

Clinical Trial Protocol

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EU Clinical Trial No.	2023-508377-82-00	
UTN	U1111-1300-2310	
Boehringer Ingelheim Trial No.	1368-0130	
BI Investigational Medicinal Product(s)	Spesolimab	
Title	Lunsayil LTE: An extension trial assessing long-term spesolimab treatment in patients with Hidradenitis Suppurativa (HS)	
Lay Title	A study to test long-term treatment with spesolimab in people with a skin condition disease called hidradenitis suppurativa (HS) who took part in a previous study with spesolimab	
Clinical Phase	II/III	
Clinical Trial Leader	Phone: Fax:	
Coordinating Investigator	Phone: Fax:	
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Original Protocol Date	15 Nov 2023	Page 1 of 107
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date	15 Nov 2023
Boehringer Ingelheim trial number/ EU CT number/ Universal Trial Number	1368-0130 2023-508377-82-00 U1111-1300-2310
Title of trial	Lunsayil LTE: An extension trial assessing long-term spesolimab treatment in patients with Hidradenitis Suppurativa (HS)
Coordinating Investigator	██████████ ██████████ Phone: +██████████ Fax: +██████████
Trial site(s)	Multi-centre trial conducted in approximately 40 countries
Clinical phase	II/III
Trial rationale	Hidradenitis suppurativa (HS) is a debilitating inflammatory skin disease characterised by recurrent inflammatory nodules, painful abscesses and tunnels that may be draining a malodourous exudate. Lesions characteristically occur in the axillary, groin, infra-mammary, and/or anogenital regions of the body. Significant pain is associated with HS and lesion sequelae include scarring and psychological distress. The average age of onset is during the early 20s. The prevalence of HS is estimated to be 0.3% globally, ranging from 0.2% to 0.6%, with variability across geographic settings. Until recently, the TNF-alpha inhibitor adalimumab, was the only biologic therapy approved for the treatment of active moderate to severe HS. In adalimumab Phase III studies, a clinical response (HiSCR50) rate of 42%-59% versus placebo response of 26%-28% was achieved at Week 12. Secukinumab, an anti-IL17A mAb, was approved for HS in June 2023 in Europe. In secukinumab Phase III studies, HiSCR50 was achieved at a rate of 42%-45.0% at Week 16, versus a placebo response rate of 31%-34%. Long-term safety information is pertinent in the treatment of HS, where it is expected that only chronic treatment may control its inflammatory manifestations. In parallel, it is important to assess the sustained level of benefit/risk ratio of chronic treatment. Therefore, extending spesolimab Phase II and III studies will provide important safety and efficacy information beyond 1 year of treatment duration.

Benefit-risk assessment and ethical considerations	Spesolimab has shown good 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.
Trial objective(s)	The primary objective of this trial is to assess the long-term safety of spesolimab in participant s with HS who have completed approximately 8 to 12 months of spesolimab treatment in part 1 or part 2 of trial 1368-0098 and trial 1368-0100.
Trial endpoints	The primary endpoint is the occurrence of treatment emergent adverse events (TEAE) up to the end of maintenance treatment period including REP (i.e., 16 weeks after the last trial treatment).
Trial design	This 92-week, multi-regimen, Phase II/Phase III extension trial investigates the long-term safety of spesolimab in participant s with HS who have completed treatment in previous parent trials.
Total number of trial participants randomised	Approximately 550 participants from Part 1& Part 2 of trial 1368-0098 and trial 1368-0100 may enter this long-term extension trial.
Number of trial participants per treatment group	Participants in this trial will continue on the same dosing regimen that they were on the parent trials.
Diagnosis, main inclusion and exclusion criteria	Participants with HS who have completed the treatment with spesolimab in the parent HS trial. Inclusion criteria • Signed and dated written informed consent in accordance with ICH Harmonized Guideline for Good Clinical Practice (ICH-GCP) and local legislation prior to admission to the trial • Participants must be within the defined Residual Effect Period corresponding to 16 weeks since last spesolimab administration. • Participants who have completed treatment in the parent HS spesolimab trial (1368-0098 or 1368-0100) without premature discontinuation and are willing and able to continue treatment in this trial. • 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. Exclusion criteria • Women who are pregnant, nursing, or who plan to become pregnant while in the trial. • Use of any drug considered by the investigator likely to interfere with the safe conduct of the trial since the last visit of the parent trials. • Participants who require/ intend to use certain restricted medications such as immunomodulatory biologics or other investigational drugs/devices during the course of the trial.

	• Relevant chronic or acute infections including human immunodeficiency virus (HIV) and viral hepatitis. The corresponding laboratory tests will be performed at Visit 1. A participant can be re-screened if the participant was treated and is cured from the acute infection. • Severe, progressive, or uncontrolled condition such as renal, hepatic, haematological, endocrine (especially untreated diabetes mellitus), pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof. • Any new documented active or suspected malignancy except appropriately treated basal cell carcinoma, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix. • History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients. • Major surgery (major according to the investigator's assessment) planned during this extension trial (e.g. hip replacement, aneurysm removal, stomach ligation), as assessed by the investigator. • Any suicidal behaviour in the past 2 years (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour). • Presence of acute demyelinating polyneuropathy.
Trial intervention and test product(s)	Spesolimab
Dose and mode of administration	
Duration of treatment	76 weeks
Statistical methods	Given the objective of this trial and the nature of the trial, no hypothesis testing will be conducted. All statistical assessments will be performed in descriptive manner to understand safety and efficacy profiles of spesolimab better. Some analysis of selective efficacy assessments may be further performed in exploratory manner.

Clinical Trial Protocol

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	Screening	Treatment Period- Year 1																										
Visit	1 *	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
Weeks																												
Time window for visits (day)	-7	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
Visit type (S: Site visit/R: Remote visit)	S	S	S	S	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	R	S	
	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IHS4 ¹¹	X						X						X						X						X			
	X						X						X						X						X			
HASI	X						X						X						X						X			
	X																											
HS-IGA	X						X						X						X						X			
Pain NRS ^{12,17}		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
^{3,17}	X						X						X						X						X			
^{13,17}	X						X						X						X						X			
IXRS contact ¹⁴	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X	
Surgeries by type and number ¹⁹	X				X				X				X					X			X				X			
Hospitalization	X				X				X				X					X			X				X			
ICU/ER use (number of days, overnight stays)	X				X				X				X					X			X				X			
WPAI-HS ^{13,17}	X						X						X						X						X			
Concomitant treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Patient’s Daily Diary ¹⁵	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X	
Review returned Patient’s Daily Diary ¹⁵		X	X	X	X		X		X		X		X		X		X		X		X		X		X		X	
Self-administration questionnaire for s.c. Spesolimab, if applicable (to be completed by trial personnel supervising self administration) ⁸			X	X	X																							
All AEs/ SAEs/ AESIs ¹⁸	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

IHS4: International Hidradenitis Suppurativa Severity Score System, HASI: Hidradenitis Suppurativa Area Severity Index,

, IHS4: International Hidradenitis Suppurativa Severity Score System; HiSCR: Hidradenitis suppurativa clinical response

*V1 of this extension trial should preferably be performed during the EoT visit of the parent trial (1368-0098; 1368-0100). When the visits are performed on the same day, duplicate procedures across studies are performed only once during the EoT/V1. First trial drug administration is planned at Visit 2 after results of safety and infection tests will be available to confirm eligibility criteria. If further work up is required e.g., a re-test of safety labs, the screening period may be extended by up to 7 more days.

If these visits are not performed on the same day, then either all Visit 1 procedures need to be performed at that visit or a modification of procedures will be considered after discussion with the sponsor. If a participant is unable to roll over on the day of the EoT Visit of the parent trial because of medical reasons, then they can be permitted to roll over preferably within 2 weeks of the EoT Visit of the parent trial. During this gap, if required, participant can take systemic and topical antibiotics in case of disease worsening, flare, or according to investigator best clinical judgement. However, biologics and immunomodulators are not allowed for HS and non-HS indications. No participant can enter this trial if more than 16 weeks have elapsed between last administration of IMP at parent trials and V1 of 1368-0130 trial (See Section [3.3.2](#) Inclusion criteria).

Flow chart – Year 2

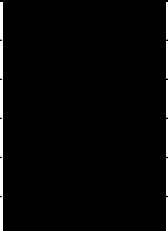
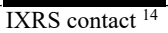
	Treatment period - Year 2											
Visit	28	29	30	31	32	33	34	35	36	37	38	39
Weeks	54	56	58	60	62	64	66	68	70	72	74	76
Time window for visits (day)	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Visit type (S: Site visit/R: Remote visit)	R	S	R	S	R	S	R	S	R	S	R	S
Physical examination ¹ Complete (C) or targeted (T)		T		T		T		T		T		T
Vital signs ²		X		X		X		X		X		X
Weight				X						X		
Local tolerability assessment ³	X	X	X	X	X	X	X	X	X	X	X	X
Infection testing ⁴												
Pregnancy test ⁵		X		X		X		X		X		X
Safety laboratory tests ⁶				X						X		
12-lead ECG ⁷				X						X		
Administer trial drug ⁸	X	X	X	X	X	X	X	X	X	X	X	X
PK Sampling ⁹				X						X		
ADA/NAb Sampling ⁹				X						X		
Blood sample (Serum soluble protein biomarkers)				X						X		
Hs-CRP				X						X		

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[illegible]

Flow Chart – End of Treatment and End of Study visits

	End of treatment ¹⁶	End of study
Visit	40	41
Weeks	78	92
Time window for visits (day)	±3	n/a
Visit Type (S: Site visit/R: Remote visit)	S	S
Physical examination ¹ Complete (C) or targeted (T)	C	T
Vital signs ²	X	X
Weight	X	X
Local tolerability assessment ³		
Infection testing ⁴	X	
Pregnancy test ⁵	X	X
Safety laboratory tests ⁶	X	X
12-lead ECG ⁷	X	X
PK Sampling ⁹		X
ADA/NAb Sampling ⁹		X
Blood sample (Serum soluble protein biomarkers)		X
		
 inflammatory nodule/ non-inflammatory nodule/ draining tunnel count/non-draining tunnel count	X	
Columbia-Suicide Severity Rating Scale (C-SSRS) ¹⁰	X	X
		
	X	
IXRS contact ¹⁴	X	
Surgeries by type and number ¹⁹	X	X
Hospitalization	X	X

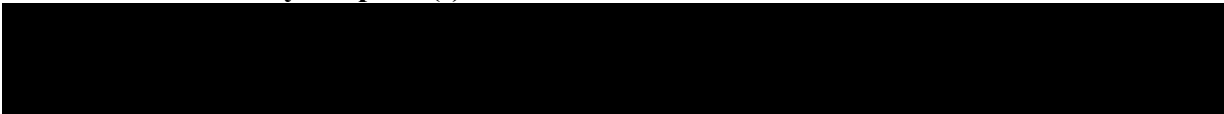
	End of treatment ¹⁶	End of study
Visit	40	41
Weeks	78	92
Time window for visits (day)	±3	n/a
Visit Type (S: Site visit/R: Remote visit)	S	S
ICU/ER use (number of days, overnight stays)	X	X
	X	
Concomitant treatment	X	X
Review returned Patient's Daily Diary ¹⁵	X	
All AEs/ SAEs/ AESIs ¹⁸	X	X

FOOTNOTES TO FLOW CHARTS:

1. Complete physical examination includes general appearance as well as evaluation of all organ systems and it shall be done at screening and EOT visit. 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. Targeted physical examination is planned for every site visit, unless complete physical examination is required by investigator. See Section [5.2.1](#) for more details.
2. Vital signs will be assessed pre dose as well as approximately 10 minutes post dose. Measurement of pre-dose vital signs should precede blood sampling to avoid the impact of blood sampling on vital signs at all dosing visits. Vital signs include systolic and diastolic blood pressure, pulse rate, respiratory rate and temperature measurement. Refer to Section [5.2.2](#) for further information.
3. The investigator will assess local tolerability at the administration site of spesolimab during site trial drug administration and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction, e.g. "swelling", "induration", "heat", "redness", "pain", and any other findings should be reported as an adverse event. Site staff shall ask participant during site visit if any local tolerability reaction occurred during home trial drug administration.
4. Infection testing: at screening; repeat the test approximately once a year and at EOT visit. See Section [5.2.3](#) for complete list of testing required. For South Africa only, tuberculosis infection testing should be done approximately at 6 months intervals. 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 Visit 1.
5. Women of childbearing potential only. Urine pregnancy testing should be done prior to administration of trial drug at visits as indicated in [Flow Chart](#). In case of a positive urine pregnancy test, a serum pregnancy test will be done. Trial 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 judgement.
6. It is preferred, but trial participants do not need to be fasted for blood sampling for the safety laboratory testing. At visits with trial drug administration, blood samples shall be taken prior to trial drug administration. Safety laboratory tests include clinical chemistry, haematology, coagulation, and urinalysis and will be performed by the Central Lab.
7. ECG measurements should always precede blood sampling and drug administration. The ECG measurements need to be conducted at timepoints indicated in the [Flow Chart](#). Additional ECG measurements may be performed if the investigator deems it clinically indicated.

8. The first trial drug dose will be administered at the site by a HCP/qualified trial personnel. Participants will be trained to self-administer the trial drug at each of the next three visits (V 3, 4 and 5) under the supervision of the HCP/qualified trial personnel at the site. Starting from visit 6 participant may opt to self-administer trial drug at home in between monthly onsite visits, Refer to Section [6](#) for more details. At visits with self administration of IMP at the site, trial personnel must supervise the self-administration by participant and complete the self-administration questionnaire for s.c. spesolimab. The questionnaire captures information whether the participant did injections of spesolimab correctly or not (See Section [5.6](#). and Appendix [10.11](#). Participant must complete e-diary to document IMP administration at home. Site will review diaries during every onsite visit.
9. At trial visits with trial drug administration pre-dose PK/ADA/NAb samples will be obtained approximately within 2 hours prior to start of trial drug administration.
10. At Visit 1, the C-SSRS baseline/screening scale will be completed. At all subsequent visits the “since last visit” scale will be completed.
11. IHS4 will be derived from lesions count by a trained health care professional
12. Trial participant eDiaries will be handed to trial participants after being trained with the objective to collect information about Numerical Rating Scale Pain. Data for pain shall be recorded by trial participant daily 7 days prior to each visit. Site staff will review the diaries from trial participants at visits indicated in the [Flow Chart](#) to assess pain (and analgesic use, and other interventions to manage pain to be recorded in eDiary as well as in eCRF) since last visit. See [Section 5.1.1](#).
13. [REDACTED]
14. Site has to contact IXRS as indicated in the [Flow Chart](#) to assign trial medication. Starting at V5, IXRS will also provide the option to allocate medication kits for use for the next upcoming remote (home) visit.
15. Trial participant's diaries returned by participants must be reviewed while trial participant is in consultation, so that any information can be clarified in an interview with trial participant, if needed.
16. For participant who discontinue trial medication before their scheduled end of treatment, an early EOT visit has to be scheduled. Subsequently EOS visit 16 weeks after the last dose of trial medication has to be performed.
17. All patient reported outcomes (PROs) should be completed by the participant on his/her own in a quiet area/room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other members of the site staff team.
18. Please refer to [Section 5.2.6.2.1](#) for AEs / SAEs collection
19. Occurrence of HS-related surgeries by type and number of surgeries by type / incision, wide excision, skin graft, etc. to be collected as indicated in the [Flow Chart](#).

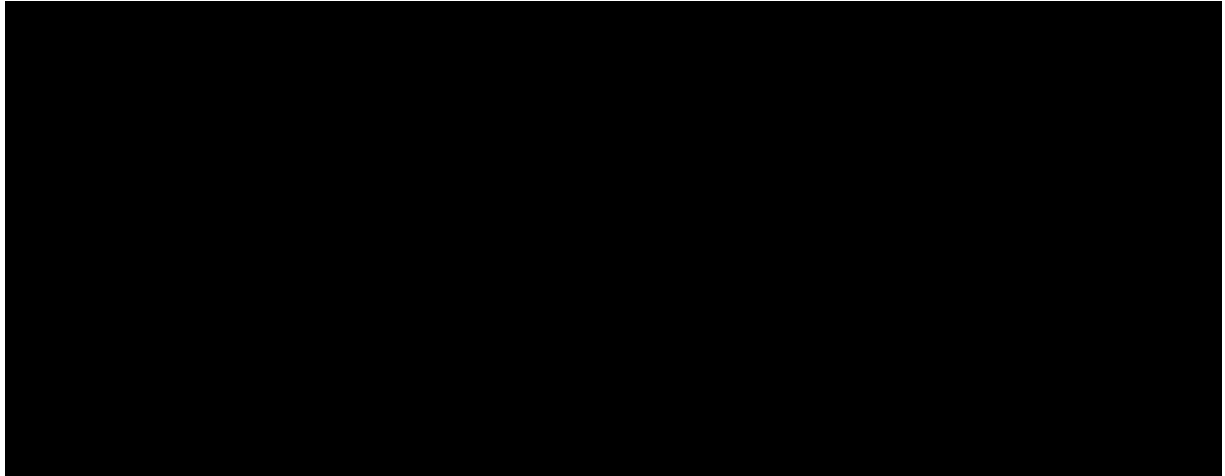
TABLE OF CONTENTS

TITLE PAGE	1
FLOW CHART	5
TABLE OF CONTENTS	12
ABBREVIATIONS AND DEFINITIONS.....	16
1. INTRODUCTION.....	21
1.1 MEDICAL BACKGROUND	21
1.2 DRUG PROFILE	21
1.3 RATIONALE FOR PERFORMING THE TRIAL	25
1.4 BENEFIT - RISK ASSESSMENT.....	26
1.4.1 Benefits.....	26
1.4.2 Risks	27
1.4.3 Discussion.....	31
2. TRIAL OBJECTIVES AND ENDPOINTS.....	32
2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS.....	32
2.1.1 Main objectives.....	32
2.1.2 Primary endpoint(s).....	32
2.1.3 Secondary endpoint(s)	32
	
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION	34
3.1 OVERALL TRIAL DESIGN.....	34
3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)	35
3.3 SELECTION OF TRIAL POPULATION	36
3.3.1 Main diagnosis for trial entry	36
3.3.2 Inclusion criteria	36
3.3.3 Exclusion criteria	37
3.3.4 Discontinuation of trial participants from treatment or assessments.....	38
3.3.4.1 Discontinuation of trial treatment	38
3.3.4.2 Withdrawal of consent to trial participation	40
3.3.4.3 Discontinuation of the trial by the sponsor	40
4. TREATMENTS.....	41
4.1 INVESTIGATIONAL TREATMENTS	41
4.1.1 Identity of the Investigational Medicinal Products.....	41
4.1.2 Selection of doses in the trial and dose modifications.....	41
4.1.3 Method of assigning trial participants to treatment groups	41
4.1.4 Drug assignment and administration of doses for each trial participant.....	42
4.1.5 Blinding and procedures for unblinding.....	43
4.1.5.1 Blinding.....	43

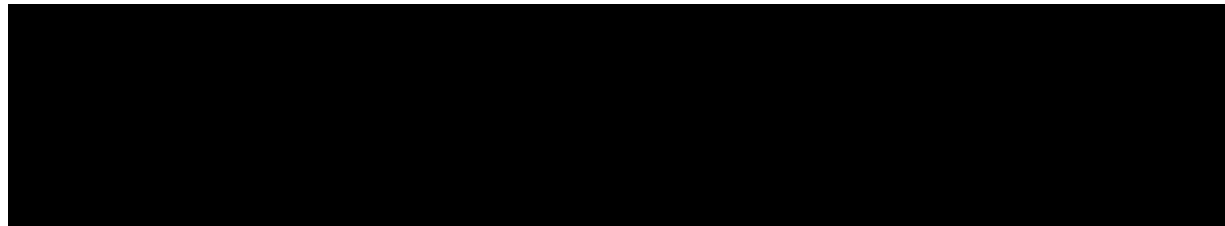
4.1.5.2	Unblinding and breaking the code	43
4.1.6	Packaging, labelling, and re-supply	43
4.1.7	Storage conditions	43
4.1.8	Drug accountability	43
4.2	OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS	44
4.2.1	Other treatments and emergency procedures	44
4.2.2	Restrictions	46
4.2.2.1	Restrictions regarding concomitant treatment	46
4.2.2.2	Concomitant medication	46
4.2.2.3	Antibiotic use during the trial	46
4.2.2.4	Analgesics use during the trial	47
4.2.2.5	Lesion intervention	47
4.2.2.6	Contraception requirements	47
4.2.2.7	Restrictions on diet and lifestyle	48
4.3	TREATMENT COMPLIANCE	48
5.	ASSESSMENTS	49
5.1	ASSESSMENT OF EFFICACY	49
5.1.1	Trial Participant Diary	51
5.2	ASSESSMENT OF SAFETY	51
5.2.1	Physical examination	51
5.2.2	Vital signs	51
5.2.3	Safety laboratory parameters	52
5.2.4	Electrocardiogram	55
5.2.5	Other safety parameters	56
5.2.5.1	Local tolerability	56
5.2.5.2	Suicidal risk assessment by the C-SSRS	56
5.2.6	Assessment of adverse events	57
5.2.6.1	Definitions of AEs	57
5.2.6.1.1	Adverse event	57
5.2.6.1.2	Serious adverse event	57
5.2.6.1.3	AEs considered “Always Serious”	58
5.2.6.1.4	Adverse events of special interest	58
5.2.6.1.5	Intensity (severity) of AEs	60
5.2.6.1.6	Causal relationship of AEs	60
5.2.6.2	Adverse event collection and reporting	61
5.2.6.2.1	AE Collection	61
5.2.6.2.2	AE reporting to the sponsor and timelines	62
5.2.6.2.3	Pregnancy	62
5.3	DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS	63
5.3.1	Assessment of pharmacokinetics	63
5.3.2	Methods of sample collection	63
5.3.2.1	Plasma sampling for pharmacokinetic analysis	63
5.3.2.2	Sampling for ADA/Nab assessment	63

5.5	BIOBANKING	65
5.6	OTHER ASSESSMENTS.....	65
5.7	APPROPRIATENESS OF MEASUREMENTS	65
6.	INVESTIGATIONAL PLAN.....	66
6.1	VISIT SCHEDULE.....	66
6.2	DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS	68
6.2.1	Screening period.....	68
6.2.2	Treatment period(s)	69
6.2.3	Follow-up period and trial completion.....	70
7.	STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE.....	71
7.1	NULL AND ALTERNATIVE HYPOTHESES	71
7.2	PLANNED ANALYSES	71
7.2.1	General considerations	71
7.2.1.1	Analysis sets.....	72
7.2.2	Handling of Intercurrent Events	72
7.2.3	Primary objective analyses.....	72
7.2.4	Secondary objective analyses	72
7.2.5	Further objective analyses.....	72
7.2.6	Safety analyses.....	73
7.2.7	Other Analyses	73
7.2.8	Interim Analyses	74
7.3	HANDLING OF MISSING DATA	74
7.4	RANDOMISATION	74
7.5	DETERMINATION OF SAMPLE SIZE	74
8.	INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE	75
8.1	TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT	75
8.2	DATA QUALITY ASSURANCE	76
8.3	RECORDS	76
8.3.1	Source documents	76
8.3.2	Direct access to source data and documents.....	78
8.3.3	Storage period of records	78
8.4	EXPEDITED REPORTING OF ADVERSE EVENTS	78
8.5	STATEMENT OF CONFIDENTIALITY AND TRIAL PARTICIPANT PRIVACY	78
8.5.1	Collection, storage, and future use of biological samples and corresponding data	79
8.6	TRIAL MILESTONES.....	80
8.7	ADMINISTRATIVE STRUCTURE OF THE TRIAL	80
9.	REFERENCES.....	82

9.1	PUBLISHED REFERENCES.....	82
9.2	UNPUBLISHED REFERENCES.....	83
10.	APPENDICES	84
10.1	TRIAL PARTICIPANT FEEDBACK.....	84



10.10	DIAGNOSIS OF ANAPHYLAXIS	104
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11	DESCRIPTION OF GLOBAL AMENDMENT(S)	107
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ABBREVIATIONS AND DEFINITIONS

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
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
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
CA	Competent authority
CDC	Complement-dependent cytotoxicity
CKD-EPI	Chronic kidney disease Epidemiology Collaboration
C _{max}	Maximum concentration
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
DBL	Database Lock
DILI	Drug induced liver injury

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
FDA	Food and Drug Administration
FUP	Follow-up
FOR	Field Observation Report
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



HIV	Human immunodeficiency virus
HODS	Hidradenitis suppurativa odour and drainage scale
HS	Hidradenitis suppurativa



hs-CRP	High-sensitivity c-reactive protein
HT29	Hypertriptoid-29
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
IFN γ	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
IXRS	IXRS®3 System Management
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
K2EDTA	Dipotassium ethylenediaminetetraacetic acid
KO mutation	Knockout mutation
LDH	Lactic Dehydrogenase
LPLT	Last patient last treatment
mAb	Monoclonal antibody
MCID	Minimal Clinical Important Difference
MedDRA	Medical Dictionary for drug regulatory activities
MoA	Mode of Action
MRD	Multiple rising dose
mRNA	Messenger RNA
NAb	Neutralizing antibody
N count	Inflammatory nodule count
NF- κ B	Nuclear factor-kappa B

NOAEL	No-observed-adverse-effect level
NRS	Numerical rating scale
NRS30	Reduction of 30% in numerical rating scale
OLE	Open label extension
OPU	Operative unit
PASI	Psoriasis Area and Severity Index
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PFS	Pre-filled syringes
PGA	Physician global assessment
PGI-S	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
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
q2w	Once every 2 weeks
qw	Every week
RAs	Regulatory authorities
RCTC	Rheumatology common toxicity criteria
REP	Residual effect period
RNA	Ribonucleic acid
RS	Randomised set
s.c.	Subcutaneous
SAE	Serious adverse event
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
TS	Treated set
TSAP	Trial statistical analysis plan
TST	Tuberculin-skin testing
UC	Ulcerative colitis
ULN	Upper limit of normal
US	Ultrasound
vs.	Versus
WBC	White Blood Cell
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 malodorous 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 sequelae 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 (dT) represents a high unmet medical need.

1.2 DRUG PROFILE

Mode of action

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

Spesolimab binds to human IL36R with a binding avidity of less than 1 pM. Spesolimab inhibits IL36 ligand-stimulated NF- κ B activation in HT29 and transformed epithelial cells and in primary human dermal fibroblasts or intestinal myofibroblasts with IC90 values in a consistent range of 0.7 to 3.7 nM. Spesolimab also inhibits IL8 release in primary human intestinal myofibroblasts and IFN γ secretion in human Peripheral Blood Mononuclear Cells PBMC stimulated with IL36 α , IL36 β , or IL36 γ 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 nondepleting therapy in vivo.

Spesolimab does not bind to IL36R from common toxicology species. Therefore, meaningful toxicity studies of the molecule cannot be performed in any animal species with spesolimab. However, hazard identification studies of the mode-of-action (MoA) of IL36R inhibition were performed in mice using a mouse specific anti-IL36R monoclonal antibody (Boehringer Ingelheim (BI) 674304), which is a mouse IgG2a monoclonal antibody with rat variable regions. In a 13-week intravenous (i.v.) toxicity study of BI 674304 in mice, no adverse effects of IL36R antagonism were seen at a dose (50 mg/kg, twice weekly) that was 5-fold higher than the dose that was protective in an experimental mouse colonic inflammation model. In the 26-week toxicity study, male and female mice (20-30/sex/group at 0, 10 and 50 mg/kg/day) were administered BI 674304 twice weekly for 26 weeks by i.v. injection via the caudal vein. There were no BI 674304-related changes in clinical observations, body weights, food consumption, ophthalmology, clinical pathology parameters (haematology, clinical chemistry), organ weights, macroscopic or microscopic examinations. The no-observed adverse-effect level was considered to be 50 mg/kg/day.

The in vitro cytokine release and tissue cross-reactivity assays demonstrate that the risk of transient cytokine release in humans is low and that, as expected, spesolimab stains epithelium in a variety of tissues. There were no signs of local irritation after single, 1mL injections of the s.c. formulation in rabbits. These preclinical toxicology data support chronic spesolimab dosing in humans.

Spesolimab or placebo was administered to 78 healthy volunteers at single ascending i.v. doses from 0.001 mg/kg to 10 mg/kg body weight. Safety and tolerability of all tested i.v. doses was good. There were no drug-related serious adverse events (SAEs). AEs categorized as related to treatment were observed in 3/120 (15.0%) subjects in the placebo group and in 7/58 (13.8%) subjects treated with spesolimab. The most frequent treatment-emergent AEs were nasopharyngitis (spesolimab: 21%; placebo: 15%), headache (spesolimab: 9%; placebo: 15%), influenza like illness (spesolimab: 7%; placebo: 10%), and diarrhoea (spesolimab: 3%; placebo: 10%). There were two AEs of moderate intensity (injection site haematoma, headache); all remaining AEs were of mild intensity. There was no apparent relationship between the frequency of AEs and the dose.

There were no relevant changes compared to placebo for laboratory safety, including clinical chemistry, haematology, coagulation parameters, and urinalysis. No clinically relevant changes were observed in 12-lead electrocardiogram (ECGs), vital signs, and cardiomonitoring.

Key PK characteristics

Pharmacokinetics (PK) analysis showed that exposure (AUC_{0-tz} and C_{max}) to spesolimab increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg.

[REDACTED]

Overall, PK data so far suggests target-mediated drug disposition kinetics for spesolimab. Anti-drug antibodies (ADA) were detected in 8 participants, 3 of those had pre-existing levels. Pharmacodynamic (PD) effects in this First in Human Single Rising Dose (SRD) trial [[c09985235-01](#)] were assessed by indirect target engagement of IL36R by spesolimab using an ex-vivo whole blood stimulation assay. [REDACTED]

[REDACTED]

In a multiple rising dose (MRD) trial, spesolimab or placebo have been administered to healthy volunteers at multiple ascending i.v. doses of 3, 6, 10 and 20 mg/kg given qw for 4 weeks (i.e. 4 administrations) or a single dose of 20 mg/kg (8 subjects each, 3:1 on active or placebo). Overall, spesolimab was well tolerated. There were no dose dependent AEs, AEs considered to be dose limiting and no SAEs. In all cases the AEs were of mild or moderate intensity. Furthermore, there were no clinically relevant abnormalities on treatment with spesolimab with respect to safety laboratory, vital signs, or ECGs as assessed by a central reader. For further details and most recent results refer to the current Investigator's Brochure (IB) [[c03320877-12](#)].

[REDACTED]

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 IC₉₀ 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 [[c03320877-12](#)].

Data from clinical studies

For a more detailed description of the spesolimab profile, please refer to the current IB [[c03320877-12](#)].

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 participants with moderate to severe HS was investigated during 12-week: a loading dose of spesolimab 3600 mg i.v. (1200 mg i.v. q1w ×3) or matching placebo was followed by maintenance subcutaneous (s.c.) dosing of 1200 mg spesolimab q2w or matching placebo [[c37475396](#)]. In this trial, 52 participants were

randomised in a 2:1 ratio to the spesolimab group (35 patients) or the placebo group (17 participants) on Day 1 [c37475396]. No formal statistical analyses were performed. The key efficacy result was a marked positive signal on the reduction of dT count and of abscess count at Week 12, in line with the hypothesised mechanism of action of spesolimab in HS. Overall, spesolimab was well tolerated and safety data were generally in line with what seen in previous spesolimab-trials in other indications. The overall incidence rate of AEs was similar between spesolimab (77.8%) and placebo (87.5%). The incidence of drug-related AEs was higher with spesolimab treatment (41.7%) than with placebo (18.8%), largely due to injection-site reactions. No AEs leading to death, no severe AEs, and no protocol-defined AEs of special interest (systemic hypersensitivity including infusion reaction and anaphylactic reaction, severe infections [according to RCTC grading], opportunistic and mycobacterium tuberculosis infections, or hepatic injury) were reported.

Open label extension (OLE) trial 1368-0067

A total of 45 participants (86.5%) continued in the OLE trial, 1368-0067 [data on file] where all participants were switched to a lower dose of spesolimab than in 1368-0052, at least up to Week 12. The primary endpoint of the ongoing trial 1368-0067 (OLE study) is safety. Overall, spesolimab was well tolerated and safety data were generally in line with what seen in previous spesolimab-trials in other indications. Although this extension trial is not controlled, efficacy data from an interim analysis at Week 12 (i.e. 24 weeks of spesolimab treatment for participants from the active treatment group in 1368-0052), indicate that the efficacy of spesolimab in HS on dT and abscess counts may be sustained up to Week 24. As per protocol pre-defined clinical criteria, a majority of participants was up titrated to a higher dose of spesolimab at this same Week 12 (or Week 24) time-point.

1.3 RATIONALE FOR PERFORMING THE TRIAL

The main rationale of this extension trial is to collect additional long-term safety and efficacy data of spesolimab in eligible HS patients who completed their treatment with spesolimab in parent trials.

Hidradenitis suppurativa (HS) is a debilitating inflammatory skin disease characterised by recurrent inflammatory nodules, painful abscesses and tunnels that may be draining a malodourous exudate. Lesions characteristically occur in the axillary, groin, infra-mammary, and/or anogenital regions of the body. Significant pain is associated with HS and lesion sequelae 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].

Until recently, the TNF-alpha inhibitor adalimumab, was the only biologic therapy approved for the treatment of active moderate to severe HS. In adalimumab Phase III studies, a clinical response (HiSCR50) rate of 42%-59% versus placebo response of 26%-28% was achieved at Week 12. Secukinumab, an anti-IL17A mAb, was approved for HS in June 2023 in Europe. In secukinumab Phase III studies, HiSCR50 was achieved at a rate of 42%-45.0% at Week 16, versus a placebo response rate of 31%-34% [R23-2963]. Long-term safety information is pertinent in the treatment of HS, where it is expected that only chronic treatment may control its inflammatory manifestations. In parallel, it is important to assess the sustained level of

benefit/risk ratio of chronic treatment. Therefore, extending spesolimab Phase II and III studies will provide important safety and efficacy information beyond 1 year of treatment duration.

The trial of exploratory and probable valid biomarkers will mostly be hypothesis-generating or supportive to endpoints. There findings will be used to expand the understanding of HS and spesolimab, thereby allowing correlation of patient subgroups with differential responses to treatment.

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 participants with HS if spesolimab development in this indication proves to be successful. Of note, spesolimab is currently approved in multiple countries worldwide 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

Preclinical profiles of spesolimab and clinical data from healthy volunteers and patient trials suggest that spesolimab is safe, tolerable and may address an unmet medical need in patients with HS by an anti-inflammatory mechanism of action (for details see the latest version of spesolimab IB [c03320877-12]). 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.

In 1368-0052 (proof of clinical concept [PoCC]) trial, 52 participants with HS were randomised in a 2:1 ratio to the spesolimab group (35 participants) or the placebo group (17 participants). As the key efficacy results, a marked positive signal on the reduction of dT count and abscess count, which are a high unmet medical need in HS, was observed at Week 12, in line with the hypothesised mechanism of action of spesolimab in HS. A total of 45 participants rolled over to 1368-0067 (OLE) trial, of which the primary endpoint is safety. In 1368-0052 trial and ongoing 1368-0067 trial, overall, spesolimab was well tolerated, and safety data were generally in line with what was seen in previous spesolimab-trials in other indications. For more details, see Section [1.2](#).

Trial 1368-0098 consists of 2 parts: a dose finding phase (Phase IIb), designed to primarily support the decision on optimal spesolimab dosing in participants with moderate to severe HS, but also collect data on subcutaneously administered loading dose 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 participants with moderate to severe HS. Trial participants completing the 48-week treatment either in Part 1 (Phase IIb) or Part 2 (Phase III) of trial 1368-0098 will be offered to roll over this trial where the participants will receive long term active spesolimab

maintenance treatment. Trial participants experiencing worsening of HS will have the possibility to receive rescue treatment according to the dispositions described in Section [4.2](#). Trial participants who fail to rescue treatment or cannot receive further trial medication (i.e. unbearable AEs) will discontinue and switch to available standard of care at the investigator's discretion, refer to Section [3.3.4](#). This will limit the duration of spesolimab exposure in trial participants who are no longer benefitting from treatment of spesolimab.

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](#).

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 7.6 of IB [[c03320877-12](#)].

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.	Participants 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].
Infections (serious, severe, opportunistic)	Inhibition of the immune response with an immunomodulating 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 participants with mild to moderate infections was seen in the spesolimab treatment group than in the placebo treatment group.	Screening procedures for infections are defined for this trial. Participant 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.

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	Nevertheless, there was no indication of an increased frequency of participants with severe, serious, and opportunistic infections in association with spesolimab treatment.	
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]	Participant 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.
Peripheral neuropathy	Three cases reported by the investigator as Guillain- Barré syndrome (GBS) were received in 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 trial 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	Timely detection, evaluation, and follow-up of suspected peripheral neuropathies to ensure participant' safety. Use of dedicated questions to elicit neurologic history during screening and exclusion criteria to avoid selection of participant with acute demyelinating neuropathy. Targeted follow-up questions to gather detailed information in case of any event during trial to ensure proper decision making.

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	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.	
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 part of site feasibility assessment. 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.
Suicidal ideation and behaviour*	Increased risk of suicidal ideation and behaviour is present in the population of participant with HS	'Baseline/ screening' version of C-SSRS will be administered with the aim to exclude participant 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 behaviour 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

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
		treatment discontinuation criteria (see Section 3.3.4.1).
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 participants with HS and not specifically due to the mechanism itself*

Regarding reactions to injections, specific safety measures will be taken during the trial. Following the injection, 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 trial (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 Childbearing Potential (WOCBP) in this trial 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 [Flow Chart](#)) and contraceptive methods; see Section [4.2.2.3](#).

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 participants 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

2.1.1 Main objectives

The primary objective of this trial is to assess the long-term safety of spesolimab in participants with HS who have completed approximately 8 to 12 months of spesolimab treatment in Part 1 or Part 2 of trial 1368-0098, and trial 1368-0100.

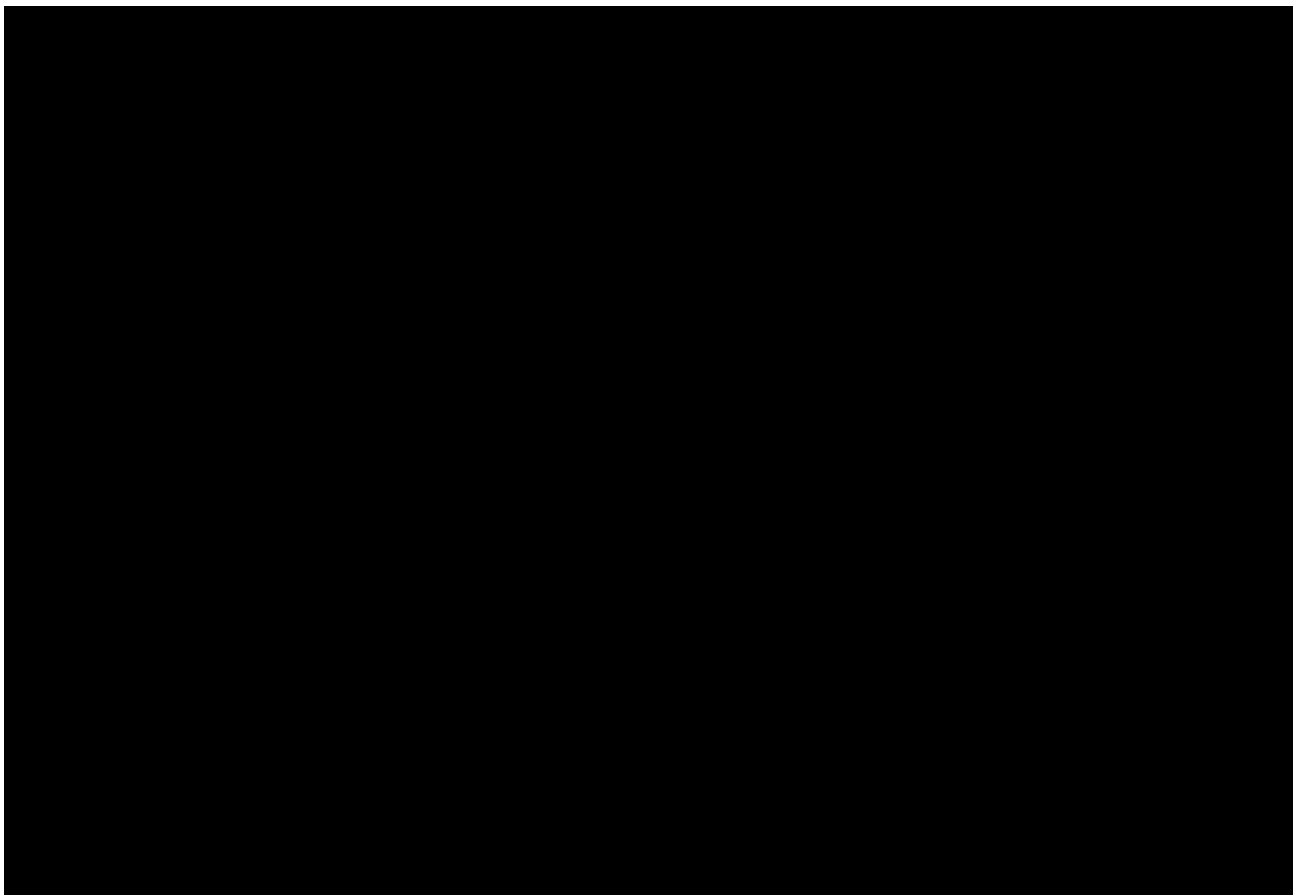
2.1.2 Primary endpoint(s)

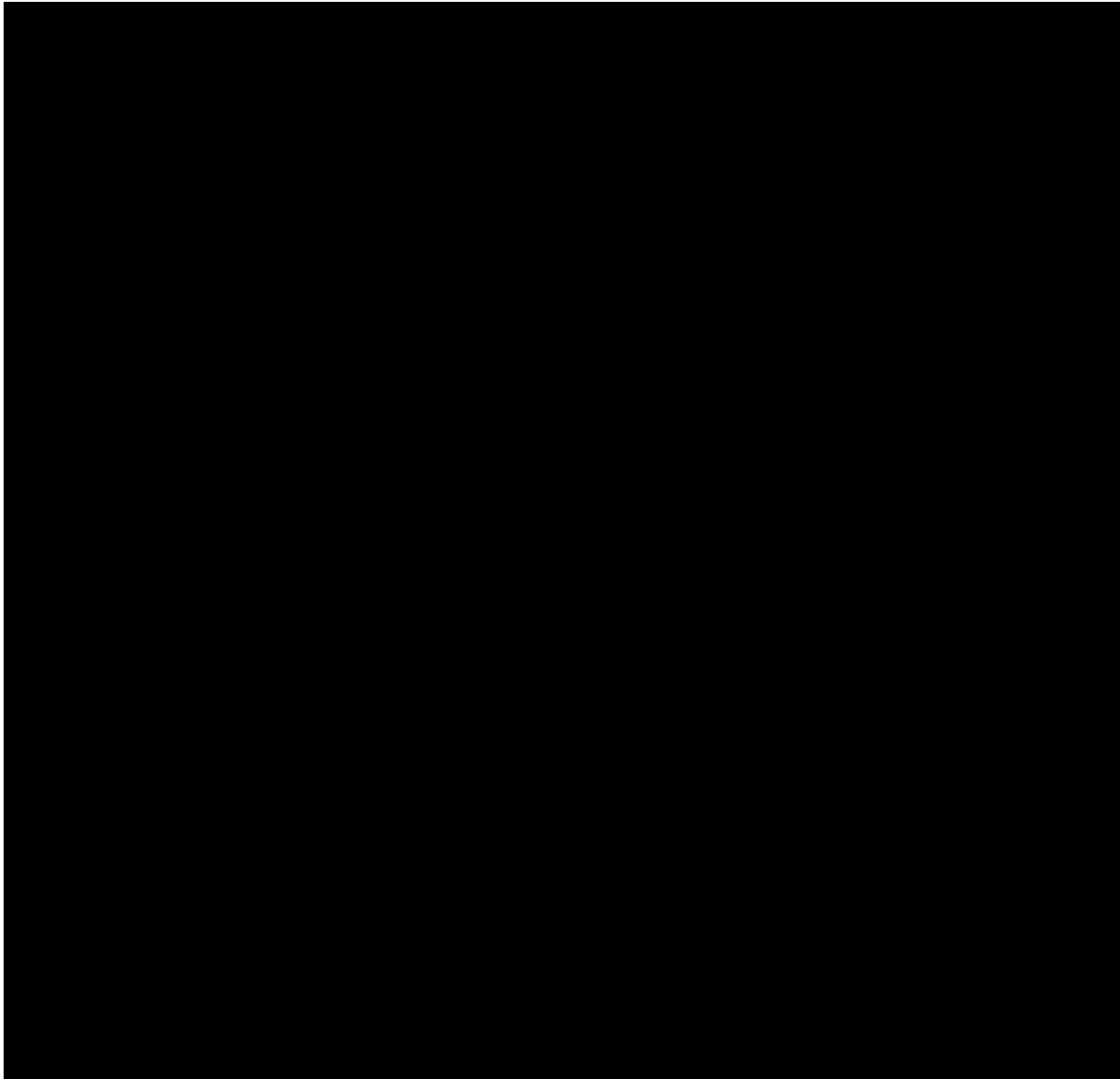
The primary endpoint is the occurrence of treatment emergent adverse events (TEAE) up to the end of maintenance treatment period including REP (i.e., 16 weeks after the last study treatment).

Note: TEAEs are defined as all adverse events occurring between start of treatment in the extension trial and the end of its residual effect period. Adverse events that start before first drug intake in the extension trial and deteriorate under treatment during the extension trial will also be considered as ‘treatment-emergent’.

2.1.3 Secondary endpoint(s)

Not applicable.





3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This 92-week, multi-regimen, Phase II/III extension trial investigates the long-term safety of spesolimab in participants with HS who have completed their treatment in the randomised, double-blind, placebo-controlled, Phase IIb/III trial 1368-0098 or Phase III, randomised, double-blind, placebo-controlled replicate trial 1368-0100.

Ideally, the end of treatment (EoT) visit of the preceding trial is the baseline visit (V1) of this extension trial; but no participant can enter this trial if more than 16 weeks have elapsed between the last administration of IMP at parent trials and V1 of 1368-0130 trial.

Approximately [REDACTED] participants from Part 1 & Part 2 of trial 1368-0098 and trial 1368-0100.

Participants in this trial will continue on the same dosing regimen that they were in the parent trials. This trial will be kept blinded, until blinded parent trials are unblinded. This is to prevent inadvertent unblinding of the parent trial. Once the parent trial is unblinded and an optimal dose is finalized based on risk/benefit analysis, all participants may be shifted to the final dose. There will be no change in the dosing regimen prior to the decision on final dose.

HS is a chronic disease with periods of activity and remission. If participants experience flare and/or disease worsening, protocol specified concomitant medications can be given. If the participant needs restricted medications to control the flare and/or disease worsening, the participant will have to be discontinued from the trial.

This extension trial consists of a [REDACTED]-week treatment period followed by a 16-week safety follow-up period ([Figure 3.1: 1](#)).

Subcutaneous administration of spesolimab will be done by a health care professional (HCP)/qualified site personnel at the site at first dosing visit. At the following three on-site visits trial participants / caregivers may self-administer spesolimab under supervision of HCP/qualified personnel. Afterwards participants/caregivers may opt to self-administer trial drug at home (under supervision of HCP remotely) between site administration after comprehensive training by site and specific instructions on transporting and storage of trial drug are provided. If the trial participant is not able/confident to perform self-administration, the subject will be allowed to return to the site for administration of the medication. Trial participants who are not willing to self-administer spesolimab can continue to receive the drug at the site.

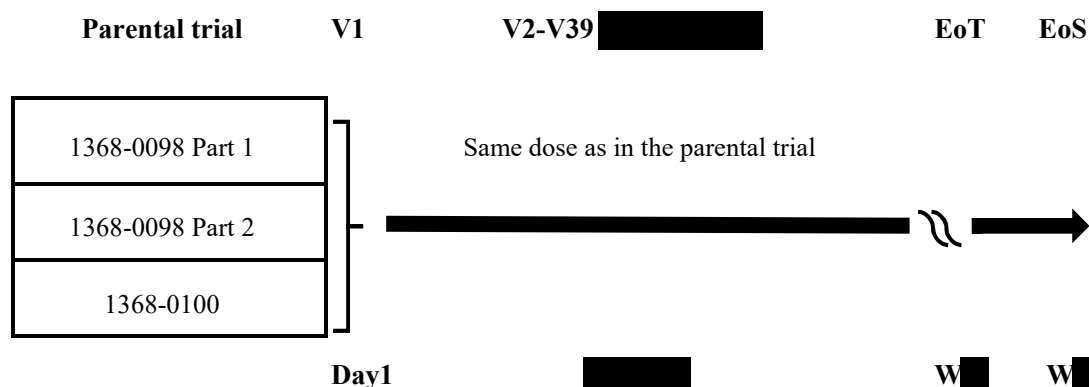


Figure 3.1: 1 Trial design

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

Participant entering this extension trial have all been treated with spesolimab for at least 8 months in a prior placebo (up to Week 16) controlled trial. The primary objective of this extension trial is long term safety assessment of spesolimab treatment in HS. Therefore, the trial design is a continuation of parent trials treatment with adaptation considering a duration of treatment [REDACTED] weeks for each participant. For participants who terminate trial drug prematurely in this extension trial, the subsequent visit will be replaced by an early EoT visit followed by an end of study (EoS) visit [REDACTED] weeks after the last trial drug administration.

An independent DMC will evaluate safety and efficacy data on a continuous basis. For details, please see Section 8.7.

The hybrid trial management approach was chosen to make the trial participation more convenient for participant by reducing travel burden and time spent at the site.

Approximately 60% of the visits are expected to occur at the site. The remaining visits should be conducted remotely, the participant will interact with the investigator and/or site personnel via a video conferencing feature. For the method of visit (on-site or remote), please refer to the [Flow Chart](#). Prior to implementation of remote visits, it is essential to assess country, site and participant's consent, suitability/operational feasibility. Further details about self-administration of s.c injections is allowed under the supervision of HCP / qualified site personnel (via video app etc.). Local regulatory and legal requirements need to be considered (for more details See Section 4.1.4).

If requested by a trial participant or deemed necessary by the investigator at any time, an on-site trial visit can be conducted, either in place of or in addition to a prespecified remote visit. Similarly, site personnel should be ready to address any concerns, questions, or event reporting from participants outside the prespecified follow-up time points.

Feedback on clinical trial experience

This trial will include an option for participants to complete 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 [10.1](#)).

3.3 SELECTION OF TRIAL POPULATION

Participants in this long-term extension trial will be rolled-over from previous parent HS trials with spesolimab with aim to offer active long-term treatment. Participants must have completed the treatment in the previous trial and must meet the eligibility criteria for this extension trial.

The total number of participants depends on how many eligible participants roll over from preceding parent trials. Approximately [REDACTED] participants from Part 1 & Part 2 of trial 1368-0098 and trial 1368-0100 may enter this long-term extension trial.

A log of all participants enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF.

If retrospectively it is found that a trial participant has been enrolled in error (i.e. 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 as to whether continued trial participation is possible.

3.3.1 Main diagnosis for trial entry

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

Please refer to Section [8.3.1](#) (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

1. Signed and dated written informed consent in accordance with ICH Harmonized Guideline for Good Clinical Practice (ICH-GCP) and local legislation prior to admission to the trial.
2. Participants must be within the defined Residual Effect Period corresponding to [REDACTED] weeks since last spesolimab administration.
3. Participants who have completed treatment in the parent HS spesolimab trial (1368-0098 or 1368-0100) without premature discontinuation and are willing and able to continue treatment in this trial.
4. WOCBP¹ 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.

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

3.3.3 Exclusion criteria

1. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
2. Use of any drug considered by the investigator likely to interfere with the safe conduct of the trial since the last visit of the parent trials.
3. Use of immunomodulatory biologics or investigational agents since the last visit of the parent trials.
4. Participants who require / intend to use certain restricted medications such as immunomodulatory biologics or other investigational drugs/devices during the course of the trial.
5. Relevant chronic or acute infections including human immunodeficiency virus (HIV) and viral hepatitis. The corresponding laboratory tests will be performed at Visit 1. A participant can be re-screened if the participant was treated and is cured from the acute infection.
6. Active or latent Tuberculosis (TB) (participants are required to be tested during the Visit 1):
 - Participants will be screened with Interferon Gamma Release Assay (IGRA) such as QuantiFERON®-TB-Gold Plus or T-spot.
 - Participants with active tuberculosis should be excluded.
 - Participants with positive IGRA are excluded unless they have completed treatment for active or latent tuberculosis per investigator discretion. Under exceptional circumstances and only after discussion with the sponsor, Tuberculin-Skin testing (TST) can be performed if IGRA is not available. A tuberculin skin test reaction $\geq 10\text{mm}$ ($\geq 5\text{mm}$ if receiving $\geq 15\text{mg/d}$ prednisone or other immunosuppressant) is considered positive. Participants with a positive TST are excluded unless they have completed treatment as above. Participants with indeterminate QuantiFERON®-TB-Gold Plus or invalid/borderline T-spot may be retested with IGRA (once).
 - If presence of untreated latent tuberculosis is established, then treatment should be initiated and completed according to local guidelines.
7. Severe, progressive, or uncontrolled condition such as renal, hepatic, haematological, endocrine (especially untreated diabetes mellitus), pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof.
8. Any new documented active or suspected malignancy except appropriately treated basal cell carcinoma, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
9. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.
10. Major surgery (major according to the investigator's assessment) planned during this extension trial (e.g. hip replacement, aneurysm removal, stomach ligation), as assessed by the investigator.

11. Any condition which in the opinion of the investigator affects the safety of the participants, the participants' ability to participate in this trial or could compromise the quality of data.
12. Any suicidal behaviour in the past 2 years (i.e. actual attempt, interrupted attempt, aborted attempt, or preparatory acts or behaviour).
13. Any suicidal ideation of type 4 or 5 on the C-SSRS in the past 3 months (i.e. active suicidal thoughts with method and intent but without specific plan, or active suicidal thoughts with method, intent and plan).
14. Currently enrolled in another investigational device or drug trial, except for 1368-0098 or 1368-0100.
15. 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
16. Previous participation in this trial
17. Presence of acute demyelinating polyneuropathy
18. Participants with body weight less than 40kg.

3.3.4 Discontinuation of trial participants from treatment or assessments

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

Every effort should be made to keep the participants in the trial: if possible on treatment, or at least to collect important trial data. Measures to control the withdrawal rate include appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial IMP or withdraw consent to trial participation and the reason (if provided) must be documented in the trial participant files and CRF. If applicable, consider the requirements for AE collection and reporting (see Section [5.2.6.2](#)).

3.3.4.1 Discontinuation of trial treatment

If a trial participant discontinues treatment but agrees to remain in the trial, they should attend further trial visits to ensure their safety and to collect important trial data.

An individual trial participant will discontinue trial IMP if:

- The trial participant wants to discontinue trial IMP. 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 he / she 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 biologics, investigational products/devices, IL-36 receptor inhibitors (as mentioned in Section [4.2.2](#)), for any indication. Use of other immunomodulatory drugs might lead to discontinuation after investigator-sponsor discussion.
- The trial participant can no longer receive trial IMP for medical reasons such as surgery, serious or severe drug induced liver injury attributable to the trial IMP (see Section [5.2.6.1.4](#)), other AEs, other diseases, or pregnancy
- The trial participant develops suicidal ideation of type 4 or 5 in the Columbia-Suicide Severity rating Scale (C-SSRS) or any suicidal behaviour
- The trial participant is unable to receive trial treatment consecutively for 16 weeks or more for any reason.
- In case a trial participant becomes pregnant during the trial the IMP should be discontinued (see 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.

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

Trial participants who discontinue treatment permanently and prematurely prior to the planned EoT visit, should be registered as discontinued from treatment in IXRS. These participants should follow the scheduled visits as much as possible as defined in the [Flow Chart](#); the EoT visit procedures should be conducted either immediately or as soon as possible, followed by the Follow-up visit (EoS) 16 weeks after the last trial drug administration date. All efforts should be made to keep the trial participant in observation for at least 16 weeks after the last dose of the trial drug for safety reasons.

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.

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

Even if the IMP is discontinued, the trial participants will remain in the trial and, given their agreement, undergo the procedures for early treatment discontinuation and follow-up as outlined in the [Flow Chart](#) and Section [6.2.3](#).

In case of a temporary reason, trial IMP should be restarted if medically justified; please see Section [4.1.4](#).

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 IMP discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after IMP discontinuation (see Section [3.3.4.1](#)).

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 GCP, 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/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 Matching placebo solution for injection

Substance:	Placebo matching to spesolimab
Pharmaceutical formulation:	Solution for injection
Unit strengths:	Placebo matching spesolimab pre-filled syringes (fill volume: 2 mL)
Mode of administration:	Subcutaneous injection
Posology:	See Section 3.1

Table 4.1.1: 2 Test product spesolimab solution for injection

Substance:	Spesolimab
Pharmaceutical formulation:	Solution for injection
Unit strengths:	
Mode of administration:	Subcutaneous injection
Posology:	(See Section 3.1)

4.1.2 Selection of doses in the trial and dose modifications

dose ranging trial 1368-0098 Part 1 is available and justifies adjustments to preserve or optimize participant benefit/risk positive ratio.

4.1.3 Method of assigning trial participants to treatment groups

Participant will be treated with spesolimab as indicated in the [Flow Chart](#) and Section . An Interactive Response Technology (IXRS) system will be used in this trial in order to dispense medication kits as well as manage initial/re-supply ordering of medication kits. The trial site will be required to complete the appropriate module within the IXRS system. The investigator will receive all necessary instructions to access the IXRS system from the sponsor or chosen provider. Detailed IXRS transactions and procedures will be documented in the user requirement specifications mutually agreed to by the sponsor and the IXRS provider. Note that the medication number is different from the patient number.

The IXRS system will be set-up with the option to dispense the IMP kits for the next upcoming remote visit to allow for home IMP administration (where permitted locally) as well as reserve IMP kits in case of any unexpected damage of IMP kits for home administration. Participants will be thoroughly trained and provided with packaging material

for transportation of IMP from site to their home. Detailed instructions on home drug administration and storage are provided in the ISF.

4.1.4 Drug assignment and administration of doses for each trial participant

Participant will be treated with spesolimab as indicated in the [Flow Chart](#) and Section [3.1](#). The medication will be assigned via IXRS. Detailed instructions for use and handling of spesolimab syringes are provided in the ISF.

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

s.c. dosing (Visit 2- EOT visit)

Trial participants will receive s.c. injections. The s.c. injection site should not be close to a vein, and it should avoid sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses. Detailed instructions for use and handling of prefilled syringes are provided in the ISF. The first trial drug dose will be administered at the site by a HCP/qualified study personnel. Participant/caregiver may then be trained to self-administer the trial drug at each of the next three visits under the supervision of the HCP/qualified study personnel at the site. Starting from Visit 6 participant may opt to self-administer trial drug at home (under supervision of HCP remotely) in between monthly onsite visits. Refer to Section [6](#) for more details. At visits with self-administration of IMP at the site, study personnel must supervise the self-administration by participant and complete the self-administration questionnaire for s.c. spesolimab. The questionnaire captures information whether the participant did injections of spesolimab correctly or not (See Appendix [10.11](#)). Participant must complete e-diary to document IMP administration at home. Site will review diaries during every onsite visit.

Monitoring after administration

Trial participants should be closely monitored for AEs, including signs and symptoms of injection site or systemic hypersensitivity reactions 1 hour following trial drug administration. Trial personnel should observe the injection site for signs of redness, swelling or hardness. They should also ask trial participants about itching, dizziness or shortness of breath. Trial participants should observe the injection site for signs of redness, swelling or hardness after IMP administration at home. They should notify site personnel in case they experience redness, swelling or other changes at the injection site. 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.

Dose modifications or dose adjustments are not permitted except as per protocol (see [Section 3.1](#)). If a dose was missed or trial treatment was temporary discontinued due to any reason, it must be discussed with the Clinical Trial Leader if the dose can be given later or if the treatment can be re-started.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Participant, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this extension will remain blinded. Once an optimal dose is finalized for phase III based on risk/benefit analysis, all participants may be shifted to the final dose. The access to the randomisation code for Visit 1 will be kept restricted until its release for analysis.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IXRS. 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.

4.1.6 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 IXRS system, which will also monitor expiry dates of supplies available at the sites. 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).

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 IMP 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
- Availability of FDA Form 1572 (if applicable)

The IMP is not allowed to be used outside the context of this protocol and 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, inventory at the site, use by each trial participant, and the return to the sponsor or warehouse/drug distribution centre or alternative disposal of unused products in alignment with the sponsor, if applicable. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the IMP and trial participants. The investigator or designee will maintain records that adequately document that trial participants were provided the doses specified by this clinical trial protocol and reconcile all IMPs received from the sponsor. At the time of return to the sponsor, the investigator or designee must verify that all unused or partially used IMP supplies have been returned by the trial participant and that no remaining IMP 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 injection reaction and anaphylactic reaction. In case of systemic hypersensitivity including injection reaction and anaphylactic reaction emerging during or after injection(s) of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to:

- Immediately stop further injections
- 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 systemic hypersensitivity, based on trial participant's clinical course and medical judgment, the injection(s) may be continued in case of mild or moderate systemic hypersensitivity (according to Common Terminology Criteria for Adverse Events (CTCAE) grading in section of the ISF) at lower speed with gradual increase to complete the injections

as detailed in the Instructions for Preparation and Handling of spesolimab / placebo in the ISF. Information about the maximum time between the start of preparation and completion of administration of the solution to the 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 [10.10 \[R11-4890\]](#)) 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.

Active/Latent TB: Tuberculosis testing with IGRA (Quantiferon Gold or T-spot) will be repeated every 52 weeks (as per [Flow Chart](#)). If positive, active tuberculosis must be ruled out. Participants with active tuberculosis must discontinue IMP and active tuberculosis must be reported as an AESI. If latent tuberculosis that was not previously treated per local guidelines is identified, participant may continue IMP if treatment of latent TB is initiated and completed as per local guidelines.

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.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

Medications that are restricted during the trial are detailed in [Table 4.2.2: 1](#).

Please see Section [3.3.4.1](#) for withdrawal information regarding the use of restricted medications.

Table 4.2.2: 1 Restricted Medications

Medication	From Day 1 to EOT
Parenteral antibiotics ¹	Restricted for HS
Systemic corticosteroids ²	Restricted for HS
Immunomodulatory/Immunosuppressive biologics ³	Restricted for HS and non-HS indications
Other systemic immunomodulatory and immunosuppressive agents	Restricted for HS and non-HS indications
Topical JAK inhibitors	Restricted for HS
Live vaccines ⁴	Restricted

1. Systemic antibiotics are allowed under specific conditions when orally administered, please see Section [4.2.2.1](#).

2. Systemic corticosteroids as short courses, i.e., approximately 1- 2 weeks at the discretion of the investigator, can be used when required for indications other than HS.

3. Use of immunomodulatory/immunosuppressive biologics for any indication may lead to discontinuation of spesolimab.

4. For seasonal influenza vaccines select inactivated vaccines (not live vaccine)

4.2.2.2 Concomitant medication

The following section provides 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.

Concomitant medications refer to any medications taken from screening until EOS, for HS or non-HS indications. All concomitant medications must be captured in the source document and recorded in the eCRF.

4.2.2.3 Antibiotic use during the trial

- Systemic antibiotics are permitted for HS disease worsening (as defined per protocol).
- Doxycycline or an acceptable oral alternative (parenteral antibiotics are not allowed) as per investigator might be used up to 2 weeks for each episode of disease worsening.
- Systemic antibiotics can be used for non-HS indications.

4.2.2.4 Analgesics use during the trial

Opioid analgesics other than tramadol are restricted for HS. Use of opioid analgesics under certain circumstances can be allowed after discussion with sponsor. For non-HS indications opioid analgesics can be allowed as per investigator discretion.

If a trial participant is on a non-opioid analgesic for HS and non-HS indication (e.g. osteoarthritis), the participant may continue the analgesic treatment.

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.

4.2.2.5 Lesion intervention

Lesion intervention as concomitant non-drug therapy are allowed in the event that an acutely painful lesion occurs and requires immediate intervention. Only 2 types of interventions are allowed in this trial:

1. intra-lesional steroid injection of triamcinolone up to 20 mg can be used for a single lesion at one time.
2. 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 source document and recorded in the eCRF.

Definitions:

- HS disease worsening is defined as total AN count is 150% of baseline (V1) AN count. For example, for a baseline AN count of 10, disease worsening should be interpreted as an AN count of 15 and above.
- Rescue medication: the treatment of HS disease worsening and includes systemic antibiotics and/or immunosuppressive biologics such as TNF-inhibitors.

4.2.2.6 Contraception requirements

Throughout the trial and for a period of at least 16 weeks after the last dose of IMP, women of childbearing potential 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.

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

Or trial participants must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the trial participant. Complete abstinence (refraining from heterosexual intercourse) is considered a highly effective method of contraception only if it is in line with the preferred and usual lifestyle of the trial participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to trial IMP, and withdrawal are not acceptable methods of contraception.

Female participants

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

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.

4.2.2.7 Restrictions on diet and lifestyle

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

4.3 TREATMENT COMPLIANCE

Administration of the subcutaneous injection will be done by a trained healthcare professional or by the participant trained to perform self IMP administration under the supervision of HCP (in person or remote). The measured plasma concentrations will provide additional confirmation of compliance.

Trial participants are requested to bring all remaining trial IMP, including empty package material, with them when attending visits.

Based on subcutaneous injection counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorized by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of s.c. injections (4 injections per dose) actually received} \times 100}{\text{Number of s.c. injections (4 injections per dose) should have been received as per protocol}}$$

If the number of doses taken is not between 80-120%, site staff will explain to the trial participant the importance of treatment compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

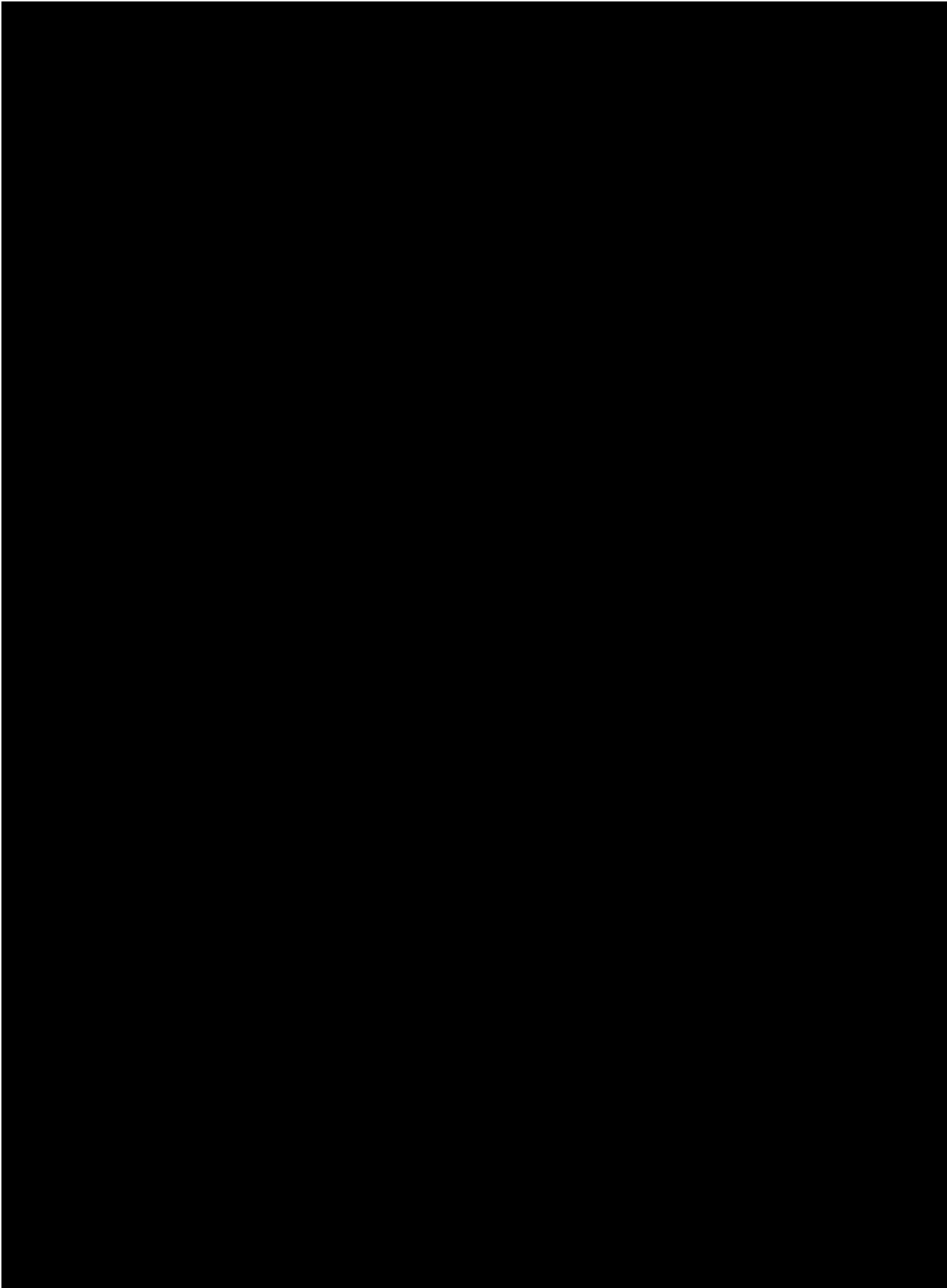
The further endpoints of the trial are specified in Section [2.2.2](#).

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

1. Hidradenitis Suppurativa Clinical Response (HiSCR50)

The HiSCR50 is one of the most well-known and widely used outcome assessments in HS clinical trials. The HiSCR50 is defined as at least a 50% reduction from baseline in the total AN count, with no increase in the abscess or dT count [[R20-2976](#)]. HiSCR50 will be evaluated at the time-points mentioned in the [Flow Chart](#). Details are provided in Appendix [10.2](#).

time-points
mentioned in the [Flow Chart](#), and the detail is provided in Appendix [10.3](#).



5.1.1 Trial Participant Diary

The Patient Global Assessment of HS Pain will be completed on a diary and collected on a daily basis during the 7 days prior to the next scheduled visit as per [Flow Chart](#).

For the daily assessments (7 days prior to visit), 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

5.2.1 Physical examination

A complete physical examination will be performed at screening and at the end of treatment visit. This examination includes, at a minimum, general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. For all other visits indicated in the [Flow Chart](#), 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 body weight will be performed at the time points specified in the [Flow Chart](#). 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 [Flow Chart](#), prior to blood sampling. This includes systolic and diastolic blood pressure and pulse rate (electronically or

by palpation count for 1 minute) in a seated position after 5 minutes of rest. At dosing visits for subcutaneous drug administration, vital signs evaluations will be performed pre-dose and, again, approximately 10 minutes after the end of trial drug administration. Measurement of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements.

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

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in [Table 5.2.3:1](#), and the sampling time points are shown in the [Flow Chart](#).

It is preferred, but trial participants do not have to be fasted for the blood sampling for safety laboratory tests. 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 AEs (refer to Section [5.2.6](#)).

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

The central laboratory will transfer the results of the analysis to the sponsor or delegate.

Table 5.2.3:1 Safety laboratory tests

Category	Test name
Haematology	Hematocrit (Hct)
	Hemoglobin (Hb)
	Glycosylated Hbc (HbA1c) (Only at baseline)
	Red Blood Cell Count/ Erythrocytes
	Reticulocyte Count
	White Blood Cells / Leukocytes
	Platelet Count/ Thrombocytes
Automatic WBC differential	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)
Manual differential WBC (if automatic differential WBC is abnormal)	Neutrophils, bands (Stabs)
	Neutrophils, polymorphonuclear (PMN)
	Eosinophils
	Basophils
	Monocytes
Coagulation	Lymphocytes
	Activated partial thromboplastin time (aPTT)
	Prothrombin time (PT)
Enzymes	INR
	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

Category	Test name
Substrates	Glucose
	BUN (blood urea nitrogen)
	Uric acid
	Creatinine ²
	eGFR (estimated by CKD-EPI formula) (only at Visit 1)
	Bilirubin Total
	Bilirubin Direct (if total is elevated)
	Bilirubin Indirect (if total is elevated)
	Troponin (Reflex, in case of elevated CK)
	Protein, total
	Albumin
	C-Reactive Protein (CRP & hs-CRP) (high sensitivity)
	Cholesterol, total
	Triglycerides
	LDL-Cholesterol
	HDL-Cholesterol
Electrolytes	Calcium
	Sodium
	Potassium
	Chloride
	Bicarbonate
Specific gamma-globulin quantification	IgE ¹ , IgG
Urine Pregnancy test (only for WOCBP)	Human Chorionic Gonadotropin in urine
Serum Pregnancy test (only for WOCBP if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Urinalysis (dipstick)	Urine Nitrite
	Urine Protein
	Urine Glucose
	Urine Ketone
	Urobilinogen
	Urine Bilirubin
	Urine RBC/ Erythrocytes / Blood
	Urine WBC/ Leukocytes
	Urine pH
	Specific gravity
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

Category	Test name
Urine (only at Visit 1)	Albumin (quantitative)

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 standardized
CREJ	Creatinine, Jaffe, Not IDMS	creatinine	Jaffe reaction, Not IDMS standardized

Table 5.2.3: 2 Infection testing at Visit 1, 27, and EoT

Functional lab group	Test name
Infection Testing	Hepatitis B Surface Antigen (qualitative) Hepatitis B core Antibody Hepatitis B Surface Antibody (qualitative) (Only for Japan) HBV-DNA PCR(quantitative) ¹ QuantiFERON®-TB Gold Plus ^{2,3} Hepatitis C Antibody (qualitative) HIV-1, and HIV-2 Antibody (qualitative)

¹A HBV-DNA PCR test should be conducted if Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative. Positive HBV DNA PCR meets exclusion or discontinuation criteria. (Only for Japan: Positive Hepatitis C antibody should be confirmed with Hepatitis C RNA PCR.

²At V1, if the 1st QuantiFERON® (or if applicable, T-Spot®) -TB test result is suspected false positive or indeterminate, a retest may be performed once. If the retest QuantiFERON®-TB test result is indeterminate, a TST (i.e. PPD skin test) to rule out TB can be performed at the site. A tuberculin skin test reaction $\geq 10\text{mm}$ ($\geq 5\text{mm}$ if receiving $\geq 15\text{mg/d}$ prednisone or other immunosuppressant) is considered positive.

<For Japan> T-Spot® TB test may be performed at local labs instead of QuantiFERON®-TB test.

³ In subjects with a negative QuantiFERON®-TB test or TST (i.e., PPD skin test) the test should be repeated once a year and at EOT.

5.2.4 Electrocardiogram

The 12-lead ECG must be administered at timepoints shown in the [Flow Chart](#) by a qualified technologist, and results will be recorded. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in the participant's medical record.

Clinically relevant abnormal findings will be reported either as baseline conditions (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](#). Please refer to the current list of "Always Serious AEs" provided in eDC.

5.2.5.1 Local tolerability

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

5.2.5.2 Suicidal risk assessment by the C-SSRS

Suicidal thoughts and behaviour will be assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS) [[R08-1147](#)] (Appendix [10.9](#)). 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. For remote visits, the trained site personnel will administer the C-SSRS via tele/videoconferencing.

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 participants 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 AE of special interests (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 related or not.

The following should also be recorded on the appropriate eCRF(s):

- Worsening of the underlying disease (for definition, see Section [4.2.2.3](#)) or of other pre-existing conditions.
- Changes in vital signs, ECG, physical examination findings, and / or laboratory test results, if judged clinically relevant by the investigator

5.2.6.1.2 Serious adverse event

An SAE is defined as any AE that 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” and “AE reporting to sponsor and timelines”.

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; see Section [5.2.6.2.2](#).

The following are considered as AESIs:

Systemic hypersensitivity including 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 [10.10](#) [[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, posttransplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), TB, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffeii, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas’ disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), hepatitis C virus progression [[R17-2617](#)].

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](#).

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 that occur after the first dose of IMP:

1. AST or ALT elevation $\geq 3 \times \text{ULN}$ and total bilirubin $\geq 2 \times \text{ULN}$ measured at the same visit, or in samples drawn within 30 days of each other, OR
2. AST or ALT elevation $\geq 3 \times \text{ULN}$ and INR $\geq 1.5 \times \text{ULN}$ measured at the same visit, or in samples drawn within 30 days of each other, OR
3. AST or ALT elevation $\geq 3 \times \text{ULN}$ 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 $\geq 5 \times \text{ULN}$

These laboratory findings constitute a hepatic injury alert, and participants showing any of these laboratory 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 laboratory results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary, in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI Checklist should be followed.

Additionally, with participants having a normal AST and ALT at baseline, the emergence of an isolated AST or ALT elevation between ≥ 3 -fold and $< 5 \times$ ULN requires repeat testing within 72 hours. DILI Checklist is not required unless repeat testing triggers alerts 1, 2, 3, or 4.

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

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

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

The following events should lead to immediate discontinuation of trial IMP (active or comparator) in participants with abnormal AST and ALT at baseline.

- Hepatic injury alerts number 1, 2, or 3
- AST or ALT $> 5 \times$ baseline or > 500 U / L (whichever occurs first)
- Any magnitude of ALT or AST elevation above baseline and any new or worsening signs and / or symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$)

Following completion of the DILI Checklist, if the Boehringer Ingelheim IMP cannot be excluded as a possible cause of the DILI event, discontinuation should be made permanent without rechallenge.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of AEs should be classified and recorded in the eCRF 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 Boehringer Ingelheim IMP, 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 a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the IMP
- 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 IMP exposure
- Evidence that the event is reproducible when the IMP is reintroduced

- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or comedications)
- 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 no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of IMP exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of IMP administration; an allergic reaction weeks after discontinuation of the IMP concerned)
- Continuation of the event despite the withdrawal of the IMP, 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 IMP concerned
- Disappearance of the event even though trial IMP treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

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 Boehringer Ingelheim paper SAE form should be used; see Section [5.2.6.2.2](#).

The following must be collected and documented by the investigator:

- From the first dose of trial medication of this trial until the individual participant's EoS:
 - all AEs (serious and non-serious) and all AESIs.

Note: All AEs that started in the parent trial (onset date in parent trial) and are still ongoing until the first dose of the extension trial 1368-0130 are to be re-recorded in the extension trial eCRF with the same information as it was recorded in the parent trial.

For further details specific to the AE reporting in the eCRF, see the Trial Specific Instructions for CRF Completion in the ISF.

- After a participant's EoS visit in the extension trial 1368-0130:

- the investigator does not need to actively monitor the participant for new AEs but should but should only report new malignancies or the exacerbation of existing malignancies, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call.

Reporting of SAEs will be done via the eCRF in the EDC system until clinical database is available for data entry. After database lock, reporting will be done only via paper SAE form.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs that are relevant for the reported SAE or AESI on the AE eCRF immediately (within 24 hours of becoming aware of the event) triggering a data transfer to the sponsor's unique entry point. The country-specific process will be described in the ISF. On 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 must be provided. For follow-up information, the same rules and timelines apply as for initial information. All AEs / SAEs, including those persisting after an 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 Boehringer Ingelheim 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 IMP, the investigator must report any IMP 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 IMP 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 (Parts 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, an SAE and / or AESI associated with the pregnancy must be reported as described in Section [5.2.6.2.2](#).

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

There is no endpoint pertaining to PK. Spesolimab concentrations will be reported descriptively. No PK parameters will be calculated. PK data may be incorporated into a pooled pharmacometrics analysis with other spesolimab trials. Also, ADAs will be measured, and their impact on PK will be assessed. The relationship between PK and selected efficacy endpoints, biomarkers, and AEs may be assessed. PK and demographic data together with treatment assignments and dosing information may be made available to individuals outside of the trial team for the purpose of PK dataset generation in accordance with sponsor's standard procedures.

Trial participants do not have to be fasted for the PK and ADA/Nab blood sampling. Refer to the [Flow Chart](#) 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. At trial visits with trial drug administration, pre-dose PK/ADA/Nab samples will be obtained approximately within 2 hours prior to start of s.c. injection.

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 trial samples will be discarded after completion of the additional investigations but not later than 5 years upon the final trial report has been signed.

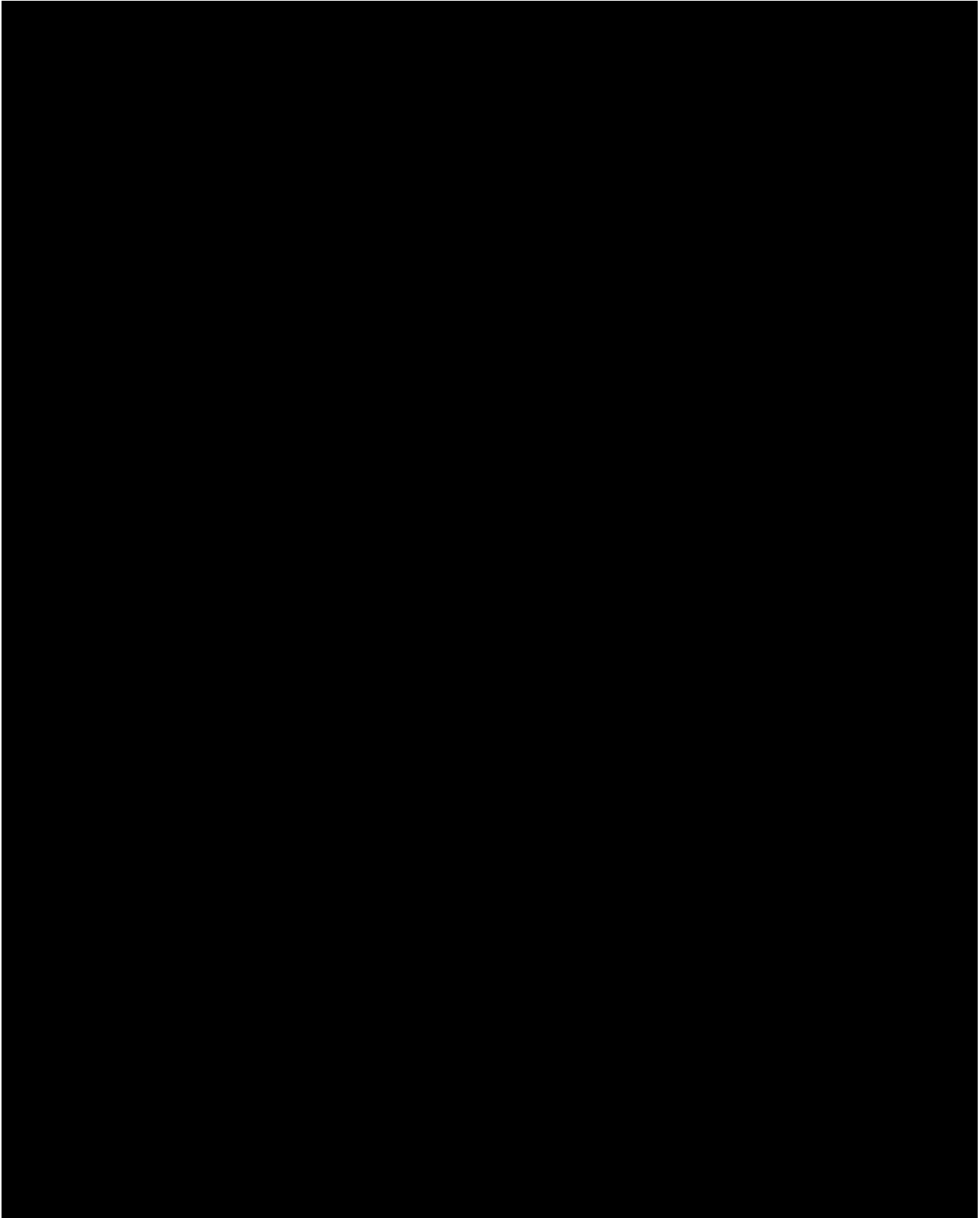
5.3.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of spesolimab plasma concentrations, approximately 3.0 mL of blood will be taken from a forearm vein into a K2EDTA (ethylenediaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the [Flow Chart](#) 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 K2EDTA anticoagulant blood-drawing tube at the time-points listed in the [Flow Chart](#) 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 [Flow Chart](#) 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.



5.5 BIOBANKING

Not applicable.

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.

Self-administration questionnaire for s.c. spesolimab

At Visits 3,4,5 trial drug may be self-administered under supervision of trial personnel. Trial personnel must supervise the self-administration by participant /caregiver and complete the self-administration questionnaire for s.c. spesolimab. The questionnaire captures information whether the participant did injections of spesolimab correctly or not (See Appendix [10.11](#)).

5.7 APPROPRIATENESS OF MEASUREMENTS

All methods used in this trial are standard methods.

6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstance (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, but will not be limited to, virtual trial participant visits and assessments, home healthcare nurse visits, direct-to-participant shipments of IMP, direct-from-participant shipments of IMP, or biological sample pick up from the participant's home. The implementation of these measures will depend on the participant's consent, operational feasibility, and local laws and regulations. Such alternative measures will be described in the participant information. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

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

The trial consists of a screening period, treatment period and a follow-up period:

Screening period:	up to 1 week
Treatment period:	76 weeks
Follow-up period:	16 weeks

V1 of this extension trial should preferably be performed during the EoT visit of the parent trial (1368-0098; 1368-0100). When the visits are performed on the same day, duplicate procedures across studies are performed only once during the EoT/V1. First trial drug administration is planned at Visit 2 after results of safety and infection tests will be available to confirm eligibility. If further work up is required e.g., a re-test of safety labs, the screening period may be extended by up to 7 more days.

If these visits are not performed on the same day, then either all V1 procedures need to be performed at that visit or a modification of procedures will be considered after discussion with the sponsor. If a participant is unable to roll over on the day of the EoT Visit of the parent trial because of medical reasons, then they can be permitted to rollover preferably within 2 weeks of the EoT Visit of the parent trial. During this gap, if required, participant can take systemic and topical antibiotics in case of disease worsening, flare, or according to investigator best clinical judgement. However, biologics, immunomodulators and opioid analgesics are not allowed for HS and non-HS indications. No participant can enter this trial if more than 16 weeks have elapsed between last administration of IMP at parent trial and V2 of 1368-0130 trial (See inclusion criteria Section [3.3](#)).

All participants are to adhere to the visit schedule specified in the [Flow Chart](#) with a time window for rescheduling. Any deviations from the planned visit schedule are to be documented. If any visit has to be rescheduled, subsequent visits should follow the original visit schedule. Additional visits for the purpose of retesting laboratory parameters or AE monitoring may be included as deemed necessary by the Investigator.

Approximately 40% of the visits may be conducted remotely from the participant's home using a videoconferencing platform offering the Investigator and/or site personnel a direct line of oversight and communication with the participant (with local approval). If the participant does not feel comfortable with remote visits, including IMP self-administration, these can be replaced by site visits. However, such modification has to be arranged with the site personnel in a timely manner.

The type of visit, on-site visit, or remote (home) visit, will be documented in the clinical history and it will be reflected in the eCRFs. Trial procedures to be performed at each visit are listed in the [Flow Chart](#) and the respective protocol sections. Please, refer to [Section 5](#) for explanations of procedures.

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

At visits requiring safety labs and urine pregnancy test procedures, they should take place prior to the trial drug administration. Pre-dose PK/ADA samples will be obtained approximately within 2 hours prior to s.c. injections 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 [Flow Chart](#)):

1. C-SSRS
2. PROs
3. AE and concomitant therapy collection
4. Physical examinations (including pre-dose vital signs)
5. ECG
6. Abscess, inflammatory nodule count, non-inflammatory nodule count
7. Draining tunnel count, non-draining tunnel count
8. [REDACTED]
9. Blood and urine sampling, urine pregnancy testing (if applicable), pK, ADa/NAbs, and biomarkers.
10. Assign (IXRS)/Administer trial drug
11. Local tolerability
12. 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 participant 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.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

In the event of force majeure or other disrupting circumstance, remote visits may 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 not 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
- [REDACTED]

Those questionnaires will be available in electronic format; paper versions will be provided as backup, but electronic versions are strongly preferred. These questionnaires should be answered by the participant at all timepoints indicated in the [Flow Chart](#). If a paper backup needs to be used is used, participant must confirm completion and return the paper copies at the next onsite visit.

6.2.1 Screening period

Visit 1 (V1) should preferably be performed in one visit combined with End of Treatment visit of parent trials 1368-0098 or 1368-0100. Procedures performed at the last visit of parent trials should not be repeated at V1 of 1368-0130 trial.

After participants have been informed about the trial, written informed consent in accordance with GCP and the local legislation must be obtained prior to performing any trial related procedures. Informed consent date will be reported in the eCRF.

Once consent is obtained, the participant is considered to have started the screening process and is assigned a unique patient number by the IXRS system. The participant is to be recorded on the enrolment log and be registered in the IXRS system as a screened participant. Trial requirements, including the procedure for the follow-up of prematurely withdrawn participant, must be fully explained to the participant and written informed consent obtained prior to initiating any trial-related evaluation. The importance of staying in the trial until completion of all requirements is to be emphasized.

During the screening visit, demographics information will be collected. This includes:

- Age (in years) on the day of informed consent
- Sex (male or 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 characterize the participant population and as a basis for contraception requirements.
- Ethnicity and race in order to sufficiently characterize the participant population, to support possible subgroup analyses if needed, unless not acceptable according to local regulations

Baseline conditions

This refers to chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, ECG, safety labs, and any condition requiring therapy (excluding HS).

- Baseline conditions from the parent trials need to be re-considered and those which are still ongoing after signing the informed consent of the extension trial need to be re-recorded with the same information in the eCRF of the extension trial.
- Any new baseline condition needs to be recorded in the eCRF of the extension trial (for example, a missed baseline condition from the parent trial)

Any clinically relevant findings identified from the physical examination, ECG, or safety labs (unless reflective of a known baseline condition, e.g. chronic anemia) at screening should be reported as AEs and do not need to be recorded as baseline conditions.

Medical history

Past medical history reported in the parent trial eCRF is not re-recorded in the extension trial eCRF. If some historical information was missed in the parent trial, it should be recorded to the parent trial if it is not yet locked. If the parent trial is already locked, the missed information can be entered in the extension trial eCRF. If a new condition developed but recovered during the parent trial this can be recorded in the extension trial if considered relevant information by the investigator.

Re-screening

- If a participant results in a screen failure (i.e. does not meet the eligibility criteria) the participant must be registered as a screen failure in IXRS system. However, re-screening of a previously screen failed participant will be permitted once per participant. Details of IXRS procedures can be found in the IXRS 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 [Flow Chart](#).

6.2.2 Treatment period(s)

The treatment period is lasting from Visit 2 until End of Treatment (EOT) Visit. For the comprehensive list of the trial procedures required during these visits please refer to the [Flow Chart](#) and its footnotes. See also Section [5.2](#) for details of all safety assessments.

Upon completion of screening and confirmation of participant eligibility, participant can directly be assigned to blind s.c. maintenance treatment. Trial drug allocation via the IXRS system and administration of trial drug should be the last activity at visits with trial drug administration, with the exception of post dose vital signs assessments. Details relating to trial drug administration are provided in [Section 4.1.4](#).

6.2.3 Follow-up period and trial completion

For the comprehensive list of the trial procedures required at the EOT and the EoS visits please refer to [Flow Chart](#) and its footnotes.

The EoS visit will take place at the end of the REP which is 16 weeks after last injection of trial medication.

Participant who discontinues trial treatment prematurely should undergo the EoT visit as soon as possible, and the EoS Visit 16 weeks thereafter. If a participant discontinues the trial during a scheduled treatment visit then the visit is considered an EoT visit.

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

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

For all treated participant, termination of trial medication (EoT) and trial completion (EoS) must be recorded on the corresponding eCRF.

A trial participant is considered to have completed the trial if one of the following applies:

- Completion of planned follow-up period i.e. EoS Visit completed)
- Lost to follow-up
- Refusal to be followed-up
- Death

Treatment completion is defined as a trial participant having completed treatments until planned EoT visit (Week 78).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This multi-regimen, extension trial is designed to collect the long-term safety and efficacy of spesolimab in eligible participants with HS who have completed trial treatments in their parent trials and to keep participant's access to the treatments as far as they are considered beneficial.

The primary objective of this trial is to assess the long-term safety of spesolimab in participant with HS who have completed approximately [REDACTED] of spesolimab treatment in Part 1 or Part 2 of trial 1368-0098 and trial 1368-0100.

Approximately [REDACTED] participants may enter this trial and the entry will be made participant by participant level once he/she has completed treatments at the end of treatment (EoT) visit specifically at following timing which are considered equivalent at Day 1 on this trial: at Week [REDACTED] on Part 1 of trial 1368-0098, at Week [REDACTED] on Part 2 of trial 1368-0098 or at Week [REDACTED] on trial 1368-0100.

The primary endpoint is the occurrence of treatment emergent adverse events (TEAE) up to the end of maintenance treatment period including residual effect period (REP; i.e., [REDACTED] weeks after the administration of the last trial treatment).

7.1 NULL AND ALTERNATIVE HYPOTHESES

Given the objective of this trial and the nature of the trial, no hypothesis testing will be conducted. All statistical assessments will be performed in descriptive manner to understand safety and efficacy profiles of spesolimab better. [REDACTED]

7.2 PLANNED ANALYSES

7.2.1 General considerations

Important protocol deviations of the protocol will include deviations of key inclusion and exclusion criteria, concomitant medication use of restricted medications, and any other deviations of . the protocol deemed important by the trial team. All decisions concerning important protocol deviations will be made prior to the final database lock (DBL) for this extension trial.

As described in Section [4.1.2](#), participant receive the same dosing regimen as in their parent trials until information from dose ranging trial 1368-0098 Part 1 has been available and optimal dosing regimen has been confirmed. All participants with wrong trial treatment will be listed.

Standard statistical parameters (number of non-missing values, mean, standard deviations, median, quartile, minimum and maximum) or frequency table including participant frequencies and percentages will be calculated where appropriate.

7.2.1.1 Analysis sets

Enrolled Set (ES): composed of all participants who have signed informed consents. Trial participant disposition will be based on ES.

Treated Set (TS): composed of all participants who have received at least 1 dose of trial treatment. All baseline characteristics, safety and efficacy analyses will be based on TS.

For efficacy and safety listings, all collected data will be presented denoted with the population inclusion flag for ES.

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

7.2.2 Handling of Intercurrent Events

The primary endpoint of this trial is the occurrence of treatment emergent adverse events (TEAEs). For safety and efficacy endpoints, the expected intercurrent event of interest in this trial is permanent trial treatment discontinuation. The strategy for handling intercurrent events is as follows:

While-on-Treatment: This is the effect of trial treatment while participants are taking the treatments. Intercurrent events will be handled by default using the while-on-treatment approach as defined in ICH E9(R1), with the trial treatment period defined as the period from the first administration of trial treatment (in this trial) to the end of the residual effect period (REP) following last administration of trial treatment (i.e., ■ weeks after the administration of the last trial treatment).

Further details will be discussed in the trial statistical analysis plan (TSAP).

7.2.3 Primary objective analyses

Number and percentage of participant with treatment emergent adverse events (TEAEs) will be presented for the primary endpoint based on Treated Set (TS). Treatment-emergent is defined as the first administration of trial treatment on this trial until the end of trial treatment period including residual effect period (REP), namely the last administration of trial treatment plus ■ weeks.

Refer to Section [7.2.6](#) for further details.

7.2.4 Secondary objective analyses

There are no secondary objectives planned in this trial.

7.2.5 Further objective analyses

Further endpoints are listed in Section [2.2.2](#).

For continuous endpoints, the efficacy data will be presented based in descriptive manner

over time where any data collected.

For time to event endpoints, Kaplan-Meier estimates of the event-free/failure probabilities as well as median time-to-event will be estimated along with 95% confidence interval in exploratory manner.

For binary endpoints, the efficacy data will be presented over time where any data collected.

TS will be used for all the analysis unless otherwise specified.

7.2.6 Safety analyses

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard Boehringer Ingelheim summary tables and listings will be produced. All AEs with an onset between start of trial treatment and end of the REP, a period of Week 16 as defined in Section [1.2](#) after the last dose of trial treatment, will be assigned to the on-treatment period for evaluation.

In general, safety analyses will be descriptive in nature and will be based on Boehringer Ingelheim standards. TS will be used for safety analysis.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs, i.e. all AEs occurring between the start of treatment and the end of the REP. For AEs that start before first administration of trial treatment and deteriorate under treatment, AEs on or after deterioration will be considered ‘treatment-emergent’, unless otherwise specified.

Frequency, severity, and causal relationship of AEs 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 the start of treatment.

7.2.7 Other Analyses

Pharmacokinetics

Please refer Section [5.3.1](#) and further information will be available in the TSAP.

Biomarker analysis

Please refer Section [5.4](#) for the biomarker assessments. The analysis for these assessments will be mainly descriptive.

Further details will be discussed in the TSAP.

7.2.8 Interim Analyses

No interim analysis is planned at this moment for this non-pivotal trial. However, considering the trial objective to collect long-term safety and efficacy on the use of spesolimab in this population, multiple data look may be performed once all participants have been unblinded in order to support regulatory interactions, publication and other purposes. These will be further discussed in the TSAP and/or a separate analysis plan with the purpose. But the primary analysis may be conducted while the data collection for selected other analyses is still ongoing.

Regardless, if these analyses will be conducted, then it will be documented in the decision log.

7.3 HANDLING OF MISSING DATA

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

Further details will be discussed in the TSAP.

7.4 RANDOMISATION

This is a multi-regimen trial and treatment assignments have been determined in the parent trials, which will be carried over to this trial. No randomization procedure is included in this trial.

7.5 DETERMINATION OF SAMPLE SIZE

Given the descriptive nature of this trial, no sample size calculation has been performed. The sample size of this OLE is determined based on the sample size of the preceding parent trials (1368-0098, 1368-0100).

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for GCP, relevant Boehringer Ingelheim SOPs, 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 the trial participants and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to 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 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 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 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 be 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 designee, IRB / IEC, or 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 [4.1.5.2](#) for rules about emergency code breaks. For drug accountability, refer to Section [4.1.8](#).

8.3.1 Source documents

A detailed description of the transmission of electronic data (i.e. data flow) is provided in the data management plan.

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 attributable, legible, contemporaneous, original, and accurate. 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 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 been properly removed or redacted from all copies of the participant's 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 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 of trial IMP
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory] and end date [if available])
- SAEs (onset date [mandatory] and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of participant's participation in the trial (end date; in case of premature discontinuation, document the reason)
- Prior to allocation of a trial participant to a treatment in 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 diary 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 and 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 consent forms. 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 circumstance (e.g. pandemic or war; see Section [6](#)), site access may be restricted, thus limiting the ability to perform standard site monitoring activities on site, such as source data review and source data verification. Therefore, some of these activities may be performed remotely or replaced by centralized 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 site(s):

The trial site(s) must retain the source and essential documents (including ISF) according to the contract or local requirements valid at the time of the end of the trial (whichever is longer).

Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

Boehringer Ingelheim is responsible for fulfilling their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND TRIAL PARTICIPANT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of participant data in accordance with the principles 7 and 12 of the World Health Organization ICH-GCP handbook. Individual participant data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred
- The participant must be informed that their personal trial-related data will be used by the sponsor in accordance with local data protection law. The level of

disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent

- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, appropriate IRB / IEC members, and inspectors from regulatory authorities
- The sponsor has implemented privacy and security controls designed to help protect participants' personal data, including information security controls, firewalls, incident detection, and secure transfer measures
- In the event of an accidental or unlawful destruction, loss, alteration, unauthorized disclosure, or access to personal data ("breach"), the sponsor has implemented procedures and measures to promptly address and mitigate any risk to the participant. In the event of a breach, the sponsor will notify the appropriate regulatory authorities and/or the participant(s) in accordance with applicable data protection law
- The contract between sponsor and trial sites specifies the responsibilities of the parties related to data protection, including the handling of data security breaches and respective communication and cooperation of the parties
- Information technology systems used to collect, process, and store trial-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access

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 must be in accordance with the separate biobanking informed consent
- The Boehringer Ingelheim 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, including 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 IMP (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial IMP 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 sponsor will prepare a clinical trial report within 1 year from the end of trial (6 months for paediatric trials).

The sponsor will notify the IEC / competent authority in each participating EU member state about all required 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 1 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.

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 and include members who are independent of Boehringer Ingelheim. DMC members will include physicians experienced in the treatment of the disease under investigation and a statistician.

The DMC will evaluate safety and 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 decision by Boehringer Ingelheim, will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs / IECs, and to investigators as required by local law. The tasks and responsibilities of the DMC are specified in a charter.

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

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

Boehringer Ingelheim 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, Clinical Research Associates (CRAs), and investigators of participating countries

In the participating countries, the trial will be performed by the respective local or regional Boehringer Ingelheim organisation (Operative Unit [OPU]) in accordance with applicable regulations and Boehringer Ingelheim 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 Boehringer Ingelheim according to Boehringer Ingelheim SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to Boehringer Ingelheim SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory service, and an IXRS vendor will be used in this trial. Details will be provided in the IXRS manual and central laboratory manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

- R20-3184 Zouboulis CC, Marmol V del, Mrowietz U, et al. Hidradenitis suppurativa/acne inversa: criteria for diagnosis, severity assessment, classification and disease evaluation. *Dermatology (Basel)*; 2015; 231(2); 184-190
- R20-3177 Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol*; 2015; 29; 619-644.
- R20-3046 Kimball AB, Kerdel F, Adams D, et al. Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomized trial. *Ann Intern Med*; 2012; 157; 846-855.
- R05-2548 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) - a simple practical measure for routine clinical use. *Joint Ann Mtg of the British Association of Dermatologists and the Canadian Dermatology Association*, Oxford, 6/Jul/1993 - 10/Jul/1993; *Clin Exp Dermatol*; 1994; 19; 210-216.
- R22-3282 Phan K, Charlton O, Smith SD. Global prevalence of hidradenitis suppurativa and geographical variation: systematic review and metaanalysis. *Biomed Dermatol*; 2020; 4; 2
- R23-2963 Kimball AB, Jemec GBE, Alavi A, et al. Secukinumab in moderate-to-severe hidradenitis suppurativa (SUNSHINE and SUNRISE): week 16 and week 52 results of two identical, multicenter, randomized, placebo controlled, double-blind phase 3 trials. *Lancet*; 2023; 401(10378); 747-761.
- R11-4890 Sampson HA, et al. Second symposium on the definition and management of anaphylaxis: summary report second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium 2nd Symp of the National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis (FAA) Network on the Definition and Management of Anaphylaxis ; *J Allergy Clin Immunol*; 2006; 117(2); 391-397.
- R17-3632 Mahil SK, Catapano M, Meglio P di, et al. An analysis of IL-36 signature genes and individuals with IL1RL2 knockout mutations validates IL-36 as a psoriasis therapeutic target. *Sci Transl Med*; 2017; 9; ean2514
- R20-3156 Kirby JS, Thorlacius L, Villumsen B, Ingram JR, Garg A, Christensen KB, et al. The Hidradenitis Suppurativa Quality of Life (HiSQOL) score: development and validation of a measure for clinical trials. *Br J Dermatol*; 2020; 183; 340-348.
- R08-1147 Posner K. State of the science: measurement of suicidal adverse events and the Columbia Suicide Severity Rating Scale. 47th NCDEU Ann Mtg, Boca Raton, 11/Jun/2007 - 14/Jun/2007; 2007; 15
- R20-3045 Zouboulis CC, Tzellos T, Kyrgidis A, et al, European Hidradenitis Suppurativa Foundation Investigator Group. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. *Br J Dermatol*; 2017; 177; 1401-1409.

- R20-2976 Kimball AB, Sobell JM, Zouboulis CC, Gu Y, et al. HiSCR (Hidradenitis Suppurativa Clinical Response): a novel clinical endpoint to evaluate therapeutic outcomes in patients with hidradenitis suppurativa from the placebo-controlled portion of a phase 2 adalimumab study. *J Eur Acad Dermatol Venereol*; 2016; 30; 989-994.
- R17-2617 Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. *Ann Rheum Dis*; 2015; 74; 2107-2116.
- R23-3832 Garg A, Zema C, Ciaravino V, Roller R, et al. Validation of the hidradenitis suppurativa investigator global assessment: a novel hidradenitis suppurativa-specific investigator global assessment for use in interventional trials. *JAMA Dermatol*; 2023; 159(6); 606-612.

9.2 UNPUBLISHED REFERENCES

c03320877-12
c09985235-01

c18789185-01

c37475396

10. APPENDICES

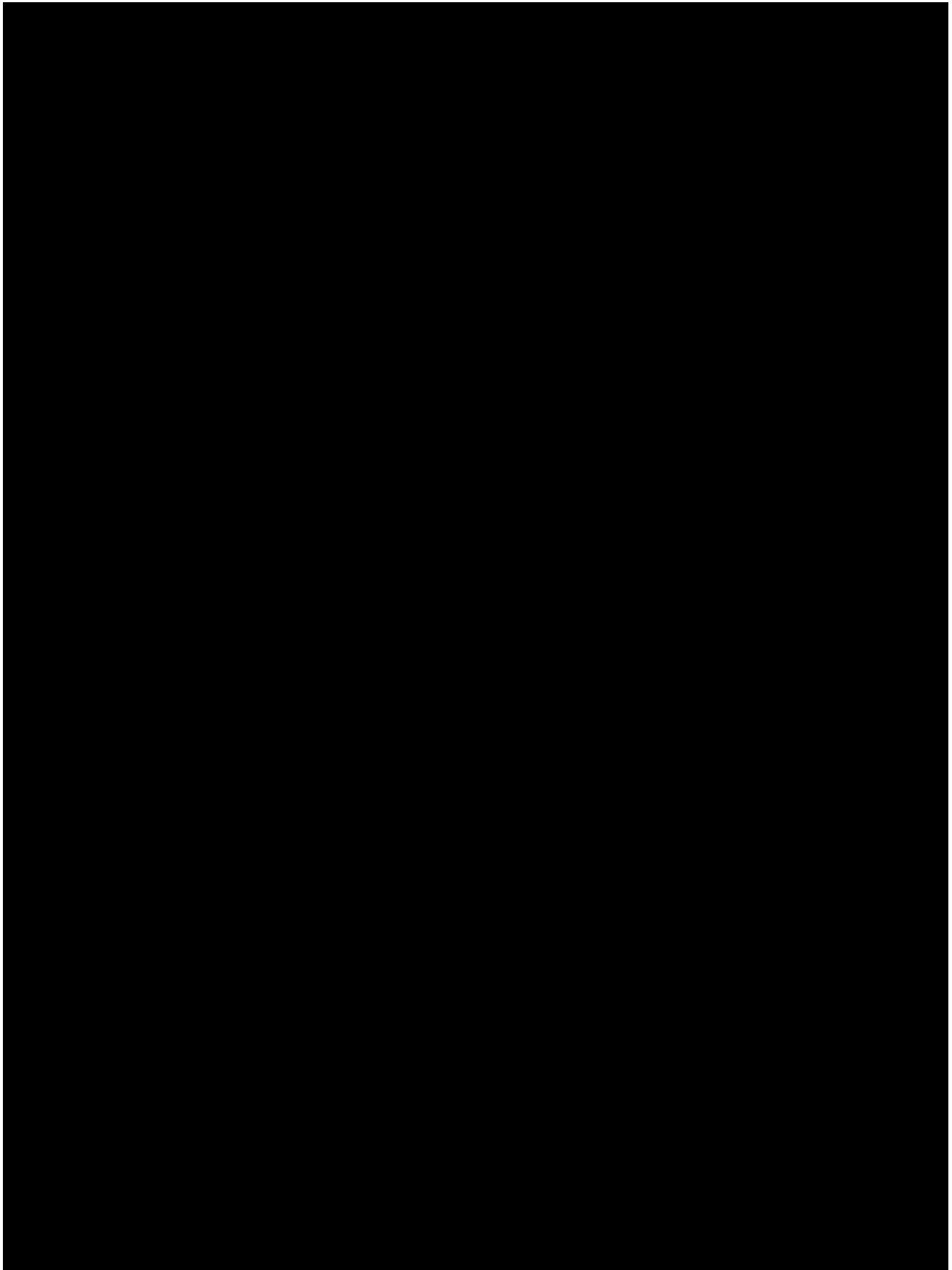
10.1 TRIAL PARTICIPANT FEEDBACK

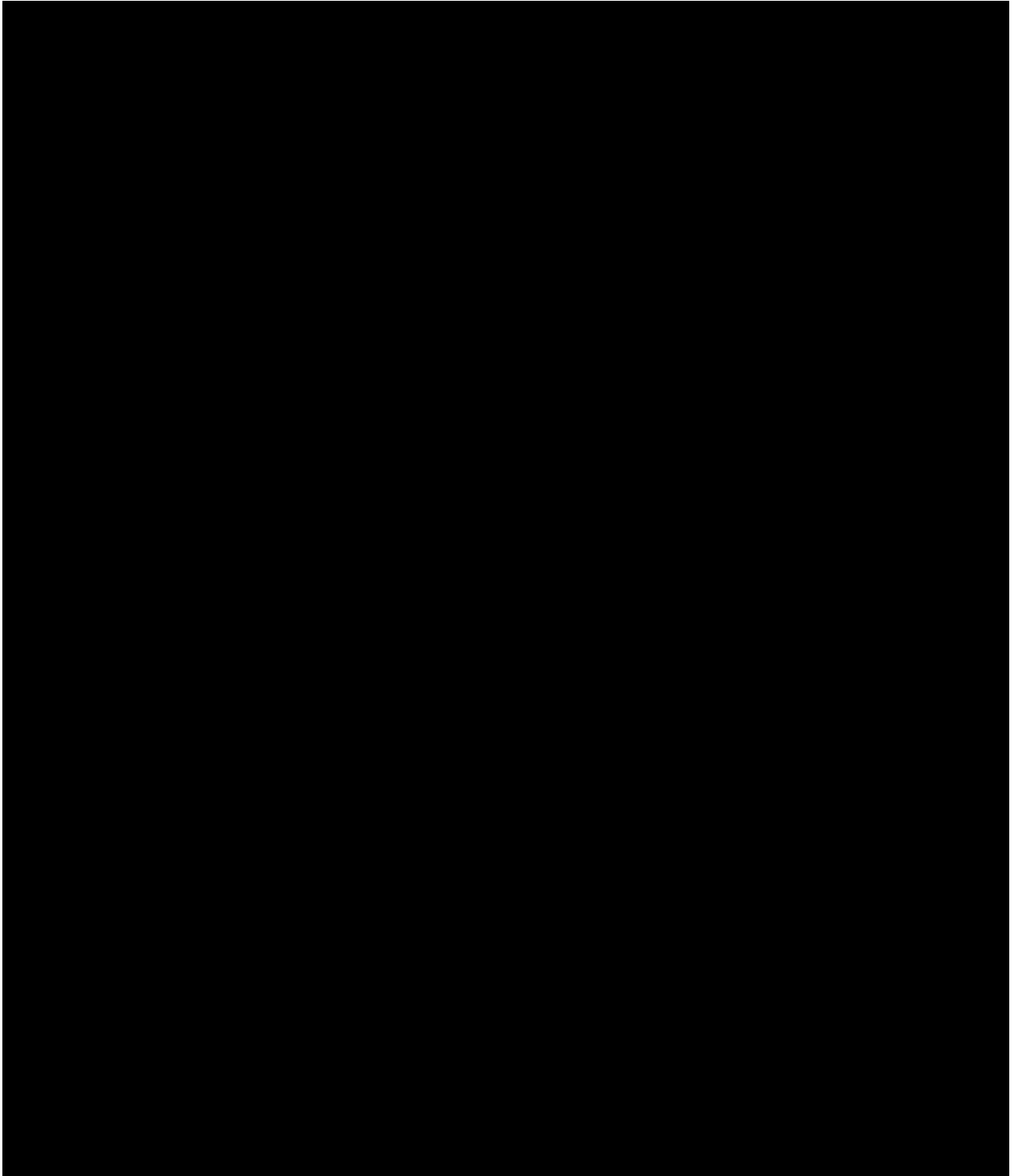
Trial Participant Feedback Questionnaires:

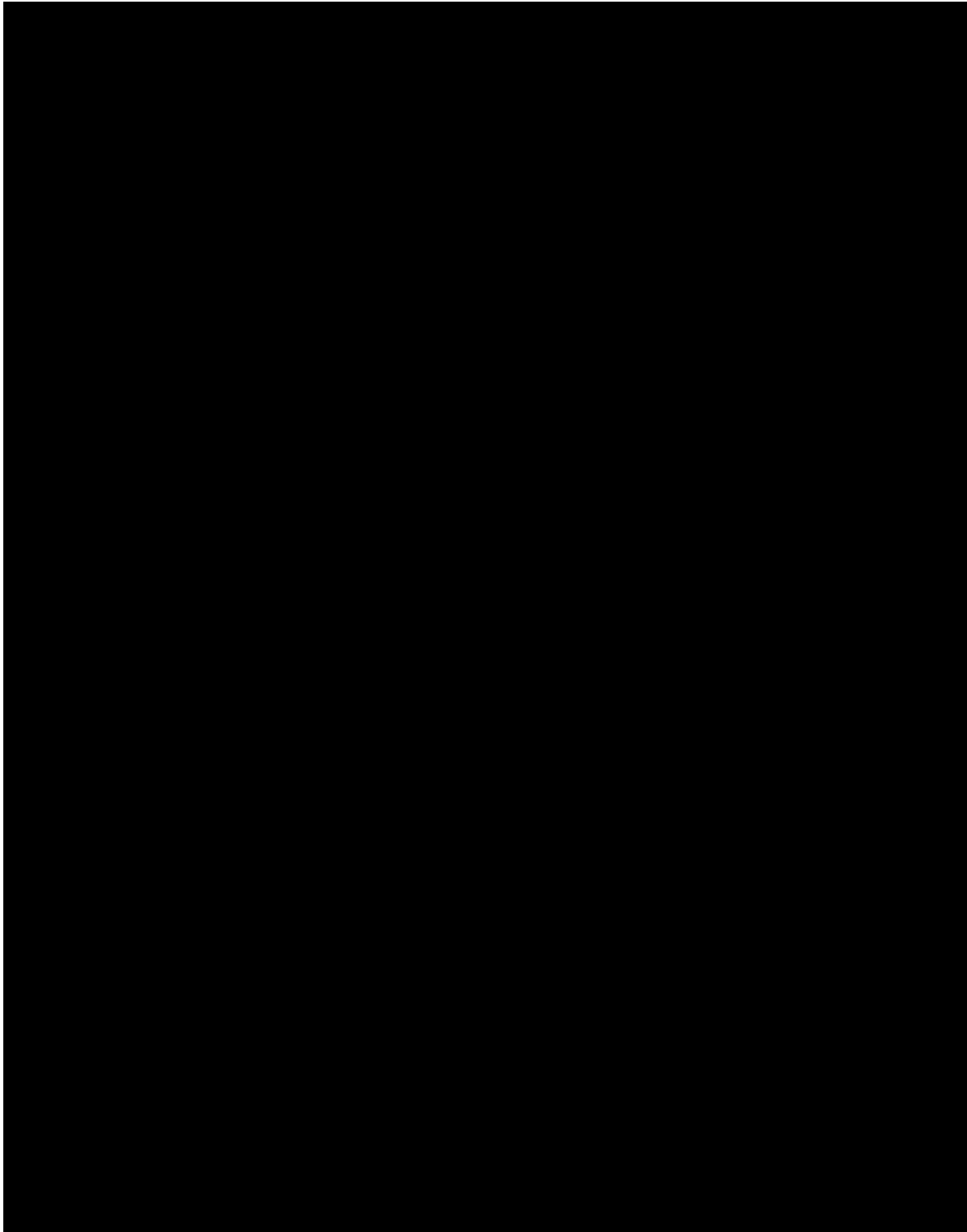
This trial will include an option for participants to complete questionnaires, 'Trial Participant Feedback Questionnaire', to provide feedback on their clinical trial experience. Individual participant level responses will not be reviewed by investigators. Responses will be used by the sponsor to understand 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 where applicable and after consent of the trial participant. Providing feedback is optional and not required for participation in the trial.

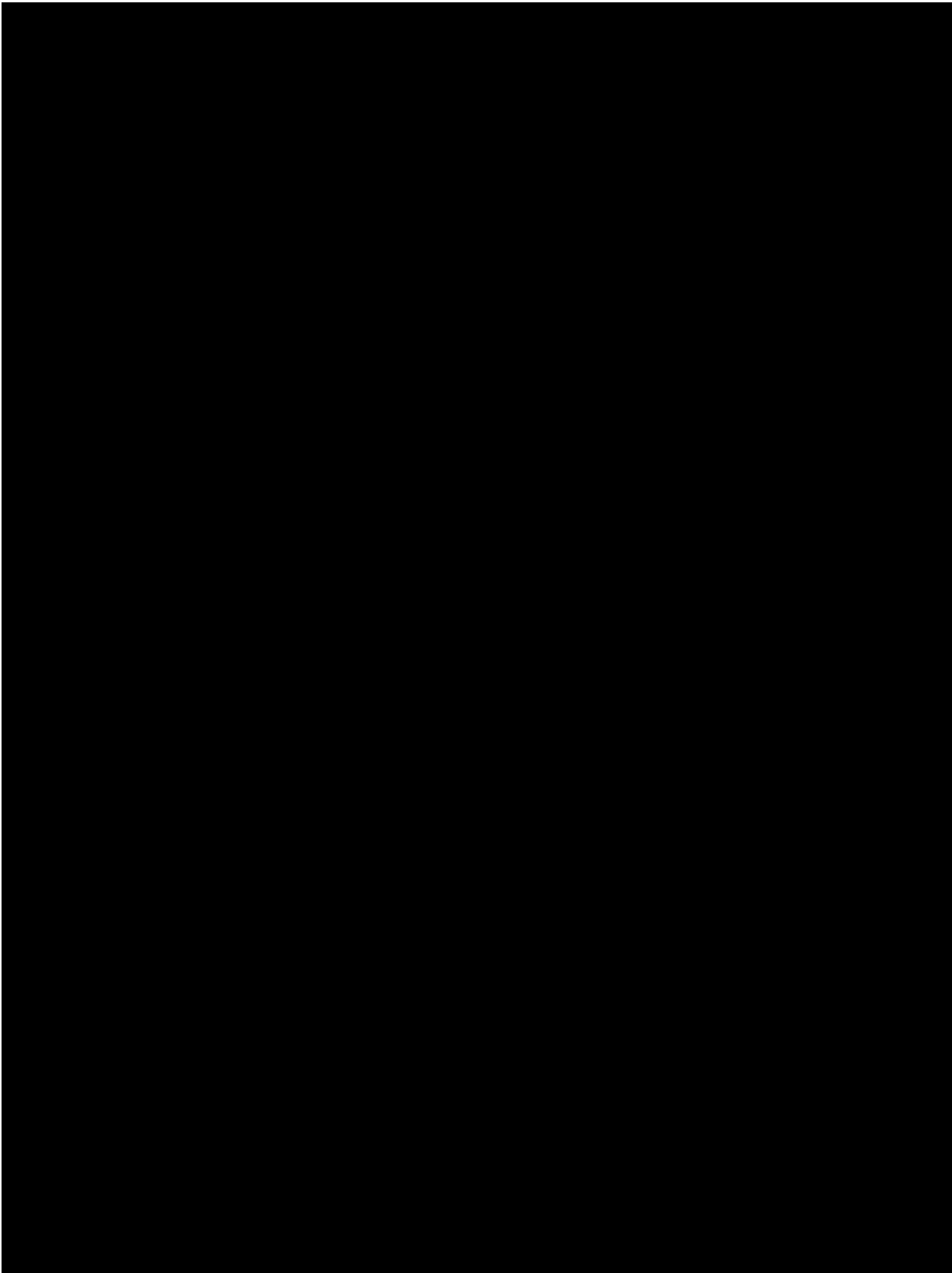
Caregiver Feedback Questionnaires:

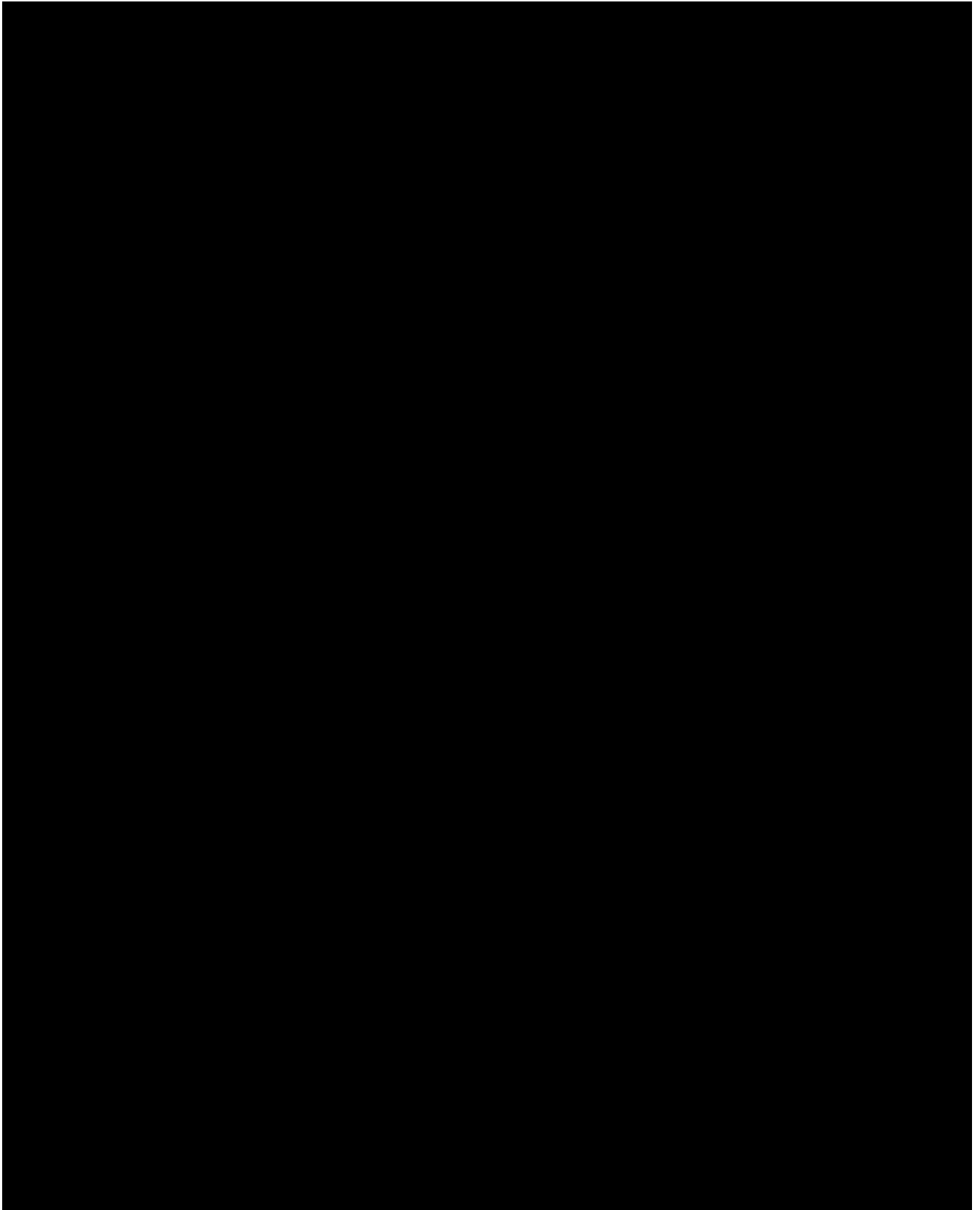
If applicable, this trial will include an option for caregivers to complete questionnaires, 'Caregiver Feedback Questionnaire', to provide feedback on the clinical trial experience. Individual caregiver level responses will not be reviewed by investigators. Responses will be used by the sponsor to understand 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 and after consent of the caregiver. Providing feedback is optional and not required for participation in the trial.

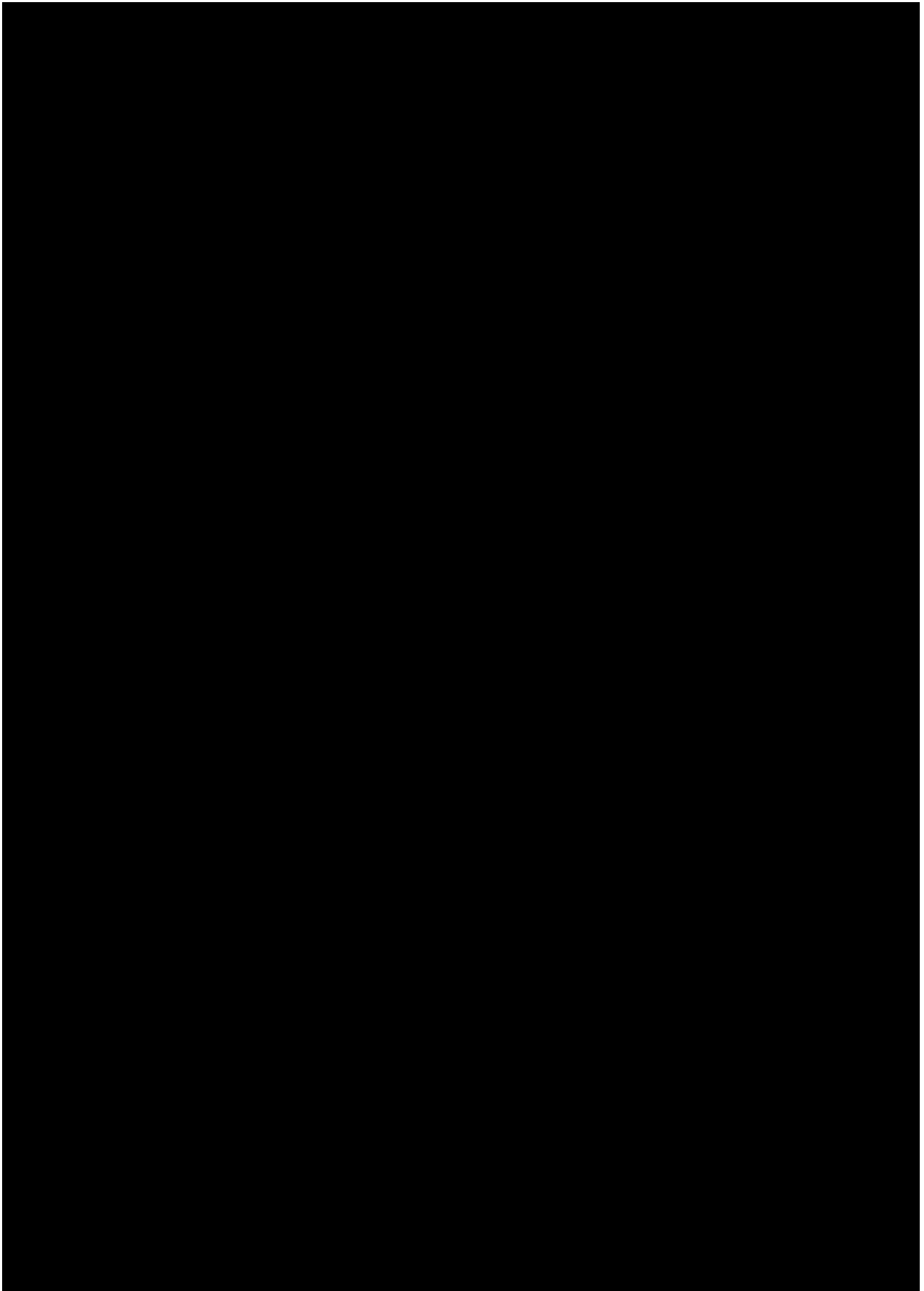


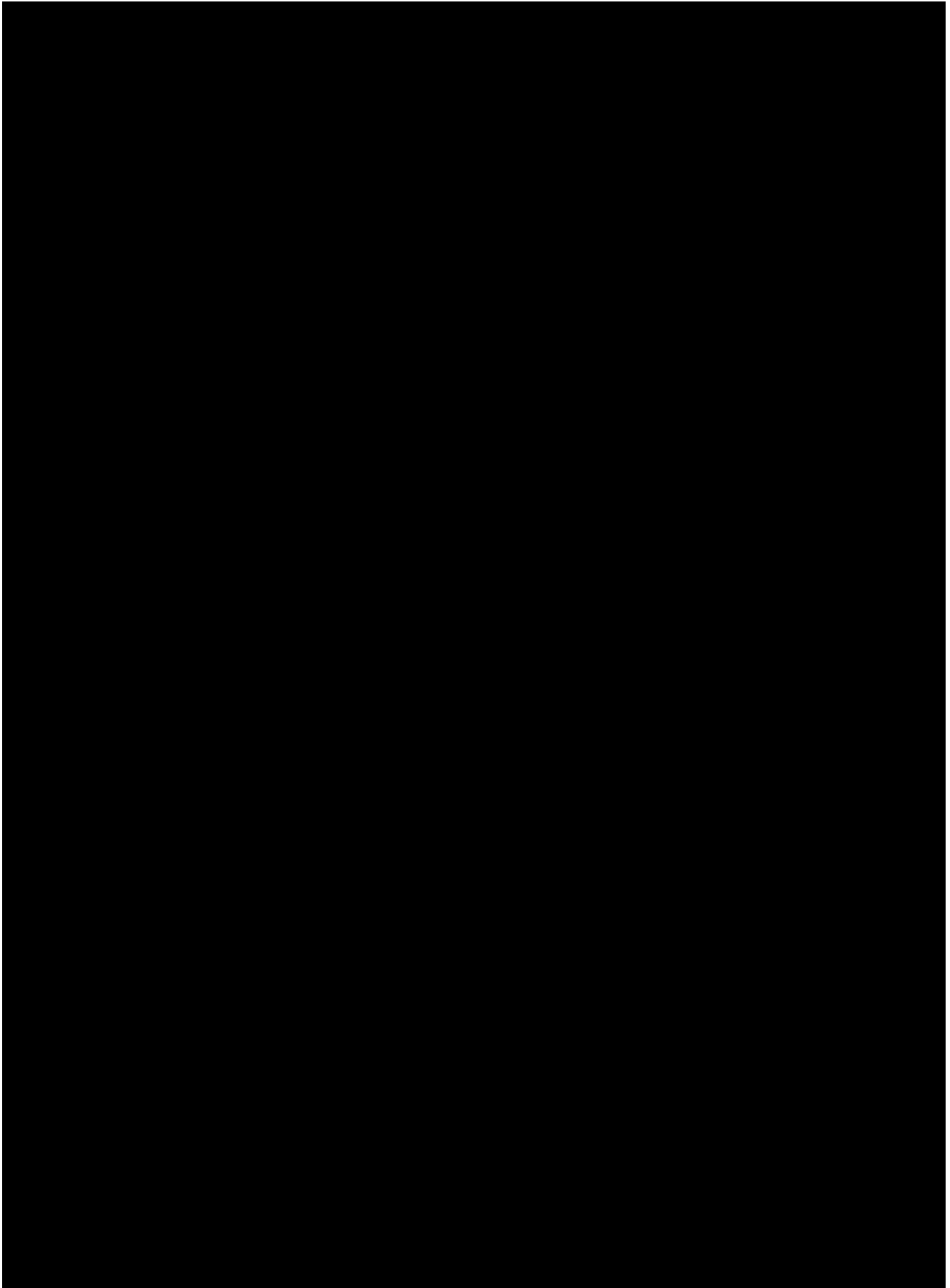


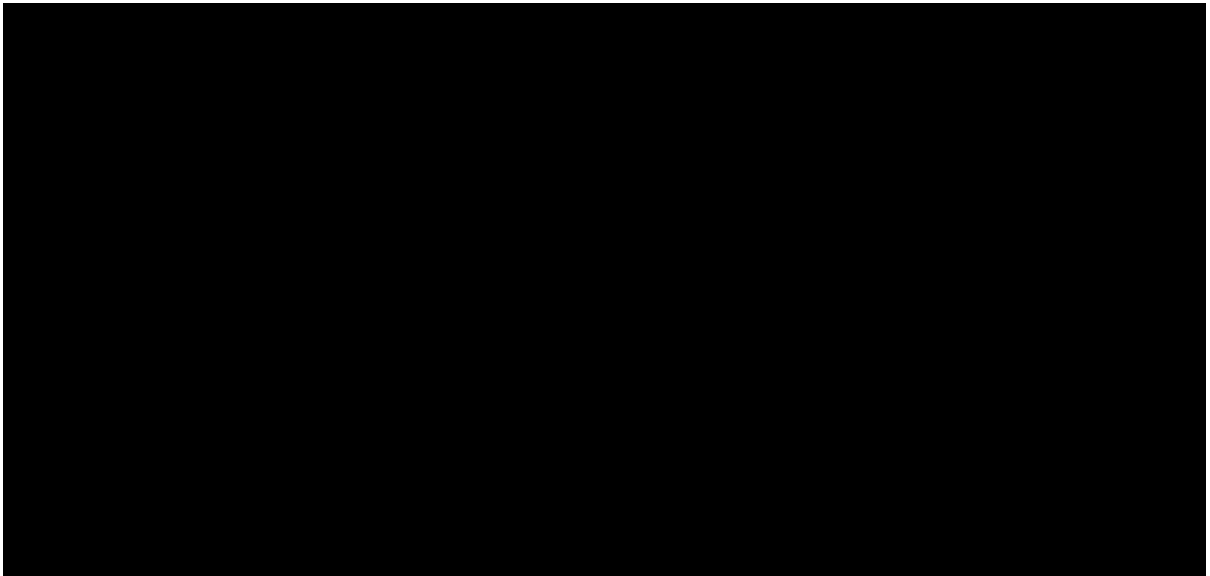


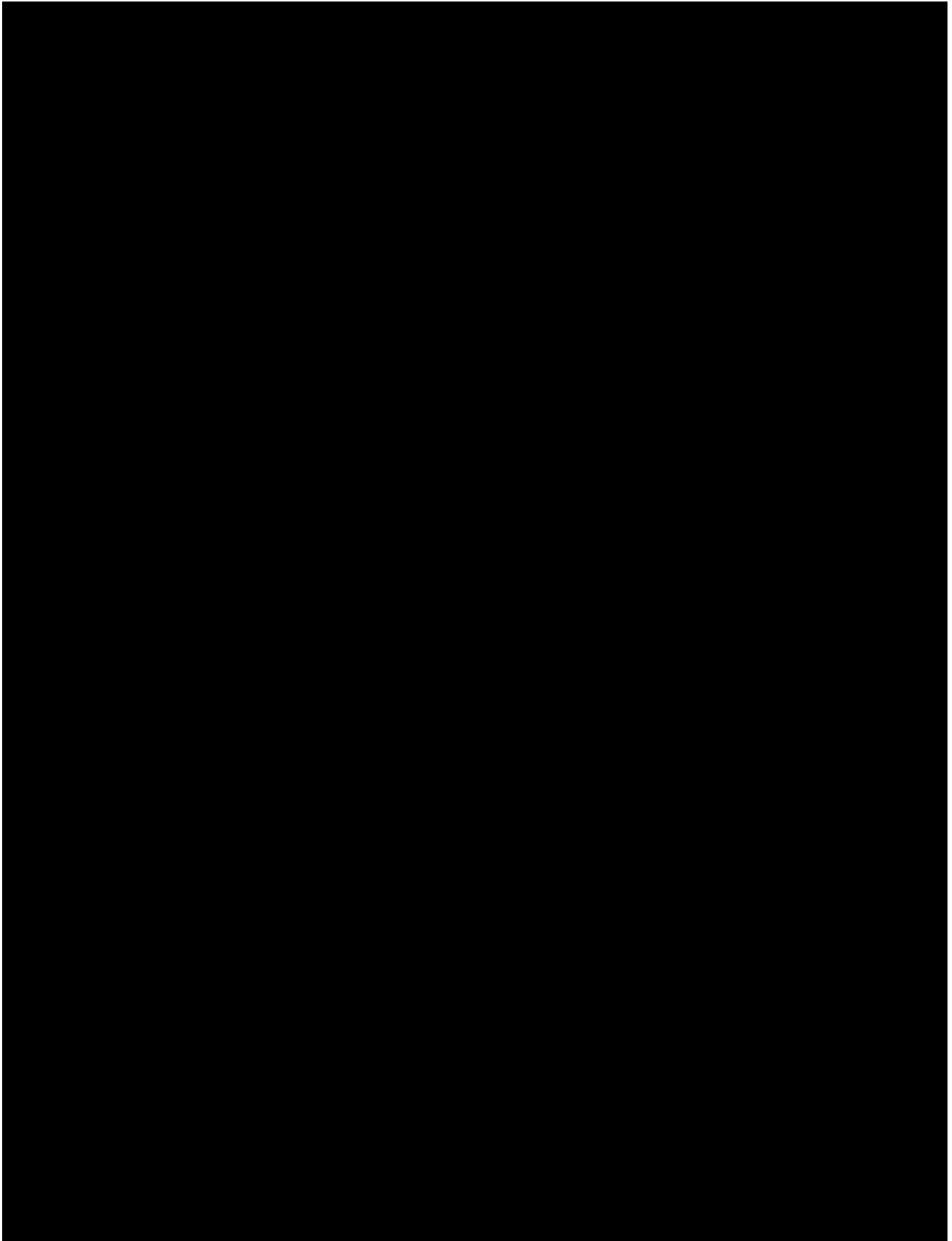


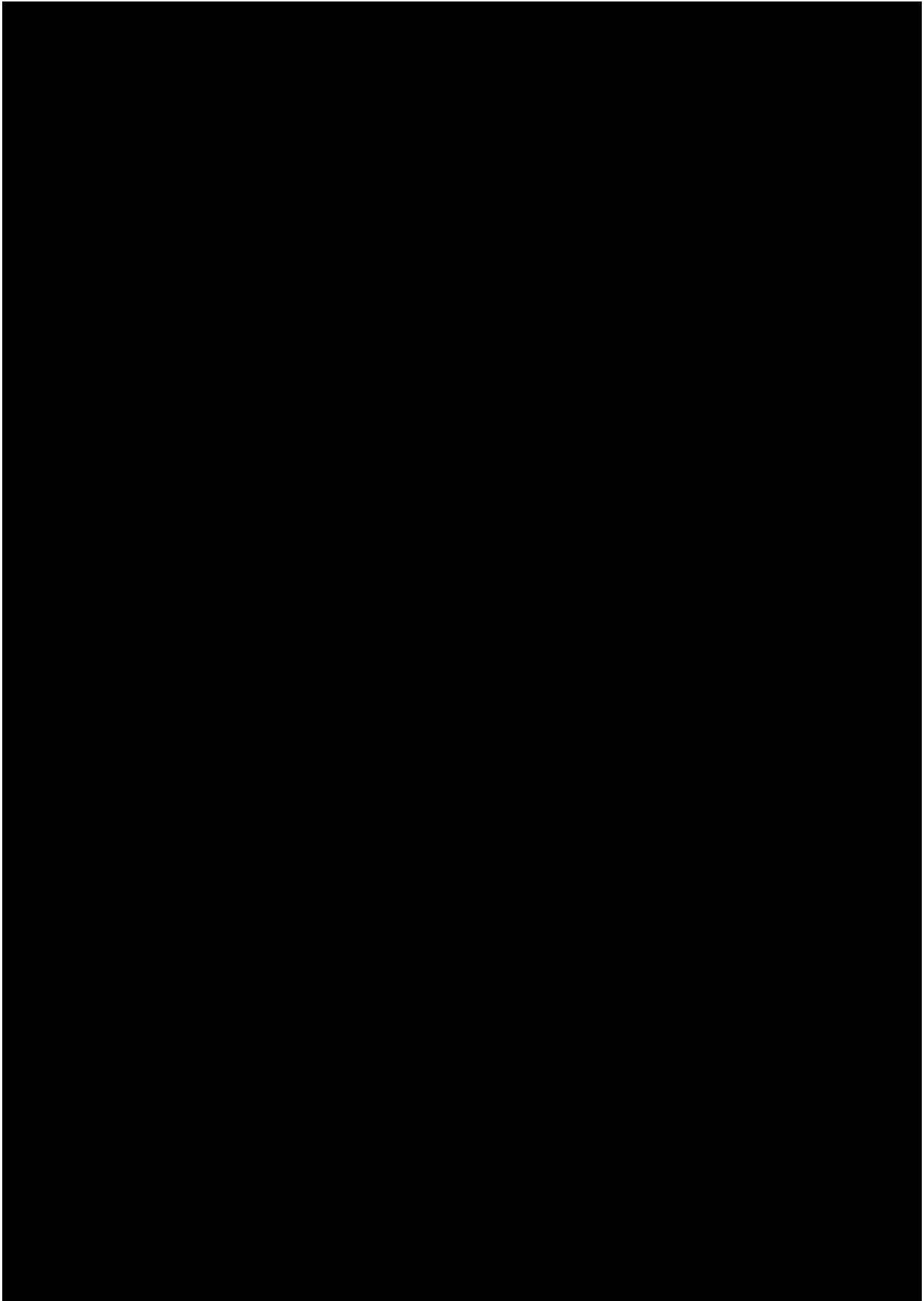




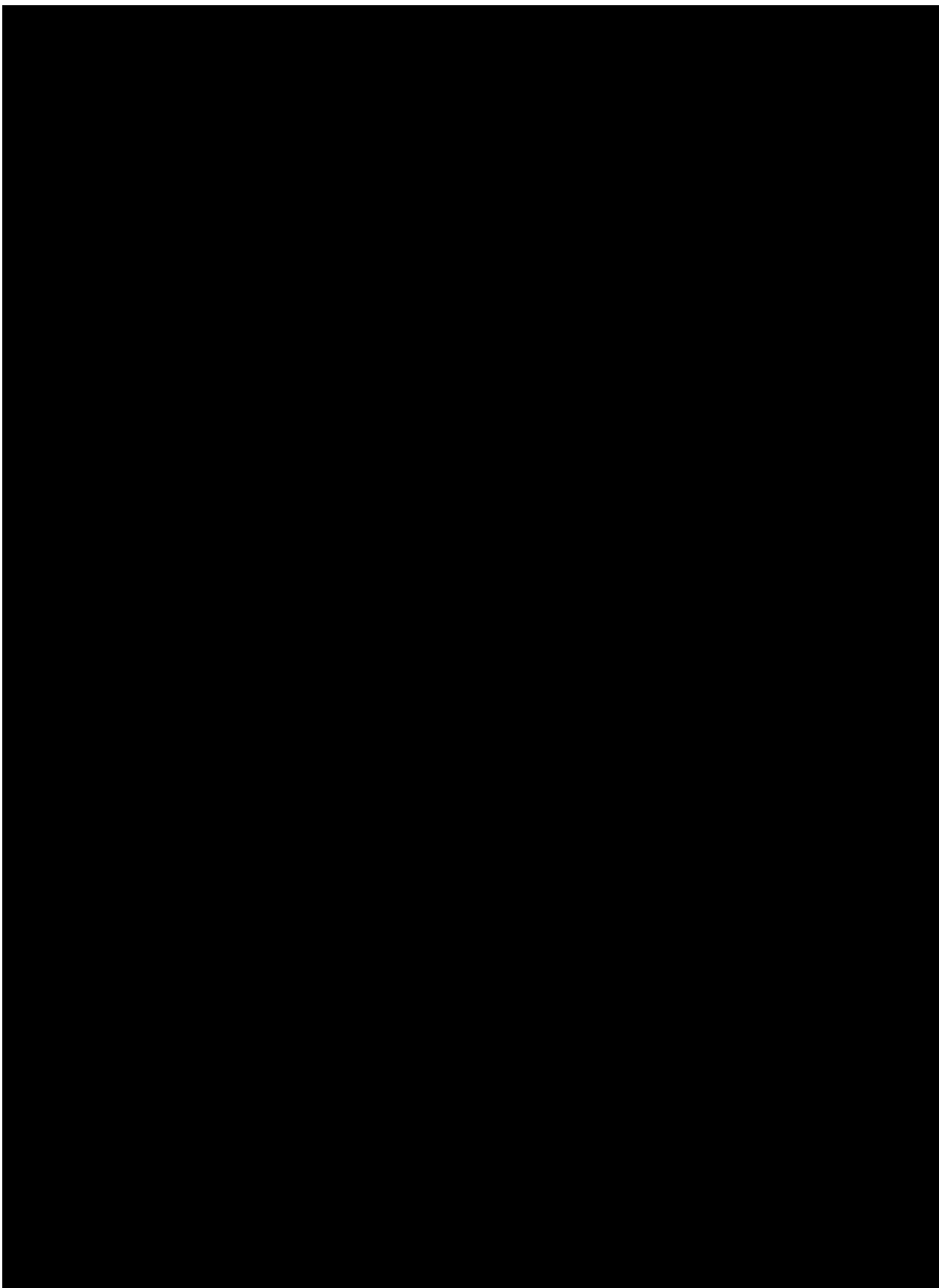


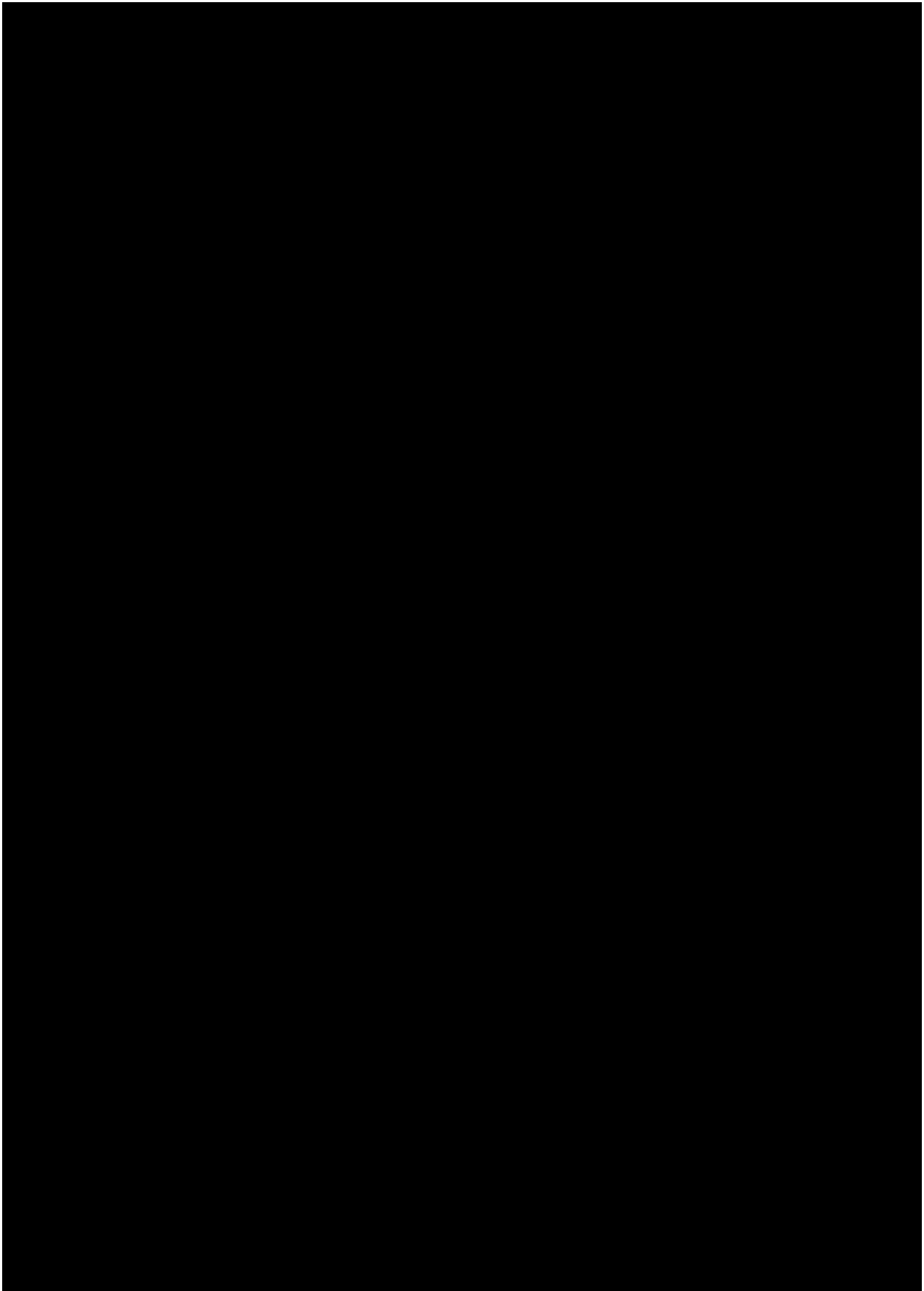


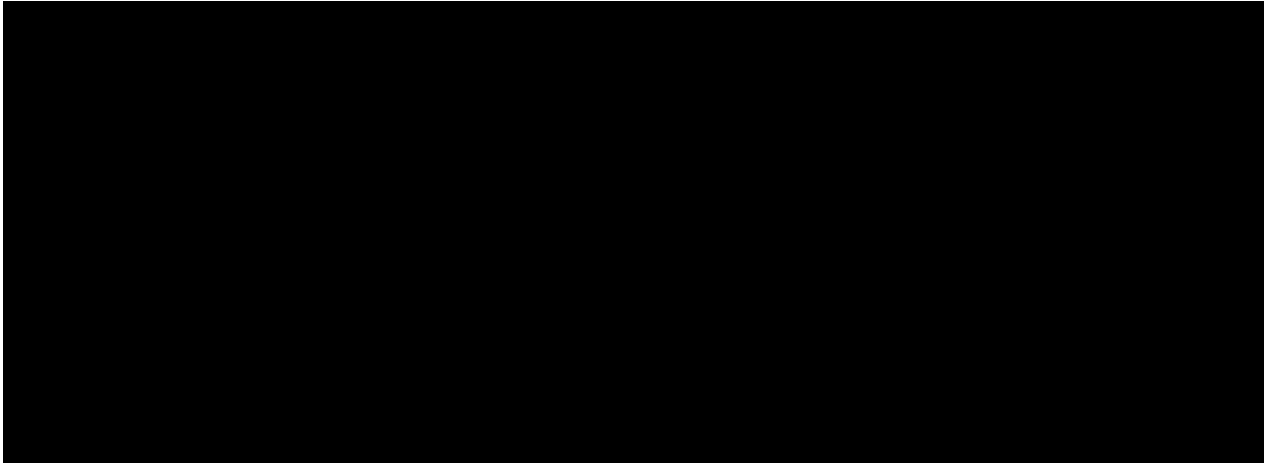


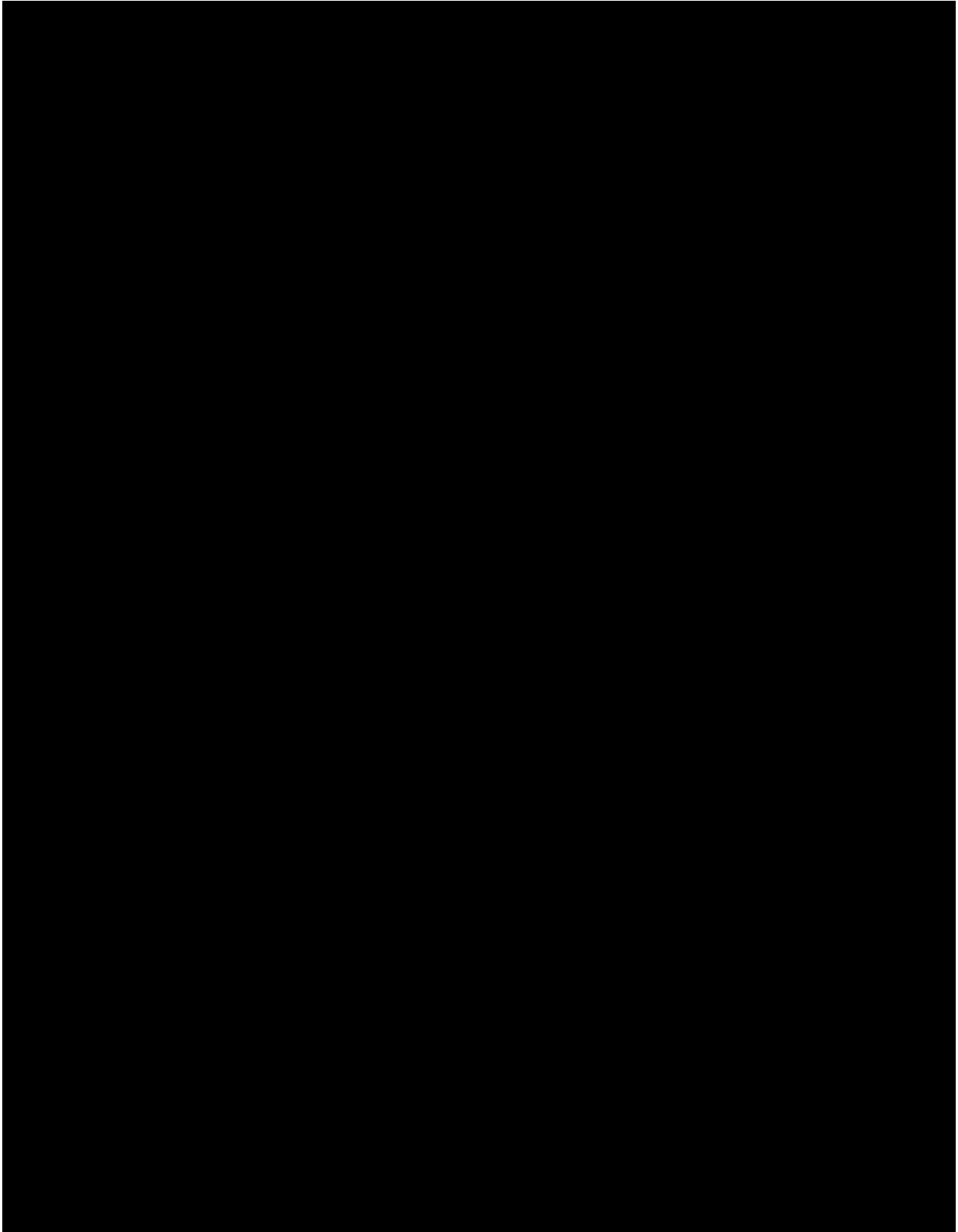


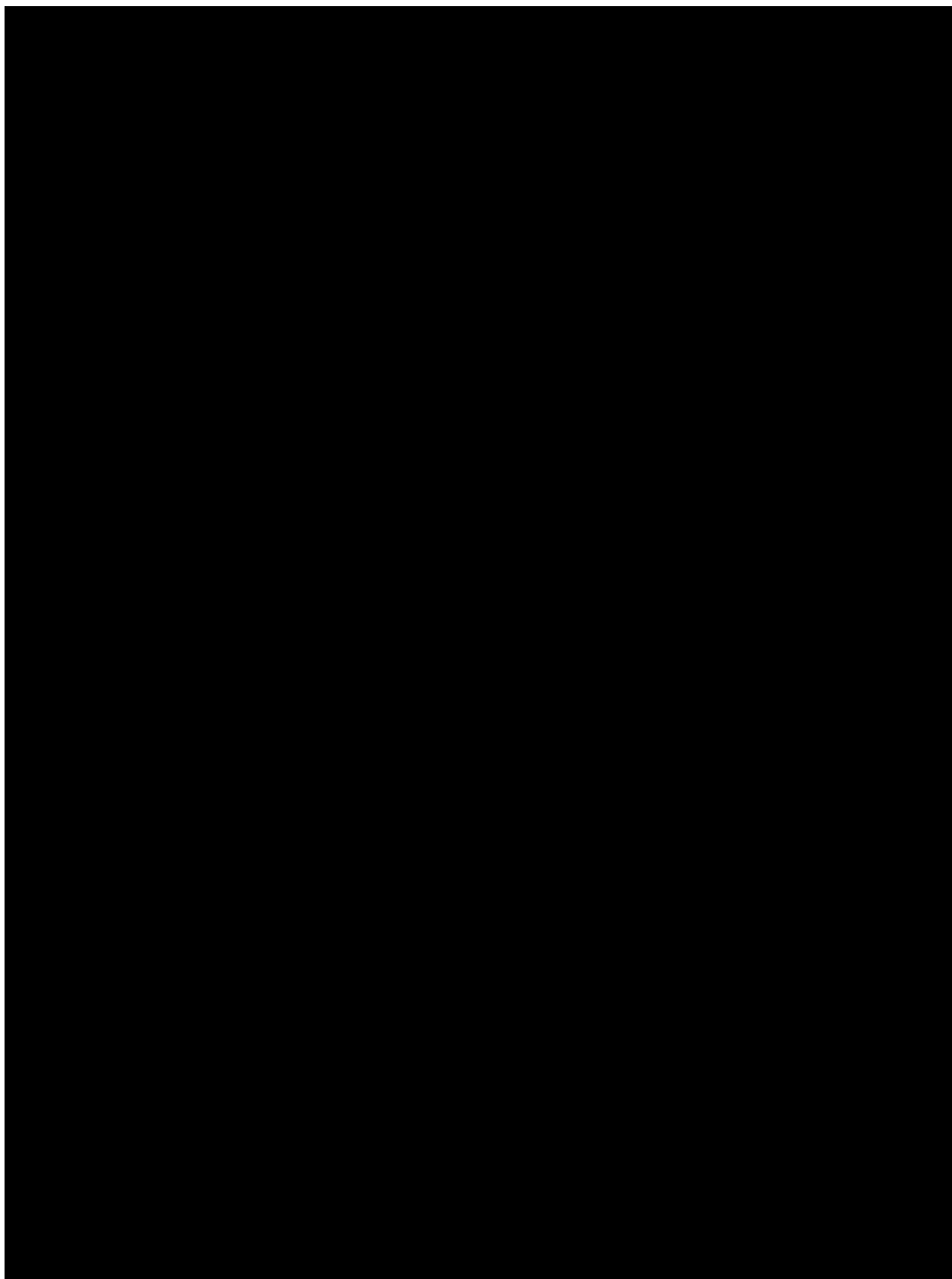


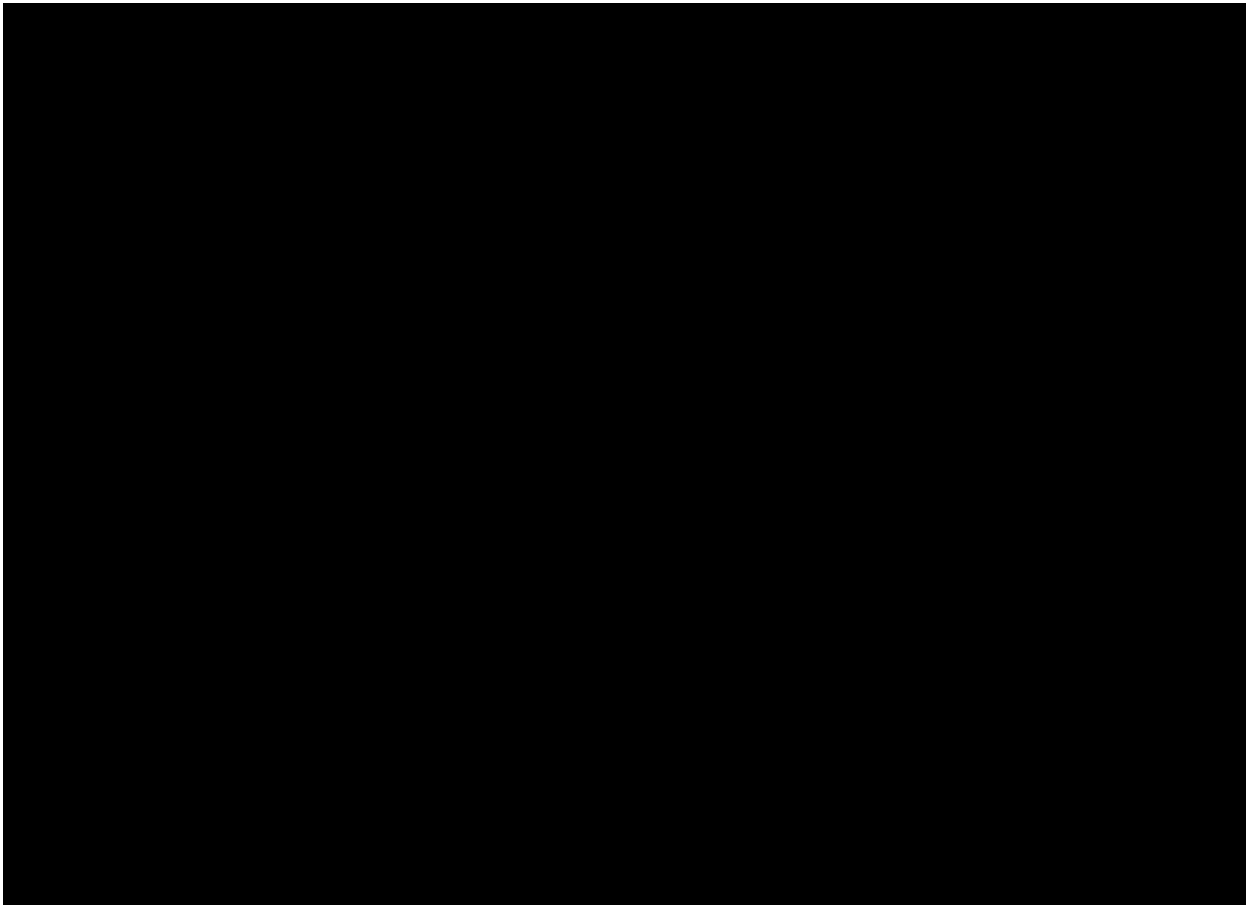


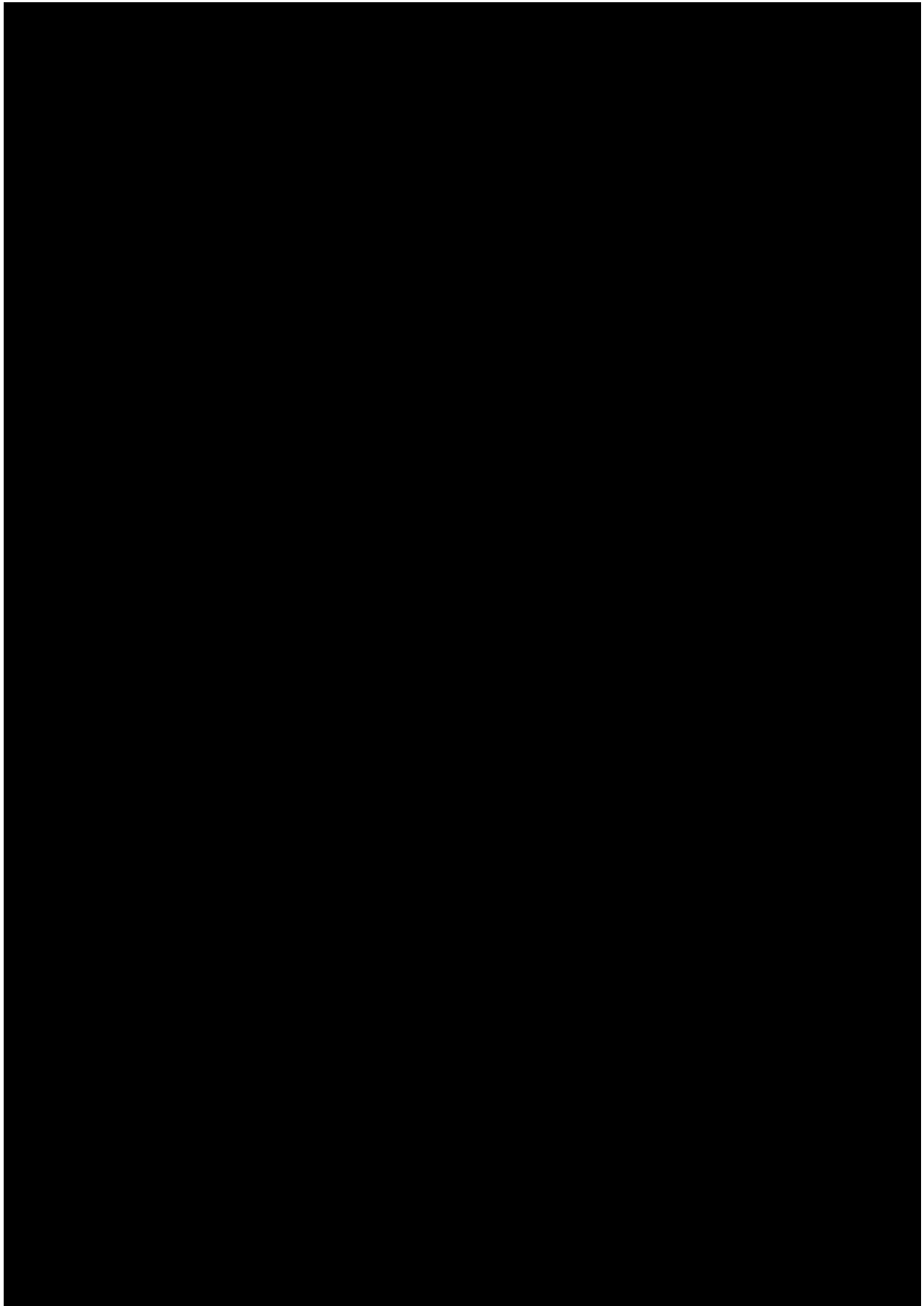


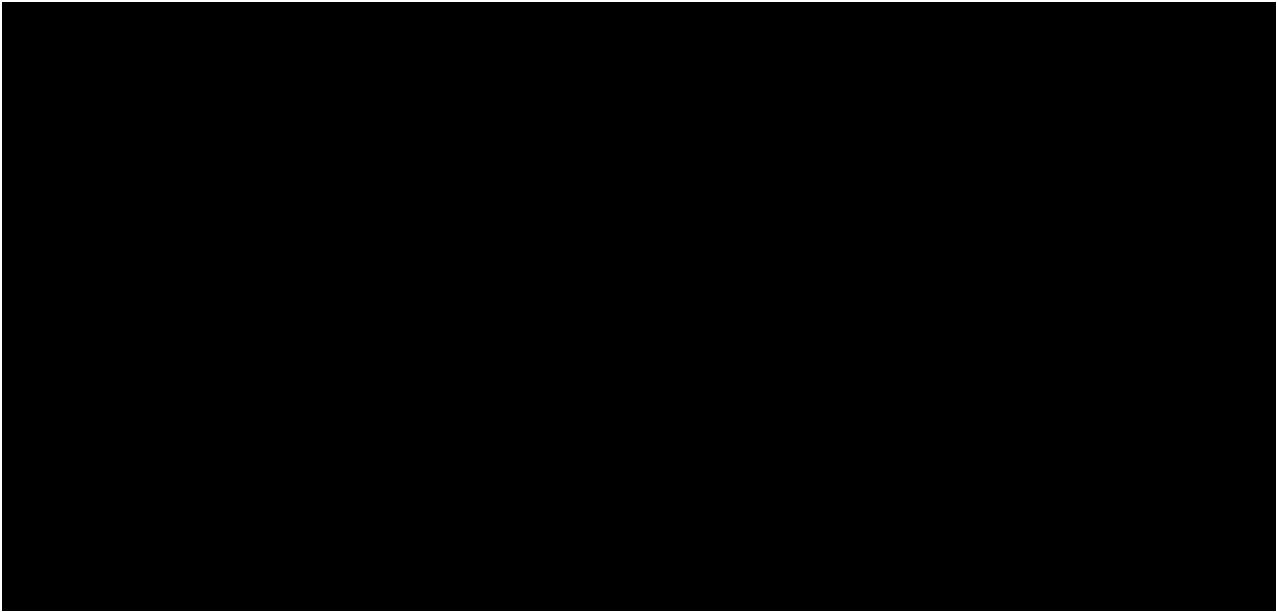












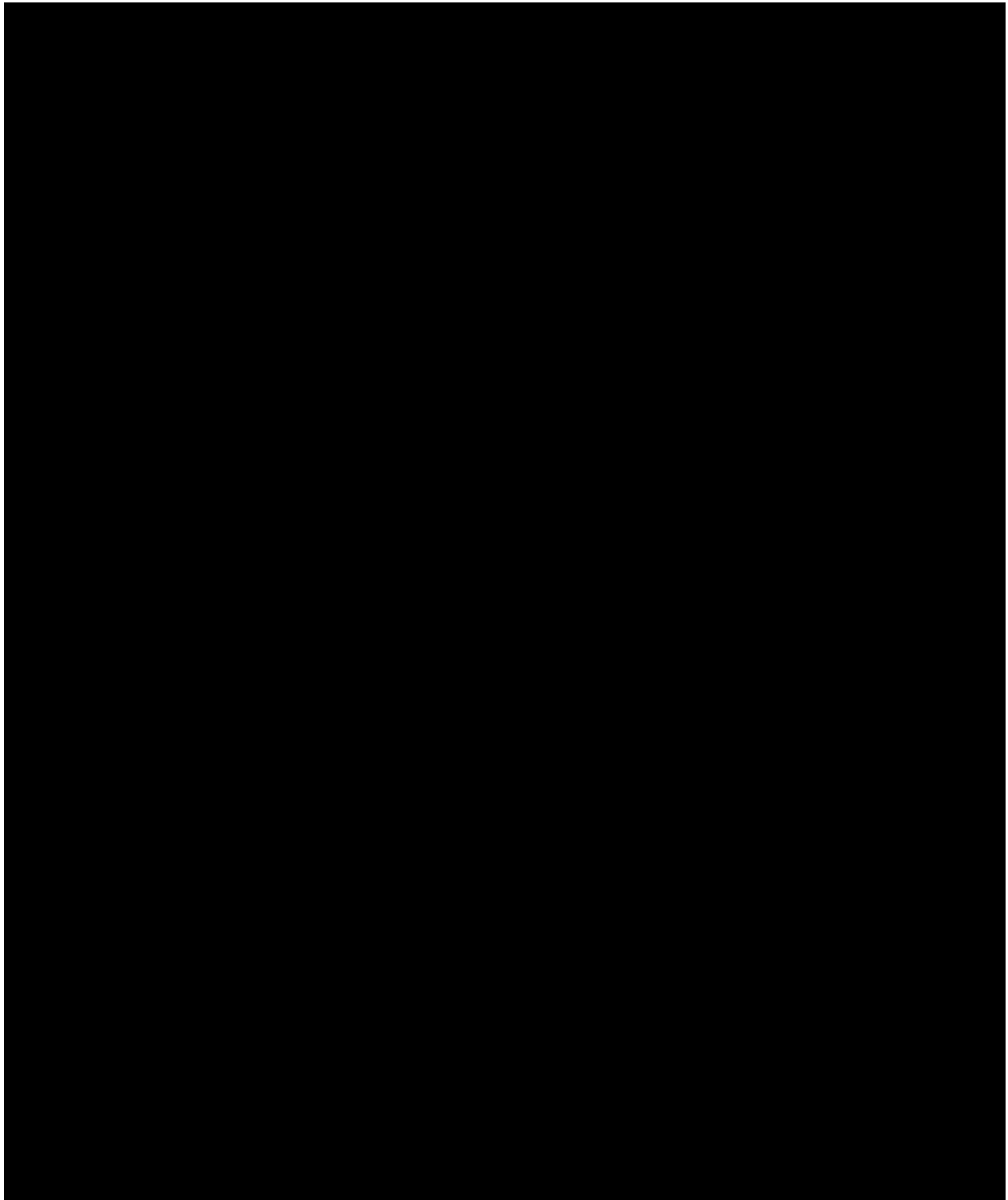
10.10 DIAGNOSIS OF ANAPHYLAXIS

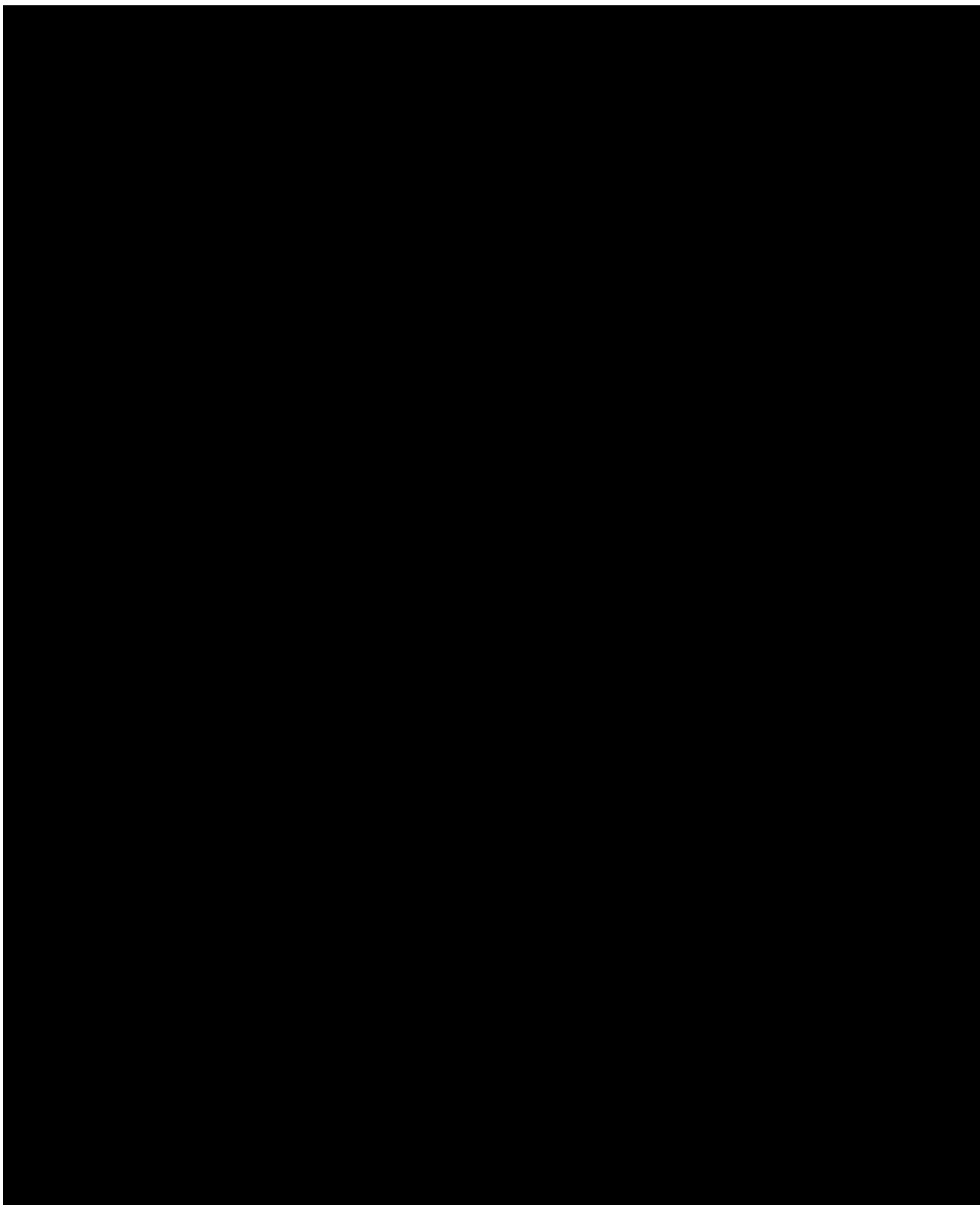
Clinical criteria for diagnosing anaphylaxis ([R11-4890](#)).

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 (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
<i>AND AT LEAST ONE OF THE FOLLOWING</i>
a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., 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 (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to <u>known</u> allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg +[2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.





11 DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

APPROVAL / SIGNATURE PAGE**Document Number:** c43157289**Technical Version Number:**1.0**Document Name:** 1368-0130-clinical-trial-protocol

Title: Lunsayil LTE: An extension trial assessing long-term spesolimab treatment in patients with Hidradenitis Suppurativa (HS)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Biostatistics		29 Nov 2023 08:31 CET
Approval-Clinical Trial Leader		29 Nov 2023 09:13 CET
Approval-Clinical Program Leaders		01 Dec 2023 15:00 CET
Approval		04 Dec 2023 03:01 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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