment will be both reproducible and

nonpredictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

Stratification of the randomization will be performed for TNFi-naive population versus TNFi-failure population. Approximately 33 patients from TNFi-naive population and 12 patients from TNFi−failure population are planned to be randomized. Once either subpopulation has recruited the planned number of patients, the screening of that subpopulation may be considered to be closed.

Within each stratum, patients will be randomized in a 2:1 randomization ratio to receive Sepsolimab vs placebo. The randomization will be done in blocks to achieve balanced allocation.

The process of randomization is done via an IRT.

7.5 DETERMINATION OF SAMPLE SIZE

This is a proof of clinical concept trial to explore a benefit of spesolimab over placebo in terms of the primary endpoint, percent change from baseline in total abscess and inflammatory nodule count at Week 12 based on the MMRM method.

With reference to the pivotal trials of Adalimumab [R20-3157] which is the only approved biologic for HS, it is expected that patients on placebo arm could achieve approximately a 20% reduction after 12 weeks of treatment. In contrast, it is expected patients on spesolimab arm could achieve a 60% to 65% reduction which is around 40% to 45% superior to placebo. The standardized deviation is assumed to be 45% for each arm.

The pivotal trials of Adalimumab [R20-3157] shows that the primary endpoint, percent change from baseline in total abscess and inflammatory nodule count at Week 12, is skewed in both active treatment arm and the placebo arm. Under such situation of skewness, for primary endpoint, MMRM method is still valid as the asymptotic normality of the distribution of the point estimate still holds. However, the commonly used “exact” methods for calculating sample size become inappropriate in this case, as they are based on a normality assumption of the data. Therefore, a simulation method is used to calculate the sample size as below:

Step 1: Data for the primary endpoint for both arms are generated from Gamma distributions respectively to allow for skewed distributions. The distributions for the percent change are parameterized using the published summary statistics from Adalimumab trial data [R20-3157]. The 10,000 datasets are generated

Step 2: For each repetition of the 10,000 iterations, the mean difference between the two arms is calculated. The proportion of iterations with a difference of at least 30% in favor of Spesolimab is calculated for each parameterization setting.

It is assumed that there is no missing data for the primary endpoint so the final primary endpoint analysis using MMRM is expected to be on complete data. Therefore, in the sample size calculation, the mean difference between two arms derived from the simulation above,

which only considers the single time point of interest (at week 12) should approximate the week 12 estimate derived from the MMRM method using all time points over time. All calculations are performed on R version 3.3.2 and the results are summarized in Table 7.5:1.

Table 7.5: 1 Probabilities to observe at least 30% difference on % change from baseline in total abscess and inflammatory nodule count at Week 12 for spesolimab (30 pts) vs.placebo (15 pts)

Assumed % change from baseline for spesolimab (SD) vs. Placebo (SD)	Probabilities to detect at least 30% difference for spesolimab vs. placebo
-20% (45%) vs -50% (45%)	0 %
-20% (45%) vs -20% (45%)	2.3%
-50% (45%) vs -20% (45%)	49.9%
-55% (45%) vs -20% (45%)	62.9%
-60% (45%) vs -20% (45%)	75.4%
-62% (45%) vs -20% (45%)	80.1%
-65% (45%) vs -20% (45%)	85.2%
-50% (45%) vs -30% (45%)	23.8%
-55% (45%) vs -30% (45%)	35%
-60% (45%) vs -30% (45%)	49.3%
-65% (45%) vs -30% (45%)	62.4%

Therefore, with an expected 62% reduction from baseline in total abscess and inflammatory nodule count at Week 12 on spesolimab and 20% reduction on placebo, the probabilities to detect at least 30% difference of spesolimab relative to placebo is 80.1%.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally acceptable representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally acceptable representative.

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see section 8.3.2). The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging (e.g. photographs) or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Patient reported outcome forms (including diary) and corresponding investigator assessment form.
- ECG results (original or copies of printouts)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed"). The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.
The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A DMC will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.
The DMC will evaluate unblinded safety and efficacy data in order to recommend whether the trial should continue, be modified or stopped due to safety or ethical concerns. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.
The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to
1. manage the trial in accordance with applicable regulations and internal SOPs,
2. direct the clinical trial team in the preparation, conduct, and reporting of the trial,
3. ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service, and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 TIME SCHEDULE FOR PHARMACOKINETIC (PK), ANTIDRUG ANTIBODY (ADA) AND NEUTRALIZING ANTIBODY (NAB) BLOOD SAMPLING

Table 10.1: 1 Time schedule for PK/ADA/Nab blood sampling during treatment

Treatment Course	Visit	Day	Time Point [hh:min]	CRF Time /PTM	Event	Sample No.
	2	1	Just before drug administration	-1:00	PK/ADA/ Nab Blood	1
	3	8 (±1)	Just before drug administration	-1:00	PK Blood	2
	4	15 (±1)	Just before drug administration	-1:00	PK/ADA/ Nab Blood	3
	5	29 (±3)	Just before drug administration	-1:00	PK/ADA/ Nab Blood	4
	6	43 (±3)	Just before drug administration	-1:00	PK Blood	5
	7	57 (±3)	Just before drug administration	-1:00	PK/ADA/ Nab Blood	6
	8	71 (±3)	Just before drug administration	-1:00	PK Blood	7
	EOT	See Flowchart			PK/ADA/ Nab Blood	8
	FUP 1	See Flowchart			PK/ADA/ Nab Blood	9
	EoS	See Flowchart			PK/ADA/ Nab Blood	10

10.2 HIDRADENITIS SUPPURATIVA CLINICAL RESPONSE (HISCR)

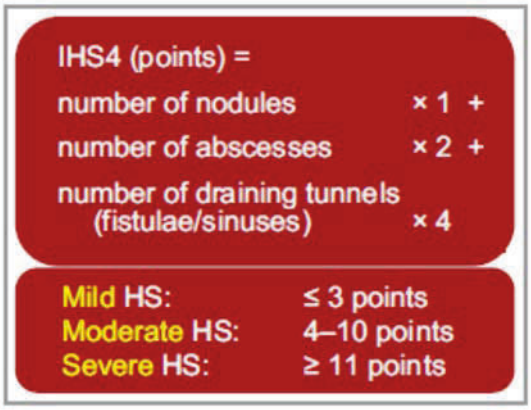
Defined as at least a 50% reduction from baseline in the total abscess and inflammatory nodule count, with no increase in the abscess or draining fistula count.

	Patient 1			Patient 2		
	Baseline	Week 12	HiSCR Criteria	Baseline	Week 12	HiSCR Criteria
Total abscess and inflammatory nodule (AN) count	20	10	✓	20	10	✓
Abscesses	5	5	✓	5	8	✗
Inflammatory nodules	15	5	✓	15	2	✓
Draining fistulas	4	4	✓	4	2	✓

Fig. Source: HUMIRA Hidradenitis Suppurativa Clinical Response (HiSCR) Data (humiradermpro.com)

10.3 INTERNATIONAL HIDRADENITIS SUPPURATIVA SEVERITY SCORE SYSTEM (IHS4)

International Hidradenitis Suppurativa Severity Score System (IHS4). A nodule (inflammatory nodule) is a raised, threedimensional, round, infiltrated lesion with a diameter of >10 mm. An abscess is a tender but fluctuating mass with a diameter of >10 mm, surrounded by an erythematous area; the middle of an abscess contains pus. A draining tunnel is a raised, tender but fluctuating longitudinal mass of variable length and depth, ending at the skin surface, and sometimes oozing a fluid. Fistulae and sinuses are examples of tunnels.



Source: the European Hidradenitis Suppurativa Foundation Investigator Group, Zouboulis C.C., Tzellos T., Kyrgidis A., Jemec G.B.E., Bechara F.G., et al. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS 4), a novel dynamic scoring system to assess HS severity . Br J Dermatol. 2017 Nov; 177 (5): 1401-1409.

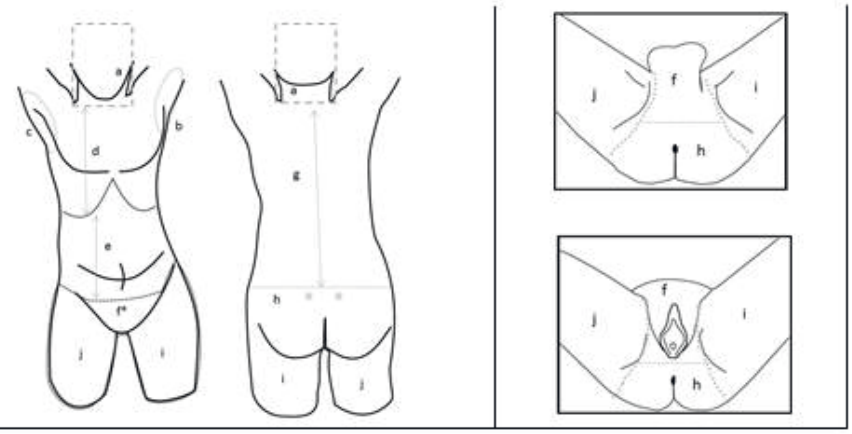
10.4 HIDRADENITIS SUPPURATIVA PHYSICIAN GLOBAL ASSESSMENT (HS-PGA)

The Physician Global Assessment Tool for hidradenitis suppurativa (HS-PGA)[a]	
Clear	No abscesses, draining tunnels, inflammatory nodules or noninflammatory nodules
Minimal	No abscesses, draining tunnels or inflammatory nodules and the presence of noninflammatory nodules
Mild	No abscesses or draining tunnels and 1–4 inflammatory nodules, or 1 abscess or draining tunnel and no inflammatory nodules
Moderate	No abscesses or draining tunnels and ≥5 inflammatory nodules, or 1 abscess or draining tunnel and ≥1 inflammatory nodule, or 2–5 abscesses or draining tunnels and <10 inflammatory nodules
Severe	2–5 abscesses or draining tunnels and ≥10 inflammatory nodules
Very severe	>5 abscesses or draining tunnels

10.5 HIDRADENITIS SUPPURATIVA AREA AND SEVERITY INDEX (HASI)

HASI is modelled after the Psoriasis Activity and Severity Index (PASI).
Four classic signs of HS-related inflammation (erythema, thickness, drainage, tenderness) are included.
Each variable in HASI is scored on a Likert scale (0–3) for each predetermined body region.
For BSA assessment, the number of palms (one palm indicated 1% of the patient's BSA) involved for each body region (head, right axilla, left axilla, anterior chest, back, anterior bathing trunk, posterior bathing trunk, other) is assessed.
This is converted to a percentage of that region.

Hidradenitis suppurativa Area and Severity Index (HASI)



Body Site	Reference BSA	Extent of BSA Involved by Active HS		Percentage BSA Involved by Active HS						
				0	1-9%	10-29%	30-49%	50-69%	70-89%	90-100%
a. Head & Neck	18%									
b. Left Axilla	2%									
c. Right Axilla	2%									
d. Chest	9%									
e. Abdomen	9%		AND							
f. Pubis & Genitals	2%									
g. Back	18%									
h. Buttocks including Intergluteal Cleft	9%									
i. Left Thigh	9%									
j. Right thigh	9%									

	Inflammatory Color Change (AVERAGE red, purple, or other color depending on skin color)				Inflammatory Induration (AVERAGE inflammatory swelling of skin, NOT skin elevation due to scarring)				Open Skin Surface (Extent of exuberant granulation tissue, erosions & ulceration, single or multiple)				Tunnels (Extent of tunneling lesions, single or multiple, draining and non-draining)			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None, Closed	Mild, Limited	Moderate	Extensive	None, Closed	Mild, Limited	Moderate	Extensive
Body Site	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
a. Head & Neck																
b. Left Axilla																
c. Right Axilla																
d. Chest																
e. Abdomen																
f. Pubis & Genitals																
g. Back																
h. Buttocks including Intergluteal Cleft																
i. Left Thigh																
j. Right thigh																

10.6 PAIN NUMERICAL RATING SCALE (NRS)

Please rate the severity of your Hidradenitis suppurativa (HS) pain in the past 24 hours at its worst? **Please mark the number on the 0 to 10 scale below**										
0	1	2	3	4	5	6	7	8	9	10
No pain										Worst possible pain

10.7 DERMATOLOGY LIFE QUALITY INDEX (DLQI)

DERMATOLOGY LIFE QUALITY INDEX **DLQI**

Hospital No: Date:
Name: Score:
Address: Diagnosis:

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

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

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

Please check you have answered EVERY question. Thank you.

10.8 HIDRADENITIS SUPPURATIVA QUALITY OF LIFE (HIS-QOL)

This questionnaire is designed to measure how Hidradenitis Suppurativa (HS) impacts you.

PLEASE READ THESE DIRECTIONS:

It is important to:

1. **Think about your HS** over the past 7 days

2. Think about ***your HS only***, not another condition.

3. **For each line select the single best option**

Please select the single best option for each item

In the past 7 days, how much has your HS caused problems with:	**UNABLE TO DO due to my HS**		Extremely	Very much	Moderately	Slightly	Not at all
1. Walking (not for exercise)	[ ]						
2. Exercising (for example: swimming, jogging, biking, yoga, aerobics)	[ ]						
3. Sleeping							
4. Washing yourself							
5. Getting dressed							
6. Your concentration							

In the past 7 days, how have your current or potential new HS lesions influenced:	Extremely	Very much	Moderately	Slightly	Not at all
7. What you wear to avoid discomfort					

In the past 7 days, how bothered have you been by:	Extremely	Very much	Moderately	Slightly	Not at all
8. Pain					
9. Itch					
10. Drainage					
11. Odor					

Please select the single best option for each item

In the past 7 days, how much has HS caused you to feel:	Extremely	Very much	Moderately	Slightly	Not at all
12. Down or depressed					
13. Embarrassed					
14. Anxious or nervous					

In the past 7 days, how much has HS:			Extremely	Very much	Moderately	Slightly	Not at all
15. Made sexual activity difficult	I am not sexually active [ ]	UNABLE TO DO **due to my HS** [ ]					
16. Affected your desire for sexual activities							

In the past 7 days, how much has HS:			Extremely	Very much	Moderately	Slightly	Not at all
17. Influenced your ability to work or study	I do not work or study [ ]	UNABLE TO DO **due to my HS** [ ]					

10.9 FACIT-FATIGUE

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circl or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

10.10 PATIENT GLOBAL IMPRESSION OF CHANGE (PGI-C)

Please choose the response below that best describes the overall change in your Hidradenitis Suppurativa (HS) since you started taking the study medication.

(Choose one box only)

[1] ___ Much better
[2] ___ A little better
[3] ___ No change
[4] ___ A little worse
[5] ___ Much worse

10.11 PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)

Please choose the response below that best describes the overall severity of your Hidradenitis Suppurativa (HS) over the past week:

[0] ___ None
[1] ___ Mild
[2] ___ Moderate
[3] ___ Severe

10.12 COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

10.12.1 Columbia-Suicide Severity rating Scale (C-SSRS) baseline version

COLUMBiA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it… and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐

5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ***Type # (1-5)*** _____ ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** ***Type # (1-5)*** _____ ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	_____	_____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	_____	_____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	_____	_____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	_____	_____

Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of aborted _____	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐

Suicidal Behavior: Suicidal behavior was present during the assessment period?		**Yes No** ☐ ☐	**Yes No** ☐ ☐
Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

10.12.2 Columbia-Suicide Severity rating Scale (C-SSRS) since last visit version

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

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SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (4) Can control thoughts with a lot of difficulty	____

(3) Can control thoughts with some difficulty	(5) Unable to control thoughts (0) Does not attempt to control thoughts	
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you	(4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain	(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** **No** ☐ ☐ Total # of Attempts _____ **Yes** **No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** **No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** **No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** **No** ☐ ☐
Suicide:	**Yes** **No** ☐ ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).	*Enter Code*

2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	_____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

10.13 DIAGNOSIS OF ANAPHYLAXIS

Clinical Criteria for diagnosing anaphylaxis [R11-4890]

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 (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. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
b. 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.
*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less han (70 mm Hg +[2 x age] from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Date of amendment		05 July 2021
EudraCT number **EU number**		2020-003672-40
BI Trial number		1368-0052
BI Investigational Medicinal Product(s)		Spesolimab (BI 655130)
Title of protocol		Randomized, double-blind, placebo-controlled, study of spesolimab in patients with moderate to severe hidradenitis suppurativa
Global Amendment due to urgent safety reasons		No
Global Amendment		☒
Section to be changed		Protocol Title
Description of change		From Randomized, double-blind, placebo-controlled, study of spesolimab in patients with moderate **or** severe hidradenitis suppurativa To Randomized, double-blind, placebo-controlled, study of spesolimab in patients with moderate **to** severe hidradenitis suppurativa
Rationale for change		HS severity grading is not a binary value
Section to be changed		Flowchart
Description of change		The line of "Patient's Global Assessment of HS Pain" has been deleted.
Rationale for change		It's part of the Patient's Diary.
Section to be changed		Flowchart
Description of change		Footnote #1 has been updated with the addition of the text in bold: 1 Day of Randomization / Day of first intake of randomized medication. **If needed, some visit 2 assessments may be conducted 2 days before or after the actual visit date after consultation with the Sponsor.** Footnote #6 has been updated with the addition of the text in bold: It is preferred but patients do not have to be fasted for the blood sampling for the safety laboratory. At visits with study drug administration this should be done prior to the study drug administration. See Table 5.2.3:2 for detailed information of the tests. **If needed, safety lab**

		samples for Visit 2 can be drawn within 48 hours before the actual visit date.
Rationale for change		Introduce flexibility for investigators and patients
Section to be changed		2.1.3 Secondary endpoint(s) and Protocol synopsis
Description of change		The following secondary endpoints were rephrased as: • Achievement of Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. • Achievement of PGA score of 0 or 1 at Week 12. • Achievement of at least 30% reduction from baseline in Numerical Rating Scale (NRS30) in Patient's Global Assessment of HS Pain at Week 12. • Occurrence of complete elimination of draining fistulas at Week 12 • Occurrence of at least one flare (defined as at least 25 % increase in AN count with a minimum increase of 2 relative to baseline) up to Week 12. And a secondary safety endpoint was added: • The occurrence of Treatment Emergent Adverse Events (TEAEs)
Rationale for change		Clarification as per Country Authority request.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		3.3.2 Inclusion Criteria and Protocol synopsis
Description of change		Criterion #3: the following sentence has been added to the criterion "(If IHS4 scoring is not available, equivalent scoring based on scoring systems as HS-PGA or Hurley are acceptable based on documented investigator assessment)"
Rationale for change		Clarification needed because maybe IHS4 was not in use at the time the patient was diagnosed.

Section to be changed		Exclusion criteria.
Description of change		Exclusion criterion 2: added: Systemic non-biologic immunomodulatory and/or immunosuppressive agents use within 4 weeks (or 5 half lives, whichever is longer) of visit 2.
Rationale for change		Consistency with other protocol sections.
Section to be changed		3.3.3 Exclusion criteria.
Description of change		Exclusion criterion 4 has been deleted • Patients who must or choose to continue the intake of restricted medications (see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
Rationale for change		To avoid duplicates.
Section to be changed		3.3.3 Exclusion criteria.
Description of change		Exclusion criteria 2 bullet points 1 and 2 had been re-worded adding the text in bold: • Topical corticosteroids **over HS lesions** within 1 week of Visit 2.
Rationale for change		To be more precise and clearer.
Section to be changed		3.3.3 Exclusion criteria.
Description of change		#3 reworded as: "Prior exposure to any immunosuppressive biologic other than TNFi for HS" #4 added: "Prior exposure to IL-36R inhibitors including spesolimab."
Rationale for change		Clarification
Section to be changed		3.3.3 Exclusion criteria
Description of change		Exclusion criterion 14 has been updated as follows: • Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in AST or ALT or alkaline phosphatase, **or** >2-fold ULN elevation in total bilirubin. **Patients with Gilbert´s syndrome can be included unless total bilirubin elevation is >5-fold ULN at screening visit and unless proportions of bilirubin fractions are inconsistent with diagnosis of Gilbert´s syndrome.**
Rationale for change		Changed as per Country Authority request.
Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		The following scenarios were added to this section: • Systemic antibiotics for HS before week 4.

		• Systemic antibiotics for HS without meeting criteria for disease worsening (as defined in section 4.2.2.2) • Influenza live vaccines are not longer permitted. Updated also in section 4.2.2.1. • If a hepatic injury alert (as defined in Section 5.2.6.1.4) is confirmed without identification of an alternative cause in the work-up according to the "DILI checklist" the patient should not receive subsequent doses of trial treatment. • The patient develops suicidal ideation or any suicidal behaviour (details on grading are given in Section 4.2.1.4 only to avoid duplicated information)
Rationale for change		Consistency with other protocol sections
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Trial treatment may be restarted after a temporary reason for treatment discontinuation on a case by case basis and after consultation with the sponsor. **Reasons for temporary treatment discontinuation may include but are not limited to pandemic lockdown, temporary hospitalization, severe infections, hepatic injury if an alternative cause is identified and patient has recovered as per investigator.**
Rationale for change		Reasons for temporary interruption (in bold above) have been added at Country Authority recommendation.
Section to be changed		4.2.1.4 Suicidality
Description of change		The following clarification in bold was added: **In case the patient develops suicidal ideation of type 4 or 5 in the C-SSRS (i.e. active suicidal thoughts with method and intent but without specific plan, or active suicidal thoughts with method, intent and plan) or any suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior), the patient should immediately** be referred to a mental health professional for further work-up and permanently discontinue trial treatment.
Rationale for change		Clarification
Section to be changed		4.2.2.2 Rescue treatment
Description of change		1 The following sentence was deleted: If a patient receives rescue treatment, the decision to maintain the patient on trial treatment will be

		decided with discussion between the investigator and sponsor. 2 The following was added: "In this trial, immunosuppressive biologics are not allowed"
Rationale for change		1 As per country Regulatory Authority request 2 Clarification
Section to be changed		4.2.2.3 Antibiotic use during the trial
Description of change		For HS disease worsening, the following was added: At or after week 4, if the patient requires systemic antibiotics for disease worsening as per the investigator, **monotherapy with either doxycycline 100mg orally twice daily or alternative as per investigator discretion, may be used for a maximum period of 2 weeks, and not more than a total of 4 weeks during the entire course of the trial.** Concomitant use of systemic antibiotic therapy for treatment of HS **other than for disease worsening, or before week 4**, is not allowed **and will lead patient to permanent treatment discontinuation (see Section 3.3.4.1).**
Rationale for change		As per country Regulatory Authority request
Section to be changed		Table 5.2.3:2 Safety Laboratory Tests
Description of change		Electrolytes: Bicarbonate was deleted from the list Specific gamma-globulin quantification: IgG has been deleted from the list. Substrates: The related footnote was changed from "At **baseline** and at EoT or EOS (as applicable) visits, a blood sample will be obtained to measure hs-CRP. This analysis will be done in the local laboratory" to "At **screening** and at EoT or EOS (as applicable) visits, a blood sample will be obtained to measure hs-CRP. This analysis will be done in the local laboratory"
Rationale for change		Bicarbonate and IgG: not longer mandated as per BI Standard. HS-CRP: Correction. Consistency with Flowchart.
Section to be changed		5.2.6.1.4 Adverse events of special interest
Description of change		The text in bold has been added: Hepatic injury A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

		• an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, **or in samples drawn within 30 days of each other**
Rationale for change		Update.
Section to be changed		6.2 Details of trial procedures at selected visits.
Description of change		It has been clarified that study visit procedures can be done within the corresponding visit window. The suggested sequence of procedures has been revisited.
Rationale for change		Patient centricity
Section to be changed		7.5 Determination of Sample Size
Description of change		More detailed rationale and justification for the calculated sample size is provided.
Rationale for change		As per country Regulatory Authority request
Section to be changed		All applicable sections
Description of change		New IB v9 dated on 20 May 2021 is used for reference instead of version 6
Rationale for change		New version of IB v9 dated on 20 May 2021 is now available
Section to be changed		All applicable sections
Description of change		BI655130 replaced by Spesolimab
Rationale for change		Consistency

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	05 Jul 2021 11:35 CEST
Approval-Biostatistics		06 Jul 2021 03:22 CEST
Approval-Medical Monitor		06 Jul 2021 13:23 CEST
Approval-[redacted] Medicine		07 Jul 2021 18:47 CEST
Approval-Team Member Medicine		12 Jul 2021 09:15 CEST
Verification-Paper Signature Completion		12 Jul 2021 10:29 CEST

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Meaning of Signature	Signed by	Date Signed