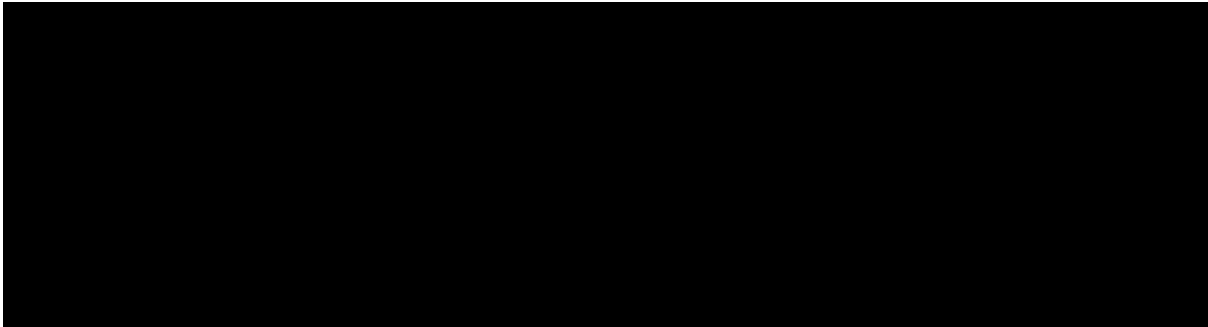
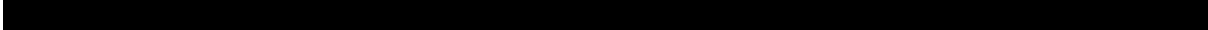
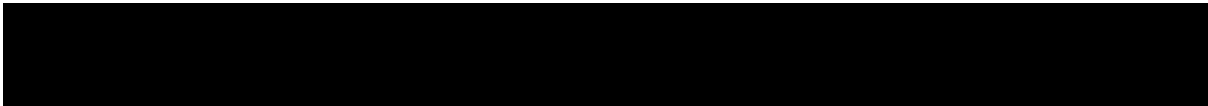


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Global ID_Version:	228892_161051_2.0
BI Trial No.:	1368-0130
Title:	A study to test long-term treatment with spesolimab in people with a skin condition disease called hidradenitis suppurativa (HS) who took part in a previous study with spesolimab
Investigational Product(s):	Spevigo [®] , Spesolimab
Responsible trial statistician(s):	Tel:
Date of statistical analysis plan:	30 Jul 2025
Version:	2.0
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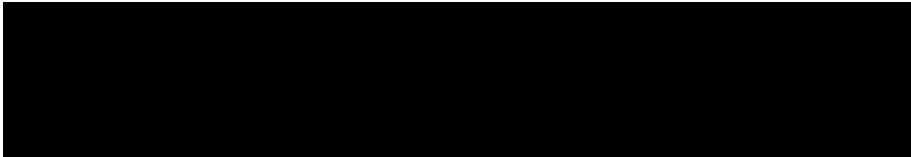
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2. LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AdT	Abscess and draining fistula/tunnel (dT)
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine amino transferase
AN	Abscess and inflammatory count
AST	Aspartate amino transferase
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
BMI	Body Mass Index
CRP	C-Reactive protein (CRP & hs-CRP)
C-SSRS	Columbia-Suicide Severity Rating Scale (R&D+M)
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Report
CTR	Clinical Trial Report
DILI	Drug-induced liver injury
DLQI	Dermatology Life Quality Index
dT	Draining fistula/tunnel
ECG	Electrocardiogram
eCRF	electronic case report form
EDMS	Electronic document management system
EMA	European Medicines Agency
EoS	End of Study
EoT	End of Treatment
ES	Enrolled Set



HS	Hidradenitis Suppurativa
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[REDACTED]	
ICH	International Council of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU/ ER	Intensive Care Unit/ Emergency Room
IE	Intercurrent Event
[REDACTED]	

iPD	Important protocol deviation
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing antibody
NRS	Numerical Rating Scale
PK	Pharmacokinetics (R&D+M)
PKPD	Pharmacokinetics Pharmacodynamics
PKS	Pharmacokinetic Set
PT	Preferred Term
q2w	Once every 2 weeks
REP	Residual Effect Period
RUN	Data Ready for Unblinding Notification
s.c.	Subcutaneous
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Events
TMF	Trial master file
TS	Treated Set
TSAP	Trial statistical analysis plan
UDAEC	User-Defined Adverse Event Categories
ULN	Upper Limit of Normal
WHO-DD	World Health Organisation – Drug Dictionary
[REDACTED]	

3. INTRODUCTION

This trial statistical analysis plan (TSAP) describes the statistical analysis required for 1368-0130 clinical trial report (CTR). Since the development of spesolimab determined to be terminated for hidradenitis suppurativa (HS) at the end of 2024, CTR will be generated in abbreviated manner following BI reference document “Clinical Trial Report Type” ([9.1](#)).

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of endpoints required for abbreviated CTR.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study.

The latest SAS® Version at the time of reporting will be used for all analyses unless otherwise specified.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

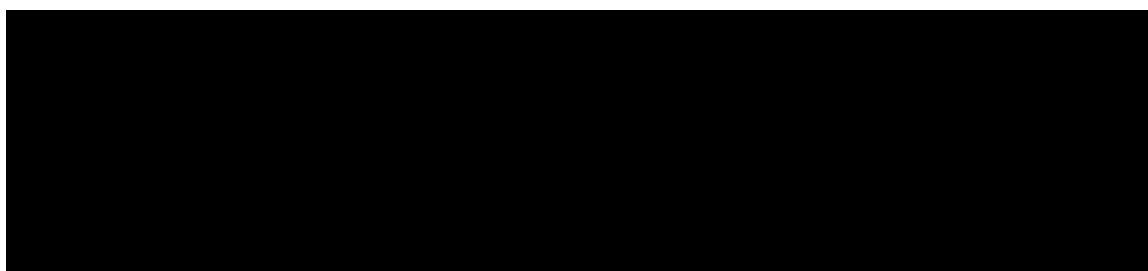
4.1 ENDPOINTS INCLUDED IN THE CTR

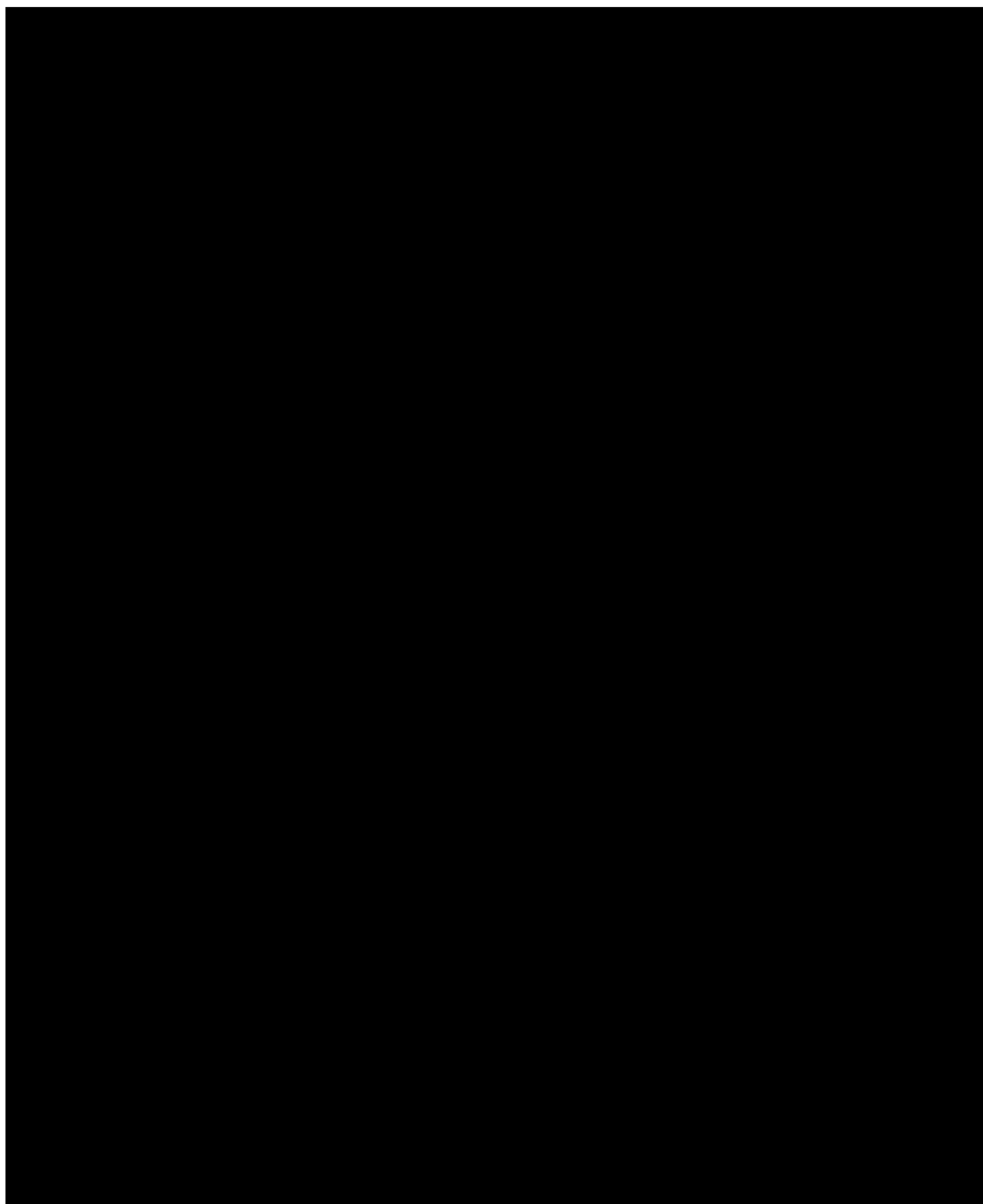
As stated in the [Section 3](#), CTR will be generated in abbreviated manner due to termination of spesolimab development for HS. Since the analysis outputs will also be used in the submission documents for other spesolimab indications, the following endpoints will be summarized/ analysed in addition to fundamental safety endpoints required for abbreviated CTR listed in the BI reference document “Clinical Trial Report Type” ([9.1](#)).

- Disposition (CTR Appendix Section 15.1.1)
- Definition of analysis sets (CTR Appendix Section 15.1.2)
- Demographics and baseline characteristics (CTR Appendix Section 15.1.4)
 - Demographic data
 - Baseline characteristics
 - Concomitant disease
 - Concomitant medication use
- Extent of exposure to study drug (CTR Appendix Section 15.1.5)
- Safety evaluation (CTR Appendix Section 15.3)
 - Adverse events (AEs)
 - Including adverse events of special interest (AESI) and user-defined adverse event categories (UDAEC)
 - Clinical laboratory evaluation
 - Vital signs and local tolerability
- Clinical pharmacokinetics evaluation (CTR Appendix Section 15.6)
- Anti-drug antibody (ADA) evaluation (CTR appendix section 15.8)

4.2 ENDPOINTS PLANNED IN THE CTP, WHICH WILL BE EXCLUDED IN THE CTR

Since efficacy evaluations are not required for abbreviated CTR nor the other dossiers, the following endpoints discussed on the clinical trial protocol as further endpoints will not be analysed and outputs will not be generated.





4.3 OTHER CHANGES

Per the CTP, patients from 1368-0098 Part 1, 1368-0098 Part 2 and 1368-0100 planned to be enrolled on this trial if patients meet criteria. However, 1368-0098 Part 2 and 1368-0100 were not initiated because of the termination of the HS program development. Therefore, only

some patients from 1368-0098 Part 1 have been enrolled on this trial. The longest exposure to study therapy among enrolled patients is about up to 22 weeks.

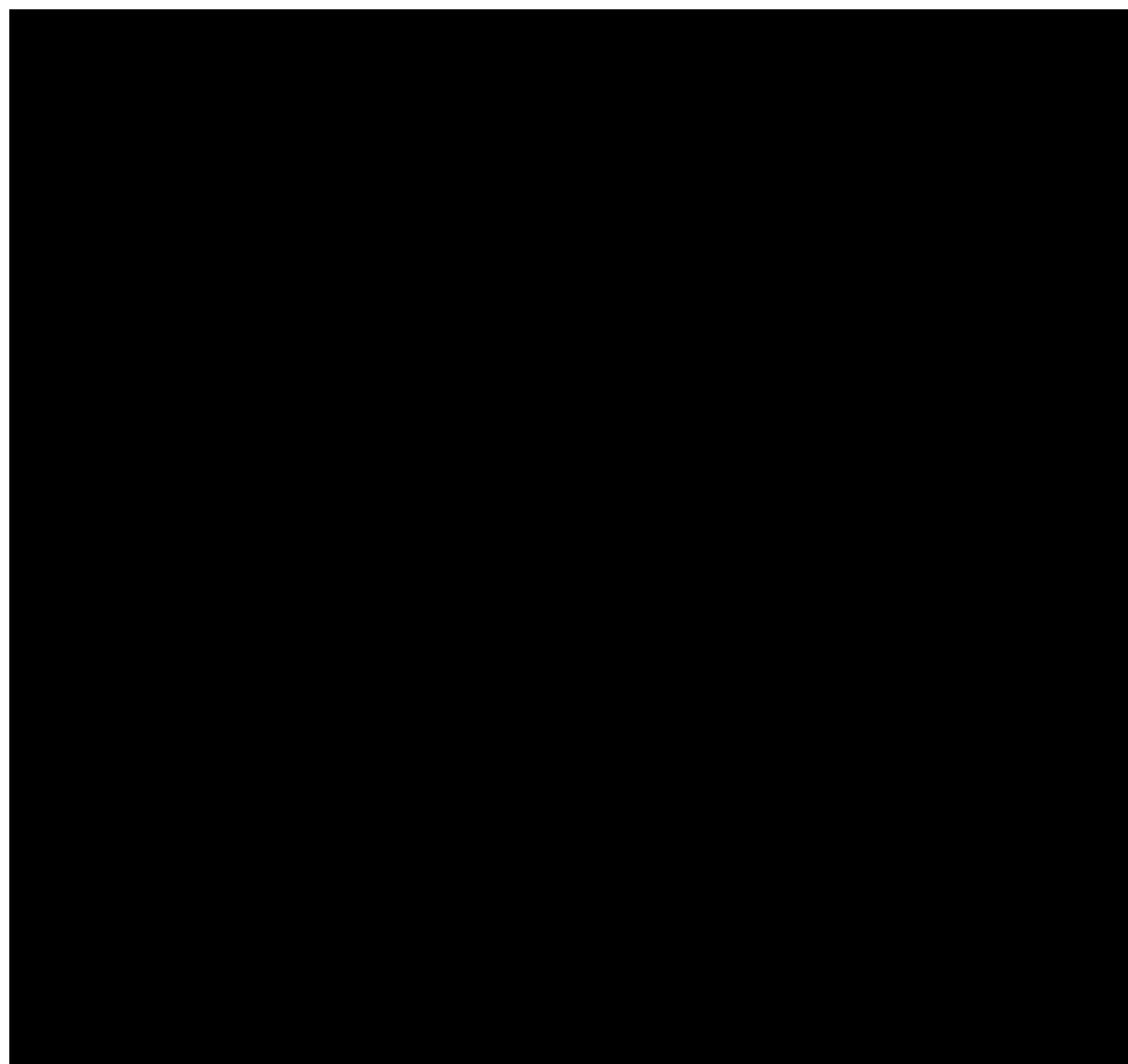
5. ENDPOINTS(S)

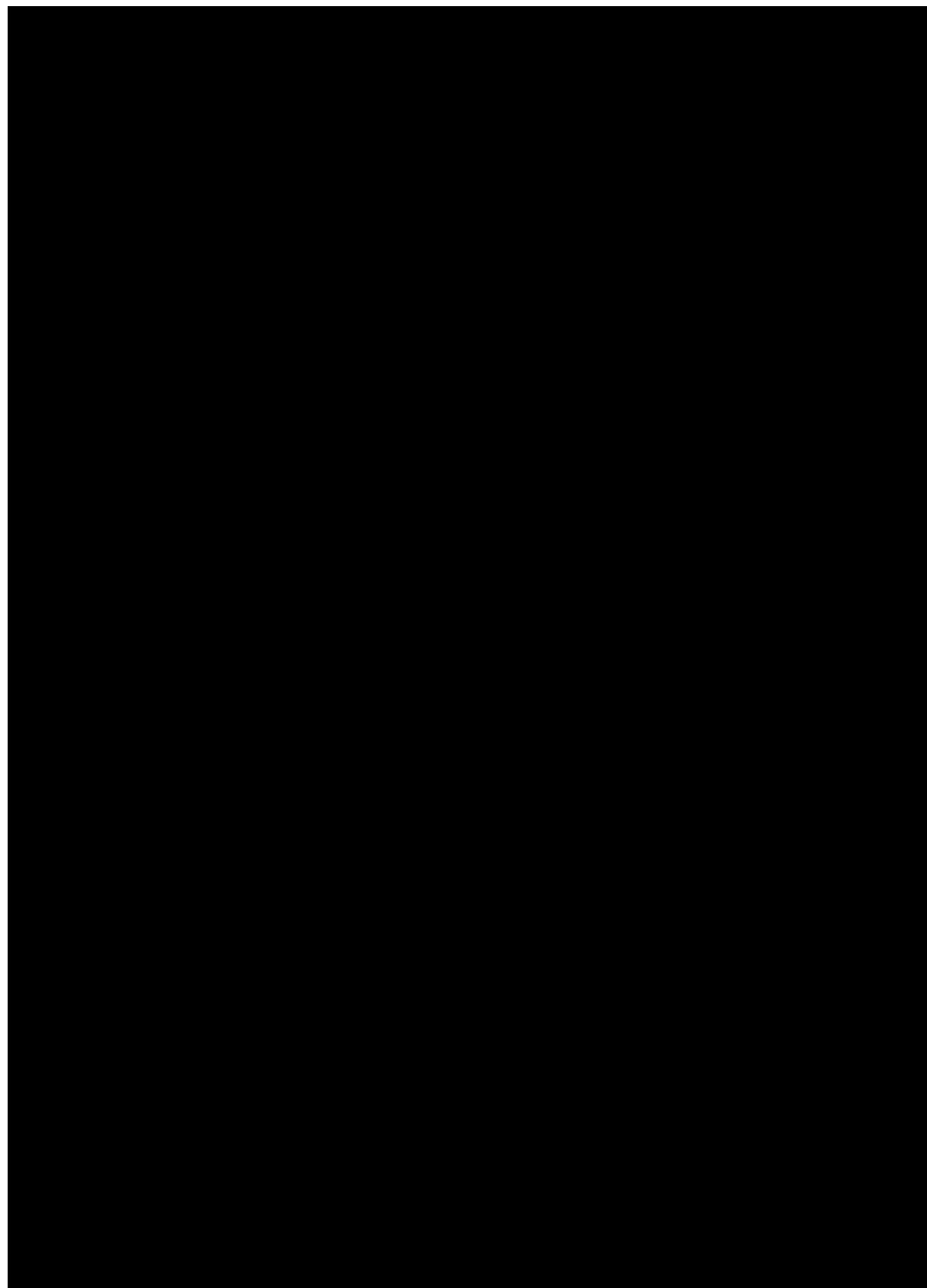
5.1 PRIMARY ENDPOINT(S)

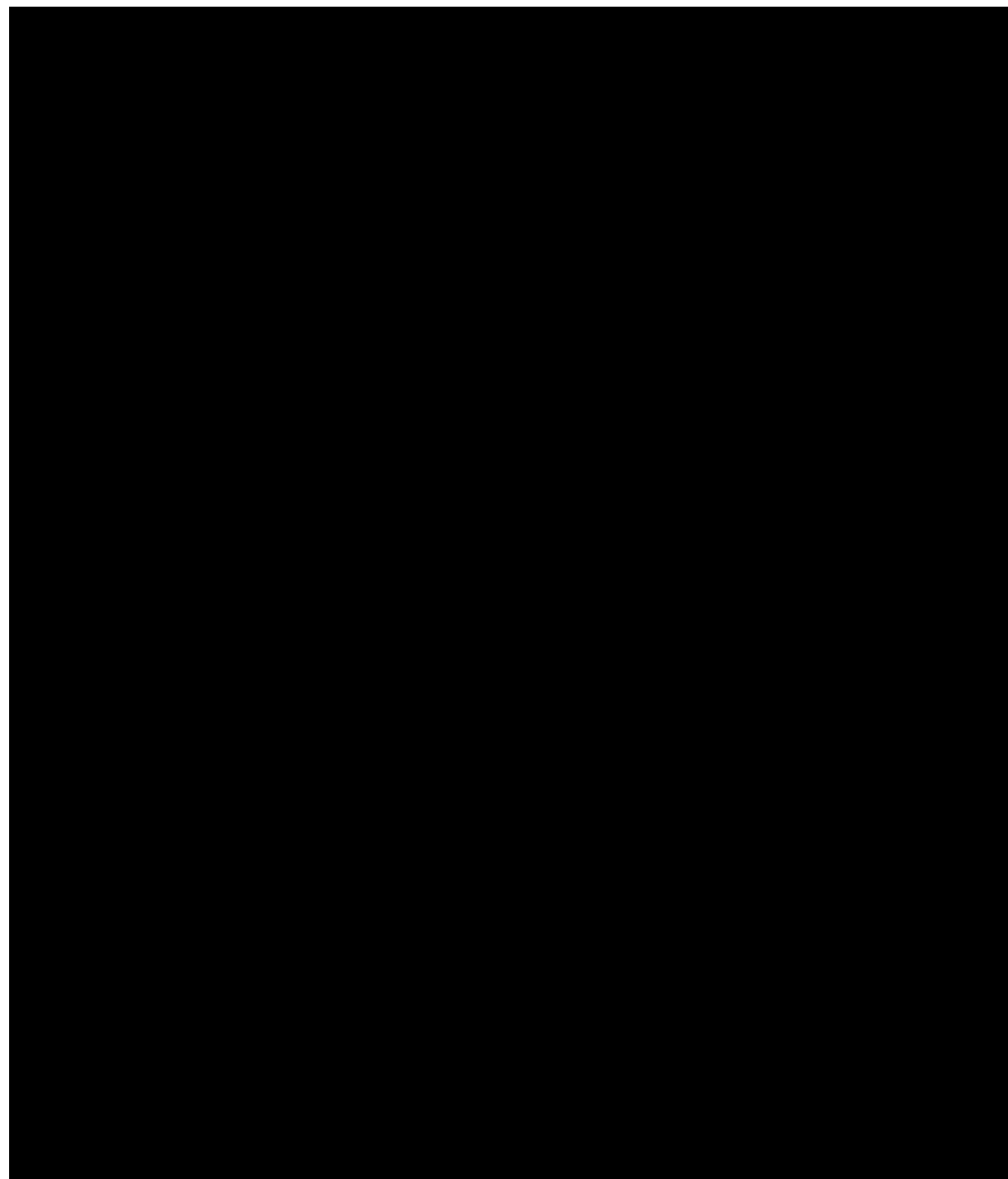
The primary endpoint of this trial is defined in CTP as the occurrence of treatment emergent adverse events (TEAE) up to the end of maintenance treatment period including REP (i.e., [REDACTED] weeks after the last study treatment).

5.2 SECONDARY ENDPOINT(S)

There is no secondary endpoints defined on this trial.







6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Analysis periods are defined relative to date of informed consent and that of the first administration of spesolimab.

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Table 6.1: 1 Analysis periods of the study according to informed consent or study treatment

Study analysis period	Description	Start (included)	End (included)
Off-treatment-period	Off-treatment period	Date of last administration of trial treatment + 113 days	latest of either date of end of study (EoS) visit or last contact date.
Screening-period	Screening	Earliest of (Date of informed consent, first screening procedure)	Date/time of start of first administration of trial treatment minus 1 minute if time is collected. Otherwise, date of start of first administration of trial treatment minus 1 day
Treatment-period	Treatment period	First administration of trial treatment in this trial	Date/time of last administration of trial treatment plus residual effect period (16 weeks= 112 days at 11:59 pm) if time is collected. Otherwise, date of last administration of trial treatment + 112 days.

The following labels for the treatment groups for all analysis will be used according to first administration of spesolimab on this trial:

-
-
-
-

6.2 IMPORTANT PROTOCOL DEVIATIONS

Each protocol deviation must be assessed to determine whether it is an important protocol deviation (iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (iPD)" [\(9.7\)](#).

Handling of iPDs in analysis is included in the DV domain specifications and stored within the Trial Master File (TMF) in Electronic Document Management System (EDMS).

iPD will not be summarized and listed only.

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6.3 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., 16 weeks after the administration of the last trial treatment).

6.4 SUBJECT SETS ANALYSED

The following analysis sets will be defined for analysis.

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

Treated Set (TS): composed of all participants who received at least 1 dose of trial treatment. All baseline characteristics and safety analyses will be based on TS. The analysis is based on actual treatment received. For safety listings, all collected data will be presented denoted with the population inclusion flag for ES.

Pharmacokinetic Set (PKS): composed of all participants who received at least 1 dose of spesolimab and had at least 1 evaluable spesolimab plasma concentration on this trial 1368-0130. Displays of spesolimab concentrations will be based on PKS.

Anti-Drug Antibody Analysis Set (ADA analysis set): composed of all participants who received at least 1 dose of trial treatment and had at least 1 evaluable anti-drug antibody (ADA) sample during 1368-0130 trial. ADA will be summarized on ADA analysis set.

Treatment arm will be based on actual treatment received, regardless of analysis set.

Table 6.4: 1 Subject sets analysed

Class of analysis	Subject set			
	Enrolled Set (ES)	Treated Set (TS)	PKS	ADA analysis set
Disposition	X			
Analysis set	X			
Demographic & baseline characteristics		X		
Baseline condition & medical history		X		
Exposure & compliance		X		
Concomitant medication		X		
Plasma concentration			X	
Safety		X		
ADA				X

ADA: anti-drug antibody;



6.6 HANDLING OF MISSING DATA AND OUTLIERS

Missing or incomplete AE dates are imputed according to BI standards ([9.2](#)).

Missing data and outliers of PK data are handled according to BI standards ([9.3](#)).

For incomplete information on the date of first diagnosis, time since first diagnosis will be calculated as follows:

- If the year of first diagnosis is unknown, time since first diagnosis will be set to missing.
- If day and month of the first diagnosis are unknown, time since first diagnosis will be calculated as if diagnosed on the 30th June of that year.
- If only the day of the first diagnosis is unknown, time since first diagnosis will be calculated as if diagnosed on the 15th of that month.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Unless otherwise specified, measurements reported with date and time and taken prior to start of administration of trial treatment on this trial will be considered pre-treatment values;

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measurements reported with a date only (and no time) and taken on the day of first administration of trial treatment on this trial will also be considered pre-treatment values. These pre-treatment values will be assigned to visits according to the nominal visit number as recorded on the eCRF or as provided by the laboratory.

Baseline is defined as the last measurement collected prior to the start of administration of the trial treatment on the parent trial, unless otherwise specified.

Pharmacokinetic (PK) concentrations collected prior to/on the date of administration of spesolimab of parent trial will be taken as pre-treatment values. And baseline is defined as the last measurement collected prior to the start of administration of spesolimab of parent trial.

Measurements taken after start of administration of trial treatment on this trial will be considered either on- or off-treatment values based on the definition in [Section 6.1](#), and will be assigned to visits for statistical analysis, if applicable, as defined below.

Analysis of AE data, potentially clinically significant abnormal laboratory values, concomitant medication or non-drug therapies, as well as use of rescue medication will not be based on visits. Frequency tables for these data will be using on-treatment data and categorized based on their occurring/starting dates. Therefore, no assignment to time windows will be necessary for such data.

The derivation of the last value, minimum value and maximum value of laboratory and vital signs data will consider all on-treatment values (whether or not selected in any time window; see [Table 6.7:1](#) for definition of the on-treatment period) within the period of interest; these will be derived for analysis of laboratory and vital signs data.

Table 6.7:1 Time windows for safety assessments to visits for statistical analysis

Visit no.	Week	Day	Window (per CTP)	Start (per CTP)	End (per CTP)
1 ^A	Screening	-7 to 1		-7	1
2			+3	11	17
3			+3	25	31
4			+3	39	45
5			+3	53	59
6			+3	67	73
7					
8			+3	96	101
9			+3	109	115
10			+3	123	129
11			+3	137	143
12			+3	151	157
13			+3	165	171
14					
15			+3	193	199

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16	Week 30	Day 210	+3	207	213
17	Week 32	Day 224	+3	221	227
18	Week 34	Day 238	+3	235	241
19	Week 36	Day 252	+3	249	255
20	Week 38	Day 276	+3	273	279
21	Week 40	Day 280	+3	277	283
22	Week 42	Day 294	+3	291	297
23	Week 44	Day 308	+3	305	311
24	Week 46	Day 322	+3	319	325
25	Week 48	Day 336	+3	333	339
26	Week 50	Day 350	+3	347	353
27	Week 52	Day 364	+3	361	367
28	Week 54	Day 378	+3	375	281
29	Week 56	Day 392	+3	389	395
30	Week 58	Day 406	+3	403	409
31	Week 60	Day 420	+3	417	423
32	Week 62	Day 434	+3	431	437
33	Week 64	Day 448	+3	445	451
34	Week 66	Day 462	+3	459	465
35	Week 68	Day 476	+3	473	479
36	Week 70	Day 490	+3	487	493
37	Week 72	Day 504	+3	501	507
38	Week 74	Day 518	+3	515	521
39	Week 76	Day 532	+3	529	535
40 ^C	Week 78	Day 546	+3	543	549
	(EoT)				
41 ^C	Week 92	Day 644	Na	644	644
	(EOS)				

For patients who discontinue the treatment early and are not willing to follow the whole visit schedule:

- EOS LD^B +112 -

All days are counted relative to the day of screening, which is defined as Day 1 (Week 0) on Visit 1. Day 1 should be preferably performed during the end of treatment (EoT) of the parent trial (1368-0098). First administration of trial therapy on this trial is planned at Week 1 on Visit 2, after results of safety and infection tests will be available to confirm eligibility criteria.

^A Measurements at screening are still on treatment period of parent trial as they are within residual effect period (REP). Some measurements at screening are considered baseline on this trial and may be listed only.

^BLD= Last dose.

^C For patients who discontinue trial treatment prematurely should undergo the End of Treatment as soon as possible.

7. PLANNED ANALYSIS

The primary objective of this trial is to assess the long-term safety of spesolimab in

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participant with HS who have completed approximately 8 to 12 months of spesolimab treatment in Part 1 of trial 1368-0098, although treatment exposures expect to be much shorter from the original plan.

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

Only descriptive statistics are planned for the clinical trial report (CTR) of this trial.

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all subjects in the respective subject set regardless of whether they have non-missing values or not).

The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be presented by treatment for demographic variables and baseline characteristics, based on the TS. More details could refer to [Section 5.4.1](#).

For continuous demographic variables listed in [Table 7.1:1](#), they will be presented by the number and percentage of patients in the categories defined in [Table 7.1:1](#).

Table 7.1:1 Categories for demographic variables and baseline characteristics

Variable	Categories
Age	< 30 years 30 to < 65 years ≥ 65 years
Weight	≤60 kg >60 to ≤90 kg >90 kg
BMI	< 25 kg/m ² 25 to < 30 kg/m ² ≥ 30 kg/m ²
Time since first diagnosis#	≤ 1 year > 1 to ≤ 5 year > 5 to ≤ 10 years > 10 years

#time since first diagnosis are calculated based on diagnosis date collected on parent trial, 1368-0098 Part 1.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report.

Concomitant diseases (i.e., baseline conditions) and concomitant non-drug therapies will be coded according to the most recent version of Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medications will be coded according to the most recent version of the World Health Organization – Drug Dictionary (WHO-DD).

Concomitant diseases which are present at start of the trial will be descriptively summarized by treatment based on the TS.

A medication/non-drug therapy will be considered concomitant to treatment, if it

- Is ongoing at the start of first trial treatment of this trial or
- Starts within the on-treatment period (see [Section 6.1](#) for the definition)

A medication/non-drug therapy will be considered as prior medication/non-drug therapy, if the end date of the medication/therapy is at any time prior to the start of first trial treatment on this trial, including medication/therapy initiated during parent trial.

Concomitant medication use (excluding rescue medication) taken at any time during the on-treatment period (cf. [Section 6.1](#)) will be summarized by treatment based on TS, with frequency and percentage of patients by Anatomical Therapeutic Chemical 3 (ATC3) class and preferred name.

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Concomitant use of non-drug therapies (excluding rescue therapy) taken any time during the on-treatment period (cf. [Section 6.1](#)) will be summarized by treatment based on TS, with frequency and percentage of patients.

Use of rescue medication will be summarized separately based on TS.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. Treatment compliance (see [Section 5.4.2](#) for the definition and calculation) will be summarized by treatment and period on TS using descriptive statistics (N, mean, SD, minimum, median, maximum).

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

Number and percentage of patients with treatment emergent adverse events (TEAEs) will be presented for the primary endpoint based on Treated Set (TS) in descriptive manner.

The expected intercurrent event (IE) is permanent treatment discontinuation. The main analysis will use while-on-treatment policy to handle IE, where treatment period is defined as the period from first administration of trial treatment to the end of residual effect period (REP) following last administration of trial treatment.

See further details on the [Section 7.8.1](#).



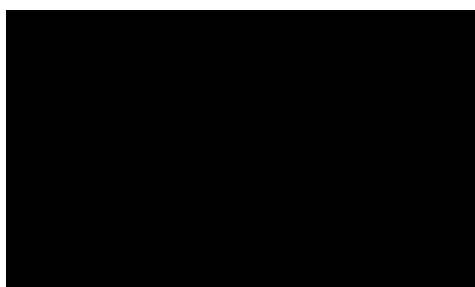
7.5 SECONDARY OBJECTIVE ANALYSIS

No secondary objective is set on this trial.



7.7 EXTENT OF EXPOSURE

Exposure of trial treatment will be summarize based on TS. The number of patients who received a dose of trial treatment will be tabulated. The amount of total dose and duration of exposure will be summarized by descriptive statistics (n, mean, SD, minimum, maximum median) for overall treatment period, The duration of exposure will be summarized categories by 8 weeks. Actual categories will be adjusted upon the observations of the longest duration of exposure among patients.



7.8 SAFETY ANALYSIS

All safety analyses will be performed on the Treated Set (TS) following BI standards. Data will be summarized descriptively without any imputation based on data available.

As the onset time of an AE will not be collected in the trial, any AE which occurs on the same day as a treatment dose will be assigned to the on-treatment period defined in [Table 6.1:1](#). For safety assessments by visits, if time is not collected, data on the same day of a treatment dose will be treated to be “prior treatment” except for scheduled local tolerability and post-dose vital signs assessments.

Off-treatment data will be listed only.

7.8.1 Adverse Events

Unless otherwise specified, adverse events (AEs) start in parent trial (1368-0098) and worsening in the this trial will be in scope of reporting, in addition to AEs that newly started in the this trial. AEs starting in parent trial and ongoing in the current trial without worsening will be reported in parent trial.

The analyses of AEs will include all on-treatment events during the whole on-treatment period. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

AEs will be coded with the most recent version of MedDRA®. Patients will be analysed according to the actual treatment received.

The analysis of AEs will be based on the concept of treatment emergent adverse events (TEAE). That means that all AEs occurring between first administration of trial treatment on this trial till 112 days after last administration of trial treatment will be assigned to the on-treatment period.

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

Time at risk [patient years] = (date of onset of AE – date of first administration of trial treatment + 1) / 365.25

If, for a patient, the selected treatment emergent adverse event didn't occur during the above defined treatment period (per [Table 6.1:1](#)) then the time at risk will be censored at the earliest of date of death, last contact date per EoS page, or the end of the above defined treatment period.

For each selected treatment emergent AE, the exposure adjusted incidence rate will be calculated as:

Incidence rate [1/100 Patient years (pt-yrs)] = 100 * number of patients with TEAE / Total TEAE-specific time at risk [patient years].

The analyses of AEs will be descriptive in nature. Analyses of AEs will be based on the exposure adjusted incidence rates (per 100 patient years), as well as the number of patients with AEs. System organ classes (SOCs) (if applicable) will be sorted according to the standard sort order specified by the European Medicines Agency (EMA), preferred terms (PTs) (if applicable) will be sorted by total frequency (within SOC).

For further details on summarization of AE data, please refer to "Handling of missing and incomplete AE dates" ([9.2](#)).

An overall summary of AEs will be presented. This overall summary will also include summary for the class of investigator reported adverse events of special interest (AESIs) defined in the CTP as well as user-defined adverse events categories (UDAEC). Both definitions are available below.

According to ICH E3 ([9.9](#)), in addition to Deaths and serious adverse events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted). An overall summary of adverse events will be presented.

The frequency of subjects with AEs will be summarized by treatment, primary system organ class and preferred term. AEs which were considered by the investigator to be drug related will be summarized separately. Separate tables will also be provided for subjects with SAEs, subjects with AEs leading to study drug discontinuation, subjects with AESIs and subjects with UDAEC. AEs will also be summarized by maximum intensity based on the Common Terminology Criteria for Adverse Event (CTCAE) grading system.

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5% (in preferred terms) will be summarized by treatment, primary system organ class and preferred term. The frequency of subjects with

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SAEs will also be summarized.

7.8.1.1 Adverse events of special interest (AESI)

The following are considered as AESIs (see Section 5.2.6.1.4 of CTP):

- Systemic hypersensitivity including anaphylactic reaction
- Severe infection
- Opportunistic and mycobacterium tuberculosis infections
- Peripheral neuropathy
- Potential severe Drug Induced Liver Injury (DILI)

7.8.1.2 User-defined adverse event categories (UDAEC)

The UDAEC categories are described below and will be evaluated.

Table 7.8.1.2: 1 Project MEDDRA search criteria for User Defined Adverse Events Concepts

User-defined AE category	Category
<i>Hypersensitivity</i>	
Hypersensitivity ALL	All of the categories below
Anaphylactic reaction, narrow	Narrow SMQ “Anaphylactic reaction”
Angioedema, narrow	Narrow SMQ “Angioedema”
Hypersensitivity, narrow	Narrow SMQ “Hypersensitivity”
<i>Infections (serious/severe, opportunistic)</i>	
Infections 'ALL'	All of the categories below
Opportunistic infections	Narrow SMQ "Opportunistic infections"
Tuberculosis infections	Sub-BIcMQ “Tuberculosis related terms”, narrow BIcMQ "Infections", narrow sub-search 8.2 “Tuberculosis related terms”
Severe infections	SOC "Infections and infestations" with AETOXGR >= 3 OR AESEV = 'Severe'. Not derived for studies where both severity variables are collected. SOC "Infections and infestations" – AEs of at least severe
Serious infections	CTCAE grade (>= 3) or any severe events SOC “Infections and infestations” with [AECOND: AESER =1] SOC “Infections and infestations” – SAEs
<i>Malignancies</i>	
Malignant tumours	Narrow sub-SMQ “Haematological malignant tumours”, Narrow sub-SMQ “Non-Haematological malignant tumours” Narrow Sub-SMQ “Malignant tumours”
Malignant skin tumours	Broad Sub-SMQ “Skin malignant tumours”
Skin melanomas	HLT Skin melanomas (excl. Ocular)

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Non-melanoma skin cancer (NMSC)	Broad Sub-SMQ “Skin malignant tumours” excluding HLT Skin melanomas (excl. Ocular)
Malignancies excluding non-melanoma skin cancer (NMSC)	Sub-SMQ “Malignant tumours” excluding NMSC defined above

User-defined AE category	Category
3 - point MACE for Monitoring 3-point MACE for Monitoring	BICMQ “Major Adverse Cardiovascular Events” with Narrow sub-search 1.1 “3-point MACE (part1/2) for monitoring” Narrow sub-search 1.2 “3-point MACE (part2/2) for monitoring” and AE outcome=fatal *
Depression Depression	Broad sub-SMQ "Depression (excl suicide and self-injury)"
Suicidal ideation and behavior (SIB) sub-SMQ "Suicide/self-injury"	sub-SMQ "Suicide/self-injury"
DRESS# Narrow DRESS (Drug reaction with eosinophilia and systemic symptoms syndrome)	Narrow SMQ "Drug reaction with eosinophilia and systemic symptoms syndrome"
Peripheral Neuropathy, Narrow Guillain-Barré Syndrome Peripheral Neuropathy Demyelination	Narrow SMQ “Guillain-Barré syndrome” Narrow SMQ “Peripheral Neuropathy” Narrow SMQ “Demyelination”

* This is achieved by retrieving all cases found either by running subsearch 1 in narrow scope (BICMQ search ID 32019093) or subsearch 2 (BICMQ search ID 32019094).

DRESS algorithmic search will be presented as a listing.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (9.4). Note that data from the central laboratory will be used for all displays described below, unless otherwise specified.

For continuous safety laboratory parameters, normalized values will be derived.

Normalization means transformation to a standard unit and to a standard reference range. The process of normalization, handling of repeat values at the same visit for by-visit displays, as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data. All analyses considering multiple times of the ULN (as described below) will be based on standardized and not normalized values. For continuous safety laboratory parameters, differences to baseline will be calculated. For all outputs, the last assessment before the first treatment at Day 1 is chosen as the baseline value.

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Only patients with at least one available post-baseline value will be included in the analysis of an individual laboratory parameter. All individual laboratory data will be listed. Values outside the reference range will be flagged.

For derivation of the last value, the minimum value, and the maximum value, all values during the on-treatment period will be considered. These will be derived for analysis of laboratory, vital signs and local tolerability data. For identification of potentially clinically significant abnormal laboratory values, all values during on-treatment period will also be considered.

Descriptive statistics of laboratory values over time and for the difference from baseline on-treatment will be based upon normalized values, including summaries of the last value on treatment, the minimum value on treatment and the maximum value on treatment and corresponding change from baseline. Graphical displays via box plots will be produced for the last value, minimum and maximum value on treatment for each continuous laboratory endpoint.

Laboratory values will be compared to their reference ranges; shift tables will be provided for the number of patients with a specific CTCAE grade at baseline versus the CTCAE grade at the last measurement on treatment, as well as the worst grade on treatment; laboratory parameters with exception to this display type are described in the company standards (9.5). These analyses will be based on converted laboratory values. The display of laboratory data using the CTCAE grades will be done based on BI standards (9.5).

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on converted lab values, i.e. using SI units. These rules will be listed in the SDL appendix of the CTR. Frequency tables will summarize the number of patients with potentially clinically significant abnormalities. Patients having an abnormal lab value at baseline will be presented separately. A separate listing will present potentially clinically significant abnormal lab values; for each functional lab group all patient's lab values will be listed, if there exists at least one lab value with clinically significant abnormality within the group.

The frequency of patients with AST or ALT elevations $\geq 3\text{xULN}$, $\geq 5\text{xULN}$, $\geq 10\text{xULN}$, and $\geq 20\text{xULN}$ will be displayed based on standardized laboratory values. To support analyses of liver related adverse drug effects, the frequency of subjects with AST and/or ALT $\geq 3\text{xULN}$ combined with the elevation of total bilirubin $\geq 2\text{xULN}$, from samples drawn within 30 days of each other, will be displayed, stratified by alkaline phosphatase $< 2\text{xULN}$ and $\geq 2\text{xULN}$ (a subject can potentially be in both alkaline phosphatase strata in case of multiple AST/ALT and bilirubin elevations). The start of the 30-day time span is triggered by each liver enzyme elevation above the defined thresholds. This analysis will be based on standardized laboratory values.

A graphical analysis of ALT and total bilirubin will be performed: the so-called eDISH plot. The peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. The measurements displayed for total bilirubin and ALT may, or may not, occur on the same date. Two reference lines, 2xULN for

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total bilirubin and 3xULN for ALT, are drawn onto the graph to divide the plane into four quadrants. Normal cases are in the lower left quadrant, potential drug-induced liver injury (DILI) cases are in the upper right quadrant (potential Hy's Law quadrant), while the lower right quadrant is known as the Temple's corollary range ($ALT \geq 3xULN$ and total bilirubin $< 2xULN$). The display will be repeated for AST and total bilirubin.

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report.

The analyses of vital signs (blood pressure, pulse rate, body temperature, respiratory rate) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see [Section 6.7](#)) will be provided, including the last value, the minimum value and the maximum value during on-treatment period.

Clinically relevant findings in vital signs data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

Abnormal findings in 12-lead ECG will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.5 Local Tolerability

Local tolerability will be summarized during on-treatment period and by visit, with the frequency and percentage of patients who experienced any symptoms by severity/intensity.

7.8.6 Acne episodes

The occurrence and characteristics of historical acne episodes will be summarised by treatment with frequency and percentage of patients. The characteristics of any acne episodes which occur during the treatment period will be displayed overall; Separate displays of the characteristics of those acne episodes which had a) a suspected medical history risk factor, b) a suspected concomitant medication risk factor, and c) a relatedness to spesolimab, will also be presented. If only few records for the acne episodes, listings will be provided instead of summary tables.

7.9 OTHER ANALYSIS

7.9.1 Biomarker analyses

██████████ will be descriptively summarized by visit as continuous variables. For each marker the absolute value and percent change from baseline will be analysed per treatment group via

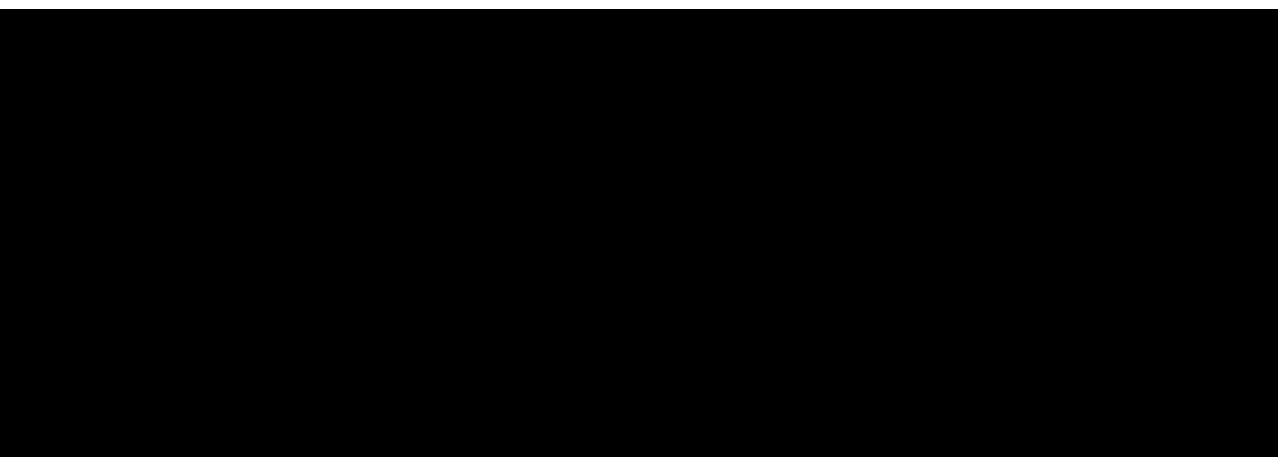
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- Mean, standard deviation, median, Q1, Q3, normalized IQR ($0.7413 \times \text{IQR}$), minimum, maximum, gMean
- Error bars for the median with Q1 being the lower end and Q3 the upper end of the bars of the respective outcome variable will be calculated for each time point. This information will be displayed graphically in conjunction with the median.
- Line plots presenting individual values of hs-CRP over time. Beside the individual patient lines also a median line will be depicted in all plots for a better visual interpretation.

All plots with absolute values will include upper limit of the normal range, if a normal range is available.



7.9.3 Immunogenicity

Analysis of anti-drug antibody (ADA) and assessments of ADA impact on PK will be performed based on the complete administration data of spesolimab from both the parent trial 1368-0098 and this trial data 1368-0130. Analysis of assessments of ADA impacts on safety will be performed based on this trial data only for the CTR.

The ADA status and frequency of patients with ADA to spesolimab will be presented by visit. The number of subjects with ADA status positive/negative at any time will be presented. ADA parameters (e.g. treatment-induced ADA positive subjects, transient ADA response and persistent ADA response) will also be presented by visit and cumulatively for the overall study duration in this trial. Further exploratory assessments of the ADA data will be performed once data is available and these will be described, if done, in the CTR.

Further analyses based on ADA data will be performed for safety-based analysis with the following ADA status and endpoints.

Patient is considered ADA positive (+) if he/she had at least 1 positive ADA sample in this trial. Otherwise, patient is considered ADA negative (-).

ADA by safety-based endpoints will be summarized for ADA analysis set.

- Safety-based subgroup analysis (using e.g. hypersensitivity safety events)
 - The number of ADA positive subjects with safety ‘event’ after the first ADA development will be compared with (i) the number of ADA positive subjects with safety ‘event’ before the first ADA development, and (ii) the number of ADA positive subjects with safety ‘event’ before the first ADA development and/or ADA negative subjects with the safety ‘event’. The timing of the onset of ADA development will be considered in two ways: 1) at the visit where ADA+ event was first observed, or, 2) at the visit immediately before the ADA+ event was first observed.

8 TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The restricted access to treatment information will be removed and be released once the parent trial (1368-0098 part I) has been unblinded for reporting purpose.

The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study/Follow-up visit and all data has been entered and cleaned as defined in the “Data Ready to be Unblinded and / or Final Trial Closure Notification” (RUN) form.

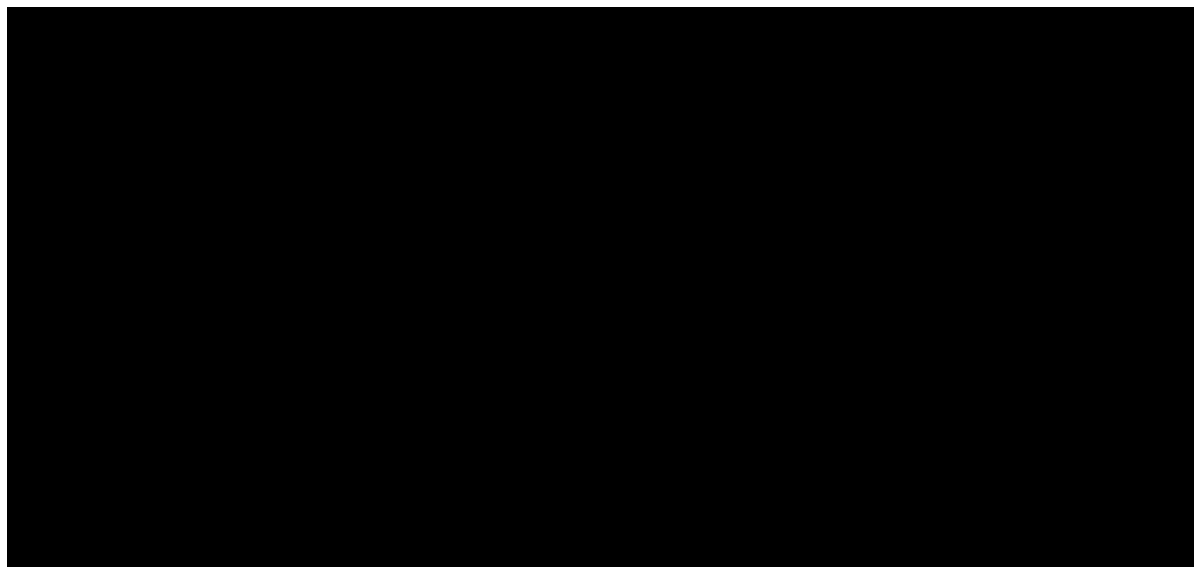
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9 REFERENCES

9.1	<i>BI-VQD-11777-S-G_40-113_AD-02</i> : "Clinical Trial Report Type", current version, group/owning department "Med Clinical Development & Operations", DMS for controlled documents
9.2	<i>BI-KMED-BDS-HTG-0035</i> : "How to Guide: Handling of Missing and Incomplete AE dates", current version, KMED
9.3	<i>BI-KMED-TMCP-HTG-0025</i> : "How to Guide: Standards and Processes for Analyses Performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, KMED
9.4	<i>BI-KMED-BDS-HTG-0042</i> : "How to Guide: Handling, Display and Analysis of Laboratory Data", current version, KMED.
9.5	<i>BI-KMED-BDS-HTG-0036</i> : "How to Guide: CTCAE Grading for Laboratory Values", current version, KMED.
9.6	<i>001-MCS-80-606</i> : "Management of Non-Compliances, Audit and Inspection Responses", current version, group / owning department "Med Quality Medicine", DMS for controlled documents.
9.7	<i>BI-VQD-12045_40-413</i> : "Identify and Manage Important Protocol Deviations (iPD)", current version, group / owning department "Med Clinical Development & Operations", DMS for controlled documents.
9.8	REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, European Commission webpage.
9.9	<i>CPMP/ICH/137/95</i> : "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version, EMA webpage.
9.10	<i>001-MCS-30-475_RD-01</i> : "Biomarker: Intended Use & Implementation Statement (IUIS) (template)", current version, group / owning department "Med Translational Medicine Clinical Pharmacology", DMS for controlled documents.



11 HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	18-Feb-25	[REDACTED]	N.A.	This is the final TSAP
2.0	08-Aug-25	[REDACTED]	Section 2 Section 6 Section 7 Section 7.8.1.2 Section 11	Format corrections