TRIAL STATISTICAL ANALYSIS PLAN

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	Page 1 of 51

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1. TABLE OF CONTENTS

TITLE PAGE 1

1. TABLE OF CONTENTS 2

LIST OF TABLES 4

2. LIST OF ABBREVIATIONS 5

3. INTRODUCTION 8

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY 9

5. ENDPOINTS(S) 10
5.1 PRIMARY ENDPOINT(S) 10
5.2 SECONDARY ENDPOINT(S) 10
5.2.1 Key secondary endpoint(s) 10
5.2.2 Secondary endpoint(s) 10
[redacted]
6. GENERAL ANALYSIS DEFINITIONS 14
6.1 TREATMENT(S) 14
6.2 IMPORTANT PROTOCOL DEVIATIONS 16
6.3 INTERCURRENT EVENTS 16
6.4 SUBJECT SETS ANALYSED 17
[redacted]
6.6 HANDLING OF MISSING DATA AND OUTLIERS 19
6.6.1 Withdrawals 19
6.6.2 Efficacy data 19
6.6.3 Safety data 20
6.6.4 PK data 21
6.6.5 Biomarker data 21
6.6.6 Time since first diagnosis 21
6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS 21

7. PLANNED ANALYSIS 26
7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 28
7.2 CONCOMITANT DISEASES AND MEDICATION 28
7.3 TREATMENT COMPLIANCE 29
7.4 PRIMARY OBJECTIVE ANALYSIS 29
7.5 SECONDARY OBJECTIVE ANALYSIS 29
7.5.1 Key secondary objective analysis 29
7.5.2 Secondary objective analysis 29
7.6 FURTHER OBJECTIVE ANALYSIS 30
7.6.1 Further efficacy endpoints 30

7.6.2 Use of rescue therapy 30
7.6.3 Other analysis 31
7.7 EXTENT OF EXPOSURE 31
7.8 SAFETY ANALYSIS 31
7.8.1 Adverse Events 31
7.8.2 Laboratory data 34
7.8.3 Vital signs 36
7.8.4 ECG 36
7.9 OTHER ANALYSIS 36
7.9.1 Biomarker analyses 36
7.9.2 Immunogenicity 36
7.9.3 PK / PD analyses 37
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION 39
9. REFERENCES 40

[redacted]

11. HISTORY TABLE 51

LIST OF TABLES

Table 6.1: 1 Flow chart of analysis phases of the study 15
Table 6.4: 1 Overview of use of patient analysis sets by class of endpoint and handling of estimand and missing data 18
[redacted]
Table 6.7: 1 Time windows for assignment of vital signs to visits for statistical analysis...23
Table 6.7: 2 Time windows for assignment of DLQI, PGI-S, PGI-C, HiSQoL, Pain NRS safety lab, and biomarker to visits for statistical analysis 24
Table 6.7: 3 Time windows for assignment of all the other efficacy assessments except those mentioned in Table 6.7: 2 to visits for statistical analysis. 25
Table 7.1: 1 Categories for summary of continuous variables 28
Table 7.8.1: 1 Project MEDDRA search criteria for User Defined Adverse Events Concepts 33
Table 11: 1 History table 51

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glosssary

Term	Definition / description
ADA	Anti-drug antibodies
ADS	Analysis dataset
AdT	total abscess, inflammatory nodule and draining tunnel
AE	Adverse event
AESI	Adverse event of special interest
ALQ	Above the upper limit of quantification
ALT	Alanine aminotransferase
AN	Abscess and inflammatory nodule
ANdT	Abscess, inflammatory nodule and draining fistula/tunnel
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC3	Anatomical-Therapeutic-Chemical classification level 3
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
BSA	Body surface area
CARE	Clinical data analysis and reporting environment
CGI	Clinical Global Impression
C_{max}	Maximum measured concentration of the analyte in plasma
CRF	Case report form
CRP	C-reactive protein
CTA	Clinical Trial Application
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting

Term	Definition / description
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
EC	Estimand concept
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
ES	Enrolled set
EudraCT	European union drug regulating authorities clinical trials
FACIT	Functional Assessment of Chronic Illness Therapy
FUP	Follow-up
gCV	Geometric coefficient of variation
GCP	Good Clinical Practice
gMean	Geometric mean
GPP	Generalized pustular psoriasis
HASI	HS Area and Severity Index
HS	Hidradenitis suppurativa
HS-PGA	HS Physician Global Assessment
HiSCR	Hidradenitis suppurativa clinical response
m-HiSCR	Modified - Hidradenitis suppurativa clinical response
HS-CRP	High-Sensitivity C-Reactive Protein
IHS4	International Hidradenitis Suppurativa Severity Score System
IHS4-55	At least a 55% reduction from baseline in IHS4
IL-36	Interleukin 36
IL-36R	Interleukin 36 Receptor
NRS	numerical rating scale
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
HiS-QoL	Hidradenitis suppurativa quality of life
iPD	Important protocol deviation
ICEs	Intercurrent events
i.v.	intravenous
MAA/BLA	Market Authorization Application/Biologics Licence Application

Term	Definition / description
MedDRA	Medical Dictionary for Regulatory Activities
DLQI	Dermatology Life Quality Index
Nab	Neutralising antibody
NRI	No response imputation
OC	Observed cases
OR	Original results
OLE	Open Label Extension
PD	Pharmacodynamic(s), protocol deviation
PE	Primary endpoint
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter set
PPS	Per protocol set
PT	Preferred term
Q1	1st quartile
Q3	3rd quartile
RAGe	Report appendix generator
REP	Residual effect period
RNA	Ribonucleic acid
RPM	Report planning meeting
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listing
SI	Système international d’unités
SOC	System organ class
TS	Treated set
TSAP	Trial statistical analysis plan
UDAEC	User-defined Adverse Event Category
ULN	Upper limit of normal range
VAS	Visual analogue scale
MCMC	Markov Chain Monte Carlo

3. INTRODUCTION

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 the primary and secondary variables and other data.

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, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.”

The statistical analyses will be performed within the validated working environment CARE, including SAS^{TM} (current Version 9.4, by [redacted], and a number of SAS^{TM}-based tools (e.g., macros for the analyses of AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

Analyses of the biomarker and gene expression data are described in a separate biomarker TSAP, unless otherwise specified in this document.

Since the primary aim of this study is to collect long-term safety and efficacy data on the use of spesolimab (BI 655130) in adult patients with Hidradentis suppurativa (HS), 1 interim analysis when all the rolled over patients reach Week 12 in this trial will be done over the 2-year conduct phase of this trial in order to support, for example, regulatory interactions, Clinical Trial Applications (CTA), and Market Authorization Application/Biologics Licence Application (MAA/BLA)submissions, but also to provide important safety and efficacy information to the sponsor to guide further development of the compound, and to the investigators via IB updates and publications. Any data cut-off to be used for the reporting of trial data at interim will be presented in either a separate data cleaning plan, or in an appendix to this TSAP. If considered appropriate, an access plan may be developed at the time of the interim which describes those personnel who will be allowed access to the results of the interim data analysis.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses stated in the CTP (latest version) will be performed as planned with the following adaptations.

Considering the categorical nature of PGI-S and PGI-C, the frequency over time will be presented for these further endpoints instead of absolute change from baseline as planned in CTP.

The below further efficacy endpoints, which were not specified in the CTP, have been added:
- Percent change from baseline (%) in total abscess and draining fistula (AdT) count over time.
- Percent change from baseline (%) in total abscess, inflammatory nodule and draining fistula/tunnel (ANdT) count over time.
- Proportion of patients with achievement of m-HiSCR response over time.
- Proportion of patients with achievement of IHS4-55 response over time.
- Percent change from baseline (%) in total inflammatory nodule count up over time.
- Percent change from baseline (%) in total abscess count up to over time.
- Achievement of complete elimination of draining fistulas over time.
- Achievement of complete elimination of abscess over time.
- Proportion of patients with achievement of HiSCR over time.
- At least 30% reduction from baseline in Numerical Rating Scale (NRS30) in Patient’s Global Assessment of HS Pain over time.

5. ENDPOINTS(S)

For estimand and handling of missing data and the occurrence of inter-current events, unless otherwise specified, see Section 6.3, Section 6.4 and Section 6.6. For the specification of baseline definition, unless otherwise specified, see Section 6.7.

For the summary of all efficacy data, only those observations which were collected during the on-treatment period will be used.

Baseline for safety data, unless otherwise specified, is the last value prior to initiation of treatment in current 1368-0067 study.

Regarding the analyses of the change from baseline by visit or compared to baseline by visit for efficacy endpoints, unless otherwise specified, we will use last measurement collected prior to initiation of spesolimab as baseline. i.e.,

- For prior spesolimab arm in 1368-0052, the baseline in parent trial is used, which refers to the last measurement collected prior to initiation of treatment in 1368-0052.
- For prior placebo arm in 1368-0052, the baseline in current trial is used, which refers to the last measurement collected prior to initiation of treatment in 1368-0067.

5.1 PRIMARY ENDPOINT(S)

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

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

Secondary endpoints are defined as described below:

- Percent change in [redacted] abscess and inflammatory nodule (AN) count from baseline (%) up to Week [redacted]
- Percent change in [redacted] draining fistula (DF) count from baseline (%) up to Week [redacted] (*Only patients with at least 1 draining fistula at baseline will be used for analysis*).
- Hidradenitis suppurativa Clinical Response (HiSCR) up to Week [redacted]
- Change from baseline in International Hidradenitis suppurativa Severity Score System (IHS4) value up to Week [redacted]
- Hidradenitis suppurativa Physician Global Assessment (HS-PGA) score of 0 or 1 up to Week [redacted]
- Absolute change from baseline in Hidradenitis suppurativa Area and Severity Index (HASI) score up to Week [redacted]
- At least one flare (defined as at least [redacted] in AN count with a minimum [redacted]

of [redacted] relative to baseline) up to Week [redacted]
- At least [redacted] from baseline in Numerical Rating Scale (NRS30) in Patient's Global Assessment of HS Pain up to Week [redacted]

[redacted]

[redacted]

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on the treatment to be administered, assignment to treatment, and selection of dose, cf. Section 4 of the CTP.

The study phases are defined relative to first dose at Day 1 as below:

Table 6.1: 1 Flow chart of analysis phases of the study

Study analysis phase	**Description**	**Start (included)**	**End (included)**
Screening phase	Screening	Earliest of (Date of informed consent, first screening procedure)	Date/time of start of the first study dose minus 1 second.
Treatment phase & Residual effects period	On-treatment period	Date/time of start of the first study dose regardless of infusion or injection (Day 1)	Earliest of: i) Date of last study drug regardless of infusion or injection + 112 days at 23:59, ii) cut-off for interim analysis if applicable.
Follow-up phase[1] (if applicable)	Off-treatment period (if applicable)	Date of end of last study dose + 113 days at 0:00 a.m.	Latest of: i) Date of EOS visit; ii) last contact date on trial termination page at 11:59 p.m.

Dates are defined individually per patient. If more than one date is associated with a specific visit, measurements associated with a specific date are assigned to a study analysis phase according to the rules specified in the table. An analysis phase will not extend beyond the start date of the following phase.

[1] The off-treatment period (i.e. Follow-up phase) only exists if the date of EoS visit or the last contact date is after the date of end of last administration + 112 days.

Treatments will be labelled for final analysis as follows:

Tables will be displayed also by prior treatment from parent trial for final analysis:

- "Prior Placebo" (applicable to analysis for whole on-treatment period, i.e., including infusion loading at Day 1 for placebo patients from parent trial]
    - "Prior Placebo + uptitration at Week [redacted] (applicable to analysis for whole on-treatment period, i.e., including infusion loading at Day 1 for placebo patients from parent trial and after dose escalation]
    - "Prior Placebo + Other" (applicable to analysis for whole on-treatment period, i.e., placebo patients from parent trial who received [redacted] dose [redacted] during all [redacted] period or who were early discontinued before Week [redacted]])

- "Prior Speso" (applicable to analysis for whole on-treatment period, i.e., including [redacted] at Day 1 for speso patients from parent trial, before and post dose escalation)
    - "Prior Speso + uptitration at Week [redacted]" (applicable to analysis for whole on-treatment period, i.e., including [redacted] at Day 1 for speso patients from parent trial and after dose escalation)
    - "Prior Speso + Other" (applicable to analysis for whole on-treatment period, i.e., speso patients from parent trial who received [redacted] during all [redacted] [redacted] or who were early discontinued before Week [redacted])

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all patients in the database (i.e., enrolled patients). Consistency check listings (for identification of violations of time windows) and a list of protocol deviations will be provided to be discussed at the RPM/DBLM/ CQM. At this meeting, it will be decided whether a discrepant data value can be used in analyses or whether it must be queried in the clinical database. 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)" (3).

If any iPDs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM/CQM minutes via an accompanying Excel spreadsheet (3). The following table contains the categories which are considered to be iPDs in this trial. If the data show other iPDs, for example, based on monitor visits to the sites, then this table will be supplemented accordingly by the time of the RPM/DBLM/CQM. Not all iPDs will lead to exclusion from analysis sets. Certain iPDs may lead patients to being excluded from all the analyses.

As this is an open label, long term safety trial, all analyses will be performed based on the treated population only. Since no confirmatory efficacy testing is planned, no efficacy related iPDs leading to exclusion from analysis set are defined.

6.3 INTERCURRENT EVENTS

The expected intercurrent events (ICEs) of interest in this trial are:

- Use of rescue therapy (while still on treatment), as defined in Section 5.4.3
- Treatment discontinuation without restricted medication, flagged by medical review if occurring
- Treatment discontinuation with restricted medication, flagged by medical review if occurring

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

Hybrid Strategy (EC-H): All intercurrent events except for the administration of rescue therapy will be handled using the treatment policy approach. Rescue therapy will be handled using the hypothetical approach, under the scenario in which the intercurrent event would not occur. This will be used as the **primary strategy** of implementing the Estimand Concept (EC), allowing the effects of adherence, i.e., regardless of treatment discontinuation, but excluding the effects of rescue therapy.

No deaths are expected in this trial. In the unlikely event of a death occurring, it will be handled using a hypothetical approach for each strategy.

6.4 SUBJECT SETS ANALYSED

The following analysis sets will be defined for this trial:

Enrolled Set (ES)
This patient set includes all patients who signed informed consent. It will be used for analyses of patient disposition.

Safety Analysis Set (SAF):
This patient set includes all patients who received at least one dose of study drug in trial 1368-0067. This is the main analysis set for efficacy and safety. Patients will be analyzed according to the actual treatment received.

Safety Set ADA (SAF-ADA)
This patient set includes all patients who received at least one dose of study drug and had at least one evaluable ADA sample in trial 1368-0067. This is the main analysis set for ADA impact on efficacy and safety. Patients will be analyzed according to the actual treatment received.

The discussion of all exceptional cases and problems and the decisions on the allocation of patients to populations will be made at the RPM/DBLM at the latest.

Table 6.4: 1 Overview of use of patient analysis sets by class of endpoint and handling of estimand and missing data

Class of endpoint		
	ES	**SAF**
Disposition	OR	
Compliance and exposure		OR
iPD		OR
Demographic/baseline characteristics		OR
Concomitant medication		OR
Primary endpoint		OR
Secondary binary efficacy endpoints		OC-NRI: for binary efficacy endpoints
Secondary continuous efficacy endpoints		OC for continuous efficacy endpoints.
Further efficacy endpoints		OC for continuous efficacy endpoints. OC-NRI: for binary efficacy endpoints
Plasma concentration & ADA		OR
Efficacy endpoints by ADA impact		OC for continuous efficacy endpoints OC-NRI for binary efficacy endpoints
AE		OR
Lab data, vital signs		OC-IR

For explanation of the different approaches with regard to missing data see Section 6.6.
OC = observed cases excluding values after any use of rescue medication.
OC-IR = observed cases including also values after any use of rescue medication.
OC-NRI = values after any use of rescue medication will be censored and impute with non-responder..
OR = original results.
NRI = Non-Response Imputation, cf. Section 6.6.2.

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Section 7.3 of the CTP describes the handling of missing data.

The original results (OR) approach implies the presentation of data exactly as observed (not using time windows and not setting values to missing).

OR analysis will be performed on parameters and endpoints that are either not affected by patients' rescue therapy use (e.g., plasma concentration level of spesolimab, rescue therapy itself), or, it is not meaningful to apply any imputation rule for the replacement of missing values.

6.6.1 Withdrawals

The reasons for withdrawal from treatment will be reported as indicated on the eCRF.

6.6.2 Efficacy data

Based on the different reasons for patients' data missing for different endpoints, various approaches will be used to assess the impact of missing data on the efficacy endpoints of this trial, depending upon the type of the endpoint (cf. Table 6.4: 1) Approaches to be applied are described below.

Missing data imputations will be performed using all available on-treatment data observed up to the respective analysis cut-off date, if applicable.

Some efficacy endpoints are defined with a particular binary outcome, i.e. Achievement of PGA score of 0 or 1. Then imputation is planned to take place only at the binary level, i.e., the

PGA score itself as a ordinal variable will not be imputed, but the binary endpoints derived based on these scores will be imputed, unless otherwise specified.

Continuous efficacy endpoints

For interim analysis planned at week [redacted] those efficacy endpoints up to Week [redacted] which are continuous in nature, the use of a restricted maximum likelihood (REML)-based mixed effect model with repeated measures (MMRM) approach, if applicable, will ensure that missing data are handled implicitly, via a missing at random assumption, by the statistical model.

For final analysis, the efficacy endpoints during on-treatment period will be displayed descriptively using following methods:

- Observed cases (OC) approach will include all collected data, without imputation for any missing data. Such an OC approach will exclude all values measured after intake of a rescue therapy.

Binary efficacy endpoints

For all binary endpoints (i.e. endpoints that are either 1 (patient responded) or 0 (patient did not respond)), the following will be performed as the primary imputation approach (analysis type: No Response Imputation [NRI]):

- If there are data at visits both before and after the visit with a missing outcome, then impute as success only if both neighbouring visits also represent a success (independent of whether the preceding and following observations were selected for analysis based on time windows described in Section 6.7 and no rescue treatment has been given during this period);
- Otherwise, impute as a failure.

OC-NRI method will be used to display the binary data.

6.6.3 Safety data

With respect to safety evaluations, it is not planned to impute missing values. For safety data that are displayed by time point (or visit) of measurement, the Observed cases (OC-IR: with no imputation for any missing data, which will include values after any rescue medication or treatment discontinuation.) approach will be used.

For safety data that are not displayed by visit such as AE and possibly clinically significant laboratory abnormality, original results (OR) will be used.

The only exceptions where imputation might be necessary for safety evaluation are AE dates and start and stop dates for concomitant medications. Missing or incomplete AE dates are imputed according to BI standards (10).

Partial start and stop dates for concomitant medications, rescue, and historical medication for HS will be imputed to enable subsequent calculation (but not for display) by the following "worst case" approach:

- If the day of the end date is missing, then the end date is set to last day of the month (or to the patient's trial completion date, if it is earlier than the last day of the month).
- If the day and month of the end date are missing then the end date is set to 31st of December of the year (or to the patient's trial completion date, if it is earlier than the 31st of December of the year).
- If the day of the start date is missing then the start date is set to first day of the month (except for rescue therapy, where the first dosing day will be used if first dosing happened in the same month).
- If the day and month of the start date are missing then the start date is set to 1st January of the year (except for rescue therapy, where the first dosing day/month will be used if first dosing happened in the same year).
- All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

If a concomitant medication was ticked to be ongoing, it is expected that the end date is missing and will not be imputed for display purposes.

6.6.4 PK data

Missing data and outliers of PK data are handled according to BI standards (11).

6.6.5 Biomarker data

The handling of other biomarkers e.g. RNA expression will be specified in a separate document.

6.6.6 Time since first diagnosis

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

Measurements reported with date and time and taken prior to start of administration of trial treatment will be considered pre-treatment values. Measurements reported with a date only (and no time) and taken on the day of first administration of trial treatment 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, unless otherwise specified, is defined as the last measurement collected prior to the start of administration of the trial treatment.

For the baseline defined in efficacy endpoints like "change from baseline" or "compared to baseline", unless otherwise specified, is defined as the last measurement before initiation of treatment (cf. Section 5).

Baseline for time to event endpoints, is defined as the last measurement collected prior to the start of administration of the trial treatment in the current extension trial 1368-0067.

For analysis of anti-drug antibodies (ADA), 2 different baselines will be used for the clinical trial report (CTR). For the analysis of ADA impact on pharmacokinetic (PK), the entire course of treatment is to be considered and assessments prior to initial trial of the parent trial (1368-0052) is considered baseline. Details will be discussed on the trial CTR.
For the analysis of ADA impact on safety and efficacy endpoints, baseline is defined as the first evaluable sample collected prior to treatment administration at baseline of this trial 0067.

Measurements taken after start of administration of trial treatment 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 therapy 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 6.1: 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.

All other safety, efficacy and biomarker measurements will be assigned to visits based on extended time windows around the planned visit dates, defined relative to the day of first trial treatment (which is scheduled for Visit 2). These extended time windows are defined in Table 6.7: 1, Table 6.7:2, Table 6.7:3.

Table 6.7: 1 Time windows for assignment of vital signs to visits for statistical analysis.

Visit number	Visit label	Planned day	Time window [day]				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
1	Week0	Day1	n/a	1[A]	1	1[A]	1
2	Week[redacted]	Day[redacted]	+-2	[redacted]	[redacted]	[redacted]	[redacted]
3	Week[redacted]	Day[redacted]	+-2	[redacted]	[redacted]	[redacted]	[redacted]
4	Week[redacted]	Day[redacted]	+-2	[redacted]	[redacted]	[redacted]	[redacted]
5	Week[redacted]	Day[redacted]	+-2	[redacted]	[redacted]	[redacted]	[redacted]
6	Week[redacted]	Day[redacted]	+-2	[redacted]	[redacted]	[redacted]	[redacted]
7	Week[redacted]	Day[redacted]	+-2	[redacted]	[redacted]	[redacted]	[redacted]
8	Week[redacted]	Day[redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
…	…	…	…	Planned date-3	Planned date+3	End of extended window of last visit+1	Midpoint of planned days between current visit and next visit
53	Week[redacted] EoT	Da[redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
54	Week[redacted] (FUP1)	Da[redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
55	Week[redacted] (EOS)	Da[redacted]	+-10	[redacted]	[redacted]	[redacted]	[redacted]
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 first treatment of current study, which is defined as Day 1.

* For the patients who enter OLE trial, V1 is strongly recommended to be performed during the EOT of the preceding parent trial.

[A] Note that measurements made at Day 1 and assigned to the on-treatment period (because mistakenly made after start of trial treatment) via assessment on date & time (i.e. safety laboratory) will not be assigned to Day 1. Such data will be listed only.

[B] LD= Last dose.

Table 6.7: 2 Time windows for assignment of DLQI, PGI-S, PGI-C, HiSQoL, Pain NRS safety lab, and biomarker to visits for statistical analysis

Visit number	**Visit label**	**Planned day**	**Time window [day]**				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
1	Week0	Day1	n/a	1 [A]	1	1 [A]	22
3	Week [redacted]	Day [redacted]	+-2	[redacted]	[redacted]	[redacted]	[redacted]
5	Week [redacted]	Day [redacted]	+-2	[redacted]	[redacted]	[redacted]	[redacted]
7	Week [redacted]	Day [redacted]	+-2	[redacted]	[redacted]	[redacted]	[redacted]
8	Week [redacted]	Day [redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
10	Week [redacted]	Day [redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
12	Week [redacted]	Day [redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
14	Week [redacted]	Day [redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
16	Week [redacted]	Day [redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
18	Week [redacted]	Day [redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
20	Week [redacted]	Day [redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
22	Week [redacted]	Day [redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
24	Week [redacted]	Day [redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
…	…		…	[redacted]	[redacted]	[redacted]	Midpoint of planned days between current visit and next visit
52	Week [redacted]	Day [redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
53	Week [redacted] EoT	Day [redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
54	Week [redacted] (FUP1)	Day [redacted]	+-3	[redacted]	[redacted]	[redacted]	[redacted]
55	Week [redacted] (EOS)	Day [redacted]	+-10	[redacted]	[redacted]	[redacted]	[redacted]
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 first treatment of current study, which is defined as Day 1.

* For the patients who enter OLE trial, V1 is strongly recommended to be performed during the EOT of the preceding parent trial.

[A] Note that measurements made at Day 1 and assigned to the on-treatment period (because mistakenly made after start of trial treatment) via assessment on date & time (i.e. safety laboratory) will not be assigned to Day 1. Such data will be listed only.

[B] LD= Last dose.

Table 6.7: 3 Time windows for assignment of all the other efficacy assessments except those mentioned in Table 6.7: 2 to visits for statistical analysis.

Visit number	Visit label	Planned day	Time window [day]				
			Window (per CTP)	Start (per CTP)	End (per CTP)	Start (extended)	End (extended)
1	Week0	Day1	n/a	1 [A]	1	1 [A]	1
2	Week[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Week[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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 first treatment of current study, which is defined as Day 1.

* For the patients who enter OLE trial, V1 is strongly recommended to be performed during the EOT of the preceding parent trial.

[A] Note that measurements made at Day 1 and assigned to the on-treatment period (because mistakenly made after start of trial treatment) via assessment on date & time (i.e. safety laboratory) will not be assigned to Day 1. Such data will be listed only.

[B] LD= Last dose.

7. PLANNED ANALYSIS

Final trial analysis is planned to be performed at the end of the study once all patients have completed the study (including any follow-up period) if applicable. As specified in CTP in Section 7.2.7, multiple interim analyses may be done over the 2-year conduct phase of this trial. The corresponding snapshot will be taken for the interim analysis and data only up to the cut-off will be included into the analysis.

First interim analysis up to Week [redacted]

The interim analysis is planned after all patients in current study finishing their Week [redacted] visit or early discontinued before the visit, and a snapshot will be performed. All data collected up to Week [redacted] dosing will be included in this interim analysis.

Final analysis

Final trial analysis will be performed once all patients have completed the trial; at that time point, a final database lock will be done.

General Remarks

The format of the listings and tables will follow the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries" (9) and those generated for PK will follow BI guideline " Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics" (11).

The individual values of all patients will be listed, including those collected during the off-treatment period. Listings will generally be sorted by country, centre number, patient number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (see Section 7.8.1 below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

N:	number of non-missing observations
Mean:	arithmetic mean
SD:	standard deviation
Min:	minimum
Q1:	lower quartile
Median:	median
Q3:	upper quartile
Max:	maximum

For PK analyte concentrations, the following descriptive statistics will additionally be calculated: variables:

CV:	arithmetic coefficient of variation
gMean:	geometric mean
gCV:	geometric coefficient of variation

The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations.

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries" (9).

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 treated patient set. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there are actual missing values. Percentages will be based on all patients in the respective patient set whether they have non-missing values or not unless there is another particular specification.

Disposition of the patient population participating in the trial will be summarised by presentation of the frequency of patients enrolled, treated, enrolled but not treated, who completed all doses of trial medication as planned, who completed the trial (EOS), who prematurely discontinued study treatment, by reason and who withdrew from the trial, by reason. Summary statistics of patients who did the dose modification at Week 12 and patients who discontinued due to no change observed at Week 24 after dose modification (according to Table 3.1: 1 in CTP) will be also displayed. The frequency of patients with iPDs will be presented; iPDs will be listed per patient.

To better illustrate the long-term disposition of entire maintenance treatment (cf. Section 6.1), a summary table regarding patient status over time will be added. The cumulative frequency of patients for the following categories will be displayed based on [redacted]-week intervals:

- Ongoing on study medication, i.e., without early treatment discontinuation by the time point
    - Intake of rescue medication
    - Up-titrate the dose to [redacted]
    - Any of the above
- Pre-maturely stopped study medication, i.e., discontinued study medication by the time point
    - Intake of rescue medication
    - Up-titrate the dose to [redacted]
    - Any of the above
- Ongoing but not achieved the visit, if due to the cut-off of interim analysis
    - Intake of rescue medication
    - Up-titrate the dose to [redacted]

  - Any of the above

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Descriptive statistics will be presented for demographic parameters and baseline characteristics, based on the SAF.

Characteristics of the trial disease will be displayed for patients receiving at least 1 dose of study drug.

For the continuous variables described below, the following categories will be defined in Table 7.1: 1, and presented according to the number and percentage of patients in each category:

Table 7.1: 1 Categories for summary of continuous variables

Variable	Categories
Age	<30 years 30 to <65 years ≥65 years
Body 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

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. Analyses of concomitant diseases and medication will be based on the SAF.

Concomitant diseases (i.e. baseline conditions) and concomitant non-drug therapies will be coded according to the most recent version of MedDRA. Concomitant medications will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

Concomitant diseases which are present at start of the study will be descriptively summarized.

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

- starting prior to day of first trial treatment OR on treatment in 1368-0052
- ongoing at the start of trial treatment or

- starting within the on-treatment period (see Section 6.1 for a definition of study analysis phases).

Concomitant medication use (excluding rescue therapy) will be summarized with frequency and percentage of patients by preferred name. Summaries will be presented for

- starting prior to day of first trial treatment OR on treatment in 1368-0052
- concomitant medication starting any time during the on-treatment period (cf. Section 6.1)

Concomitant use of non-drug therapies (excluding rescue therapy) taken any time during the on-treatment period (cf. Section 6.1) will be summarized with frequency and percentage. Summaries will be presented for

- starting prior to day of first trial treatment OR on treatment in 1368-0052
- concomitant non-drug therapies starting any time during the on-treatment period (cf. Section 6.1).

Use of rescue therapy will be summarized separately (see Section 7.6.2).

7.3 TREATMENT COMPLIANCE

Treatment compliance (see Section 5.4.4 for the definition and calculation) will be summarized for the SAF using descriptive statistics (N, mean, SD, minimum, median, maximum) for day 1, maintain period and overall treatment period. The number and percentage of patients with the following overall compliance categories will be presented:

- "<80% of planned",
- "80 to 120% of planned" and
- ">120% of planned".

7.4 PRIMARY OBJECTIVE ANALYSIS

Refer to Section 7.8.1 for the description for adverse events including the primary endpoint.

7.5 SECONDARY OBJECTIVE ANALYSIS

7.5.1 Key secondary objective analysis

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 Secondary objective analysis

For continuous secondary endpoints, the primary analysis will implement the hybrid strategy (EC-H) of handing ICE defined in Section 6.3. Any data collected after the ICE will be censored for the timepoint afterwards, i.e., only data prior to the ICE will be considered.

Descriptive summaries and graphical displays (line plots) will be produced using OC method for continuous secondary endpoints and binary secondary endpoints respectively.

7.6 FURTHER OBJECTIVE ANALYSIS

Analysis of further endpoints is described in Section 7.2.4 of the CTP. All analyses of further endpoints will be performed for the SAF.

7.6.1 Further efficacy endpoints

For each of the further endpoint described below, hybrid strategy will be used to handle intercurrent events which lead to data censoring as described for the primary endpoint.

Continuous further endpoints
The further continuous and binary endpoints will be evaluated in a descriptive manner using OC method as section 7.2.4 in CTP, by visit if applicable.

Questionnaires will be descriptively summarized by visit.

Binary further endpoints
Descriptive statistics will be displayed based on the OC-NRI approach for each of the binary further endpoint, by visit if applicable.

7.6.2 Use of rescue therapy

Summary of use of rescue therapy

Frequency of use of rescue therapy, as identified on the eCRF, from Day 1 up to the end of reporting period, will be summarized with the number and percentage of patients by preferred name.

Time to first use of rescue therapy

The time to event will be defined as the start date of first rescue therapy use minus the date of first drug administration, plus 1 day. If patient has no rescue therapy, the time to first use of rescue therapy will be censored on the patient level at the last contact day up to the end of reporting period.

A Kaplan-Meier analysis of time to the first use of rescue therapy will be presented. KM-estimates of the survival/failure probabilities at weekly intervals, as well as the median time-to-event will be provided. Confidence intervals will be based on two-sided $\alpha = 0.05$.

7.6.3 Other analysis

Since there's dose modification at week [redacted] and and re-assessment week [redacted] according to the Table 3.1: 1 in CTP, descriptive summaries for the status of HS-PGA grade change at Week [redacted] and Week [redacted] by responder status at baseline will be provided.

7.7 EXTENT OF EXPOSURE

An overall table will summarize the entire treatment period. The number of subjects who received a dose of trial drug will be tabulated. Treatment exposure will be assessed as the total dose of treatment [mg] administrated for the loading stage, the maintenance stage, as well as the overall dose across the two stages, which will be summarised by descriptive statistics (N, mean, SD, minimum, median, maximum). The total duration of exposure [days] will also be displayed.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the safety analysis set.

All safety analyses will be performed following BI standards for overall on-treatment period. No hypothesis testing is planned. OC-IR and OR methods will be used for safety reporting. AE and possibly clinically significant laboratory abnormalities will be analysed under OR (as defined in Section 6.6.3); the safety data by visit, i.e., laboratory, vital signs and local tolerability, will be analysed under OC-IR (as defined in Section 6.6.3).

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 "post treatment". 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

AEs will be coded with the most recent version of MedDRA.

For AEs in current trial, we will summarize AEs start in 1368-0052 and still ongoing in current trial 1368-0067 plus new AEs start in current trial.

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. System organ classes (SOC, if applicable) will be sorted according to the standard sort order specified by the EMA, preferred terms (PT, if applicable) will be sorted by total frequency (within SOC).

For details on summarization of AE data, please refer to "Handling and summarization of adverse event data for clinical trial reports and integrated summaries" (15) and "Handling of missing and incomplete AE dates" (10).

The analysis of AEs will be based on the concept of TEAEs. This means that all AEs will be assigned to the screening period, on-treatment period (i.e. treatment phase plus REP) or off-treatment period (i.e. follow up) as defined in Section 6.1. Since only the start date of an AE is collected (without start time), any AE occurrence on the same day as the first spesolimab administration will be assigned to the on-treatment phase.

Exposure-adjusted adverse event incidence rates for TEAE will be calculated using the following approach:

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

   Time at risk [subject years] = (date of onset of AE – first treatment start date in current study +1) / 365.25

2) If, for a subject, the selected TEAE didn't occur, then the time at risk will be censored at min (date of death, last contact date per EoS page, cut-off date for the interim analysis, or the end of on-treatment period). For each selected TEAE, the exposure adjusted incidence rate will be calculated as:

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

An overall summary of AEs will be presented. This overall summary will include summary statistics for the class of other significant AEs (sponsor definition based on ICH E3) and for the class of AESIs.

The following is considered an AESI in this trial:

- Systemic hypersensitivity including infusion reaction and anaphylactic reaction
- Severe infections (according to RCTC grading)
- Opportunistic and mycobacterium tuberculosis infections
- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - an elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood draw sample, or in samples drawn within 30 days of each other
    OR
  - aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN.

In addition, user defined adverse event concepts (UDAEC) identified through specific search criteria will be reported separately (see Table 7.8.1: 1)

Table 7.8.1: 1 Project MEDDRA search criteria for User Defined Adverse Events Concepts

User-defined AE category		
	Label	Description
Hypersensitivity	Hypersensitivity ALL	Combined search strategy based on the three individual UDAECs described below
	Anaphylactic reaction, narrow	Narrow SMQ “Anaphylactic reaction”
	Angioedema, narrow	Narrow SMQ “Angioedema”
	Hypersensitivity, narrow	Narrow SMQ “Hypersensitivity”
Infections (serious/severe, opportunistic)	Infections 'ALL'	terms from combined search with sort order # in (20, 30, 40, 21, 22) Sort order if applicable to project or trial
	Opportunistic infections	SMQ "Opportunistic infections", narrow
	Tuberculosis infections	sub-BIcMQ “Tuberculosis related terms”, narrow BIcMQ "Infections", sub-search 8.2 “Tuberculosis related terms” narrow
	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" of at least severe RCTC grade (>= 3) or any severe events
	Serious infections	SOC “Infections and infestations” with [AECOND: AESER = 1] SOC “Infections and infestations” with "intensity= serious"
Malignancies	Malignant tumours	sub-SMQ “Haematological malignant tumours”, narrow, sub-SMQ “Non-Haematological malignant tumours”, narrow
	Malignancies excluding NMSC	sub-SMQ “Malignant tumours” excluding terms from search with sort order #=340 Sub-SMQ “Malignant tumours” excluding NMSC, where NMSC is defined above
Torsades de Pointes	Torsades de Pointes	Broad sub-SMQ “Torsade de pointes/QT prolongation”
Depression	Depression	sub-SMQ "Depression (excl suicide and self-injury)", broad

User-defined AE category		
	Label	Description
Suicidal ideation and behavior (SIB)	sub-SMQ "Suicide/self-injury"	
DRESS	DRESS (Drug reaction with eosinophilia and systemic symptoms syndrome), broad	SMQ "Drug reaction with eosinophilia and systemic symptoms syndrome", broad Algorithm: A or (B and C and D) or (B and C and E) or (B and D and E)
	DRESS (Drug reaction with eosinophilia and systemic symptoms syndrome), narrow	SMQ "Drug reaction with eosinophilia and systemic symptoms syndrome", narrow Only category A

* this is achieved by retrieving all cases found either by running subsearch 1 in narrow scope (BIcMQ search ID 32019093) or subsearch 2 (BIcMQ serach ID 32019094)

The frequency of patients with AEs will be summarised by prior treatment from parent trial, primary SOC and PT. AEs which were considered by the investigator to be drug related will be summarised separately. Separate tables will also be provided for patients with SAEs, patients with AESIs, patients with AE leading to discontinuation of the trial medication, and patients with other significant AEs (as described previously). AEs will also be summarized by maximum intensity.

For disclosure of AE data on ClinicalTrials.gov, the frequency of patients with non-serious AEs occurring with an incidence of greater than 5% (in PTs) will be summarised by treatment, primary SOC and PT. The frequency of patients with SAEs and drug related SAEs will also be summarised respectively.
For disclosure of AE data in the EudraCT register, the frequency of non-serious AEs with an incidence of greater than 5 % (in PTs) and the frequency of SAEs will be summarised.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (12). 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. Normalisation means transformation to a standard unit and to a standard reference range. The process of normalisation, 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 (12). 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.

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 entire treatment period will be considered under OR. 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 entire treatment period will also be considered under OR.

Descriptive statistics of laboratory values over time and for the difference from baseline on-treatment (see Section 6.7) will be based upon normalized values and provided by visit (including follow up) under OC-IR, including summaries of the last value on-treatment, the minimum value on-treatment, and the maximum value on-treatment. Graphical displays via box plots will be produced for the change from baseline, over time, 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 RCTC grade at baseline versus the grade at the last measurement on treatment, as well as the worst grade on treatment. These analyses will be based on standardized laboratory values.

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 1 lab value with clinically significant abnormality within the group.

The frequency of patients with AST or ALT elevations ≥3xULN, ≥5xULN, ≥10xULN, and ≥20xULN will be displayed based on standardized laboratory values. To support analyses of liver related adverse drug effects, the frequency of patients with AST and/or ALT ≥3xULN combined with a total bilirubin ≥2xULN in a 30 day period after AST/ALT elevation will be displayed, stratified by alkaline phosphatase <2xULN and ≥2xULN (a patient 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 the ALT, AST and total bilirubin during the on-treatment period will also be performed; the so called eDISH plot. In the graph, for each subject, 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 or total bilirubin and ALT may, or may not, occur on the same date. Two reference lines, 2xULN for total bilirubin and 3xULN for ALT, are drawn onto the graph in order to divide the plane into 4 quadrants. Normal cases are in the lower left quadrant, potential DILI cases are in the upper right quadrant (Hy's Law quadrant), while the lower right quadrant is known as the Temple's corollary range (ALT ≥3xULN and total bilirubin <2xULN).

Clinically relevant findings in laboratory 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.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate, body temperature, respiratory rate) and body weight 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.

No separate listing or analysis of ECG data will be prepared.

7.9 OTHER ANALYSIS

7.9.1 Biomarker analyses

The following biomarkers will be analysed and reported as a part of the CTR:

- HS-CRP

Results on other biomarkers (e.g. RNA expression, serum and plasma biomarkers) may or may not be reported in the CTR, depending e.g. on the availability of the data. In case they are reported outside the CTR the analysis will be defined in a separate document (in case they are reported in the CTR, the analysis will be described in the CTR).

For the analysis of biomarkers, log transformed data will be used where deemed necessary.

7.9.2 Immunogenicity

Analysis of ADA and assessments of ADA impact on PK will be performed based on the complete administration data of spesolimab from both 1368-0052 and this trial data 1368-0067. Analysis of assessments of ADA impacts on safety and efficacy endpoints will be performed based on this 1368-0067 trial data only for the clinical trial report (CTR).

The ADA status and titre as well as frequency of patients with ADA to spesolimab will be presented by visit. Descriptive statistics of ADA titre (for ADA positive patients, when available) will be provided by visit. The number of subjects with ADA status positive/negative at any time will also 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. Further exploratory assessments of the ADA data will be performed once data are available and these will be described, if done, in the CTR.

Further analyses based on ADA data will be performed for efficacy-based and safety-based analysis with the following ADA and neutralizing antibody (NAb) status and endpoints.

Patient is considered ADA positive (+) if he/she had at least 1 positive ADA sample in the trial. Otherwise, patient is considered ADA negative (-). Patient is considered NAb positive (+) if he/she had ADA positive and at least 1 NAb positive sample in the trial. Patient is considered NAb negative (-) if he/she had ADA positive but no NAb positive sample OR if he/she is considered ADA negative.

- efficacy-based subgroup analysis as described in Section 6.4
    - ADA positive and ADA negative subjects (at Week 12 or later time), or
    - Neutralising antibody (Nab) positive and NAb negative subjects (at Week 12 or later time)
- Safety-based subgroup analysis (using e.g. hypersensitivity safety events)
    - ADA positive and ADA negative subjects (at any time), or
    - NAb positive and NAb negative subjects (at any time), or before ADA development (including subjects with events either before their first ADA positive sample or without ADA positive sample throughout) and after ADA development (including subjects with events from the time point of their first ADA positive sample onwards). This approach takes into account the time when ADA actually developed and when the safety event occurred in relationship to ADA.

7.9.3 PK / PD analyses

No PK parameters will be calculated.

The descriptive analysis of spesolimab plasma concentrations will be based on the PKS.

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to ‘ALL CALC’, the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to ‘DESC STATS’ the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition ‘TIME VIOLATION’ or ‘TIME DEVIATION’ the value can be used for further analyses based on actual times. If ACEXCO is set to ‘HALF LIFE’ the value will be excluded from half-life calculation only; the value is included for all other analyses.

Further details are given in (11).

No formal analysis of pharmacokinetic/pharmacodynamic relationships is planned. The relationship between PK and selected efficacy endpoints, biomarkers and AEs may be assessed.
Any further exploratory analyses, if done, will be described in the CTR or in a separate report.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

Due to the first dose of current study is blinded, the treatment information will be loaded into the trial database after the unblinding of parent trial 1368-0052.

9. REFERENCES

1.	*BI-VQD-23790-S-G_50-415_AD-02 (v5.0):* "Project Analysis Dataset (PADS) Template (template) ", current version, Group "Biostatistics & Data Sciences", IDEA for CON.
2.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note for Guidance on Statistical Principles for Clinical Trials, current version.
3.	*BI-VQD-12045_40-413 (v3.0):* " Identify and Manage Important Protocol Deviations (iPD) ", current version; IDEA for CON
4.	*BI-KMED-BDS-HTG-0041*: "How to Guide: Analysis and Presentation of AE Data from Clinical Trials", current version, KMED
5.	*001-MCS-40-106_RD-03:* "Clinical Trial Protocol general template for Phase I-IV", current version, Group "Clinical Operations", IDEA for CON.
6.	*001-MCS-80-60*6: "Management of Non-Compliances", current version, Group "Quality Medicine", IDEA for CON.
7.	*001-MCS-40-135_RD-01:* "Integrated Quality and Risk Management Plan", current version, Group "Clinical Operations", IDEA for CON.
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.	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
10.	*BI-KMED-BDS-HTG-0035*: "Handling of missing and incomplete AE dates", current version; IDEA for CON
11.	*BI-KMED-TMCP-HTG-0025 (v1.0):* "How to Guide: Standards and Processes for Analyses Performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, KMED.
12.	*BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON
13.	*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 - 10 Jul 1993. Clin Exp Dermatol 1994; 19; 210-216.
14.	*R20-3156:* Kirby et al. The Hidradenitis Suppurativa Quality of Life (HiSQoL) score: development and validation of a measure for clinical trials. British Journal of Dermatology (2020) 183, pp340–348

15.	*001-MCG-156:* "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON
16.	*R20-3045:* The European Hidradenitis Suppurativa Foundation Investigator Group, Zouboulis C.C., TzellosT., Kyrgidis A., Jemec G.B.E., Bechara F.G., et al. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS 4), a novel dynamic scoring system to assess HS severity. Br J Dermatol. 2017 Nov; 177 (5): 1401-1409.

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11. HISTORY TABLE

Table 11: 1 History table

Version	**Date (DD-MMM-YY)**	**Author**	**Sections changed**	**Brief description of change**
1.0	**12-Jan-2024**	[redacted]	None	This is the final TSAP.
2.0	**04-Jun-2024**	[redacted]	Section 6.4 Subject sets analysed Section 6.7 Baseline, time windows and calculated visits Section 7.9.2 Immunogenicity	Following clarifications and changes and made on immunogenicity (anti-drug antibody (ADA)): • Section 6.4 Safety set ADA (SAF ADA) to be added • Section 6.7 Definitions of baseline of ADA is added • Section 7.9.2 (1) data included in the ADA analysis (2) Definitions of ADA and NAb (Neutralizing antibody) positive are clarified.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval	[redacted]	04 Jun 2024 17:28 CEST
Approval-Clinical Program [redacted]		04 Jun 2024 17:39 CEST
Approval		05 Jun 2024 13:29 CEST
Approval-Project Statistician		05 Jun 2024 16:12 CEST
Approval-Medical Writer		06 Jun 2024 09:56 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed