Clinical Trial Protocol

	Document Number:	**c40061625-02**
EudraCT No. **EU Clinical Trial No.**	2022-501074-19-00	
BI Trial No.	1368-0098	
BI Investigational Medicinal Product	Spevigo®, spesolimab	
Title	Randomised, double-blind, placebo-controlled, Phase IIb/Phase III study to evaluate the efficacy and safety of spesolimab in patients with moderate to severe hidradenitis suppurativa. Lunsayil 1.	
Lay Title	A study to test whether spesolimab helps people with a skin disease called hidradenitis suppurativa	
Clinical Phase	IIb/III	
Clinical Trial Leader	[redacted]	
Coordinating Investigator		
Current Version and Date	Final Version 2.0 02 Nov 2023	
Original Protocol Date	02 Dec 2022	Page 1 of 177

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date **Latest revision date**	Final protocol Version 1, 02 Dec 2022
BI trial number **EU CT number**	1368-0098 2022-501074-19-00
Title of trial	Randomised, double-blind, placebo-controlled, Phase IIb/Phase III study to evaluate the efficacy and safety of spesolimab in patients with moderate to severe hidradenitis suppurativa. Lunsayil 1.
Coordinating Investigator	[redacted]
Trial sites	Multi-centre trial conducted in approximately 40 countries
Clinical phase	IIb/III
Trial rationale	Hidradenitis suppurativa (HS) is an inflammatory skin disease characterised by recurrent inflammatory nodules, painful abscesses and fistulous tracts also called tunnels that may be draining a malodourous exudate. Patients with HS have one of the lowest quality of life measures of any dermatologic disease. Spesolimab is a humanised, selective antibody that blocks the activation of the interleukin-36 receptor (IL-36R). It is hypothesised that by interfering with this mechanism, spesolimab may decrease neutrophilic and other immune cells influx in lesions, thereby directly impact abscesses and draining fistulas, a high unmet medical need in HS. No other IL-36 receptor antagonist is currently approved, that would provide information on identified risks in molecules of this class. Study 1368-0098 consists of 2 parts: a dose finding Phase IIb (Part 1), designed to primarily support the decision on optimal spesolimab dosing in patients with moderate to severe HS with existing draining tunnels (dT); a confirmatory Phase III (Part 2), designed to confirm positive benefit/risk ratio of spesolimab in HS.

Benefit-risk assessment and ethical considerations	Spesolimab has shown acceptable tolerability so far in clinical trials of multiple indications. Considering the medical need for development of a more effective and well tolerated drug for the therapy of HS, the benefit of this trial is considered to outweigh the potential risks. The placebo control until [redacted] is required to control for investigator bias and/or beneficial effects of being in a clinical trial. By switching placebo recipients to active treatment from [redacted] this protocol ensures an opportunity for all trial participants to receive active investigational medicinal product (IMP) treatment during the study.
Trial objectives	**Part 1 (Phase IIb)** The primary objectives of the dose finding phase are as follows: (1) to demonstrate a non-flat dose response curve, evaluate the quantitative treatment effect size, and evaluate the dose-response relationship based on the primary endpoint of percent change from baseline in dT count at [redacted] (2) to determine an optimal dose for Part 2 by incorporating information of available safety and of efficacy based on the primary endpoint of percent change from baseline in dT count at [redacted] The secondary objectives are as follows: (1) to demonstrate non-flat dose response curve based on selected secondary and further efficacy endpoints at [redacted] (2) to evaluate the quantitative treatment effect size of percent change from baseline in dT count at [redacted] and absolute change from baseline in International Hidradenitis Suppurativa Severity Score System (IHS4) value at [redacted] (3) to evaluate the sustainability of spesolimab efficacy up to [redacted] and up to [redacted] (4) to assess safety of spesolimab. The secondary objectives will be served by selected secondary and further efficacy endpoints, as well as safety endpoints. **Part 2 (Phase III)** The primary objective of the confirmatory phase is to demonstrate superiority of [redacted] of spesolimab (identified on the basis of Phase IIb data analysis) against placebo in the mean percent change from baseline in dT count at [redacted] The secondary objectives are as follows: (1) to demonstrate superiority of spesolimab against placebo for the key secondary endpoints. (2) to assess safety of spesolimab.

Trial endpoints	**Part 1 (Phase IIb)** **Efficacy** Primary endpoint Percent change from baseline in dT count at [redacted] Secondary endpoint • Percent change from baseline in dT count at [redacted] • Absolute change from baseline in IHS4 value at [redacted] • Absolute change from baseline in IHS4 value at [redacted] **Safety** Occurrence of treatment emergent adverse events (TEAEs). **Part 2 (Phase III)** Final endpoints for Part 2 will be supported by study results available at the time of Part 1 primary analysis. **Efficacy** Primary endpoint Percent change from baseline in dT count at [redacted] Key secondary endpoints The followings are considered as potential key secondary endpoints. These may be amended according to Part 1 results. • Absolute change from baseline in IHS4 value at [redacted] • Absolute change from baseline in Hidradenitis Suppurativa Area Severity Index (HASI) score at [redacted] • Achievement of Hidradenitis Suppurativa Clinical Response (HiSCR50) at [redacted] HiSCR50 is defined as at least a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in dT count relative to baseline. • Percent change from baseline in abscess count at [redacted] • Achievement of at least a 50% reduction in dT count at [redacted] relative to baseline. • Achievement of at least a 50% reduction in abscess and dT (AdT) count at [redacted] relative to baseline. • Achievement of at least a 50% reduction in ANdT count at [redacted] relative to baseline. • Achievement of at least 30% reduction from baseline in Numerical rating Scale (NRS30) in Patient's Global Assessment of HS pain at [redacted] **Safety** Occurrence of TEAEs.

Trial design	**Part 1 (Phase IIb) and Part 2 (Phase III)** International, multi-center, placebo-controlled, double blind, randomised trial assessing the efficacy and safety of spesolimab versus placebo in patients with moderate to severe HS over [redacted]
Total number of trial participants randomised	**Part 1 (Phase IIb)** [redacted] **Part 2 (Phase III)** [redacted]
Number of trial participants per treatment group	**Part 1 (Phase IIb)** [redacted] **Part 2 (Phase III)** [redacted]

Diagnosis, main inclusion and exclusion criteria	**Part 1 (Phase IIb) and Part 2 (Phase III)** Diagnosis: Moderate to severe HS based on IHS4 criteria. **Part 1 (Phase IIb)** Main inclusion criteria (additional criteria clarifications may be found in the body of protocol): • Of full age of consent at screening. • Moderate to severe HS, based on IHS4 criteria, for at least 6 months prior to and including Baseline visit. • HS lesions in [redacted] distinct anatomic area. • Biologic naive or TNFi-exposed for HS. • For biologic naïve, inadequate response to an adequate course of appropriate oral antibiotics for treatment of HS in the last 1 year prior to the Baseline visit, as per investigator discretion • Total AN count [redacted] • Total dT count [redacted] Main exclusion criteria: • Use of restricted medications that interferes with the assessment of HS. • Prior exposure to any immunosuppressive biologic other than TNFi for HS. • Prior exposure to IL-36R inhibitors including spesolimab. **Part 2 (Phase III)** For inclusion and exclusion criteria, except for potential criteria which will be confirmed after analysis of Phase IIb results, the same criteria as Part 1 (Phase IIb) will need to be met.
Trial intervention and test product	Spesolimab

Dose and mode of administration	**Part 1 (Phase IIb)** By group up to Visit 14 [redacted] • High dose group [redacted] • Medium dose group [redacted] • Low dose group [redacted] By group from Visit 14 [redacted] • From Visit 14 [redacted] trial participants in high and medium dose groups will receive [redacted] • From Visit 14 [redacted] trial participants in low dose group will receive [redacted] • Based on inadequate clinical response as per protocol, up-titration [redacted] will be possible when applicable (low dose group). From Visit 23 [redacted] on, trial participants will continue to receive the previously assigned dosing regimen until the results of primary analysis [redacted] are available. Upon availability of the Phase IIb primary analysis efficacy and safety results, the dosing regimen might be adapted from Visit 23 [redacted] through amendment. **Part 2 (Phase III)** The dosing regimen will be selected based on Phase IIb primary analysis.
Comparator product	Placebo.

Dose and mode of administration	**Part 1 (Phase IIb)** • Up to Visit 14 [redacted] but not including this visit, matching. • From Visit 14 [redacted] trial participants in the placebo group will be switched to [redacted] Visit 23 [redacted] • From Visit 23 [redacted] on, trial participants will continue to receive the previously assigned dosing regimen until the results of primary analysis [redacted] are available. Upon availability of the Phase IIb primary analysis efficacy and safety results, the dosing regimen might be adapted from Visit 23 [redacted] through amendment. **Part 2 (Phase III)** • Up to [redacted] matching.From [redacted] trial participants in the placebo group will be switched to a dose regimen selected on the basis of Phase IIb.
Duration of treatment	**Part 1 (Phase IIb)** Administration of treatment will be up to [redacted] The final assessment of treatment effect will be on [redacted] (EoT visit). **Part 2 (Phase III)** Administration of treatment will be up to [redacted] The final assessment of treatment effect will be on [redacted] (EoT visit).

Statistical methods	**Part 1 (Phase IIb)** [redacted] To account for the repeated nature of the data and the covariates in the model, [redacted] Percent change from baseline in dT count will be used as the response variable [redacted] The [redacted] include fixed categorical effects of treatment at each visit, [redacted] at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements. **Part 2 (Phase III)** The primary endpoint is percent change from baseline in dT count at [redacted] Restricted maximum likelihood estimation based on a mixed-effect model for repeated measures analysis will be used to obtain adjusted means for the treatment effects. This model will include categorical fixed effects for treatment at each visit, [redacted] at baseline, and categorical baseline dT count at each visit. The primary treatment comparisons will be the contrast between treatment at [redacted] Significance tests will be based on adjusted treatment differences using a one-sided α of 0.025.

FLOWCHART

Part 1 (Phase IIb): Flowchart will be consolidated for Part 2 (Phase III) based on the primary analyses and/or interim analyses of Part 1.

Trial Periods	Screening	Treatment Period - up to [redacted]																				
Visit	**1**	**2** Baseline	**3**	**4**	**5**	**6**	**7***	**8**	**9***	**10**	**11**	**12**	**13**	**14**	**15***	**16**	**17**	**18**	**19**	**20***	**21**	**22***	**23**
Day	[redacted]																						
Time window for visits (days)	n.a.	none	±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
[redacted]																							

FLOWCHART

Part 1 (Phase IIb): Flowchart will be consolidated for Part 2 (Phase III) based on the primary analyses and/or interim analyses of Part 1. (cont.)

Trial Periods	**Screening**	**Treatment Period - up to** [redacted]																				
Visit	**1**	**2** **Baseline**	**3**	**4**	**5**	**6**	**7***	**8**	**9***	**10**	**11**	**12**	**13**	**14**	**15***	**16**	**17**	**18**	**19**	**20***	**21**	**22***	**23**
Day	[redacted]																						
Time window for visits (days)	n.a.	none	±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
[redacted]																							

FLOWCHART

Part 1 (Phase IIb): Flowchart will be consolidated for Part 2 (Phase III) based on the primary analyses and/or interim analyses of Part 1. (cont.)

Trial Periods	Screening	Treatment Period - up to [redacted]																				
Visit	**1**	**2** Baseline	**3**	**4**	**5**	**6**	**7***	**8**	**9***	**10**	**11**	**12**	**13**	**14**	**15***	**16**	**17**	**18**	**19**	**20***	**21**	**22***	**23**
Day [redacted]																							
Time window for visits (days)	n.a.	none	±1	±1	±1	±1	±1	±1	±1	±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
[redacted]																							

Trial Periods	Treatment Period – after [redacted] up to [redacted]								EoT	Safety Follow-Up
Visit	**24***	**25**	**26***	**27**	**28***	**29**	**30***	**31**	**EoT**[2]	**EoS**
Day [redacted]										[redacted] admin or 98 days from EoT.
Time window for visits (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7
[redacted]										

FLOWCHART

Part 1 (Phase IIb): Flowchart will be consolidated for Part 2 (Phase III) based on the primary analyses and/or interim analyses of Part 1. (cont.)

Trial Periods	Treatment Period – after [redacted] up to [redacted]								EoT	Safety Follow-Up
Visit	**24***	**25**	**26***	**27**	**28***	**29**	**30***	**31**	**EoT[2]**	**EoS**
Day	[redacted]									[redacted] 98 days from EoT.
Time window for visits (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7
[redacted]										

FLOWCHART

Part 1 (Phase IIb): Flowchart will be consolidated for Part 2 (Phase III) based on the primary analyses and/or interim analyses of Part 1. (cont.)

Trial Periods	**Treatment Period – after [redacted] up to [redacted]**								**EoT**	**Safety Follow-Up**
Visit	**24***	**25**	**26***	**27**	**28***	**29**	**30***	**31**	**EoT[2]**	**EoS**
Day	[redacted]									[redacted] or 98 days from EoT.
[redacted]										
Time window for visits (days)	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7
[redacted]										
All adverse events[19]	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X
[redacted]										
Completion of patient participation										X

HiSCR: Hidradenitis Suppurativa Clinical Response, IHS4: International Hidradenitis Suppurativa Severity Score System, HASI: Hidradenitis Suppurativa Area Severity Index, HS-PGA: Hidradentis Suppurativa Physician's Global Assessment, DLQI: Dermatology Life Quality Index, HiS-QoL: Hidradenitis Suppurativa Quality of Life, PGI-C: Patient Global Assessment of Change, PGI-S: Patient Global Assessment of Severity, HODS: Hidradenitis odour and drainage scale, HADS: Hospital Anxiety and Depression Scale, C-SSRS: Columbia-Suicide Severity rating Scale, IHS4: International Hidradenitis Suppurativa Severity Score System

* Visits should happen at site. However, for Visits 7, 9, 15, 20, 22, 24, 26, 28, and 30, trial participants will be offered the possibility to have home nursing visits if locally allowed. In exceptional circumstances (i.e. pandemic, conflict, other), visits might take place by phone just to collect safety information.

1 Day of randomisation/day of first intake of randomized medication. If needed, some Visit 2 assessments may be conducted within 2 days before or after the actual visit date after consultation with the sponsor.

2 Trial participants who discontinue trial treatment prematurely should undergo the End of Treatment (EoT) visit as soon as possible. All trial participants [redacted] are expected to complete EoT visit, and EoS visit [redacted] after their last trial drug intake or [redacted] from EoT. For trial participants entering the [redacted] the EoT visit will be their EoS visit in trial 1368-0098 (see also footnotes #10 and #20).

3 X^c is a complete physical examination. X^t is a targeted physical examination. See Section 5.2.1. If home visits take place for Visits 7, 9, 15, 20, 22, 24, 26, 28, and 30, instead of visits at site, a targeted physical examination may be done by a home-nurse.

4 Measurements of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements at all dosing visits. Additional assessments of vital signs should be performed approximately at 10 minutes post-dose for [redacted] and approximately 5 minutes and 1 hour post dose for [redacted] See Section 5.2.2.

5 Women of childbearing potential only. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed at all other visits indicated in the Flowchart. In case of a positive urine pregnancy test, a serum pregnancy test will be done. Urine pregnancy testing should be done prior to administration of study drug. Study drug should only be administered in case of a negative test result. More frequent testing should be done if required by the local regulation or per investigator judgment.

6 It is preferred, but trial participants do not have to be fasted for the blood sampling for the safety laboratory. At visits with study drug administration, this should be done prior to the study drug administration. See Table 5.2.3: 1 for detailed information of the tests. If needed, safety lab samples for Visit 2 can be drawn within 48 hours before the actual visit date. If screening visit is done less than 7 days earlier of Visit 2 (baseline), safety laboratory test can be omitted at Visit 2.

7 Infection testing: at screening and at EoT visit. See Section of safety laboratory parameters for complete list of testing required (see Table 5.2.3: 2). For Japan only, if there is no chest X-ray test or CT taken within 3 months prior to Visit 1, it should be taken at screening visit. For South Africa only, tuberculosis infection testing should be done approximately at 6 months intervals. For this reason, participants from South Africa QuantiFERON testing should be done at visit 19.

8 ECG measurements should always precede blood sampling and drug administration. The ECG measurements need to be conducted at timepoints indicated in the Flowchart. Additional ECG measurements may be performed if the investigator deems it clinically indicated.

9 [redacted]

10 Trial participants who terminate study drug early should do the EoT visit as soon as possible. These participants will then do EoS visits, [redacted] after last study drug administration. When this discontinuation happens before Visit 14 [redacted], in addition to safety follow up assessment, trial participants ideally should also continue visits for assessments of efficacy until [redacted] as per Flowchart.

11 Desoxyribonucleic Acid (DNA) banking sample is optional. This sampling is only possible if the trial participant agreed by signing a separate informed consent. For details, please see Section 5.5.

12 Skin biopsy is mandatory at selected sites and should be sampled under ultrasound (US) guidance. For all other sites it is optional. Sites without the US required capabilities cannot perform skin biopsies. See Section 5.4.4.

13 US lesion evaluation is mandatory at selected sites with US capabilities. For all other sites it is optional. See Section 5.4.3.

14 IHS4 is used to classify trial participant's severity at baseline. IHS4 will be derived from lesions count by a trained health care professional

15 Trial participant diaries will be handed to trial participants with the objective to collect daily information about NRS Pain and Pruritus from baseline, after being trained, till Visit 19 [redacted] After Visit 19, NRS pain and NRS pruritus will be collected on a daily basis during the 7 days prior to the next scheduled visit (prior to Visit 23, Visit 27, Visit 31, and EoT visit). Site staff will collect the diaries from trial participants at visits indicated in the Flowchart to assess pain and pruritus since last visit. See Section 5.1.1.

16 At Screening, the C-SSRS baseline/screening scale will be completed. At all subsequent visits the "since last visit" scale will be completed.

17a At Visit 2, instructions for paper version of patient's daily diary will be dispensed to trial participants. Site staff should provide adequate training. Two weekly diaries and one additional [redacted]

17b Once electronic diary is available instructions for electronic diary will be dispensed to trial participants. Site staff should provide adequate training. Trial participant diary captures [redacted] until Visit 19. From Visit 23, trial participants will record data for pain and pruritus during the last 7 days before the applicable visits (one daily diary on the last 7 days before the next scheduled visit). Analgesic use and other interventions to manage pain will be collected at the same time points, but in paper format.

18 Trial participant's diaries returned by participants must be reviewed while the trial participant is in the consultation, so that any information can be clarified in an interview with the trial participant, if needed.

19 For local tolerability at the administration site of the IMP, the investigator will perform an assessment during the study drug administration visit and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction, e.g. "swelling", "induration", "heat", "redness" should be evaluated and reported as adverse events.

20 All trial participants completing [redacted] of the trial may be [redacted]

21 For South Africa only, tuberculosis infection testing should be done approximately at 6 months intervals. For this reason, participants from South Africa [redacted]

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ABBREVIATIONS AND DEFINITIONS

AD	Atopic Dermatitis
ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AdT	Abscess and draining fistula/tunnel count
AE	Adverse event
AESI	Adverse event of special interest
ALCOA	Attributable, legible, contemporaneous, original, accurate
ALT	Alanine aminotransferase
AN	Abscess and inflammatory nodule
AN count	Abscess and inflammatory nodule count
ANdT count	Abscess, inflammatory nodule, and draining fistula/tunnel count
AST	Aspartate aminotransferase
AUC	Area under the curve
BI	Boehringer Ingelheim
BSA	Body Surface Area
CA	Competent authority
CDC	Complement-dependent cytotoxicity
CKD-EPI	Chronic kidney disease Epidemiology Collaboration
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CQM	Clinical quality monitoring
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	Clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver injury
DLQI	Dermatology life quality index
DMC	Data monitoring committee

DNA	Desoxyribonucleic Acid
dT	Draining fistula/tunnel
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EoS	End of study
EoT	End of treatment
EQ-5D-5L	EuroQol 5 dimensions 5-level
EU	European Union
EudraCT	European Union drug regulating authorities clinical trials
FACIT	Functional assessment of chronic illness therapy
FAS	Full Analysis Set
FDA	Food and Drug Administration
FUP	Follow-up
GBS	Guillain-Barré syndrome
GCP	Good clinical practice
GMP	Good manufacturing practice
GPP	Generalized pustular psoriasis
HAs	Health authorities
HADS	Hospital anxiety and depression scale
HASI	Hidradenitis suppurativa area and severity index
HiSCR	Hidradenitis suppurativa clinical response
HiS-QoL	Hidradenitis suppurativa quality of life
HIV	Human immunodeficiency virus
HODS	Hidradenitis suppurativa odour and drainage scale
HS	Hidradenitis suppurativa
hs-CRP	High-sensitivity c-reactive protein
HT29	Hypertriptoid-29
HV	Healthy Volunteers
I&D	Incision and Drainage
i.v.	Intravenous
IB	Investigator’s brochure

IC90	90% of maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent ethics committee
IFNγ	Interferon gamma
Ig	Immunoglobulin
IGRA	Interferon gamma release assay
IHS4	International hidradenitis suppurativa severity score system
IL(-)36	Interleukin 36
IL(-)36R	Interleukin 36 receptor
IL(-)36RN	Interleukin 36 receptor antagonist
IMP	Investigational medicinal product
ISPOR	International Society for Pharmacoeconomics & Outcomes Research
IPDs	Important protocol deviations
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional review board
IRT	Interactive response technology
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
K_2EDTA	Dipotassium ethylendiaminetetraacetic acid
KO mutation	Knockout mutation
LPLT	Last patient last treatment
LTE	Long Term Extension
MCID	Minimal Clinical Important Difference
[redacted]	
MedDRA	Medical Dictionary for drug regulatory activities
[redacted]	
MRD	Multiple rising dose
mRNA	Messenger RNA
NAb	Neutralizing antibody
N count	Inflammatory nodule count
NETosis	Neutrophil extracellular trap-osis

NF-κB	Nuclear factor-kappa B
NOAEL	No-observed-adverse-effect level
NRI	Non response imputation
NRS	Numerical rating scale
NRS30	Reduction of 30% in numerical rating scale
OPU	Operative unit
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PFS	Pre-filled syringes
PGA	Physician global assessment
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
POAB	Patient organisation advisory board
PoCC	Proof of Clinical Concept
PPD	Purified protein derivative
PPS	Per-protocol set
PPP	Palmoplantar pustulosis
PROs	Patient reported outcomes
PSPV	Patient Safety Pharmacovigilance
PT	Preferred term
PTM	Planned Time
q2w	Once every 2 weeks
qw	Every week
RAs	Regulatory authorities
RCTC	Rheumatology common toxicity criteria
REP	Residual effect period
RNA	Ribonucleic acid
ROW	Rest of the world
RS	Randomised set
s.c.	Subcutaneous
SAE	Serious adverse event

SAF	Safety Analysis Set
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SDTM	Standard Data Tabulation Model
SFQ	Site Feasibility Questionnaire
SoC	Standard of care
SOP	Standard operating procedure
SPI	Stability and Packaging Information
SRD	Single rising dose
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis
TBA	Trial Bio Analyst
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse events
TMF	Trial master file
TNF	Tumor necrosis factor
TNFi	Tumor Necrosis Factor inhibitor
~~TS~~	~~Treated set~~
TSAP	Trial statistical analysis plan
TST	Tuberculin-skin testing
UC	Ulcerative colitis
ULN	Upper limit of normal
US	Ultrasound
vs.	Versus
WHO	World Health Organisation
WOCBP	Woman of childbearing potential
WPAI-HS	Work Productivity and Activity Impairment Questionnaire for HS

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Hidradenitis suppurativa (HS) is an inflammatory skin disease characterised by recurrent inflammatory nodules, painful abscesses and fistulous tracts also called tunnels that may be draining a malodourous exudate. Patients with HS 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. Significant pain is a major symptom and lesion sequalae include scarring, and psychological distress. The average age of onset is during the early 20s [R20-3184]. The prevalence of HS is estimated to be 0.3% globally, ranging from 0.2% to 0.6%, with variability across geographic settings [R22-3282].

Treatment often begins with topical or oral antibiotics, such as topical clindamycin and oral tetracycline, followed by the use of other antibiotics if there is no improvement. When topical medications and oral antibiotics fail, or the disease has progressed, biologics are recommended [R20-3177]. Adalimumab is the only approved biologic, with a Hidradenitis Suppurativa Clinical Response (HiSCR50: at least a 50% reduction in the total abscess and inflammatory nodule [AN] count with no increase in abscess count and no increase in draining fistulas/tunnels [dT] count relative to baseline) rate of 42% to 59% versus placebo response rate of 26% to 28%, with a schedule of weekly subcutaneous dosing. When drug treatment management is insufficient or ineffective, surgery is the only option, leading to burdensome healing periods.

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 report to be unsatisfied with the level of control offered by currently available treatment options. 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 relief from or improvement in pain, drainage (including explosive openings) and fatigue.

Clearly, current therapeutic options have their limitations, and there is a high need for safe and effective treatment that provides rapid control and fast resolution of skin signs and symptoms. In particular, reduction of draining tunnels (dTs) represents a high unmet medical need.

1.2 DRUG PROFILE

Mode of action
Spesolimab is a humanised, selective antibody that blocks the activation of the human interleukin-36 receptor (IL-36R). IL-36 is a potent activator of neutrophil infiltration. In patients with generalised pustular psoriasis (GPP), spesolimab treatment rapidly stopped the flare and cleared pustules, the primary lesions in GPP.

HS and GPP have similarity in neutrophil infiltration. IL-36 alpha, beta, and gamma mRNA expression are upregulated in lesioned skin in HS patients, with a decrease in IL36RN expression [R20-3047]. In the context of HS, neutrophils are shown to undergo neurophil

extracellular trap-osis (NETosis) leading to secretion of type I interferons [R20-3155]. Navrazhina et al. showed that in HS lesional skin, a IL-36/IL-17 mediated feed forward mechanism may play a role in the pathogenesis of dTs [R22-2400]. It is hypothesised that by interfering with this mechanism, spesolimab may decrease neutrophilic and other immune cell infiltrations, thereby directly impact abscesses and dTs, a high unmet medical need in HS.

Key pharmacokinetic and immunogenicity characteristics

Spesolimab has been characterised by typical IgG1 monoclonal antibody pharmacokinetics (PK). PK data showed that exposure increased with increasing dose in a dose proportional manner from 0.3 mg/kg to 20 mg/kg following intravenous (i.v.) administration of spesolimab to healthy volunteers. In healthy volunteers, the geometric mean spesolimab clearance (gCV%) was 0.146 (23.3%) L/day. The corresponding terminal half-life was 28.8 (25.1%) days. The clearance in GPP patients was approximately 25% higher.

Comparing the exposures between the 300 mg subcutaneous (s.c.) dose and 300 mg i.v. dose, a s.c. bioavailability of ~70% was determined. No differences in PK were observed between Caucasians and Japanese subjects.

Immunogenicity

In healthy volunteers, ADA to spesolimab was developed with a median onset time ranging 4-17 weeks across trials. Overall, the ADA incidence was comparable between i.v. and s.c. administration. The ADA incidence appeared to be higher in females, though the maximum titer was comparable between males and females. Following single dose administrations of s.c. or i.v. spesolimab, the ADA incidence rate was 39%-52% in females, compared with 19~24% in males. The impact of ADA on spesolimab PK was overall mild in healthy volunteers. Following i.v. administration, lowered spesolimab concentration was only observed in 1 subject in trial 1368-0001, and possibly in 2-3 subjects in trial 1368-0043 (all with maximum titer greater than 11 400). Following s.c. administration, ADA formation may have contributed to the lowered spesolimab concentrations in some volunteers with maximum titer higher than 11 400 in trial 1368-0029.

Details of immunogenicity results in other indications can be found in the current Investigator's Brochure (IB) [c03320877-11].

Residual Effect Period (REP)

The REP of spesolimab is 16 weeks. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

Data from non-clinical studies

Non-clinical pharmacology

Spesolimab binds to human IL-36R with a binding avidity of less than 1 pM. Spesolimab inhibits IL36 ligand-stimulated NF-κB activation in HT29 cells and transformed epithelial cells and in primary human dermal fibroblasts or intestinal myofibroblasts with IC_{90} values in a consistent range of 0.7 to 3.7 nM. Spesolimab also inhibits IL8 release in IL36-stimulated human dermal fibroblasts and IFNγ secretion in human peripheral blood mononuclear cell (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.

Toxicology

Spesolimab does not bind to IL-36R from common toxicology species. Therefore, meaningful toxicity studies of the molecule cannot be performed in any animal species with spesolimab. However, hazard identification studies of the mode-of-action of IL-36R inhibition were performed in mice using a mouse specific anti-IL-36R monoclonal antibody (BI 674304). Details of results concluding to a no-observed-adverse-effect level (NOAEL) of 50 mg/kg/day can be found in the current IB [c03320877-11].

Data from clinical studies

This section presents the high-level summary of results from clinical studies. For a more detailed description of the spesolimab profile, please refer to the current IB [c03320877-11].

First in human single rising dose trial 1368-0001 [c09985235-01]

Spesolimab has been administered as a single i.v. dose to healthy volunteers. A total of 78 subjects were randomised within 11 sequential dose groups to active drug (dose range: 0.001 to 10 mg/kg body weight) or placebo. In total, 58 subjects received spesolimab and 20 subjects received placebo. All subjects completed the trial according to the protocol.

In total, 49 out of 78 subjects (62.8%) were reported with at least 1 AE while on-treatment (spesolimab: 36 out of 58 subjects [62.1%]; placebo: 13 out of 20 subjects [65.0%]). All AEs were of mild or moderate intensity. There were no serious AEs, no AEs that led to discontinuation of trial drug, no protocol-specified AEs of special interest and no other significant AEs according to project definition. All AEs were resolved by the end of the trial. No relevant changes were observed in safety laboratory tests, vital signs, and ECGs. Importantly, there were no relevant differences in frequencies of subjects with treatment emergent AEs between the treatment groups, and no dose-dependency was observed.

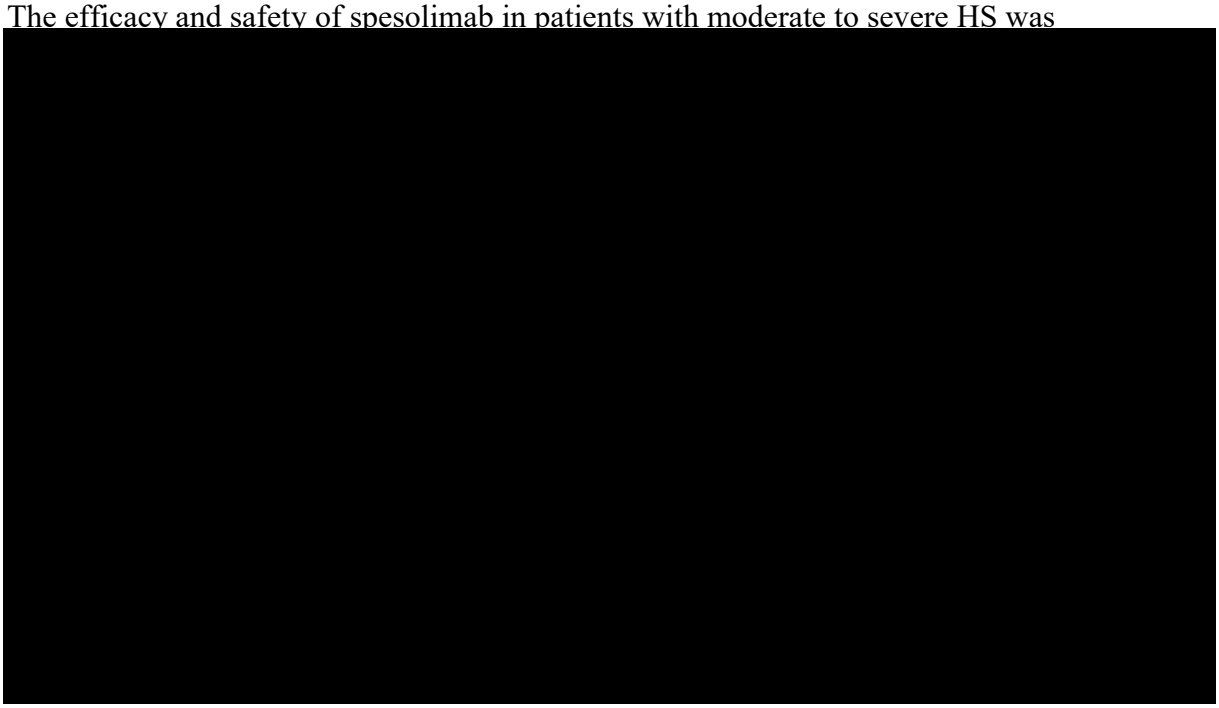
Multiple rising dose trial 1368-0002 [c18789185-01]

In a multiple rising dose trial, spesolimab or placebo have been administered to 40 healthy volunteers at multiple ascending intravenous (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 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.

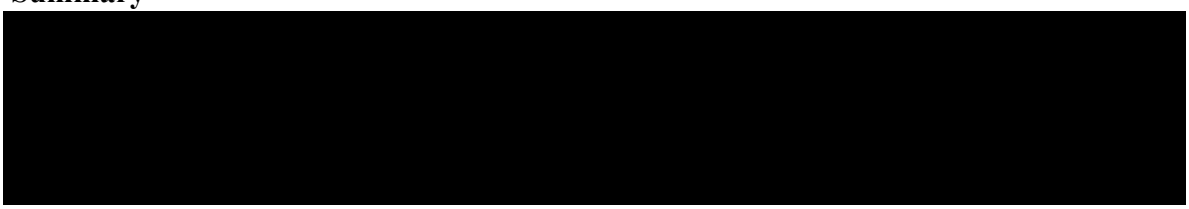
Phase IIa trial 1368-0052

The efficacy and safety of spesolimab in patients with moderate to severe HS was



Open label extension (OLE) trial 1368-0067

Summary



1.3 RATIONALE FOR PERFORMING THE TRIAL

Study 1368-0098 consists of 2 parts: a dose finding phase (Phase IIb), designed to primarily support the decision on optimal spesolimab dosing in patients with moderate to severe HS, but also collect data on [redacted] and accrue long term safety/efficacy experience on optimal spesolimab dosing once available; a confirmatory phase (Phase III), designed to confirm the efficacy and safety of optimal spesolimab dosing in patients with moderate to severe HS.

Based on the medical background (see Section 1.1) and drug profile (see Section 1.2), there is an unmet medical need in HS, and spesolimab may directly have a positive impact on this high unmet medical need. In addition, no other IL-36 receptor antagonist is currently approved, to provide information on identified risks in molecules of this class. Therefore, the knowledge of the safety and risk profile of compounds in this class is limited. To perform this trial will provide further efficacy and safety profile of spesolimab for further development, which may help to provide alternative treatment option for patients with moderate to severe HS.

The study of [redacted] will mostly be hypothesis-generating or supportive to endpoints. These findings will be used to expand our understanding of the disease HS and the investigational compound, e.g. by learning more about the drug mechanism or the biology of the disease, to correlate patient subgroups with differential responses to treatment and/or to prognosis, [redacted]

In order to be able to address future scientific questions, trial participants will be asked to voluntarily [redacted] (please see Section 5.5. If the trial participant agrees, banked samples may be used for [redacted] and drug [redacted]

1.4 BENEFIT - RISK ASSESSMENT

Spesolimab potential benefit in HS and associated risk is still at an early stage of definition. Participation in this trial may help providing future benefit to patients with HS if spesolimab development in this indication proves to be successful. Of note, spesolimab is currently approved in the USA for the treatment of GPP flare at the dose of 900 mg i.v, followed by an additional 900 mg i.v. dose if symptoms persist. HS is a different skin disease and required a separate clinical development to establish spesolimab benefit/risk ratio in this indication.

1.4.1 Benefits

Before initiation of this trial, approximately [redacted] have been exposed to [redacted] of spesolimab regardless of dose. 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 the latest version of spesolimab IB [c03320877-11]). Subsequently, several clinical studies exploring efficacy and safety of spesolimab in different indications have been conducted or are ongoing.

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.

1.4.2 Risks

No other IL-36 receptor antagonist is currently approved, that would provide further information on identified risks in molecules of this class. The knowledge of the safety and risk profile of compounds in this class is still considered limited. However, the safety profile of spesolimab is considered acceptable based on available data from completed trials.

In order to protect the trial participant's safety during conduct of this trial, an independent Data Monitoring Committee (DMC) will periodically review clinical trial safety data. For details, please see Section 8.7. In addition to the AE tracking, planned interim analysis at [redacted] of Part 1 of the trial will also contribute to the monitoring of any safety signal (see Section 7.2.8).

For potential risks, Table 1.4.2: 1 lists the possible risks for spesolimab as well as theoretical risks derived from general safety considerations of immunomodulatory drugs and from this trial specific procedures. For details on treatment-related risks, refer to Section 1.2 and IB [c03320877-11].

Table 1.4.2: 1 Overview of trial-related and potential risks

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Systemic hypersensitivity reaction	After administration of any biologic agent or protein, there is a possibility of occurrence of immediate (such as anaphylaxis) or delayed (such as drug reaction with eosinophilia and systemic symptoms) adverse immune reactions.	Patients with a history of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients are excluded from the trial. In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to interrupt and treat the condition. Systemic hypersensitivity reaction is defined as an adverse event of special interest (AESI); see Section 5.2.6.1.4. It is subject to close monitoring and investigators are requested to assess these conditions using the criteria discussed in the statement paper from Sampson HA [R11-4890].

Table 1.4.2: 1 Overview of trial-related and potential risks (cont.)

Infections (serious, severe, opportunistic)	Inhibition of the immune response with an immune-modulating biologic may increase the risk of infections. A recent characterisation of individuals with homozygous IL-36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL-36 signaling pathway inhibition may not substantially compromise host defenses [R17-3632]. In clinical trials with spesolimab, a higher proportion of patients with mild to moderate infections was seen in the spesolimab treatment group than in the placebo treatment group. Nevertheless, there was no indication of an increased frequency of patients with severe, serious, and opportunistic infections in association with spesolimab treatment.	Screening procedures for infections are defined for this trial. Patients with any relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis or tuberculosis are excluded from the trial. Treatment of infections should be initiated promptly according to standards of care. Severe infections and opportunistic infections are considered AESIs for this trial; see Section 5.2.6.1.4. These conditions and serious infections are subject to close monitoring.

Table 1.4.2: 1 Overview of trial-related and potential risks (cont.)

Malignancies	Inhibition of the immune response with an immunomodulatory drug may potentially impair immune defences and thus theoretically decrease immune defence against malignancies. A recent characterisation of individuals with homozygous IL-36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL-36 signaling pathway inhibition does not compromise host defenses [R17-3632]	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 investigator should discontinue treatment with spesolimab. Diagnostics and treatment have to be initiated according to local standard of care. Malignancies represent always serious adverse events and are subject to close monitoring; see Section 5.2.6.1.3.

Table 1.4.2: 1 Overview of trial-related and potential risks (cont.)

Peripheral neuropathy	Three cases reported by the investigator as Guillain-Barré syndrome (GBS) were received in ongoing clinical trials with spesolimab. Case #1 was from the Phase II open label extension trial 1368-0017/ indication UC. Case #2 was from the Phase II open label extension trial 1368-0024/ indication PPP. Case #3 was from the Phase II open label extension trial 1368-0067/indication HS. 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. 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. A causal association with spesolimab for any of the reported cases was assessed to be unlikely as per independent external expert adjudication.	Timely detection, evaluation, and follow-up of suspected peripheral neuropathies to ensure patients´ safety. Use of dedicated questions to elicit neurologic history during screening and exclusion criteria to avoid selection of patients with acute demyelinating neuropathy. Targeted follow-up questions to gather detailed information in case of any event during trial to ensure proper decision making.

Table 1.4.2: 1 Overview of trial-related and potential risks (cont.)

Trial procedures		
Blood sampling Inflammation of the wall of the vein. Injuring of a nerve while inserting the venous catheter, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.	General risk, acceptable in framework of trial participation. As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of lightheadedness and/or fainting. In rare cases, the puncture site can also become infected, or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain.	Evaluation of the medical expertise of the trial sites is a part of site feasibility assessment. To ensure participant safety, all events or symptoms reported will be managed according to the judgment of the investigator. These risks will be addressed by careful safety monitoring and risk mitigation measures such as (a) pressure on the puncture site for approximately 5 minutes after the needle extraction, is recommended. (b) close clinical monitoring for AEs. (c) selection of experienced sites and site staff. (d) safety recommendations provided in laboratory manual.
Skin biopsy	Can cause local bruising, inflammation, nerve damage and pain.	These risks will be addressed by careful safety monitoring and risk mitigation measures such as (a) close clinical monitoring for AEs. (b) selection of experienced sites and site-staff. (c) staff training.

Table 1.4.2: 1 Overview of trial-related and potential risks (cont.)

Other risks		
Administration of placebo	If the trial participant is randomised to receive a placebo, the participant's condition could get worse during the trial.	The placebo control is required to control for investigator bias and/or beneficial effects of being in a clinical trial. The rationale for switching placebo trial participants to active treatment at Visit 14 [redacted] is to give these trial participants the opportunity to receive active investigational medicinal product (IMP) treatment from that visit. The use of rescue medication is foreseen in this trial for participants experiencing a worsening of their HS condition; see Section 4.2.3.
Suicidal ideation and behaviour*	Increased risk of suicidal ideation and behaviour is present in the population of patients with HS	'Baseline/ screening' version of C-SSRS will be administered with the aim to exclude patients with active moderate to severe symptomatology present within a specified time prior to the screening or screening visit. 'Since last visit' version of C-SSRS will be administered with the aim to monitor trial participant's safety during the trial and to initiate actions for the participant's safety if such actions are deemed necessary. All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior represent SAEs and are subject to close monitoring; see Section 5.2.5.2. Participants with C-SSRS score of 4 or 5 have the trial treatment discontinuation criteria (see Section 3.3.4.1)

Table 1.4.2: 1 Overview of trial-related and potential risks (cont.)

Drug-induced liver injury (DILI)	Although rare, a potential for DILI is under constant surveillance by sponsors and regulators. Therefore, DILI is considered as a standard risk in all BI development programs.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure trial participant' safety (see also Section 5.2.6.1.4). Trial treatment discontinuation criteria as well as criteria for trial treatment restart are implemented for relevant cases.

* This is due to a higher risk in the population of patients with HS and not specifically due to the mechanism itself

Regarding reactions to injections/infusions, specific safety measures will be taken during the trial. Following the injection/infusion the trial participants will be monitored for reactions at the site according to the Instructions for Preparation and Handling of Spesolimab/Placebo which can be found in the Investigator Site File (ISF). Local tolerability will be carefully monitored in this study (see Section 5.2.5.1).

Based on the findings in the non-clinical 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 minimise the risk of unintentional exposure of an embryo or fetus to the investigational drug, WOCBP must agree to the requirements for the pregnancy testing (see Flowchart) and contraceptive methods; see Section 4.2.2.3.

1.4.2.1 Coronavirus disease 2019

At the time of this original protocol, the COVID-19 pandemic is active in many countries. Given the unique circumstances created by the pandemic, specific consideration has been given to the benefits and risks of the trial as they relate to the pandemic and potential SARS-CoV-2 infection; see Appendix 10.21.

1.4.3 Discussion

Based on the drug profile (see Section 1.2), there is no mechanism- or compound-related safety concerns of spesolimab. It is expected that trial participants with moderate to severe HS will not be exposed to unacceptable, undue risks, and AEs.

In the context of the unmet medical need and anticipated benefit of spesolimab, based upon the available non-clinical and clinical information (see Section 1.2), the benefit risk evaluation of the compound is favourable.

Considering the medical need for the development of a better tolerated and more effective treatment for patients with moderate to severe HS, the expected benefit outweighs the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

Final endpoints for Part 2 will be supported by study results available at the time of Part 1 primary analysis

2.1.1 Main objectives

Study 1368-0098 consists of 2 parts: dose finding Phase IIb (Part 1), designed to find the optimal dose in patients with moderate to severe HS for Phase III development; confirmatory Phase III (Part 2), designed to assess the efficacy and safety of spesolimab in patients with moderate to severe HS. Patients recruited in Part 1 cannot participate in Part 2.

Part 1 (Phase IIb)
The dose finding phase (Part 1) will characterise the dose-response curve and exposure-response relationship and will support identifying the dose of spesolimab providing the most adequate benefit/risk to patients with moderate to severe HS by assessing 3 dosing regimens (for detailed dosing regimens, please see Section 3.1 and Section 4.1.4) and placebo.

The primary objective of dose finding phase are as follows (for summary measure of treatment effect, please see Section 2.1.2):
(1) to demonstrate a non-flat dose response curve, evaluate the quantitative treatment effect size, and evaluate the dose-response relationship based on the primary endpoint of percent change from baseline in dT count at [redacted]
(2) to determine an optimal dose candidate for Part 2 by incorporating information of available safety and of efficacy based on the primary endpoint of percent change from baseline in dT count at [redacted]

The secondary objectives are as follows:
(1) to demonstrate non-flat dose response curve based on selected secondary and further efficacy endpoints at [redacted]
(2) to evaluate the quantitative treatment effect size of percent change from baseline in dT count at [redacted] and absolute change from baseline in International Hidradenitis Suppurativa Severity Score System (IHS4) value at [redacted]
(3) to evaluate the sustainability of spesolimab efficacy up to [redacted]
(4) to assess safety of spesolimab.
The secondary objectives will be served by selected secondary and further efficacy endpoints, as well as safety endpoints (for list of secondary and further endpoints, please see Section 2.1.3 and Section 2.2.2).

The primary and secondary analyses will be based on Full analysis set (FAS), defined as trial participants randomised in Part 1 and having received at least 1 dose of study drug. Treatment comparisons will be performed regardless of treatment adherence.

Part 2 (Phase III)
Because of the use of modelling, [redacted] in Part1.

The confirmatory phase aims to provide substantial evidence of the efficacy, safety, and tolerability of spesolimab in comparison to placebo in trial participants with moderate to severe HS.

Part 2 will not be conducted if the analysis of Part 1 (Phase IIb) at [redacted] data cut-off does not conclude to potential of spesolimab for demonstrated clinical benefit versus placebo in terms of effect size and sustainability. The dose [redacted] for Part 2 (Phase III) will be based on all available data at the time of primary analysis when last trial participant complete Visit 10 [redacted]

The primary objective of the confirmatory phase (Part 2) is to demonstrate superiority of one dosing regimen [redacted] of spesolimab (identified on the basis of Phase IIb data analysis) against placebo in the [redacted] from baseline in [redacted]

The secondary objectives are as follows:
(1) to demonstrate superiority of spesolimab against placebo for the key secondary endpoints (please see Section 2.1.3).
(2) to assess safety of spesolimab.

The primary and secondary analyses will be based on the TS, defined as trial participants randomised in Part 2 and having received at least 1 dose of study drug. Treatment comparisons will be performed regardless of treatment adherence.

2.1.2 Primary endpoints

Part 1 (Phase IIb)
Percent change from baseline in dT count at [redacted]

Part 2 (Phase III)
Percent change from baseline in dT count at [redacted]

2.1.3 Secondary endpoints

Part 1 (Phase IIb)
Efficacy
Secondary endpoint

- Percent change from baseline in dT count at [redacted]
- Absolute change from baseline in IHS4 value at [redacted]
- Absolute change from baseline in IHS4 value at [redacted]

Safety

Occurrence of treatment emergent adverse events (TEAEs)

Part 2 (Phase III)

Efficacy

Key secondary endpoints

The following key secondary endpoints will be considered. These may be amended according to Part 1 results:

- Absolute change from baseline in IHS4 value at [redacted]
- Absolute change from baseline in Hidradenitis Suppurativa Area Severity Index (HASI) score at [redacted]
- Achievement of Hidradenitis Suppurativa Clinical Response (HiSCR50) at Week 16: HiSCR50 is defined as at least a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in dT count relative to baseline.
- Percent change from baseline in abscess count at [redacted]
- Achievement of at least a 50% reduction in dT count at [redacted] relative to baseline.
- Achievement of at least a 50% reduction in abscess and dT (AdT) count at [redacted] relative to baseline
- Achievement of at least a 50% reduction in ANdT count at [redacted] relative to baseline.
- Achievement of at least 30% reduction from baseline in Numerical rating Scale (NRS30) in Patient's Global Assessment of HS pain at [redacted]

Safety

Occurrence of TEAEs.

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

Further objectives are to evaluate further measures of efficacy including effect size up to [redacted] the pharmacokinetics (PK), the immunogenicity (anti-drug antibody [ADA] and neutralizing antibody [NAb]) of spesolimab, and to explore biomarkers related to changes in HS and IL36 pathway after treatment (assessment of gene expression levels in skin biopsies and whole blood, evaluation of serum proteomics and imaging markers acquired by ultrasound [US]).

2.2.2 Further endpoints

For further endpoints, time-point defined as "at each scheduled assessment" refers to scheduled assessment for the related outcome as per Flowchart. More details and additional further endpoints may be defined in the TSAP.

Part 1 (Phase IIb)

Efficacy

Lesion counts clinical endpoints

- Percent change from baseline in dT count at each scheduled assessment.
- Achievement of at least 50% reduction from baseline in dT count at each scheduled assessment.
- Occurrence of complete elimination of dT at each scheduled assessment.
- Time to first occurrence of complete elimination of dT during the treatment period.
- Percent change from baseline in abscess count at each scheduled assessment.
- Achievement of at least 50% reduction from baseline in abscess count at each scheduled assessment.
- Occurrence of complete elimination of abscess at each scheduled assessment.
- Percent change from baseline in total AdT count at each scheduled assessment.
- Achievement of at least 50% reduction from baseline in AdT count at each scheduled assessment.
- Percent change from baseline in inflammatory nodule (N) count at each scheduled assessment.
- Percent change from baseline in total ANdT count at each scheduled assessment.
- Achievement of at least 50% reduction from baseline in ANdT count at each scheduled assessment.

Response-, score-, and flare-related clinical endpoints

- Achievement of HiSCR50 at each scheduled assessment.
- Absolute change from baseline in IHS4 value at each scheduled assessment.
- Achievement of IHS4-55 response (defined as at least 55% reduction from baseline) at each scheduled assessment.
- Absolute change from baseline in HASI score at each scheduled assessment.
- Achievement of Physician's Global Assessment (PGA) score of 0 or 1 at each scheduled assessment.
- Occurrence of at least one HS flare at each scheduled assessment: defined as at least 25 % increase in AN count with a minimum increase of 2 relative to baseline.
- Time to first occurrence of HS flare during the treatment period.

Patient reported outcomes (PROs)

- Achievement of at least 30% reduction from baseline in Numerical rating scale (NRS30) in Patient’s Global Assessment of HS pain at each scheduled assessment.
- Absolute change from baseline in Hidradenitis Suppurativa Quality of Life (HiS-QoL) total score at each scheduled assessment.
- Absolute change from baseline in FACIT-Fatigue scale score at each scheduled assessment.
- Absolute change from baseline in Dermatology Life Quality Index (DLQI) score at each scheduled assessment.
- Absolute change from baseline in Patient Global Impression of Change (PGI-C) score over time.
- Absolute change from baseline in Patient Global Impression of Severity (PGI-S) score over time.

- Change from baseline in Hidradenitis Suppurativa odour and drainage scale (HODS) at each scheduled assessment.
- Change from baseline in NRS Pruritus at each scheduled assessment.
- Change from baseline in Hospital Anxiety and Depression Scale (HADS) at each scheduled assessment.

Part 2 (Phase III)
Efficacy

- Achievement of HiSCR50 at each scheduled assessment.
- Percent change from baseline in dT count at each scheduled assessment.
- Achievement of at least 50% reduction from baseline in dT count at each scheduled assessment.
- Occurrence of complete elimination of dT at each scheduled assessment.
- Time to first occurrence of complete elimination of dT during the treatment period.
- Percent change from baseline in abscess count at each scheduled assessment.
- Achievement of at least 50% reduction from baseline in abscess count at each scheduled assessment.
- Occurrence of complete elimination of abscess at each scheduled assessment.
- Percent change from baseline in total AdT count at each scheduled assessment.
- Achievement of at least 50% reduction from baseline in AdT count at each scheduled assessment.
- Percent change from baseline in N count at each scheduled assessment.
- Absolute change from baseline in IHS4 value at each scheduled assessment.
- Achievement of IHS4-55 response (defined as at least 55% reduction from baseline) at each scheduled assessment.
- Absolute change from baseline in HASI score at each scheduled assessment.
- Achievement of at least 30% reduction from baseline in Numerical rating scale (NRS30) in Patient's Global Assessment of HS pain at each scheduled assessment.
- Percent change from baseline in total ANdT count at each scheduled assessment.
- Achievement of at least 50% reduction from baseline in ANdT count at each scheduled assessment.
- Achievement of PGA score of 0 or 1 at each scheduled assessment.
- Absolute change from baseline in HiS-QoL total score at each scheduled assessment.
- Absolute change from baseline in FACIT-Fatigue scale score at each scheduled assessment.
- Absolute change from baseline in DLQI score at each scheduled assessment.
- Absolute change from baseline in PGI-C score over time.
- Absolute change from baseline in PGI-S score over time.
- Change from baseline in HODS at each scheduled assessment.
- Change from baseline in NRS Pruritus at each scheduled assessment.
- Change from baseline in HADS at each scheduled assessment.
- Occurrence of at least one HS flare at each scheduled assessment: defined as at least 25 % increase in AN count with a minimum increase of 2 relative to baseline.
- Time to first occurrence of HS flare during the treatment period.

- Work Productivity and Activity Impairment Questionnaire for HS (WPAI-HS) - change from baseline in WPAI-HS at each scheduled assessment.
- EQ-5D-5L- change from baseline in EQ-5D at each scheduled assessment.
- Number of surgeries
- Days of hospitalisation
- Days out of work/unemployment
- Number of emergency room visits
- Steroid free time/remission
- Hormonal therapy free time (in women)
- Antibiotics free time/remission

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is an international, Phase IIb/III multi-center, double-blind, placebo-controlled, randomised trial assessing the efficacy and safety of spesolimab versus placebo in patients with moderate to severe HS. Approximately [redacted] participants in Part 1 (Phase IIb) and [redacted] participants in Part 2 (Phase III) will be randomised. A sufficient number of trial participants will be screened to meet this randomisation target. Trial participants recruited in Part 1 cannot participate in Part 2. An overview of trial design is presented in Figure 3.1: 1.

Part 1 (Phase IIb)
Trial participants will be enrolled (screened) into the trial at Visit 1, and treatment will be initiated at Visit 2.

Screening and randomisation
After signing the informed consent, trial participants will enter the screening period for up to 28 days, and if all eligibility criteria are met, trial participants will be randomised in a [redacted] ratio to either active group, including high dose, medium dose, and low dose group, or placebo group [redacted] The randomisation will be stratified for [redacted] and [redacted] at baseline [redacted] For stratification, the details are described in Section 7.4.

At least approximately [redacted] participants from [redacted] population (meaning a corresponding [redacted] and a maximum of approximately [redacted] participants from [redacted] population (meaning a corresponding [redacted] are planned to be randomised, respectively. These participants who were previously [redacted] might have had a primary or a secondary failure of [redacted] Primary failure of [redacted] is defined as lack of efficacy after at least 3 months of treatment with an agent [redacted] (patients who never responded), and secondary failure is defined as loss of clinical efficacy in a trial participant after initial response to an agent [redacted] (patients who initially responded but then relapsed). Additionally, [redacted] might have [redacted] due to AE or stopped for other reason.

Approximately [redacted] participants with baseline [redacted] and [redacted] participants with baseline [redacted] are planned to be randomised, respectively.

No stratification beyond those prior described [redacted] will be applied for the trial participants.

Study [redacted] in the Flowchart represents the [redacted] is used for Day 1.

Treatment phase

Once randomised, trial participants will start a treatment period of [redacted] Administration of treatment will be up to [redacted] The final assessment of treatment effect will be on [redacted] (EoT visit).

For the first [redacted] according to the assigned dose group, trial participants will be administered an initial [redacted] dose of spesolimab [redacted] high dose group], [redacted] [medium dose group], or [redacted] [low dose group] [redacted] at Visit 2 [redacted] Visit 3 [redacted] Visit 4 [redacted], and Visit 5 [redacted] or matching placebo. From Visit 6 [redacted] to Visit 9 [redacted] (both inclusive), trial participants will be administered a [redacted] of spesolimab (either [redacted] [high dose group], [redacted] [medium dose group], or [redacted] [low dose group] according to the assigned dose group), or matching placebo. For trial participants initially randomised to spesolimab group, from Visit 10 [redacted] to Visit 31 [redacted] (both inclusive), the participants will be administered a [redacted] dose of spesolimab: either [redacted] (high and medium dose group) or [redacted] low dose group) [redacted] according to the assigned dose group).

From Visit 14 [redacted], there is an option of increasing the dose to the maximum subcutaneous dose of [redacted] (applied to low dose treatment group participants only, via IRT in a blinded manner) if they have [redacted] compared to baseline and the investigator agrees with the dose increase.

For trial participants initially randomised to placebo group, from Visit 10 [redacted] to Visit 13 [redacted] (both inclusive), the participants will be administered a matching placebo [redacted] Visit 14 [redacted] to Visit 31 [redacted] (both inclusive), the participants will be [redacted] dose of spesolimab [redacted]

From Visit 23 [redacted] on, trial participants will continue to receive the assigned dosing regimen, at least until the results of [redacted] are available. Upon availability of the Phase IIb (Part 1) primary analysis efficacy and safety results, the dosing regimen may be adapted from Visit 23 [redacted]. For more detailed drug assignment and administration of doses for each trial participant, please see Section 4.1.5.

Follow-up phase and end of study

Trial participants completing EoT visit [redacted] of the study may roll over to an [redacted] if they agree and meet the eligibility criteria [redacted] These trial participants are not required to complete a safety follow-up period, and their EoT visit will be considered also their end of study (EoS) visit, which is the [redacted]

Trial participants, who permanently discontinue trial drug earlier than Visit 31 [redacted] or do not qualify to enter the LTE trial for any other reason, will be invited to do the EoT visit instead of the next planned visit and will then enter a safety follow-up period [redacted]

Part 2 (Phase III)
Part 2 (Phase III) will start after completion of primary analysis of Part 1 (Phase IIb), assessment of further development benefit, interaction with HAs, and approval by IRB/EC in participating countries.

Screening and randomisation

After signing the informed consent, trial participants will enter the screening period for up to 28 days, and if all eligibility criteria are met, trial participants will be randomised in a 1:1 ratio to either active group or placebo group. The randomisation will be stratified for [redacted] and [redacted] Recruitment ratios guidance for [redacted] trial participants will be reviewed and revised, if needed, after the primary analysis of Part 1 is available and in light of the consolidated entry criteria for Part 2. Approximately [redacted] participants with baseline [redacted] are planned to be randomised, respectively.

Treatment phase

Once randomised, trial participants will start a treatment period of [redacted] (treatment administered period is from Visit 2 [redacted] to [redacted], both inclusive, and an assessment done at [redacted]). From Visit 2 [redacted] prior to [redacted] is not inclusive), trial participants will be administered [redacted] of spesolimab with selected dosing regimen based on primary analysis of Part 1 (Phase IIb) or matching placebo. From [redacted] to [redacted] (both inclusive), all participants (both initially randomised to spesolimab group and placebo group) will be administered a [redacted] of spesolimab with selected dosing regimen based on primary analysis of Part 1 (Phase IIb).

Follow-up phase and end of study

Same rule is applied as Part 1. Please see "*Follow-up phase and end of study*" in Part 1.

IC = Informed Consent, V = Study Visit, W = Week (study weeks), FUP = Follow Up, EoT = End-of-Treatment, EoS = End-of-Study, REP = Residual Effect Period

a
b Upon availability of the efficacy and safety results of (Part 1)
c If trial participants meet criteria for inadequate clinical response and the investigator agrees with participants in low dose spesolimab group can be from to on; see Section 3.1.
d
e after last dose or from EoT
f Part 2 will start after of Part 1 assessment of further development benefit, interaction with HAs, and approval by IRB/EC

Figure 3.1: 1 Trial design

An overview of all relevant trial activities is provided in the Flowchart. For visit schedules and details of trial procedures at selected visits, refer to Section 6.1 and Section 6.2, respectively.

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

Overall, an operationally seamless Phase IIb (Part 1)/Phase III (Part 2) design is selected to streamline spesolimab development in HS while ensuring trial participant safety and flexibility to inform Phase III design with Phase IIb-generated evidence.

Primary and secondary endpoints selection for Phase IIb (Part 1)

[redacted] Draining tunnels are lesions with high impact for the trial participants, and drainage represents one of the highest unmet needs based on two BI Patients Organisation Advisory Boards (see below in this section). The pathophysiology of dT suggests a potential key role for the blockade of IL36 receptor activation by spesolimab. [redacted] Therefore, it is planned to use [redacted] as the primary endpoint which would not be possible to evaluate in patients without any [redacted] at baseline.

[redacted]

Overall feasibility of the trial

BI considers selection and development of clinically meaningful outcomes assessments that remain a high unmet need such as % [redacted] to be an appropriate tool being used for what it is intended for, evaluating novel therapies targeting moderate to severe HS patients suffering from [redacted] Prior to implementing [redacted] endpoint for Part 2 of trial 1368-0098, BI is planning to work with external experts in the HS field and create and define validation plans (i.e. establishment of content validity and other measurement properties) for this endpoint in parallel to Part 1 (Phase IIb), [redacted]

Placebo controlled treatment for both Part 1 (Phase IIb) and Part 2 (Phase III)

The placebo control is required to control for investigator bias and/or beneficial effects of being in a clinical trial. The rationale for switching placebo trial participants to active treatment at [redacted] is to give these participants the opportunity to receive active investigational medicinal product (IMP) treatment [redacted] For the benefit-risk assessment of using placebo, please see Section 1.4.

Dose ranging for Part 1 (Phase IIb)

Data from prior studies of spesolimab in HS are indicative of a need for dose ranging work and for further investigations over the efficacy profile of this molecule in HS. The primary analysis will be conducted after all trial participants complete [redacted] In addition, a

[redacted] will be conducted after all trial participants complete [redacted] visit. [redacted] Additionally, the exposure-response relationship for the key efficacy endpoints will be characterised using population PKPD modelling approaches that will be defined and reported separately. [redacted]

[redacted] *dose up to* [redacted] *for Part 1 (Phase IIb)*
The potential benefit of the [redacted] dosing regimen will be determined with up to [redacted] data, limiting unnecessary over exposure until [redacted] if no benefit is shown.

[redacted] *dose group for Part 1 (Phase IIb)*
A [redacted] group is needed for a robust modelling approach. From [redacted] trial participants in this group may be [redacted] the dose of [redacted] based on clinical response, as per protocol.

For more information regarding selection of doses in the trial, please see Section 4.1.2.

DMC
An independent DMC is involved in monitoring of overall safety and efficacy. For details, please see Section 8.7.

Feedback on trial design from patient or patient organisation
On [redacted] a Patient Organisation Advisory Board (POAB) meeting was held with the objective to seek patient and patient organisation input and advice to inform the HS programme concerning the following topics: dosing and administration, clinical trial endpoints, Patient Reported Outcomes (PROs) and long-term trial participation.

On [redacted] the second POAB meeting was held with the following objectives:

- Gain feedback on the design of the trial
- Confirm what supporting materials should be used in the trial
- Understand what psychological support is needed

On [redacted] the third POAB meeting was held with the following objectives:

- Get additional feedback to improve management of visit procedures and patient facing materials targeted for trial participants.
- Get feedback about the ICF content, design and administration.

The input received from these meetings has been considered whenever possible to add flexibility and to have a more patient centric protocol.

Feedback on clinical trial experience
This trial will include an option for participants to complete anonymised questionnaires to provide feedback on their clinical trial experience. Providing this feedback is not required for trial participation, and information collected from these questionnaires will not be analysed as part of the clinical data for the trial (see Appendix 10.19).

3.3 SELECTION OF TRIAL POPULATION

A total of approximately [redacted] in Part 1 (Phase IIb) and [redacted] in Part 2 (Phase III) will be randomised in this trial. A sufficient number of participants will be screened to meet this randomised goal. Trial participants will be recruited across multiple sites in multiple countries. The minimum planned number of participants per site [redacted]

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

A trial screening log collecting information on patients considered for participation and reason not enrolled (=signed informed consent) if applicable will be maintained. This screening log will be maintained in the Investigator Site File (ISF). Also, a log of all participants 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. Even for screen failure participants, a minimum of information will be collected: participant number, inform consent version and date, demographics, eligibility and reason for screen failure. In case of a SAE during the screening period, information on SAE, relevant other AEs, and concomitant treatment will be collected.

If retrospectively it is found that a trial participant has been randomised in error (=did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment, a decision will be made whether continued trial participation is possible or not.

Trial participants can be re-screened (see also Section 6.2.1). The previous participant number will be provided by [redacted] and the information will be collected in the eCRF.

3.3.1 Main diagnosis for trial entry

Patients aged 18 years or older, with moderate to severe HS will be included in the trial if those patients fulfil all the inclusion criteria and do not meet any of the exclusion criteria.

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

3.3.2 Inclusion criteria

Part 1 (Phase IIb)

1. Of full age of consent (according to local legislation, at least ≥ 18 years) at screening.
2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
3. Moderate to severe HS, based on IHS4 criteria, at least 6 months prior to and including Baseline visit, as determined by the investigator through participant interview and/or review of the medical history (if IHS4 scoring is not available for the period before screening, equivalent scoring based on scoring systems as HS-PGA or Hurley are acceptable on the basis of documented investigator assessment)
4. HS lesions [redacted] anatomic areas [redacted]
5. Biologic naive or [redacted] for HS.
6. For biologic naïve, inadequate response to an adequate course of appropriate oral antibiotics for treatment of HS in the last 1 year prior to the Baseline visit, as per investigator discretion. All participants must have previous exposure to antibiotics for HS.
7. Total AN count of [redacted] at Baseline visit.
8. Total dT count [redacted] Baseline visit
9. Women of childbearing potential (WOCBP) must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly, for the duration of the trial and [redacted] after last administration. A list of contraception methods meeting these criteria and instructions on the duration of their use is provided in the participant information and in Section 4.2.2.3

Part 2 (Phase III)
Except for potential criteria, which will be confirmed after primary analysis of Phase IIb results, the same inclusion criteria as Part 1 (Phase IIb) will need to be met.

3.3.3 Exclusion criteria

Part 1 (Phase IIb)

1. Participants who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
2. Prior exposure to any immunosuppressive/immunomodulatory biologic other than TNFi for HS.
3. Prior exposure to IL-36R inhibitors including spesolimab.
4. Treated with any investigational device or investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives of the drug, whichever is longer, prior to Visit 2 (Baseline visit)
5. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Women who stop nursing before the study drug administration do not need to be excluded from participating.

6. Participants with history of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.
7. Participants with a transplanted organ (with exception of a corneal transplant >12 weeks prior to screening) or who has ever received stem cell therapy (e.g., Remestemcel-L)
8. Participants with any documented active or suspected malignancy or history of malignancy within 5 years prior to the screening visit, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or *in situ* carcinoma of uterine cervix.
9. Participants with active or latent tuberculosis (TB) (trial participants are required to be tested during the screening visit):
   - participants with active TB should be excluded.
   - participants will be screened with Interferon Gamma Release Assay (IGRA) such as QuantiFERON or T-spot. Participants with positive IGRA are excluded, unless they have completed treatment for active or latent TB per investigator discretion, at the time of screening. Participants with untreated latent tuberculosis may be included if treatment of latent tuberculosis as per local guidelines is initiated prior to randomization and completed during the course of the trial.
   - participants with indeterminate QuantiFERON or invalid/borderline T-spot may be retested with IGRA (once), and if inconclusive, should have a PPD skin test. Under certain conditions (e.g. unavailability of additional IGRA testing tubes, inability to process the IGRA [availability of freezer, centrifuge, etc.]), Tuberculin-Skin testing (TST) may be considered for retesting, but this should be discussed with the sponsor on a case-by-case basis.
   - Under exceptional circumstances and only after discussion with sponsor, PPD skin test, also called TST, can be performed if IGRA is not available or inconclusive. A tuberculin skin test reaction ≥10 mm (≥5 mm if receiving ≥15 mg/d prednisone or other immunosuppressant) is considered positive. Patients with a positive TST are excluded, unless they have completed treatment as above.
   - (Only for Japan: If there is no chest X-ray test or CT taken within 3 months prior to Visit 1, it should be taken as tuberculosis screening test.)
10. Participants with active systemic infection within 2 weeks of Visit 2 (Baseline visit). These participants can be re-screened after completed treatment of the acute infection, as per investigator discretion.
11. Participants with relevant chronic infections as determined by the investigator, including human immunodeficiency virus (HIV) or viral hepatitis. The corresponding laboratory tests will be performed during screening. In case of a positive hepatitis C antibody test, a positive reflex testing for Hepatitis C RNA PCR is considered positive. For hepatitis B, exclusion criterion is met with positive Hepatitis B surface antigen; positive HBV DNA PCR (HBV DNA PCR is done in case of positive Hepatitis B core antibody and negative Hepatitis B surface antigen). A patient can be re-screened if the patient was treated and is cured from the acute infection.
12. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to first study drug administration (Visit 2-Baseline visit) or planned during the study (e.g. hip replacement, aneurysm removal, stomach ligation)
13. Participants with severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in AST, ALT, or alkaline phosphatase, **or** >2-fold ULN elevation in total bilirubin at screening visit. Trial participants with Gilbert´s

syndrome can be included unless total bilirubin elevation was >5-fold ULN at screening visit and unless proportions of bilirubin fractions are inconsistent with diagnosis of Gilbert´s syndrome.

14. Participants at screening with a severe, progressive, or uncontrolled condition as renal, hepatic, haematological, endocrine, pulmonary, cardiac, neurologic, cerebral, psychiatric disease (including history or suspicion of chronic alcohol or drug abuse) other than HS, or signs and symptoms thereof, in the opinion of the investigator would compromise the safety of the participant or the quality of the data, and would make the study participant unreliable to adhere to the protocol, to comply with all study visits/procedures, or to complete the trial.
15. Planned use of laser or other hair removal procedures over HS-affected areas during the trial period.
16. Participants with any suicidal ideation of type 4 or 5 on the C-SSRS in the past 12 months prior to screening visit (i.e. active suicidal thoughts with method and intent but without specific plan, or active suicidal thoughts with method, intent and plan)
17. Participants with any suicidal behavior in the past 2 years prior to screening visit (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behavior)
18. Previous enrolment in this trial (exception: trial participants re-screened)
19. Presence of acute demyelinating polyneuropathy.
20. Confirmed or suspected acute SARS-CoV-2 infection. Participants who recovered from a SARS-CoV-2 infection may be eligible: 14 days or more from first symptoms or from first PCR test confirmation to randomisation, whichever is shorter AND at least 14 days without SARS-CoV-2 symptoms. If local criteria are stricter, they will apply.
21. Trial participants who weigh <40 kg.

Part 2 (Phase III)
Except for potential criteria, which will be confirmed after analysis of Phase IIb results, the same criteria as Part 1 (Phase IIb) will need to be met.

3.3.4 Discontinuation of trial participants from treatment or assessments

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

In case of premature permanent discontinuation of trial treatment, the EOT visit procedures will be done at the earliest, followed by a safety follow up visit [redacted] after the last drug administration. For those trial participants with premature discontinuation happening before visit 14 [redacted] in addition to safety follow up assessment, trial participants ideally should also continue visits for assessment of efficacy up to Visit 14 [redacted] as per Flowchart. For these cases only the IMP administration will be skip.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the source documents and in the CRF.

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

If the reason for discontinuation is an AE, please follow the requirements for AE collection reporting (see Section 5.2.6.2). If the reason for discontinuation is death, this should be reported on the SAE form as well, regardless of causal relationship.

3.3.4.1 Discontinuation of trial treatment

An individual trial participant will discontinue trial treatment if:

- The trial participant wants to discontinue trial treatment. The trial participant will be asked to explain the reasons but has the right to refuse to answer.
- The trial participant has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of the investigator, the safety of the trial participant cannot be guaranteed as participant is not willing or able to adhere to the trial requirements in the future.
- The trial participant uses/requires certain restricted medications, such as immunosuppressive / immunomodulatory biologics, investigational products/devices, IL-36 receptor inhibitors (as mentioned in Section 4.2.2), for any indication.
- The trial participant can no longer receive trial treatment as per physician's discretion (such as surgery, adverse events, other diseases)
- The trial participant should not receive subsequent doses of trial treatment if a hepatic injury alert (see Section 5.2.6.1.4) is confirmed without identification of an alternative cause in the work-up according to the "DILI checklist".
- The trial participant develops suicidal ideation of type 4 or 5 in the Columbia-Suicide Severity rating Scale (C-SSRS) or any suicidal behaviour (see Section 4.2.1 on Individual stopping rules related to specific AEs)
- The trial participant is unable to receive trial treatment consecutively for [redacted] or more for any reason
- If the participant experiences an infection with SARS CoV 2 (as confirmed by local standards) or any significant systemic infection based on the investigator's judgement, interruption of study medication should be considered. The participant may resume trial treatment following recovery of the infection if the participant is expected to derive clinical benefit, at the discretion of the investigator.
- In case a trial participant becomes pregnant during the study the IMP should be discontinued. The pregnancy will be followed as described in Section 5.2.6.2.3
- If peripheral neuropathy is suspected, treatment with spesolimab must 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

In case the infusion of study drug is permanently discontinued before the whole amount of the prepared solution has been administered to the trial participant, every effort should be made to complete all remaining study assessments of the visit.

Trial participants who discontinue treatment permanently and prematurely prior to the planned EoT visit [redacted] should be registered as discontinued from treatment in IRT. These participants should follow the scheduled visits as much as possible as defined in the Flowchart: the EoT visit procedures should be conducted either immediately or as soon as

possible, followed by the Follow-up visit (EoS) [redacted] after the last trial drug administration date. All efforts should be made to keep the trial participant in observation for at least [redacted] after the last dose of the study drug for safety reasons. All trial participants should have an EoS visit and assessments as per Flowchart must be done during the EoS visit.

For all trial participants, the reason for permanent discontinuation from trial treatment (e.g. AEs) must be recorded according the options available in the CRF. This data will be included in the trial database and reported.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war; please see Section 6), physical participant visits to the sites may not be feasible or may need to be restricted to ensure participant safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue trial treatment. Where permitted by local law and regulations, trial medication may be shipped directly to the participants' home in agreement with the sponsor. In that case, a home visit service would assist the participant with medication administration. In case these options cannot be locally implemented, the IMP will be temporarily discontinued.

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

3.3.4.2 Withdrawal of consent to trial participation

Trial participants may withdraw their consent to trial participation at any time without the need to justify the decision.

If a trial participant wants to withdraw consent, the investigator should be involved in the discussion with the trial participant 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.

Withdraw of consent is when the trial participant declines any further participation in the clinical trial and is confirmed when the patient meets all of the below:
- Does not want to take trial medication any longer and
- Does not want to continue to come to the site/clinic for protocol scheduled trial visits after treatment discontinuation and
- Does not want to be contacted periodically and
- Does not want to be contacted at the end of the trial and
- Does not provide access to the own health records

If any of these is not met, then it is not a withdrawn of consent.

3.3.4.3 Discontinuation of the trial by the sponsor

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

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 GCPs, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further treatment and follow up of trial participants affected will occur as described in Section 3.3.4.1.

The investigator/the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the investigational medicinal products

Table 4.1.1: 1 Test product spesolimab solution [redacted]

Substance:	Spesolimab (Spevigo®)
Pharmaceutical formulation:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strengths:	Spesolimab [redacted]
Posology:	See Section 3.1. [redacted]

Table 4.1.1: 2 Test product BI matching placebo solution [redacted]

Substance:	Placebo matching to spesolimab
Pharmaceutical formulation:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strengths:	[redacted]
Mode of administration:	
Posology:	See Section 3.1. [redacted]

Table 4.1.1: 3 Test product spesolimab solution [redacted]

Substance:	Spesolimab (Spevigo®)
Pharmaceutical formulation:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strengths:	Spesolimab [redacted]
Mode of administration:	[redacted]
Posology:	See Section 3.1.

Table 4.1.1: 4 Test product BI matching placebo solution [redacted]

Substance:	Placebo matching to spesolimab
Pharmaceutical formulation:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strengths:	[redacted]
Mode of administration:	
Posology:	See Section 3.1.

4.1.2 Selection of doses in the trial and dose modifications

Part 1 (Phase IIb)
The main trial objectives of Part 1 in this trial is provided in Section 2.1.1.

[redacted] dosing regimens are defined (for details, see Section 3.1) in this trial: one middle dosing regimen (middle dose group) [redacted] one higher dosing regimen (high dose group); and one lower dosing regimen (low dose group). [redacted] Taken together, trial participants randomised to active treatment in 1368-0052 received [redacted] then [redacted] starting [redacted] Those randomised to placebo in 1368-0052 received placebo until Week 10. Starting [redacted] and after final evaluation of Study 1368-0052 (EoT visit), the former placebo trial participants [redacted] Thereafter all trial participants were continued [redacted]

Safety for the lower and medium dosing regimen is supported by the safety profile observed in Study [redacted]

In the healthy volunteer (HV) study (1368-0002), 6 healthy volunteers were exposed to the highest 20 mg/kg dose. In those 6 trial participants, no serious adverse event (SAE) or adverse event of special interest (AESI) were reported. At PT level, the most frequently reported treatment-emergent AEs (more than 20% of the trial participants who received spesolimab in the MRD part) were nasopharyngitis, headache, and injection site erythema. All AEs resolved by the end of the trial or were followed up sufficiently. No relevant changes were observed in safety laboratory tests, vital signs, and ECGs. Based on these safety findings from the 1368-0002 study, the highest dose planned for the 1368-0098 study can be considered as acceptable.

Table 4.1.2: 1 [redacted]

[redacted]

1. Observed exposures in HV study (gMean, n=4)
2. [redacted] AUC from [redacted] for comparison purpose

[redacted]

After the last dose is administered at [redacted] final efficacy, PK, and ADA/NAb assessments will be made at the end of the dosing interval, [redacted] after the last dose at [redacted] (EOT visit). The last safety assessment will be done [redacted] after the last administration. Prolonging Part 1 participants treatment with spesolimab beyond [redacted] allows to: 1) switch prior placebo recipients to active treatment, 2) explore further how spesolimab efficacy and safety profile is maintained, and 3) explore further potential immunogenicity of spesolimab in HS patients, up to approximately 1 year.

Part 2 (Phase III)
Dose regimens to serve trial objectives of Part 2 (Phase III), defined in Section 2.1.1, will be selected according to Part 1 (Phase IIb) results. Justification of selecting the dose regimens will be clarified in an amended CTP.

4.1.3 Method of assigning trial participants to treatment groups

For both Part 1 and Part 2, after the assessment of all in- and exclusion criteria, each eligible trial participant will be randomised to a treatment group at Visit 2 according to a randomisation plan, please see Section 7.4.Randomisation codes will be generated through a validated software and kept blinded to the trial team, sites and trial participants. Access to the codes will be controlled and documented.

An [redacted] The investigator will receive all necessary instructions to access the [redacted] from the sponsor. Detailed [redacted] functions and procedures will be documented in the user requirement specifications mutually agreed to by the sponsor and the [redacted]

4.1.4 Blinding and procedures for unblinding

4.1.4.1 Blinding

Part 1 (Phase IIb)
Trial participants, investigators, central reviewers, and everyone (except for specified project members [e.g. PK]) involved in trial conduct or with any other interest in this double-blind trial will remain blinded regarding the randomised treatment assignments until the database is declared ready for final analysis according to the sponsor's SOPs.

Further details, regarding the timepoint of unblinding the database for analyses including primary, interim, and final analysis, are documented in the TSAP or logistics plan.

The randomisation codes will be provided to bioanalytics before the last trial participant completed the [redacted] visit of Phase IIb (Part 1) of the trial to exclude placebo samples from the PK and ADA analysis. Bioanalytics will not disclose the randomisation code or the results of their measurements until the database lock.

For the primary analysis at [redacted] and interim analysis at [redacted] a respective team ("shadow team") independent of the main trial team will be formed to conduct the necessary analysis and reporting steps and ensure to maintain the blind and restrict access to the randomisation codes from the main trial team. Details of data transfer, timelines, and involved trial functions during this process will be described in a separate logistics plan which will also specify details on data access.

Part 2 (Phase III)
Trial participants, investigators, central reviewers, and everyone involved in trial conduct, trial analysis, or with any other interest in this double-blind trial will remain blinded regarding the randomised treatment assignments until the database is declared ready for analysis according to the sponsor's SOPs. Further details, regarding the timepoint of unblinding the database for analysis, will be documented in the TSAP.

The responsible bioanalyst of the external bioanalytical laboratory will receive the randomisation codes prior to last trial participant completed to allow for the exclusion from the analyses of PK and ADA samples taken from placebo trial participants.

The TBA may receive unblinding data from the external bioanalytical laboratory after the last trial participant completed the last visit but prior to official unblinding of the analysis database at the end of the trial for preparation of data transfer e.g. check file structure prior to data upload and SDTM transformation and bioanalytical report writing. Bioanalytics will not disclose the randomisation code or the results of their measurements until the database lock.

Part 1 (Phase IIb) and Part 2 (Phase III)
The access to the randomisation code will be kept restricted until its documented release per sponsor SOP.

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

4.1.4.2 Emergency unblinding and breaking the code

Emergency unblinding will be available to the investigator via IXRS and emergency service. It must only be used in an emergency when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The treatment allocation should not be disclosed to the sponsor unless this is explicitly requested. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

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

4.1.5 Drug assignment and administration of doses for each trial participant

Trial participants for Part 1 will be treated with spesolimab or matching placebo as indicated in the Flowchart and Section 3.1. Trial participants for Part 2 treatment schedule will be simplified, based on the results from Part 1 data available when the primary analysis will be conducted. Therefore, the rest of this section applies to study participants in Part 1. This section will be duly amended to include any change applied to drug administration for study participants in Part 2 after the Part 1 primary analysis has been conducted.

As briefly described in Section 4.1.3, the medication will be assigned [redacted]

There are no special requirements on drug administration in relation to meals. Administration of study medication should occur after ECG and after blood sampling.

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.

[redacted] **(Visits 2, 3, 4, and 5** [redacted]
Trial participants will receive [redacted] spesolimab or matching placebo. The administration of the trial medication will be done by a trained health care professional. Detailed instructions for the preparation of the [redacted] the [redacted] and the [redacted] [redacted] are provided in the ISF. The administration of [redacted] doses will be done at site.

[redacted] **(Visit 6 to 31** [redacted]
Trial participants will receive [redacted] of spesolimab or matching placebo. [redacted] provided in the ISF. [redacted] is allowed.

Monitoring after administration
Trial participants should be closely monitored for AEs, including signs and symptoms of [redacted] hypersensitivity reactions, for 2 hours after the first dose of trial drug administered at Day 1 (Visit 2) and 1 hour following all other doses of trial drug. Study personnel should observe the [redacted] They should also ask trial participants about itching, dizziness or shortness of breath. Trial participants should be advised to notify site personnel in case they experience redness, swelling or other changes at the [redacted] 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, see Section 5.2.6 about AE reporting.

In case of safety concerns, e.g. due to [redacted] it is in the discretion of the investigator or his/her designee to adapt the [redacted] and - provided no further safety concern exist - [redacted] Further, based on [redacted] medical judgment he/she will provide medications such as steroids, etc, as needed (see Section 4.2.1 for handling of [redacted]. Detailed instructions for handling of [redacted] are also provided in the "Instructions for Pharmacist" document placed in the ISF. Pre-medications for further [redacted] might be considered and will be agreed on between investigator and BI clinical monitor.

Dose modifications or dose adjustments are not permitted except as per protocol (see Section 3.1 possible [redacted] from [redacted] of Part 1 (implemented by IRT if applicable as per allocated blind treatment group). In exceptional cases of missed or delayed visits, if any of these visits have to be rescheduled, the date of subsequent visit should be calculated from baseline (Visit 2). After Visit 5 [redacted], 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.

Table 4.1.5: 1 Placebo controlled period of Part 1 (Up to Visit 14 [redacted]

Administration of trial drug
[redacted]

Table 4.1.5: 2 Overview of treatment course from Visit 15 [redacted] up to Visit 31 [redacted]

Administration of trial drug
[redacted]

From Visit 23 [redacted] on, trial participants will continue to receive the previously assigned dosing regimen until the results of primary analysis [redacted] are available. Upon availability of the Phase IIb (Part 1) primary analysis efficacy and safety results, the dosing regimen may be adapted from Visit 23 [redacted]

Table 4.1.5: 3 Dosage and treatment schedule for the [redacted]

Visit 2 (baseline)	Visit 3	Visit 4	Visit 5
[redacted]			

Table 4.1.5: 4 Dosage and treatment schedule for the [redacted]

[redacted]

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an [redacted] which will also monitor expiry dates of supplies available at the sites.

The label will be prepared according to EU Regulation No. 536/2014, Annex 6, Section D. Omitting certain particulars with the following justifications:

- "Investigator" was omitted from the label because patient cards are used.
- Additionally, each kit assigned to a patient will be registered as such in the IXRS. "Visit number" is omitted from the label as each kit assigned to a participant has a kit number and it be registered in the [redacted]

Should local regulations outside the EU require these particulars, they will be added to the country-specific label text.

For 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. The shipping, labelled storage conditions and the available stability data used for assessment in the event of a temperature excursion described in the Stability and Packaging Information (SPI) is reflected in the Mini-tag® profile. The Mini-tag® is validated and is the leading temperature monitoring system used for IMP in this trial. Site staff will be trained on its usage by the time the medication is received at site. For details of storage conditions, please refer to the ISF. A Mini-tag® status site 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.

For more details, please see the relevant instructions in the ISF.

4.1.8 Drug accountability

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

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

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

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 trial participant, and the return to the sponsor or warehouse/drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse/drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational medicinal product and trial participants. The investigator or designee will maintain records that document adequately that the trial participants were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator or designee must verify that 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 hypersensitivity including [redacted] and anaphylactic reaction
In case of systemic hypersensitivity including [redacted] and anaphylactic reaction emerging during or after [redacted] of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to

- Immediately interrupt the [redacted]
- Treat with systemic antihistamines, i.v. steroids, and in case of a severe allergic reaction (eg, anaphylactic reaction) epinephrine

Also draw a plasma sample for IgE and ADA as detailed in the Laboratory Manual (ISF). Please initiate the evaluation of histamine, serum tryptase, and complement components.

In case of [redacted] based on trial participant's clinical course and medical judgment, the [redacted] be re-initiated/the [redacted] be continued in case of mild or moderate [redacted] (according to Common Terminology Criteria for Adverse Events (CTCAE) grading in section of the ISF) at lower speed with gradual increase to complete the [redacted] as detailed in the Instructions for Preparation and Handling of spesolimab/placebo in the ISF. In any case, the total duration of [redacted] should not exceed [redacted] Information about the maximum time between the start of [redacted] trial participant is detailed in the Instructions for Pharmacist filed on the ISF.

In case of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA (Appendix 10.20 [R11-4890]) suspected to be caused by the trial medication, the investigator should permanently discontinue treatment with spesolimab.
When a delayed hypersensitivity reaction is suspected, please draw a blood sample for laboratory assessment and evaluate for signs of extra-cutaneous organ involvement. The decision to discontinue treatment and/or restart treatment after resolution of the reaction should be based on reaction type and severity. See Section 3.3.4 for reference.

Severe infections (according to CTCAE grading in Section 15 of the ISF), serious infections, opportunistic or mycobacterium tuberculosis infections
Treatment of the infection should be initiated promptly according to local standard of care. No further trial medication should be administered until the active infection has been resolved. Treatment with spesolimab may be restarted when the trial participant has recovered according to investigator's assessment. See Section 3.3.4 for reference.

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. See Section 3.3.4 for reference. Diagnostics and treatment must be initiated according to local standard of care (SoC).

Suicidality
In case a trial participant develops suicidal ideation of type 4 or 5 in the Columbia-Suicide Severity rating Scale (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 trial participant should immediately be referred to a mental health professional for further work-up and permanently discontinue trial treatment. See Section 3.3.4 for reference.

Overall, the choice of SoC treatment will be left at the discretion of the investigator. The sponsor will not provide/supply SoC treatments to the sites.

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Trial participants must not participate in another investigational drug or device trial or receive other investigational treatment(s) while enrolled in this trial.

The following medications/medication classes are restricted during trial treatment and prior to Visit 2 for durations as specified in Table 4.2.2.1: 1. Please see Section 3.3.4 for withdrawal information regarding the use of restricted medications.

Table 4.2.2.1: 1 Restricted medications in Part 1 (Phase IIb)*

Medications/ medication classes	Washout period prior to V2 (baseline)	V2 to V14	From V14 to EoT
Systemic antibiotics[1]	4 weeks	Restricted for HS except for HS-disease worsening after V6 (definition in Section 4.2.3)	Restricted for HS except for HS-disease worsening after V14
Systemic corticosteroids[2]	2 weeks	Restricted for HS. For non-HS indications, only short courses are allowed[2]	Restricted for HS[2]
Immunosuppressive/ immunomodulatory biologics	12 weeks or 5 half-lives whichever is longer	Restricted for HS and non-HS indications	Restricted for HS and non-HS indications
Other systemic non-biologic immunomodulatory and immunosuppressive agents	4 weeks or 5 half-lives whichever is longer	Restricted for HS and non-HS indications	Restricted for HS and non-HS indications
Live vaccines[3]	6 weeks	Restricted	Restricted
Opioid analgesics	2 weeks	Restricted for HS and non-HS indications	Restricted for HS[4]
Spironolactone[5]	1 week	Restricted for HS and non-HS indications	Restricted for HS
Metformin[5]	1 week	Restricted for HS and non-HS indications	Restricted for HS
Topical cannabis oil	1 week[6]	Restricted for HS	Permitted
Systemic medicinal cannabis	3 weeks	Restricted for HS and non-HS indications	Restricted for HS
Topical corticosteroids for HS[7]	2 weeks	Restricted for HS	Restricted for HS up to Visit 23.
Topical JAK inhibitors	12 weeks	Restricted for HS	Restricted for HS up to Visit 23

* Restricted medications are expected to be revised and adapted if needed for Part 2 (Phase III)

1 Some conditions apply on the use of systemic antibiotics, please see Section 4.2.3.1.

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 Live vaccines are restricted for 16 weeks after the last dose of spesolimab.

4 After Visit 14 [redacted] opioid analgesics other than tramadol are restricted for HS.

5 Restricted if used for HS. If used for non-HS indication, dose should be stable for at least 12 weeks prior to V2. Metformin and spironolactone can be initiated for non-HS indications after Visit 14 [redacted]

6 Restricted if used over HS-affected areas. Other alternative therapies for HS are restricted, unless permitted after discussion with the investigator and trial team.

7 Prior to Visit 23 [redacted], topical corticosteroids are allowed for non HS indications for areas not concurrently involved by HS.

8 Use of immunomodulatory/immunosuppressive biologics other than [redacted] for HS meets exclusion criterion #2.

4.2.2.2 Restrictions on diet and lifestyle

No specific restrictions on diet or lifestyle of the trial participants are required.

4.2.2.3 Contraception requirements

Throughout the trial, and for a period of at least [redacted] after last trial drug administration, WOCBP 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. A list of contraception methods meeting these criteria is provided in the participant information.

Female trial participants
Examples of acceptable methods of birth control for this trial:

- 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 (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised sexual partner with documented absence of sperm

OrTrial participants must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the trial participant. Periodic abstinence (e.g., calendar, ovulation, symptomthermal, post-ovulation methods), declaration of abstinence for the duration of exposure to study drug, and withdrawal are not acceptable.

Male trial participants
Because of the negative outcome of the completed BI teratogenicity study, a double barrier method of contraception is not required. Contraception of male trial participants and female partners of male trial participants are not required. Systematic collection of pregnancy data in female partners of clinical trial participant is not required [c03320877-11].

4.2.3 Concomitant medications/interventions

The following sections provide definition of certain terms used in this trial and additional information on certain concomitant medications and lesion interventions. The sponsor will not provide/supply these treatments to the sites.

Any medication received by trial participant from Visit 1 should be recorded in the appropriate concomitant medications page in the eCRF.

Rescue medication is defined as the treatment for HS disease worsening and includes systemic antibiotics and/or immunosuppressive biologics such as TNF-inhibitors.

HS Disease worsening is defined as total AN count is 150% of baseline AN count. For example, for a baseline AN count of 10, disease worsening should be interpreted as an AN count of 15 and above.

4.2.3.1 Antibiotic use during the trial

Non-HS use
From randomisation up to Visit 14 [redacted] systemic antibiotics can be used for indications other than HS for a duration of less than or equal to 4 weeks. The same restriction applies to the period from Visit 14 [redacted] to Visit 23 [redacted], with a maximum of 4 consecutive weeks of systemic antibiotics allowed for non-HS indications.

HS use (as defined above in Section 4.2.3):

- At or after Visit 6 [redacted], if the trial participant requires systemic antibiotics for HS disease worsening (as defined above in Section 4.2.3) , monotherapy with doxycycline 100 mg orally twice daily may be used for a maximum period of 2 weeks, and not more than a total of 4 weeks up to Visit 23 [redacted]. After V23 [redacted], systemic antibiotics can be used for HS disease worsening (duration as per investigator discretion).
- Please refer to the ISF for alternative oral antibiotics allowed in this trial.
- Parenteral antibiotics are restricted for HS until [redacted] based on roll over status.

Concomitant use of systemic antibiotic therapy for treatment of HS other than the above is not allowed.

4.2.3.2 Analgesics use during the trial

Opioid analgesics are restricted for HS and non-HS indications up to Visit 14 [redacted] After Visit 14 [redacted] opioid analgesics other than tramadol are restricted for HS. After Visit 14, opioid analgesics can be allowed for non-HS indications as per investigator discretion.

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

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

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

4.2.3.3 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 in this trial: intra-lesional steroid and Incision and Drainage (I&D).

- If I&D is performed, only over the counter antiseptic wash can be used. Concomitant medications associated with the lesion intervention must be captured in the medical records.

- Intralesional steroid injections of triamcinolone up to [redacted] can be used for a single lesion at one time.

Up to Visit 14 [redacted] a total of two protocol-allowed interventions are permissible. After Visit 14 [redacted] up to Visit 23 [redacted], a total of two protocol-allowed interventions are permissible. For each period, an intervention can maximally occur on two different lesions at the same time or on the same lesion at two different study visits. From Visit 23 [redacted] to EoT, there are no restriction in the number of lesion interventions.

Lesions that have been subjected to intervention should not be counted in future assessments.

4.3 TREATMENT COMPLIANCE

[redacted]Compliance will be verified by the CRA authorized by the sponsor.

[redacted]

Treatment compliance is defined as good if between 80-120% of scheduled [redacted] as per protocol are received. If the treatment compliance is not between 80-120%, site staff will be reminded about the importance of treatment compliance. However, randomised participants will not be discontinued for poor compliance without prior discussion with the monitor or designee.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

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

Efficacy assessments are primarily based on the reduction of HS lesions count evaluated by the investigator (or appropriately qualified delegate). Adequate identification and counting of draining tunnels, abscesses, and inflammatory nodules are key and require careful training. As much as possible, the same or a reduced number of well-trained evaluators should be assessing lesions at one investigative site to reduce unspecific variability as much as possible. [redacted]

Efficacy will also be assessed in this study according to patient's reporting outcomes including the assessment of skin pain, pruritus, but also drainage and odour, Dermatology Life Quality Index, HiS-QoL.

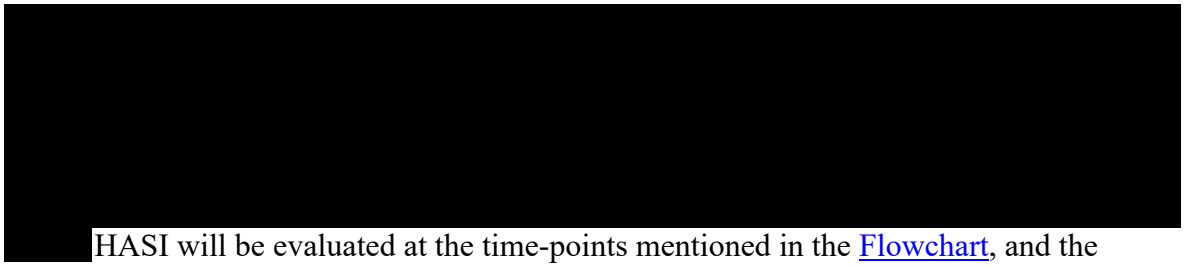
The description of specific scores, index, or PROs used as efficacy outcome is provided below.

Part 1 (Phase IIb) and Part 2 (Phase III)

1. **International Hidradenitis Suppurativa Severity Score System (IHS4)**
   The IHS4 is a validated, clinical scoring system for dynamic assessment of HS severity. Determining IHS4 requires counting nodules, abscesses and dT/sinus tracts making it straightforward to apply in clinical trials [R20-3045]. IHS4 will be evaluated at the time-points mentioned in the Flowchart, and the detail is provided in Appendix 10.4.

2. **Hidradenitis Suppurativa Clinical Response (HiSCR50)**
   The HiSCR50 is one of the most well-known and widely used outcome assessment in HS clinical trials. The HiSCR50 is defined as at least a 50% reduction from baseline in the total AN count, [redacted] [R20-2976]. HiSCR50 will be evaluated at the time-points mentioned in the Flowchart. Appendix 10.3.

3. **Hidradenitis Suppurativa Area and Severity Index (HASI)**
   The HASI is modelled after the Psoriasis Activity and Severity Index (PASI). Four classic signs of HS-related inflammation (erythema, induration, open ulcer, and dTs) are included. Each variable in HASI is scored on a Likert scale (0-3) for each predetermined body region. [redacted] This is converted



HASI will be evaluated at the time-points mentioned in the Flowchart, and the detail is provided in Appendix 10.5.

4. **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, minimal, mild, moderate to severe, or very severe) based on abscesses, dT, inflammatory nodule, and non-inflammatory nodule [R20-3046]. HS-PGA will be evaluated at the time-points mentioned in the Flowchart, and the detail is provided in Appendix 10.6.

5. **Pain Numerical Rating Scale (NRS Pain)**
   The HS Pain NRS is an endpoint for the assessment of HS-related pain severity for clinical trials with patients with HS. The Patient Global Assessment of HS Pain will be used to assess the worst HS pain. Ratings will range from 0 (no HS pain) to 10 (HS pain as bad as you can imagine). It is a unidimensional measure of pain intensity and can be administered daily with minimal trial participant burden. Recall period is 24 h and response is given by an 11-point scale ranging from 0 to 10; see Appendix 10.7.

6. **Pruritus Numerical Rating Scale (NRS Pruritus)**
   The HS Pruritus NRS is an endpoint for the assessment of HS-related pruritus severity for clinical trials with patients with HS. The Patient Global Assessment of HS Pruritus will be used to assess the worst HS pruritus. Ratings will range from 0 (no itch) to 10 (HS worst imaginable itch). It is a unidimensional measure of pruritus intensity and can be administered daily with minimal trial participant burden. Recall period is 24 h and response is given by an 11-point scale ranging from 0 ("no itch") to 10 ("worst imaginable itch"). Trial participants are asked to rate the intensity of their itch using this scale; see Appendix 10.8.

7. **Dermatology Life Quality Index (DLQI)**
   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, see Appendix 10.9.

   The DLQI will be analysed under six headings as shown in Table 5.1: 1 [R05-2548].

Table 5.1: 1 DLQI

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

[redacted]

8. **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. [redacted]

9. **Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue)**
The FACIT-Fatigue is a 13-item questionnaire [R10-6433], [R07-4311], [R16-0029] that assesses self-reported fatigue and its impact upon daily activities and function. Answers are based on a 5-point Likert scale. Responses of "not at all", "a little", "somewhat", "quite a bit", and "very much" are available for each question and correspond to scores of 0, 1, 2, 3, and 4, respectively (total score range: 0-52). [redacted]

10. **Patient Global Impression of Change (PGI-C)**
The PGI-C is a 1-item tool assessing the change of HS by start of taking the study medication by 5-point Likert-type scale. The first assessment of PGI-C is performed at Visit 6 [redacted] and after that, as indicated in the Flowchart. The tool is required for anchoring of other instruments and endpoints, see Appendix 10.12.

11. **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 first assessment of PGI-S is performed at Visit 2 [redacted]. The tool is required for anchoring of other instruments and endpoints; see Appendix 10.13.

12. **Hidradenitis Suppurativa odour and drainage scale (HODS)**
    The HODS is an 8-item scale developed to assess the HS-related drainage and odour in patients. It covers two domains: drainage (5 items) and odour (3 items). The response options range from 1-5. Higher scores depict worse outcome of the concept being assessed; see Appendix 10.14.

13. **Hospital Anxiety and Depression Scale (HADS)**
    The HADS is an instrument for screening anxiety and depression in non-psychiatric populations. The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale; see Appendix 10.15.

Part 2 (Phase III) only

14. **Work Productivity and Activity Impairment Questionnaire for HS (WPAI-HS)**
    WPAI-HS is 6-item instrument to assess the effect of hidradenitis suppurativa on ability to work and perform normal daily activities; see Appendix 10.16.

15. **EuroQol 5 dimensions 5-level (EQ-5D-5L)**
    Assessment of changes in quality of life using the EuroQol-5D-5L. The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'; see Appendix 10.17.

[redacted]

The Patient Global Assessment of HS Pain and HS Pruritus will be completed on a diary (one scale for pain and another for pruritus), on a daily basis by trial participants from Visit 2 [redacted] through Visit 19 [redacted] After Visit 19, NRS pain and NRS pruritus will be collected on a daily basis during the 7 days prior to the next scheduled visit as per Flowchart. For details, refer to the Flowchart.

For the daily assessments, trial participants should be instructed that, before they go to bed, they complete the assessment based on a recall period of the "last 24 hours" and respond to the items. This training should be documented in trial participant clinical records.

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

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on the following observations and examinations:

- Physical examination
- Vital signs
- Clinical laboratory values (haematology, clinical chemistry, coagulation, infection testing and urinalysis)
- 12-lead ECG
- AEs
- Serious AEs (SAEs)
- Intensity of AEs assessed by CTCAE grading version 5.0 (refer to ISF for details)
- Suicidality

The detailed corresponding observations and examinations are described in the following respective subsection.

5.2.1 Physical examination

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

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

For subsequent visits, targeted physical examinations will be done. Targeted physical examination should include examination of the skin (involved areas) and examination pertinent to adverse events or abnormal results from lab test, ECG and/or vital signs.

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

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

5.2.2 Vital signs

Vital signs will be evaluated at the time-points specified in the Flowchart. This includes temperature, respiratory rate, systolic and diastolic blood pressure, and pulse rate (electronically or by palpation count for 1 minute). The results must be included in the trial participant's source documents. Measurement of vital signs should precede blood sampling at all visits.

[redacted]
At dosing visits, vital sign evaluations will be performed pre-dose and additional evaluations will be taken post-dose, approximately 5 and 60 minutes after [redacted] The investigator should evaluate the clinical significance of the results. Clinically abnormal findings will be reported as baseline condition or AEs.

[redacted]
At dosing visits for [redacted] administration, vital signs evaluations will be performed pre-dose and, again, approximately 10 minutes after the end of drug administration. At Visit 6 [redacted] and Visit 7 [redacted] additional measurements will be performed approximately 60 minutes post-dose [redacted]

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 Flowchart. More frequent blood sampling than the defined in the Flowchart may be done whenever the investigator deems necessary. Unscheduled safety laboratory examinations will be reported in the CRF along with the results.

It is preferred, but trial participants do not have to be fasted for the blood sampling for the safety laboratory. Instructions regarding sample collection, sample handling/processing, and sample shipping are provided in the Laboratory Manual in the ISF.

All analyses will be performed by a central laboratory, and the respective reference ranges will be provided 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 baseline conditions or AEs (please refer to Section 5.2.6). A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed and should be repeated until normalisation or stabilisation or until an alternative explanation has been found. Abnormal laboratory values will be graded for intensity by using CTCAE Version 5.0 criteria.

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. The amount of blood taken from the trial participant concerned will be increased due to this additional sampling.

Table 5.2.3: 1 Safety laboratory tests

Functional lab group	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

Table 5.2.3:1 Safety laboratory tests (cont.)

Functional lab group	Test name
Substrates	Glucose
	BUN (blood urea nitrogen)
	Uric acid
	Creatinine[2]
	eGFR (estimated by CKD-EPI formula) (only at screening)
	Bilirubin Total
	Bilirubin Direct (if total is elevated)
	Bilirubin Indirect (if total is elevated)
	Troponin (Reflex, in case of elevated CK)
	Protein, Total
	Albumin
	C-Reactive Protein (CRP and hs-CRP [high sensitivity – CRP])
	Cholesterol, total
	Triglycerides
	LDL-Cholesterol
	HDL-Cholesterol
Specific gamma-globulin quantification	IgE[1]
Hypersensitivity	Complement C3
	Complement C4
	Complement total
	Histamine
	Tryptase
Urine Pregnancy test (only for female patients of childbearing potential)	Human Chorionic Gonadotropin in urine
Serum Pregnancy test (only for female patients of childbearing potential at screening. At later visits only if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Hormones (only at screening)	TSH (free T3 and free T4 in case of abnormal TSH result)
Urinalysis (dipstick)	Urine Nitrite
	Urine Protein
	Urine Glucose
	Urine Ketone
	Urobilinogen
	Urine Bilirubin
	Urine RBC/Erythrocytes
	Urine WBC/Leukocytes
	Urine pH

Table 5.2.3:1 Safety laboratory tests (cont.)

Functional lab group	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 screening)	Albumin (quantitative)
Infection Testing	See Table 5.2.3: 2

1 Only in case of allergic reaction
2 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 standardised
CREJ	Creatinine, Jaffe, Not IDMS	creatinine	Jaffe reaction, Not IDMS standardised

Table 5.2.3: 2 Exclusionary laboratory tests (including infection and pregnancy testing)

Functional lab group	Test name
Infection Testing	Hepatitis B Surface Antigen (qualitative) Hepatitis B Surface Antibody (qualitative) (Only for Japan) Hepatitis B core Antibody (qualitative) HBV-DNA PCR (quantitative) at screening (Visit 1) and EOT Visit[1] Hepatitis C Antibody (qualitative)[6] HIV-1, and HIV-2 Antibody (qualitative) QuantiFERON®-TB-Gold Plus[2,3,4,5] T-spot TB test
Serum pregnancy test (only for female trial participants of childbearing potential)	Human Serum Chorionic Gonadotropin

1 A HBV-DNA PCR should be done if Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative. These evaluations should be conducted at screening and at the EOT visit. (Only for Japan: a HBV-DNA PCR should be done if Hepatitis B core Antibody and/or Hepatitis B Surface Antibody is positive and Hepatitis B Surface Antigen is

negative. These evaluations should be conducted at screening and at the EOT visit. If HBV DNA level is undetectable at screening, the patient can participate in this trial. But HBV DNA level will be monitored at least every 6 months.)

2 There is the trial site option to perform a PPD skin test. (Only for Japan: Chest X-ray test or CT chest should be done if not done within 3 months prior to Visit 1.)

3 Trial participants 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 trial participants with a negative IGRA or PPD skin test, the test should be repeated at the EoT visit. Results of the PPD test should be collected in the CRF.

5 Only for South Africa: Additionally, the tuberculosis infection testing will be repeated approximately 6 months from baseline [redacted] On clinical suspicion of Tuberculosis, infection testing can be performed as per the investigator's discretion at any time during the study.

6 Positive Hepatitis C antibody should be confirmed with Hepatitis C RNA PCR.

The investigator will use the exclusionary lab test results for the assessment of the participants' eligibility for the trial. The infection testing will be repeated at EoT visit as per defined criteria.

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons. Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in participant's medical record.

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

5.2.5 Other safety parameters

Trial participants with a history of malignancy (except for specific cancers) will be excluded from this trial per the exclusion criteria (Section 3.3.3). All cases of malignancies that are detected during the trial will be reported as SAEs, see Section 5.2.6.

5.2.5.1 Local tolerability

Local tolerability at the administration site of trial medication will be assessed by the investigator during the study drug administration visit and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction, e.g. "swelling", "induration", "heat", "redness", "pain", and other findings should be reported as an adverse event, see Section 5.2.6.

[redacted]

Suicidal thoughts and behaviour will be assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) [R08-1147]. The C-SSRS is a semi-structured, investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal 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 baseline/screening scale of the C-SSRS will be administered for eligibility confirmation and the follow-up scale at all visits for assessment of suicidality.

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 trial participants. 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. Free text entries are allowed for; the investigator has to directly evaluate the scale and write a report. In this trial, paper forms will be used for the assessment of the C-SSRS, and results will be transcribed into the e-CRF.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the Screening Visit/Visit 1 (using the 'baseline/screening' version) with the aim to exclude patients with active moderate to severe symptomatology within a specified time prior to the screening or screening visit. The lifetime and the past year history of suicidal ideation and behaviour will also be recorded. After the screening visit, the assessment 'since last visit' version will be performed at each visit. The investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated, or reports may be validated by a consulting psychiatrist or other mental health professional expert. If there is a confirmed positive report of suicidal behaviour or suicidal ideation type 4 or 5 after start of trial (see Section 3.3.4.1 for reference about discontinuation), the investigator is to immediately interview the trial participant and/or is to consult a mental health professional. If the positive report is confirmed, appropriate actions for the trial participant'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 separate SAEs by the investigator. For 'Self-injurious behaviour, without suicidal intent', standard AE/SAE reporting rules are to be applied. For each negative report (suicidal ideation type 1, 2, or 3) after the start of the trial, the investigator is to decide on the basis of clinical judgment whether it represents an AE as defined in the protocol, and if it is considered an AE, then it must be reported accordingly.

5.2.6 Assessment of adverse events

Data and information necessary for the thorough assessment of AEs, SAEs, and AESIs will be reported to the sponsor via eCRF. This may include specific data and information not prospectively specified in this protocol.

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 trial participant 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 considered drug-related or not.

The following should also be recorded on the appropriate eCRFs, BI SAE form (if applicable):

- Worsening of the underlying disease (for definition, see Section 4.2.3) or of other pre-existing conditions.
- Changes in vital signs, ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator.

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

5.2.6.1.2 Serious adverse event

A 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 participant 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 participant 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.

For Japan only: an event that possibly leads to disability will be handled as “deemed serious for any other reason” and, therefore, reported as an SAE.

5.2.6.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined in Section 5.2.6.1.2. The latest list of “Always Serious AEs” can be found in the eDC system. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.6.2, subsections “AE Collection” (Section 5.2.6.2.1) and “AE reporting to sponsor and timelines” (Section 5.2.6.2.2).

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:
Systemic hypersensitivity including infusion reaction and anaphylactic reaction
Any suspicion of severe infusion reaction systemic/hypersensitivity reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (Appendix 10.20 [R11-4890]), see Section 4.2.1 for "Other treatments and emergency procedures".

Severe infections (according to CTCAE grading in Section 15 of the ISF)
(See Section 4.2.1 for "Other treatments and emergency procedures")

Opportunistic and mycobacterium tuberculosis infections
These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, post-transplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis [zygomycosis, rhizopus, mucor, lichtheimia], scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression [R17-2617].

Potential Severe DILI
A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by any of the following alerts (alterations) of hepatic laboratory parameters:
1. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation ≥3x ULN and total bilirubin (TBIL) ≥2x ULN measured at the same visit, or in samples drawn within 30 days of each other, OR
2. AST or ALT elevation ≥3x ULN and INR ≥1.5x ULN measured at the same visit, or in samples drawn within 30 days of each other, OR
3. AST or ALT elevation ≥3x ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%), OR
4. AST or ALT elevation ≥5x ULN

These laboratory findings constitute a hepatic injury alert, and participants showing any of these lab abnormalities need to be followed up according to the "DILI checklist" provided in the eDC system.

In case of clinical signs or symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, TBIL) 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. Additionally, with participants having a normal AST and ALT at baseline, the emergence of an isolated AST or ALT elevation between ≥3-fold and <5x ULN requires repeat testing within 72 hours. DILI Checklist is not required unless repeat testing triggers alerts 1, 2, 3, or 4, mentioned above.

The following events should lead to immediate discontinuation of trial treatment (active or comparator):

- Hepatic injury alert numbers 1, 2, or 3
- Hepatic injury alert number 4, if persists >2 weeks
- AST or ALT elevation >8x ULN

Following completion of the DILI Checklist, if the BI investigational drug cannot be excluded as a possible cause of DILI event, then discontinuation should be made permanent without rechallenge. If an alternate causality, e.g. acute viral hepatitis, is confirmed by the DILI Checklist evaluation, then BI investigational drug may be re-started, if warranted.

Peripheral neuropathy
Any event suspected or diagnosed as peripheral neuropathy would be considered as an AESI. For the treatment interruption rules, please see Section 3.3.4.1.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of AEs should be classified and recorded in the CRF according to the CTCAE version 5.0.

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the AE and the BI investigational compound, 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 as follows:

- The event is consistent with the known pharmacology of the trial 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 as follows:

- 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 trial drug concerned)
- Continuation of the event despite the withdrawal of the medication, considering 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
- There is an 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 participant files.

Per default SAEs/AESIs should be reported via the eCRF in the EDC system. If the EDC system is not or no longer available (e.g. after database lock), the BI paper SAE form should be used; please see Section 5.2.6.2.2.

For trial participants not rolling over to LTE trial, the following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual participant's end of trial (usually the EoS visit, please see Section 6.2.3):
  all AEs (serious and non-serious) and all AESIs
- After the individual participant's end of trial:
  the investigator does not need to actively monitor the participant for new AEs but should only report any occurrence of cancer of new histology and trial drug-related SAEs and trial drug-related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call; those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2), but not on the CRF

For trial participants rolling over to LTE trial the following must be collected and documented on the appropriate CRF(s) by the investigator or delegated:

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

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the AE or SAE eCRF pages to the sponsor's unique entry point immediately (within 24 hours of becoming aware of the event), the country specific process will be described 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 in addition.

With receipt of any further information on these events, follow-up reports have 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 participant'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. Should the EDC system not be available for more than 24 hours, reporting must occur via the BI paper SAE forms.

For Japan:
The investigator must report medical device (prefilled syringes) failure of the trial medication that leads to AEs, SAE and/or AESI or is judged as a potential cause for leading SAEs by the investigator on the Product/Device Complaints Form to the sponsor. Please refer the instruction in ISF for further reporting requirements of medical device (prefilled syringes) failure accompanied with AEs, SAE and/or AESI or judged as a potential cause for leading SAEs.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a trial participant 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 Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for 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 Studies is to be completed. However, if there is an SAE and/or AESI associated with the pregnancy, it must be reported in accordance with the rules and timeline as described in Section 5.2.6.2.2.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

[redacted]

Spesolimab concentrations will be reported descriptively. [redacted]

Trial participants do not have to be fasted for the PK and ADA/NAb blood sampling. Refer to the Flowchart for the time points of PK and ADA/NAb sample collection. Date and exact time of drug administration and PK and ADA/NAb sampling will be recorded on CRFs. See for reference Appendix 10.1. At study visits with study drug administration, pre-dose PK/ADA/NAb samples will be obtained approximately within 2 hours prior to start of [redacted] At [redacted] Day 1, post-dose PK samples will also be obtained approximately 5 minutes after end of [redacted]

5.3.2 Methods of sample collection

Handling procedures can be found in the laboratory manual in the ISF. Samples will be stored in a freezer set at the analytical laboratory until the finalisation of the clinical trial report (CTR). The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.3.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of spesolimab plasma concentrations, approximately 3.0 mL of blood will be taken from a forearm vein into a K_2EDTA (ethylendiaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the Flowchart under PK sampling. The plasma samples may be used for further methodological investigations, (e.g. stability testing) however, only data related to the analyte will be generated by these additional investigations.

5.3.2.2 Sampling for ADA/NAb assessment

For ADA assessment, approximately 3.0 mL of blood will be taken from a forearm vein into a K_2EDTA anticoagulant blood-drawing tube at the time-points listed in the Flowchart under plasma ADA/NAb sampling. For NAb assessment, approximately 3.0 mL of blood will be taken from a forearm vein into a serum blood drawing tube at the time-points listed in the Flowchart under ADA/NAb sampling.

The plasma/serum samples may be used for further methodological investigations, e.g.for further investigations to characterise ADA response or to address Health Authority questions regarding the results/methodology, however only data related to the anti-drug antibodies will be generated by these additional investigations.

5.3.3 Analytical determinations

Spesolimab plasma concentrations will be determined by a validated assay.

The presence of ADA to spesolimab will be assessed via a tiered approach using a validated assay (screening, confirmatory, and titration analysis, as appropriate). Time-points that are confirmed positive may be further characterised using a validated NAb assay.

5.3.4 Pharmacokinetic - pharmacodynamic relationship

No formal analysis of pharmacokinetic/pharmacodynamic relationships is planned.
If the data suggest a pharmacokinetic/pharmacodynamic relationship of special parameters, e.g., an exploratory analysis may be performed.
Correlation between drug concentration and response may be made if adequate data are available. In addition, exploratory correlations may also be made between drug concentration and AEs.
Data may also be used to develop pharmacokinetic/pharmacodynamic models using nonlinear mixed effect modelling techniques, if feasible. For this purpose, data may also be combined with data from other trials. Modelling activities will be planned and documented separately according to internal and external guidelines and Standard Operating Procedures (SOP).

5.4 ASSESSMENT OF BIOMARKERS

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in Section 5.1 and Section 5.2.

[redacted]The further objectives, related to exploratory biomarkers, are specified in Section 2.2.1.

[redacted]

5.4.1 Biochemical and cellular biomarkers

[redacted]

[redacted]

5.4.3 Imaging biomarkers

[redacted]

5.4.4 Methods of sample collection

Detailed instructions on sampling, preparation, processing, shipment, and storage of samples are provided in the laboratory manual in ISF. For sampling time-points, refer to the Flowchart.

Whole blood for gene expression analysis
For the assessment of RNA expression, whole blood will be collected from a forearm vein and stored according to standard procedure provided in ISF.

Skin biopsy and US lesion evaluation
For the skin biopsies, one punch biopsy from lesional skin will be collected at Visit 2 [redacted] and Visit 10 [redacted]. An additional paired non-lesional skin biopsy will also be collected at baseline.

Selected trial sites with US capability
At selected trial sites with US capability, skin biopsies (lesional and non-lesional) will be obtained as mandatory. Skin biopsies will be done under US guidance to ensure optimal skin biopsy selection and increase the quality of sampling.

[redacted]

All other trial sites (i.e. other than selected trial sites)
Skin biopsies (lesional and non-lesional) and US lesion evaluation with US imaging will be optional.

Study samples
The study samples will be discarded after completion of any investigations, but not later than 2 years after the biomarker report has been signed. Any leftover samples or derived material from pre-specified analyses (e.g. RNA, DNA, and blood) may be used for method development/validation but will be destroyed no later than 2 years after the biomarker report has been signed. Exceptions are remainders of study samples for which a participant has voluntarily accepted a biobanking option and has provided a signed ICF (see Section 5.5).

[redacted]

5.4.5 Analytical determinations

Serum, whole blood and skin biomarkers will be analysed using established parameters for each analyte and the corresponding matrix.

Characteristics of the analytical methods for the analysis of the biomarkers will be given in detail in an accompanying technical/biomarker report.

The biomarker assay analysis of all biomarker 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. And this approach may also imply that not all collected samples will be analysed, especially in case of termination of the project/trial.

[redacted]

5.5 BIOBANKING

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

Unspecified DNA banking:
An additional blood sample for DNA banking will be collected in [redacted] at Visit 2 (see Flowchart). [redacted]

5.6 OTHER ASSESSMENTS

Assessments PROs
Administration of paper or electronic PRO (PRO/ePRO) assessments will be in accordance with the guidance from regulatory authorities and international societies (e.g. ISPOR). Trial participants are required to fill PRO/ePRO assessments on their own in a quiet area/room at the frequency as specified in the CTP, without being influenced by the investigator or other members of the trial team. The PRO/ePRO assessments are to be completed by the participant without any help from or interpretation/translation by other people. If this is not possible, the PRO/ePRO assessments are not to be done.
The completion of PRO/ePRO assessment by the participant and the mode of administration will be documented.

Photo images
Photographs of trial participant's skin affected areas are collected to document clinical condition during the clinical trial, i.e. before and during the treatment. Photo images will be mandatory at selected sites who will also be collecting skin biopsies and US images for lesion evaluation. All trial participants in the selected sites must accept photoimaging. For all other sites, photoimaging will be optional. An informed consent on photoimaging and related signature must be obtained from the concerned trial participants. Trial participants accepting the photoimaging to be taken must sign an informed consent.

Trial participants who consent will have photographs taken at the designated study visits listed in the Flowchart.

The skin photo images will be obtained using a standardised software and supplied to the trial site by a digital imaging vendor. The photographs taken using this software are automatically

uploaded to the vendor's central secured server using an encrypted data transfer and anonymous subject allocation. Training and detailed instructions will be provided by the imaging vendor.

5.7 APPROPRIATENESS OF MEASUREMENTS

All methods used in this trial are standard methods.

6. INVESTIGATIONAL PLAN

The trial will be conducted worldwide as multinational trial at multiple sites experienced in the management of dermatologic diseases, including dermatological conditions such as HS.

The regions and clinical sites will be selected based on the availability of patients with HS and their experience in conduct of clinical trials and use of the clinical assessments.

Part 2 investigational plan will be detailed in an amendment based on Part 1 safety and efficacy available data at the time of Part 1 primary analysis. The following text of this section applies to Part 1 of the study described in this protocol.

All trial participants are to adhere to the visit schedule as specified in the Flowchart. Each visit date (With its window) up to EoT is to be counted from Visit 2 [redacted] at Day 1 (first trial drug administration day). If any of these visits have to be rescheduled, the date of subsequent visit should be calculated from Day 1.

For trial participants not rolling over to LTE trial, FUP refers to Follow-up visit which will be scheduled [redacted] after last study drug administration. EoT refers to the End of Treatment visit at [redacted] (or earlier if a trial participant terminates study drug before [redacted]

EoS refers to End of Study visit which will be scheduled [redacted] after last study drug administration (after REP period). It is considered to be the safety follow-up and it should happen 112 days after the last drug administration or 98 days after the EoT visit.

For trial participants rolling over to LTE trial, EoT and EoS dates will be the same. These patients will not undergo the safety follow-up period because they will be followed in the LTE trial. For these trial participants EoT visit of this trial and first visit of the LTE trial should occur the same day.

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

In the event of force majeure or other disruptive circumstances (e.g., pandemic, war) the execution of the investigational plan as per this clinical trial protocol may not be feasible. With the consent of the participant, the sponsor and investigator may agree on alternative, back-up or rescue methodology which may include virtual trial participant visits and assessments, home healthcare nurse visits, or bio-sample pick up from the participant's home. The implementation of these measures will depend on participant's consent, operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

Reported Outcomes (PROs) assessments:
Patient Reported outcomes should be completed by the trial participants on their own at site, or on their own at home (only applicable when paper versions are used). During the completion of the PROs, the participants should be in a quiet area/room and, as much as possible, with limited interaction (only checking comfort of participants) with the investigator

or other members of the study team. Questionnaires could be filled within 24 hours prior to scheduled visit for the PRO assessment. There is no specific order for the PROs completion. PROs are listed in Section 2.2. as secondary/further endpoints. Electronic or paper version of PROs and diaries will be implemented based on availability, feasibility, translations, etc.

6.1 VISIT SCHEDULE

Study procedures to be performed at each visit are listed in the Flowchart and the respective protocol sections. Please, refer to Section 5 and Appendix 10 for explanations of procedures.

Visits may take place as site visits. However, Visits 7, 9, 15, 20, 22, 24, 26, 28, and 30 could be performed as home visits if acceptable according to local laws and regulations, see Flowchart as reference for procedures to be held during home visits. The type of visit, on-site visit or trial participant's home visit, will be documented in the clinical history and it will be reflected in the eCRFs. The trial procedures conducted/collected during an on-site visit are equivalent to trial procedures conducted at trial participant's home visit. Oversight on the type of visits will be ensured during CQM.

Site staff will agree with the trial participant how they would like to be reminded in advanced about their visits, i.e. phone call prior the scheduled visit or through another procedure agreed with the trial participant.

In those visits requiring safety labs and urine pregnancy test procedures, they should take place prior to the study drug administration. Pre-dose PK/ADA samples will be obtained approximately within 2 hours prior to [redacted] administration.

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

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

1. C-SSRS
2. PROs
3. Patient diaries (all diaries to be handled/completed by 1st day of the visit)
4. AE and concomitant therapy collection; smoking/tobacco/nicotine status
5. Physical examinations (including pre-dose vital signs)
6. ECG
7. Draining fistula count
8. Abscess and inflammatory nodule count
9. HiSCR, IHS4, HS-PGA, and HASI assessment
10. Photographs of skin lesions
11. US lesion evaluation (if applicable. See Section 5.4.3)
12. Skin biopsies (done guided by US)
13. Blood and urine sampling, urine pregnancy testing (if applicable), PK, ADA/NAb, and biomarkers.
14. Assign (IRT)/Administer study drug
15. Local tolerability
16. Post-dose vital signs

In exceptional cases, if standard visits at the trial site 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 trial participants 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.

All deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

In the event of force majeure or other disrupting circumstances remote visits may have to be performed as follows: by video call or phone, whatever is available and feasible for each trial participant. Video call is the preferred option as C-SSRS interview benefits from body language and eye contact information that can be missed by phone.

If a participant is not able or willing to come to the site for a trial visit, remote visits (by video call or phone) should be performed instead. The following assessment can be done remotely:

- Collection of adverse events from last visit
- Any change in concomitant therapies from last visit
- C-SSRS

NRS for pain and pruritus, DLQI, HiS-QoL, FACIT-Fatigue scale, Patient Global Impression of Change (PGI-C), Patient Global Impression of Severity (PGI-S), HADS, HODS. – Those questionnaires will be available in paper or electronic format. These questionnaires should be answered by the participant. Participants will be supplied with the questionnaires to be filled out at home. The questionnaires should be answered on the day of the remote visit or within the visit window range and sent back to the site thereafter.

Home Healthcare Nurse

Only for visits where a Home Healthcare Nurse is an option, the following assessments can be done at the participant's home, when applicable according to the Flowchart:

- C-SSRS
- Physical examination
- Vital signs
- Administration of study medication
- NRS Pain and NRS pruritus: Review completed Patient's Diary in case paper version is used. Or oral check completed when electronic version is used
- Review paper HS pain medication diary
- AEs collection
- Concomitant therapy review

And remind the trial participant about the date for the next study visit.

The study medication will be sent from site to the patient's home by courier. The nurse performing the home visit should check that the medication is fit for use. After the visit is completed, the nurse should send to site the documentation from the visit. The used and unused medication will be returned to site by the courier vendor (within 72 hours after the visit) for accountability purposes and destruction.

Safety lab, as per Flowchart

If blood sampling for central lab at the trial site is not possible, in exceptional cases (e.g., due to COVID-19 pandemic, travel restrictions, central lab kit stock out issues, etc.), the safety lab analyses can be performed at a local lab until central lab testing becomes available. The results of the local lab tests must be transferred to the investigator to ensure medical review and proper documentation of the lab results with clinical relevance for safety on the clinical records and in the eCRFs as AEs.

Under these exceptional circumstances, standard collection of lab values, must be included in eCRFs by site staff as accreditation/reference ranges are required.

6.2.1 Screening period

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

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

Screening (Visit 1) should normally take place no more than 28 days before Visit 2. Visit 1 procedures may be completed over multiple physical visits, if needed. The time window for Visit 1 may be extended at the discretion of the CT Manager in conjunction with the CT Leader on a case by case basis.
For the comprehensive list of the trial procedures required at the Screening Visit (Visit 1) please refer to Flowchart. Trial participants who have a laboratory test value that makes their participation uncertain may have the test repeated to determine eligibility; however, the result must be available prior to Visit 2 (Day 1). Baseline conditions and medical history will be assessed during screening.

During the screening visit, the following demographics information will be collected:

- Age on the day of informed consent (in years)
- Sex (male, female in order to describe the trial participant`s sex at birth)
- Gender identity (male, female, non-binary, not answered, or other in order to describe how the trial participant self-identifies, regardless of their genotypic or phenotypic

sex) if 1) locally accepted (i.e. based on HA/EC/IRB acceptance, independent of acceptance by investigators or participants), 2) investigators are willing to ask, and 3) participants are willing to reply
- For women of childbearing potential, yes/no in order to characterise the patient population and as a basis for contraception requirements
- Ethnicity and race in order to sufficiently characterise the patient population, to support possible subgroup analyses

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

Infection screening
Infection testing will include tuberculosis, hepatitis B, hepatitis C, and HIV assessments (see Section 3.3.3 and Table 5.2.3: 2).

Medical History
Medical history of HS, including the previous treatment, will be collected and reported in the eCRF.

Information on clinically significant previous and concomitant illnesses, other than HS, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the screening visits will be recorded as medical and surgical history at screening on the Baseline Condition page in the eCRF.

Fitzpatrick skin type
Assessment on the type of skin should be done using the Fitzpatrick skin type scale, see Appendix 10.22 for reference.

Patients who fail screening (i.e. does not meet the eligibility criteria) following Visit 1 assessments should be registered as a screen failure in [redacted]

Re-Screening
Re-screening of a previously screen failed patient will be permitted only once in a case by case basis in agreement with the Sponsor. Details of [redacted] procedures can be found in the [redacted] manual located in the Investigator Site File (ISF).

For the comprehensive list of the trial procedures required at the Screening Visit (Visit 1) please refer to the Flowchart.

Re-screened patients will need to sign a new informed consent before any re-screening procedures and will be given a new unique trial participant number. Trial participant numbers from screen-failed participants cannot be re-used. If a patient is re-screened and there are valid screening determinations from his/her previous participation in the trial, like for

example safety labs, performed within 28 days prior to baseline (visit 2), these do not need to be repeated.

6.2.2 Treatment period

When eligibility of the patient to participate in the trial is confirmed, randomisation via [redacted] will be performed at Visit 2. The administration of treatment is from Visit 2 [redacted] to Visit 31 [redacted]. The final assessment of treatment effect will be on [redacted] (EoT visit). Procedures described in the Flowchart for each visit should be performed.

Baseline (Visit 2) and following site visits can be done in two consecutive days, or within the corresponding time window for visits (±1 or ±3 day) range, if needed. If this is the case, then it is important to keep certain procedures together. This is the proposal the site should follow in relation to the procedures listed in Section 6.1:

Day 1:
1. C-SSRS
2. PROs
3. Patient Diaries (to review from last visit and hand out new diaries to be completed)
4. AE and concomitant therapy collection; smoking/tobacco/nicotine status
5. Abscess and inflammatory nodule count
6. Draining fistula count
7. HiSCR, IHS4, HS-PGA, and HASI assessment
8. Photographs of skin lesions
9. US lesion evaluation (if applicable. See Section 5.4.3)
10. Skin biopsies (done guided by US)

Day 2:
3. AE
4. Physical examinations (including pre-dose vital signs)
5. ECG
12. Blood and urine sampling, urine pregnancy testing (if applicable), PK, ADA/NAb, and biomarkers.
13. Assign [redacted]/Administer study drug
14. Local tolerability
15. Post-dose vital signs

For the CRFs, the visit date should be the first date of that visit procedures.

[redacted]
During the [redacted] of the treatment period, the [redacted] are administered at [redacted] visits (Visit 2 to Visit 5) with [redacted] of spesolimab or matching placebo. Please see the Flowchart, Section 3.1 and Section 4.1.4 for further details.

[redacted] Period
From Visit 6 to Visit 31, [redacted] are administered [redacted] will be used at each visit. Please see the Flowchart, Section 3.1 and Section 4.1.4 for further details.

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

6.2.3 Follow-up period and trial completion

Treatment completion
Treatment completion is defined as a trial participant having completed treatments till planned EoT visit [redacted]. A trial participant is considered to have completed the trial in case any of the following applies:

- Completion of planned follow-up period (= End-of-trial Visit completed)
- Lost to follow-up
- Refusal to be followed-up
- Death

For all randomized patients, termination of trial medication (EoT) and trial completion (EoS) must be recorded on the corresponding CRFs. For trial participants completing the randomized trial treatment regularly at [redacted] (EoT) and not rolling-over to the LTE trial, safety follow-up visits will be performed at Follow-up visit (EoS visit).

All trial participants not entering the LTE trial are expected to complete EoT visit, and EoS visit [redacted] after their last trial drug intake (Visit 31) or [redacted] after EoT visit.

Trial participants who roll over to the LTE trial will complete their participation in the trial at [redacted] (EoT visit). However, if for whatever reason these patients rolling over to the LTE trial have not been randomized after [redacted] from the EoT, safety follow-up visit will be performed [redacted] after their last trial drug intake. During this period AEs and AESI should be collected, see Section 5.2.6.2.1.

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 returned to a medically acceptable level.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The trial consists of two parts, Part 1 (Phase IIb) and Part 2 (Phase III) which, for the purpose of statistical analyses, are considered independent.

7.1 NULL AND ALTERNATIVE HYPOTHESES

Part 1 (Phase IIb)

Statistical hypotheses to be tested for the primary endpoint are:

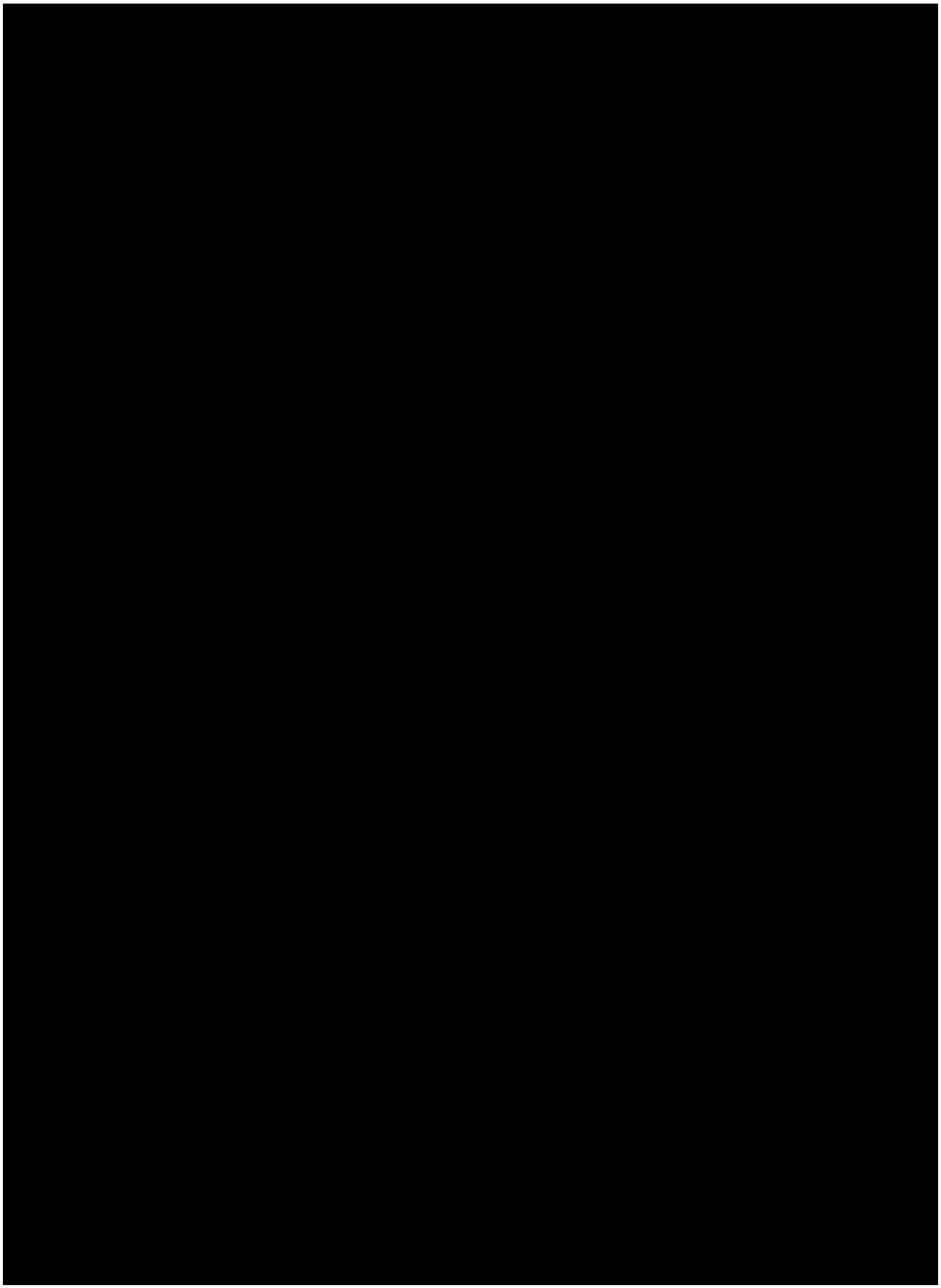
The null hypothesis is that there is a flat dose response curve comparing the placebo and the spesolimab dose groups on the primary endpoint of percent change from baseline in dT count at [redacted] The alternative hypothesis is that there is a non-flat dose response curve indicating a benefit of spesolimab over placebo. These hypotheses testing are non-confirmatory.

[redacted]

All secondary endpoints of Phase IIb (Part 1) will be evaluated in an exploratory manner; no adjustment for multiple testing is needed.

Part 2 (Phase III)

[redacted]



[redacted]

7.2 PLANNED ANALYSES

7.2.1 General considerations

All statistical analysis sets are defined by study part (Part 1 (Phase IIb), Part 2 (Phase III)). Analysis sets of two study parts will always be independent.

For each study part the following analysis sets will be defined for statistical analyses:

Entered Set (ES): This trial participant set includes all trial participants who signed informed consent. The ES will be used for the analyses of trial participant disposition.

Randomised Set (RS): This trial participant set includes all randomized trial participants.

Full analysis set (FAS): This trial participant set includes all trial participants who are randomised and received at least one dose of study drug. The FAS is the main analysis set for Part 1/2 (Phase IIb/III) ~~safety and~~ efficacy analyses. Patients will be analyzed according to their planned treatment group.

Safety Analysis Set (SAF): This subject set includes all subjects who were randomized and received at least one dose of study drug. This is the main analysis set for safety. Subjects will be analyzed according to the actual treatment received.

Further analysis sets will be defined in the TSAP, if needed.

Data from trial participants who are screened but not randomized will be listed but not included in any summary statistics or inferential statistics.

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

7.2.2 Handling of intercurrent events

Part 1 (Phase IIb)

The expected intercurrent events of interest in this trial are:

- Use of rescue therapy
- Treatment discontinuation without restricted medication

- Treatment discontinuation with restricted medication

The strategies for handling intercurrent events in this trial are as follows:

Primary strategies for primary and secondary endpoints:

All intercurrent events will be handled using the treatment policy approach as defined in ICH E9(R1). Use of "treatment policy" approach disregards the intercurrent event and uses the value of the variable regardless of the occurrence of the intercurrent event.

No deaths are expected in this trial. In the unlikely event of death occurring, it will be handled using a hypothetical approach as defined in ICH E9(R1). Use of the "hypothetical approach" considers the effect of what would have happened if the intercurrent event did not occur.

Table 7.2.2: 1 Primary strategies for handling of intercurrent events as per ICH E9(R1): Part 1

Intercurrent event	**Primary strategy for primary endpoint**	**Primary strategy for secondary endpoints**
Use of rescue therapy	Treatment policy	Treatment policy
Treatment discontinuation without restricted medication	Treatment policy	Treatment policy
Treatment discontinuation with restricted medication	Treatment policy	Treatment policy
Death	Hypothetical	Hypothetical

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy.

Any intercurrent events that are not listed will be decided by blinded review based on the general principle outlined, and corresponding strategies will be documented in the TSAP.

Part 2 (Phase III)

The expected intercurrent events of interest in this trial are:

- Use of rescue therapy
- Treatment discontinuation without restricted medication
- Treatment discontinuation with restricted medication

The strategies for handling intercurrent events in this trial are as follows:

Primary strategies for primary and key secondary endpoints:

All intercurrent events will be handled using the treatment policy approach as defined in ICH E9(R1). Use of "treatment policy" approach disregards the intercurrent event and uses the value of the variable regardless of the occurrence of the intercurrent event.

No deaths are expected in this trial. In the unlikely event of death occurring, it will be handled using a hypothetical approach as defined in ICH E9(R1) for continuous endpoints, and a mixture of hypothetical and composite strategy as defined in ICH E9(R1) for binary endpoints. Use of the "hypothetical approach" considers the effect of what would have happened if the intercurrent event did not occur. Use of the 'composite approach' considers that a poor outcome will be expected.

Table 7.2.2: 2 Primary strategies for handling of intercurrent events as per ICH E9(R1): Part 2

Intercurrent event	**Primary strategy for primary endpoint**	**Primary strategy for key secondary endpoints**	
		Continuous	Binary
Use of rescue therapy	Treatment policy	Treatment policy	Treatment policy
Treatment discontinuation without restricted medication	Treatment policy	Treatment policy	Treatment policy
Treatment discontinuation with restricted medication	Treatment policy	Treatment policy	Treatment policy
Death	Hypothetical	Hypothetical	Hypothetical/ Composite

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand for each main analysis in this protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy.

Any intercurrent events that are not listed will be decided by blinded review based on the general principle outlined, and corresponding strategies will be documented in the TSAP.

7.2.3 Primary objective analyses

Part 1 (Phase IIb)

The primary endpoint for Phase IIb is percent change from baseline in dT count at [redacted]

The primary analysis consists of a [redacted] of quantitative treatment benefit.

[redacted] is used to evaluate several possible dose response models (patterns), and to identify the best-fitting model or subset of models.

To account for the repeated nature of the data and the covariates in the model, [redacted] will be carried out in SAS and covariate adjusted fixed effect estimates of average

response for each dose group and the covariance matrix will be extracted from the fit and used for [redacted]

Percent change from baseline in dT count will be used as the response variable in the [redacted] The [redacted] will include fixed categorical effects of treatment at each visit, [redacted] status at baseline, and categorical baseline dT count at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-trial participant measurements.

The placebo effect in percent change from baseline in dT count at [redacted] is assumed to be -10%, and the maximum effect in percent change from baseline in dT count at [redacted] within the investigated dose range relative to placebo is assumed to be -30%. The following model assumptions and resulting graphs (Figure 7.2.3: 1) have been selected for [redacted] to cover both plausible and a diverse range of dose response patterns. Planned total dose before [redacted] will be used to evaluate dose response curve.

- Linear
- Exponential: [redacted]
- Emax: [redacted]
- SigEmax: [redacted]
- BetaMod: [redacted]

The optimal contrasts corresponding to the candidate models will be shown in the TSAP. For the final evaluation these contrasts will be updated using the estimated means for each dose group and the estimated variance-covariance matrix extracted from the primary analysis model.

A non-flat dose response is established if at least one dose response pattern is statistically significant, rejecting the null hypothesis of a flat dose response relationship over percent change from baseline in dT count at [redacted] jointly for each of the candidate dose response models with a contrast test controlled for the family-wise type I error rate at 1-sided α of 0.05.

If non-flat dose-response is established, the statistically significant (best fitting) model(s) from the above candidate set are refitted to the data to generate new estimates for all model parameters. If more than one model is significant, the weighted average model will be evaluated to identify the [redacted] for Part 2 [redacted]. The target dose(s) can be estimated from each significant model by accounting for safety. Doses within the dose range investigated will be considered.

In addition to the results from [redacted], a beneficial treatment effect relative to placebo will be evaluated.

Baseline is defined as the last available data collected at Visit 2 prior to administration of first dose of study medication, or last available screening data if Visit 2 data are missing.

The primary analysis will be performed using the TS, as defined in Section 7.2.1. All available data from the TS in each active treatment arm and the placebo arm up to Week 8 will be used. Trial participants will be analysed according to the stratum to which they belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomisation and is therefore consistent with regulatory guidance.

In the primary analysis intercurrent events are handled with treatment policy approach, except for death (unexpected), see Section 7.2.2.

Part 2 (Phase III)

The primary endpoint for Phase III part is percent change from baseline in dT count at [redacted]

Restricted maximum likelihood estimation based on a mixed-effect model for repeated measures analysis will be used to obtain adjusted means for the treatment effects. This model will include categorical fixed effects for treatment at each visit, [redacted] status at baseline, and categorical baseline dT count at each visit. The primary treatment comparisons will be the contrast between treatment at [redacted]

Significance tests will be based on adjusted treatment differences using a one-sided α of 0.025. The primary treatment comparison will be the contrast of percent change from baseline in dT count at [redacted] between treatments.

Full details will be specified in the TSAP.

Baseline is defined as the last available data collected prior to administration of first dose of study medication.

The primary analysis will be performed using the TS, as defined in Section 7.2.1. All available data from the TS in the active treatment arm and the placebo arm up to [redacted] will be used. Trial participants will be analysed according to the stratum to which they belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomisation and is therefore consistent with regulatory guidance.

In the primary analysis intercurrent events are handled with treatment policy approach, except for death (unexpected), see Section 7.2.2.

7.2.3.1 Sensitivity analyses

For each study part

Sensitivity analyses based on different missing data imputation scheme will be specified in the TSAP.

Further details will be specified in the TSAP.

7.2.3.2 Subgroup analyses

[redacted] A complete list of subgroup analyses will be specified in the TSAP.

7.2.3.3 Supplementary analyses

A complete list of supplementary analyses will be specified in the TSAP.

7.2.4 Secondary objective analyses

All secondary endpoints are specified in Section 2.1.3.

Part 1 (Phase IIb)

Secondary endpoints

Continuous endpoints will be analysed using a [redacted] effect of baseline of outcome measures at each visit. Visit will be treated as repeated measure with an unstructured covariance matrix for the within trial participant variability and all visits with planned measurements of the outcome variable as well as all dose groups (placebo, low dose, medium dose and high dose) will be included in the model. The TSAP will specify approaches to be taken to resolve possible non-convergence issues, including if necessary the selection of a simpler covariance structure.

[redacted] will also be used for selected secondary endpoints to evaluate the treatment effect of multiple dose regimens of spesolimab vs. placebo, if needed.

Any p-values presented for secondary endpoints will be considered nominal in nature and no adjustment for multiplicity will be made.

All secondary endpoints will be summarized descriptively.

Same as for the primary endpoint, the primary analysis of secondary endpoints will be performed on the TS using a treatment policy approach for handling the intercurrent events except for death (unexpected), see Section 7.2.2.

Part 2 (Phase III)

[redacted]

[redacted]

7.2.5 Further objective analyses

All further endpoints are specified in Section 2.2.2 and will be considered exploratory in nature.

Part 1 (Phase IIb)

Continuous further endpoints will be analysed using [redacted] Time to event further endpoints will be analysed using Kaplan-Meier plot or by Cox regression model if needed. Binary further endpoints will be summarized descriptively via frequency tables or by logistic regression model if needed. Count further endpoints will be summarized descriptively or by negative binomial model if needed.

Further details will be specified in the TSAP if needed.

The PK concentration or parameters will be summarized descriptively.

Part 2 (Phase III)

[redacted]

Further details will be specified in the TSAP if needed.

The PK concentration or parameters will be summarized descriptively.

7.2.6 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, a period of 16 weeks after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

The safety analysis will be performed by treatment at onset.

Safety analyses will be based on the TS. 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 treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’. Adverse events will be summarized by treatment at onset, and the treatment at onset of AE for the drug-related AE.

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

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 summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of trial participants with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared with findings before start of treatment.

Further details will be specified in the TSAP.

7.2.7 Other analyses

Immunogenicity

Details on immunogenicity data analyses will be specified in the TSAP.

Biomarker analyses

Biomarker results may or may not be reported in the CTR. In case they are reported outside the CTR, the biomarker analysis plan will be defined in a separate document (otherwise the biomarker analysis plan will be described in the TSAP).

7.2.8 Interim analyses

The primary analysis for Part 1 will be conducted after the last trial participant completes the [redacted] visit. A respective team ("shadow team") independent of the main trial team will be formed to conduct the necessary analyses and ensure to maintain the blind and restrict access to the randomisation codes from the main trial team. Details of this process will be described in a separate logistics plan which will also specify details on data access. The trial team members, trial participants, and investigators will remain blinded until the end of Part 1. The sponsor will make a decision for proceeding into Part 2 (Phase III). This recommendation will include the selection of appropriate dose(s) for Part 2 and may also include modification to inclusion/exclusion criteria, sample size and endpoints. The sponsor intends to seek health authority feedback on the cumulative data available after Part 1 [redacted] and the resulting proposed final design for Phase III to assess the benefit/risk of spesolimab in HS.

The [redacted] for Part 1 will be conducted after the last trial participant completes the [redacted] visit and the efficacy effect size will be evaluated. Trial participants and investigators will remain blinded until the end of this study part.

No adjustment of the family-wise Type I error for Part 2 is needed after Part 1 (Phase IIb), as the analysis sets of Part 1 (Phase IIb) and Part 2 (Phase III) are independent.

7.3 HANDLING OF MISSING DATA

Part 1 (Phase IIb)

Efficacy endpoints

In the primary analysis of primary and secondary endpoints, missing data will not be imputed except for death (unexpected), where a poor outcome will be assigned. The mixed effect model will handle missing data based on a likelihood method under the 'missing at random assumption'. Sensitivity analyses for handling missing primary and secondary endpoints data will be specified in the TSAP.

Full details on the handling of missing data will be specified in the TSAP prior to unblinding.

Safety endpoints

Missing or incomplete AE dates will be imputed according to BI standards. Other missing safety data will not be imputed.

PK endpoints

Handling of missing PK data will be performed according to the relevant Corporate Procedure (001-MCS-30-476). PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

Part 2 (Phase III)

Efficacy endpoints

In the primary analysis of primary and continuous key secondary endpoints, missing data will not be imputed except for death (unexpected), where a poor outcome will be assigned. The mixed effect model will handle missing data based on a likelihood method under the 'missing at random assumption'.

Sensitivity analyses for handling missing primary and continuous key secondary endpoints data will be specified in the TSAP.

In the primary analysis of binary key secondary endpoints, a No Response Imputation (NRI) approach will be applied to the missing visits up to [redacted] that is, imputing as a failure to achieve a response in the visits with missing endpoint score, however:

- If there are available data at the visits both before and after the visit with a missing outcome, then impute as a success only if both the preceding and the following measurement indicate success.
- Otherwise, impute as a failure to achieve a response (i.e. no response imputation)

NRI is a conservative imputation scheme because it assumes that missing data due to any reason is related to treatment failure.

Sensitivity analyses for handling missing binary key secondary endpoints data will be specified in the TSAP.

Full details on the handling of missing data will be specified in the TSAP prior to unblinding.

Safety endpoints

Missing or incomplete AE dates will be imputed according to BI standards. Other missing safety data will not be imputed.

PK endpoints

Handling of missing PK data will be performed according to the relevant Corporate Procedure (001-MCS-30-476). PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.4 RANDOMISATION

Part 1 (Phase IIb)

Stratification for Japan versus rest of the world (ROW) will be performed in order to assure that sufficient trial participants per treatment group are recruited specifically to support individual country submission to HAs in Japan; these strata will be treated as operational strata and will not be included into the analyses of efficacy endpoints.

Separate randomisation lists will be prepared for Japan and ROW. In ROW randomisation list, the randomisation will be stratified by [redacted] at baseline [redacted] and baseline [redacted] Stratification will be done by the IRT system. Eligible trial participants from ROW will be parallel randomized in blocks to double-blind treatment, and will be randomized to spesolimab high dose, spesolimab medium dose, spesolimab low dose or placebo in a 1:1:1:1 ratio. In Japan randomisation list, the randomisation will not be stratified within the [redacted] system. Eligible trial participants from Japan will be parallel randomized in blocks to double-blind treatment, and will be randomized to spesolimab high dose, spesolimab medium dose, spesolimab low dose and placebo in a 1:1:1:1 ratio.

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size for each randomisation list (ROW/Japan) will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

Part 2 (Phase III)

The randomisation will be stratified by [redacted] at baseline [redacted] and baseline [redacted] Stratification will be done by the [redacted] system. Eligible trial participants will be parallel randomized in blocks to double-blind treatment and will be randomized to spesolimab at selected dose regimen or placebo in a 1:1 ratio.

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

Part 1 (Phase IIb)

The probability of success of this trial is defined as the probability to obtain a significant test for non-flat dose-response curve for primary endpoint.

The sample size calculation in this part is based on an assumed standard deviation of 50% for the primary endpoint, as well as on the pre-specified models listed in Section 7.2.3. The maximum effect in percent change from baseline in dT count at [redacted] within dose range relative to placebo is assumed to be [redacted]. The mean percent change from baseline in dT count at [redacted] is assumed to be [redacted] for placebo. These estimates are derived from [redacted]

The following power has been evaluated for the candidate set of possible dose response patterns based on current expectation (Table 7.5: 1).

[redacted]

Calculations were performed using R version 4.0.5.

Part 2 (Phase III)

Results from the [redacted] No data on the treatment effect of spesolimab beyond [redacted] is available. Assuming the treatment effect of spesolimab on HS could be maintained at least up to [redacted] the mean percent change from baseline [redacted] for spesolimab at selected dose regimen.

For sample size calculation for the primary endpoint in Part 2, a common standard deviation (SD) of 50% for percent change from baseline in [redacted] is assumed for both spesolimab at selected dose regimen and placebo groups. The [redacted]

[redacted] considering one-sided alpha of 2.5%.

Sample size may be reassessed based on efficacy effect size from [redacted]

Calculations were performed using R version 4.0.5.

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 Harmonised Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC, the EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997), 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 will be treated as “protocol deviation”.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the treating physician of the trial participant.

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to participation in the trial, written informed consent must be obtained from each participant (or the participant’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 form, and any additional participant-information form retained by the investigator as part of the trial records. A signed copy of the informed consent (main, specific for optional procedures, biogenetics) and any additional participant information must be given to each participant or the participant’s legally accepted representative.

The investigator or delegate must give a full explanation to trial participants based on the participant information form. A language understandable to the trial participant should be chosen, technical terms and expressions avoided, if possible.

The trial participant must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the trial participant’s own free will with

the informed consent form after confirming that the trial participant understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial participant 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 regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual trial participants will be provided by the sponsor. See Section 4.1.4.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial participant. 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 participant 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 trial participant, documented in their medical records, would be acceptable.
Copies of source data necessary for imaging biomarkers (i.e. US) will be sent to an external supplier for a centralised reading. For further details, please refer to the ISF and/or imaging manual. Before sending or uploading those copies, the investigator must ensure that all participant identifiers (e.g. participant's name, initials, address, phone number, social security

number) have properly been removed or redacted from any copy of the participants' source documents.

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

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

- Participant signed informed consent
- Participant identification: sex, year of birth (in accordance with local laws and regulations)
- Participant participation in the trial (substance, trial number, participant number, date participant was informed)
- Dates of participant's visits, including dispensing and administration of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date [mandatory], and end date [if available])
- Serious adverse events (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Patient reported outcome forms (including diary) and corresponding investigator assessment form completed on paper
- ECG results (original or copies of printouts) trace and assessment of normal or abnormal
- Completion of participant's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a trial participant 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 participant or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the participant eligible for the clinical trial

In addition to paper forms, Patient Reported Outcome forms and dairy can be completed on an e-device provided by an external vendor. During conduct of the trial, access to the data will be possible via the vendor portal. Data from e-PRO and Central lab will be directly uploaded into CDR system for downstream data analysis. After completion of the trial a copy of the collected data will be sent to the applicable sites for archiving.

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 always be available 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 or delegate will also monitor compliance with the protocol and GCP.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war; please see Section 6), site access may be restricted, thus limiting the ability to perform standard site monitoring activities on site such as on-site source data review and source data verification. Therefore, some of these activities may be performed remotely or replaced by centralised monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations.

8.3.3 Storage period of records

Trial sites:
The trial sites 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.

AE/AESI are processed in the global Safety Database and assessed for the company causal relationship as well as the expectedness of the event according to the reference safety information. Individual Case Safety Reports (ICSR) are subsequently reported according to local Regulations. Reporting to the EMA will be done via E2B transmission of ICSRs to the Eudravigilance CT Module.

8.5 STATEMENT OF CONFIDENTIALITY AND TRIAL PARTICIPANT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of trial participant data in accordance with the principles 7 and 12 of the WHO GCP handbook.
To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a participant identification number instead of the trial participant's name. The code is only available at the site and must not be forwarded to the sponsor. In case participant's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the trial participant will be redacted by the site prior to forwarding. Access to the participant files and clinical data is strictly limited: personalised treatment data may be given to the trial participant's personal physician or to other appropriate medical personnel responsible for the trial participant's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.
A potential data security breach will be assessed regarding the implications for rights and privacy of the affected persons. Immediate actions as well as corrective and preventive

actions will be implemented. Respective regulatory authorities, IRBs/IECs and trial participants will be informed as appropriate.

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

8.6 TRIAL MILESTONES

The **first act of recruitment** represents the **start of the trial** and is defined as the date when the first trial participant in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last trial participant in the whole trial ("Last Participant Completed").

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

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The initiation of the Phase III will be driven by the results of the Primary analysis at [redacted] and the interim analysis at [redacted] of the Phase IIb.
The IEC/competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all trial participants 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 trial participant (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

A DMC will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician.

The DMC will evaluate safety data, efficacy data as detailed in the DMC charter. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter. The relevant documents (minutes of DMC meetings, contracts etc.) will be stored in the TMF.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader 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 (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

In the participating countries, the trial will be performed by the respective local or regional BI-organisation (Operative Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.

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, a central images service, and an IRT vendor will be used in this trial. Details will be provided in the [redacted] Manual and Central Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 [redacted]

[redacted]

10.2 TRIAL [redacted]

[redacted]

Trial period	Treatment period
[redacted]	

10.3 HIDRADENITIS SUPPURATIVA CLINICAL RESPONSE (HISCR)

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

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

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

10.4 INTERNATIONAL HIDRADENITIS SUPPURATIVA SEVERITY SCORE SYSTEM (IHS4)

International Hidradenitis Suppurativa Severity Score System (IHS4). 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.

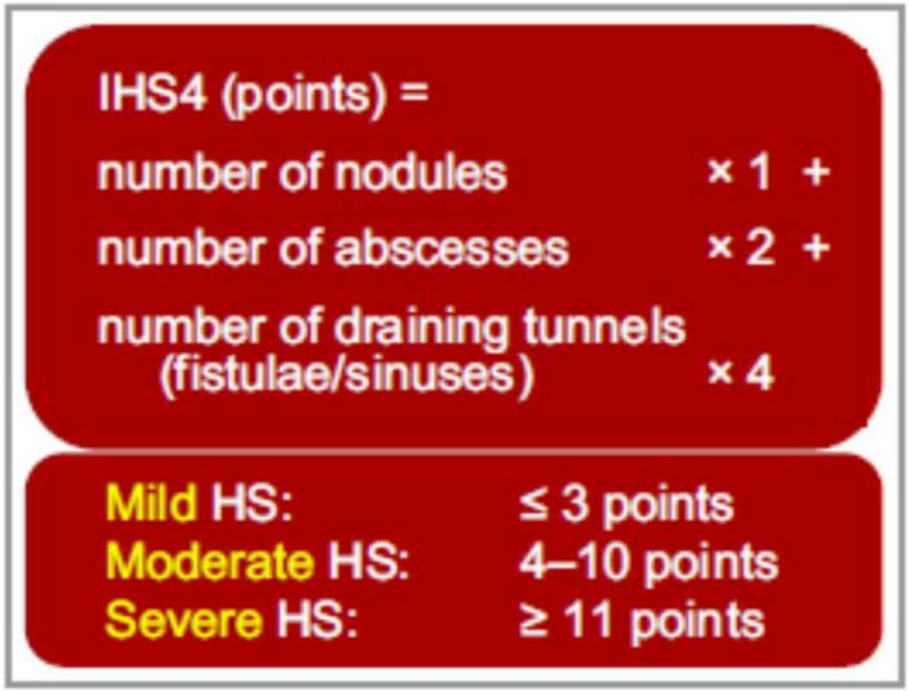
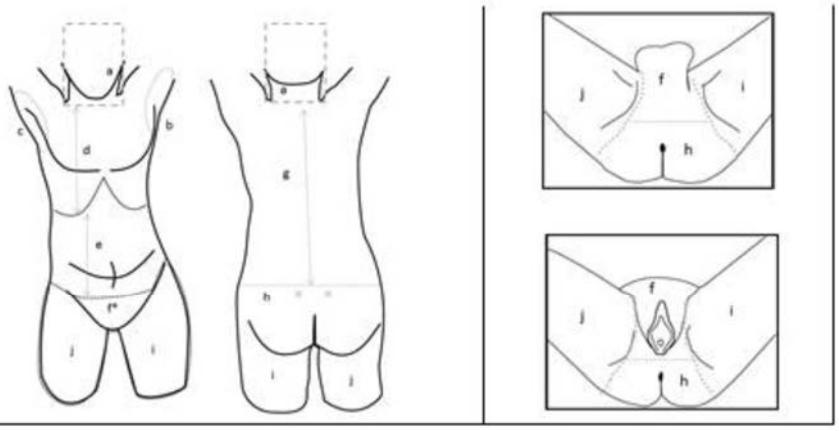


Fig. source: [R20-3045].

10.5 HIDRADENITIS SUPPURATIVA AREA AND SEVERITY INDEX (HASI)

Hidradenitis suppurativa Area and Severity Index (HASI)



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

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

10.6 HIDRADENITIS SUPPURATIVA PHYSICIAN GLOBAL ASSESSMENT (HS-PGA)

Hidradenitis Suppurativa – Physician's Global Assessment (HS-PGA). Score

Explanation	
Clear (score = 0)	No abscesses, no draining fistulae, no inflammatory nodules, and no noninflammatory nodules
Minimal (score = 1)	No abscesses, no draining fistulae, no inflammatory nodules but presence of noninflammatory nodules
Mild (score = 2)	No abscesses, no draining fistulae and 1–4 inflammatory nodules, or 1 abscess or draining fistula and no inflammatory nodules
Moderate (score = 3)	No abscesses, no draining fistulae and ≥5 inflammatory nodules, or 1 abscess or draining fistula and ≥1 inflammatory nodule, or 2–5 abscesses or draining fistulae and <10 inflammatory nodules
Severe (score = 4)	2–5 abscesses or draining fistulae and ≥10 inflammatory nodules
Very severe (score = 5)	>5 abscesses or draining fistulae

10.7 PAIN NUMERICAL RATING SCALE (NRS PAIN)

2. Pain

Please rate the severity of your hidradenitis suppurativa (HS) pain when it was at its worst in the previous 24 hours

On a scale of 0 to 10, with 0 being 'no pain' and 10 being the 'worst possible pain', how would you rate your Hidradenitis Suppurativa pain at its worst during the previous 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No pain										**Worst possible pain**

10.8 PRURITUS NUMERICAL RATING SCALE (NRS PRURITUS)

Pruritus (itch) NRS

On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the worst moment during the previous 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No itch										Worst itch imaginable

The NRS is comprised of one item and represents the numbers 0 ("no itch") to 10 ("worst imaginable itch"). Trial participants are asked to rate the intensity of their itch using this scale. It features high reliability and concurrent validity and is a popular choice for all patients due to its simple format.

Time needed for completion: 1 minute
It can be interpreted as follows: NRS= 0 - no pruritus
NRS <3 - mild pruritus
NRS > 3< 7 - moderate pruritus
NRS > 7< 9 - severe pruritus
NRS > 9 - very severe pruritus

10.9 DERMATOLOGY LIFE QUALITY INDEX (DLQI)

DERMATOLOGY LIFE QUALITY INDEX **DLQI**

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

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

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

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

Please check you have answered EVERY question. Thank you.

10.10 HIDRADENITIS SUPPURATIVA QUALITY OF LIFE (HIS-QOL)

HiSQOL: Hidradenitis Suppurativa Quality Of Life

This questionnaire is designed to measure the impact of

Hidradenitis Suppurativa (HS), also known as acne inversa, on you.

PLEASE READ THESE DIRECTIONS:

It is important to:

1. Think about your HS **over the past 7 days.**
2. Think about **your HS only**, not another condition.
3. For each item select the **single best option.**

Please select the single best option for each item

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

In the past 7 days, how has HS influenced:	Extremely	Very much	Moderately	Slightly	Not at all
7. What you wear to avoid discomfort					

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

Please select the single best option for each item

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

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

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

10.11 FACIT-FATIGUE

FACIT Fatigue Scale (Version 4)

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

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

10.12 PATIENT GLOBAL IMPRESSION OF CHANGE (PGI-C)

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

(Choose one box only)

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

10.13 PATIENT GLOBAL IMPRESSION OF SEVERITY (PGI-S)

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

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

10.14 HIDRADENITIS SUPPURATIVA ODOUR AND DRAINAGE SCALE (HODS)

Hidradenitis Suppurativa Odor and Drainage Scale - Drainage

Drainage Definition: Secretion, blood, stains.

	No drainage	Mild drainage*	Moderate drainage**	Severe drainage***	Very severe drainage****
1. In the past 7 days, what was the usual amount of drainage from your hidradenitis suppurativa?					
• Head and Neck	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
• Armpits	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
• Trunk	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
• groins	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
• Buttocks	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
• Genital Perianal area	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
• Other area	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
2. In the past 7 days, what was the worst amount of drainage from your hidradenitis suppurativa?	No drainage	Mild drainage*	Moderate drainage**	Severe drainage***	Very severe drainage****
• Head and Neck	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
• Armpits	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
• Trunk	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
• groins	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
• Buttocks	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
• Genital Perianal area	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
• Other area	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
In the past 7 days…	Never	Rarely	Sometimes	Often	Always
1. I felt embarrassed about my drainage…	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
2. The drainage interfered with my sex life…	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
3. How often did the drainage from your Hidradenitis Suppurativa lesions make you select specific clothing?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

*Drainage fully controlled, no dressing needed
**Drainage controlled, dressings may be required, wear time 2-3 days
***Drainage uncontrolled, dressings required, dressing may be overwhelmed in less than 1 day
****Drainage uncontrolled, dressings required, dressings need to be changed 3 or more times a day

Hidradenitis Suppurativa Odor and Drainage Scale (HODS) – Odor

Odor Definition: unpleasant smell, bad smell

	No odor at all	Slight odor	Moderate odor	Strong odor	Very strong odor
1. In the past 7 day, what was the typical odor that you perceived coming from your hidradenitis suppurativa affected areas?	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
	Never	Rarely	Sometimes	Often	Always
2. In the past 7 days, I felt embarrassed about my odor…	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐
3. In the past 7 days, my odor interfered with my sex life	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐

10.15 HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Hospital Anxiety and Depression Scale (HADS)

GL Assessment

Name: _____ Date: _____

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

FOLD HERE

A	D			A	D
		I feel tense or "wound up"	**I feel as if I am slowed down**		
3		Most of the time	Nearly all the time		3
2		A lot of the time	Very often		2
1		From time to time, occasionally	Sometimes		1
0		Never	Never		0
		I enjoy the things I used to enjoy	**I get a sort of anxious feeling like "butterflies" in the stomach**		
	0	Definitely	Never	0	
	1	Not quite so much	Occasionally	1	
	2	Only a little	Often	2	
	3	Hardly at all	Very often	3	
		I get a sort of frightened feeling as if something awful is about to happen	**I have lost interest in my appearance**		
3		Very definitely and fairly badly	Definitely		3
2		Yes, but not too badly	Often I don't take as much care as I should		2
1		Sometimes, but it doesn't worry me	Sometimes I don't take as much care as I should		1
0		Never	I take just as much care as ever		0
		I can laugh and see the funny side of things	**I feel restless as if I have to be on the move**		
	0	As much as I always could	Definitely	3	
	1	Not quite so much now	Quite a lot	2	
	2	Definitely not so much now	Not very much	1	
	3	Never	Never	0	
		Worrying thoughts go through my mind	**I look forward with enjoyment to things**		
3		A great deal of the time	As much as I ever have		0
2		A lot of the time	Somewhat less than I used to		1
1		Not too often	Much less than I used to		2
0		Almost never	Rarely		3
		I feel cheerful	**I get sudden feelings of panic**		
	3	Never	Very often	3	
	2	Not often	Often	2	
	1	Sometimes	Not very often	1	
	0	Most of the time	Never	0	
		I can sit at ease and feel relaxed	**I can enjoy a good book, radio or television program**		
0		Always	Often		0
1		Usually	Sometimes		1
2		Not often	Not often		2
3		Never	Very seldom		3

Please make sure you have answered all the questions.

	A	D
TOTAL		

HADS - United States/English - Version of 30 Jan 17 (updated 22 Feb 21) - Mapi.
ID058941 / HADS_AU5.0_eng-US.doc

10.16 WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE FOR HS (WPAI-HS)

Work Productivity and Activity Impairment Questionnaire: Hidradenitis Suppurativa, V2.0 (WPAI: Hidradenitis Suppurativa)

The following questions ask about the effect of your hidradenitis suppurativa on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your hidradenitis suppurativa? *Include hours you missed on sick days, times you went in late, left early, etc., because of hidradenitis suppurativa. Do not include time you missed to participate in this study.*

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your hidradenitis suppurativa affect your productivity while you were working?

   Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If hidradenitis suppurativa affected your work only a little, choose a low number. Choose a high number if hidradenitis suppurativa affected your work a great deal.

   Consider only how much hidradenitis suppurativa affected productivity while you were working.

Hidradenitis suppurativa had no effect on work	0 1 2 3 4 5 6 7 8 9 10	Hidradenitis suppurativa completely prevented me from working

   CIRCLE A NUMBER

6. During the past seven days, how much did your hidradenitis suppurativa affect your ability to do your regular daily activities, other than work at a job?

   By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If hidradenitis suppurativa affected your activities only a little, choose a low number. Choose a high number if hidradenitis suppurativa affected your activities a great deal.

   Consider only how much hidradenitis suppurativa affected your ability to do your regular daily activities, other than work at a job.

Hidradenitis suppurativa had no effect on my daily activities	0 1 2 3 4 5 6 7 8 9 10	Hidradenitis suppurativa completely prevented me from doing my daily activities

   CIRCLE A NUMBER

WPAI: Hidradenitis Suppurativa V2.0 (US English)

10.17 EUROQOL 5 DIMENSIONS 5-LEVEL (EQ-5D-5L)

Health Questionnaire

English version for the USA

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

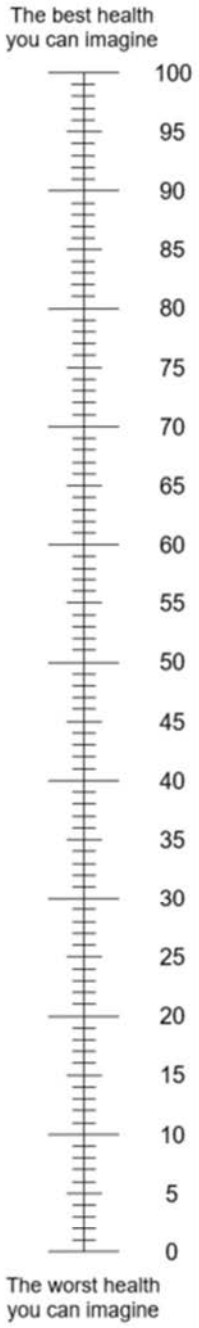
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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[redacted]

COLUMBiA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

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

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

5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes No** ☐ ☐	**Yes No** ☐ ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** ***Type # (1-5)*** _____ ***Description of Ideation*** Past 12 Months - ***Most Severe Ideation:*** ***Type # (1-5)*** _____ ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	_____	_____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	_____	_____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	_____	_____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	_____	_____

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

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

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? If yes, describe:		
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐	**Yes No** ☐ ☐

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

2 = Behavior likely to result in death despite available medical care			

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

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

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____

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

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

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

10.19 TRIAL PARTICIPANT FEEDBACK

Optional Trial Participant Feedback Questionnaires:
This trial will include an option for participants to complete anonymised questionnaires, 'Trial Participant Feedback Questionnaire', to provide feedback on their clinical trial experience. Individual participant level responses will not be reviewed by investigators. Responses will be used by the sponsor to understand where improvements can be made in the clinical trial process. These questionnaires will not collect data about the participant's disease, symptoms, treatment effect, or AEs and therefore will not be part of the trial data or clinical trial report. The questionnaires will be implemented after local regulatory approval, when applicable, and after consent of the trial participant. Providing feedback is optional and not required for participation in the trial.

10.20 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.

10.21 COVID-19 RISK ASSESSMENT

Table 10.21: 1 Overview of trial-related risks due to COVID-19

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product: BI 655130		
SARS-CoV-2 infection	Similar to other immune modulating biological treatments, spesolimab may potentially increase the risk of infections. However, the available pharmacological, non-clinical and clinical data do not indicate an increased risk of contracting SARS-CoV-2 or severe clinical courses due to the treatment with BI 655130. Furthermore, according to the Centers for Disease Control and Prevention there is limited information regarding risk factors for severe COVID-19 disease. However, 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. So , participants with moderate to severe Hidradenitis suppurativa may be at risk of a severe clinical course of COVID-19.	Even though the risks associated with BI 655130 treatment are considered low, 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 spesolimab clinical trial protocol (CTP), please refer to Section 1.4.2.1. Also, potential participants with active or recent SARS-CoV-2 infection will only be included upon full recovery (see Section 3.3.3). A suspected SARS-CoV-2 infection while in the trial will be confirmed with an immediate PCR or antigen test. If positive, the participant will follow the local quarantine rules and should be treated, as any other acute infection, with standard of care. Trial treatment may be continued based on the discretion of the investigator (see Section 3.3.4.1). Then, treatment may be resumed following recovery from SARS-CoV-2 infection if clinical benefit is expected.

Table 10.21: 1 Overview of trial-related risks due to COVID-19 (cont.)

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Trial procedures		
	Trial conduct and protocol-defined procedures are not expected to increase the risk of contracting SARS-CoV-2 or to aggravate the course of an infection.	
Other risks		
Risk of contracting SARS-CoV-2	Travelling to the site or being at the site for trial visits may potentially increase the risk of contracting SARS-CoV-2.	The number of site visits is limited to the minimum required for the successful conduct of the trial. Further protective measures (e.g. social distancing, wearing masks) are recommended to be taken. Measures are in place to ensure continued participant treatment, monitoring, and safety even if site visits are not possible (see Section 4.1 and Section 6.2).

10.22 FITZPATRICK SKIN TYPE SCALE

The Fitzpatrick skin type (or phototype) depends on the amount of melanin pigment in the skin. This is determined by constitutional colour (white, brown, or black skin) and the effect of exposure to ultraviolet radiation (tanning).

Fitzpatrick skin type		
Skin type	Typical features	Tanning ability
I	Pale white skin, blue/green eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

11. CONFIDENTIALITY STATEMENT DESCRIPTION OF GLOBAL AMENDMENT(S)

Date of amendment		02 Nov 2023
EudraCT number **EU CT number**		2022-501074-19-00
BI Trial number		1368-0098
BI Investigational Medicinal Product(s)		Spevigo®, spesolimab
Title of protocol		Randomised, double-blind, placebo-controlled, Phase IIb/Phase III study to evaluate the efficacy and safety of spesolimab in patients with moderate to severe hidradenitis suppurativa. Lunsayil 1.
Global Amendment due to urgent safety reasons		Add "x" ifapplicable
Global Amendment		X
Section to be changed		[redacted]

[redacted]

Date of amendment		02 Nov 2023
[redacted]		

Date of amendment		02 Nov 2023

[redacted]

Date of amendment		02 Nov 2023

[redacted]

Date of amendment		02 Nov 2023
[redacted]		

Date of amendment		02 Nov 2023

[redacted]

Date of amendment		02 Nov 2023
[redacted]		

Date of amendment		02 Nov 2023

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Date of amendment		02 Nov 2023

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APPROVAL / SIGNATURE PAGE

Document Number: c40061625 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-02

Title: Randomised, double-blind, placebo-controlled, Phase IIb/Phase III study to evaluate the efficacy and safety of spesolimab in patients with moderate to severe hidradenitis suppurativa. Lunsayil 1.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	03 Nov 2023 13:20 CET
Approval-Biostatistics		03 Nov 2023 14:42 CET
Approval-Clinical Program [redacted]		03 Nov 2023 16:22 CET
Verification-Paper Signature Completion		04 Nov 2023 14:58 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed