TRIAL STATISTICAL ANALYSIS PLAN

c38234149-01

BI Trial No.:	1368-0008
Title:	Mechanism of Action and Clinical Effect of BI 655130 in Patients with fistulizing Crohn's Disease Revised protocol # 04
Investigational Product:	Spesolimab
Responsible trial statisticians:	[redacted] Phone: Fax: [redacted] Phone: Fax:
Date of statistical analysis plan:	10 FEB 2022 SIGNED
Version:	Final 1

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADA	Anti-drug antibodies
ADS	Analysis Dataset
ALQ	Above the upper Limit of Quantification
BI	Boehringer Ingelheim
BLQ	Below the lower Limit of Quantification
BM	Biomarker
CARE	Clinical data analysis and reporting environment
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CPFM	combined perianal fistula remission
CRP	C-Reactive Protein
EC	enterocutaneous
eCRF	Electronic case report form
EDC	Electronic Data Capture
ENTS	Entered set
ES	Enrolled set
FAS	Full Analysis Set
FC	fold change
FDR	False Discovery Rate
HMGB1	High-Mobility-Group-Protein B1
hsCRP	high sensitivity C-Reactive Protein
ICH	International Conference On Harmonisation
IL	Interleukin
iPD	Important Protocol Deviations
ISF	Investigator Site File
LLOQ	Lower Limit Of Quantification
MedDRA	Medical Dictionary For Regulatory Activities
MMP-12	Matrix Metalloproteinase-12
MPO	Myeloperoxidase
nAb	Neutralizing Antibodies

Term	Definition / description
NGAL	Neutrophil Gelatinase-Associated Lipocalin
NRI	no response imputation
OC	observed case
OC-IR	observed cases including rescue
OR	original results
PFM	perianal fistula remission
PFR	perianal fistula response
RAGe	Report appendix generator
RAM	Report Alignment Meeting
RCTC	Rheumatology Common Toxicity Criteria
RS	Randomised Set
RSS	RNA Sequencing Set
SAF	Safety Set
SD	Standard Deviation
SDL	Subject data listing
TOM	Trial Oversight Meeting
UDAEC	User Defined Adverse Event Categories
ULOQ	Upper Limit Of Quantification

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 revised CTP 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 and its amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomisation.

The trial is divided into a Screening Cohort and a Study Cohort. The analyses of both cohorts are described in the TSAP.

Study data as collected in the eCRF will be stored in a trial database within the BRAVE EDC system. All study data including external data will then be uploaded to the CDR data warehouse.

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by [redacted]), 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).

Analyses of gene expression will be performed using R version 3.0.2 or later (R Core Team (2013). R: A language and environment for statistical computing. [redacted]) in conjunction with limma package version 3.18.13 or later ([redacted]: linear models for microarray data, Bioinformatics and Computational Biology Solutions Using R and Bioconductor 397-420, 2005).

This TSAP fully specifies the planned analyses for the primary analysis which is performed once all randomised patients have completed the first 12 weeks of the trial (Week 12 Primary Analysis). It also specifies the planned analyses for the complete trial data (Final Trial Analysis).

In addition, a preliminary PK analysis will be performed before the trial is unblinded for the primary analysis. This analysis will include only descriptive summaries of PK data.

Week 12 Primary Analysis

Once all patients have completed the week 12 (i.e., Visit 6) assessment, a preliminary database lock will be performed. Since the patients will be treated for another 12 weeks, patients and investigators must remain blinded. Details regarding the unblinding process at the time of the primary analysis are described in a logistics plan.

For all patients, data of treatment period 1 will be included in the primary analysis. In addition, data up to end of trial will be included for all patients to the time of the preliminary database lock. The analysis of treatment period 1 is considered the Primary Analysis. Data of treatment period 2 are considered as supportive data.

The week 12 primary analysis will include the following data: disposition, baseline characteristics and demographics, concomitant medications including rescue medications, exposure data, primary and secondary endpoint data, some further efficacy endpoints (CDAI, PDAI, SES-CD, IBDQ, CRP and faecal calprotectin) and adverse events.

Final Trial Analysis

The final trial analysis of all data will be performed once all treated patients have completed the trial (up to Visit 10); at that time point, a final database lock will be done and all trial data will be reported.

It may happen that data of treatment period 1 that are analysed in the Week 12 analysis are subsequently changed due to corrections. Only few minor changes are expected and the results of treatment period 1 for the efficacy analysis up to Week 12 are considered the primary results.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in this TSAP are in accordance with the statistical methods planned in the CTP (based on Global Amendment 3).

Referring to CTP Section 7.3.2 (Secondary endpoint analyses), 95% CIs for the rate difference will be provided. The analysis is incorrectly described in the CTP as rate difference. The secondary endpoints are the proportion of patients with a pre-determined event at Week 12. Therefore, CIs for the risk difference will be provided.

5. ENDPOINTS

All primary and secondary endpoints are only applicable for the Study Cohort.

Descriptions of endpoints refer to the Study Cohort only, if not stated otherwise.

5.1 PRIMARY ENDPOINT

CTP Section 2.1.2: *The primary endpoint is the total number of deregulated genes at week 4 comparing changes in gene expression from baseline between the two treatment groups. Thereby, deregulation of a gene is defined based on the baseline adjusted mean difference to placebo of gene expression fulfilling the following criteria:*

- *FDR adjusted p-value ≤ 0.05*
- *|fold change| ≥ 1.5*
- *genes can be annotated with Ensembl identifiers (version 84 or later)*

Gene expression is analysed based on biopsies (curettage and inner fistula orifice) via RNA sequencing;

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoints

Secondary efficacy endpoints are as defined in Section 2.1.3 of the CTP:

- proportion of patients with perianal fistula response at week 12
- proportion of patients with perianal fistula remission at week 12
- proportion of patient with combined perianal fistula remission at week 12

Perianal fistula response is defined as closure of at least 50% of external openings, no drainage / discharge despite gentle finger compression of fistulas that were draining at baseline and without new emerging fistulas.

Perianal fistula remission is defined as closure of all external openings, no drainage / discharge despite gentle finger compression of fistulas that were draining at baseline and without new emerging fistulas.

Combined perianal fistula remission is defined as closure of all external openings, no drainage / discharge despite gentle finger compression of fistulas that were draining at baseline and without new emerging fistulas, AND absence collections of >2 cm, confirmed by MRI in at least two of three dimensions – blinded and centrally read).

In general, the derivations of perianal fistula response, remission, and combined perianal fistula remission at a given visit are Boolean functions based on the following, where a perianal fistula refers to an external opening:

Let

- v indicate a given analysis visit;
- $o(v)$ indicate the count of closed perianal fistulas that were draining at baseline at analysis visit v;
- $\rho(v)$ indicate the count of open perianal fistulas that were draining at baseline at analysis visit v;
- $\epsilon(v)$ be the number of newly emerged perianal fistulas from the baseline to analysis visit v;

then perianal fistula response (PFR) for a given patient x is

$$PFR(x) = \begin{cases} 0, & if \dfrac{o(v)}{o(v) + \rho(v)} < 0.5 \; or \; \epsilon(v) > 0 \\ 1, & if \dfrac{o(v)}{o(v) + \rho(v)} \geq 0.5 \; and \; \epsilon(v) = 0 \end{cases}$$

, and perianal fistula remission (PFM) for a given patient x is

$$PFM(x) = \begin{cases} 0, & if \; \rho(v) > 0 \; or \; \epsilon(v) > 0 \\ 1, & if \; \dfrac{o(v)}{o(v) + \rho(v)} = 1 \; and \; \epsilon(v) = 0 \end{cases}$$

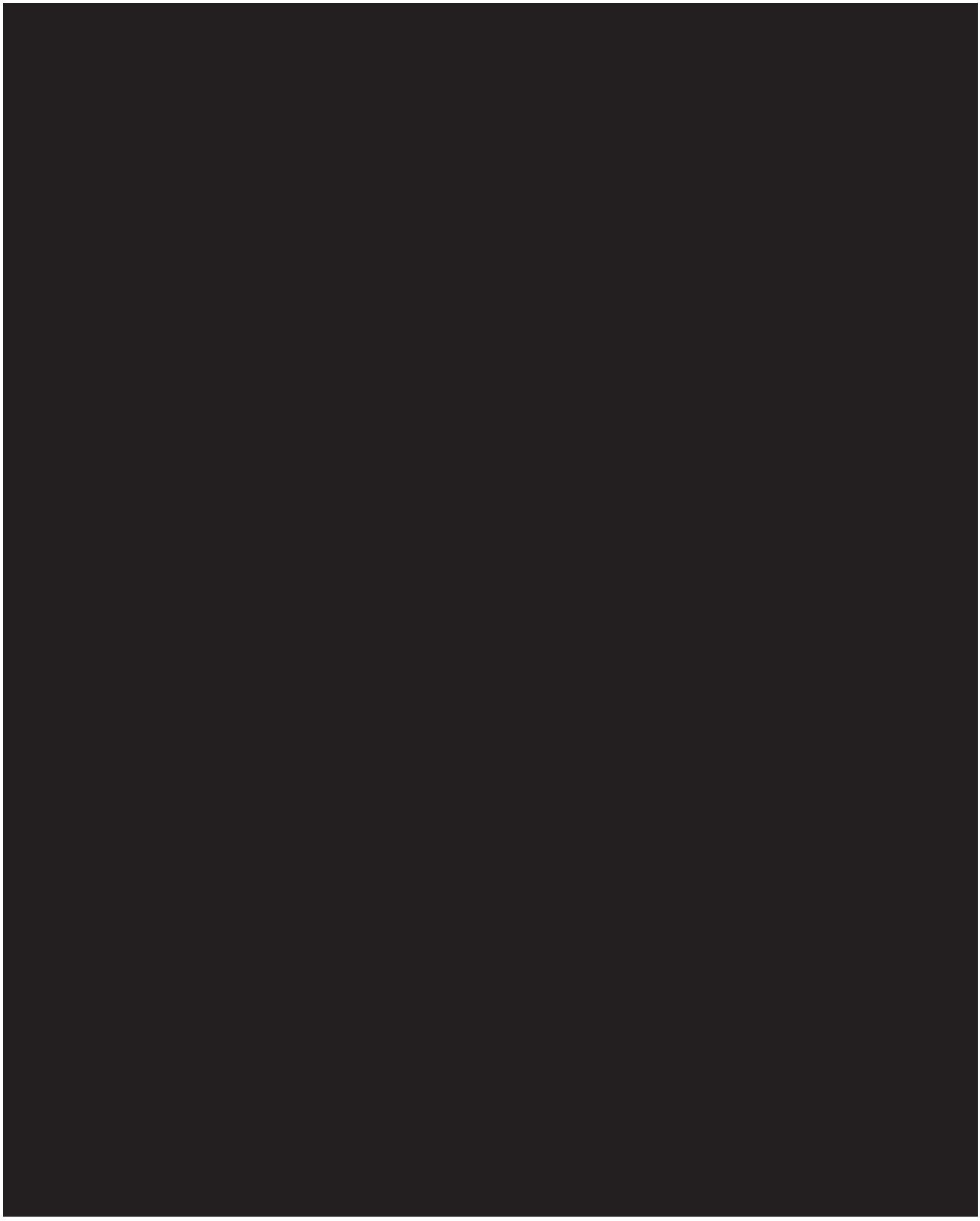
, and combined perianal fistula remission (CPFM) for a given patient x is

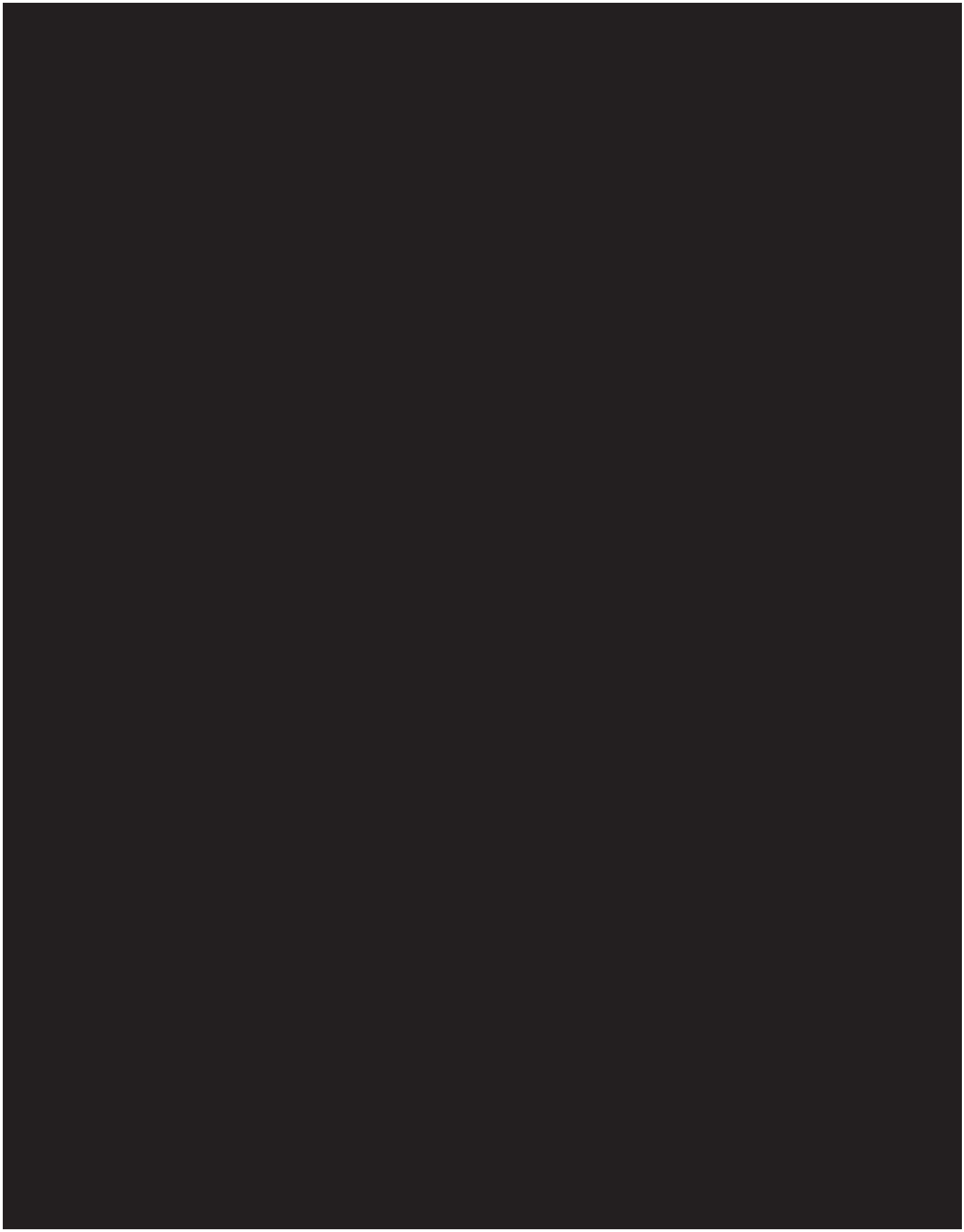
$$CPFM(x) = \begin{cases} 0, & if \; \rho(v) > 0 \; or \; \epsilon(v) > 0 \; or \; collections > 2cm \\ 1, & if \; \dfrac{o(v)}{o(v) + \rho(v)} = 1 \; and \; \epsilon(v) = 0 \; and \\ & \qquad collections \leq 2cm \end{cases}$$

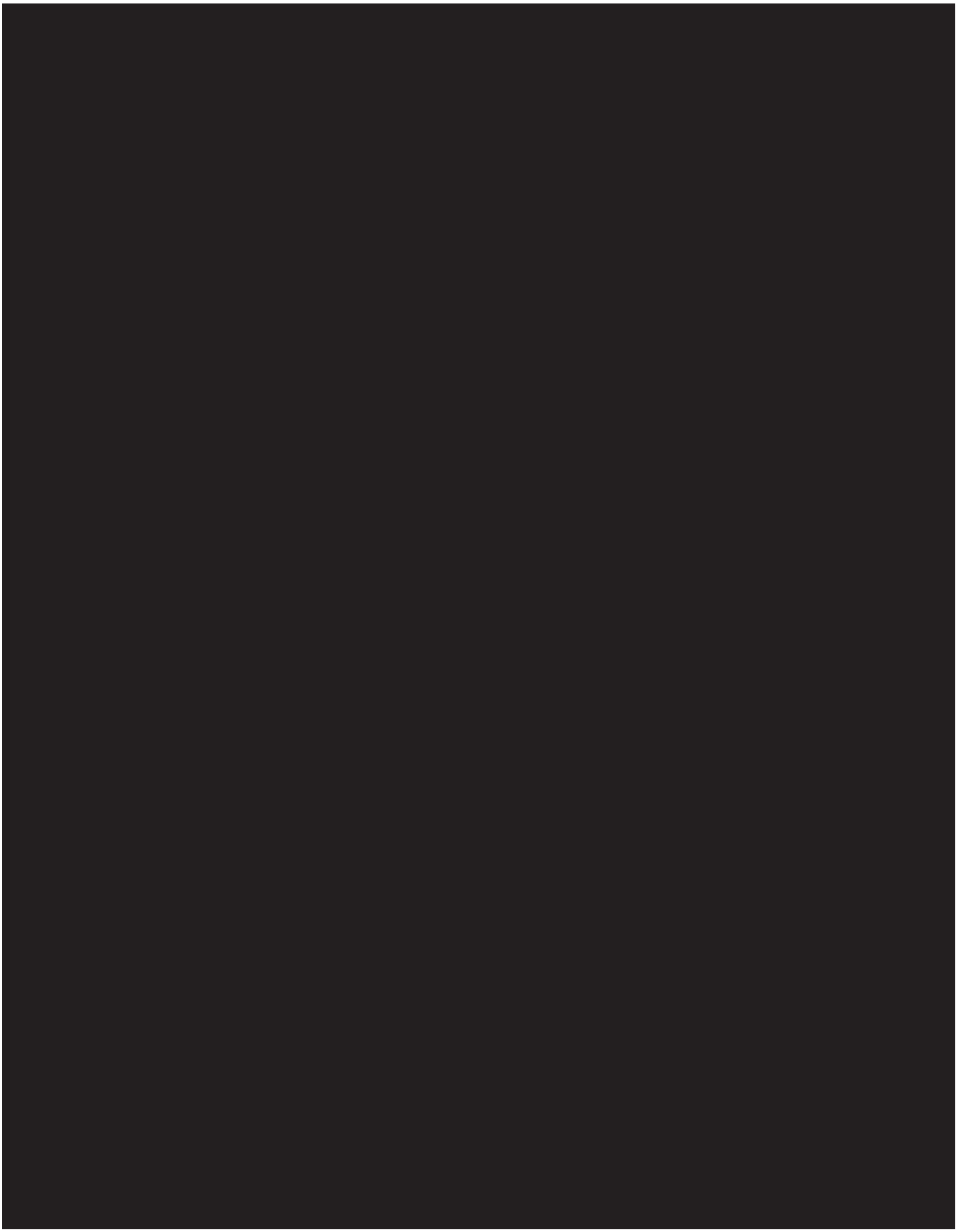
Note that these endpoints are derived based on the information reported on the CRF remission and response and CRF MRI form at the respective post-baseline visit. Data from CRF Fistula Characteristics (Visit 1c) form will not be used as fistula related surgery performed after Visit 1c reduced the number of open and draining fistulas in a few cases. The post-baseline data collected on the CRF remission and response refer to the draining fistulae existing after surgery.

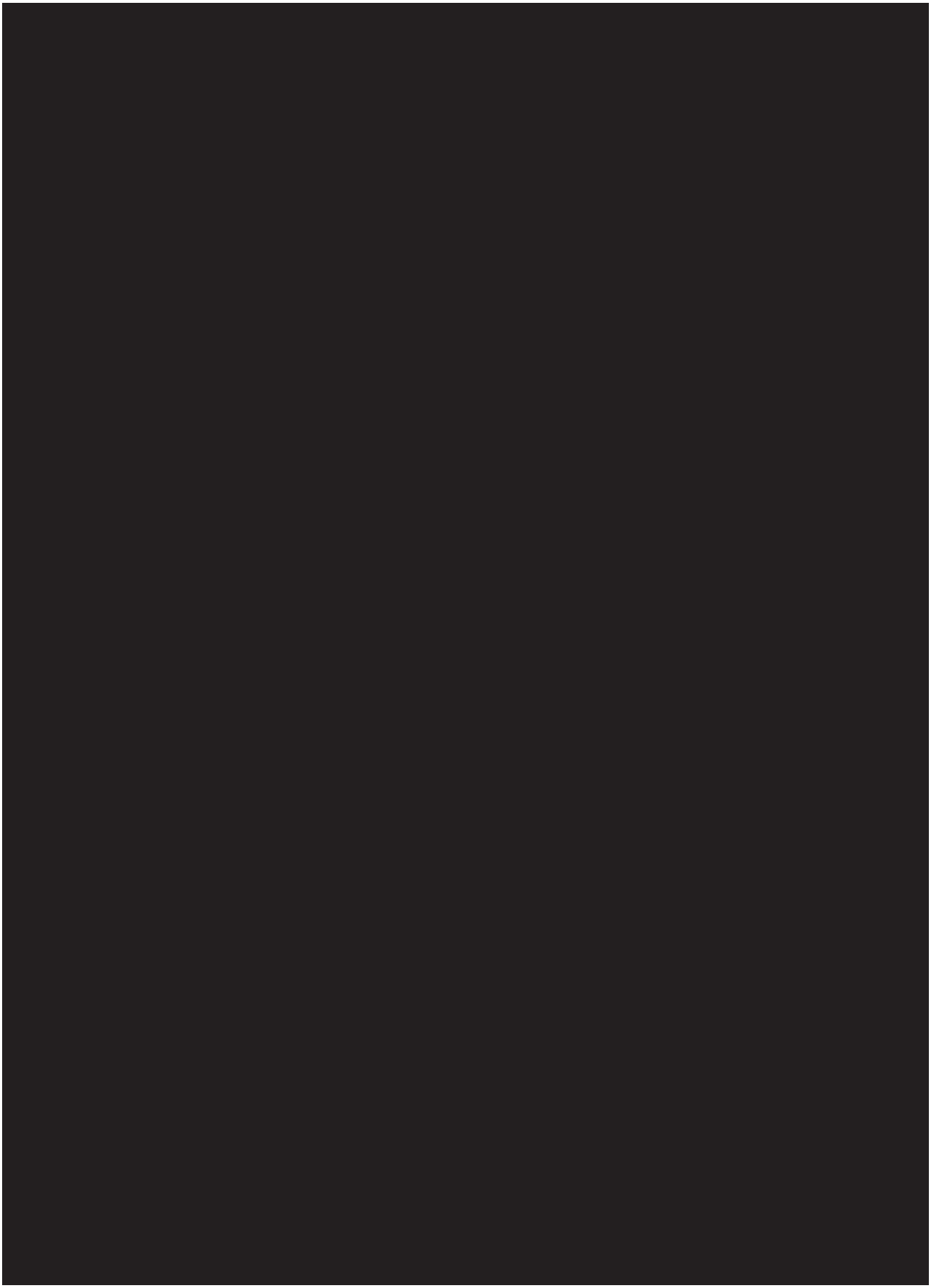
Furthermore, the seton will be removed during fistula preparation visit Week 4, hence neither response nor remission can be observed at that visit. Therefore, in general fistula characteristics data of Week 4 will not be used for any analyses. Week 4 data will only be listed.

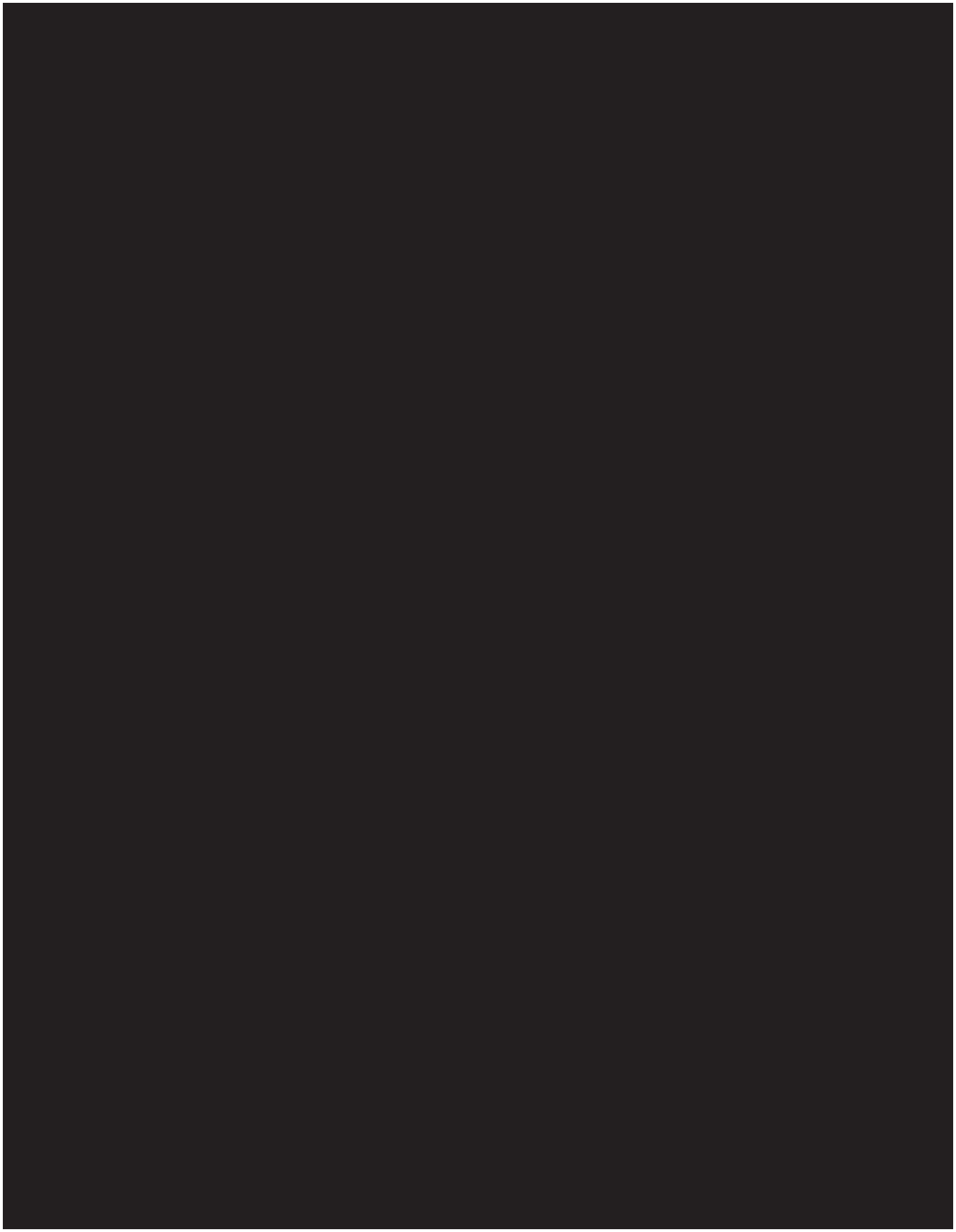
Also note that the number of newly emerged perianal fistulas on the remission and response form since Visit 1c is the cumulative number up to the visit under consideration.

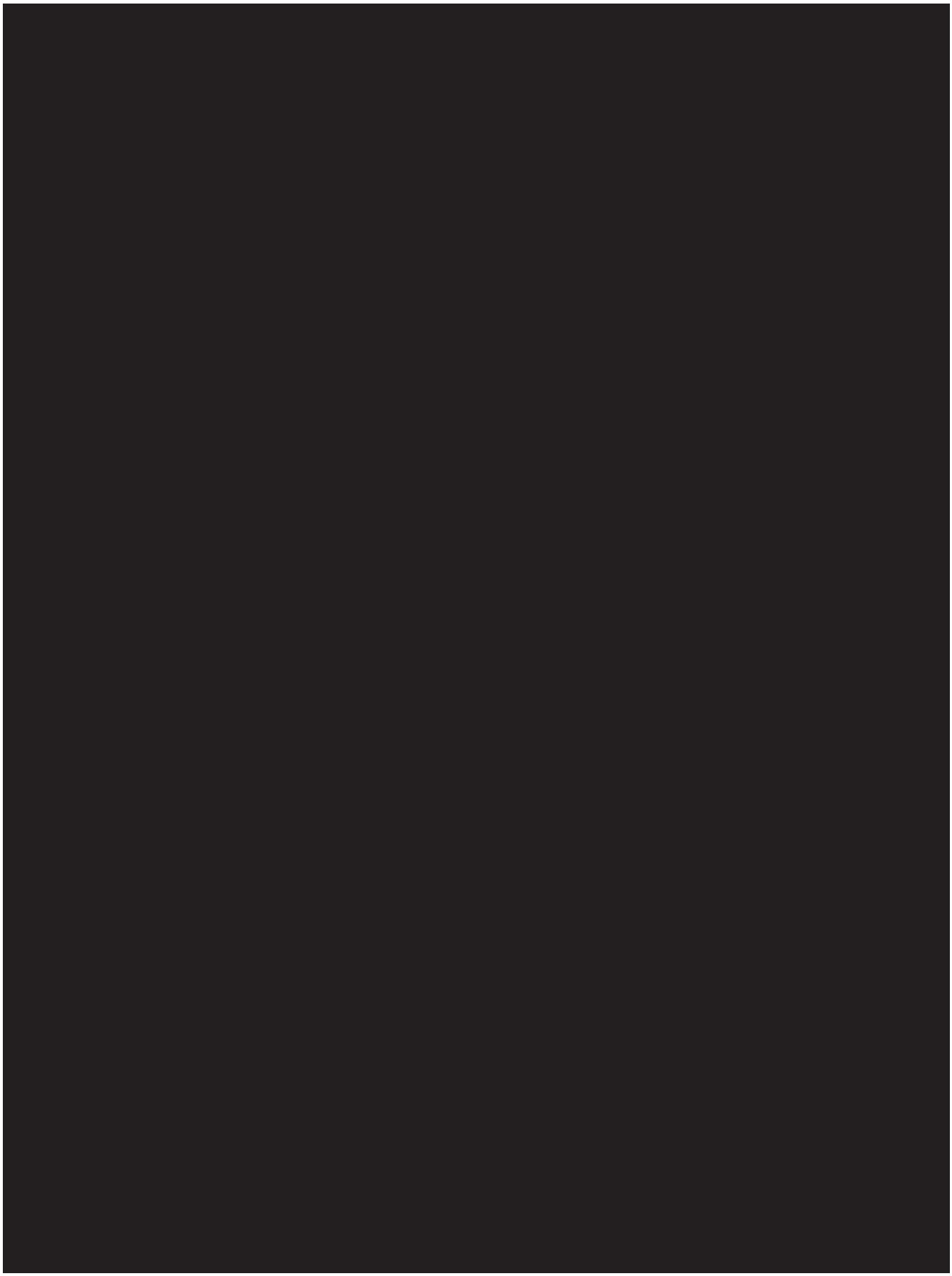


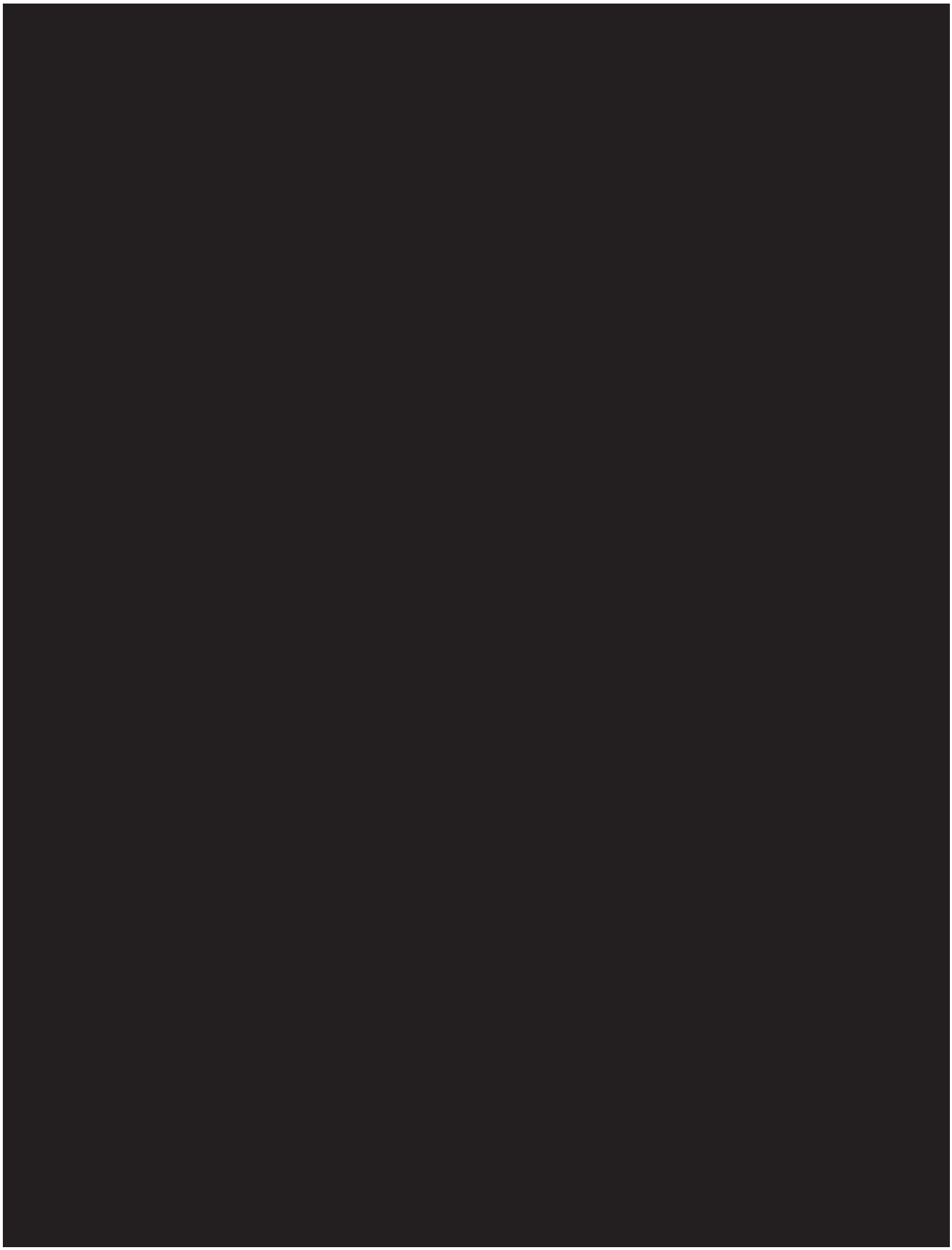












6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignments of dose groups, and selection of doses, cf. Section 4 of the CTP.

The trial is divided into a Screening Cohort and a Study Cohort.

Patients of the Screening Cohort will only be treated with the standard of care for their disease. The patients will not be treated with trial medication and they will undergo only few additional study related procedures.

The Study Cohort is split into two treatment periods. The patients will be randomised to receive spesolimab 1200 mg i.v. or matching Placebo for treatment period 1. Depending on the outcome at Week 12 (achievement of combined perianal fistula remission after treatment period 1), patients will stay on their randomised treatment or switch from Placebo to active treatment. Trial medication will be administered intravenously at Week 0, 4, and 8 during treatment period 1 and at Week 12, 16, and 20 during treatment period 2.

In general, results of Study Cohort will be presented separately from results of the Screening Cohort, i.e., in different tables. Selected summaries (e.g., demographics) will be prepared for the whole trial in addition, i.e., combining data of both cohorts.

Event data of the Study Cohort will be assigned to one of the two treatment periods. Events which occurred after first study drug administration (planned at Visit 2) and before the first study drug administration after the determination of the combined perianal fistula remission outcome (planned at Visit 6) are assigned to treatment period 1. Events occurring after the first study drug administration after the determination of the combined perianal fistula remission outcome (planned at Visit 6) are assigned to treatment period 2.

Three treatment sequences are assigned in this trial (“Pbo-Pbo”, “Pbo-Speso”, and “Speso-Speso”). The analysis phases for the Study Cohort are defined in Table 6.1.1.

Generally, visit based data (e.g., laboratory data and vital signs) will be analysed for treatment period 1 by treatment (”Pbo” and ”Speso”, i.e., the treatment the patient initially received in period 1 independent of the treatment in period 2) and over the whole trial by treatment sequence (“Pbo-Pbo”, “Pbo-Speso”, “Speso-Speso” and “Speso”). The treatment sequence “Pbo-Pbo” includes only patients who stay on Placebo after Visit 6 (Week 12). Similarly, the treatment sequences “Pbo-Speso” and “Speso-Speso” include only patients who received Spesolimab during treatment period 2. “Speso” includes all patients initially randomized (for efficacy analysis) or initially receiving (for safety analysis) Spesolimab in treatment period 1 and includes also patients who were not treated in treatment period 2.

Statistical analysis of event data (e.g., AEs) of the Study Cohort will be done by treatment (“Pbo” and “Speso”) for treatment period 1. Over the whole trial the following treatments and treatment sequences will be presented: “Pbo (Pbo-Pbo)”, “Pbo (Pbo-Speso)”, “Speso (Pbo-Speso)”, “Speso (Speso-Speso)”, “Speso”, “Total Pbo” and “Total Speso”. “Pbo (Pbo-Pbo)”

includes all events occurring during treatment with Placebo in patients who stay on Placebo after Week 12 assessment and “Pbo (Pbo-Speso)” includes all events occurring during treatment with Placebo in patients who switched to Speso at Visit 6 (Week 12). “Speso (Pbo-Speso)” includes all events occurring during treatment with spesolimab in patients initially receiving/randomized to Placebo. Similarly, “Speso (Speso-Speso)” includes all events occurring during treatment with spesolimab in patients who received spesolimab as first treatment and who stay on spesolimab after Week 12 assessment. “Speso” includes all patients initially randomized (for efficacy analysis) or initially receiving (for safety analysis) Spesolimab in treatment period 1 and includes all patients who were not treated during treatment period 2. ”Total Pbo”/“Total Speso” includes all events which occurred during treatment with Placebo/spesolimab regardless of the initial treatment.

Table 6.1: 1 Flow chart of analysis phases for the Study Cohort

Study analysis phase	Period	Sequence	Treatment	Label	Start (included)	End (included)
Screening		-	-	**Screening**	Date of informed consent	Date/time of start of infusion of first randomized study drug (Pbo or Speso) minus 1 minute
On-treatment	**Period 1**	**Pbo-Pbo** or **Pbo-Speso**	**Pbo**	**Pbo**	Date/time of start of infusion of first Pbo (Day 1)	Date/time of start of infusion of first Pbo or Speso on or after Visit 6 minus 1 minute or in case of early termination during period 1 date of end of infusion of last Pbo prior to Visit 6 date + REP (112*24 h) at 11:59 p.m. (up to date of individual patient EoS)
		Speso-Speso	**Speso**	**Speso**	Date/time of start of infusion of first Speso (Day 1)	Date/time of start of infusion of first administration of Speso on or after Visit 6 minus 1 minute or in case of early termination during period 1 date of end of infusion of last Speso prior to Visit 6 date + REP (112*24 h) at 11:59 p m. (up to date of individual patient EoS)
	Period 2	**Pbo-Pbo**	**Pbo**	**Pbo (Pbo-Pbo)**	Date/time of start of infusion of first Pbo on or after Visit 6	Date of end of infusion of last administration of Pbo + REP (112*24 h) at 11:59 p m. (up to date of individual patient EoS)
		Pbo-Speso or **Speso-Speso**	**Speso**	**Speso (Pbo-Speso)** or **Speso (Speso-Speso)**	Date/time of start of infusion of first Speso on or after Visit 6	Date of end of infusion of last administration of Speso + REP (112*24 h) at 11:59 p m. (up to date of individual patient EoS)
Follow-up[1]		-	-	**F/U**	Date of end of infusion of last study drug (Pbo or Speso) + REP (112*24 h) at 12:00 a m.	Latest of: i) Date of EOS visit; ii) last contact date on End of Study page at 11:59 p m.

[1] Follow-up phases might not exist, e.g. if the patient's trial termination date is within 112 days after last administration of spesolimab or placebo.

In CTR Section 15 (but not in Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE tables), the following totals will be provided in addition:

- "**Total Pbo"**, defined as the total over all on-treatment phases involving Placebo (i.e., "Pbo" in Period 1 and "Pbo (Pbo-Pbo)" in Period 2)

- "**Total Speso"**, defined as the total over all on-treatment phases involving Speso (i.e., "Speso" in Period 1 and "Speso (Pbo-Speso)" and "Speso (Speso-Speso)" in Period 2)

CTR Section 15, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE displays will present results for the on-treatment phase only.

In CTR Section 15 AE tables (but not in Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE tables), the following totals will be provided in addition:

- "**Total on-trt"**, defined as the total over all on-treatment phases, including placebo and spesolimab
- "**Overall**" (across treatment), where appropriate.

"Overall" is applicable in disposition, demographics and baseline characteristics, and compliance summaries. "Total Speso" should also be presented in safety tables. Where applicable, output columns should be arranged in the order as given above.

Events will be assigned the study phases and treatment periods based on the event start date.

AEs occurring during the screening or the follow-up phase will be listed only.

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 enrolled in this trial.

Consistency check listings (for identification of deviations of protocol-defined time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the trial oversight meetings, the report planning meetings and the report alignment meeting (TOMs/RPMs/RAM). At these meetings, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important protocol deviation (iPD). For definition of iPDs, and for the process of identification of these, refer to the BI reference document "Identify and Manage Important Protocol Deviations (IPD)" (2).

If any iPDs are identified, they are to be summarised into categories and will be captured in the TOMs minutes and in the decision log. Categories which are considered to be iPDs in this trial are defined in the DV domain (excel Spreadsheet). If the data show other iPDs, the definition in the DV domain will be supplemented accordingly by the time of the TOMs/BRPMs/RAM.

Not all iPDs will lead to exclusion from analysis sets. iPDs leading to exclusion from analysis sets are indicated as such in the DV domain.

All iPDs and all COVID-19 related PDs will be summarised and listed.

6.3 PATIENT SETS ANALYSED

The following analysis sets will be defined for this trial:

- Enrolled set (ES)
  This patient set includes all patients of the Screening Cohort and of the Study Cohort who signed informed consent.
  It will be used for analyses for disclosure of AE data.

- Enrolled set – Screening Cohort (ES-Screen)
  This patient set includes all patients of the Screening Cohort who signed informed consent.
  It will be used for analyses of patient disposition for the Screening Cohort.

- Entered set (ENTS) – Screening Cohort
  The entered set includes all patients of the Screening Cohort who entered the trial ("Will the subject enter the study?" is ticked "Yes" on the Eligibility page of the eCRF).

- Enrolled set– Study Cohort (ES-Study)
  This patient set includes all patients of the Study Cohort who signed informed consent. It will be used for analyses of patient disposition for the Study Cohort.
  [In case a patient is re-screened, the last attempt will be considered.]

- Randomised set (RS) – Study Cohort
  The randomised set includes all randomised patients, whether treated or not.
  Since patients in the Screening Cohort will not be randomised, RS only contains patients of the Study Cohort.
  It is expected that the RS and the FAS (see below) will not differ. Therefore, all analyses will be performed on the FAS.

- Safety set (SAF) – Study Cohort
  The safety set includes all patients who were randomised and treated with any amount of study drug. The treatment assignment will be determined based on the actual treatment the patient received.
  Since patients in the Screening Cohort will not be randomised, SAF only contains patients of the Study Cohort.

- Full analysis set (FAS) – Study Cohort
  The full analysis set includes all patients of the Study Cohort who provided a baseline value and at least one post-baseline value for at least one secondary endpoint or further efficacy endpoint.

- RNA sequencing set (RSS) – Study Cohort
  This patient set includes all patients in the safety set who provide a valid baseline and at least one valid post-baseline observation for at least one gene expression variable of

biopsy. This patient set will be used for analyses related to RNA sequencing. By definition of the safety set, RSS only contains patients of the Study Cohort.

Handling of Treatment Misallocations in Analysis Sets

If a patient is randomized but took incorrect treatment during the study, then the following will apply for safety reporting:

If a patient randomized to Placebo inadvertently is administered a dose of spesolimab during the first 12 weeks of the trial then that patient will be reported in the spesolimab treatment arm (treatment period 1 and 2) for all safety analyses. If a patient is randomized to spesolimab and was only administered placebo during the first 12 weeks of the trial then that patient will be reported in the placebo treatment arm (treatment period 1). If a patient is randomized to spesolimab and was only administered placebo during the entire trial (that is, within both first and last 12 weeks) then that patient will be reported in the placebo treatment arm (treatment period 1 and 2).

Primary endpoint analysis:

If a patient is randomized to placebo/spesolimab but received spesolimab /placebo on Day 1 then then that patient will be reported in the spesolimab/placebo treatment arm, respectively. Note that study drug the patient was not randomized to was administered at Week 4 or later does not affect the primary endpoint analysis since biopsies are scheduled pre-dose at Week 4.

Table 6.3: 1 Patient sets analysed

Class of endpoint	Patient set					
	ES	ENTS	ES-Screen/ ES-Study	SAF	FAS	RSS
Disposition	OR[2]	OR[1]	OR		OR	
Exposure and compliance				OR		
iPD		OR[1]			OR	
Demographic/baseline endpoints		OR[1]			OR	
Primary endpoint and further endpoints related to gene expression data						OR
Secondary efficacy endpoints					NRI OC-IR[S]	
[redacted]					[redacted]	
Safety endpoints				OR OC-IR		
Use of rescue medication					OR	
[redacted]				[redacted]		

[1] The patient set will be used for analysis of the Screening Cohort data.
[2] The patient set will be used for analysis combined data of the Screening Cohort and the Study Cohort.
[S] sensitivity analysis
NRI = no response imputation, OR = original results, OC = observed case, OC-IR = observed cases including rescue
For explanation of the different approaches with regard to missing data see Section 6.6.

[redacted]

6.5 POOLING OF CENTRES

It is planned that up to 8 patients will be entered into the Screening Cohort and approximately 20 patients will be entered into the Study Cohort. The trial will be conducted in multiple centres across several countries and a small number of patients entered per centre can be expected. Given the low number of patients per centre, separate analyses by centre are not meaningful and not desirable. All patients from all centres will be pooled for statistical analysis.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Section 7.5 of the CTP describes the handling of missing data.

Based on the different reasons for patients' data missing, different approaches will be used to assess the impact of missing data on the endpoints of this trial, depending upon the type of the endpoint. The following approaches are applied in this trial:

- The original results (OR) approach implies the presentation of data exactly as observed (not using time windows as described in Section 6.7 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.

- Observed cases (OC) approach will include all collected data, without imputation for any missing data but all values measured after any use of rescue medication will be excluded from the analysis. Note that patients that took rescue treatment are not kept in the denominator for categorical endpoints at subsequent time points.

- Observed cases including rescue (OC-IR) approach is an extension of the OC approach which includes additionally all values which were measured after rescue medication intake.

- The no response imputation (NRI) approach is applied for binary endpoints. Missing values will be imputed described in the following:
  1. If a patient takes a rescue medication (as defined in Section 5.4.3) for the treatment of disease under study or died due to any cause , then all data subsequent to the intake of such rescue will be considered to be missing.
  2. For endpoints which are measured at multiple visits, if there are data at visits both before and after the visit with a missing outcome, then impute as success only if both neighbouring visits also represent a success (independent of whether the preceding and following observations were selected for analysis based on time windows described in Section 6.7), and there is no intervening rescue treatment use.

  For all patients with a missing visit outcome, impute as a failure to achieve a response.

- Imputation technique last observation carried forward (LOCF): The LOCF approach will be used as the imputation strategy to replace missing values either at intermediate visits or due to early withdrawal from the trial. The last available value, excluding baseline, will be carried forward to all subsequent visits within the on-treatment period at which a measurement is missing. Values measured after the day of first rescue medication intake (as defined in Section 5.4.3) will be set to missing and the missing values within the on-treatment period will be imputed by LOCF.

The following sections describe which imputation approach is used for the different endpoints.

6.6.1 Withdrawals

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

6.6.2 Efficacy endpoints

CTP Section 7.5: *No imputations for the primary endpoint […] are planned.*

Further binary efficacy endpoints which are measured at multiple visits will be analysed using NRI imputation strategy.

[redacted]

6.6.3 Safety endpoints

CTP Section 7.5: *With respect to safety evaluations, it is not planned to impute missing values.*

For safety data that are displayed by time point (or visit) of measurement, the OC-IR approach as described above will be applied (cf. Section 6.6).

The only exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates" (3)).

Partial start and stop dates for concomitant medications and rescue, as well as historical medication for Crohn's Disease 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 last contact 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 last contact date, if it is earlier than the 31st of December of the year).
- If the day of the start date is missing the start date is set to first day of the month (except for rescue medication, where the first dosing day of the treatment period will be used if first dosing of the treatment period happened in the same month).
- If the day and month of the start date are missing then the start date is set to 1st January of the year (except for rescue 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.

[redacted]

6.6.6 RNA sequencing data

The data will be presented using the OR analysis strategy.

[redacted]

6.6.8 Time since first diagnosis

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

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

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For the Screening Cohort, the study day will be defined relative to the day of Visit 2, which is defined as Day 1. The start date of Visit 2 will be used in case the Visit 2 procedures are split over several days. For the Study Cohort, study day will be defined relative to the day of first infusion of trial treatment (Day 1).

The following descriptions refer to the analysis of the Study Cohort.

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

Adverse events reported without time on the day of first drug administration in treatment period 1 are considered as on-treatment AEs in treatment period 1. AEs reported without time on the day of first drug administration in treatment period 2 are considered as on-treatment AEs in treatment period 2. In addition, treatment-emergent adverse events which are reported with a date only (and no time) and which occur on the day preceding the first administration of trial treatment in the subsequent extension trial will be considered treatment-emergent AE in this parent trial.

Baseline, unless otherwise specified, is defined as the last measurement collected prior to the start of administration of the trial treatment. For the analysis of the gene expression values (primary endpoint), baseline is the measurement at Visit 1c.

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 (Table 6.7: 1).

Analysis of AE data, concomitant medication or non-drug therapies, as well as use of rescue medication will not be based on visits. Therefore, no assignment to time windows will be necessary. Frequency tables for these data will be using on-treatment data only.

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

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

Visit			Time window (days)		
name	Visit label	Planned day	Window	Start (inclusive)	End (inclusive)
V1a	Screening	-35 to -22	n/a		
V1b	Screening	-35 to -21	n/a		
V1c	Screening	-21	n/a		
V2	Baseline	1	n/a	-35 [A]	1 [A]
Planned on-treatment visits [B]					
V3	Week 2	15	-13/+4	2	19
V4	Week 4	29	-9/+14	20	43
V5	Week 8	57	-13/+14	44	71
V6	Week 12	85	-13/V6	72	Date of Visit 6
V7	Week 16	113	-13/+14	100	127
V8	Week 20	141	-13/+14	128	155
V9	Week 24/EoT	169	-13/+14	156	186
End of study[C]					
V10	Week 36/EoS	253		187[D]	Day of last value

Days are counted relative to the day of first 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 infusion of trial treatment) via assessment on date and time (i.e. safety laboratory) will not be assigned to Day 1. Such data will be listed only.
[B] Only 'on-treatment' data (i.e. measured within the REP following intake of last dose) are included.
[C] All data, irrespective of whether 'on-treatment' or 'off-treatment', are included.
[D] Data reported on Day 232 or later will be used for by visit analysis. Other data mapped before Day 232 will be listed only.

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

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 later value will be selected.

Assignment of efficacy observations to visits based on time windows will be based on the non-imputed (observed) data after setting values after rescue medication intake to missing (if applicable, i.e. for the "LOCF" and "NRI" approaches and the "OC" approach defined in Section 6.6). Visits which were not assigned a value based on time windows will thereafter

be imputed for the NRI approaches defined in Section 6.6. Imputation of efficacy endpoints (binary as well as continuous) will be performed based on all available observations, irrespective of whether the observation was selected in any time window.

For derivation of 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, all values during the on-treatment period (including unscheduled and repeated measurements) will be considered; these will be derived for analysis of laboratory and vital signs data. For identification of potentially clinically significant abnormal laboratory values, all values (including unscheduled and repeated measurements) will be considered.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI standards "Standards for Reporting of Clinical Trials and Project Summaries" (6).

The individual values of all patients will be listed separately for the Screening Cohort and the Study Cohort. Listings will generally be sorted by country, centre number, patient number and visit (if visit is applicable in the respective listing). In the listings the visits will be labeled, i.e., for Visit 6 the label Week 12 will be presented. AE listings will be sorted by assigned treatment (see Section 7.8.1 for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

If not stated otherwise, data will be analysed as follows. Summaries of data of the Screening Cohort will be summarized overall patients. For the Study Cohort, demographics data and baseline characteristics will be summarised by treatment arm ("Placebo" and "Speso"). Summaries of data during treatment period 1 will be presented by treatment arm. Summaries over the whole treatment period will be presented by treatment sequence ("Pbo-Pbo", "Pbo-Speso", "Speso-Speso" and "Speso") for visit-based data and by treatment ("Pbo (Pbo-Pbo)", "Pbo (Pbo-Speso)", "Speso (Pbo-Speso)", "Speso (Speso-Speso)", "Speso", "Total Pbo" and "Total Speso") for event-based data. Further details are described in Section 6.1.

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 standards "Standards for Reporting of Clinical Trials and Project Summaries" (6).

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.

For the Screening Cohort, disposition of the patient population participating in the trial will be summarised by the presentation of the frequency of patients enrolled, entered, who completed the trial and who were prematurely discontinued from trial, by reason.

For the Study Cohort, disposition of the patient population participating in the trial will be summarised by the presentation of the frequency of patients enrolled, enrolled but not randomised, randomised, randomised but not treated, treated, who completed trial medication overall/ in period 1/ in period 2, who were prematurely discontinued from trial medication overall/ in period 1/ in period 2, by reason, who completed participation in the trial overall/ in period 1/ in period 2, who were prematurely discontinued from trial overall/ in period 1/ in period 2, by reason, and who entered the extension trial 1368-0007. The summary will be presented by randomised treatment. Further disposition information may be summarised by country.

In addition, number and proportion of patients assigned to spesolimab or placebo, with at least one intake of study drug in period 2 will be presented by outcome (achievement of combined perianal fistula remission after treatment period 1) and by randomised treatment.

The frequency of patients with iPDs, also summarised by whether or not the iPD led to exclusion from the any analysis set, will be presented. An iPD might lead to an exclusion from all analyses sets or from one or more analysis sets used for the efficacy analysis (i.e., RSS and FAS). The analysis will be based on the ENTS for the Screening Cohort and based on the FAS for the Study Cohort. The frequency of patients in each of the different analysis sets will also be presented. The analysis will be performed for both cohorts.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

For the Study Cohort, demographic data and baseline characteristics will be summarised by treatment arm based on the FAS and additionally by treatment sequence. Fistula characteristics will be summarized for Visit 1a and Visit 1c separately. Number of draining fistula and number of non-draining fistula where applicable will be summarized descriptively and with categories (0,1,2,3,>3).

Demographic data will be summarised overall based on the ENTS for the Screening Cohort.

For the continuous variables described above, 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 to < 75 years ≥ 75 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 DISEASES AND MEDICATION

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.

Only descriptive statistics are planned for this section of the CTR. Analyses of concomitant diseases and medications will be based on the FAS for the Study Cohort and based on the ENTS for the Screening Cohort.

Baseline conditions and diagnosis will be summarised with frequency and percentage of patients by SOC and preferred name.

The frequency and percentage of patients with historical medication for Crohn's Disease will be displayed by defined categories (cf. Section 5.4.3) and preferred name.

A medication/no-drug therapy will be considered concomitant to a treatment, if it

- is ongoing at the time of first administration of the respective treatment in the treatment period or
- starts within the analysis phase of the respective treatment in the treatment period (cf. Section 6.1 for a definition of treatments and 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 any time prior to the start of first trial treatment.

Concomitant medication use (excluding rescue medication, historical medication for Crohn's Disease, and background medication for Crohn's Disease) will be summarised with frequency and percentage of patients by ATC3 class and preferred name. For the Study Cohort, summaries will be presented for

- prior medication taken any time prior to Day 1 (the day of start of trial treatment)
- concomitant medication taken any time during treatment period 1 (cf. Section 6.1)
- concomitant medication taken any time during treatment period 2 (cf. Section 6.1).

Background medication (eCRF) for Crohn's Disease will be analysed in the same way and presented separately. Concomitant medication and background medication in the Screening Cohort will be summarised over the whole study period.

Furthermore, the use of rescue therapy including rescue medication (eCRF) and rescue non-drug surgical therapy (cf. Section 5.4.3) will be summarised with frequency and percentage of patients together in one table by category. Summaries will be presented for rescue therapies during treatment period 1 and during treatment period 2 (similar as for concomitant medication)..

Concomitant use of non-drug therapies will be summarised with frequency and percentage of patients by SOC and preferred name. Summaries will be presented for prior non-drug therapies, concomitant non-drug therapies during treatment period 1 and during treatment period 2 (similar as for concomitant medication) for the Study Cohort. For the Screening Cohort, the summaries will be presented over the whole study duration.

7.3 TREATMENT COMPLIANCE

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

Treatment compliance (as described in Section 5.4.2) will be summarised by visit and overall via dose intensity based on the safety set using descriptive statistics (N, mean, SD, minimum, median, maximum).

For the patients who discontinued the study treatment prematurely, only the scheduled visits before premature discontinuation will be used for the calculation of overall compliance.

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

- "< 80% of planned", and
- "80% to 100% of planned"

The number of patients who received a dose will also be tabulated per visit.

7.4 PRIMARY ENDPOINTS

The analysis of the gene expression values (inner orifice/ curettage) will be done by "actual treatment" and based on the RSS. The observed results approach will be applied (i.e., no visit windowing and no imputation of missing data will be performed).

All analyses will be performed using the raw read counts for gene expression. This gene expression analysis is conducted separately for biopsy location based on inner orifice and based on curettage.

Log_2 fold changes (FC) and associated FDR adjusted p-values are calculated as described in CTP Section 7.3.1.

Primary analysis

The number of deregulated genes at Week 4 will be derived as defined in Section 7.3.1 of the CTP. The results will be presented in a frequency table by treatment separately for biopsy location (inner orifice and curettage). Percentages are calculated excluding patients who did not have a biopsy at that time point.

Graphical displays such as volcano plots are generated for visual assessments of the changes in gene regulations.

Deregulated genes will be presented in a separate listing.

[redacted]

[redacted]

7.5 SECONDARY ENDPOINTS

Secondary endpoints are defined for the Study Cohort only.

7.5.1 Key secondary endpoint

Not applicable.

7.5.2 Secondary endpoints

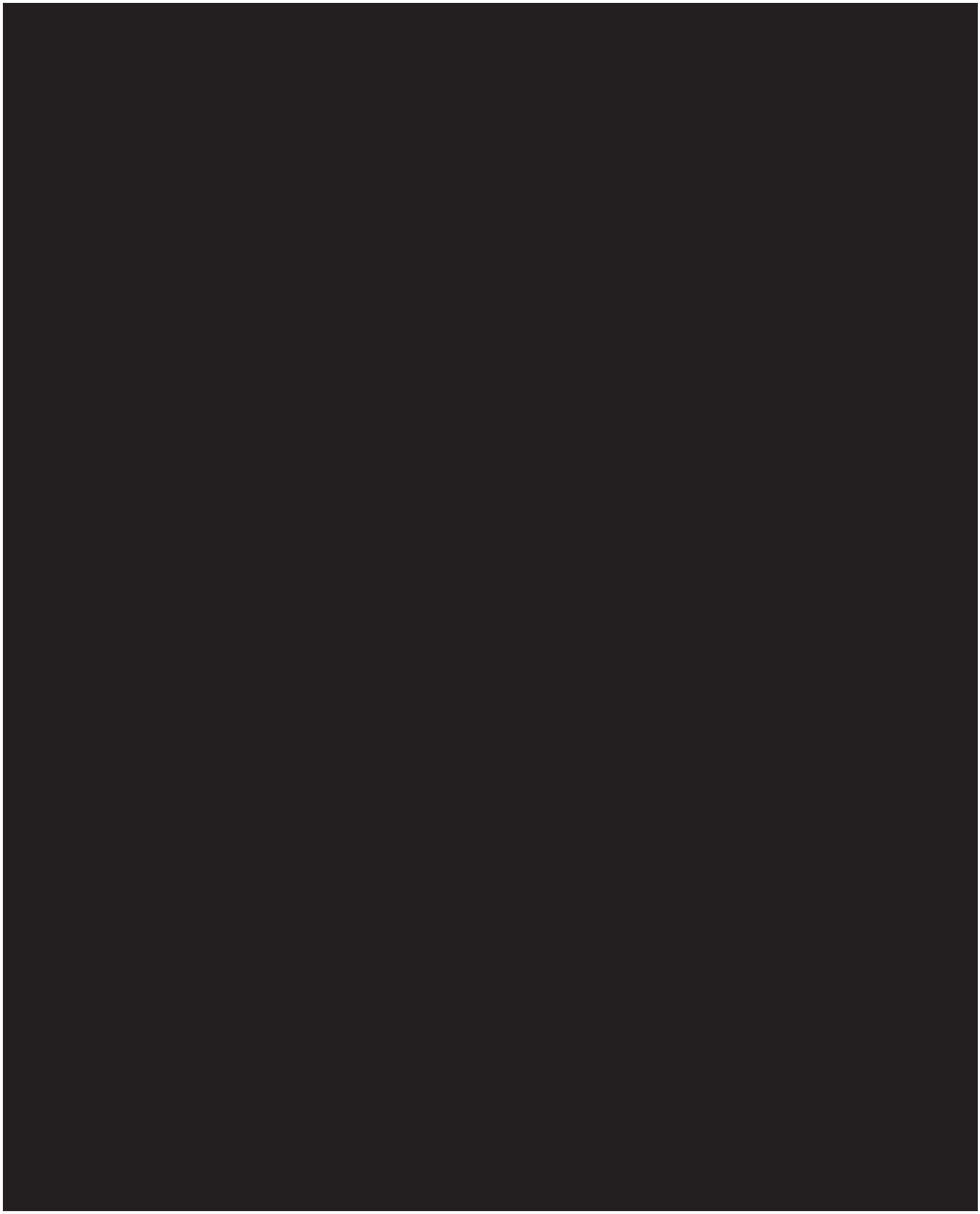
The analysis of secondary endpoints will be based on the FAS using NRI approach and will be done by "planned treatment".

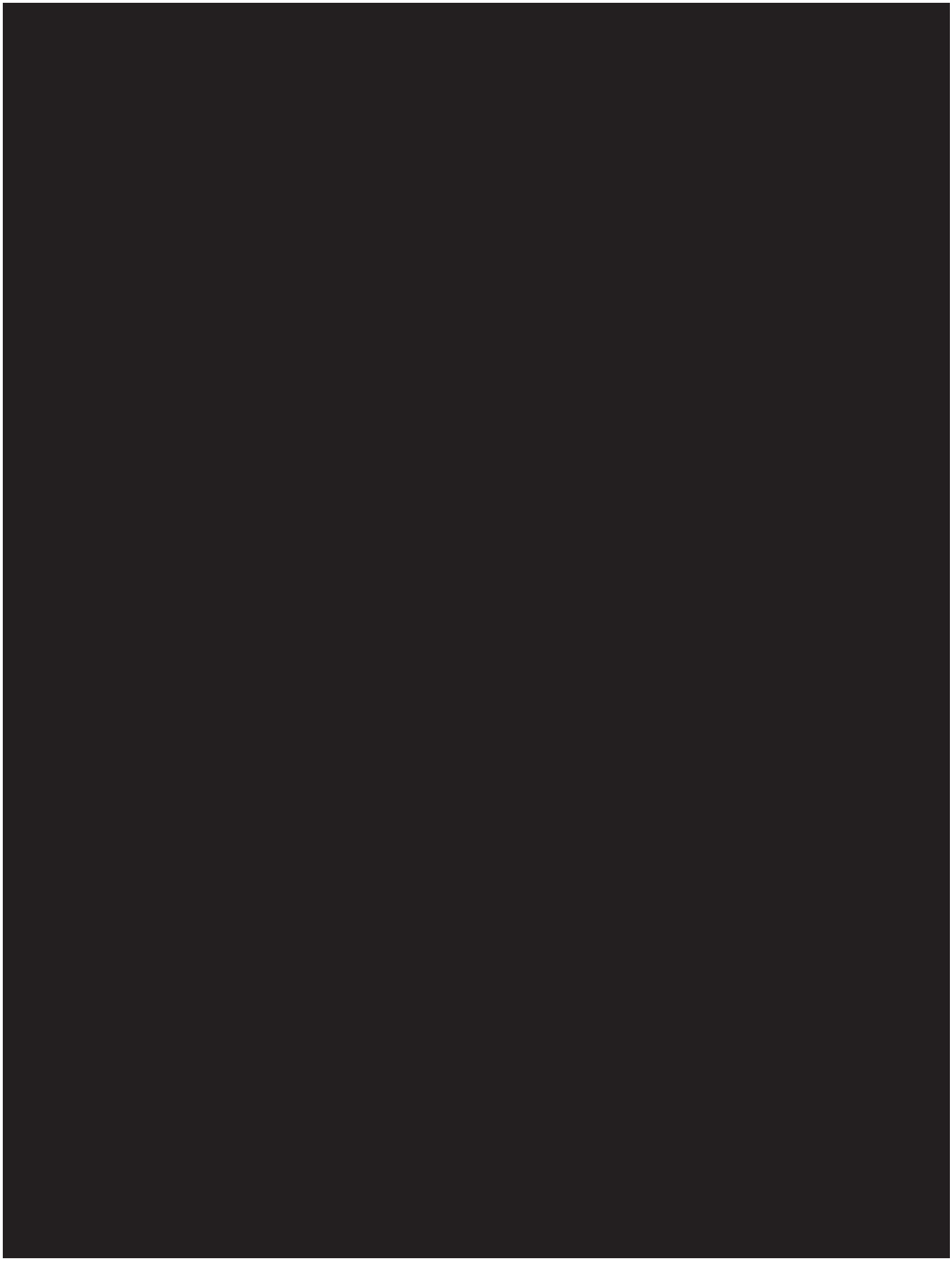
Perianal fistula response, perianal fistula remission, and combined perianal fistula remission will be derived based on reported fistula characteristic data as described in Section 5.2.2 for Week 12, and Week 24;

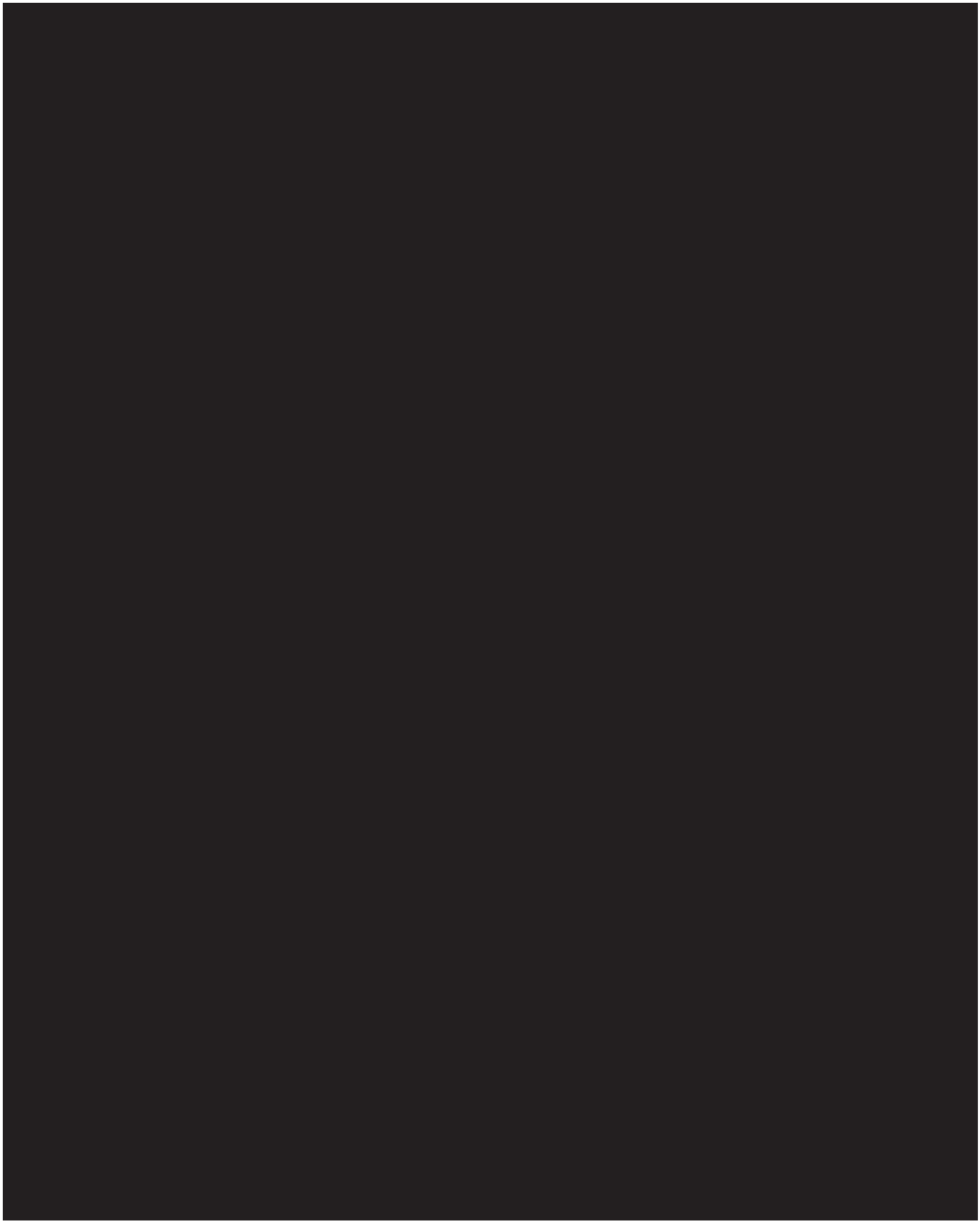
The proportion of patients at Week 12 will be summarized descriptively presenting patient frequencies and proportions together with 95% exact unconditional confidence intervals based on the score statistic for the risk difference spesolimab minus Placebo (if feasible) (cf. Additional Section 9.2.)

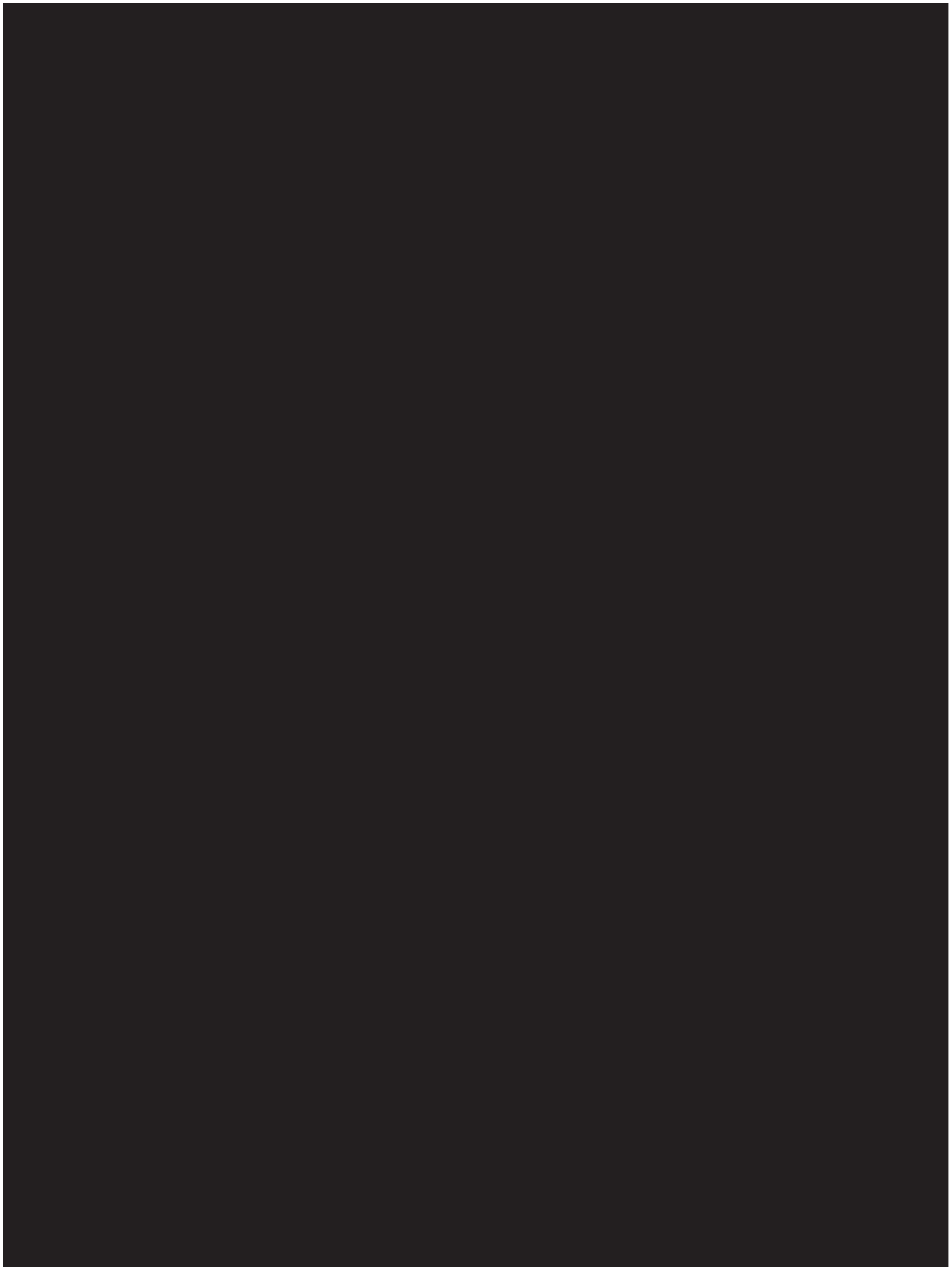
[redacted]

[redacted]









7.7 EXTENT OF EXPOSURE

Exposure (as amount administered in mg), duration of infusion (in minutes), and the number of active vials used for infusion will be summarised by descriptive statistics (N, mean, SD, minimum, median, maximum) per visit and per treatment period based on the SAF. The number and percentage of patients according to the duration of infusion will also be classified by visit and by treatment period according to the following categories:

Duration of infusion (min) categories

- Duration "< 60 min",
- Duration ">=60 min to < 120 min",
- Duration ">=120 min to < 180 min",
- Duration ">= 180 min".

The total duration of exposure and total exposure (as amount administered in mg), will be summarised by descriptive statistics by treatment period and overall based on the SAF.

7.8 SAFETY ANALYSIS

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

7.8.1 Adverse events

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

The analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and not on the number of AEs. Exposure-adjusted AE summaries will also be presented for the Study Cohort (see further details below).

For further details on summarisation of AE data, please refer to "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (3).

The analysis of AEs of the Study Cohort will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to screening, on-treatment, or follow-up phase as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1. All AEs of the Screening Cohort will be assigned to screening phase.

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

CTP Section 5.2.6.1: *The following are considered as AESIs:*

- *Infusion reactions including anaphylactic reaction (study cohort, only)*
  […]
- *Severe infections (according to RCTC grading in Appendix 10.9)*
- *Opportunistic and mycobacterium tuberculosis infections*
  […]
- *Hepatic injury (study cohort, only)*
  […]

The investigator had to classify on the eCRF whether an observed AE was an AESI or not. The investigator identified AESI will be captured from the eCRF and reported as "Investigator reported AESI" table. In addition, user defined adverse event categories (UDAEC) identified through specific search criteria will be reported separately (cf. Table 7.8.1:1)

Table 7.8.1: 1 Project standard MedDRA search criteria for User Defined Adverse Event Categories (UDAEC)

User Defined AE category	
Label	**Description**
Infections ALL	Combined search strategy based on the individual UDAECs for infections 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 ALL	Combined search strategy based on the three individual UDAECs for hypersensitivity described below
- Angioedema	Narrow SMQ "Angioedema"
- Hypersensitivity	Narrow SMQ "Hypersensitivity"
- Anaphylactic reaction	Narrow SMQ "Anaphylactic reaction"
Malignancies ALL	
- Malignant tumours	Narrow Sub-SMQ "Malignant tumours" Narrow Sub-SMQ "Haematological malignant tumours" Narrow Sub-SMQ "Non-Haematological malignant tumours"
- Non-melanoma skin cancer (NMSC)	Broad Sub-SMQ "Skin malignant tumours" excluding HLT Skin melanomas (excl. Ocular)
- Malignancies excluding NMSC	Sub-SMQ "Malignant tumours" excluding NMSC, where NMSC is defined above
Torsades de Pointes	Broad sub-SMQ "Torsade de pointes/QT prolongation"

According to ICH E3 (8), in addition to Deaths and Serious Adverse Events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced).

The exposure adjusted incidence rate (per 100 patient years) of a selected AE is defined as the number of patients experiencing the AE per treatment group during time at risk divided

by the total time of patient at risk in that treatment group to contribute an event to the analysis multiplied by 100 (per 100 patient years), where

Time at risk (patient years) = (date/time of TEAE onset–study drug start date/time +1)/ 365.25

If, for a patient, no treatment emergent AE occurred then the end of time at risk will occur at the minimum of (date of death; drug stop date+112 days; last contact date per EoS page (if patient does not enter a subsequent extension trial); one minute prior to time of first treatment in next treatment period or extension trial; analysis cut-off date (for Interim Analysis only)).

The time at risk in this situation is defined as:

Time at risk (patient years) = (end of time at risk–study drug start date + 1)/365.25

For each TEAE, the exposure-adjusted incidence rate will then be calculated as:

Incidence rate [per 100 patient years (pt-yrs)] = 100 * number of patients with TEAE /

Total TEAE-specific time at risk (patient years).

For patients who do not roll-over into a subsequent extension trial, a listing of all TEAE which occur after the individual patient's end of study will be done.

The exposure-adjusted incidence rate and frequency of patients with AEs will be summarised by treatment, primary SOC and preferred term. AEs which were considered by the investigator to be drug related will be summarised separately (for the Study Cohort only). Separate tables will also be provided for patients with SAEs, patients with AEs leading to study drug discontinuation, patients with AEs leading to dose reduction, patients with AESIs (separately for each of the four categories), and patients with UDAECs. The frequency of patients with AEs will also be summarised by worst RCTC grading, primary SOC and preferred term.

The system organ classes and preferred terms within system organ classes will be sorted by descending frequency overall treatment groups.

For disclosure of AE data on ClinicalTrials.gov, the frequency of patients with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by treatment, primary SOC and preferred term. The frequency of patients with SAEs will also be summarised.

For disclosure of AE data in the EudraCT register, the frequency of AEs, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarised.

For support of lay summaries, the frequency of patients with drug-related SAEs will be summarised by treatment, primary system organ class and preferred term.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature. The analyses will be based on BI standards "Display and Analysis of Laboratory Data" (9).

For continuous safety laboratory parameters, normalised values will be derived. Normalisation means transformation to a standard unit and to a standard reference range. The process of normalisation, handling of repeat values at the same visit for by-visit displays, as well as standard analyses for safety laboratory data are described in the BI guidance for the Display and Analysis of Laboratory Data. 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.

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 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. Since safety laboratory tests will be performed at the local laboratory of each site, this analysis will be based on normalized laboratory values only.

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 summarise the number of patients with potentially clinically significant abnormalities during the on-treatment period and without the finding at baseline. 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 ≥ 3xULN with concomitant or subsequent total bilirubin ≥ 2xULN in a 30 day period after AST/ALT elevation will be displayed, stratified by alkaline phosphatase < 2xULN and ≥ 2xULN (a patient can potentially be in both alkaline phosphatase strata in case of multiple AST/ALT and bilirubin elevations). The start of the 30 day time span is triggered by each liver enzyme elevation above the defined thresholds. Even if a patient changes treatment, i.e., if a patient

switches from Placebo to spesolimab at Week 12, the entire 30-day span is considered. This analysis will be based on standardized laboratory values.

A graphical analysis of ALT and total bilirubin during the on-treatment period will be performed; the so-called eDISH plot. The peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. The measurements displayed for total bilirubin and ALT may, or may not, occur on the same date. Two reference lines, 2xULN for 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 (potential Hy's Law quadrant), while the lower right quadrant is known as the Temple's corollary range (ALT $\geq$ 3xULN and total bilirubin < 2xULN).

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

7.8.3 Vital signs

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

7.8.4 ECG

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

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

7.8.5 Others

[redacted]

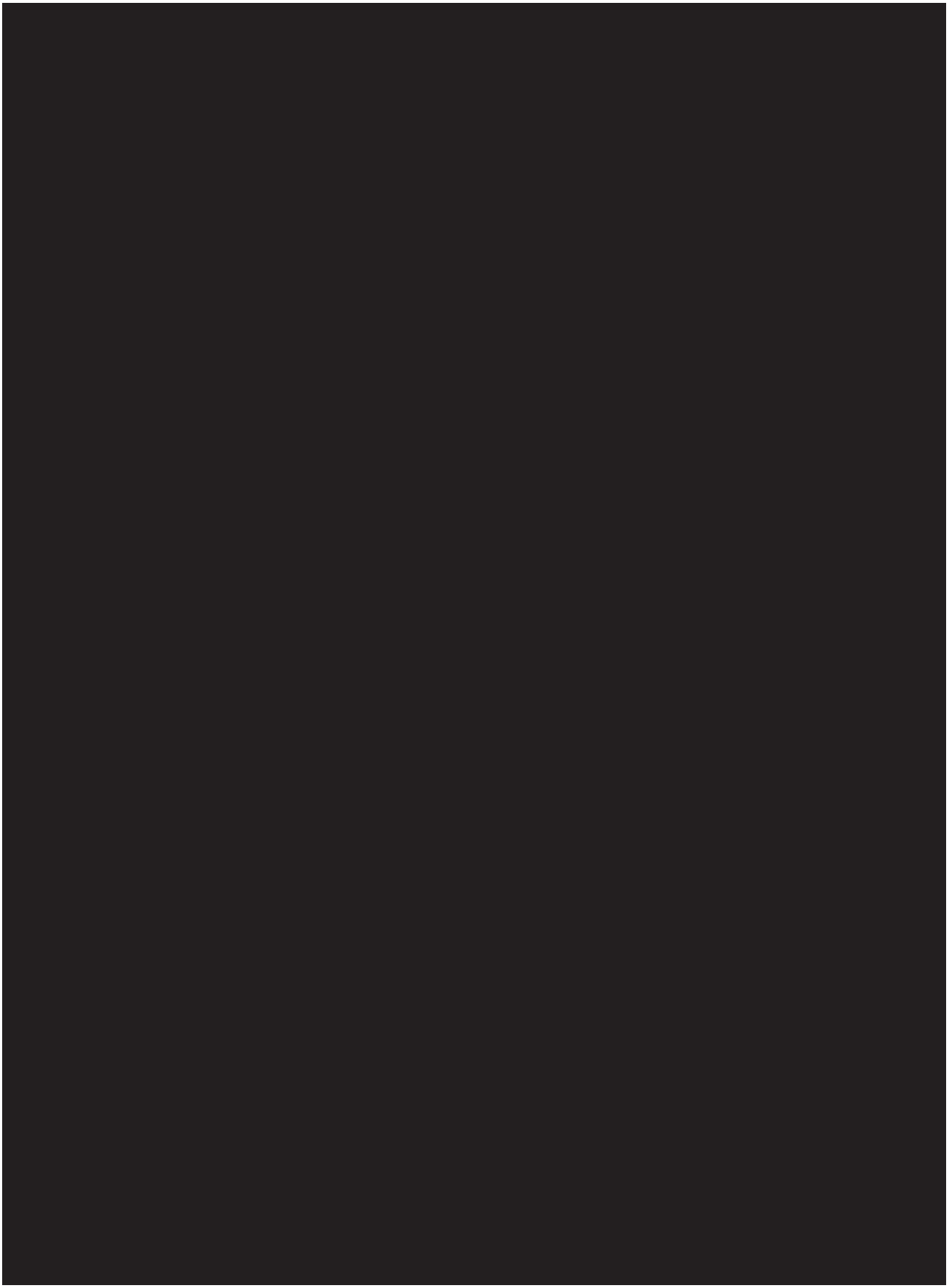
[redacted]

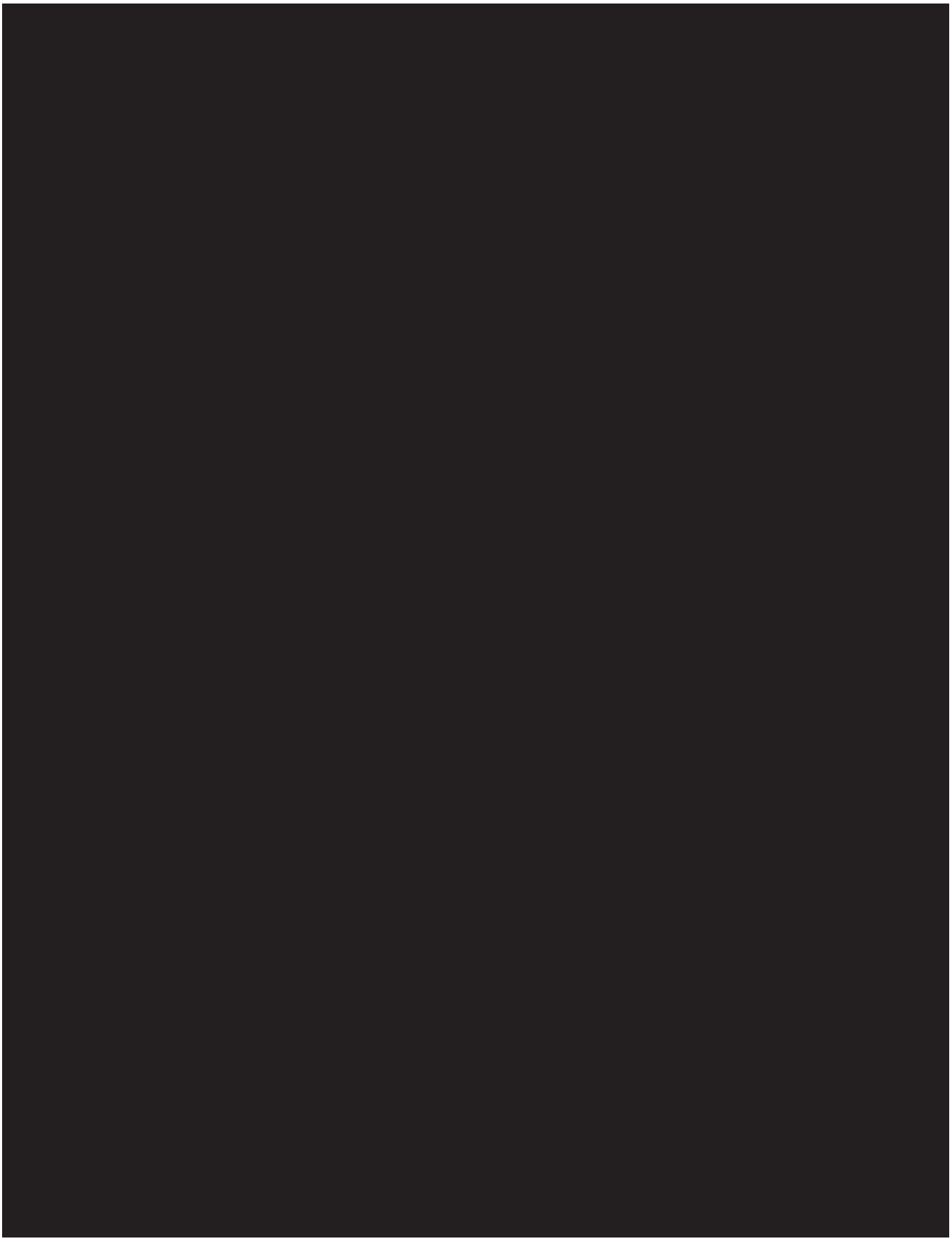
7.9 HANDLING OF DMC ANALYSES

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. 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 Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
2.	*001-MCS-40-413_1.0:* "Identify and Manage Important Protocol Deviations (iPD)", current version; IDEA for CON
3.	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
4.	*KM Asset BI-KMED-TMCP-MAN-0014*: "Noncompartmental PK/PD Analyses of Clinical Studies", current version; KMED
5.	*KM Asset BI-KMED-TMCP-MAN-0010: "*Description of Analytical Transfer Files, PK/PD Data files and ADA files", current version; KMED
6.	*KM Asset BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED
7.	*KM Asset BI-KMED-BDS-HTG-0066: "*Analysis and Presentation of AE data from clinical trials", current version; KMED
8.	*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
9.	*KM Asset BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version; KMED





10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**11-JAN-19**	[redacted]	None	This is the initial TSAP (document number c26459747) with necessary information for trial conduct
Final 1	**10-FEB-22**	[redacted]		Analyses are adapted to current BI standards, project standards and the adapted CTP. Secondary endpoint analyses based on re-calculated data, not based on investigator tick marks. Actual treatment defined with respect to safety analyses and primary endpoint analysis Details for analyses are added.