Clinical Trial Protocol

	Document Number:	**c33707086-02**
EudraCT No. **EU Trial No.**	2020-005587-55	
BI Trial No.	1368-0067	
BI Investigational Medicinal Product(s)	Spesolimab, BI 655130	
Title	An open-label, long-term extension trial of spesolimab treatment in adult patients with Hidradenitis Suppurativa (HS)	
Lay Title	A study investigating long-term treatment with spesolimab in people with a skin disease called hidradenitis suppurativa who completed a previous clinical trial.	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Tel: [redacted]	
Coordinating Investigator	[redacted] Email: [redacted]	
Version and Date	**Version:** Final Version 2.0	**Date:** 04 Jul 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	16 Dec 2020
Revision date	04 Jul 2022
BI trial number	1368-0067
Title of trial	An open-label, long-term extension trial of spesolimab treatment in adult patients with Hidradenitis Suppurativa (HS)
Coordinating Investigator	[redacted]
Trial site(s)	Multi-centre trial conducted in multiple countries
Clinical phase	II
Trial rationale	The main rationale of this extension trial is to collect additional long-term safety and efficacy data of spesolimab in HS patients.
Trial objective(s)	The primary objective of this trial is to assess the long-term safety of spesolimab in patients with HS who have completed the 1368-0052 PoCC trial and are qualified for entry into this trial. The secondary objectives are to evaluate efficacy at a lower dose than tested in PoCC trial.
Trial endpoints	The primary endpoint is the occurrence of treatment emergent adverse events (TEAEs) up to the end of the maintenance treatment period including REP (i.e., 16 weeks after the last study treatment). Secondary Endpoints: • Percentage change in total abscess and inflammatory nodule (AN) count from baseline up to Week [redacted] • Percentage change in total draining fistula (DF) count from baseline up to Week [redacted] • Hidradenitis Suppurativa Clinical Response (HiSCR) up to Week [redacted] • Change from baseline in International Hidradenitis Suppurativa Severity Score System (IHS4) value up to Week [redacted] • Hidradenitis Suppurativa Physician Global Assessment (HS-PGA) score of 0 or 1 up to Week [redacted] • Absolute change from baseline in Hidradenitis Suppurativa Area and Severity Index (HASI) score up to Week [redacted] • Occurrence of at least one flare (defined as at least [redacted] in AN count with a minimum increase of 2 relative to baseline) up to Week [redacted] • Achievement of at [redacted] from baseline in Numerical Rating Scale (NRS30) in Patient's Global Assessment of HS Pain up to Week [redacted]
Trial design	Open label, single-arm, multi-regimen, 2-year extension study in adult patients with HS who have completed their treatment in the 1368-0052 PoCC trial.

Total number of patients randomised	Approximately 45 patients will enter this trial
Number of patients per group	Number of patients per group will depend on the number of patients completing the parent (1368-0052) trial in each arm. Patients from the placebo arm of the 1368-0052 trial will be given an initial [redacted] dose of spesolimab, followed by [redacted] every [redacted] weeks. Patients from the active arm of the 1368-0052 trial will be given a loading dose of placebo followed by [redacted] spesolimab [redacted] every [redacted] weeks.
Diagnosis	Adult patients with HS who have completed their treatment in the 1368-0052 trial.
Main in- and exclusion criteria	**Main inclusion criteria** (for a complete list see Section 3.3.2): • Patients who have completed treatment in the parent HS spesolimab trial (1368-0052) without premature discontinuation. **Main exclusion criteria** (for a complete list see Section 3.3.3) • Patients who experienced study treatment-limiting adverse events during the 1368-0052 parent trial. • Use of any restricted medication or any drug considered by the investigator likely to interfere with the safe conduct of the study since the last visit of the 1368-0052 parent trial. • Any condition which in the opinion of the investigator affects the safety of the patient, the patient's ability to participate in this trial or could compromise the quality of data.
Test product(s)	Spesolimab
dose	At Visit 1 patients from the placebo group in the parent 1368-0052 trial are given [redacted] of spesolimab plus [redacted] placebo followed by [redacted] spesolimab every [redacted] weeks. At Visit 1 patients from the active group in the parent 1368-0052 trial are given [redacted] infusion of placebo plus [redacted]. spesolimab followed by [redacted] spesolimab every [redacted] weeks. Administration of study medication at Visit 1 is blinded. Refer to Section 4.1.2 for details. At Week 12, all patients will be assessed for total number of ANs and DF and HS PGA. Based on the individual responder status at baseline, decisions on further dosing will be taken as depicted in Table 3.1: 1.
mode of administration	[redacted] at Visit 1 only, and s.c. at all visits
Duration of treatment	[redacted] weeks
Statistical methods	Given the single arm and open-label nature of this trial, no hypothesis testing will be performed in the confirmatory sense. All statistical assessments will be performed in an explorative manner to better understand the efficacy and safety profile of spesolimab.

FLOW CHART – UP TO W12

Trial Periods							
Visit	**1***	**2**	**3**	**4**	**5**	**6**	**7**
Week (W)	W0	W[redacted]	[redacted]	W[redacted]	W[redacted]	W[redacted]	W[redacted]
Day	[redacted]						
Time Window for Visits	n/a	±2 days	±2 days	±2 days	±2 days	±2 days	±2 days
Informed consent	X						
Demographics	X						
Medical history	X						
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X	X	X	X	X	X
Physical examination[1] -Complete (C) or Targeted (T)	C	T	T	T	T	T	T
Height	X						
Weight	X		X		X		X
Vital Signs[2]	X[2a]	X[2b]	X[2b]	X	X	X	X
Safety Laboratory tests (blood and urine)[3]	X		X		X		X
Infection Testing[4]	X						
12 lead-ECG (local)	X		X		X		X
Pregnancy testing[5]	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X
Review of in-/exclusion criteria	X						
Local tolerability assessment[6]	X	X	X	X	X	X	X
All AEs/SAEs/AESIs	X	X	X	X	X	X	X
Pain NRS	X		X		X		X
DLQI, PGI-S, PGI-C, HiSQOL[7]	X		X		X		X
FACIT Fatigue Scale[7]	X		X		X		X
HiSCR, HS-PGA, IHS4, HASI[8]	X	X	X	X	X	X	X
Abscess count. Inflammatory nodule count. Non-inflammatory nodule count. Draining Fistula count.	X	X	X	X	X	X	X
Photography	X		X		X		X
hs-CRP	X		X		X		X
ADA/Nab[9]	X	X	X		X		X
PK Sampling[9]	X	X	X		X		X
Blood sample (Serum soluble protein biomarkers)	X		X		X		X
Blood sample for RNA sequencing	X		X		X		X
IRT contact	X	X	X	X	X	X	X
Administer study drug	X	X	X	X	X	X	X

*V1 of this extension trial should preferably be performed during the EoT visit of the parent PoCC trial (1368-0052). When the visits are performed on the same day duplicate procedures across studies are performed once during the EoT/V1. If these visits are not performed on the same day, then either all V1 procedures need to be performed at that visit or a modification of procedures will be considered after discussion with the sponsor (e.g., if V1 is within 2 days of the EoT visit of the PoCC trial, then certain visit procedures need not be repeated; however, if the gap is between 3-14 days, then align with the sponsor accordingly). If a patient is unable to roll over on the day of the EoT Visit of the 1368-0052 PoCC trial because of medical reasons, then they can be permitted to rollover within 2 weeks of the EoT Visit of the PoCC trial. During this gap, if required, patients can take systemic and topical antibiotics for disease worsening as per investigator discretion (see Section 4.2). However, biologics,

immunomodulators and opioid analgesics are not allowed for HS and non-HS indications. Any further extensions beyond 2 weeks must be discussed with the sponsor.
** At Week [redacted] of this extension trial, all patients will be assessed for the change of HS-PGA grade. The change in HS-PGA grade will be compared with the assessment at baseline of this extension trial / Week [redacted] of the 1368-0052 PoCC trial. Based on the individual responder status, decisions on further dosing will be taken as depicted in Table 3.1:1.

1. Complete physical examination includes general appearance as well as evaluation of all organ systems; Targeted physical examination includes evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities
2. Vital signs will be assessed pre dose as well as approximately 10 minutes post dose. Measurement of pre-dose vitals should precede blood sampling. Vital signs include systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature. Refer to Section 5.2.2 for further information.
    a. For the trial drug administrations at Visit 1, vitals should be captured approximately 5 minutes and 60 minutes post dose for i.v. administration and approximately10 minutes post-dose for s.c. administrations.
    b. At Visit 2 and Visit 3 additional measurements will be performed approximately 60 minutes after s.c. study drug administration.
3. Safety laboratory tests include clinical chemistry, haematology, coagulation, and urinalysis and will be performed by the Central Lab.
4. Infection testing includes tuberculosis, hepatitis B, hepatitis C, and HIV assessments. Also refer to Table 5.2.3: 1 and Section 6.2.1.2 for further instructions.
5. Women of childbearing potential only. Pregnancy testing should be done prior to administration of study drug. Study drug should only be administered in case of a negative test result. In case of a positive urine pregnancy test, a serum pregnancy test will be done.
6. The investigator will assess local tolerability at the administration site of spesolimab 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”, “pain”, and any other findings should be reported as an adverse event.
7. Patient questionnaires should be completed before any other procedures on that day, before the physician assessments, and before study drug administration.
8. Physician assessments should be done after patient questionnaires are completed and before study drug administration. HiSCR is calculated automatically by comparing the lesion count from baseline. Further details are described in Section 5.1.1.
9. Pre-dose PK/ADA/Nab samples will be obtained approximately within one hour prior to start of study drug administration.

FLOW CHART – W14 TO END OF STUDY

Trial Periods	**Maintenance Treatment Period (visits every 2 weeks)**	**End of Treatment****	**Follow-up 1 (2 weeks after last dose)**	**End of Study (16 weeks after last dose)**
Visit	**8 to 52**	**EoT**	**FUP1**	**EoS[15]**
Day	[redacted]			
Week (W)				
Time window for visits	±3 days	±3 days	±3 days	+10 days
IRT contact	X	X		
Concomitant therapy	X	X	X	X
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X	X	X
Physical examination[10]	Targeted	Targeted	Complete	Targeted
Vital signs[11]	X	X	X	X
Weight	Every second visit	X	X	X
Safety Laboratory tests (blood and urine)[12]	Every second visit	X	X	X
Pregnancy testing[13]	X	X	X	X
Infection testing[14]	X[14]	X[14]		
Local tolerability assessment	X	X		
All AEs/SAEs/AESIs[15]	X	X	X	X[15]
Pain NRS	Every second visit	X	X	
DLQI, PGI-S, PGI-C, HiSQOL[16]	Every second visit	X	X	
FACIT Fatigue Scale[16]	Every second visit	X	X	
HiSCR, HS-PGA, IHS4, HASI[17]	X[17]	X	X	
Abscess count. Inflammatory nodule count. Non-inflammatory nodule count. Draining Fistula count.[17]	X[17]	X	X	
Photography[18]	X[18]	X	X	
ADA/Nab[19]	X[19]	X	X[22]	X
PK Sampling[19]	X[19]	X	X[22]	X
hs-CRP[20]	X[20]	X		
12 lead-ECG (local)[21]	X[21]	X	X	X
Administer study drug (every 2 weeks)	X	X		

**Patients who discontinue trial treatment prematurely should undergo the EoT visit as soon as possible, the Follow-up (FUP 1) visit two weeks after last dose, and the EoS visit 16 weeks after the last dose. If a patient discontinues the study during a scheduled treatment visit then the visit is considered an EoT visit.

***Week [redacted] Patients identified as a Non-responder AND up-titrated to [redacted] at Week [redacted] must undergo a re-assessment of their HS-PGA. If there is no change or no improvement in their HS-PGA grade at Week [redacted] compared to Week [redacted] then the patient MUST be discontinued from the trial (Table 3.1: 1). The HS-PGA page and Abscess and Inflammatory Nodule count page are added as "unscheduled visits" at Week [redacted] to document the re-assessment. This assessment is recommended to be performed at the start of the visit. If the patient is discontinued at the Week [redacted] visit, then this visit can be considered the EoT visit.

Every second visit = every other visit starting from W14.

10. Complete physical examination includes general appearance as well as evaluation of all organ systems; Targeted physical examination includes evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.
11. Vital signs will be assessed pre dose as well as 10 minutes post dose. Measurement of pre-dose vitals should precede blood sampling. Vital signs include systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature.
12. Safety laboratory tests include clinical chemistry, haematology, coagulation, and urinalysis and will be performed by the Central Lab.
13. Women of childbearing potential only. Pregnancy testing should be done prior to administration of study drug. Study drug should only be administered in case of a negative test result. In case of a positive urine pregnancy test, a serum pregnancy test will be done.
14. Testing at EoT includes tuberculosis and hepatitis B. Also refer to Table 5.2.3: 1 for information on QuantiFERON testing at Weeks [redacted] and [redacted] Please also see Section 6.2.1.2 for further information.
15. After the EoS visit (=individual patient's end of the trial) the investigator should report only any cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of and only via the BI SAE form, please see Section 5.2.6.2.1.
16. Patient questionnaires should be completed before any other procedures on that day, before the physician assessments, and before study drug administration.
17. Physician assessments should be done after patient questionnaires are completed and before study drug administration. Starting from Week 14, physician assessments, abscess counts, inflammatory nodule counts, non-inflammatory nodule counts, and draining fistula counts are completed every 4 weeks for the next six months, i.e., Weeks 14, 18, 22, 26, 30, 34, 38, and then every 12 weeks thereafter, i.e., Weeks 50, 62 74, 86, 98. HiSCR is calculated automatically by comparing the lesion count from baseline. Further details are described in Section 5.1.1.
18. Photography should be completed every [redacted] weeks starting from Week [redacted]
19. PK and ADA/Nab samples are collected at Weeks [redacted], EoT, and EoS. Pre-dose PK/ADA/Nab samples will be obtained approximately within 1 hour prior to start of study drug administration.
20. hs-CRP measurements should be completed every [redacted] weeks starting from Week [redacted]
21. ECG is required every 12 weeks starting from Week [redacted]
22. PK and ADA/Nab samples will only be collected if the patient missed the EoT visit collection.

TABLE OF CONTENTS

ABBREVIATIONS

ADCC	Antibody-dependent Cellular Cytotoxicity
ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AN count	Abscess and Inflammatory Nodule
AST	Aspartate Aminotransferase
AUC0-tz	Area Under the Concentration-time Curve
BI	Boehringer Ingelheim
CA	Competent Authority
CDC	Complement-dependent Cytotoxicity
C_{max}	Maximum Plasma Concentration
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
C-SSRS	Columbia-Suicide Severity Rating Scale
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DBL	Database Lock
DCs	Dendritic Cells
DF	Draining Fistula
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoT	End of Treatment
EoS	End of Study

FACIT	Functional Assessment of Chronic Illness Therapy
FDA	U.S. Food & Drug Administration
GPP	Generalized Pustular Psoriasis
HASI	Hidradenitis Suppurativa Area and Severity Index
HBV	Hepatitis B virus
HiSCR	Hidradenitis Suppurativa Clinical Response
HiS-QoL	Hidradenitis Suppurativa Quality of Life
HIV	Human Immunodeficiency Virus
HS-PGA	Hidradenitis Suppurativa Physician Global Assessment
HS	Hidradenitis suppurativa
I&D	Incision and Drainage
i.v.	intravenous
IB	Investigator Brochure
ICH-GCP	ICH Harmonized Guideline for Good Clinical Practice
IEC	Independent Ethics Committee
IGRA	Interferon Gamma Release Assay
IHS4	International Hidradenitis Suppurativa Severity Score System
IL36	Interleukin 36
IL36R	Interleukin 36 Receptor
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
k.g.	Kilogram
LPLT	Last Patient Last Treatment
MedDRA	Medical Dictionary for Drug Regulatory Activities
m.g.	Milligram
MoA	Mode-of-action
MMRM	Mixed Effect Model for Repeated Measurements
MRD	Multiple Rising Dose
Nab	Neutralizing Antibody
NRI	Non Response Imputation
NRS	Numerical Rating Scale

OLE	Open label extension
OPU	Operative Unit
PD	Pharmacodynamic
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetics
PoC	Proof of concept
PoCC	Proof-of-clinical-concept
PPD	Purified Protein Derivative
PPP	Palmoplantar Pustulosis
PROs	Patient Recorded Outcomes
q.w.	Every Week
RA	Regulatory Authorities
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
s.c.	subcutaneous
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SoC	Standard of Care
SOP	Standard Operating Procedure
SRD	Single Rising Dose
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Events
TSAP	Trial Statistical Analysis Plan
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 study methodology; however, the disease appears to be more common than was previously considered [R20-3176].

Treatment often begins with topical or oral antibiotics. 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 (s.c.) dosing.

When the medical management is ineffective, surgery is the 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.

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 Peripheral Blood Mononuclear Cells 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 IL36R 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 IL36R inhibition were performed in mice using a mouse specific anti-IL36R monoclonal antibody (Boehringer Ingelheim (BI) 674304), which is a mouse IgG2a monoclonal antibody with rat variable regions. In a 13-week intravenous (i.v.) toxicity study of BI 674304 in mice, no adverse effects of IL36R 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 i.v. injection via the caudal vein. There were no BI 674304-related changes in clinical observations, body weights, food consumption, ophthalmology, clinical pathology parameters (haematology, clinical chemistry), organ weights, macroscopic or microscopic examinations. The no-observed-adverse-effect level 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, 1mL injections of the s.c. formulation in rabbits. These preclinical toxicology data support chronic spesolimab dosing in humans.

Spesolimab or placebo 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 serious adverse events (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%; placebo: 15%), headache (spesolimab: 9%; placebo: 15%), influenza like illness (spesolimab: 7%; placebo: 10%), and diarrhoea (spesolimab: 3%; placebo: 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 electrocardiogram (ECGs), vital signs, and cardio-monitoring. Pharmacokinetics (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 kinetics for spesolimab. Anti-drug antibodies (ADA) were detected in 8 patients, 3 of those had pre-existing levels. Pharmacodynamic (PD) effects in this First in Human Single Rising Dose (SRD) trial [c03361085] were assessed by indirect target engagement 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 (MRD) 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 20 mg/kg (8 subjects each, 3:1 on active or placebo). 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) [c03320877-10].

1.2.2 Studies in Patients

Safety and efficacy data are available from a proof of concept (PoC) study in patients with GPP. In trial 1368-0011, seven patients received a single i.v. dose of 10 mg/kg spesolimab and were monitored for 20 weeks. At week 1 after dosing, GPP Physician Global Assessment 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 GPP Area and Severity Index 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%).

Further trials are ongoing in patients with GPP, PPP, AD, UC, or CD. An independent Data Monitoring Committee (DMC) is involved in the monitoring of these trials. As of September 2020, an estimated 604 subjects have been exposed to spesolimab, out of a total of 693 subjects in the clinical development programme. No safety signal of concern has been identified in any of the ongoing trials.

1.2.3 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/or PD effects still likely to be present.

1.2.4 Summary

Spesolimab is an anti IL36R antibody with a high clinical activity to block IL36R signaling, as demonstrated in patients with GPP, 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 HS.

For a more detailed description of the spesolimab profile, please refer to the current IB [c03320877-10].

1.3 RATIONALE FOR PERFORMING THE TRIAL

Adalimumab 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 s.c. 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 IL36R antagonist currently in development for the treatment of GPP. HS and GPP may have similarity considering the presence of pustules, neutrophil infiltration, and psoriasiform hyperplasia. IL36 alpha, beta and gamma mRNA expression are upregulated in lesional skin in HS patients with a decrease in IL36RN expression [R20-3047]. Internal in situ hybridization staining of HS lesions also confirms the increased expression of ligands. IL36 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 dendritic cells (DCs) and monocytes can be activated by IL36 (internal data and published) to potentiate the antigen presenting cell function of DCs and also lead to secretion of chemokines and cytokines that can recruit more immune cells including neutrophils. IL36 is a potent activator of neutrophil infiltration and in the context of HS, neutrophils are shown to undergo NETosis leading to secretion of auxiliary medicinal products and type I Interferons [R20-3155]. Based on the role of IL36 driving TH17 and TH1 responses in GPP (published and our internal data) the hypothesis is that IL36 is also a key driver of TH17 responses in skin of HS patients. To that end, we are conducting the 1368-0052 proof-of-clinical concept (PoCC) study in moderate to severe HS patients.

The main rationale of this extension trial is to collect additional long-term safety and efficacy data of spesolimab in eligible HS patients from the 1368-0052 PoCC trial. Additional appreciable benefit for the patients of this extension study is the possibility to receive spesolimab as s.c. maintenance treatment with the aim to maintain their positive clinical response reached in the preceding PoCC trial, if they are eligible to receive further spesolimab treatment in this extension study.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Preclinical profiles of spesolimab and clinical data from healthy volunteers and patient trials suggest that spesolimab is safe, tolerable and may address an unmet medical need in patients with HS by an anti-inflammatory mechanism of action. Efficacy in HS has not been established. The data from the completed 1368-0011 PoC trial, 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 IL36R antagonist. (see: spesolimab IB, document number c03320877-10)

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 IL36R inhibition in mice (spesolimab IB, document number c03320877-10, Section 5.1.2). A recent publication has assessed the clinical phenotype and immune function in 12 healthy individuals harbouring an IL36R 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 IL36 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 20 mg/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 c03320877-10). Moreover, several clinical studies are ongoing as of May 2020, exploring efficacy and safety of spesolimab in different indications such as: Atopic Dermatitis, Ulcerative Colitis, Crohn’s Disease, GPP, and PPP. 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 no signal of a safety issue and 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.

Eligible patients completing the 1368-0052 PoCC trial will be offered to rollover into this trial to receive open-label active spesolimab maintenance treatment for up to 2 years. Patients will be re-assessed at week 12 to evaluate response and further dose modifications will be done accordingly. 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 (i.e., unbearable adverse events (AEs)) will be discontinued and switched to available standard of care (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

There are no identified or potential risks for spesolimab, based on the toxicology programme or any clinical trials conducted for this product to date. No other IL36 receptor antagonist is currently approved, providing information on identified risks in molecules of this class. The

risks shown in the table below are hypothetical in nature; these are derived from general safety considerations of immunomodulatory drugs.

In order to protect the patient's safety during conduct of this trial, an independent DMC has been established for the periodic review of clinical trial safety data. Refer to Section 8.7 for details.

Table 1.4.2:1 Overview over trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product - spesolimab		
Drug induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety. Refer to Section 5.2.6.1.4.
Systemic Hypersensitivity	After administration of any biologic agent or protein, there is a possibility of occurrence of adverse immune reactions which can be local (e.g. redness, pruritus, and or swelling at the injection site) or systemic (e.g. anaphylactic 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 SoC 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

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
		paper from Sampson HA [R11-4890]. Refer to Section 5.2.6.1.4.
Infections	Inhibition of the immune response with an immunomodulating biologic may increase the risk of infections. A recent characterization of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signaling pathway inhibition does not compromise host defenses [R17-3632].	Infection testing procedures will be established for this trial. Treatment of infections should be initiated promptly according to standards of care. Patients with infections such as human immunodeficiency virus (HIV), viral hepatitis or tuberculosis are discontinued from the trial. However, if latent tuberculosis is established during the trial, then patients can receive anti-tuberculosis treatment as per investigator discretion and continue receiving study medication as per investigator. Refer to Sections 3.3.4.1 and 6.2.1.2 Severe infections and opportunistic infections are considered AESIs for this trial. These conditions and serious infections are subject to close monitoring. Refer to Section 5.2.6.1.4.
Malignancies	Inhibition of the immune response with an immunomodulating biologic may increase the risk of a decreased immune defense against malignancies. A recent characterization of individuals with homozygous IL36R KO mutations revealed that normal immune function	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 basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	was broadly preserved suggesting that IL36 signalling pathway inhibition does not compromise host defenses. [R17-3632].	investigator should discontinue treatment with spesolimab. Diagnostics and treatment have to be initiated according to local SoC. Malignancies represent always SAEs and are subject to close monitoring. Refer to Section 5.2.6.1.3.
Peripheral Neuropathy	Three cases reported by the investigator as Guillain-Barré syndrome (GBS) were received in ongoing clinical trials with spesolimab. A panel of independent neurologists and experts in the study of neuropathies assessed the 3 cases. Only 1 met level 4 diagnostic certainty for the diagnosis of GBS (lowest level on Brighton scale of 1 to 4). In that case, there was a coincident infection with SARS-CoV-2. The other 2 cases were assessed as not GBS. Observed cases showed a heterogenous pattern. A causal association to spesolimab was assessed to be unlikely. As per assessment by the panel of external neurologists the nonspecific symptoms and findings in all three cases may best be referred to as peripheral neuropathy.	Timely detection, evaluation, and follow-up of suspected peripheral neuropathies to ensure patients´ safety. Targeted Follow up questions to gather detailed information in case of any event during trial to ensure proper decision making. Trial treatment discontinuation criteria as well as criteria for trial treatment restart are implemented for relevant cases. Refer to Section 4.2.1.4.

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
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 light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paraesthesia), 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 the laboratory manual.
Other risks		
Suicidal ideation and behaviour	Increased risk of suicidal ideation and behaviour is present in the population of patients with HS.	'Baseline/ screening' version of Columbia-Suicide Severity Rating Scale (C-SSRS) will be administered with the aim to exclude patients with active moderate or severe symptomatology present within a specified time prior to Visit 1. '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 behaviour represent SAEs and are subject to close monitoring. Refer to Section 5.2.5.1.

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 AEs, definition of opportunistic infections and mycobacterium tuberculosis infections, severe infections and systemic hypersensitivity including infusion reaction and anaphylactic reactions as AESI; (c) selection of sites experienced in treatment of HS patients with biologics; and (d) implementation of a fully independent DMC.

1.4.2.1 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 (ISF). Subcutaneous injection has been well tolerated in a small phase I study (1368-0003; see spesolimab IB, document number c03320877-10) and will be carefully monitored for local tolerability in this study. i.v. infusion, which occurs only at Visit 1, has been well tolerated in various clinical trials and will be monitored for tolerability.

1.4.2.2 Women of Child Bearing Potential

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 foetus to the investigational drug, WOCBP must agree to the requirements for the pregnancy testing and contraceptive methods. Refer to Section 4.2.2.7.

1.4.2.3 COVID-19

Currently, information about the immune response in patients with COVID-19 is sparse and inconclusive. There are some reports suggesting high-levels of pro-inflammatory cytokines in the severe cases, with much of the morbidity associated with coronavirus infection, potentially related to immune activation and inflammation. To date, there is no reliable evidence suggesting a link between SARS-CoV-2 infections and the IL36 pathway targeted by spesolimab. According to the Centers for Disease Control and Prevention 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 not well 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 AEs, as well as guidance on handling of acute infections occurring during the trial have been included in the clinical trial protocols (CTP). As any other acute infection a suspected or diagnosed COVID-19 infection should be treated according to the SoC 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 studied in trials with spesolimab are not believed to be at higher risk of COVID-19 due to their background or concomitant diseases. 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 finding. 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.

1.4.3 Discussion

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

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

The primary objective of this trial is to assess the long-term safety of spesolimab in patients with HS who have completed the 1368-0052 PoCC trial and are qualified for entry into this trial. The secondary objectives are to evaluate efficacy at a lower dose than tested in PoCC trial.

2.1.2 Primary endpoint(s)

The primary endpoint is the occurrence of treatment emergent adverse events (TEAE) up to the end of maintenance treatment period including REP (i.e., 16 weeks after the last study treatment).

2.1.3 Secondary endpoint(s)

- [redacted] change in [redacted] abscess and inflammatory nodule (AN) count from baseline up to Week [redacted].
- [redacted] change in total draining fistula (DF) count from baseline up to Week [redacted].
- Hidradenitis Suppurativa Clinical Response (HiSCR) up to Week [redacted].
- Change from baseline in International Hidradenitis Suppurativa Severity Score System (IHS4) value up to Week [redacted].
- Hidradenitis Suppurativa Physician Global Assessment (HS-PGA) score of 0 or 1 up to Week [redacted].
- [redacted] change from baseline in Hidradenitis Suppurativa Area and Severity Index (HASI) score up to Week [redacted].
- Occurrence of at least one flare (defined as at least [redacted] in AN count with a minimum increase of 2 relative to baseline) up to Week [redacted].
- Achievement of at least [redacted] from baseline in Numerical Rating Scale (NRS30) in Patient's Global Assessment of HS Pain up to Week [redacted].

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This open label, single-arm, multi-regimen, 2-year extension study investigates the long-term safety and efficacy of spesolimab in patients with HS who have completed their treatment in the 1368-0052 PoCC trial. BI trial 1368-0052 is the first trial from which patients will rollover into this extension trial. Patients rolling over into this trial must have completed the treatment period as required in the 1368-0052 PoCC trial. Ideally, the end of treatment (EoT) visit of the preceding trial is the baseline visit (V1) of this extension trial.

This extension trial consists of a [redacted] weeks treatment period followed by a [redacted] week safety follow-up period.

Approximately [redacted] patients from the 1368-0052 PoCC trial are planned to be rolled over into this open-label extension study.

Patients from the placebo arm of the 1368-0052 PoCC trial will be given an initial [redacted] dose of spesolimab plus [redacted] placebo, followed by [redacted] spesolimab [redacted] every [redacted] weeks [redacted]). Patients from the active arm of the 1368-0052 PoCC trial will be given an initial [redacted]. placebo plus [redacted] spesolimab [redacted]., followed by [redacted] spesolimab [redacted]. every [redacted]. Administration of trial medication at Visit 1 is blinded. See Section 3.1.1 for more details.

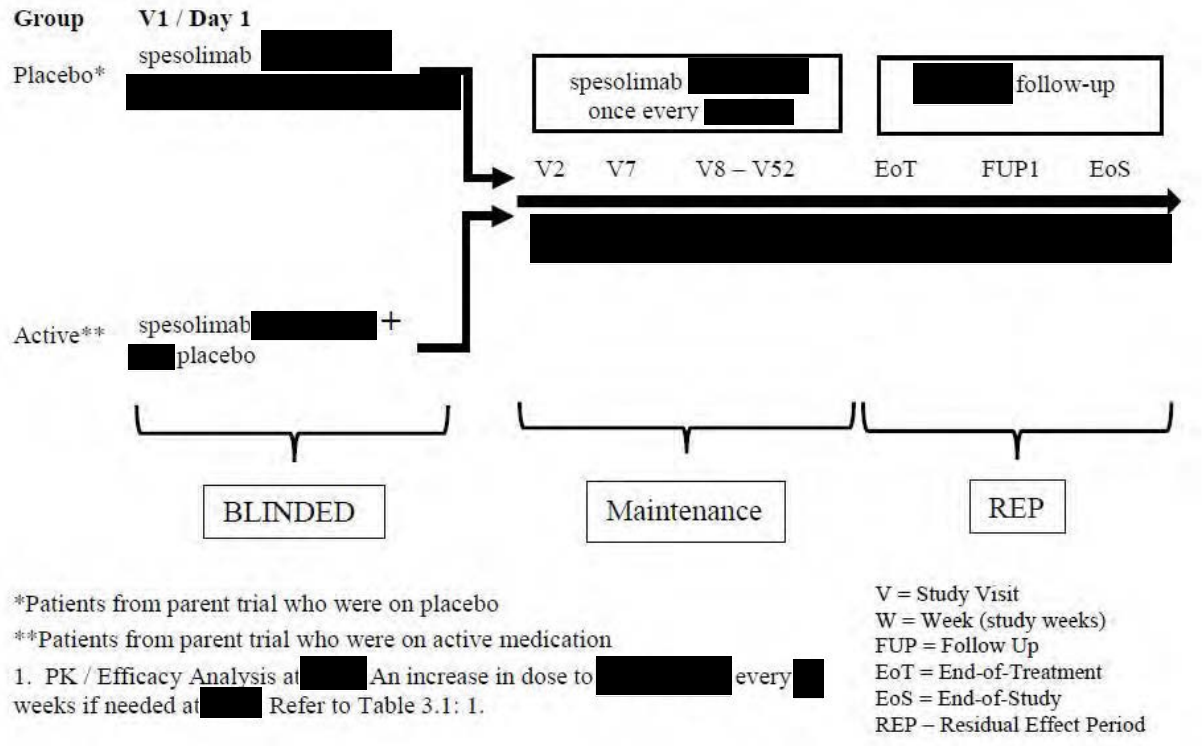
At Week [redacted] of this extension trial, all patients will be assessed for the change of HS-PGA grade. The change in HS-PGA grade will be compared with the assessment at baseline of this extension trial / Week [redacted] of the 1368-0052 PoCC trial. Based on the individual responder status decisions on further dosing will be taken as depicted in Table 3.1: 1.

Table 3.1: 1 Week 12 Dose Modification Management

Baseline	Assessment at Week 12	Management
Status from Week 12 of 1368-0052 PoCC trial	**HS-PGA grade change from baseline HS-PGA grade of this trial**	
Responder (Achieved HiSCR 50)	No change or improvement in grade (i.e., reduction by at least 1 grade)	Continue the same dose
	Worsening in grade (i.e., increase by at least 1 grade)	Option to increase the dose to [redacted]
Partial Responder (Achieved HiSCR 25 but did not achieve HiSCR 50)	Improvement in grade	Continue the same dose
	No change or worsening in grade	Increase the dose to [redacted]
Non-responder (Did not achieve HiSCR 25)	Improvement in grade	Continue the same dose
	No change or worsening in grade	Increase the dose to [redacted] Re-assess HS-PGA grade at week [redacted] and discontinue, if no change or worsening observed compared to Week [redacted]

Responder is defined as achievement of HiSCR 50 in the1368-0052 PoCC trial, partial responders are defined as patients who did not achieve HiSCR 50, but achieved at least a [redacted] in AN count relative to baseline in the 1368-0052 PoCC trial, and non-responders are defined as patients who have shown less than [redacted] in AN counts or have worsening of the disease in the 1368-0052 PoCC trial.

3.1.1 Trial Design Diagram



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

This trial will be conducted as a prospective, open-label design. The aim of the trial is to allow treatment continuation to individual patients who completed the 1368-0052 PoCC trial and evaluate the sustainability of response. Additionally, this trial provides opportunity for the patients who were on the placebo arm in the 1368-0052 PoCC trial to get access to the trial treatment. It is also designed to generate additional safety information.

Patients who prematurely discontinued the 1368-0052 PoCC trial are not eligible to participate in this study. For patients who terminate study drug prematurely in this extension study the subsequent visit will be replaced by an early EoT visit followed by an end of study (EoS) visit 16 weeks after the last study drug administration.

Interim analyses of PK, ADA, and clinical data may be performed throughout the conduct phase of this 2-year trial to support future trial applications, IB, regulatory documents and scientific publications. The final analysis of the entire trial data will start once the last patient has completed the EOT visit and final report will include all trial data. Individual patient participation is concluded when the patient has completed the last scheduled visit. The end of whole study is defined as “last patient out”; i.e., last scheduled visit completed by the last patient in the study. All the parameters will be assessed in a descriptive manner, since the trial is open-label.

An independent DMC will evaluate safety and efficacy data on a continuous basis.

3.3 SELECTION OF TRIAL POPULATION

Patients in this long-term open label extension (OLE) trial will be rolled over from the 1368-0052 PoCC trial. The total number of patients to be rolled over depends on how many eligible patients roll over from the 1368-0052 PoCC trial. The maximum number of patients eligible to rollover is approximately 45 from multiple countries and multiple sites. This OLE study aims to offer active long-term treatment to patients having completed treatment with spesolimab in the 1368-0052 PoCC trial, and an opportunity for patients on the placebo arm to get active treatment. This study will also help to characterize the safety and clinical outcome of spesolimab long-term treatment.

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.

3.3.1 Main diagnosis for trial entry

Patients with HS who have completed the treatment with spesolimab in the parent HS trial.

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. Patients who have completed treatment in the parent HS spesolimab trial (1368-0052) without premature discontinuation.
2. Signed and dated written informed consent in accordance with ICH Harmonized Guideline for Good Clinical Practice (ICH-GCP) and local legislation prior to admission to the trial.
3. 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. A list of contraception methods meeting these criteria is provided in the patient information and consent form and in Section 4.2.2.7.

3.3.3 Exclusion criteria

1. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
2. Patients who experienced study treatment-limiting adverse events during the 1368-0052 parent trial.

[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.

3. Severe, progressive, or uncontrolled condition such as renal, hepatic, haematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof.
4. Any new documented active or suspected malignancy except appropriately treated basal cell carcinoma, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
5. Use of any restricted medication or any drug considered by the investigator likely to interfere with the safe conduct of the study since the last visit of the 1368-0052 parent trial.
6. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.
7. Major surgery (major according to the investigator's assessment) planned during this extension trial (e.g. hip replacement, aneurysm removal, stomach ligation), as assessed by the investigator.
8. Any condition which in the opinion of the investigator affects the safety of the patient, the patient's ability to participate in this trial or could compromise the quality of data.
9. Any suicidal behaviour in the past 2 years (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour).
10. Any suicidal ideation of type 4 or 5 on the C-SSRS in the past 3 months (i.e. active suicidal thoughts with method and intent but without specific plan, or active suicidal thoughts with method, intent and plan).
11. Currently enrolled in another investigational device or drug trial, except for 1368-0052.
12. Previous participation in this trial.

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 Case Report Form (CRF). If applicable, consider the requirements for Adverse Event collection reporting (please see Sections 5.2.6.2.1 and 5.2.6.2).

Patients withdrawn from the trial, independent of the underlying reason, should undergo the EoT visit as soon as possible, the FUP 1 Visit two weeks after the last dose, and the EoS Visit 16 weeks after the last dose for safety reasons. This should also be proposed to patients who withdraw their informed consent.

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 develops infections such as HIV, viral hepatitis or tuberculosis. However, if latent tuberculosis is diagnosed during the trial, patients can receive anti-tuberculosis treatment as per investigator discretion and continue receiving study medication as per investigator. Refer to Section 6.2.1.2
- The patient needs to take concomitant medication such as immunosuppressive biologics, live vaccines, or other concomitant medication that interferes with the Investigational Medicinal Products (IMP) or other trial treatment. Also refer to Sections 4.2.1 and 4.2.2.
- The patient can no longer receive trial treatment for medical reasons such as surgery, serious or severe Drug Induced Liver Injury attributable to the trial drug, other adverse events, other diseases, or pregnancy. Also refer to Sections 5.2.6.1.4 and 5.2.6.2.3.
- 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 behaviour (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour). The patient should immediately be referred to a mental health professional for further work-up.
- The patient is a Non-responder on 1200 mg of IMP and there is no change or no improvement in their HS-PGA grade at Week 24 compared to Week 12.

In addition, the principal investigator may discontinue subjects at any time based on his or her clinical judgment.

For individual stopping rules related to specific AEs, please see Section 4.2.1.

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, BI 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, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart 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

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

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see Section 3.3.4.1.
3. Deviations from ICH-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 1 – BI 655130 (spesolimab) solution for injection

Substance:	BI 655130 (spesolimab)
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	[redacted]/prefilled syringe 2mL (150mg/mL)
Posology:	[redacted] every [redacted] weeks, including at Visit 1 for subjects who were on spesolimab in the parent trial. An increase in dose at W[redacted] to [redacted] mg [redacted]. every [redacted] if needed; Refer to Table 3.1: 1.
Method and route of administration:	[redacted]

Table 4.1.1: 2 Test product 2 – BI matching placebo solution for injection

Substance:	Placebo matching BI 655130 (spesolimab)
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	placebo, [redacted] prefilled syringe
Posology:	Placebo matching [redacted] at Visit 1 only for subjects who were on placebo in the parent trial
Method and route of administration:	[redacted]

Table 4.1.1: 3 Test product 3 – BI 655130 (spesolimab) solution for infusion

Substance:	BI 655130 (spesolimab)
Pharmaceutical formulation:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	[redacted]
Posology:	[redacted] Visit 1 only for subjects who were on placebo in the parent trial (Loading Dose)
Method and route of administration:	[redacted]

Table 4.1.1: 4 Test product 4 – BI matching placebo solution for infusion

Substance:	Placebo matching to BI 655130 (spesolimab)
Pharmaceutical formulation:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	Placebo [redacted]
Posology:	Placebo matching [redacted] in Visit 1 only for subjects who were on spesolimab in the parent trial
Method and route of administration:	[redacted]

4.1.2 Selection of doses in the trial and dose modifications

In the 1368-0052 PoCC trial, a fixed rather than weight-based dose regimen was selected. Early trials of therapeutic monoclonal antibodies often investigate bodyweight–based regimens to reduce the inter-subject variability in drug exposure. However, there is generally only a modest contribution of body weight to the overall PK and PD variability of monoclonal antibodies. Furthermore, monoclonal antibodies are highly target specific and offer a relatively large therapeutic window compared to new chemical entities. Therefore, most monoclonal antibodies are approved at fixed doses in antibody/target excess in order to cover target turnover and maximize efficacy [R10-6267; R13-4749; R13-4753; R13-4750; R13-4754].

In this extension trial, patients from the active arm in the parent trial will be given [redacted] every [redacted], which is half the dose of the 1368-0052 PoCC trial. This is to evaluate whether these patients would be able to sustain efficacy at a lower dose. Patients who were in the placebo arm will be given a [redacted] dose of spesolimab, followed by [redacted]. every [redacted]. The rationale is to give an opportunity to the patients from the placebo arm to be given active treatment and also to understand induction response after a placebo period. Additionally, this dose was also selected to evaluate efficacy of [redacted] dose. All the patients will be reassessed at Week [redacted] to evaluate the response and will have the option of either continuing the same dose or increasing the dose.

Data from the 1368-0052 PoCC trial will not be available prior to the 1st patient rolling over into this extension trial. When new data from the PoCC trial becomes available, the impact for this extension trial will be evaluated and if needed the dose would then be adjusted by amending this protocol.

4.1.3 Method of assigning patients to treatment groups

An Interactive Response Technology (IRT) system will be used in this trial in order to dispense medication kits as well as manage initial/re-supply ordering of medication kits. The study site will be required to complete the appropriate module within the IRT system. The investigator will receive all necessary instructions to access the IRT system from the sponsor or chosen provider. Detailed IRT transactions and procedures will be documented in the user requirement specifications mutually agreed to by the sponsor and the IRT provider. All medication kit assignments will occur in an open label fashion except for medications provided for Visit 1. Note that the medication number is different from the patient number.

4.1.4 Drug assignment and administration of doses for each patient

Patients will be treated with spesolimab as indicated in the Flow Chart and Section 3.1.1. The medication will be assigned via IRT.

At Visit 1 patients who were in the placebo arm of the 1368-0052 PoCC trial will be given an initial [redacted] dose of spesolimab plus [redacted] placebo. Patients from the active arm of the 1368-0052 PoCC trial will be given [redacted] placebo plus [redacted] spesolimab [redacted]

Detailed instructions for the preparation of the solution for infusion, the volume to be administered and the infusion rate as well as detailed instructions for use and handling of spesolimab syringes are provided in the ISF.

At all other visits all patients will receive [redacted] spesolimab [redacted] for the remainder of the trial unless an increase in dose to [redacted] is required at Week [redacted] Refer to Table 3.1: 1.

Patients have to be closely monitored for local or systemic hypersensitivity reactions for one hour following [redacted] or [redacted] study drug administration. Patients should be closely monitored for signs and symptoms of injection site or systemic hypersensitivity reactions following study drug administration. 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. Study personnel should observe the injection site for signs

of redness, swelling or hardness. They should also ask patients 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 his/her medical judgment he/she will provide medications such as steroids, etc., as needed (see Section 4.2.1 for handling of infusion reactions). Detailed instructions for handling of infusion reactions are also provided in the "Instructions for Pharmacist" document 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 Visit 1. 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. (See Section 3.3.4.1.)

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 the 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, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this extension will remain blinded to the medication provided at Visit 1 at least until the last patient from the 1368-0052 trial completes [redacted] weeks of treatment in this trial. The access to the randomisation code for Visit 1 will be kept restricted until its release for analysis.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available for the blinded medication at Visit 1 only. Although, all patients will receive spesolimab regardless at all visits. All patients at Visit 1 will be receiving placebo plus spesolimab.

4.1.6 Packaging, labelling, and re-supply

The IMP will be provided by BI or a designated contract research organization (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice. 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. 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 CTP by authorized personnel as documented in the trial staff list.

4.1.8 Drug accountability

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

- Approval of the CTP by the institutional review board (IRB) / independent ethics committee (IEC)
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site,
- Approval/notification of the regulatory authority (RA), e.g. competent authority (CA),
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated CTP,
- Availability of the proof of a medical license for the Principal Investigator, if applicable,
- Availability of U.S. Food & Drug Administration (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.

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 IMP and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all IMP 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 and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Systemic steroids dosed i.v. 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.

Any of the below 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.

4.2.1.1 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 SoC to:

- Immediately interrupt the infusion (if i.v.) or stop further injections (if s.c.).
- Treat with systemic anti-histamines, i.v. 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, i.v. 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 Rheumatology Common Toxicity Criteria (RCTC) grading) at lower speed with gradual increase to complete the infusion as detailed in the Instructions for Pharmacist in the ISF. 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 systemic hypersensitivity

(according to RCTC grading) to complete the injections as detailed in the Instructions for Use of Spesolimab Pre-filled Syringes in the ISF.

In case of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA (Appendix 10.1 [R11-4890]) suspected to be caused by the trial medication, the investigator should discontinue treatment permanently with spesolimab.

When a non-acute hypersensitivity reaction related to immune complexes (i.e., serum sickness) is suspected, please draw a sample for the laboratory assessment for circulating immune complexes.

In case of severe infections (according to RCTC grading), serious infections, opportunistic or mycobacterium tuberculosis (TB) infections, treatment of the infection should be initiated promptly according to local SoC. 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.

4.2.1.2 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 discontinue treatment with spesolimab. Diagnostics and treatment have to be initiated according to local SoC.

4.2.1.3 Suicidality

In case of signals of suicidal ideation or suicidal behaviour the patient should be referred to psychiatric work up. Overall, the choice of SoC treatment will be left at the discretion of the investigator. The sponsor will not provide/supply SoC treatment (s) to the sites. See Section 5.2.5.2.

4.2.1.4 Peripheral Neuropathy

If peripheral neuropathy is suspected, treatment with spesolimab should be temporarily discontinued until a full neurological investigation has been conducted.

After completion of the neurological investigation, treatment can be restarted based on medical judgement of the investigator.

4.2.2 Restrictions

4.2.2.1 Restrictions Regarding Concomitant Treatment

The medication (or classes of medications) listed in Table 4.2.2.1:1 are restricted for specific periods during the study (W0 - W12 and W12 through to EoT). As these restricted medications are consistent with the preceding 1368-0052 PoCC trial, patients must not have taken the medications (or classes of medications) through to the EoT Visit of the PoCC trial (which is the same day as Visit 1 in this trial). In the event that the EoT/V1 cannot be done on

the same day then a maximum 2-week gap can be allowed from the EoT Visit of the 1368-0052 PoCC trial to Visit 1 of this extension trial, systemic and topical antibiotics can be used for disease worsening as per investigator discretion. However, biologics, immunomodulators and opioid analgesics are not allowed for HS and non-HS indications. See also footnote to Visit 1 in the Flow Chart.

Table 4.2.2.1: 1 – Restricted Medications

Medication	W0 - W12	W12* - EoT
Systemic antibiotics[1]	Restricted for HS	Permitted for HS-disease worsening
Systemic corticosteroids[2]	Restricted for HS	Restricted for HS
Biologics causing immunosuppression	Restricted for HS and non-HS indications	Restricted for HS and non-HS indications
Other systemic immunomodulatory agents	Restricted for HS and non-HS indications	Restricted for HS and non-HS indications
Live vaccines[3]	Restricted	Restricted
Opioid analgesics	Restricted for HS	Restricted for HS
Spironolactone[4]	Restricted for HS and non-HS indications	Restricted for HS
Metformin[4]	Restricted for HS and non-HS indications	Restricted for HS
Topical cannabis oil[5]	Restricted for HS	Permitted
Systemic medicinal cannabis	Restricted for HS and non-HS indications	Restricted for HS
Topical corticosteroids for HS	Restricted for HS[6]	Permitted

*Following Week [redacted] dose modification management – See Table 3.1: 1

1. For more information on the use of systemic antibiotics please see Section 4.2.2.3.
2. Systemic corticosteroids as short courses, i.e., approximately 1- 2 weeks at the discretion of the investigator, can be used for indications other than HS.
3. Patients can receive seasonal influenza vaccines (excluding live attenuated vaccines).
4. Restricted if used for HS. Allowed for non-HS indications as a stable dose prior to V2 of the 1368-0052 PoCC trial.
5. Restricted if used over HS-affected areas. Other alternative therapies for HS are restricted, unless permitted after discussion with the PI and the sponsor.
6. Prior to Week [redacted], 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 defined as the treatment for disease worsening, and includes systemic antibiotics or immunosuppressive biologics such as TNF-inhibitors. The sponsor will not provide/supply these treatment(s) to the sites. As per Table 4.2.2.1: 1, immunosuppressive biologics are restricted during the entire trial. If a patient receives rescue treatment, the decision to maintain the patient on trial treatment is based on the investigator's clinical judgement.

4.2.2.3 Antibiotic Use During the Trial

Non HS use:
Systemic antibiotics can be used for indications other than HS. A maximum of 4 weeks of systemic antibiotics are allowed from Week 0 - Week 12 for non-HS indications.

HS disease worsening (as defined above in Section 4.2.2.2):
After Week 12, systemic antibiotics may be used for disease worsening as per investigator discretion.

4.2.2.4 Analgesics Use During the Trial

Opiate analgesics (except synthetic opioids such as tramadol) are restricted for HS. It can be allowed for non-HS indications as per investigator discretion.

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 from the 1368-0052 PoCC trial and is anticipated to remain stable throughout the study.

If a subject's pain (HS-related or non-HS-related) worsens after Visit 1, then non-opioid analgesic therapy may be initiated or increased.

Use of analgesics will be documented in 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, 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 from W0 – W12. An intervention can maximally occur on two different lesions at the same time or on the same lesion at two different study visits. There are no restriction in the number of lesion interventions from W12 – EoT.

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 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 (oestrogen 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 or intrauterine hormone-releasing system
- 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 centre under the supervision of the investigator or a designee. The measured plasma concentrations will provide additional confirmation of compliance.

5. ASSESSMENTS

All assessments are measured at the time points noted in the Flow Chart and preferably completed prior to study drug administration.

5.1 ASSESSMENT OF EFFICACY

5.1.1 Hidradenitis Suppurativa Clinical Response - HiSCR

The HiSCR 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 AN count, with no increase in the abscess or draining fistula count. [R20-2976] HiSCR is calculated automatically by comparing the lesion count from baseline.

5.1.2 International Hidradenitis Suppurativa Severity Score System - 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].
A nodule (inflammatory nodule) is a raised, three dimensional, 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.

5.1.3 Hidradenitis Suppurativa Physician Global Assessment - HS-PGA

This documents the physician's assessment of the patient's HS at a given time point. It scores patient disease severity as either clear or minimal or mild or moderate or severe or very severe, based on abscesses, draining fistulae, inflammatory nodule and non-inflammatory nodule.

5.1.4 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. 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).

5.1.5 Pain Numerical Rating Scale – Pain NRS

The Pain NRS is an endpoint for the assessment of HS-related pain severity for clinical trials with patients with HS. It is a unidimensional measure of pain intensity and can be administered monthly at the site. Response is given by an 11-point scale ranging from 0 to 10. The Pain NRS is completed by the patients during clinic visits. It will be used to assess the worst HS pain. Ratings will range from 0 (no HS pain) to 10 (HS pain as bad as one can imagine).

5.1.6 Dermatology Life Quality Index

The 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.

5.1.7 Hidradenitis Suppurativa Quality of Life – HiS-QoL

The 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.

5.1.8 FACIT-Fatigue Scale

The FACIT-Fatigue Scale 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 of 3-4 points in change score has been reported [R16-0029]. The recall period for items is 7 days.

5.1.9 Patient Global Impression of Change - PGI-C

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

5.1.10 Patient Global Impression of Severity - 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.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

A targeted physical examination will be performed at the time points specified in the Flow Chart. It includes evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.

Measurement of height and body weight will be performed at the time points specified in the Flow Chart.

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

5.2.2 Vital signs

This includes temperature, respiratory rate, systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. 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. Additionally, vital signs will be measured approximately 10 min post-dose after s.c. administration and approximately 5 and 60 min. post-dose in case of i.v. study drug administration. Also at Visit 2 and Visit 3 additional measurements will be performed

approximately 60 minutes after s.c. 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. For the sampling time points please see the Flow Chart.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF. Patients do not have to be fasted for the blood sampling for the safety laboratory. If blood sampling for central lab is not possible because central laboratory supplies are not available on time, safety lab analyses can be performed at a local laboratory. The results of the local lab tests must be reported to the investigator who ensures medical review and proper documentation in the eCRF.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF. The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

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 and/or the electronic data capture (eDC) system. The amount of blood taken from the patient concerned will be increased due to this additional sampling. The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.2.3:1 Infection testing at Visit 1 and EoT visit

Category	Test Name
Infection Testing	Hepatitis B virus-DNA (quantitative) at Visit 1 and EoT Visit[1] QuantiFERON®-TB-Gold Plus[2, 3, 4] Hepatitis B Surface Antigen (qualitative)[5] Hepatitis B core Antibody[5] Hepatitis C Antibodies (qualitative) [5] HIV-1, and HIV-2 Antibody (qualitative) [5] T-spot TB test

1. An 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 Visit 1 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 patients with a previously (i.e., in the previous PoCC trial or in this ongoing extension trial) negative QuantiFERON®-TB test, the test should be repeated every 52 weeks, as long as the results are negative.
5. If determined as negative at Visit 1, then there is no need to retest at the EoT Visit.

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 Bicarbonate

Category	Test Name
Substrates	Glucose BUN (blood urea nitrogen) Uric acid Creatinine[4] eGFR (estimated by CKD-EPI formula) (only at Visit 1) 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 & hs-CRP) (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol
Specific gamma-globulin quantification	IgE[1], IgG
Urine Pregnancy test (only for WOCBP)	Human Chorionic Gonadotropin in urine
Serum Pregnancy test (only for WOCBP if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes / Blood Urine WBC/ Leukocytes Urine pH Specific gravity

Category	Test Name
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 Visit 1)	Albumin (quantitative)
Interferon Gamma Release Assay (IGRA)	QuantiFERON®-TB or T-spot at EoT visit [2,3]

1. Only in case of allergic reaction
2. Patients with indeterminate QuantiFERON or invalid/borderline T-spot may be retested with IGRA (once) and if inconclusive should have a PPD skin test. .
3. In subjects with a negative QuantiFERON®-TB-Gold Plus or PPD skin test, the test should be repeated every 52 weeks (including the test at the EoT visit) as long as the results are negative.
4. 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 Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a 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 Visit 1) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

5.2.5.1 Malignancies

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

5.2.5.2 Columbia-Suicide Severity Rating Scale (C-SSRS)

Considering the characteristics of spesolimab, no penetration of blood-brain-barrier is anticipated, and a central effect triggering suicidal events is considered unlikely. The available pre-clinical and clinical data do not indicate effects of spesolimab on the central nervous system.

Pro-active screening for SIB in the HS clinical development program will be implemented with the following objectives:
- As a safety measure to exclude subjects at risk of suicidality and monitor for signs of suicidality.
- Structured data collection that may help in future assessment of potential signals around suicidality.

The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behaviour and suicidal ideation. It does not give a global score, but provides some categorical and some severity information specifically for behaviour and ideation.

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counsellor, 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 behaviour, and may be expanded to up to 17 items in case of positive responses. The investigator has to directly evaluate the scale and confirm that they evaluated and reviewed the scale. The investigator documents their evaluation and review of the scale by either,
- writing at statement in the source notes, or
- writing “reviewed” on questionnaire, signs, and dates the questionnaire.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at Visit 1 (using the ‘since last visit’ version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to the baseline visit. The life time history of SIB will also be recorded.

After the baseline visit the assessment ‘since last visit’ will be performed at each clinic or phone visit (‘since last visit’ version). 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. If there is a confirmed positive report of suicidal behaviour or suicidal ideation type 4 or 5 after start of trial, the investigator is to immediately interview the subject during the clinic visit, and/or is to consult a psychiatrist. If

the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.

All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behaviour must be reported as SAEs by the investigator. For 'Self-injurious behaviour, no suicidal intent' (Type 11) standard AE / SAE reporting rules are to be applied. For each negative report (suicidal ideation type 1, 2 or 3) after start of the trial, the investigator is to decide based on clinical judgment whether it represents an AE as defined in the CTP, and if it is considered an AE then it must be reported accordingly.

5.2.5.3 Local Tolerability

Local tolerability at the administration site of spesolimab will be assessed by the investigator during the trial 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", "pain", and any other findings should be reported as AEs (see Section 6.2.2).

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 electronic case report form (eCRF) only. However, if these abnormalities are AEs of the parent PoCC trial and still ongoing after the first dose in this extension trial, then they should not be recorded as baseline conditions. In such situations Section 5.2.6.2 should be followed.

5.2.6.1.2 Serious adverse event

A SAE is defined as any AE, which fulfils at least one of the following criteria:

- results in death,

- 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,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- 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, BI 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 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 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 10.1 [R11-4890]).

Severe infections
Refer to the RCTC grading in the ISF.

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), TB, 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), hepatitis C virus progression [R17-2617].

Potential Severe DILI

A potential severe Drug Induced Liver Injury (DILI) that requires follow-up 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 sample, or in samples drawn within 30 days of each other; or
- 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.
For patients with abnormal aminotransaminase levels between >1 and <3 x ULN at baseline:

1. An elevation of AST and / or ALT ≥3-fold the baseline value combined with an elevation of bilirubin ≥2-fold ULN or ≥2-fold the baseline value (if bilirubin is elevated at baseline), measured in the same blood sample, or in samples drawn within 30 days of each other, or,
2. Aminotransferase elevations ≥5-fold the baseline value.

For patients with abnormal aminotransaminase levels between ≥3 x ULN and <5 x ULN at baseline:

1. An elevation of AST and / or ALT ≥2-fold the baseline value combined with an elevation of bilirubin ≥2-fold ULN or ≥2-fold the baseline value (if bilirubin is elevated at baseline); measured in the same blood sample or in samples drawn within 30 days of each other, or,
2. Aminotransferase elevations ≥3-fold the baseline value.

Peripheral NeuropathyAny event suspected or diagnosed as Peripheral Neuropathy would be considered as an AESI. For the treatment interruption rules, please see Section 4.2.1.4.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) grading of AEs will be performed according to RCTC Version 2.0 developed by the Outcome Measures in Rheumatology organization [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. The following must be collected and documented on the appropriate CRF(s) by the Investigator (special notes on SAE form reporting where needed):

- From the time of the signing of the consent form in the extension trial until the end of the EoS visit all AEs (serious and non-serious) and all AESIs.

- All AEs that started in the 1368-0052 PoCC (parent) trial (onset date in parent trial) and are still ongoing after 1st IMP administration in the extension trial:

- Re-record the AE in the extension trial eCRF with the same information as it was recorded in the parent trial.
- Should the AE end during the course of the extension trial,
  - ⇨ update both - the extension trial eCRF and the parent trial eCRF. If the parent trial is already locked, update only the extension trial eCRF. In this case the update for the parent trial will be handled outside of the eCRF of the parent trial.
- However, concerning reporting on the SAE form (if applicable), the follow-up report will still be sent on the parent trial SAE form, no new SAE form is to be completed for the extension trial.
- If the intensity of an ongoing AE changes after 1st IMP administration in the extension trial:
  - ⇨ update both - the extension trial eCRF and the parent trial eCRF- with the end date for the initial/previous intensity. If the parent trial is already locked, update only the extension trial eCRF. In this case the update for the parent trial will be handled outside of the eCRF of the parent trial.
  - ⇨ The AE with the new intensity will be handled as new event; this means it is only recorded in the extension trial eCRF.
    - ⇨ Example: If the intensity increased then the new AE name/term should contain “Worsening of….” or “Exacerbation of….”.

      Considerations for reporting on the SAE form, when intensity change qualifies as worsening/exacerbation of an event that had already been reported on the SAE form:
      - corresponding follow up report to be sent on the parent trial SAE form with date of worsening as event end date.
      - extension trial SAE form to be sent as initial report for the extension trial for new event “worsening/exacerbation of….” with date of worsening as onset date.

Considerations for reporting on the SAE form, when intensity change qualifies as worsening/exacerbation of an event and requires for the first time reporting on the SAE form (meeting for the first time seriousness/AESI criteria):
- only extension trial SAE form to be sent - as initial report for the extension trial for new event "worsening/exacerbation of…." with date of worsening as onset date.

- All AEs with an end date **before** the 1st IMP administration in the extension trial, even if Informed Consent of the extension trial was already signed:

    - Record only in the eCRF of the parent trial.
    - In case of an AE reportable on the SAE form, send the update only on the SAE form of the parent trial.
    - Do not re-record in the extension trial eCRF, do not complete a new SAE form for the extension trial.

- After the EoS visit in the extension trial:

After a patient´s EoS Visit in the extension trial the investigator does not need to actively monitor the patient for new AEs but should only report new malignancies or the exacerbation of existing malignancies, 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) for the extension trial, but not on the CRF (neither on CRF for extension trial nor for parent trial).

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 immediately to the sponsor's unique entry point (within 24 hours of becoming aware of the event) (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 send 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.

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, ADA and neutralizing antibody (Nab) 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.

5.3.2 Methods of sample collection

Plasma/Serum samples may be used for further methodological investigations (ex: for future stability testing). However, only data for measuring the analyte and antibody responses to the analyte will be generated by these investigations. After completion of the trial, the plasma/serum samples may be used for further methodological investigations, e.g. for stability testing. However, only data related to the analyte and data related to the ADAs will be generated by these additional investigations. The samples will be discarded after completion of the additional investigations but not later than [redacted] years upon the final study report has been signed.

5.3.2.1 Plasma sampling for PK analysis

For quantification of spesolimab plasma concentrations, blood will be taken from a forearm vein into a K2EDTA (ethylendiaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the Flow Chart under plasma PK. Handling procedures can be found in the laboratory manual.

5.3.2.2 Sampling for ADA/Nab assessment

For ADA assessment, blood will be taken from a forearm vein into a K2EDTA anticoagulant blood-drawing tube at the time points listed in the Flow Chart under ADA/Nab. For Nab assessment, blood will be taken from a forearm vein into a serum blood-drawing tube at the

time points listed in the Flow Chart under ADA/Nab. Handling procedures can be found in the laboratory manual (see ISF).

[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.

5.4.1 Biochemical and cellular biomarkers

Serum will be collected as indicated in the Flow Chart to assess changes in protein levels of select IL36 pathway and disease related markers. The biomarker assay analysis of samples will be performed in a staged approach. The initial analysis will focus on selected time points and depending on these results a decision will be made about further analysis of all samples. This is due to the exploratory nature of the mechanism being tested and the timing of effect on candidate biomarkers in the study.

5.4.2 Pharmacogenomics biomarkers

Whole blood samples will be collected as indicated in Flow Chart 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. The biomarker analysis of samples will be performed in a staged approach. The initial analysis will focus on selected time points and depending on these results a decision will be made about further analysis of all samples. This is due to the exploratory nature of the mechanism being tested and the timing of effect on candidate biomarkers in the study.

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 Flow Chart.

[redacted]

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Photographs

Subjects will have photographs taken of their disease response during the study. The photographs will be taken at designated study visits listed in the Flow Chart. 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 Flow Chart. Each visit date (with its window) up to the EoS Visit is to be counted from Visit 1 (visit with first IMP administration). If any of these visits has to be rescheduled, the date of the subsequent visit should be calculated again from Visit 1. Additional visits (unscheduled visits) for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator. If a visit was missed due to any reason, the Clinical Trial Leader (CT Leader) must be contacted to discuss if the visit must be skipped.

For detailed description of the visit schedule and the trial procedures, please refer to the Flow Chart and its footnotes.

Details relating to study drug administration and treatment interruptions are provided in Section 4.1.4.

Study measurements and assessments are scheduled to occur 'before' trial medication administration. For planned individual plasma concentration sampling times refer to the Flow Chart. Sampling times will be recorded and used for PK analysis.

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.

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this CTP may not be feasible at a site. With the consent of the patient, sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual patient visits and assessments, home healthcare nurse visits, and direct-to-patient shipments of trial treatment. Such alternative measures may be described in a specific Crisis Management Manual as part of the initial submission package, and will also be mentioned in the patient information leaflet. The implementation of these measures will depend on patient's consent, operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart and respective CTP sections. Refer to Section 5 for explanations of the specified assessments and procedural details.

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.

Separate from the PROs above, the evaluation of efficacy assessments are to be conducted preferably by the same qualified assessor, whenever possible, throughout the study.

PROs and assessments should preferably be done prior to any study drug administration.

6.2.1 Visit 1 – Start of Treatment

For the comprehensive list of the trial procedures required at Visit 1 please refer to the Flow Chart. Study drug will start at Visit 1.

Visit 1 should preferably be performed in one visit combined with the EoT visit of the preceding 1368-0052 PoCC trial. Any duplicate procedures across the two studies are performed only once when the visit is combined. When these two visits across both studies do not occur on the same day then a modification of procedures will need to be considered. Refer to the Flow Chart for procedures that are identical across the two visits and for further information on any modification of procedures.

If a patient performs the EoT visit in the 1368-0052 PoCC study and a newly observed medical finding, for example, prohibits the patient to immediately enrol into this study, then the patient can come back for Visit 1 at a later date per the opinion of the investigator and after discussion with the sponsor. The maximum gap for enrolling into this trial is 2 weeks after the EoT in the 1368-0052 PoCC trial. During this gap, patients can take systemic and topical antibiotics for disease worsening as per the investigator discretion (see Section 4.2). However, biologics, immunomodulators and opioid analgesics are not allowed for HS and non-HS indications.

Refer to Section 4.1.4 for study drug assignment and administration. Administration of the study drug is blinded at Visit 1 only.

6.2.1.1 Informed Consent

The patient must be given sufficient time to consider participation in this extension trial. Therefore, to facilitate the logistics of Visit 1 and the consenting process, information about this extension trial should be discussed with potentially eligible patients in advance of Visit 1 of this trial. A copy of the patient information and consent form of the extension trial should be provided to potentially eligible patients preferably no later than Visit 8 of the previous 1368-0052 PoCC trial. This will provide potential patients with sufficient time to consider their possible participation in this extension trial. At Visit 1, 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. Also refer to Section 8.1.

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 evaluations. The importance of staying in the trial until

completion of all study requirements should be emphasized. No trial procedures can 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. Once informed consent is obtained, the IRT contact is to be performed by the site. IRT will assign a patient number at the time IRT registration. Collection of SAEs and AEs begins immediately after the patient has signed the consent form (please refer to Section 5.2.6.2.1). The patient should be recorded on the enrolment log.

6.2.1.2 Infection Testing

Infection testing will include TB, Hepatitis B, Hepatitis C, and HIV assessments (see Table 5.2.3:1). **The results of the Infection Testing will not be available until after the patient receives their first dose at Visit 1**. See Section 3.3.4.1 for Discontinuation Rules.

Interferon Gamma Release Assay

Patients with indeterminate / suspected false-positive QuantiFERON TB or invalid/borderline T-spot test result may have the test repeated once. If after repeat testing the QuantiFERON TB result is “indeterminate”, a PPD skin test may be performed locally. A tuberculin skin test reaction ≥10mm (≥5mm if receiving ≥15mg/d prednisone or its equivalent) is considered positive.

In patients with a previously (i.e., in the previous PoCC trial or in this ongoing extension trial) negative IGRA for TB the test should be repeated every 52 weeks, as long as the results are negative. Refer to Table 5.2.3:1.

If latent tuberculosis is diagnosed during the trial, then patients can receive anti-tuberculosis treatment as per investigator discretion and continue receiving study medication as per investigator.

6.2.2 Treatment period(s)

The treatment period is from Visit 1 to the EoT Visit at Week [redacted]. For the comprehensive list of the trial procedures required during these visits please refer to the Flow Chart and its footnotes. See also Section 5.2 for details of all safety assessments.

Refer to Section 4.1.4 for study drug administration.

For information on the collection of photographs of skin lesions, please see Section 5.6.1

6.2.3 Follow-up period and trial completion

For the comprehensive list of the trial procedures required at the EoT, FUP 1, and the EoS visits please refer to Flow Chart and its footnotes.

The FUP 1 Visit occurs 2 weeks after the EoT Visit; this is 2 weeks after the patient has received their last dose of trial medication.

The EoS visit will take place at the end of the REP which is 16 weeks after last injection of trial medication. Please also refer to the REP in Section 1.2.3. After conclusion of trial the patients will be treated according to the standard of care.

Patients who discontinue trial treatment prematurely should undergo the EoT visit as soon as possible, the FUP 1 Visit two weeks after the last dose, and the EoS Visit 16 weeks after the last dose. If a patient discontinues the study during a scheduled treatment visit then the visit is considered an EoT visit.

In the event a patient discontinues treatment and the trial prematurely and is unable to perform both FUP 1 and EoS visits, (only willing or physically can only perform one visit) then the early FUP 1 Visit procedures should be followed.

For all patients, trial completion status must be recorded on the corresponding eCRFs.

Treatment completion is defined as a patient completing the EoT Visit after receiving approximately 2 years of treatment without early discontinuation of study treatment.

Trial completion is defined as a patient having reached the EoS Visit within the specified window per protocol.

If needed in the opinion of the investigator, after the EoS visit additional visits may be scheduled for continued safety monitoring.

Abnormal assessments or lab values judged clinically relevant by the investigator will be monitored until they are returned to a medically acceptable level.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The primary objective of this trial is to assess the long-term safety of spesolimab in patients with HS who have completed the 1368-0052 PoCC trial and are qualified for entry into this trial. The secondary objectives are to evaluate efficacy at a lower dose than tested in PoCC trial.

For primary analysis of the primary endpoint, all adverse events with an onset between start of treatment and end of the REP (i.e., 16 weeks after the last study treatment) will be included.

7.1 NULL AND ALTERNATIVE HYPOTHESES

Given the single arm and open-label nature of this trial, no hypothesis testing will be performed in the confirmatory sense. All statistical assessments will be performed in an explorative manner to better understand the efficacy and safety profile of spesolimab.

7.2 PLANNED ANALYSES

7.2.1 General considerations

This trial is designed as a single arm, open-label trial in patients with HS who have completed the planned treatment period in spesolimab 1368-0052 PoCC trial.

The following patient population set will be defined in this trial for analyses:

Safety Analysis Set (SAF)
This patient set includes all patients who received at least one study treatment in this trial.

Further analysis sets will be defined in the trial statistical plan (TSAP) if necessary.

Important deviations of the protocol will include deviations of the key inclusion and exclusion criteria, 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 final database lock (DBL) for this extension trial.

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

A Clinical Trial Report (CTR) will be prepared once the final DBL for this extension trial has been performed.

7.2.2 Primary endpoint analyses

Refer to Section 7.2.5 for the description of safety analyses for the primary endpoint. The primary endpoint will be summarized based on SAF.

7.2.3 Secondary endpoint analyses

For binary endpoints, the efficacy data will be presented over time based on SAF where any data collected after the use of rescue therapy will be censored and then imputed using the Non Response Imputation (NRI) method as described in Section 7.3.

For continuous endpoints, the efficacy data will be presented over time based on SAF where any data collected after the use of rescue therapy will be censored and then may be handled by a mixed effect model for repeated measurements (MMRM).

Further, it is also of interest to explore week 12 efficacy performance of patients who were responders, partial responders and non-responders in the 1368-0052 trial respectively as defined in Table 3.1: 1.

Further details will be provided in the TSAP.

[redacted]

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, (i.e., 16 weeks after last study treatment) will be assigned to the on-treatment period for evaluation.

All 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, i.e. all adverse events occurring between start of the first treatment and end of the REP of the last treatment. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’. Safety assessments including treatment emergent adverse events, laboratories, vital signs etc. based on SAF.

Frequency, severity, and causal relationship of treatment emergent adverse events will be tabulated by system organ class (SOC) and preferred term after coding according to the current version of the MedDRA at DBL. Exposure adjusted incidence rate of all treatment emergent adverse events will also be presented.

The exposure adjusted incidence rate (per 100 subject years) of a selected treatment emergent adverse event is defined as the number of subjects experiencing the adverse event per treatment group during time at risk divided by the total time of subjects at risk in that treatment group to contribute the event to the analysis multiplied by 100 (per 100 subject year), where:

Time at risk [subject years] = (date of onset of TEAE – study drug start date + 1) / 365.25

If, for a subject, the selected treatment emergent adverse event didn't occur then the time at risk will be censored at min (date of death, last contact date per EoS page, drug stop date + 112 days, cut-off date if interim analysis performed). For each selected treatment emergent AE, the exposure adjusted incidence rate will be calculated as:

> Incidence rate [1/100 Subject years (pt-yrs)] = 100 * number of subjects with TEAE / Total TEAE-specific time at risk [subject years].

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter 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.

Vital signs, physical examinations, or other safety-relevant data observed at 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

Pharmacokinetics

Please refer to Section 5.3.1 and further information available in the TSAP.

Biomarker Analysis

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 TSAP.

Further details will be discussed in the TSAP.

7.2.7 Interim Analyses

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

As the primary aim of this study is to collect long-term safety and efficacy data on the use of spesolimab in this population, multiple interim analyses may be done over the two-year conduct phase of this trial to support, for example, regulatory interactions, Clinical Trial Application and Marketing Authorisation Application/Biologics Licencing Application submissions, but also to provide important safety and efficacy information to the sponsor to guide further development of the compound, and to the investigators via IB updates and publications.

Since patients will be enrolled into this study over a time period of several weeks and in line with the exploratory nature and open label design of the study, such analyses will be performed on demand and are not feasible to be pre-defined.

7.3 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at all visits. However, missing data will still occur and approaches to handle this are proposed below.

For the safety data, including the primary endpoint, no missing data imputations are planned.

For secondary binary efficacy endpoints, a NRI approach will be applied to the missing visits; that is, imputing as a failure to achieve a response in the visits with missing endpoint score, however:

- If there are visits with available data 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).

For secondary continuous efficacy endpoints, MMRM method may be applied to handle the missing data.

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

7.4 RANDOMISATION

This is an open-label and single arm study. No randomization of treatment group is required.

Treatment allocation of patients at Visit 1 is based on their previous treatment in the 1368-0052 PoCC trial. Patients, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this extension will remain blinded to this medication by IRT system. Afterwards, all patients will receive open-label s.c. spesolimab starting at Visit 2 onwards where no blinding is required.

7.5 DETERMINATION OF SAMPLE SIZE

Given the descriptive nature of this trial, no sample size calculation has been performed. The sample size of this OLE is determined based on the sample size of the preceding parent trial (1368-0052).

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-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 BI 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 IRB / EC and 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 accepted 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. Please also refer to Section 6.2.1.1 for special considerations prior to Visit 1.

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 or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, 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 RA. 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. 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.

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))
- SAEs (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- 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 ICH-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 World Health Organization ICH-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 RA.

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 – (Biobanking is not applicable in this trial).
- 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 – (Biobanking ICF is not applicable in this trial).

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 suspected unexpected serious adverse reactions 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 / CA 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.

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 safety data and efficacy data. The DMC will receive urgent significant safety concerns and DILI for immediate evaluation. 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 RAs/Health Authorities, 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 CT Leader, responsible for coordinating all required activities, in order to
- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers, 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 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 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 than (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)

11.1 GLOBAL AMENDMENT 1

Date of amendment		04 July 2022
EudraCT number **EU number**		2020-005587-55
BI Trial number		1368-0067
BI Investigational Product(s)		BI 655130
Title of protocol		An open-label, long-term extension trial of spesolimab treatment in adult patients with Hidradenitis Suppurativa (HS)
Global amendment due to urgent safety reasons		No
Global amendment		X

Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS, Trial Endpoints, 2.1.3 Secondary endpoints(s)
Description of change		Change the wording in two endpoints FROM: Number of patients having at least one flare (defined as at least [redacted] in AN count with a minimum increase of 2 relative to baseline) up to Week [redacted] Number of patients having at least [redacted] from baseline in Numerical Rating Scale (NRS30) in Patient's Global Assessment of HS Pain up to Week [redacted] TO: **Occurrence of** at least one flare (defined as at least [redacted] in AN count with a minimum [redacted] of [redacted] relative to baseline) up to Week [redacted]. **Achievement of** at least [redacted] from baseline in Numerical Rating Scale (NRS30) in Patient's Global Assessment of HS Pain up to Week [redacted]
Rationale for change		To better clarify and to make these two secondary endpoints more informative.

Section to be changed		Flow Chart - Up to W[redacted]
Description of change		Add footnote about dose modification at Week 12
Rationale for change		To align with Table 3.1: 1 and instructions in section 3.1

Section to be changed		Flow Charts, Footnotes #8 and #17, Section 5.1.1
Description of change		Added information that the HiSCR value is

		calculated automatically.
Rationale for change		To clarify that the HiSCR value is not required to be completed by the investigator.

Section to be changed		Flow Chart -W[redacted] to End of study, Section 3.3.4 Withdrawal of patients from treatment, 6.2.3 Follow-up period and trial completion
Description of change		Align wording FUP1 and EoS visit timelines with Flow Chart. FUP 1 is two weeks after last dose and EOS is [redacted] weeks after last dose.
Rationale for change		To have consistent wording

Section to be changed		Flow Chart – W[redacted] to End of Study
Description of change		Add footnote ***. Clarification on re-assessment of Non-responders on [redacted] at Week [redacted]
Rationale for change		To align with the information in Table 3.1: 1.

Section to be changed		Table 1.4.2:1 Risks
Description of change		The risk “Peripheral Neuropathy” was added to Table 1.4.2:1 including a summary of data and mitigation strategy.
Rationale for change		Added to inform about the newly added potential risk “peripheral neuropathy” deriving from the three cases reported as Guillain-Barré syndrome by the investigator in Spesolimab trials (details in the CTP). The cases were considered as peripheral neuropathy by the external neurologist expert panel’s assessment.

Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		Include the discontinuation of Non-responders on [redacted] at Week [redacted]
Rationale for change		To be consistent with Table 3.1: 1

Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		The patient needs to take concomitant medication such as immunosuppressive biologics, ~~systemic corticosteroids, other immunomodulators, opioid analgesics for HS,~~ live vaccines, or other concomitant medication that interferes with the Investigational Medicinal Products (IMP) or other trial treatment.
Rationale for change		To be consistent with Table 4.2.2.1: 1 – Restricted Medication.

Section to be changed		3.3.4.1 Discontinuation of trial treatment
Description of change		Added language in bold i.e. The patient can no

		longer receive trial treatment for medical reasons such as surgery, **serious or severe Drug Induced Liver Injury attributable to the trial drug**, **other** adverse events, other diseases, or pregnancy. Also refer to Section 5.2.6.1.4**.**
Rationale for change		To use standard language.

Section to be changed		4.1.4, 7th paragraph
Description of change		Add the name of the exact document, i.e., Instructions for Pharmacist, which is found in the ISF.
Rationale for change		To clarify the name of the document in the ISF.

Section to be changed		4.2.1.4 Peripheral Neuropathy
Description of change		Following information was added: “Peripheral Neuropathy” If peripheral neuropathy is suspected, treatment with Spesolimab should be temporarily discontinued until a full neurological investigation has been conducted. After completion of the neurological investigation, treatment can be restarted based on medical judgement of the investigator.
Rationale for change		Added as mitigation strategy to account for the three cases reported as Guillain-Barré syndrome in spesolimab trials. The cases were considered as peripheral expert panel’s assessment (details in the CTP).

Section to be changed		Table 4.2.2.1: 1 – Restricted Medications
Description of change		Move footnote #6 to “Restricted for HS”
Rationale for change		To clarify that topical corticosteroids are allowed prior to Week [redacted] for non-HS areas only.

Section to be changed		4.2.1.1, 3rd paragraph
Description of change		Add the name of the exact document, i.e., Instructions for Pharmacist, which is found in the ISF.
Rationale for change		To clarify the name of the document in the ISF.

Section to be changed		4.2.1.1, 4th paragraph
Description of change		Add the name of the exact document, i.e., Use of Spesolimab Pre-filled Syringes, which is found in the ISF.
Rationale for change		To clarify the name of the document in the ISF.

Section to be changed		4.2.2.1

Description of change		(W0 - W[redacted] and W[redacted] through to EoT).
Rationale for change		Change W[redacted] to W[redacted] to match the headings in the Restricted Medications Table 4.2.2.1: 1

Section to be changed		4.2.2.2
Description of change		If a patient receives rescue treatment, the decision to maintain the patient on trial treatment **is based on the investigator's clinical judgement**.
Rationale for change		To remove the need for the investigator to discuss their decision with the sponsor.

Section to be changed		4.2.2.4
Description of change		Opiate analgesics **(except synthetic opioids such as tramadol)** are restricted for HS. It can be allowed for non-HS indications as per investigator discretion
Rationale for change		This is a 2-year OLE trial with a primary endpoint of TEAE. Tramadol is added to allow for pain relief for HS or non-HS indications to help patients over this 2-year period.

Section to be changed		4.2.2.7 Contraception Requirements
Description of change		Remove the following sentence: A double barrier method of contraception is not required.
Rationale for change		Sentence is redundant and confusing. The acceptable methods of birth control are defined in this section.

Section to be changed		5.2.3 Safety laboratory parameters
Description of change		If blood sampling for central lab is not possible because central laboratory supplies are not available on time, safety lab analyses can be performed at a local laboratory. The results of the local lab tests must be reported to the investigator who ensures medical review and proper documentation in the eCRF.
Rationale for change		To prevent that an important safety laboratory analysis is not done and allow local safety analysis in emergency

Section to be changed		5.2.5.2 Columbia-Suicide Severity Rating Scale (C-SSRS)
Description of change		Remove reference to investigator having to write a report and instead confirm their review in the source notes or by writing reviewed on questionnaire, signs and dates the questionnaire
Rationale for change		To remove the requirement that required the

		investigator to write a report; not necessary.

Section to be changed		5.2.6.1.4 Adverse events of special interest
Description of change		Added Peripheral Neuropathy as an Adverse event of special interest.
Rationale for change		To update reporting requirements to ensure all cases of suspected peripheral neuropathy including non-serious ones are analyzed quickly.

Section to be changed		6.2.3 Follow-up period and trial completion
Description of change		After conclusion of trial the patients will be treated according to the standard of care.
Rationale for change		To include a statement of treatment after conclusion of trial

Section to be changed		Abbreviations; 7.2.1; 7.2.2; 7.2.5
Description of change		Treated Set (TS) replaced by SAFety analysis set (SAF)
Rationale for change		To be aligned with the Trial Statistical Analysis Plan

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Biostatistics	[redacted]	05 Jul 2022 17:10 CEST
Approval-Clinical Trial Leader		05 Jul 2022 17:39 CEST
Approval-Clinical Program [redacted]		07 Jul 2022 12:31 CEST
Approval-Principal Investigator		07 Jul 2022 15:51 CEST

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Meaning of Signature	Signed by	Date Signed