TRIAL STATISTICAL ANALYSIS PLAN

c26514524-03

BI Trial No.:	1368-0013
Title:	Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity Including Revised Protocol # 3 [c15875404-04]
Investigational Product:	Spesolimab (BI 655130)
Responsible trial statisticians:	[redacted] Tel.: [redacted] Fax:
Date of statistical analysis plan:	22 DEC 2020 SIGNED
Version:	Revised

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
[redacted]	
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
ALQ	Above the upper limit of quantification
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC3	Anatomical-Therapeutic-Chemical classification level 3
[redacted]	
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
[redacted]	
CRF	Case report form
[redacted]	
CTP	Clinical trial protocol
CTR	Clinical trial report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
ES	Enrolled set
EudraCT	European union drug regulating authorities clinical trials

Term	Definition / description
FACIT	Functional Assessment of Chronic Illness Therapy
gCV	Geometric coefficient of variation
gMean	Geometric mean
GPP	Generalized pustular psoriasis
GPPASI	Generalized Pustular Psoriasis Area and Severity Index
GPPASI 50	Achievement of a ≥ 50 % reduction in GPPASI total score compared to baseline
GPPASI 75	Achievement of a ≥ 75 % reduction in GPPASI total score compared to baseline
GPPASI 90	Achievement of a ≥ 90 % reduction in GPPASI total score compared to baseline
GPPGA	Generalized Pustular Psoriasis Physician Global Assessment
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	Interleukin
iPD	Important protocol deviation
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
NOA	Not analyzed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
NRI	No response imputation
OR	Original results
[redacted]	
PPS	Per protocol set
PSS	Psoriasis symptom scale
Q1	1st quartile
Q3	3rd quartile
RAGe	Report appendix generator

Term	Definition / description
REP	Residual effect period
RNA	Ribonucleic acid
RPM	Report planning meeting
RS	Randomized set
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listing
SI	Système international d'unités
TS	Treated set
TSAP	Trial statistical analysis plan
UDAEC	User-defined Adverse Event Category
ULN	Upper limit of normal range
VAS	Visual analogue scale

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the CTP and its amendments, 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 CTP. 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, and planning of sample size, and randomization.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SAS™-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).

Study data will be stored in a trial database within the BRAVE system.

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

This is a multicenter, randomized, double-blind, placebo-controlled Phase II study with one dose of Spesolimab/placebo in patients with GPP presenting with an acute flare of moderate to severe intensity. In total, at least 51 patients will be randomized to receive Spesolimab/ placebo (2:1). All patients will receive the dose of study medication (900 mg i.v. Spesolimab or Placebo) on Day 1 of Week 1. Based on the subsequent treatment response, patients will then be followed for 12 to 28 weeks (see Flow Chart of CTP). The primary and key secondary efficacy endpoints of the trial will be determined on Day 8. This TSAP fully specifies the analyses of the trial.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Following further endpoints are added to TSAP:

- Change from baseline in GPPGA total score, by visit
- Change from baseline in GPPGA pustulation subscore, by visit
- GPPGA clear/almost clear (modified) defined as a GPPGA total score of 0 or 1 and with all subscores < 3, by visit
- A GPPGA erythema sub-score of 0 or 1, by visit.
- A GPPGA scaling sub-score of 0 or 1, by visit.
- A GPPGA pustulation sub-score drop by at least 2 points from baseline, by visit.
- A Pain VAS drop by at least 30 points from baseline.
- Percentage change from baseline in each of GPPASI pustulation, erythema and scaling severities.
- [redacted]
- A PSS score of 0, by visit
- A FACIT-Fatigue score improvement of at least 4 points, by visit

[redacted]

For time to first achievement of GPPGA pustulation score of 0 or GPPGA score of 0 or 1, the first day should be day of randomized treatment if it is different from randomization. For Wilcoxon testing, the calculations of ranks should be also relative to Day 1.

Percentage change from baseline in GPPASI will be calculated instead of percentage reduction in GPPASI. For example, if there is 50% reduction in GPPASI score, it means % change from baseline in GPPASI is -50%.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- A GPPGA pustulation subscore of 0 indicating no visible pustules at Week 1.

For the estimand concept (EN) on the above-defined primary binary endpoint definition, death or any use of escape medication prior to week 1 will be considered to represent a non-response at the Week 1 timepoint.

See Section 9.1.2 for further details on the derivation of the GPPGA total score.

5.2 SECONDARY ENDPOINTS

Key Secondary Endpoint

- A Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 at Week 1.

The same estimand concept (EN) used for primary endpoint will be used for key secondary endpoint.

Secondary Endpoints at Week 4 (included in the statistical testing strategy):

Secondary endpoints of the study at Week 4 which are included in the statistical testing strategy in a hierarchical manner subsequent to performance of the tests on the primary and key secondary endpoints are:

- A Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI) 75 at Week 4.
- Change from baseline in Pain Visual Analog Scale (VAS) score at Week 4.
- Change from baseline in Psoriasis Symptom Scale (PSS) score at Week 4.
- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score at Week 4.

Secondary Endpoints at Week 4 (not included in the statistical testing strategy):

- A Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 at Week 4.
- A GPPGA pustulation sub-score of 0 indicating no visible pustules at Week 4.
- A GPPASI 50 at Week 4.
- The percent change from baseline in GPPASI at Week 4.

Secondary Endpoints at Week 1:

- A GPPASI 50 at Week 1.

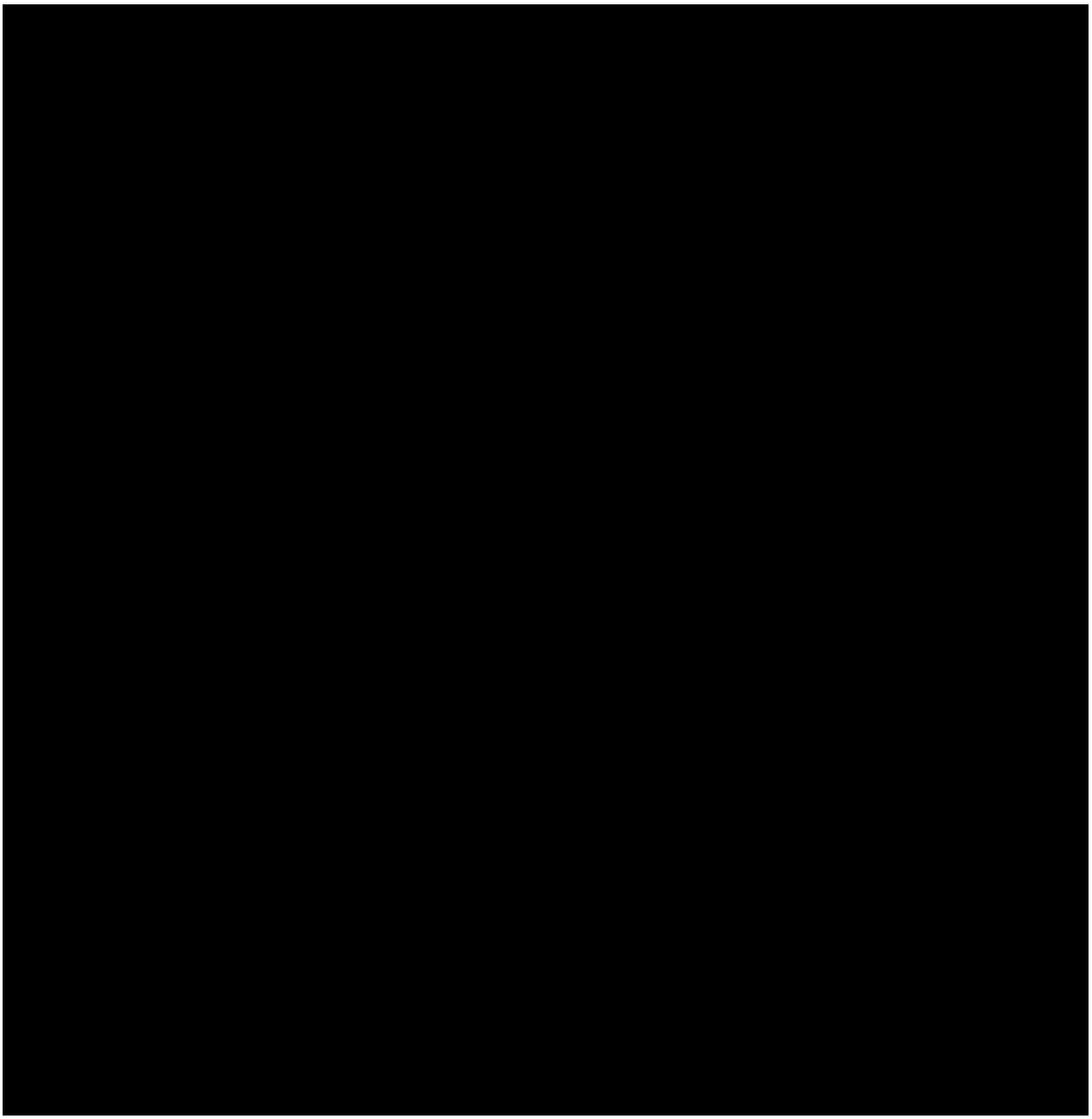
- The percent change from baseline in GPPASI at Week 1.

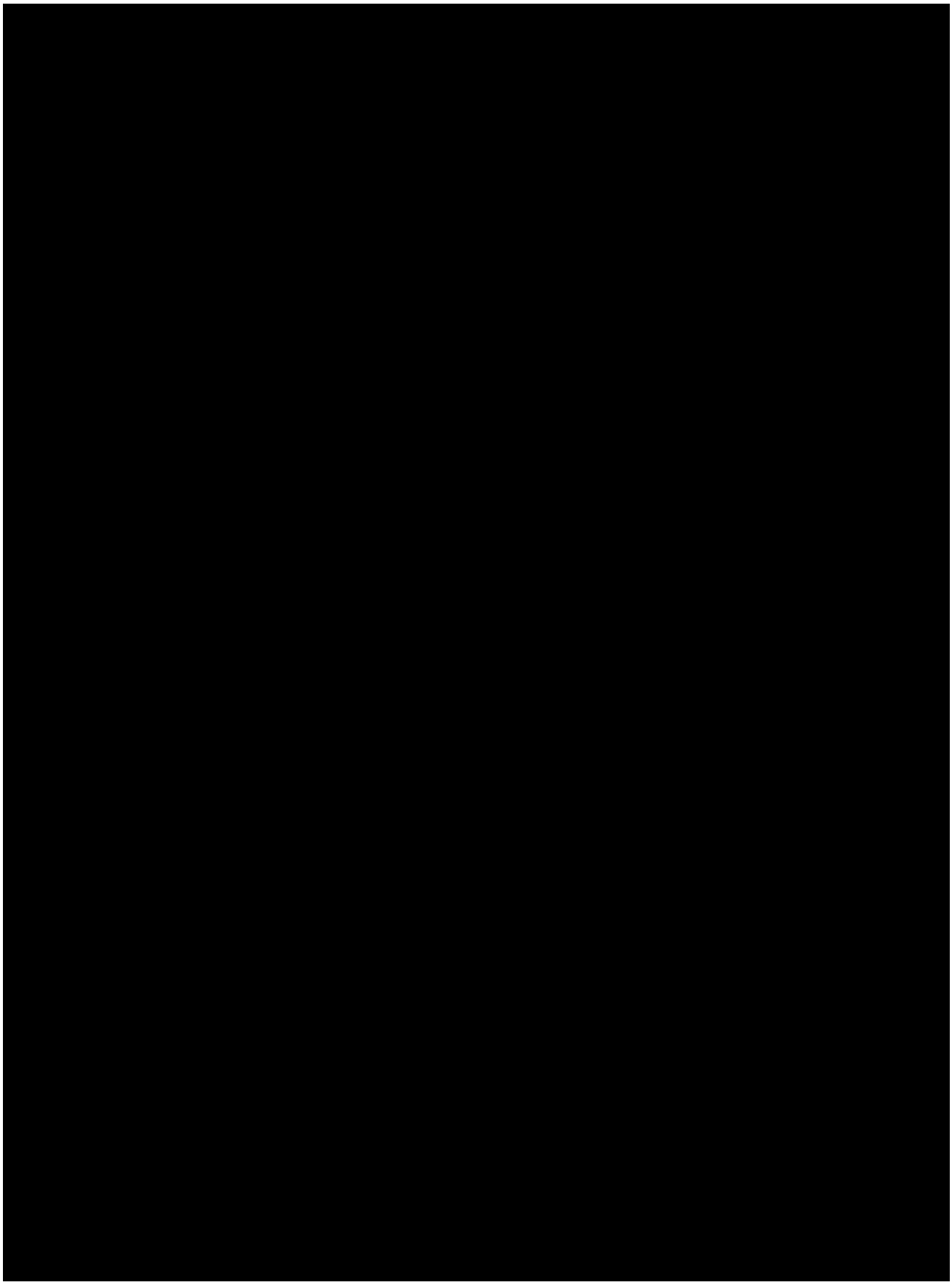
For the estimand concept (EN) on each of the above-defined binary and continuous secondary endpoint definition(s) at week 1/4, death or any use of escape medication prior to week 1/4, or OL Spesolimab use at D8 or any rescue medication with Spesolimab prior to week 4 will be considered to represent a non-response at the week 1/4 time-point.

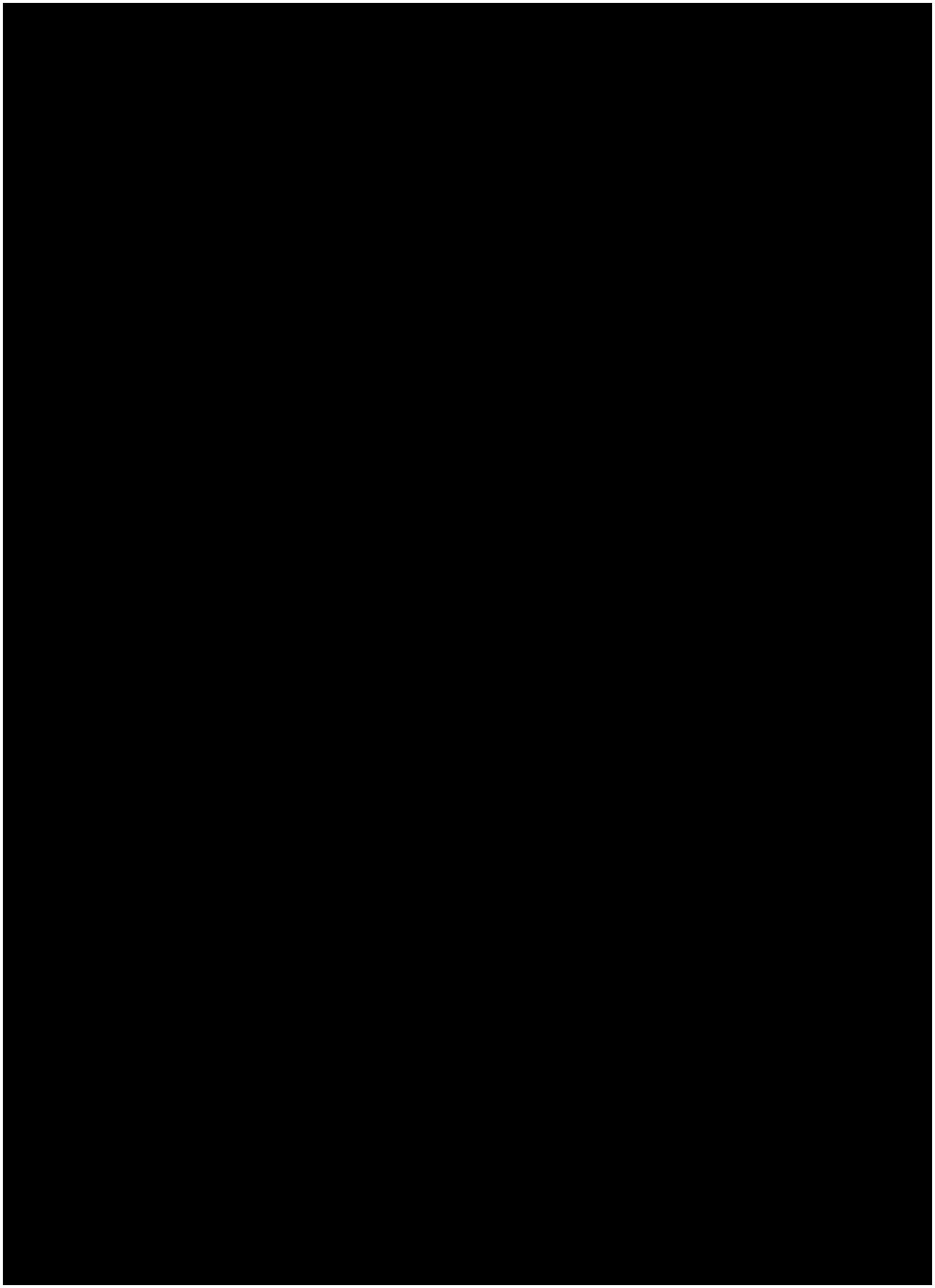
For further details on the derivation of the GPPASI score, the PSS score, and the FACIT-Fatigue score, refer to Sections 9.1.1, 9.1.5, and 9.1.3, respectively.

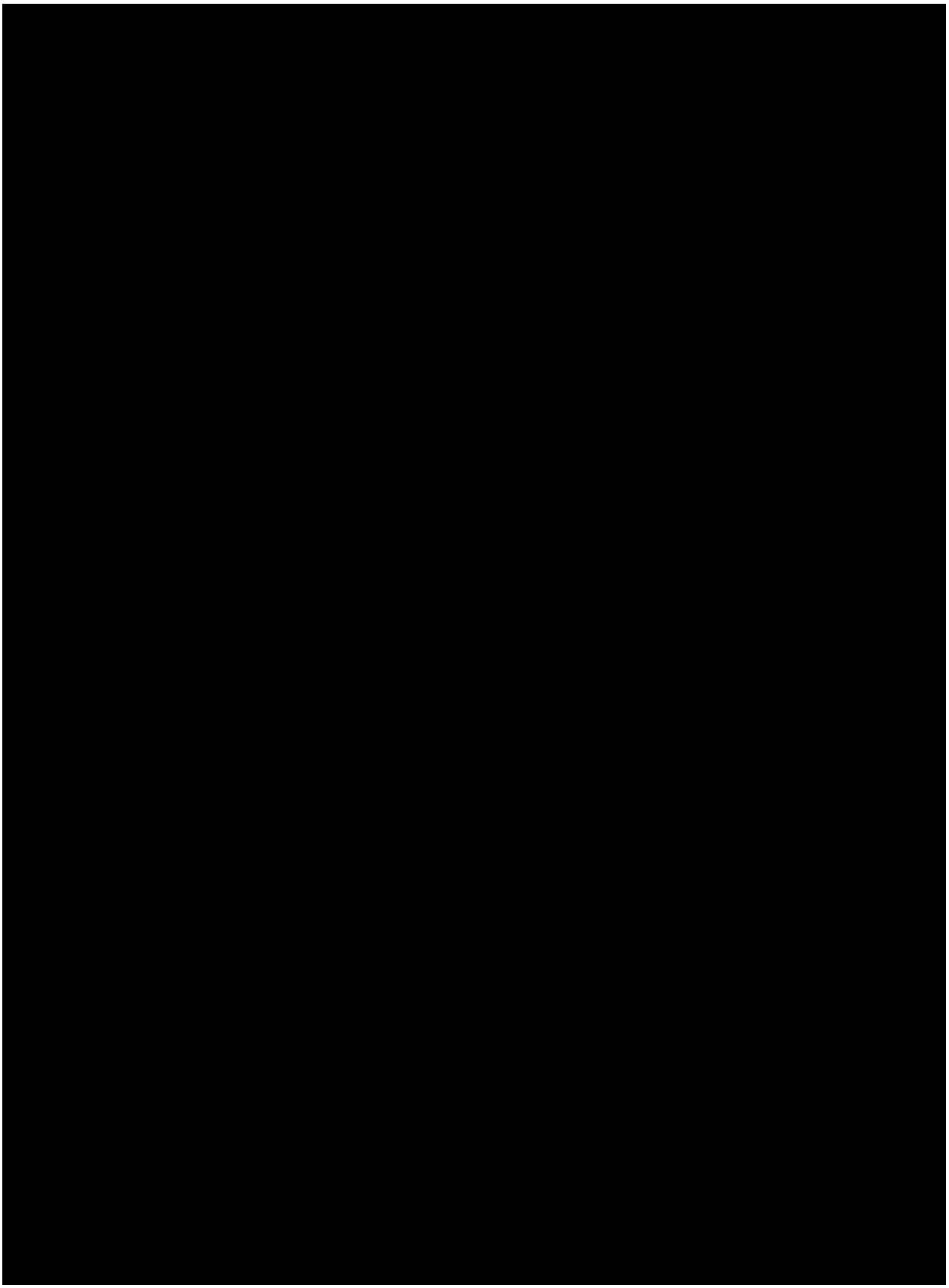
Secondary Safety Endpoints:

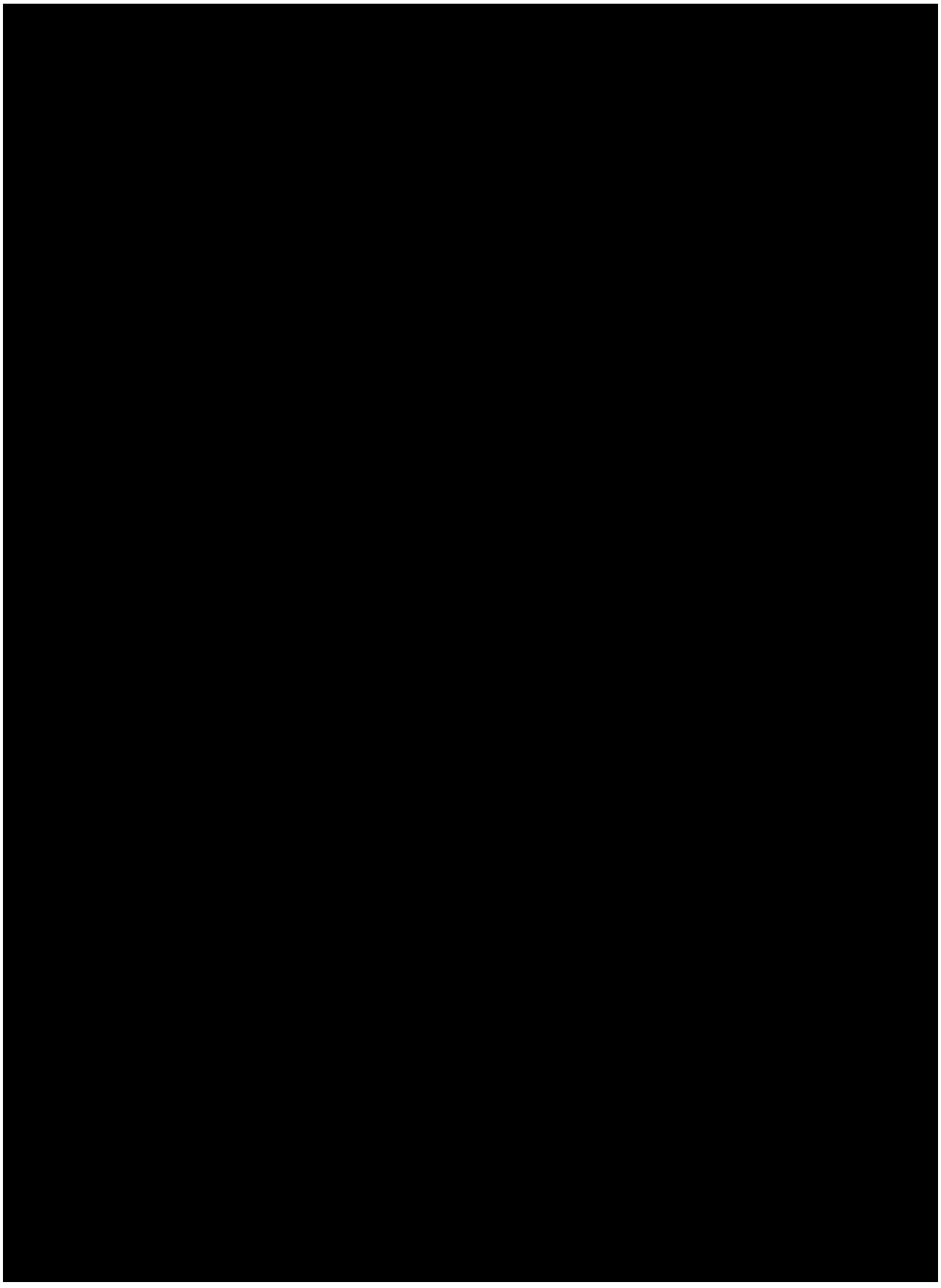
- The occurrence of Treatment Emergent Adverse Events (TEAEs).











6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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 randomized dose at Day 1 as below:

Table 6.1: 1 Flow chart of analysis phases of the study according to randomized treatment

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 infusion of randomized study treatment minus 1 minute
Treatment phase (including Residual effect period)[2]	On-treatment period	Date/time of start of infusion of randomized study treatment (Day 1)	Earliest of: i) Date of end of infusion of randomized study treatment (Day 1) + 112 days at 23:59, ii) Date/time of first dose in OLE trial 1368.25., iii) Date of end-of-study visit if there is no roll-over to 1368.25
Follow-up phase[12]	Off-treatment period	Date of end of infusion of randomized study treatment (Day 1) + 113 days at 0:00	Latest of: i) Date of End-of-Study visit; ii) last contact date on End of Study page at 23:59

Dates are defined individually per patient. 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 last contact date is after the date of end of infusion of randomized treatment + 112 days.
[2] For primary safety purpose, safety data is censored for reporting following intake of (optional) open-label Spesolimab on Day 8, or intake of rescue medication with Spesolimab for treatment of a GPP flare.

Treatment groups for the analysis phases according to the randomized/actual treatment on Day 1 (see Table 6.1: 1) will be labelled as follows:

- **"Placebo"** (i.e. randomized to receive /actual received Placebo on Day 1)
- **"Speso 900 mg IV SD"** (i.e. randomized to receive /actual received Spesolimab on Day 1)
- **"Overall"**(across treatments), where appropriate.

“Overall Total” is applicable in disposition, demographics and baseline characteristics, compliance summaries, AE, clinically significant abnormal lab values and others if needed. Where applicable, output columns should be arranged in the order as given above.

For analysis on effects of OL Spesolimab at Day 8 following randomized treatment at Day 1, patients will be categorized into four different groups (see Section 7.6.2):

- **Arm 1, "Placebo only"**(i.e. randomized to placebo treatment and not given OL Spesolimab at D8)
- **Arm 2, "Placebo + OL D8"**(i.e. randomized to placebo treatment and given OL Spesolimab at D8)
- **Arm 3, "Speso only"**(i.e. randomized to Spesolimab treatment and not given OL Spesolimab at D8)
- **Arm 4, "Speso + OL D8"**(i.e. randomized to Spesolimab treatment and given OL Spesolimab at D8)

For further analysis on safety data including REP of any non-randomized Spesolimab, individual patient's data will be separated based on the use of randomized treatment at Day 1 and non-randomized Spesolimab as follows (see Section 7.8.1):

- **"Prior non-rand. Speso "**(i.e. TEAE starting before use of any non-randomized Spesolimab are considered)
- **"Post OL Speso at D8"** (i.e. TEAE starting post OL dose at Day 8 but before rescue medication with Spesolimab are considered)
- **"Post rescue with Speso"** (i.e. TEAE starting post rescue medication with Spesolimab are considered)

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

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 deviations of time windows) and a list of protocol deviations will be provided to be discussed at the RPM/DBLM. 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). The categories of iPD are defined in the Integrated Quality and Risk Management plan (IQRMP). These categories are repeated below in order to ensure that those iPD which lead to exclusion from the PPS are suitably documented before unblinding and locking of data.

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)" (2).

If any patients fulfil the iPD categories, then they are to be summarized and will be captured in the RPM/DBLM 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 site(s), then this table will be supplemented accordingly by the time of the RPM/DBLM. Not all iPDs will lead to exclusion from analysis sets. iPDs leading to exclusion from analysis sets are indicated as such in Table 6.2: 1.

IPDs will be summarized and listed for the randomized set.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Comments	Excluded from
A		**Entrance criteria violated**		
A1		**Inclusion criteria not met**		
	A1.01	GPP per CTP not confirmed	Inclusion criterion 1	PPS#
	A1.02	Retinoids/methotrexate/cyclosporine not discontinued prior to first dose of study treatment	Inclusion criterion 2	PPS
	A1.03	Age out of range	Inclusion criterion 3 Also programmatic check required	None
	A1.04	Women of childbearing potential not to agree to use effective method of birth control;	Inclusion criterion 5	None
A2		**Exclusion criteria violated**		
	A2.01	SAPHO syndrome	Exclusion criterion 1	PPS
	A2.02	Primary erythrodermic psoriasis vulgaris	Exclusion criterion 2	PPS
	A2.03	Primary plaque psoriasis vulgaris without presence of pustules or with pustules that are restricted to psoriatic plaques	Exclusion criterion 3	PPS
	A2.04	Drug-triggered Acute Generalized Exanthematous Pustulosis (AGEP)	Exclusion criterion 4	PPS
	A2.05	Immediate life-threatening flare of GPP or requiring intensive care treatment	Exclusion criterion 5	PPS
	A2.06	Severe, progressive, or uncontrolled hepatic disease	Exclusion criterion 6	None
	A2.07a	Any restricted medication, or any drug, with potential influence on safe conduct of study	Exclusion criterion 7	PPS#
	A2.07b	Any prior exposure to Spesolimab or another IL36R inhibitor	Exclusion criterion 7	PPS#
	A2.08	Dose escalation of cyclosporine and/or methotrexate and/or retinoids within the 2 weeks prior to first study treatment	Exclusion criterion 8 Also programmatic check required	PPS#
	A2.09	The initiation of systemic agents 2 weeks prior to first study treatment	Exclusion criterion 9 Also programmatic check required	PPS#

Table 6.2: 1 Important protocol deviations (cont'd.)

Category / Code		Description	Comments	Excluded from
	A2.10	Congestive heart disease	Exclusion criterion 10	None
	A2.11	Active systemic infections during the last 2 weeks prior to first study treatment	Exclusion criterion 11	None
	A2.12	Increased risk of infectious complications	Exclusion criterion 12	None
	A2.13	Relevant chronic or acute infections including HIV or viral hepatitis.	Exclusion criterion 13	None
	A2.14	Active or Latent TB	Exclusion criterion 14	None
	A2.15	History of allergy/hypersensitivity to a systemically administered trial medication agent or its excipients	Exclusion criterion 15	None
	A2.16	Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening	Exclusion criterion 16	None
	A2.17	Currently enrolled or less than 30 days since another investigational device or drug study	Exclusion criterion 17	PPS
	A2.18	Pregnancy	Exclusion criterion 18	None
	A2.19	Major surgery within 12 weeks prior to first study treatment	Exclusion criterion 19	None
	A2.20	Clinical Evidence which would make the study participant unreliable to adhere to the protocol	Exclusion criterion 20	PPS
B		**Informed consent**		
	B1	Informed consent not available	Inclusion criterion 4; Date of informed consent missing or no signature on patient's "Declaration of Informed Consent" In this case: Patient's data will not be used at all.	All#
	B2	Informed consent too late	Informed consent date was after Visit 1	None

Table 6.2: 1 Important protocol deviations (cont'd.)

Category / Code		Description	Comments	Excluded from
C		**Trial medication and randomization**		
C1		**Incorrect trial medication**		
	C1.01	Missing medication or incorrect medication received by patients due to other reasons	At least one randomized vial was given wrongly or missing at Day 1 due to other reason. Can only be finally judged after DBL since unblinding information is required	PPS
	C1.02	Missing medication or incorrect medication received by patients due to COVID-19	At least one randomized vial was given wrongly or missing at Day 1 due to COVID-19. Can only be finally judged after DBL since unblinding information is required	PPS
C2		**Non-compliance**		
	C2.01	Non-compliance with study drug intake-- administered dose too low or too high	Study medication dose (based on infusion volume) is less than 80% or more than 120% of the total planned dose	PPS
C3		**Randomization not followed**		
	C3.01	Treated without randomisation	Patient treated according to eCRF, but not randomised according to IVRS.	PPS/RS/SAF
	C3.02	Randomization order not followed	Stratification error Programming check and also manual review after DBL	None#
C4		**Medication code broken**		
	C4.01	Medication code broken inappropriately	Medication code was broken prior to the DBL for no valid reason. Final decision at the DBL meeting based on medical judgment.	PPS#

Table 6.2: 1 Important protocol deviations (cont'd.)

Category / Code		Description	Comments	Excluded from
D		**Concomitant medication**		
D1		**Previous medication**		
	D1.01	Washout of previous medication too short	Washout period too short - See Table 4.2.2.1: 1 in CTP	PPS#
D2		**Prohibited medication use**		
	D2.01a	Use of prohibited med (with potential influence on eff. data) when not provided as an escape treatment to stabilize a worsening disease condition – prior to or up to Week 1	See the list of restricted medication in CTP, Table 4.2.2.1: 1, manual assessment at MQRM/ RPM/DBLM	PPS#
	D2.01b	Use of prohibited med (with potential influence on eff. data) when not provided as an escape treatment to stabilize a worsening disease condition – after Week 1	See the list of restricted medication in CTP, Table 4.2.2.1: 1,manual assessment at MQRM/ RPM/DBLM	None#
	D2.01c	Use of prohibited med (without potential influence on eff. data)	See the list of restricted medication in CTP, Table 4.2.2.1: 1,manual assessment at MQRM/ RPM/DBLM	None#
D3		**Change in Background medication**		
	D3.01	Background medication (methotrexate, cyclosporine, or retinoids) not stopped prior to receiving first study treatment on Day 1	Background medication continues into the treatment period	PPS#
E		**Missing data**		
F		**Study specific analysis**		
F1		**Other trial specific deviation**		
	F1.01	Study drug intake outside time window	Infusion period takes longer than 180 minutes.	None
	F1.02	Patient was administered open-label treatment at Day 8 with Spesolimab but did not qualify for this treatment per CTP requirement.	Patient was Spesolimab re-treated but did not show a GPPGA of ≥2 and a pustular sub-score ≥2 at Day 8	None
	F1.03	Patient was administered rescue treatment with Spesolimab but did not achieve flare qualification per CTP requirement.	Flare qualification requires: ≥2 point increase in GPPGA score & pustulation subscore of GPPGA ≥ 2 after achieving a clinical response (GPPGA 0 or 1)	None#

Table 6.2: 1 Important protocol deviations (cont'd.)

Category / Code	Description	Comments	Excluded from
G	**Other safety related deviations**		
G1	Pregnancy test not done for woman of child bearing potential at days of IMP treatment and not prior the IMP administration	Pregnancy test not done before randomized treatment at Day 1, OL Spesolimab at Day 8 or rescue Spesolimab	None#

PD will be detected manually;
Source: BI reference document ' Identify and Manage Important Protocol Deviations (iPD)' [001-MCS-50-413] (2, 12).

6.3 PATIENT SETS ANALYZED

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.

- Randomized Set (RS):
  This patient set includes all randomized patients. Treatment assignment will be as randomized. It will be used for analyses of patient baseline demographics and disease characteristics, and is the main set for the analyses of efficacy endpoints.

- Safety Analysis Set (SAF):
  This patient set includes all patients who were randomized and received at least one dose of study drug on Day 1. This is the main analysis set for safety. Patients will be analyzed according to the actual treatment received.

- Per-Protocol Set (PPS):
  This patient set includes all patients in the randomized set who adhered to the CTP without any iPDs which are flagged for exclusion from the PPS in the table above. The PPS will be used for sensitivity analysis on the primary and key secondary endpoints.

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

Handling of Treatment Misallocations in Analysis Sets

If a patient is randomized but not treated, they will be reported under their randomized treatment group for efficacy analysis according to RS and PPS (per the intent-to-treatment principle). By definition, however, such patients are excluded from the safety analyses since no randomized study medication was taken.

If a subject is treated but not randomized, they will be excluded from the efficacy analysis and safety analysis by definition. However, subjects under such circumstances will be described in the final clinical trial report.

If a subject is randomized but took incorrect treatment during the study, then:

- For efficacy analyses according to the RS and PPS, they will be reported under their randomized treatment group.

- For safety analyses using the SAF which are based on actual treatment:

  - If a subject is planned to receive a single dose administration of Spesolimab (randomized to 900 mg SD), then they will be reported under the Spesolimab 900 mg SD group if the subject receives at least 1 vial of randomized Spesolimab on Day

1. A subject will be assigned to the placebo treatment group only if they are treated and receive no vials of randomized Spesolimab on Day 1.

- If a subject is planned to receive placebo treatment, then they will be reported under the placebo arm if they are treated and receive no vial of randomized Spesolimab on Day 1. If the subject receives >= 1 vial of randomized Spesolimab on Day 1, then the patient will be reported as treated with Spesolimab 900 mg SD treatment group.

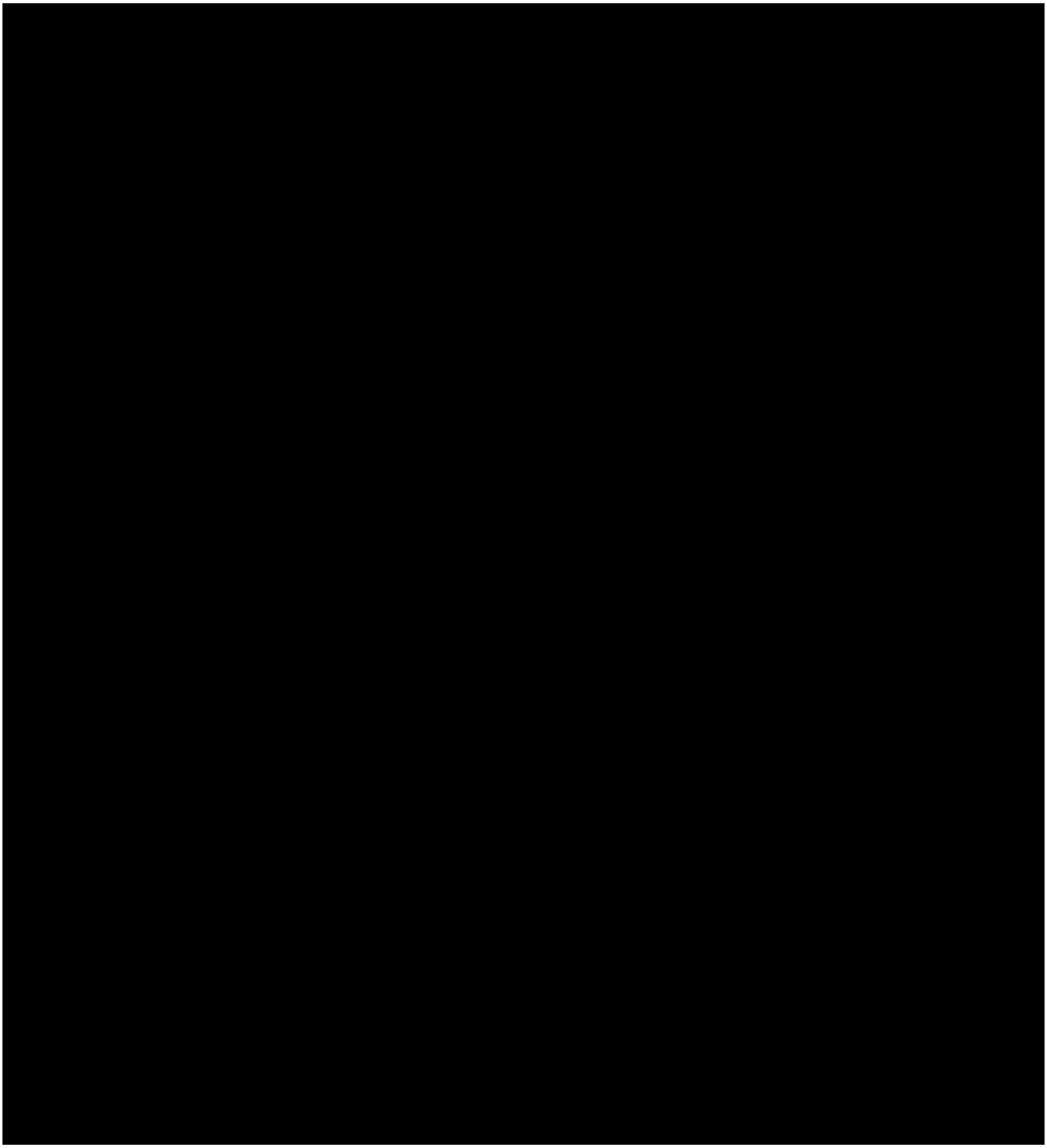
Table 6.3: 1 illustrates the data sets which are to be used for each category class of endpoints, and the approaches used with regard to missing data including estimand concepts.

Table 6.3: 1 Overview of use of patient analysis sets by class of endpoint and handling of estimand and missing data

Class of endpoint	ES	SAF	RS	PPS
Disposition	OR		OR	
Compliance and exposure		OR		
iPD			OR	
Demographic/baseline characteristics			OR	
Concomitant medication			OR	
Primary endpoint and key secondary endpoint			EN-NRI, EN-NRI[1] EN-BRI[1], EN-EM[1] EN-PC-NRI[1] OC[2], OC-IR[2]	EN-NRI[1],
Secondary binary efficacy endpoints			EN-NRI, EN-NRI[13] EN-BRI[13] OC[2], OC-IR[2]	
Secondary continuous efficacy endpoints			EN-LOCF, EN-LOCF[13] EC-MMRM[1], EC-LOCF[1] OC[2], OC-IR[2]	
[redacted]				
Safety data		OR OC-IE OC-IR[1]		
[redacted]				

sensitivity/further analysis or subgroup analysis
[2] descriptive display only
[3] for secondary endpoints included in the testing strategy only
For explanation of the different approaches with regard to missing data see Section 6.6.
EN: Primary estimand for binary and continuous endpoints. Death or any use of escape medication, or OL Spesolimab use at D8, or rescue medication with Spesolimab, prior to observing the endpoint(s) is considered to represent a non-response in the analysis of this endpoint outcome.

EN-PC: Alternative estimand for binary endpoints. Death or any use of escape medication, or OL Spesolimab use at D8, or rescue medication with Spesolimab, prior to observing the endpoint(s) is considered to represent a non-response in the analysis of this endpoint outcome. Any data after the use of restricted medication for other purpose will be censored.
EN-ID8: Alternative estimand for binary and continuous endpoints. Death or any use of escape medication, or rescue medication with Spesolimab, prior to observing the endpoint(s) is considered to represent a non-response in the analysis of this endpoint outcome.
EC: Alternative estimand for continuous endpoint. Any data post escape medication use or OL Spesolimab use at D8, or rescue medication with OL Spesolimab will be censored.
EC-ID8: Alternative estimand for continuous endpoint. Any data post escape medication use or rescue medication with OL Spesolimab will be censored.
NRI, BRI, EM, LOCF and MMRM represent analyses involving imputed data, cf. Section 6.6.2.
OC = observed cases excluding values after any use of escape medication, or OL Spesolimab use at D8, or rescue medication with Spesolimab, OC-IR = observed cases including also values after any use of escape medication, or OL Spesolimab use at D8, or rescue medication with Spesolimab, OC-IE = observed cases excluding values after any use of OL Spesolimab use at D8, or any rescue medication with Spesolimab, OC-ID8 = observed cases excluding values after any use of escape medication, or rescue medication with Spesolimab.
OR = original results.



6.5 POOLING OF CENTRES

No particular analysis is planned.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Section 7.5 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 for which 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. 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 in terms of the proportion of patients with a particular binary outcome, i.e. achievement of a GPPGA total score of 0 or 1. Then imputation is planned to take place only at the binary level, i.e., the GPPGA total score itself will not be imputed, but the binary endpoints derived based on these scores will be imputed, unless otherwise specified.

Binary efficacy endpoints for randomized dose at Day 1

The following primary imputation strategy ("NRI") will be performed after the implementation of the estimand concept:

- For endpoints which are measured at multiple visits, if there are available data at the visits both before and after the visit with a missing outcome, then impute as a success only if both 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);

- Otherwise, impute as a failure to achieve a response (i.e. no response imputation).

Other imputation schemes will be also considered for the primary and secondary binary efficacy analyses included in the hierarchical testing procedure, including (see the footnote of Table 6.6.2: 1 for the definition of EN):

- Best response imputation (BRI) after implementation of EN: impute all missing values based on the best response observed for the patient at visits prior to withdrawal/occurrence of missing data (independent of whether the observations were selected for analysis based on time windows described in Section 6.7). If there is no non-

missing data available (including baseline), then the missing value will be imputed as a non-response.

- Exhaustive method (EM) (primary endpoint and key secondary endpoint only) for EN: If fewer than 3 patients have missing data on an endpoint at Week 1 then a list of all possible treatment differences will be generated whereby each of the potential responses (response, non-response) will be imputed for each patient in an exhaustive manner. The primary endpoint analysis will be repeated for each possible combination of imputed values on missing responses and the results will be summarized in a single table.

In addition, the following methods will be implemented to display the data descriptively.

- 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 any use of escape medication, or OL Spesolimab use at D8, or rescue medication with Spesolimab.
- Observed cases including intercurrent events (OC-IR) approach is an extension of the OC approach which includes additionally all values which were measured after any use of escape medication, or OL Spesolimab use at D8, or rescue medication with Spesolimab.

With regard to the handling of missing data on the primary and key secondary binary efficacy endpoints at Week 1 and secondary binary efficacy endpoints at Week 4, which are included in the testing strategy, the following table gives an overview of the proposed estimand implementation and missing data imputation methods which are planned to be used.

Table 6.6.2: 1 Handling of estimand and missing data on binary efficacy endpoints in testing strategy

Analysis or display method	Binary efficacy endpoint observed or not	Estimand or display concept		Imputation method on missing data due to other reasons, i.e. withdrew consent, lost to follow up, data not collected, etc.
		[Week 1 and 4] Death, or use of escape medication, or [Week 4 only] OL Spesolimab use at D8 or rescue use with Spesolimab, prior to endpoint	[Week 1 and 4] Use of restricted medication for other purpose	
EN-NRI	Observed/ Not observed	Non-response	Observed	NRI
EN-BRI	Observed/ Not observed	Non-response	Observed	BRI
EN-EM	Observed/ Not observed	Non-response	Observed	EM
EN-PC-NRI	Observed/ Not observed	Non-response	Censored and then imputed by NRI	NRI
OC	Observed	Censored	Observed	n.a.
	Not observed	No imputation	No imputation	No imputation
OC-IR	Observed	Observed	Observed	n.a.
	Not observed	No imputation	No imputation	No imputation

EN: Primary estimand for binary endpoint. For week 1, death or any use of escape medication, and, for week 4, death, or any use of escape medication, or OL Spesolimab use at D8, or any rescue medication with Spesolimab, prior to observing the endpoint(s) is considered to represent a non-response.
EN-PC: Alternative estimand for binary endpoint. For week 1, death or any use of escape medication, and, for week 4, death, or any use of escape medication, or OL Spesolimab use at D8, or any rescue medication with Spesolimab, prior to observing the endpoint(s) is considered to represent a non-response. Any data after the use of restricted medication for other purpose will be censored.
OC = observed cases excluding values after any use of escape medication, or OL Spesolimab use at D8, or any rescue medication with Spesolimab, OC-IR = observed cases including also values after any use of escape medication, or OL Spesolimab use at D8, or any rescue medication with Spesolimab.
"NRI", "BRI" and "EM" (Exhaustive method) mean analyses involving imputed data, cf. Section 6.6.2.

Continuous efficacy endpoints for randomized dose at Day 1

For the primary estimand of continuous endpoints, death or any use of escape medication, or OL Spesolimab at Day 8, or any rescue medication with Spesolimab, prior to observing the endpoint(s) is considered to represent a non-response. Here the outcome of "non-response" itself is not a missing value but is the worst possible outcome of the corresponding

continuous endpoint. See Section 7.5.2 for how to display continuous endpoint with both "non-response" outcome and other numeric continuous values.

The primary imputation strategy of missing values of continuous endpoints is LOCF after the implementation of estimand concept:

- Impute the missing outcome as the last available value (including baseline) prior to the missing outcome;

Wilcoxon rank test on secondary continuous endpoints:
For secondary continuous endpoints, a rank-based approach will be used for testing as below:

> The best possible baseline values are the lowest value 0 for Pain VAS score and PSS score, and the highest value 52 for FACIT-Fatigue scale score. The worst possible post-baseline values are the highest values 100 and 16 for Pain VAS score and PSS score respectively, and the lowest value 0 for the FACIT-Fatigue scale score. Therefore, the maximum value for the worst possible change from baseline (i.e., the worst possible post-baseline value – the best possible baseline value) is 100 for Pain VAS, 16 for PSS, and -52 for the FACIT-Fatigue scale. Furthermore, the maximum value for the worst percentage change from baseline in GPPASI at Week 1 and at Week 4 will be the highest observed percentage change from baseline of all patients with non-missing GPPASI at Week 1 or Week 4, which are denoted as PT1 and PT4 respectively.

For Wilcoxon rank tests of the secondary continuous endpoints at week 1 or at week 4, worst case ranks will be assigned to those patients with death, or prior escape medication, or OL Spesolimab at D8, or rescue medication with Spesolimab cf. Section 7.5 of CTP. The ranking rules for the tests are outlined in Table 6.6.2: 2.

Table 6.6.2: 2 Ranking rules for Wilcoxon rank tests of secondary continuous endpoint on EN

	Category	**Ranking**	**Case description**	**Imputed change from baseline for further ranking score**
1	Missing data at week 1/4[1] but still alive and no use of either escape medication, OL Spesolimab at D8 or rescue medication with Spesolimab prior to Week 1/4[1].	Rank by imputed value	Patient has available data at visit prior to Week 1/4[1]	LOCF prior to Week 1/4[1]
			Patient has no prior available value	102 for Pain VAS 18 for PSS and -54 for FACIT-Fatigue scale PT1/PT4+2 for percentage change from baseline in GPPASI at Week 1/4
2	Use of escape medication, OL Spesolimab at D8 or rescue medication with Spesolimab prior to endpoint collection at Week 1/4[1] but still alive.	Rank by OL Spesolimab at D8 or time to rescue medication or time to escape medication from randomized treatment.	Patient has OL Spesolimab at D8, and has no escape medication, and no rescue medication prior to endpoint collection at Week 4	104 for Pain VAS 20 for PSS -56 for FACIT-Fatigue scale PT4+4 for percentage change from baselines in GPPASI at Week 4

Table 6.6.2: 2 Ranking rules for Wilcoxon rank tests of secondary continuous endpoint on EN (cont'd.)

	Category	**Ranking**	**Case description**	**Imputed change from baseline for further ranking score***
			Patient has rescue medication with Spesolimab x days from randomized treatment., and has no escape medication prior to endpoint collection at Week 4 (independent of whether OL Spesolimab was administered at D8 or not)	106-x/1000 for Pain VAS 22-x/1000 for PSS -58+x/1000 for FACIT-Fatigue scale PT4+6-x/1000 for percentage change from baseline in GPPASI at Week 4
			Patient has escape medication y days after randomized treatment and prior to endpoint collection at Week 1/4[1] (independent of whether OL Spesolimab was administered at D8 or not, or rescue medication was taken)	108-y/1000 for Pain VAS 24-y/1000 for PSS -60+y/1000 for FACIT-Fatigue scale PT1/4+8-y/1000 for percentage change from baseline in GPPASI at Week 1/4

Table 6.6.2: 2 Ranking rules for Wilcoxon rank tests of secondary continuous endpoint on EN (cont'd.)

	Category	**Ranking**	**Case description**	**Imputed change from baseline for further ranking score***
3	Patient died before the measurement at Week 1/4[1]	Ranked by time to death from randomized treatment.	Patient died z days after randomized treatment. (independent of the occurrence of other events)	110-z/1000 for Pain VAS 26-z/1000 for PSS -62+z/1000 for FACIT-Fatigue scale PT1/4+10-z/1000 for percentage change from baseline in GPPASI at Week 1/4

* Ranked values in this table are only for purpose of rank tests but not for any descriptive displays
[1] For percentage change from baseline in GPPASI at week 1, the imputation rule is based on the data at week 1, but for other secondary continuous endpoints, it is based on the data at week 4.

Other sensitivity analysis of continuous endpoints include an additional estimand (EC) whereby any data after use of escape medication/OL Spesolimab at D8/rescue treatment with Spesolimab will be censored. The following two methods may be used to handle the censored or missing data here:

- A mixed effect model for repeated measurements (MMRM) will be used to handle the missing cases implicitly.
- (For secondary continuous endpoints only) LOCF method will be used to impute the missing cases.

In addition, OC and OC-IR methods will be implemented to display the data descriptively if needed.

With regard to the handling of missing data on the secondary continuous efficacy endpoints at Week 4, which are included in the testing strategy, the following table gives an overview of the proposed estimand implementation and missing data imputation methods which are planned to be used.

Table 6.6.2: 3 Handling of estimand and missing data on continuous efficacy endpoints in testing strategy

Analysis or display method	Continuous efficacy endpoint observed or not	Estimand or display concept Death, or use of escape medication, or OL Spesolimab use at D8 or rescue use with Spesolimab, prior to endpoint	Imputation method on missing data due to other reasons, i.e. withdrew consent, lost to follow up, data not collected, etc.
EN-LOCF	Observed/ Not observed	Non-response	LOCF
EC-MMRM	Observed/ Not observed	Censored	MMRM
EC-LOCF	Observed/ Not observed	Censored then imputed by LOCF	LOCF
OC	Observed	Censored	n.a.
	Not observed	No imputation	No imputation
OC-IR	Observed	Observed	n.a.
	Not observed	No imputation	No imputation

EN: Primary estimand for continuous endpoint. Death or any use of escape medication or OL Spesolimab use at D8, or any rescue medication with Spesolimab, prior to observing the endpoint(s) is considered to represent a non-response.
EC: Alternative estimand for continuous endpoint. Any data post escape medication use or OL Spesolimab at D8, or rescue medication with OL Spesolimab will be censored.
OC-IR = observed cases including also values after any use of escape medication, or OL Spesolimab use at D8, or any rescue medication with Spesolimab
"LOCF" and "MMRM" mean analyses involving imputed data, cf. Section 6.6.2.

[redacted]

[redacted]

6.6.3 Safety data

With respect to safety evaluations, it is not planned to impute missing values.

The following approaches will be used for the descriptive reporting.

- Observed cases including escape medication (OC-IE) approach will include all collected data after escape medication use, without imputation for any missing data. Such an OC-IE approach will exclude all values measured after OL Spesolimab use at D8, or rescue medication with Spesolimab.
- Observed cases including intercurrent (OC-IR) approach will be applied in the same manner as defined for the efficacy data (see Section 6.6.2).

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 (4).

Partial start and stop dates for concomitant medications, and background, escape, as well as historical medication for GPP 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 escape medication, 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 escape medication, 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.

Missing start dates of open-label treatment with Spesolimab on Day 8 will be set to date of the Day 8 visit (if consistent with any specification on the month and/or year), otherwise it needs to be assessed by the trial team on an individual basis. Missing end dates will be set to the same date as the start date.

Missing start dates of rescue treatment with Spesolimab for a GPP flare will be set to the date of occurrence of the applicable flare, the date being consistent with any specification on month and/or year of the rescue treatment; other situations need to be assessed by the trial team on an individual basis.

6.6.7 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.

6.6.8 Disease characteristics

Incomplete information regarding disease characteristics will be imputed as follows:

- For calculation of "date of diagnosis of most recent flare of GPP before the trial to Visit 1", partial dates will be replaced with the first day of the month (if month and year are available, and not later than the month and year upon which Visit 1 was performed). Otherwise, the dates will not be replaced. Replacement will only be done for calculation.

- For calculation of "start date of symptoms of current flare of GPP", partial dates will be replaced with the day of the first study treatment administration (if month and year are available, and are identical to the month and year upon which first study treatment administration was performed). Otherwise, the dates will not be replaced. Replacement will only be done for calculation.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline, unless otherwise specified, refers to the last measurement collected prior to the dose of randomized Spesolimab/placebo administered at Day 1 in the study. For the analysis of biomarkers (see Section 7.6.5) baseline refers to the last measurement prior to randomized treatment administered at Day 1 but not more than 5 days earlier.

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 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.

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, concomitant medications, recurrence of flares and of rescue/escape medication use will not be based on visits therefore, no assignment to time windows will be necessary.

All other safety, efficacy [redacted] measurements will be assigned to visits based on time windows around the planned visit dates, defined relative to the day of first trial treatment, Day 1. These time windows are defined in Table 6.7: 1.

Table 6.7: 1 Time windows for assignment of efficacy, safety lab, vital signs [redacted] to visits for statistical analysis

Visit number	*Visit label*	*Planned day*	*Time window*		
			Window (per CTP)	*Start (extended)*	*End (extended)*
2	*Week 1, Day 1*	*Day 1*	*exact day*	*Day 1* [A]	*Day 1* [A]
3	*Week 1, Day 2*	*Day 2*	*exact day*	*Day 2*	*Day 2*
4	*Week 1, Day 3*	*Day 3*	*exact day*	*Day 3*	*Day 3*
5 [B]	*Week 1, Day 4*	*Day 4*	*exact day*	*Day 4*	*Day 4*
6 [B]	*Week 1, Day 5*	*Day 5*	*exact day*	*Day 5*	*Day 5*
7 [B]	*Week 1, Day 6*	*Day 6*	*exact day*	*Day 6*	*Day 6*
8 [B]	*Week 1, Day 7*	*Day 7*	*exact day*	*Day 7*	*Day 7*
9 [E]	*Week 1, Day 8*	*Day 8*	*exact day*	*Day 8*	*Day 10*
10	*Week 2*	*Day 15*	*+/- 3 days*	*Day 11*	*Day 18*
11	*Week 3*	*Day 22*	*+/- 3 days*	*Day 19*	*Day 25*
12	*Week 4*	*Day 29*	*+/- 3 days*	*Day 26*	*Day 43*
13	*Week 8*	*Day 57*	*+/- 7 days*	*Day 44*	*Day 71*
14	*Week 12* [C]	*Day 85*	*+/- 7 days*	*Day 72*	*Day 99*
Post Week 12 [D]				*Day 100*	*Day 113*
Off treatment [D]				*Day 114*	*Day of last follow-up value*

All days are counted relative to the day of randomized treatment, which is defined as Day 1.
[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] *Since visits 5-8 are optional, the assessments (if any) will not be displayed in tables or figures only if otherwise specified.*
[C] *Patients who receive rescue treatment with OL Spesolimab between Wk7-Wk12 will not have scheduled V14, however if there is any unscheduled assessment between the defined extended time window for V14, it will be still used.*
[D] *All tables and figures by visit will only report visits up to week 12 (if applicable). "Post Week 12" and "off treatment" won't be used for any tables or figures.*
[E] *For primary analysis visit (V9), only the assessments prior any non-randomized treatment will be used except for those pre-specified post-treatment assessments.*

Repeated and unscheduled efficacy, safety and other measurements will be handled similarly to scheduled measurements and will also be assigned to a time window depending upon the date of measurement.

Notice that for EN, EN-PC and EN-ID8 estimands, any observation post intercurrent events of interests (i.e., death, escape medication or rescue medication with Spesolimab for all 3 estimands or OL Spesolimab at D8 for EN and EN-PC only) will be set to be "non-response". Further, within the extended time window of a visit, if the day of the intercurrent event is prior to the date of planned visit, then a "non-response" observation will be assigned to that day. If the day of the intercurrent event is on or after the date of planned visit, then a "non-response" observation will be assigned to that day only if there is no other observation on the same day, otherwise, no additional observation will be assigned.

Only one observation per time window will be selected for statistical analysis at a particular visit – the value which is closest to the protocol planned visit day will be selected. If there are two observations which have the same difference in days to the planned day, but which are not measured on the same day, the later value will be selected. If there are two observations on the same day, the worst value will be selected.

Assignment of observations to visits based on time windows will be based on the non-imputed (observed) data after the implement of estimand concepts. For example, for EN estimand, values after death or use of escape medication, OL Spesolimab at Day 8 or rescue medication with Spesolimab should be set to be "Non-response" first before assignment of efficacy endpoints.

For visits without an assigned value based on time windows, a value will thereafter be imputed (if needed) as defined in Section 6.6. Imputation of efficacy endpoints, when applicable, will be performed based on all available observations meeting the imputation rules, irrespective of whether the observation was selected in any time window.

Tables and figures presenting results of the statistical analysis will only display visits at which the respective parameter was planned to be collected according to the CTP. Note that Visits 5-8 are optional so they will not be displayed in tables and figures only if otherwise specified.

7. PLANNED ANALYSIS

Primary analysis of study will be performed once all patients have completed 12 weeks study period or early discontinue. A snapshot will be taken for the primary analysis and all patients' data up to the cut-off date will be included into analysis.

Final trial analysis is planned to be performed at the end of the study once all randomized patients have completed the study (including any follow-up period) if applicable. Additional but limited data after primary analysis snapshot will be listed in final analysis.

A database lock for the primary analysis will be done and treatment will be un-blinded. In order to warrant the integrity of the treatment blind while the trial continues through completion, a logistics plan will be developed to describe the mechanisms that are to be put in place to assure that the patients and investigators remain blinded to both individual patient data, as well as the primary analysis results. The blind status of trial and project team members at this time will also be clarified. The logistics plan will be finalized prior to the treatment un-blind for the primary analysis.

The primary analysis and final analysis may be performed as a single analysis (at the time of trial completion), if, prior to the time of the primary analysis, the trial team agrees that the expected time interval between the planned analyses is insufficient to justify the performance of separate analyses.

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (001-MCG-159) (10). The individual values of all patients will be listed. Listings will generally be sorted by country, center 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

Statistical parameters will be displayed to a defined number of decimal places as specified in the BI guideline "Reporting of clinical trials and project summaries" (10).

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

Disposition of the patient population participating in the trial will be summarized by the presentation of the frequency of patients screened, randomized, screened but not randomized, randomized but not treated, randomized and treated, who completed trial medication (on Day 1), who were prematurely discontinued from trial medication (on Day 1), by reason, who completed participation in the trial, who were prematurely discontinued from trial, by reason, and who entered the extension trial 1368.25.

The frequency of patients with iPDs, also summarized by whether or not the iPD led to exclusion from the PPS, will be presented. The frequency of patients in each of the different analysis sets will also be presented.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

Descriptive statistics will be presented by treatment for demographic parameters and baseline characteristics, based on the RS. The presence of mutations (yes or no) in the following genotypes will be descriptively presented by treatment for the RS: IL36RN, CARD14, or, AP1S3 based on information collected via eCRF and the results for the DNA resequencing respectively.

Characteristics of the trial disease, including details on the current and past GPP flares prior to trial onset, will be displayed for randomized patients. Here the output for most recent flare will be based on “Disease Characteristics (Most Recent Flare prior to Consent)” eCRF page while other prior flares will be based on “Natural Medical History for GPP” eCRF page.

For the continuous variables described below, the following categories will be defined, 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	< 50 years 50 to < 65 years ≧ 65 years < 65 years ≧65 years
Weight	≤70 kg >70 to ≤80 kg >80 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 years > 5 to ≤ 10 years > 10 years

7.2 CONCOMITANT DISEASE AND MEDICATION

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

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.

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

- is ongoing at the start of randomized trial treatment or
- starts within the on-treatment period (see Section 6.1 for a definition of study analysis phases).

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 randomized trial treatment.

Concomitant medication use (excluding escape medications as defined in the CTP) will be summarized with frequency and percentage of patients by ATC3 class and preferred name.

The frequency and percentage of patients with historical medication for GPP will be displayed, including presentation by type of historical medication (preferred name), and by reason for discontinuation.

The frequency and percentage of patients taking either none or any background medication for GPP will be tabulated by type of background therapy (preferred name); a background therapy is assumed to be present if the medication is identified on the CONMED page of the CRF and is given for the purpose of disease under study (flagged as a background medication).

Use of escape medication, treatment with OL Spesolimab at Day 8, or rescue treatment with Spesolimab will be summarised separately (see Section 7.6.3). An escape medication is assumed if for any medication which is newly given for the disease under study and denoted for the purpose of escape use (disease worsening/not improved) per CONMED page of the CRF.

Concomitant use of non-drug therapies will be summarised with frequency and percentage. Summaries will be presented in the same manner as done for the concomitant medication use.

7.3 TREATMENT COMPLIANCE

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

Treatment compliance to the randomized study treatment will be summarised on Day 1 via dose intensity (as described in Section 5.4.6) for the SAF using descriptive statistics (N, mean, SD, minimum, median, maximum).

The number and percentage of patients with the following overall compliance categories will be presented:

- "< 80% of planned",
- ">=80 of planned"

7.4 PRIMARY ENDPOINT

The evaluation of patients achieving a GPPGA pustulation subscore of 0 at Week 1 is the primary endpoint of this trial.

Death, or any use of escape medication prior to observing the primary endpoint(s) is considered to reflect a failure to achieve the endpoint outcome, i.e. non-response. In this concept, death, or any use of escape medication after the actual assessment time point of week 1 is not considered. If time is not collected, death or any use of escape medication on or after the actual assessment day of Week 1 is not considered.

The Suissa-Shuster Z-pooled test, will be implemented to test the treatment effect on the primary endpoint on the RS (estimand EN), at a 1-sided, alpha level of 0.025. Confirmation of efficacy is then given only if the null hypothesis on the primary endpoint is rejected. In the output, the result will be reported at 2-sided alpha level of 0.05 which is more common way in CTR but it is exactly same as 1-sided alpha level of 0.025. Confidence intervals (95%) around the risk difference will be produced using the Chan and Zhang method (6).

Example SAS code for Suissa-Shuster Z-pooled test is as follows:

```
PROC FREQ DATA=data;
  TABLES treat*endpoint_bin;
  EXACT BARNARD (column=2);
RUN;
```

Example SAS code for CI of proportion difference by Chan and Zhang method is as follows:

```
PROC FREQ DATA=data;
  <WHERE treat IN ('Treatment_1','Treatment_2');>
  TABLES treat*endpoint_bin / RELRISK RISKDIFF;
  EXACT RELRISK (METHOD=SCORE column=2) RISKDIFF (METHOD=SCORE
column=2);
RUN;
```

Graphical displays (Line plots) of the response on primary endpoint will be produced over time (with 95% confidence intervals based on the Wilson score) up to, and including, Visit 14 (Week 12).

Secondary analysis for the primary endpoint will include:

- A sensitivity analysis utilizing the PPS;
- Sensitivity analyses on the RS which utilize alternative methods for the handling of missing data as described in Section 6.6.2.
- Analysis of an additional estimand (EN-PC) whereby death or any use of escape medication, prior to observing the week 1 primary endpoint will be considered to

represent a non-response. For patients who use restricted medication for other purpose prior to Week 1, data will be censored for further analysis following the restricted medication use and imputed using NRI method as described in Section 6.6.2.

- Sensitivity analyses on the RS to adjust for the potential covariates, IL36R mutation status (Yes vs No) and baseline GPPGA total score (3 vs 4) respectively.

  The proportion of patients with a response between Spesolimab and placebo will be analysed by IL36R mutation status and baseline GPPGA total score (3 vs 4) respectively, using a logistic regression approach with a logit link via PROC LOGISTIC in SAS®. Fixed classification effects will include treatment, subgroup and treatment-by-subgroup interaction term.

  The estimates from the logistic regression are on the logit scale, and the difference in proportions will be calculated as the difference between the predicted probabilities by subgroup level and treatment on the original scale.

Descriptive subgroup displays on the primary endpoint (via estimand EN) will be done for the applicable subgroups as defined in Section 6.4 using the RS.

7.5 SECONDARY ENDPOINT

7.5.1 Key Secondary endpoint

The treatment effect on the key secondary endpoints will be tested in a hierarchical manner subsequent to the test of the primary endpoint. The key secondary endpoint on the patients achieving a GPPGA score 0 or 1 at Week 1 will be analyzed in the same way as primary endpoint.

7.5.2 Secondary endpoints

Secondary endpoints included in the testing procedure

The treatment effect on the following secondary endpoint will be tested in a hierarchical manner as a part of the pre-specified testing strategy (see Section 7.2 of the CTP), subsequent to the test of the primary endpoint and key secondary endpoint:

1) The proportion of patients achieving a GPPASI 75 at Week 4,
2) The change from baseline in pain VAS score at week 4,
3) The change from baseline in PSS score at week 4, and,
4) The change from baseline in the total FACIT-Fatigue score at Week 4.

GPPASI 75 at Week 4

The primary analysis for the proportion of patients achieving a GPPASI 75 at Week 4 will be performed using the same approach as that defined for the primary analysis of the primary endpoint, based on the RS (estimand EN).

Graphical displays will be produced using the same method as described for the primary endpoint.

Sensitivity analysis for GPPASI 75 at Week 4 will include:

- Sensitivity analyses on the RS which utilize BRI respectively for the handling of missing data as described in Section 6.6.2.

Descriptive subgroup displays (via estimand EN) will be done for the applicable subgroups as defined in Section 6.4 using the RS.

Pain VAS score, PSS score, and FACIT-Fatigue score at Week 4

For the analysis of each of the continuous secondary endpoints which are included in the statistical testing strategy, the following approach will be done:

Any assessments after death, or the use of escape medication, or OL Spesolimab at D8, or rescue medication with Spesolimab, will be considered as “non-response” and assigned with worst outcome for the analysis (estimand EN). In this concept, death, or any use of escape medication or OL Spesolimab at Day 8 or of rescue medication with Spesolimab after the actual endpoint assessment time point at week 4 is not considered. If time is not collected, death, or any use of escape medication or of rescue medication with Spesolimab on or after the actual assessment day of Week 4 is not considered.

In primary analysis of the secondary continuous endpoints, “non-response” itself is not a missing value but the worst possible outcome of the endpoint. The mean of the endpoints could not be reported due to the mix of “non-response” outcomes and other numeric continuous outcomes. The Q1, median and Q3 could be still reported, however, where “non-response” will be treated as the worst outcome in the rank. If the proportion of “non-response” is high enough, Q1, median and Q3 of the endpoint could all be reported as “non-response”. For example, for a continuous endpoint where larger value indicates the better outcome, if the achieved data is (NR, NR, NR, NR, NR, NR, 2, 3, 3, 3, 5) where NR=”non-response”, then Q1 is NR, median is NR and Q3 is 3.

For each secondary continuous endpoint, the effect of Spesolimab will be evaluated by a Wilcoxon rank test using the RS. All details regarding the ranking rules for Wilcoxon test are defined in Section 6.6.2.

Example SAS code for Wilcoxon rank test is as below:

```
proc NPAR1WAY data=data wilcoxon;
    class treatment;
    var endpoint;
    exact wilcoxon;
```

run;

The difference between treatments, based on the RS, will be displayed using a modified Hodges-Lehmann (HL) estimate of the median difference (11). If a patient has died or used escape medication, or OL Spesolimab at D8, or rescue medication with Spesolimab prior to a timepoint (i.e., Week 4), then the patient's assessment at that timepoint (i.e., Week 4) will be treated as "non-response" in HL estimation. Otherwise, missing data at that timepoint (i.e., Week 4) will be imputed using LOCF method. The modification of the HL estimate is that all NR-NR comparisons on a patient level will be excluded from the calculation since they do not provide any information about the numerical estimate and they have no clear 'positioning' when calculating the median. Further the difference between a non-missing value and a non-response status should be 'large positive' or 'large negative', depending on the direction. A 95% confidence interval around the modified HL estimate of the median treatment difference will also then be calculated, adjusting for the reduced number of comparisons (due to exclusion of the NR-NR outcomes). Graphical displays of the modified HL estimate of the median treatment difference (with and without 95% confidence intervals) will be produced over time. For clarity, a full description of the modified HL method is defined as follows:

For each of the secondary continuous endpoints in the testing procedure, assume that the continuous response vector in Placebo arm is $(x_1, x_2, \ldots, x_n)$ and the continuous response vector in Spesolimab arm is $(y_1, y_2, \ldots, y_m)$, where n is the number of patients in Placebo arm and m is the number of patients in Spesolimab arm.

Step 1, In line with the standard HL approach, calculate the difference between every possible pair of x's and y's; $d_{ij}=y_j-x_i$. There will be a total of m times n such differences. For the modified version, all NR-NR comparisons are then discarded from the calculation, that is, mn-l comparisons will be performed (where l is the number of NR-NR comparisons). Note that all comparisons between a non-response and a measurement are still retained. The remaining values in the list of d_{ij} will then be ranked in ascending order and the median from the list will be picked as the modified HL estimate.

Step 2, Compute the rank of the lower confidence limit as $R_L=\frac{m\prime n\prime}{2}-Z_{0.025}\sqrt{\frac{m\prime n\prime(m\prime+n\prime+1)}{12}}$ where $Z_{0.025}$ is the z-value corresponding to a one sided 97.5% confidence interval, $m'=\sqrt{m^2-lm/n}$ and n'=m'n/m and noting that m'n'=mn-l. If R_L is a non-integer, it needs to be rounded down. The rank of the upper confidence limit will be $R_U=m'n'-R_L+1$. If the obtained R_L or R_U is not a possible value, then it should be rounded to the nearest possible value.

Step 3, Look up the values that corresponding to the ranks R_L and R_U in the remaining values in the ranked list of d_{ij}. These are the confidence limits for HL estimate.

Note that if the overall non-response rate across two arms is too high (i.e., >30%), the modified HL estimate will be no longer robust and therefore will not be displayed.

Descriptive statistics, based on RS (OC) and RS (OC-IR), will be produced, and will include n, mean, SD, min, median, and max for the individual treatment groups.

Sensitivity analysis for each of the continuous secondary endpoints will include an additional estimand (EC) whereby any data post use of escape medication/OL Spesolimab at D8/rescue treatment with Spesolimab will be censored. Two methods will be used to handle the censored or other missing values respectively:

- MMRM method (EC-MMRM),

  Continuous endpoints up to week 4 will be evaluated using an MMRM model accounting for the following sources of variation: 'baseline', 'visit' and 'treatment' as covariates, 'visit*treatment' and 'visit*baseline' as interaction effects as well as the random 'subject' effect. The unstructured covariance structure will be used to model the within patient measurements. To estimate denominator degrees of freedom the Kenward-Roger approximation will be used.

  It is expected most of patients on placebo arm may receive escape medication up to Day 8 or OL Spesolimab at Day 8. Based on "EC" estimand, then most placebo data post Day 8 may have been censored. To avoid achieving the estimates which are not robust, if from certain visits, the values of more than 70% patients are censored or missing for one treatment arm, then MMRM estimates won't consider the data from that time point for that arm.

  In the event of any model non-convergence, the methods described in Section 9.2 will be utilized to resolve this.

  Example SAS code for MMRM is as below:

```
PROC MIXED DATA=alldat cl method=reml;
  CLASS visit trt subject;
  MODEL ept = visit*trt base*visit / ddfm=kr s CL;
  REPEATED visit / subject= subject type=un r rcorr;
  LSMEANS visit*trt / pdiff=all om cl alpha=0.05 slice=visit;
RUN;
```

  Results of the MMRM (N, mean, SE and 95% CI per dose group and timepoint) will be presented in tables and displayed graphically.

- LOCF method (EC-LOCF).

In addition, subgroup displays will be done for the applicable subgroups as defined in Section 6.4 using the RS in the following two ways:

- Descriptive statistics using primary EN estimand and impute missing values using LOCF method.

- MMRM method using EC estimand,

Subgroup analysis will use MMRM model based on the alternative estimand (EC). A single MMRM model will be fitted involving all terms from the above EC-MMRM model in the sensitivity analysis except replacing the treatment-by-visit term by the treatment-by-subgroup-by-visit term.

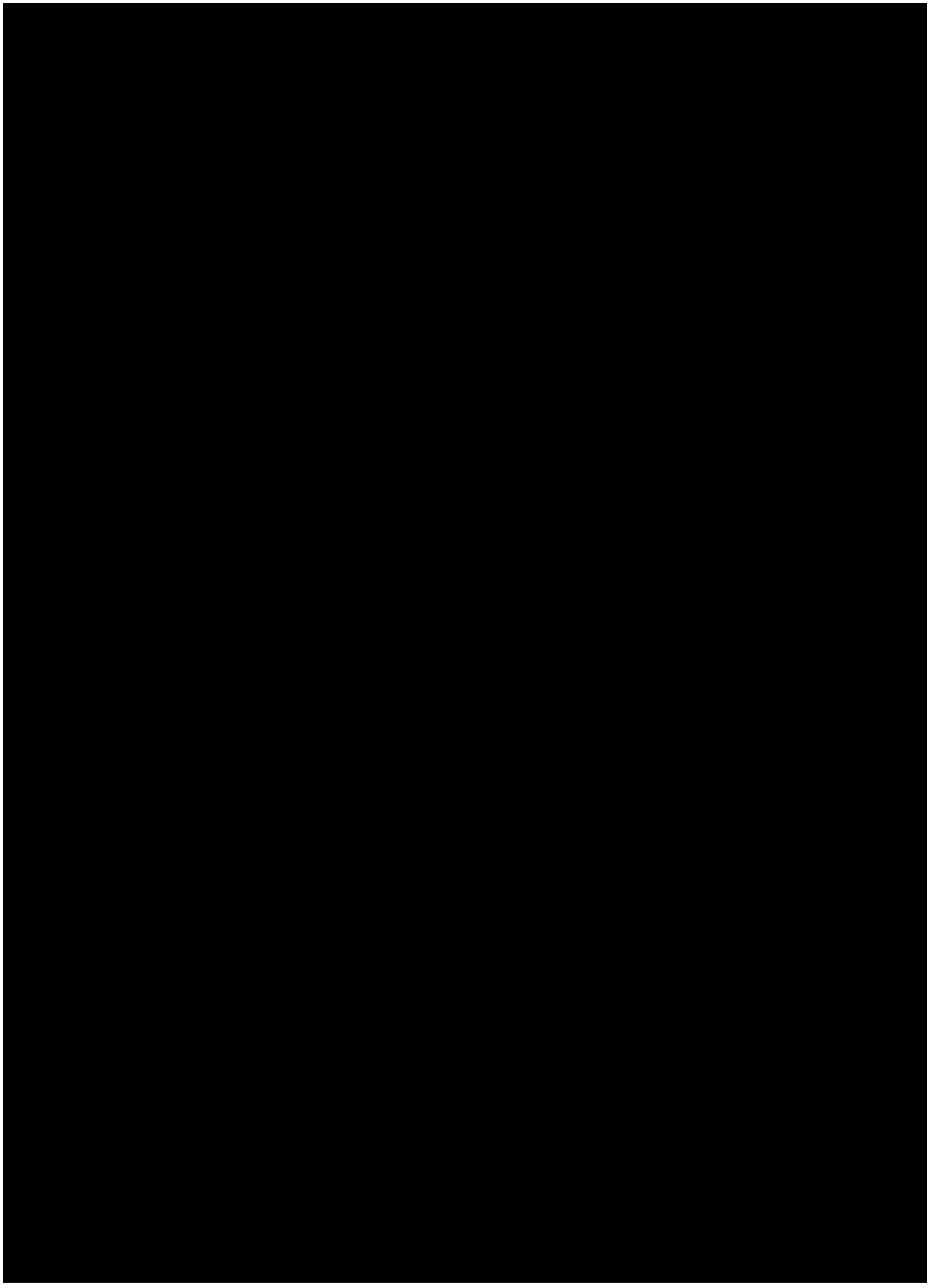
To avoid achieving the estimates which are not robust, if from certain visits, the values of more than 70% patients are censored or missing across all subgroup levels for one treatment arm, then MMRM estimates won't consider the data from that time point for all subgroups of that arm.

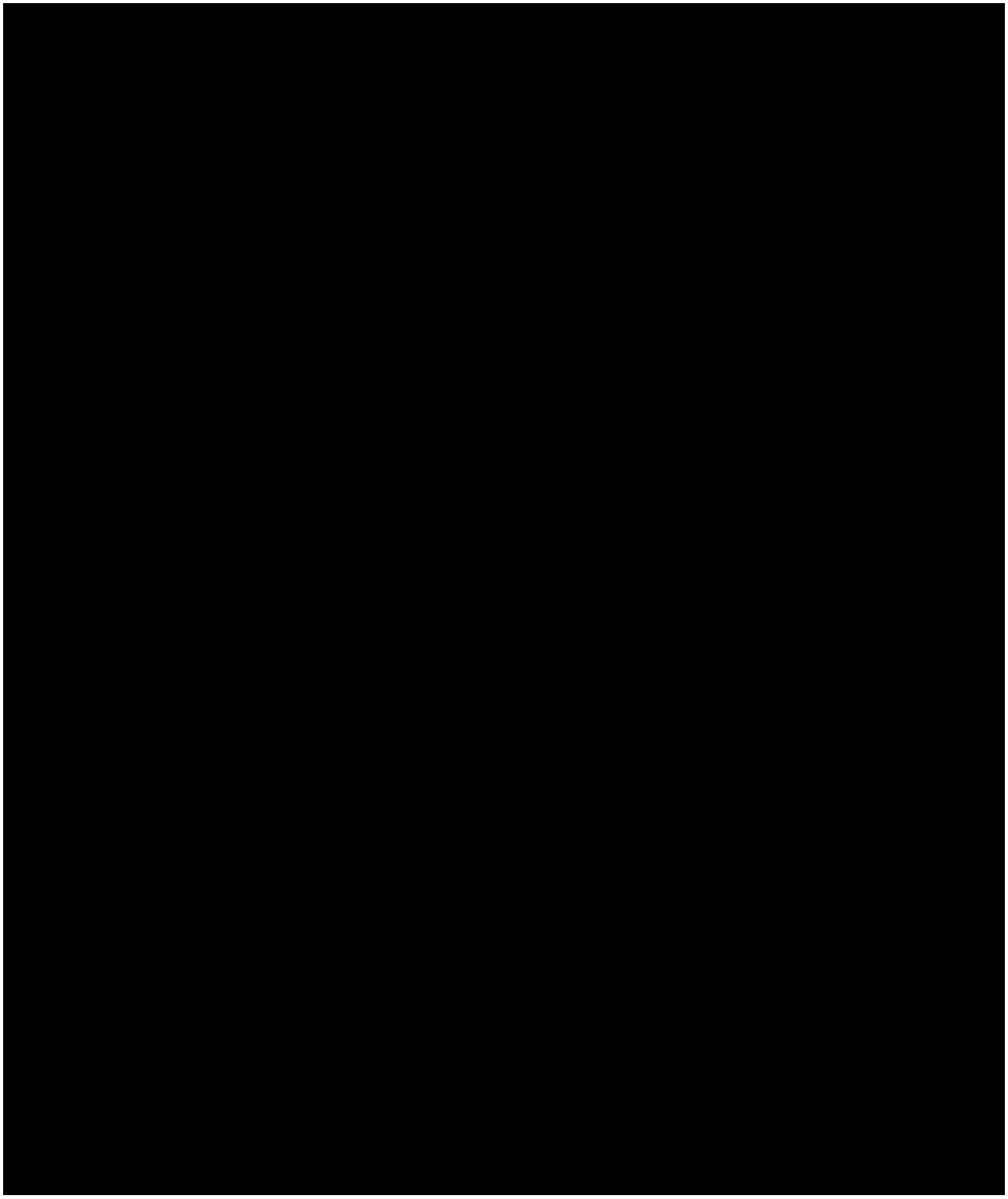
In the event of any model non-convergence, the methods described in Section 9.2 will be utilized to resolve this.

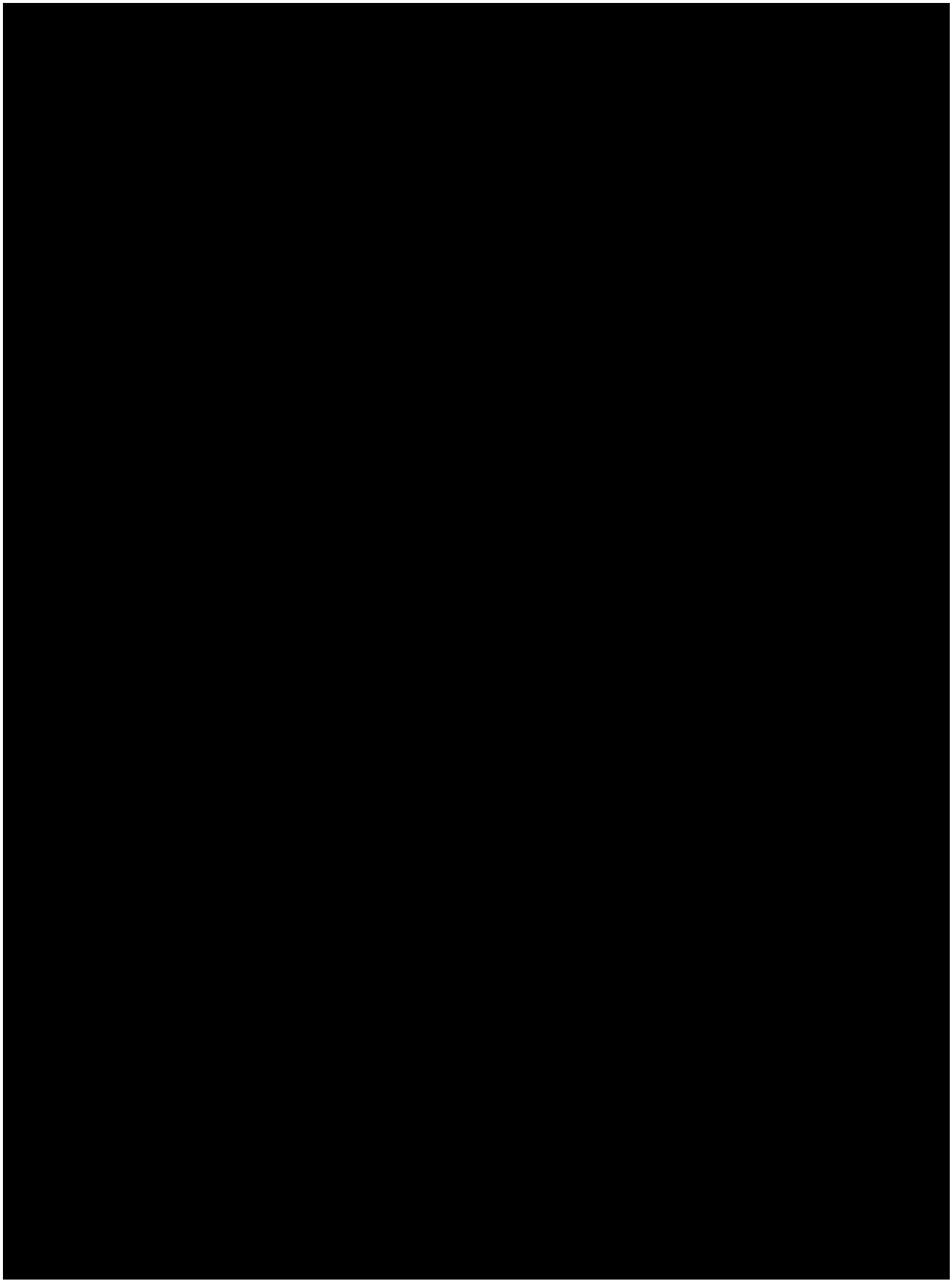
Secondary endpoints not included in the testing procedure

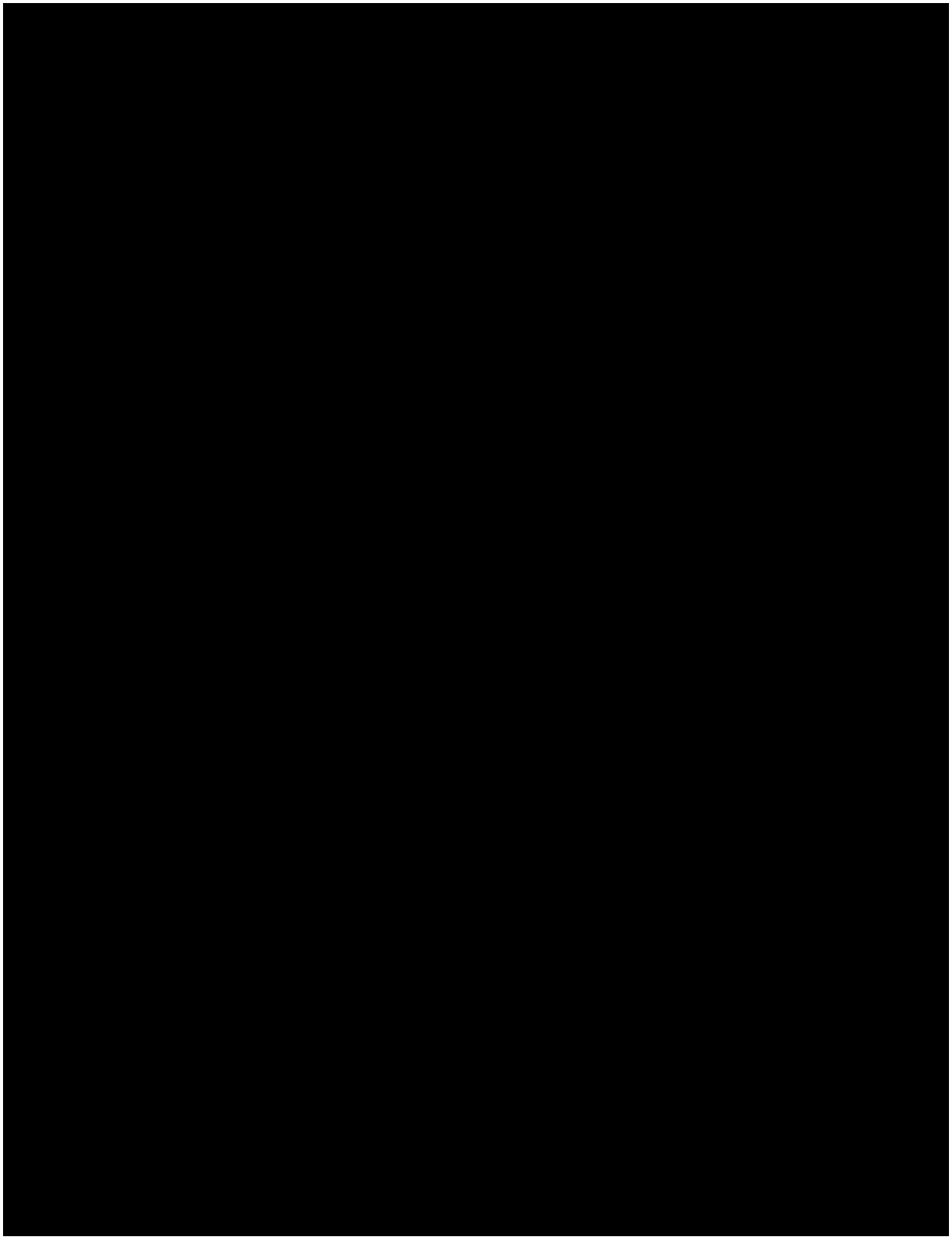
For the binary secondary endpoints (either at week 1 or at week 4) that, are not included into the statistical testing strategy, graphical displays and statistical testing using the Suissa-Shuster Z-pooled test will be performed using the primary estimand and imputation strategy (EN-NRI), as described for the primary endpoint in Section 7.4.

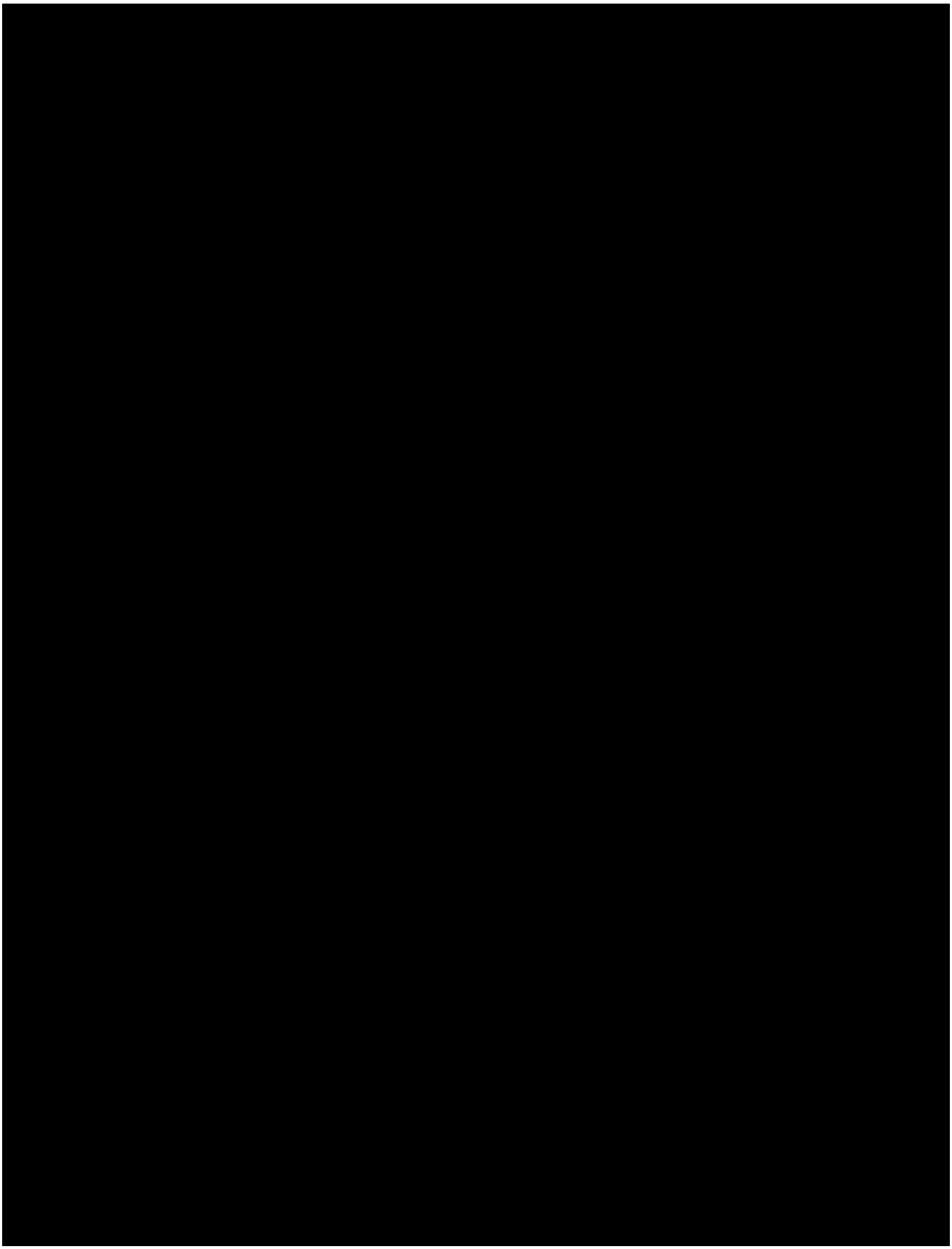
For the continuous secondary endpoints, the percentage change in GPPASI from baseline at Week 1 and Week 4, which are not included into the statistical testing strategy, the analysis will be performed using the same method as for the secondary continuous endpoints in the testing strategy. All details regarding the ranking rules for Wilcoxon rank tests are defined in Section 6.6.2 (and Table 6.6.2: 2).

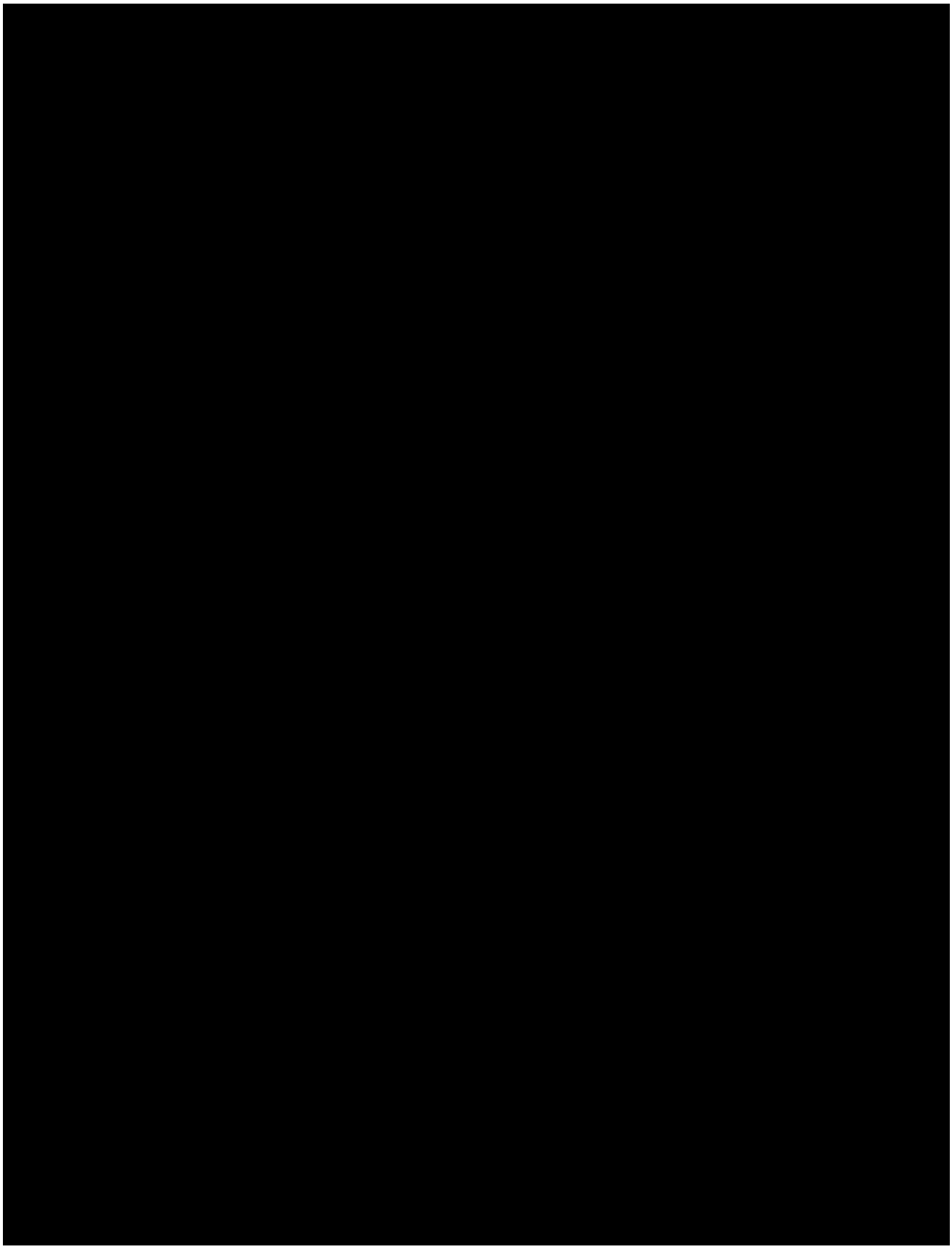


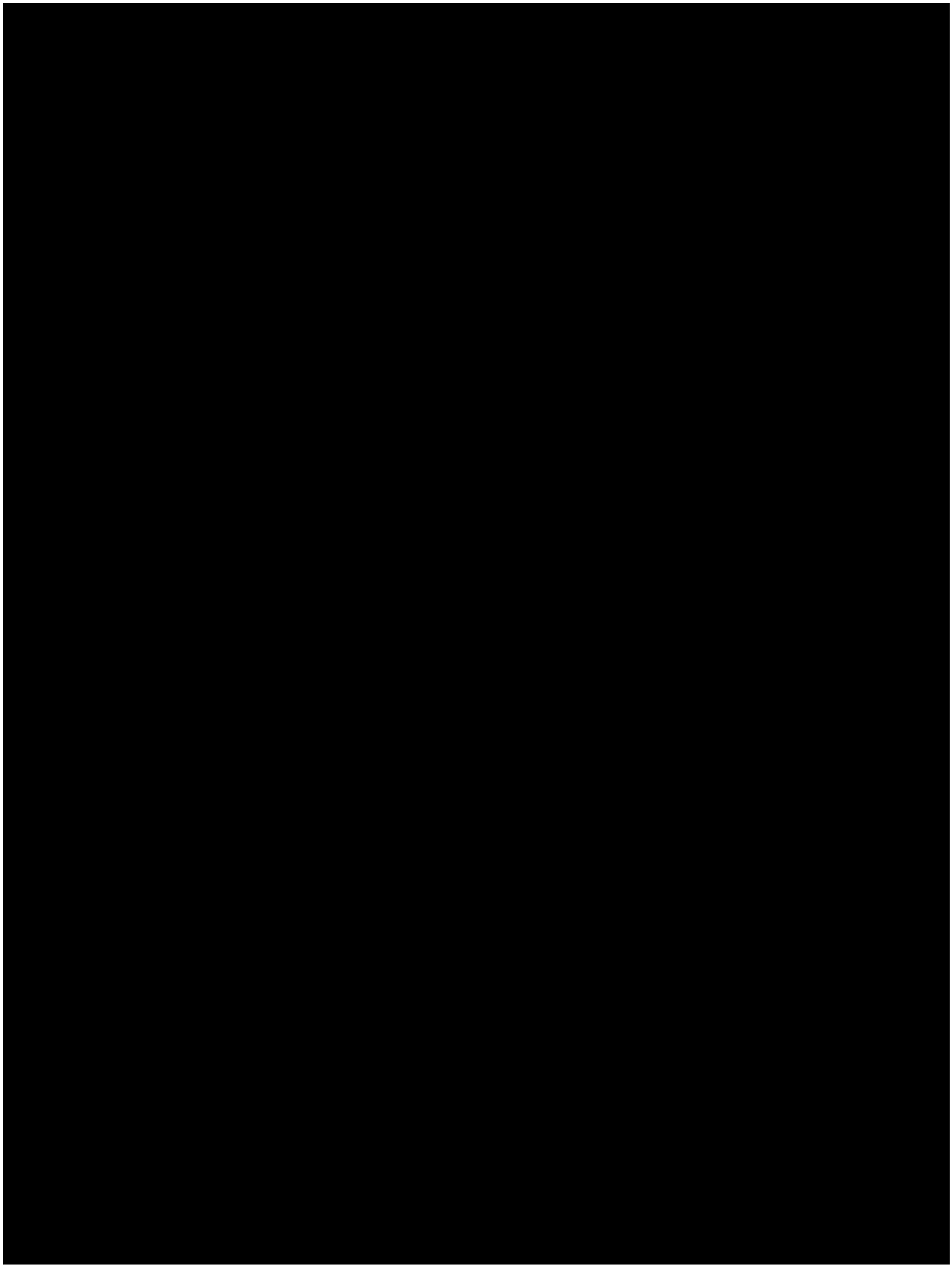


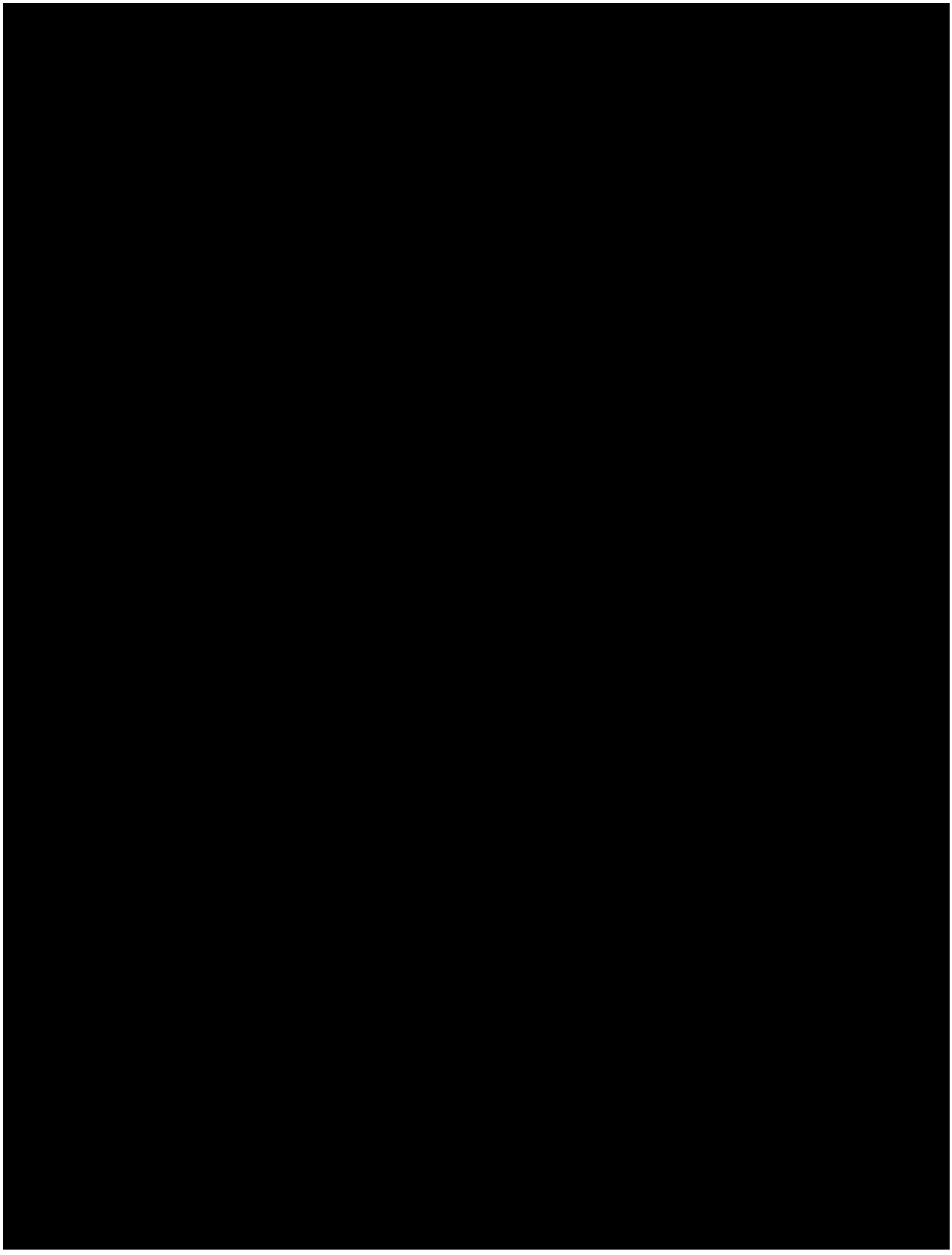












7.7 EXTENT OF EXPOSURE

The number of subjects who received a dose of randomized trial drug will be tabulated. The duration of infusion [in minutes] and the amount of treatment received [mg] will be summarised by descriptive statistics (N, mean, SD, minimum, Q1, median, Q3, maximum) on Day 1.

The number and percentage of patients according to the duration of infusion will also be classified according to the following categories:

Duration of infusion [min] categories

- Duration "< 60 min",
- Duration ">=60 min to < 120 min",
- Duration ">=120 min to < 240 min",
- Duration ">= 240 min".

The above will also be summarized for the open-label treatment with Spesolimab provided on Day 8, as well as for the rescue treatment with Spesolimab.

7.8 SAFETY ANALYSIS

All safety analyses will be performed based on the SAF following BI standards. No hypothesis testing is planned.

Primary analysis for safety data
The primary safety analysis will be done based on data through the first 12 weeks of treatment (i.e., up to Day 85)).

In the primary safety analysis, OC-IE method will be used whereby data after actual time of intake of (optional) open-label Spesolimab on Day 8, or rescue medication with Spesolimab for treatment of a GPP flare will be censored for reporting.

Since the onset time of an AE will not be collected in the trial, any AE which occurs on the same day as the first dose of randomized trial medication (Day 1) will be, conservatively, assigned to the on-treatment period. Any AE which occurs on the same day as the first dose of a non-randomized Spesolimab medication administration (i.e. for OL D8, or for rescue) will be assigned to the period commencing on the day of use of the non-randomized Spesolimab treatment. For safety assessments by visits (except for local tolerability or post-treatment vital signs), if time is not collected, data on the same day of (optional) open-label Spesolimab on Day 8, or rescue medication with Spesolimab for treatment of a GPP flare will not be excluded.

In addition, all AE tables will be repeated up to Week 1 and up to the end of REP of the randomized treatment at Day 1 respectively.

Further analysis for safety data

In further analysis of safety data, AEs of patients will be reported by treatments and their starting time periods relative to the use of randomized treatment at Day 1, OL Spesolimab at Day 8 and rescue medication with Spesolimab (see Section 6.1). That is to say, one patient may be counted in multiple treatment periods as defined below based on the use of randomized treatment at Day 1, OL Spesolimab at Day 8 and rescue medication with Spesolimab. In addition, AEs of patients post any use of randomized or non-randomized Spesolimab are summarized where two arms will be pooled:

- **"Prior non-rand. Speso "**(i.e. TEAE starting before use of any non-randomized Spesolimab are considered)
- **"Post OL Speso at D8"** (i.e. TEAE starting post OL dose at Day 8 but before rescue medication with Spesolimab if applicable are considered)
- **"Post rescue with Speso"** (i.e. TEAE starting post rescue medication with Spesolimab are considered)
- **"Post any Speso"** (i.e. TEAE starting post any randomized or non-randomized Spesolimab are considered where two arms will be pooled)

Descriptive summaries of all AE and potentially clinically significant abnormal Lab values will be repeated up to the end of REP of any of randomized treatment at D1 or non-randomized Spesolimab.

7.8.1 Adverse events

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

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

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

For analysis up to Week 1, Week 12 and the end of REP of randomized drug:

> Time at risk [subject years] = (date of onset of TEAE up to the end time of risk– randomized study drug start date + 1) / 365.25

The end time of risk will be the min (day of death, randomized drug stop date + X days, the day prior to OL Spesolimab at Day 8, the day prior to rescue medication with Spesolimab, the day prior to first dose in the extension study if patient will be rolled over or last contact date

per EoS page if patient will not be rolled over). Here X equals to 6, 84 and 112 for analysis up to Week 1, Week 12 and the end of REP of randomized drug respectively.

For the further analysis on safety data,

> Time at risk prior to non-randomized Spesolimab/ post OL Spesolimab at Day 8/post rescue medication with Spesolimab [subject years] = (date of onset of TEAE up to the end time of risk – randomized treatment date/Day 8 / date of rescue use of Spesolimab + 1) / 365.25

End of time at risk prior to any non-randomized Spesolimab will be the min of (Day 113 or the day prior to any non-randomized Spesolimab, last contact date per EoS page if patient will not be rolled over or the day prior to first dose in the extension study if patient will be rolled over).

End of time at risk post OL Spesolimab at Day 8 will be the min of (Day 8 Spesolimab date +112 or the day prior to the use of rescue medication with Spesolimab or the last contact date per EoS page if patient will not be rolled over or the day prior to first dose in the extension study if patient will be rolled over).

End of time at risk post use of rescue medication with Spesolimab will be the min of (the day of rescue medication with Spesolimab in the trial +112 or the last contact date per EoS page if patient will not be rolled over or the day prior to first dose in the extension study if patient will be rolled over).

In addition, for overall period post use of any Spesolimab,

> Time at risk overall post use of any Spesolimab [subject years] = (date of onset of TEAE up to the end time of risk – first use of any Spesolimab start date + 1) / 365.25

End of time at risk for overall post use of any Spesolimab will be min of (the day of last Spesolimab in the trial +112 or the last contact date per EoS page if patient will not be rolled over or the day prior to first dose in the extension study if patient will be rolled over).

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the exposure adjusted incidence rates (per 100 subject years), as well as the number of patients with AEs and not on the number of AEs. System organ classes (if applicable) will be sorted according to the standard sort order specified by the EMA, preferred terms (if applicable) will be sorted by total frequency (within system organ class) across all treatment columns, cf. Section 6.1.

For further details on summarization of AE data, please refer to "Handling and summarization of adverse event data for clinical trial reports and integrated summaries" (7) and "Handling of missing and incomplete AE dates" (4).

The analysis of AEs will be based on the concept of treatment emergent AEs. This means that all AEs will be assigned to the screening phase, treatment phase or follow-up phase 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 randomized Spesolimab/placebo administration will be assigned to the on-treatment period.

An overall summary of AEs will be presented. This overall summary will include summary for the class of AESIs.

The following are considered as AESIs (see Sec 5.2.6.1 of CTP):

- Hepatic injury
- Systemic hypersensitivity reactions including Infusion reactions and anaphylactic reaction
- Severe infections (according to RCTC grading in the ISF)
- Opportunistic and mycobacterium tuberculosis infections

The investigator identified AESI will be captured from the eCRF and reported as "Investigator reported AESI" table. In addition, user defined adverse event concepts (UDAEC) identified through specific search criteria will be reported separately (cf. Table 7.8.1: 1).

Table 7.8.1: 1 Project MedDRA search criteria for User Defined Adverse Event Concepts

User-defined AE category		
Label		Description
Infections (serious/severe, opportunistic)	Infections ALL	Combined search strategy based on the individual UDAECs described below; the UDAEC "severe infections (investigator-defined) will be disregarded for this search
	Opportunistic infections	Narrow SMQ "Opportunistic infections"
	Tuberculosis infections	BIcMQ "Infections": Narrow sub-search 8.2 "Tuberculosis related terms"
	Serious infections	all serious events in SOC "Infections and infestations"
	Severe infections	all events in SOC "Infections and infestations" of at least severe RCTC grade, by HLGT
Hypersensitivity	Hypersensitivity ALL	Combined search strategy based on the three individual UDAECs described below
	Anaphylactic reaction	Narrow SMQ "Anaphylactic reaction"
	Angioedema	Narrow SMQ "Angioedema"
	Hypersensitivity	Narrow SMQ "Hypersensitivity"
Malignancies	Malignant tumours	Narrow Sub-SMQ "Malignant tumours" Narrow Sub-SMQ "Haematological malignant tumours" Narrow Sub-SMQ "Non-Haematological malignant tumours"
	Malignant skin tumours	Broad Sub-SMQ "Skin malignant tumours"
	Skin melanomas	HLT Skin melanomas (excl. Ocular)
	Non-melanoma skin cancer (NMSC)	Broad Sub-SMQ "Skin malignant tumours" excluding HLT Skin melanomas (excl. Ocular)

Table 7.8.1: 1 Project MedDRA search criteria for User Defined Adverse Event Concepts (cont'd.)

User-defined AE category		
Label		Description
3-point MACE	Malignancies excluding NMSC 3-point MACE	Sub-SMQ "Malignant tumours" excluding NMSC, whereas NMSC is defined above BIcMQ "Major Adverse Cardiovascular Events" with Narrow sub-search 1.1 "3-Point MACE (part 1/2)" Narrow sub-search 1.2 "3-Point MACE (part 2/2)" *
Torsades de Pointes	Torsades de Pointes	Broad sub-SMQ "Torsade de pointes/QT prolongation"

* 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

According to ICH E3 (9), the sponsor has defined AEs which are to be classified as 'other significant'. For the current trial, these will include those non-serious AEs which were reported with 'action taken = Drug Withdrawn' or 'action taken = Dose Reduced'.

The exposure-adjusted incidence rate and frequency of patients with AEs will be summarized by treatment, primary system organ class and preferred term. AEs and serious AEs which were considered by the investigator to be drug related will be summarized separately. Separate tables will also be provided for patients with SAEs, patients with AEs leading to study drug discontinuation, patients with AEs leading to death, patients with AESIs, patients with other significant AEs (derived based upon ICH E3 (9)), UDAEC and serious UDAEC (cf. Table 7.8.1: 1) . AEs will also be summarized by maximum intensity.

For disclosure of AE data on ClinicalTrials.gov and EudraCT register respectively, the additional AE tables will be produced per requirements.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (8). 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 (8). 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 (see Section 6.7) will be calculated.

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.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be based upon normalized values and provided by visit (including follow up), including the last value on treatment, the minimum value on treatment and 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; a shift table will be provided for the number of patients with a specific RCTC grade at baseline and 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 normalized 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 patients' 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 ≥ 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 and/or AP≥ 3xULN plus 2 times the baseline with concomitant or subsequent total bilirubin ≥ 2xULN plus 1.5 times the baseline* 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.

Two graphical analyses of ALT and total bilirubin during the on-treatment period will be performed; the so-called eDISH plot. The first graph will include all patients in the SAF, while the second graph will only include those patients who do not show ALT/AST values with changes from baseline <2 x baseline and bilirubin values with changes from baseline <1.5 x baseline in SAF. For each graph, 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 total bilirubin and 3xULN for ALT, are drawn onto the graph in order to divide the plane into four 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 analyzed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate), body temperature, 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 during the on-treatment period, the minimum value during the on-treatment period, and the maximum value during the on-treatment period (see Table 6.1:1 for definition of the on-treatment period). Graphical displays via box plots will be produced for the change from baseline, over time, for each continuous vital sign endpoint.

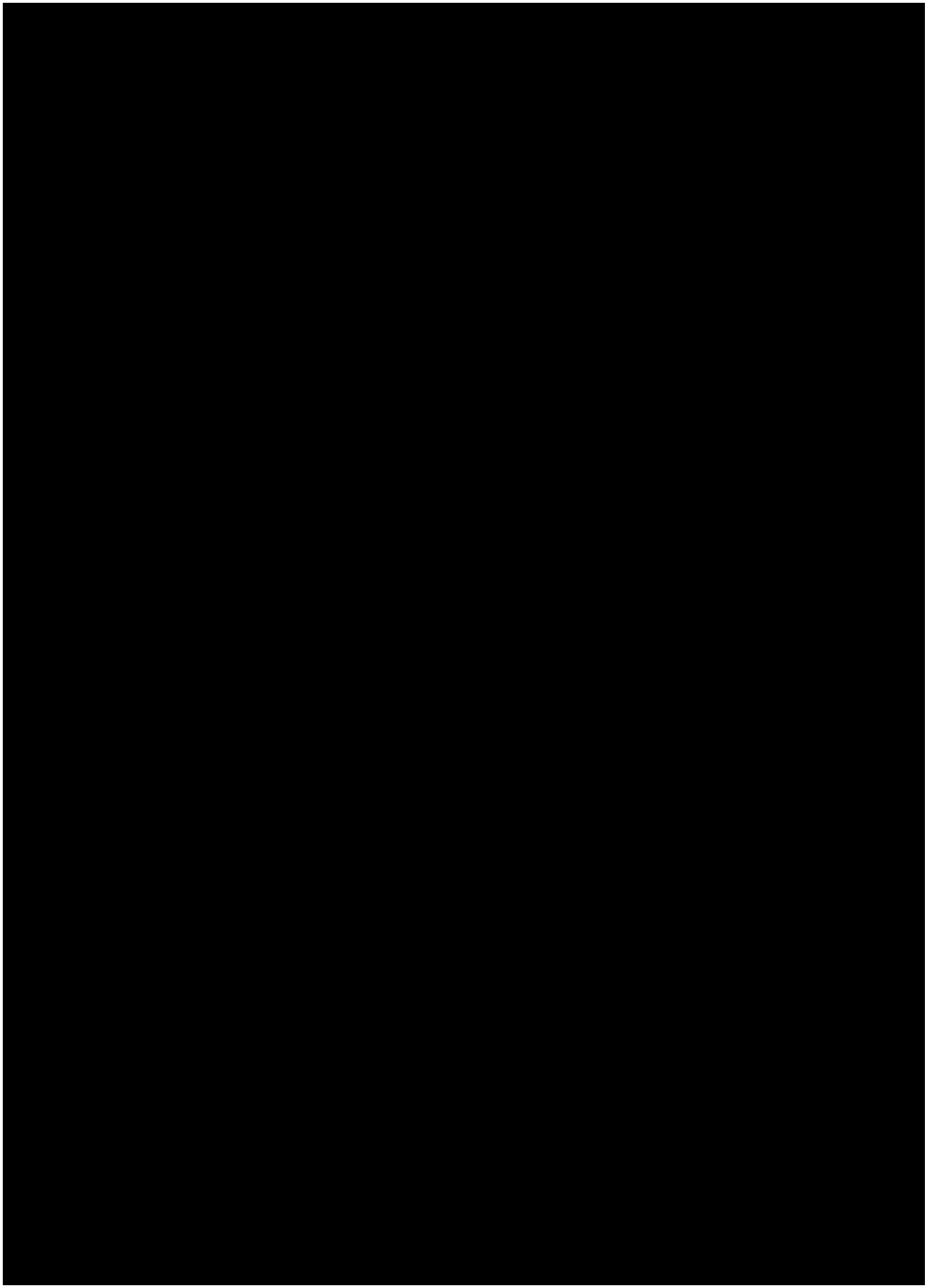
Clinically relevant findings in vital signs data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analyzed as such.

7.8.4 ECG

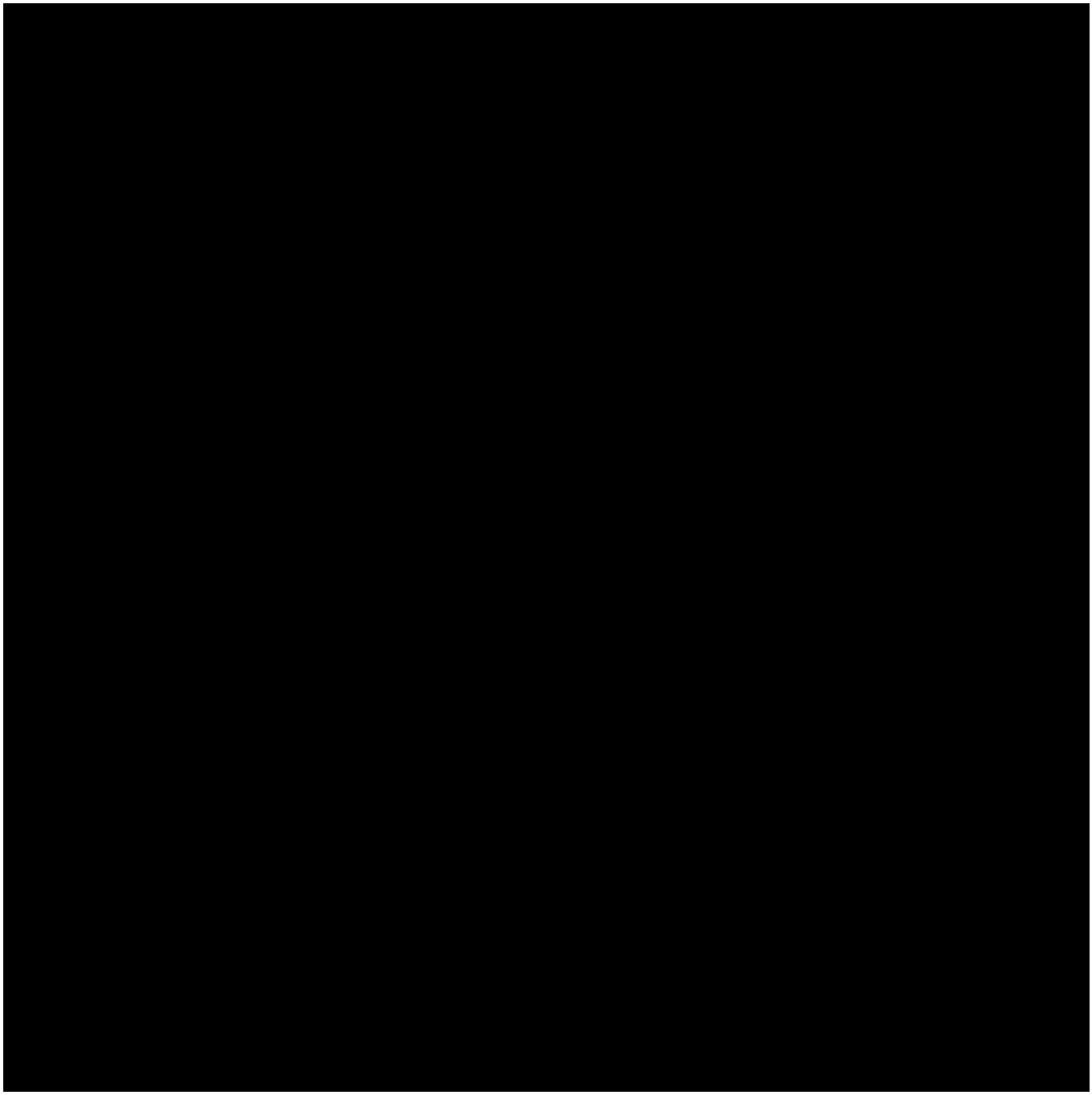
Abnormal findings in 12-lead ECG will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analyzed as such. No separate listing or analysis of ECG data will be prepared.

7.8.5 Local Tolerability

Local Tolerability will be summarized, *by visit*, with the frequency and percentage of patients who experienced any symptom by type and intensity.



[redacted]



7.9 ANALYSIS OF COVID19 IMPACT

There is currently an outbreak of respiratory disease, COVID-19 worldwide which has impacted the conduct of this trial. This public health emergency has raised more difficulties for patients to meet protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing. Site personnel or trial subjects are also under the risk to get infection with COVID-19.

Consequently, there are unavoidable protocol deviations due to COVID-19 illness and/or COVID-19 public and individual health control measures. To assess the impact on patients' safety and drug efficacy in this trial, the following analyses are planned:

Disposition, PD and iPD:
Frequency of the patient with missing visits or early discontinuation due to COVID-19 will be listed. PDs and iPDs related to COVID-19 will be also listed if any.

AE based on the periods of COVID-19 disruption

To assess whether there was any potential change in AE assessment during the COVID-19 disruption, AEs prior the disruption and post the disruption will be reported separately. It will include the following AE tables:

- Overview on TEAE
- TEAE by SOC, preferred term
- SAE by SOC, preferred term
- UDAEC

The start date for the COVID-19 disruption is chosen to be 1st March 2020.

In addition, if there is any case, COVID-19 infection will be reported separately.

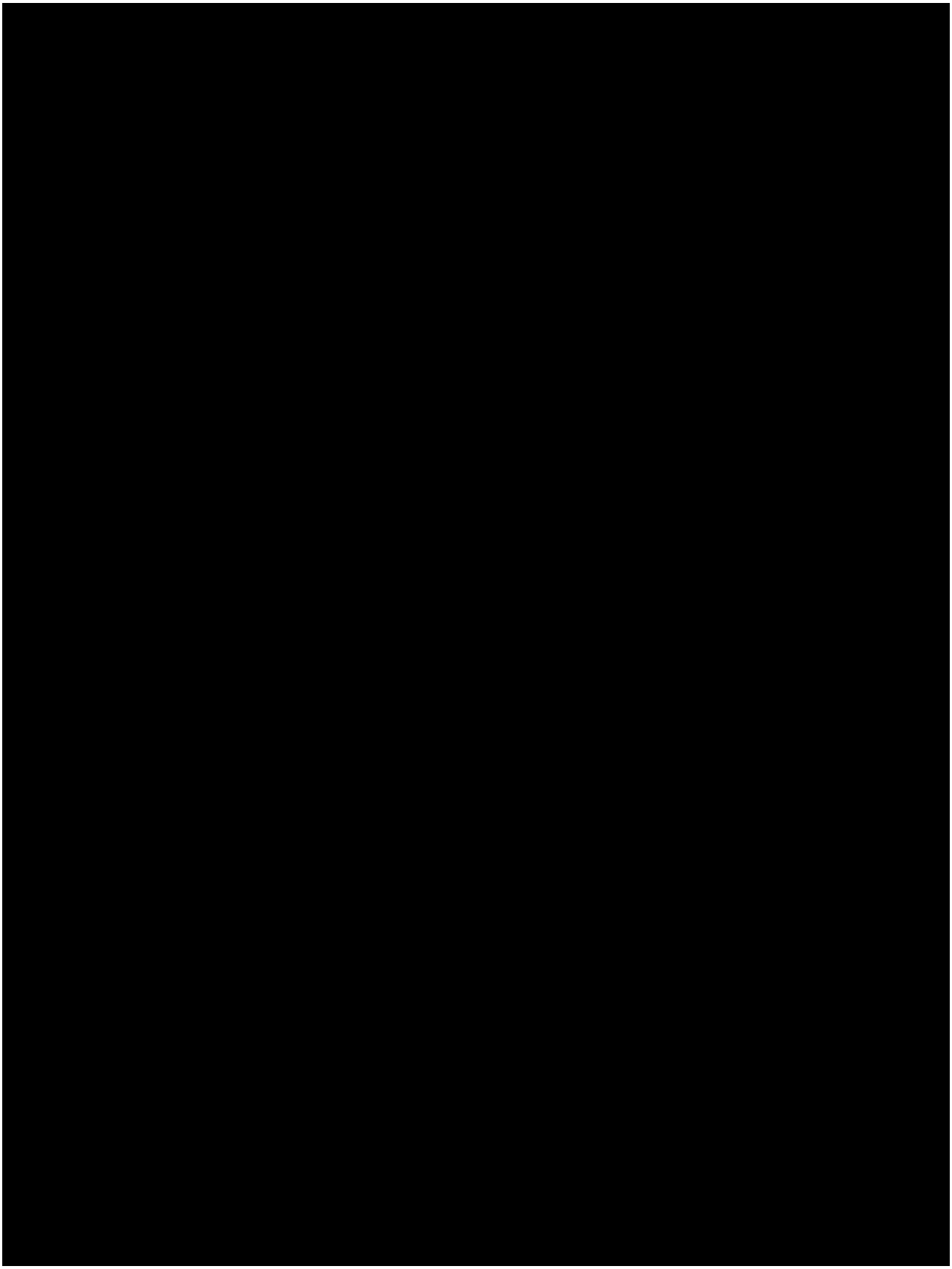
7.10 HANDLING OF DMC ANALYSES

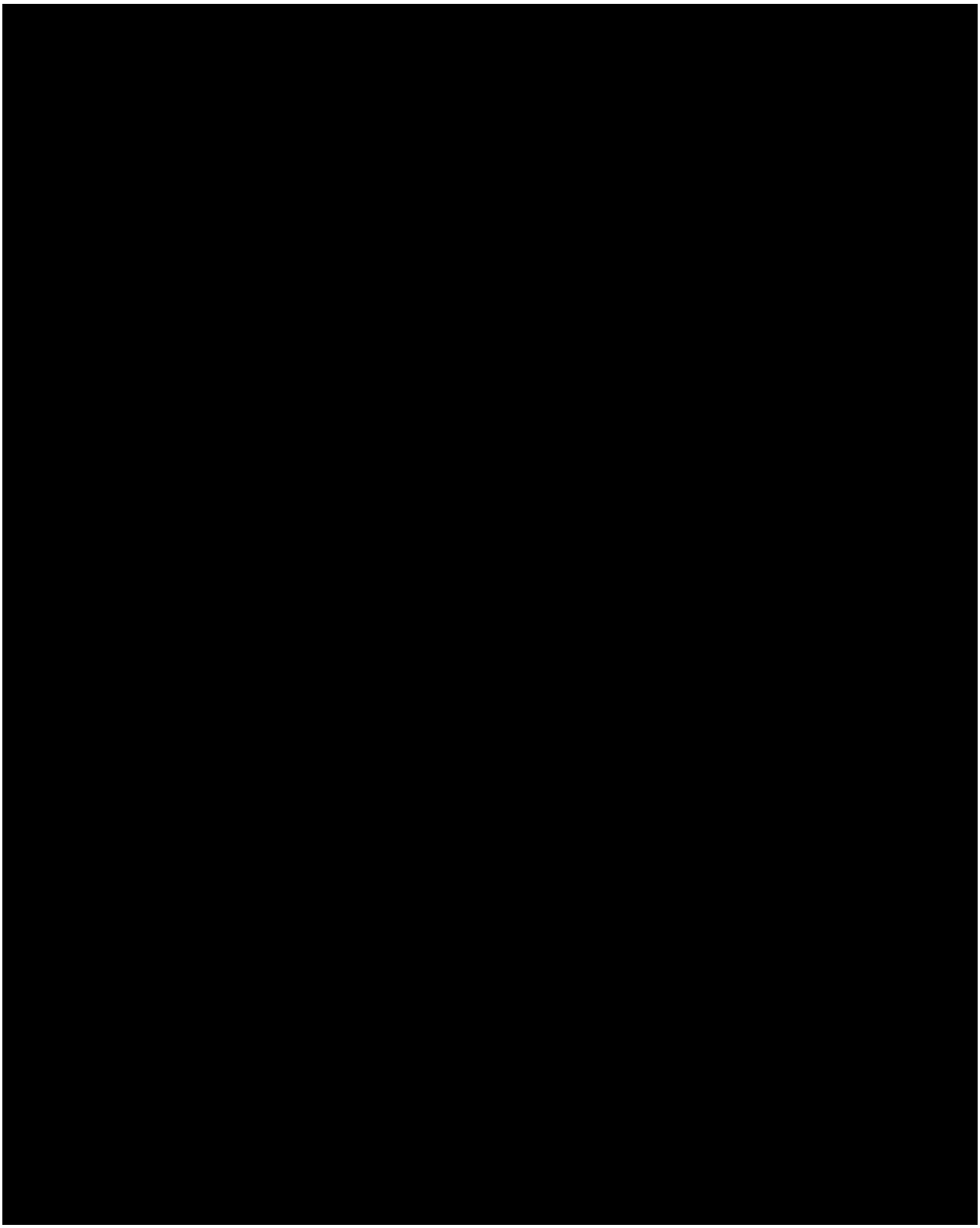
A fully external DMC, independent of the trial and project teams, will be set-up to review all available un-blinded safety data as well as selected efficacy data at regular intervals following first-patient-in. A separate DMC SAP which describes the analyses required for assessment by the DMC will be produced. Further details are provided in a DMC charter.

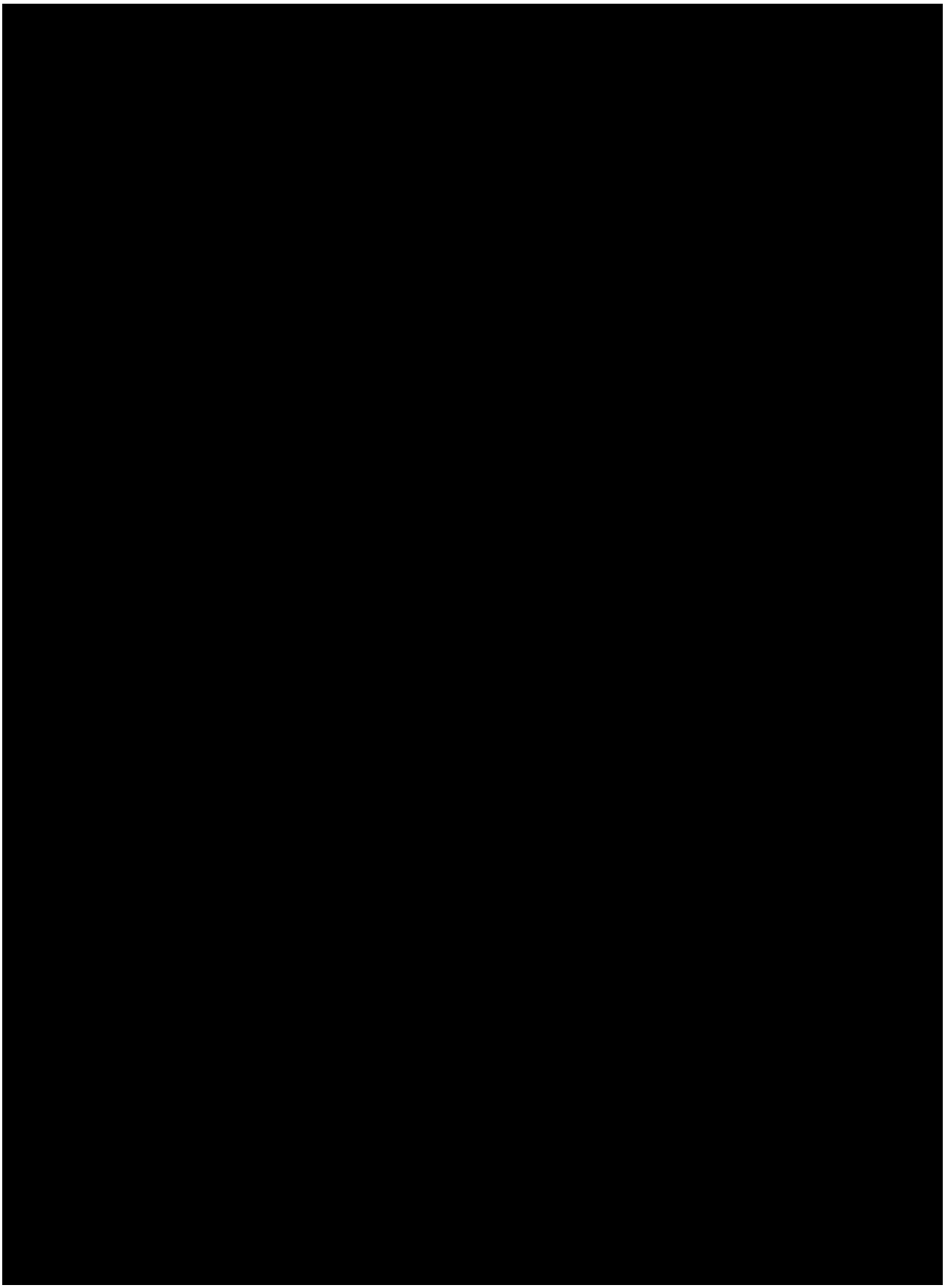
8. REFERENCES

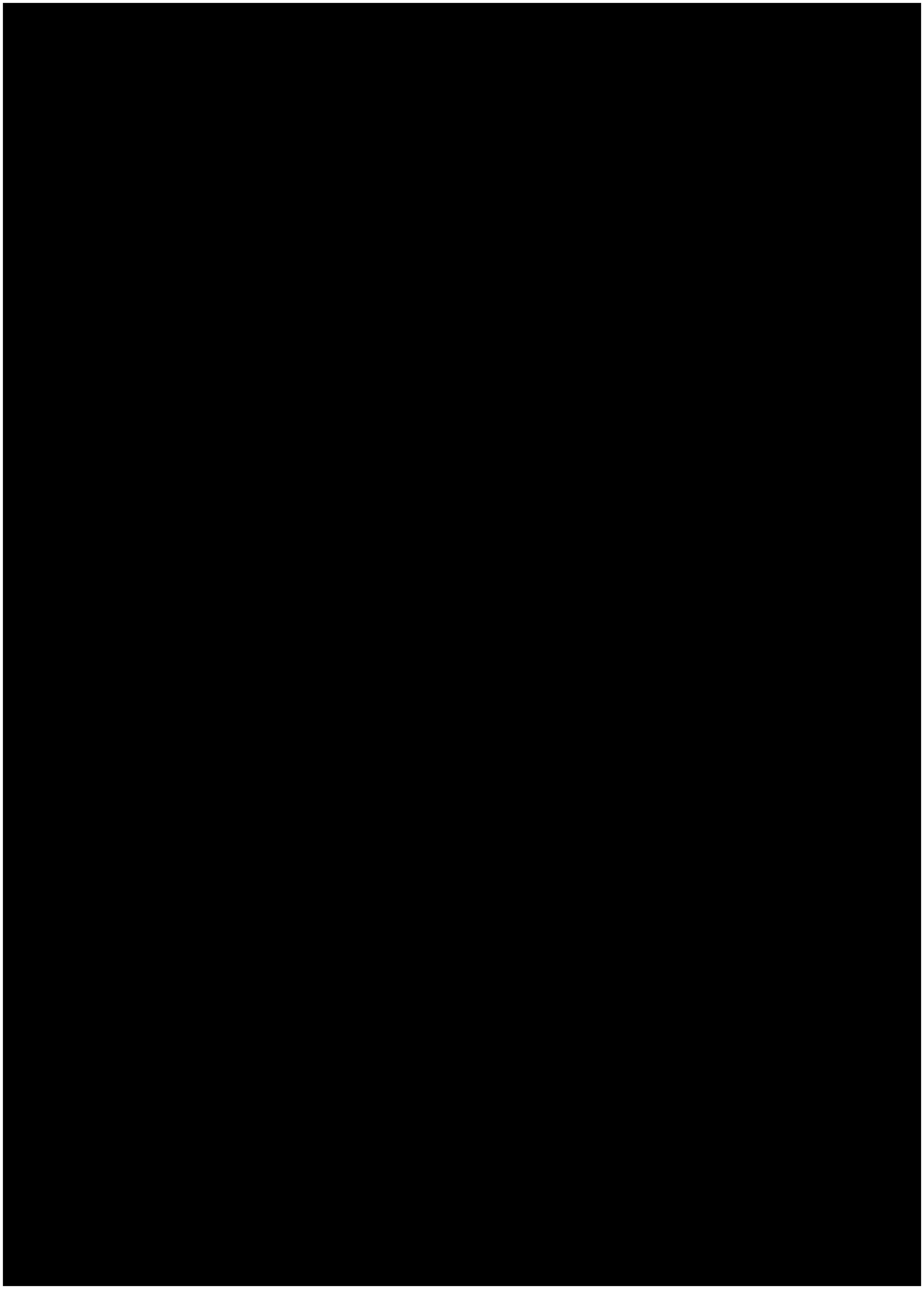
1	*CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Statistical Principles for Clinical Trials, current version
2	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3	*BI-KMED-COPS-TMP-0001:* "Important Protocol Deviation (iPD) log", current version; IDEA for CON
4	*BI-KMED-BDS-HTG-0035*: "Handling of missing and incomplete AE dates", current version; IDEA for CON
5	*001-MCS-36-472:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, Group "Biostatistics & Data Sciences", IDEA for CON
6	*Chan I S F, Zhang Z. "*Test‐based exact confidence intervals for the difference of two binomial proportions"[J]. Biometrics, 1999, 55(4): 1202-1209.
7	*001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON
8	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON
9	*CPMP/ICH/137/95*: "Structure and Content of Clinical Study Reports", ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
10	*BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
11	*R20-2984:* Hodges Jr J L, Lehmann E L. Estimates of location based on rank tests[J]. The Annals of Mathematical Statistics, 1963: 598-611.
12	*001-MCS-40-413_RD-00:* "List of References to SOP Identify and Mange Important Protocol Deviations (iPD)", current version; IDEA for CON
13	*R16-0029:* Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005;32(5):811-9.
14	*R18-1989*: Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S240-52.

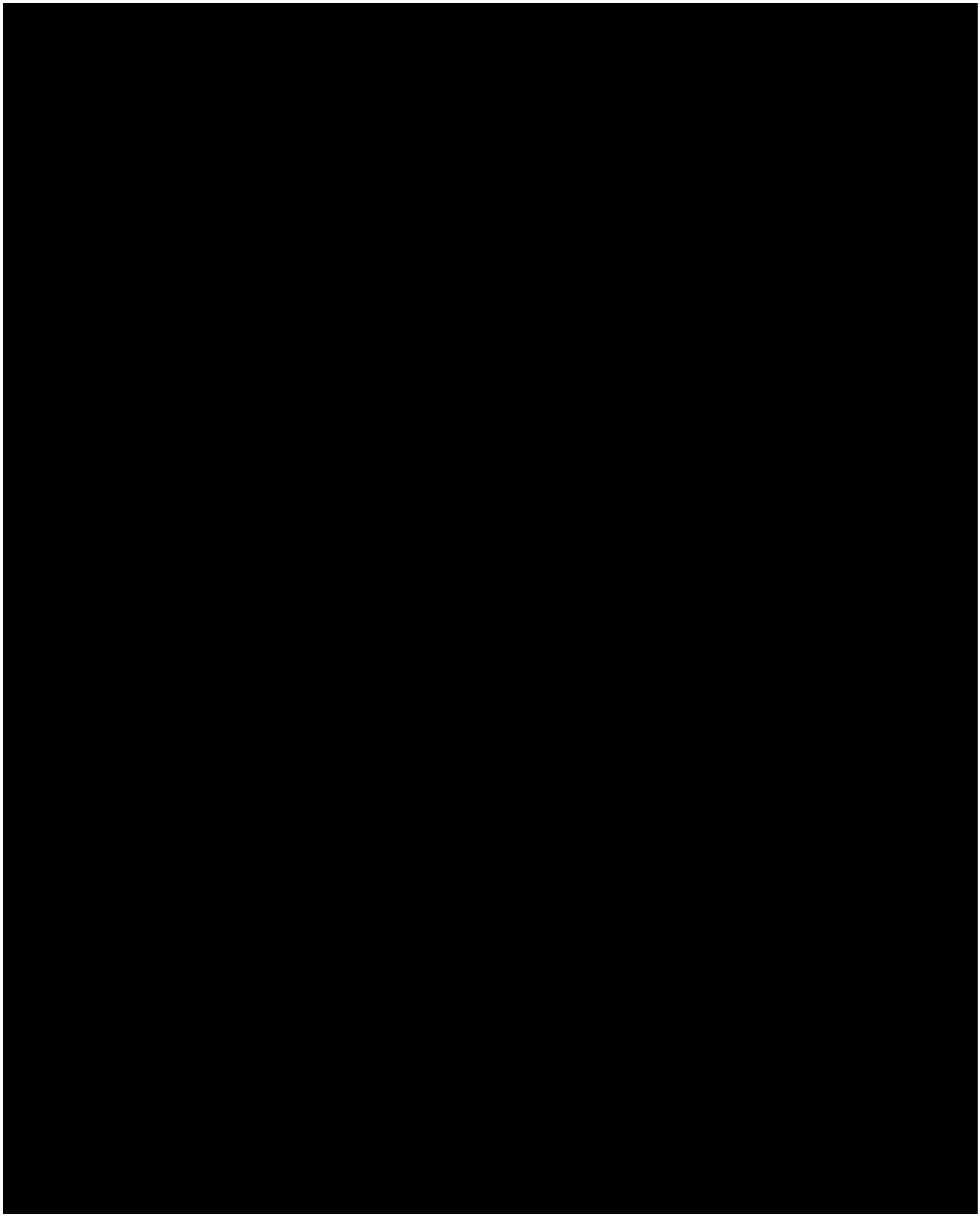
15	*R18-1990:* Rentz AM, Skalicky AM, Burslem K, Becker K, Kaschinski D, Esser D, et al. The content validity of the PSS in patients with plaque psoriasis. J Patient Rep Outcomes. 2017;1(1):4.
16	[redacted]
17	*001-MCG-741:* "Clinical subgroup analyses for local and regional Populations in Asia - Clinical Bridging Study Waiver (BSW) and Descriptive Subgroup Analysis (SGA) Reports", current version; IDEA for CON.

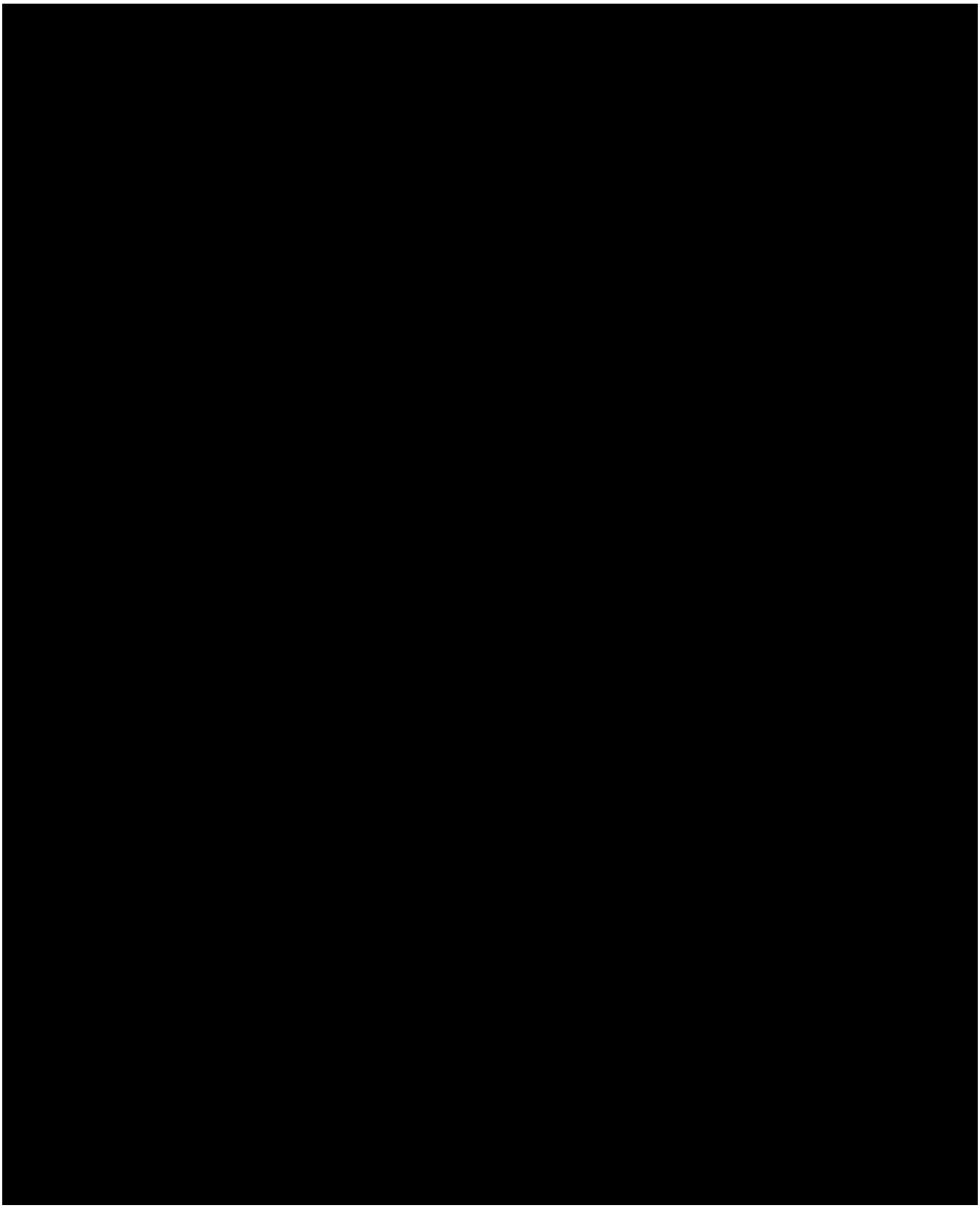


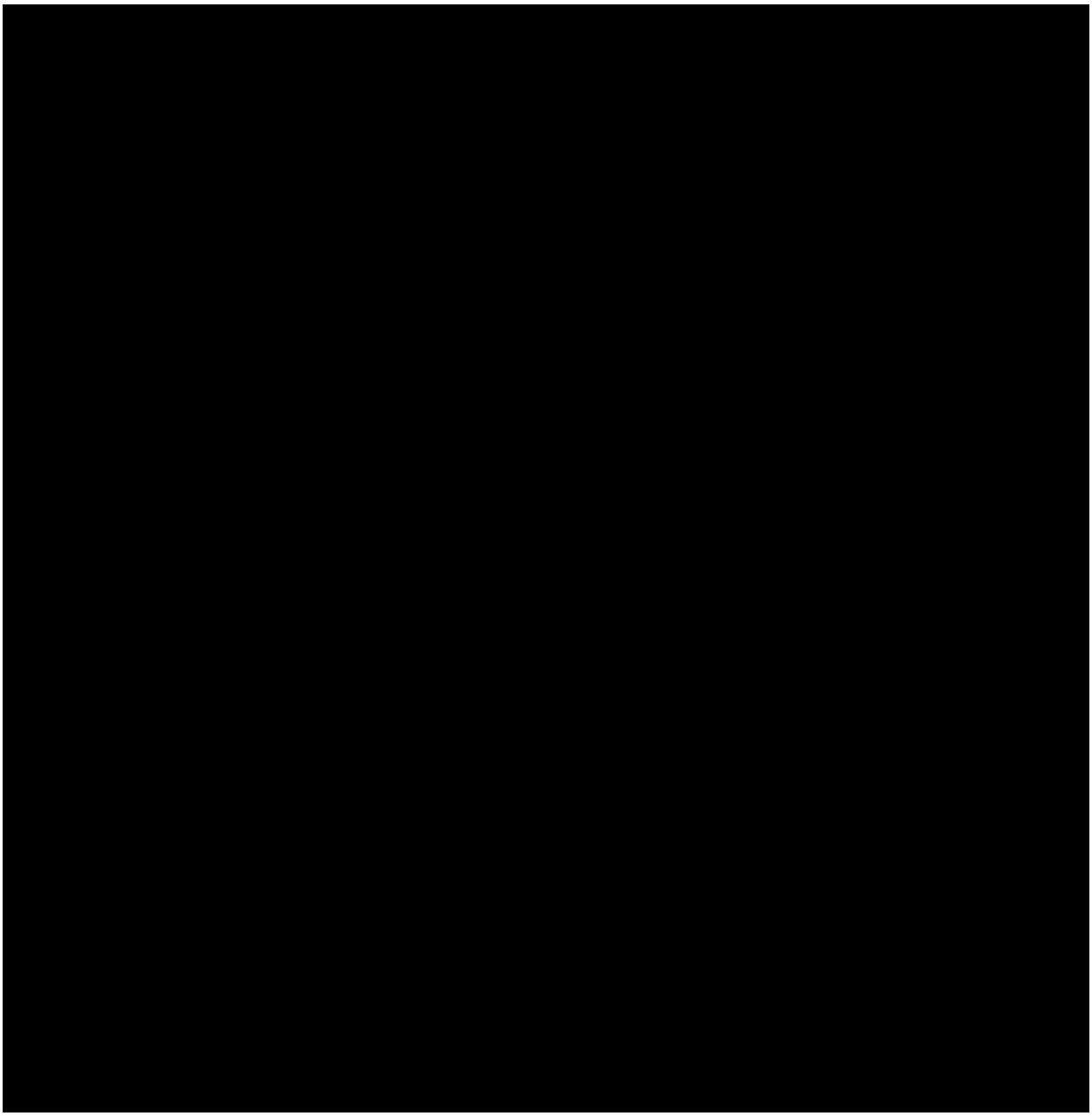












10. HISTORY TABLE

Table 10: 1 History table

Version	Date	Author	Sections changed	Brief description of change
1	**18-JAN-19**	[redacted]	None	This is the final TSAP.
2	**10-NOV-20**		All	Per CTP amendment 2, update primary and key secondary endpoints.
			All	Per CTP amendment 2, add sample size and update testing method.
			All	Per CTP amendment 3, add further endpoints for randomized treatment
			All [redacted]	[redacted]
			[redacted]	
			[redacted]	
			Section 6.1	The first dose of OLE trial was considered to define the analyses phase of this trial.
			Section 6.1 Section 7.8	Further analysis on safety data including REP of any non-randomized Spesolimab are updated.
			Section 6.2	Minor changes on iPD categories.
			[redacted]	
			Section 6.6.2	Remove MI for missing data per CTP amendment 3. Update the ranking rules for Wilcoxon ranking tests for continuous endpoints.
			Section 6.7	Update rules to assign the time windows.
			Section 7	Add the timeline for primary and final analyses per CTP amendment 3.
			Section 7.4	Add sensitivity analysis for primary endpoint per CTP amendment 3
			Section 7.5.2	Add sensitivity analyses for continuous endpoints and refine the wording.
			[redacted]	
			[redacted]	
			Section 7.8.6	Elaborate analysis on Immunogenicity
			Section 7.8.7	Add subgroup analysis of AE
			Section 7.9	Add analysis for the impact of COVID 19
			[redacted]	

Table 10.1 History table (cont'd.)

Version	Date	Author	Sections changed	Brief description of change
3	**22-Dec-2020**	[redacted]	Section 4 [redacted]	[redacted]
			Section 4	If central lab are not available, the eCRF results will be used [redacted]
			Section 6.7 [redacted]	[redacted]
			[redacted]	
			Section 7.8.1	Remove important risk as the UDAEC are not identified risks, and 3-point MACE and Torsades de Pointes are added