TRIAL STATISTICAL ANALYSIS PLAN

c37964321-02

BI Trial No.:	1425-0003
Title:	A Phase IIa, randomised, double-blind, placebo-controlled trial to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BI 706321 orally administered for 12 weeks in patients with Crohn`s Disease (CD) receiving ustekinumab induction treatment. Including Protocol Amendments 1, 2, 3 and 4 [c33919902-05]
Investigational Product(s):	BI 706321
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	02 AUG 2024
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2. LIST OF ABBREVIATIONS

Term	Definition / description
ALT	Alanine Aminotransferase
ALQ	Above the limit of quantification
ANCOVA	Analysis of covariance
AP	Abdominal Pain
ASA	Aminosalicylic Acid
AST	Aspartate Aminotransferase
BLQ	Below the limit of quantification
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CDEIS	Crohn's Disease Endoscopic Index of Severity
CRP	C-Reactive Protein
CTP	Clinical Trial Protocol
DILI	Drug Induced Liver Injury
ECG	Electrocardiogramm
EoT	End of Treatment
ES	Enrolled Set
FAS	Full Analysis Set
FCP	Fecal Calprotectin
FLF	Fecal lactoferrin
GHAS	Global Histologic Disease Activity Score
HR	Heart Rate
IBDQ	Inflammatory Bowel Disease Questionnaire
LLOQ	Lower Limit of Quantification
LOCF	Last Observation Carried Forward
NRI	Non-Response Imputation
OC	Observed Case
OR	Original Results
PBMC	Peripheral Blood Mononuclear Cell
PKS	Pharmacokinetic Set
PR	Pulse Rate

Term	Definition / description
PRO	Patient Reported Outcome
QRS	Measurement that represents the depolarization of ventricles
QT/QTc/QTcB/QTcF	Measurement representing the total time from ventricular depolarization to complete repolarization (uncorrected and corrected)
REP	Residual effect period
RHI	Robarts Histology Index
RIPK2	Receptor-Interacting Protein Kinase-2
RR	Respiration Rate
RS	Randomized set
SES-CD	Simple Endoscopic Score for Crohn's disease
SF	Stool Frequency
SOC	System Organ Class
TSAP	Trial Statistical Analysis Plan
TNF	Tumor Necrosis Factor
TS	Treated Set
ULN	Upper Limit of Normal

3. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 "Statistical Methods and Determination of Sample Size". Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

SAS® Version 9.4 or r version 4.1.0 or later will be used for all analyses.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint is absolute change from baseline in Simple Endoscopic Score for Crohn's disease (SES-CD) at Week 12.

The SES-CD is a numerical grading system generating a total score (0-56) composed of 4 variables (presence of ulcers, ulcerated surface, affected surface, and presence of narrowings), all of which are recorded in 5 segments: terminal ileum, right colon, transverse colon, left colon, and rectum (Refer to Appendix 10.3 in the CTP). The endoscopy (ileocolonoscopy) examinations at screening(baseline) and Week 12 provide information on the inflammatory status of these 5 segments. The absolute change is simply the difference calculated by subtracting the SES-CD at baseline from Week 12. A decrease in SES-CD (change less than 0) is considered as an improvement in endoscopic inflammation status while an increase is considered worsening.

Note that endoscopies are centrally read in a blinded fashion by two independent readers (Reader #1 and Reader #2). If there is agreement between the readers in the total SES-CD score then the scoring from Reader #1 will be used as the outcome and used for analysis. If there is disagreement in the total SES-CD score then the two readings are reviewed by an

adjudicator who will select either Reader #1 or Reader #2 as the outcome and used for analysis.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable. No key secondary endpoints have been defined.

5.2.2 Secondary endpoint(s)

Secondary endpoints are listed in Section 2.1.3 of the CTP and can be grouped into the following categories of assessments:

- Endoscopic(efficacy):
  - Percent change in SES-CD from baseline at Week 12
  - Endoscopic response (defined as >50% SES-CD reduction from baseline, or for an induction baseline SES-CD of 4, at least a 2 point reduction from induction baseline) at Week 12
  - Endoscopic response (defined as >50% SES-CD reduction from baseline, or for an induction baseline SES-CD of 4, at least a 2 point reduction from induction baseline) at Week 48
  - Endoscopic remission (defined as SES-CD score of ≤2) at week 12
  - Endoscopic remission (defined as SES-CD score of ≤2) at week 48.

  Percent change from baseline in SES-CD is calculated as:

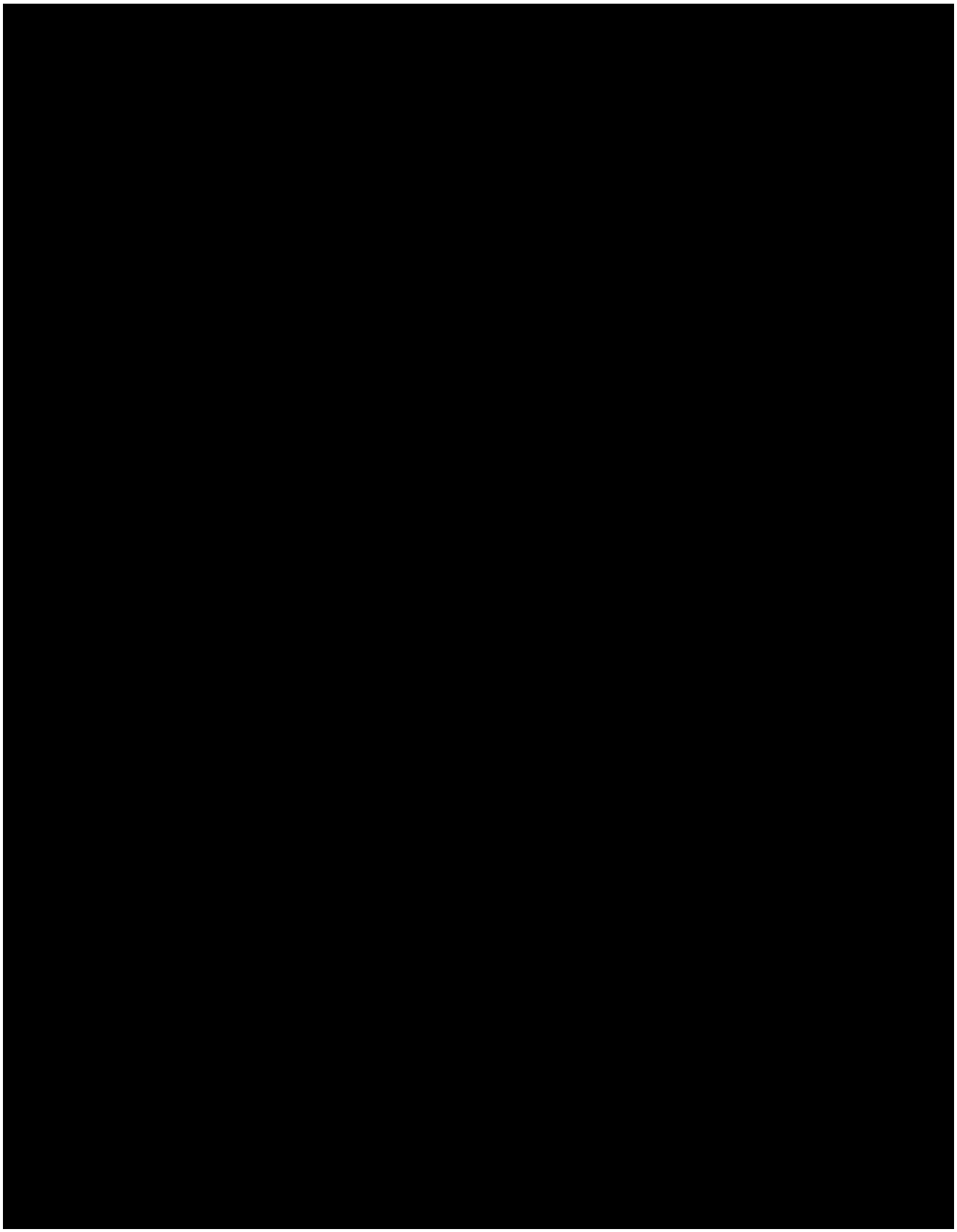
$$\frac{\text{Absolute change in SES-CD}}{\text{SES-CD at baseline}} \text{ x } 100$$

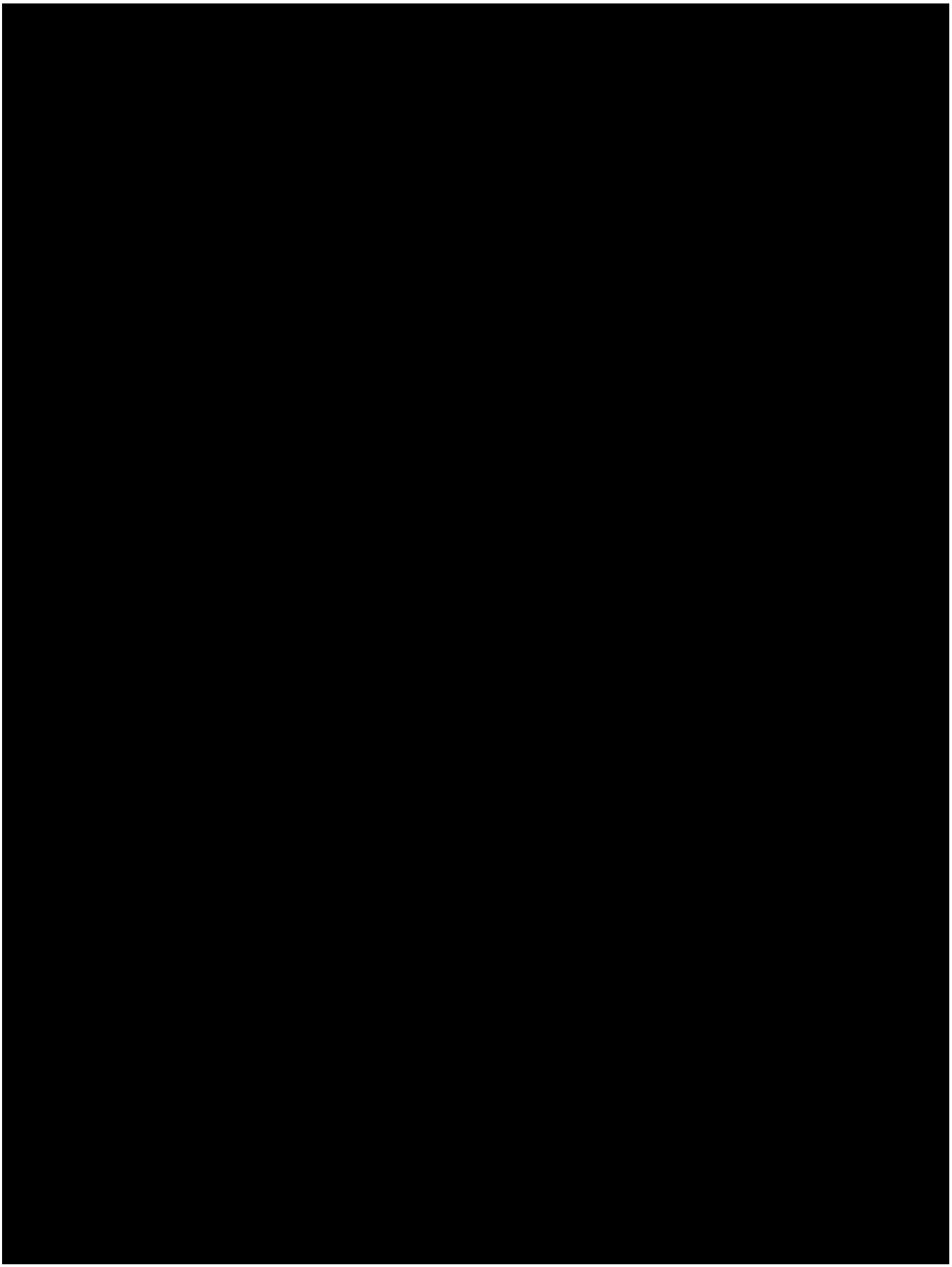
- Biological (biomarkers):
  - Biological remission, defined as CRP < 5 mg/L and faecal calprotectin (FCP) < 250 ug/g at week 12
  - Biological remission, defined as CRP < 5 mg/L and faecal calprotectin (FCP) < 250 ug/g at week 48

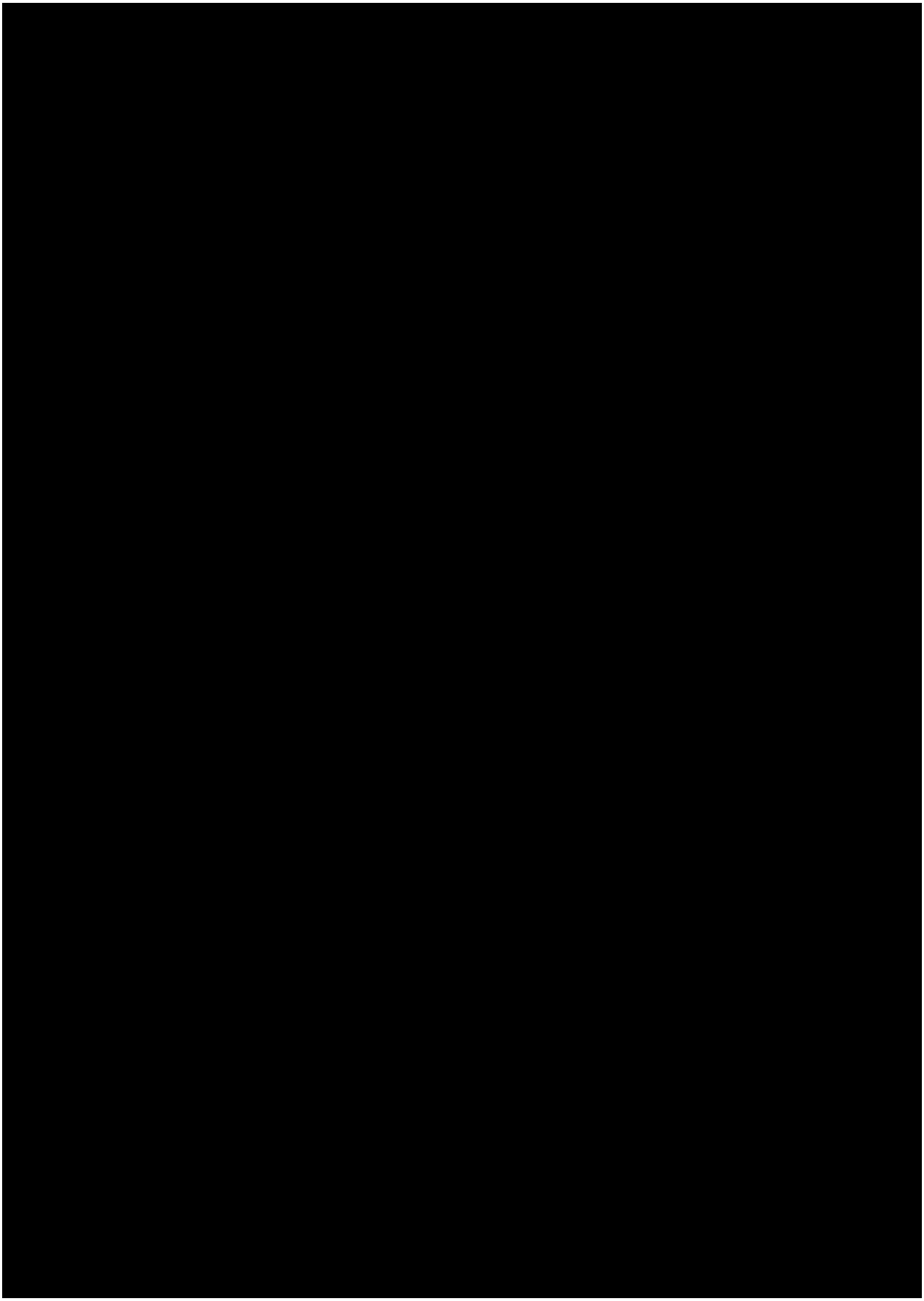
- Clinical (efficacy):
  - Clinical remission at week 12, defined as a Crohn's Disease Activity Index (CDAI) score of <150
  - Clinical remission at week 48, defined as a CDAI score of <150
  - Clinical response at week 12, defined by a CDAI reduction from baseline of at least 100 points, or a CDAI score of <150

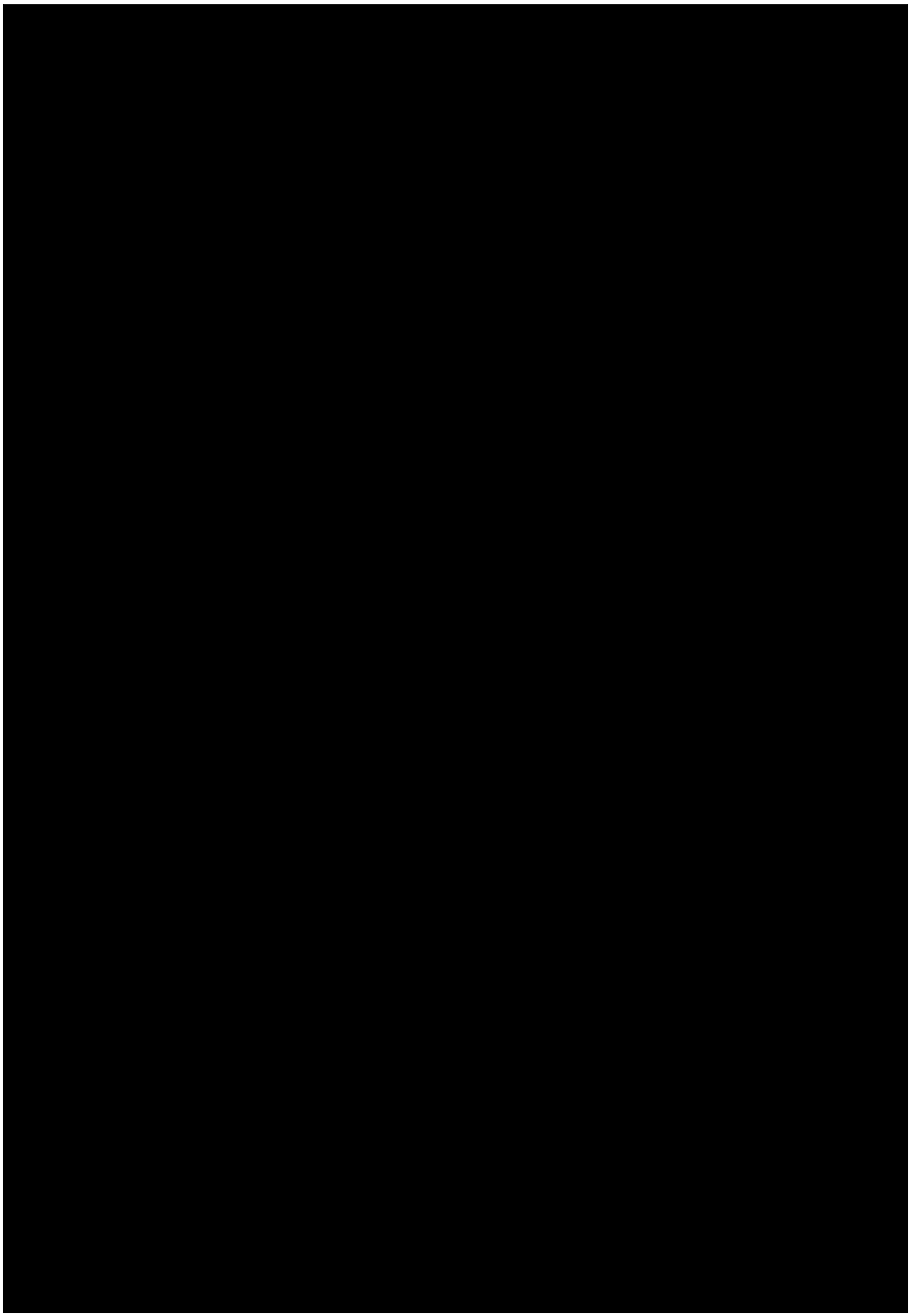
    Refer to Appendix 10.4 in the CTP and Section 10.2 below for details of the CDAI score calculation. Details for handling of missing CDAI data can be found in Section 6.6.1.

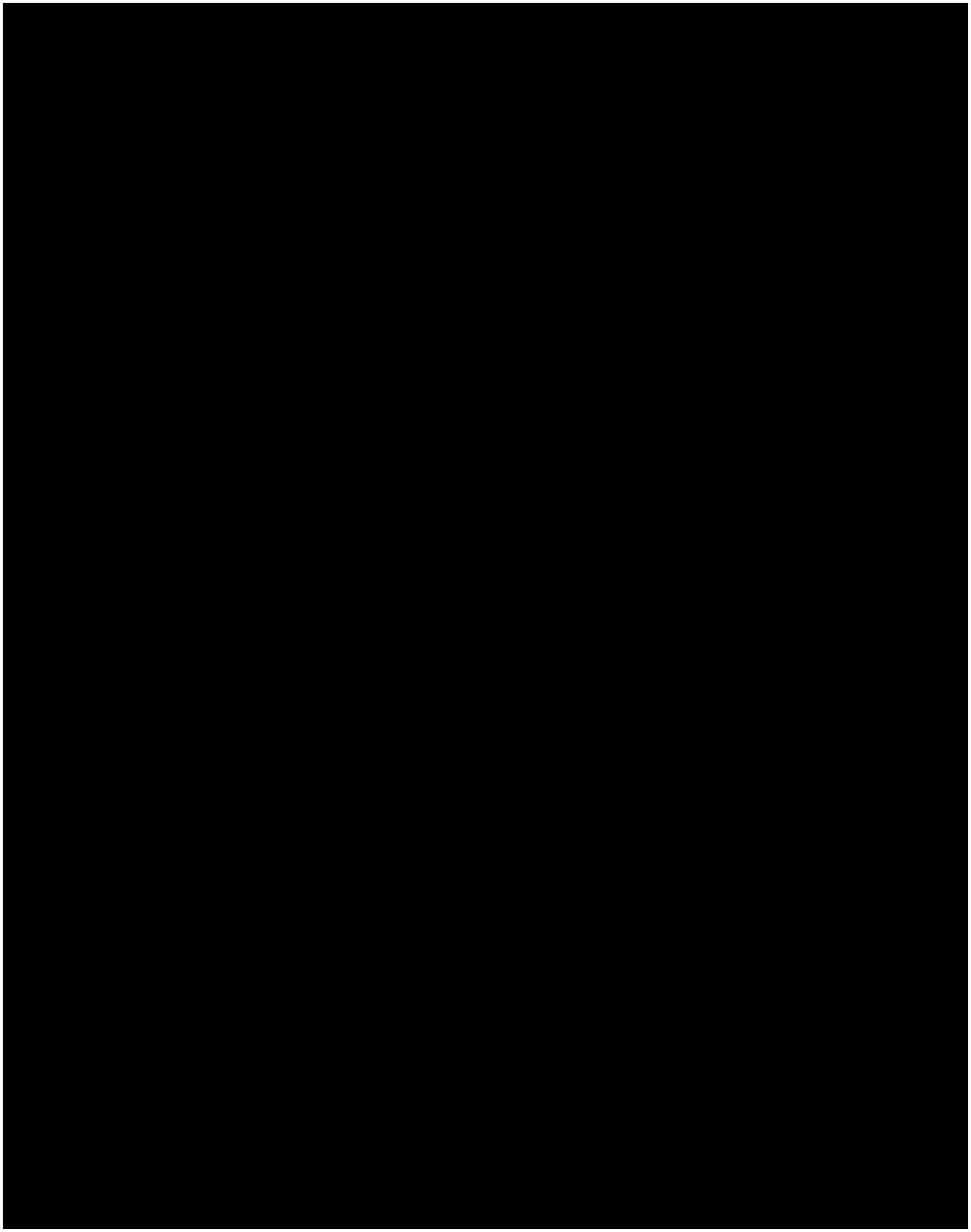
- Safety:
    - Number of patients with treatment-emergent adverse event (TEAE) through end of treatment (EoT) and the REP period (i.e. through Visit 9)











6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic study information on treatments to be administered, assignment of treatment groups, selection of doses, refer to CTP Section 4.

The trial is divided into a Screening period, a randomized blinded induction period with patients receiving either placebo or BI 706321 + ustekinumab, and an unblinded follow-up treatment period where all patients continue to receive ustekinumab (refer to CTP Section 3.1). Start and end dates/times for these periods are defined in Table 6.1: 1.

Table 6.1: 1 Trial phases

Study analysis phase	Description	Start (included)	End (included)
Screening period	Screening	Earliest of (Date of informed consent, first screening procedure)	Earlier date/time of either first administration of BI 706321 or first i.v. of ustekinumab - 1 minute.
Induction period	On-treatment period (blinded)	Earlier date/time of either first administration of BI 706321 or first i.v. of ustekinumab (Day 1)	Last date of administration of BI 706321 at 11:59 p.m.
Follow-up period	Off-treatment, on ustekinumab s.c. alone	Last date of administration of BI 706321 + 1 day at midnight (0:00)	Date of the end of study participation on the End of Study (e)EOS CRF at 11:59 p.m.
Induction+ Follow-up period	Covers entire trial period for reporting	Earlier date/time of either first administration of BI 706321 or first i.v. of ustekinumab (Day 1)	Date of the end of study participation on the End of Study (e)EOS CRF at 11:59 p.m.

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

A residual effect period (REP) of 16 days after the last intake of BI 706321/placebo has been defined. For safety analyses, data up to end of the REP will be considered as on-treatment for the induction period with BI 706321/placebo + ustekinumab. For efficacy analyses, data up to 1 day after last treatment intake of BI 706321/placebo will be considered as on-treatment for the induction period. In general, tabulations over time and AE reporting will be produced separately for the induction period or the induction+follow-up period (i.e. separate tables for the Follow-up period will not be produced)

All patients will be analysed “as treated” for safety and efficacy in case of mix-ups in randomisation and treatment administration.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Protocol deviations that affect the rights or safety of the study participants, or can potentially influence the primary outcome measurement in a non-negligible way will be considered as

important protocol deviations (iPDs). IPDs will be identified and documented according BI SOPs (2).

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS. Other relevant documentation of details related to iPDs will also be stored in the TMF (e.g. in the decision log).

6.3 SUBJECT SETS ANALYSED

The following patient sets will be defined for analysis:

Subject analysis sets:

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

- Randomised set (RS)
  - All randomised patients, treated or not.

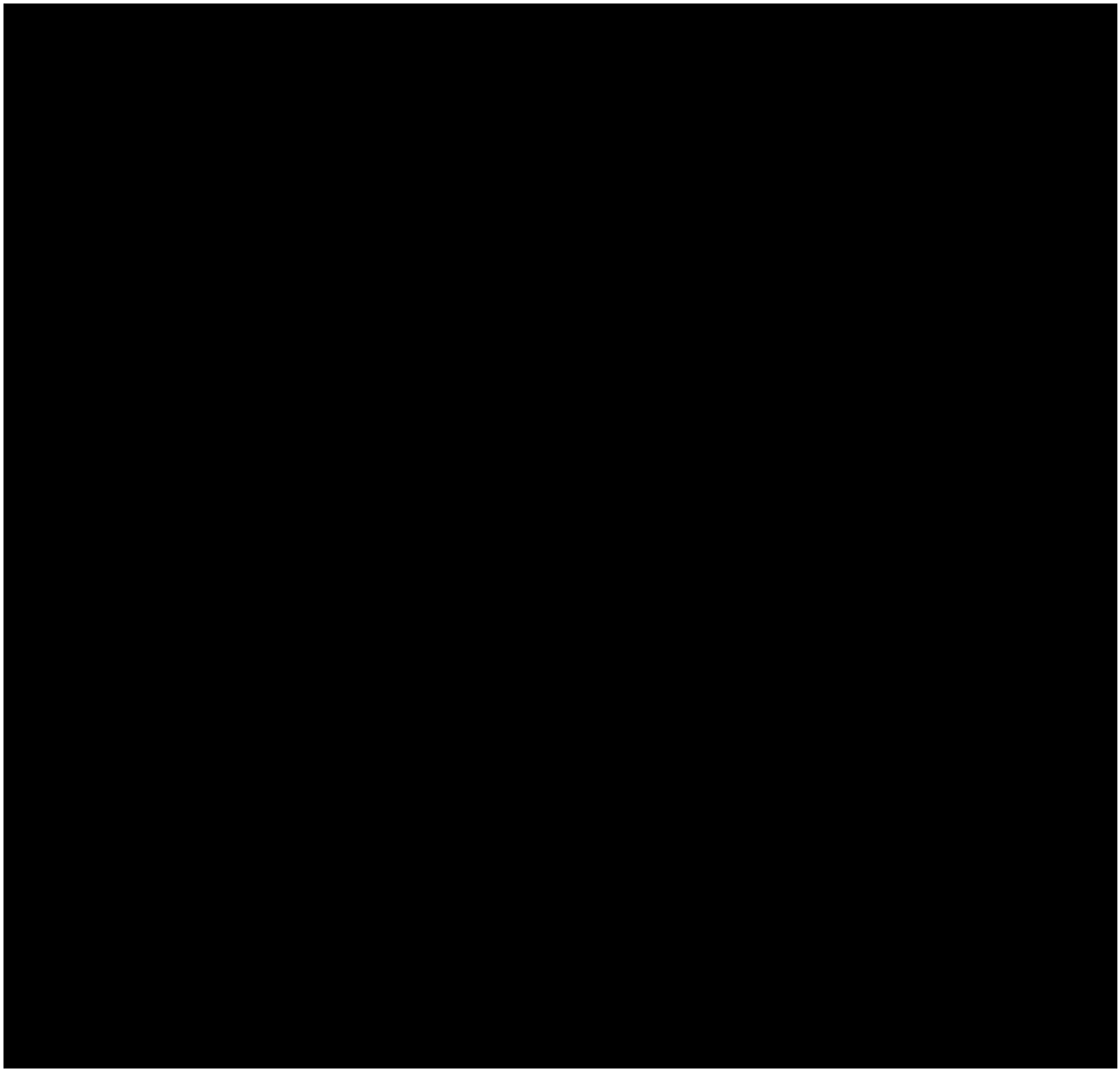
- Full analysis set (FAS)
  - All patients in the RS who received at least 1 dose of trial medication and have analysable post-baseline data (observed or imputed) in at least one efficacy/biological/histological parameter. Treatment assignment will be as treated.

For each planned analysis, Table 6.3: 1 shows which subject set will be used for which class of endpoints.

Table 6.3: 1 Subject sets analysed

Class of endpoint	FAS
Primary	primary analysis
Secondary and further endpoints:	
Efficacy	X
Biomarkers (blood, stool, and histopathological)	X
RNA Seq based endpoints	X
Pharmacokinetic endpoints	X
Safety endpoints & treatment exposure	X
Demographic/baseline endpoints	X

Note that the number of patients with available data for an endpoint may differ. For details, see section “Handling of missing data”.



6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

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 as well as the time point. 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.
- The non-response imputation (NRI) approach is applied for binary endpoints. Missing values will be imputed described in the following:
    - 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)
- 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 at which a measurement is missing. If there are on-treatment values measured after the day of CD medication increase or addition, these will be set to missing and the missing values within the on-treatment period will be imputed by LOCF.
- Imputation technique Baseline observation carried forward (BOCF): This will be applied in certain instances where there are no post baseline measurements.

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

6.6.1 Efficacy data

Handling of missing data for endoscopy data

Based on the CTP and requirements of for completing the endoscopy procedure, the following scenarios could occur if a patient discontinues BI 706321 prior to Week 12:

1. A patient may only have a baseline SES-CD value if the patient has less than 6 weeks of treatment with BI 706321/placebo
2. A patient may have an early post-baseline SES-CD value that falls within the Week 8 visit window if the patient has at least 6 Weeks of treatment.

For the primary analysis of change from baseline in SES-CD score, BOCF imputation will be applied to SES-CD scores in scenario 1 above and LOCF will be applied in scenario 2.

Imputation for a sensitivity analysis is also planned:

For patients with an early post baseline endoscopic assessment as described above, a simple linear regression equation based on the change from baseline to Week 8 will be used to impute the Week 12 SES-CD score and change from baseline. The equation to derive the Week 12 value will be:

$$\text{Week 12 SES} = \frac{\text{SES at Week 8} - \text{SES at Baseline}}{(\text{Date of Week 8 SES} - \text{Date of Baseline SES})} \text{ x } 85$$

After these observations are imputed, multiple imputation will be used handle missing Week 12 data where there is no post baseline value.

If no patients with missing Week 12 endoscopic assessments have a post-baseline measurement then multiple imputation will be used to impute the change from baseline to week 12.

The SAS procedure PROC MI will be used to generate 10 complete sets of data with Week 12 changes from baseline in SES-CD. All variables in the primary analysis model will be included in the imputation model. Example SAS code can be found in Section 10.7.3.

Note that this sensitivity analysis will only be performed if there are more than 10% of the patients only have a baseline visit without having any post baseline visit.

Handling of missing data for CDAI:

The CDAI is derived based on eight components: number of liquid stools, extent of abdominal pain, general well-being, occurrence of extraintestinal manifestations, need for antidiarrheal drugs, presence of abdominal masses, haematocrit, and body weight. Refer to Additional Section 10.2 for a detailed description of the CDAI score derivation.

PRO components: If there are less than 4 days of any diary data (1. number of liquid or soft stools, 2. abdominal pain rating, or 3. general well-being rating) of the 7 days included in the visit window described in Section 10.2, then the window will be shifted backward, 1-day at a time, until there are a least 4 non-missing values to use to calculate the average. The average of these 4 days will be multiplied by 7 then the weighting factor for the CDAI component. If a daily average cannot be calculated then the component from the previous post baseline visit will be carried forward. For the CDAI calculation at Visit 5 (Day 15), days prior to Visit 4 (Day 8) will not be used.

If at least one of the six assessments regarding extra-intestinal manifestations is missing, the score is set to missing.

If haematocrit or deviation from ideal weight is not available then the last post baseline observation will be carried forward to calculate the CDAI total score used for analysis.

The CDAI score is set to missing if any of the eight components is missing.

If the CDAI score at the visit is missing after the above imputations, then the post-baseline CDAI score shall be imputed by the last (post-baseline) observation carried forward (LOCF).

[redacted]

6.6.2 Safety data

With respect to safety evaluations, it is not planned to impute missing values for AEs, safety laboratory values, vital signs, or ECG data. 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 will be imputed according to BI standards (see "Handling of missing and incomplete AE dates" (3)).

Partial start and stop dates for concomitant medications, background, and historical medication for CD 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 end of study participation from End of Study eCRF. 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 end of study participation from End of Study eCRF, 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.
- If the day and month of the start date are missing then the start date is set to 1st January of the year.
- All other cases need to be assessed by the trial team on an individual basis, using the above points as guidance.

For safety data that are displayed by time point (or visit) of measurement, the OC approach will be used.

6.6.3 Pharmacokinetic data

Missing data and outliers of PK data are handled according to (1).

6.6.4 Biomarkers

Biological/Histological endpoints:

This includes changes from baseline in haemoglobin, albumin, CRP, FCP, [redacted]). No imputation of missing data will be performed.

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

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

Baseline, unless otherwise specified, is defined as the last measurement collected prior to the start of administration of the trial treatment. For the SES-CD score (primary endpoint), baseline is the measurement from the ileocolonoscopy performed along with the screening procedures.

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).

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)
V1	Screening	-28 to -1 [A]	n/a		
V2	Baseline	1	n/a	-28	1 [B]
Planned on-treatment visits [C]					
V3	Day 4	4	-2/+1	2	5
V4	Week 1	8	-2/+3	6	11
V5	Week 2	15	-3/+7	12	22
V6	Week 4	29	-6/+14	23	43
V7	Week 8	57	-13/+14	44	71
V8	Week 12/EoT	85	-13/+14	72	99
Follow-up period[D]					
V9	Week 16	113	-13/+28	100	141
V10	Week 24	169	-27/+27	142	196
V11	Week 32	224	-27/+28	197	252
V12	Week 40	281	-28/+27	253	308
V13	Week 48/EoS	336		309	Day of last value

Days are counted relative to the day of first treatment, which is defined as Day 1.
[A] Baseline ileocolonscopy can be up to 6 weeks (-42 days) prior to Day 1 if patient is re-screened.
[B] 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 and time (i.e. safety laboratory) will not be assigned to Baseline. Such data will be listed only
[C] Only 'on-treatment' data (i.e. BI 706321/Placebo + Ustekinumab measured within the REP following intake of last dose) are included.
[D] All "off-treatment" data, irrespective of whether on or off open label ustekinumab are included.

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.

For safety laboratory data - in the case of an unscheduled repeat visit (i.e. a separate sample is measured for the same visit) the worst value of the repeated observations will be selected first and then the above rule will be applied.

Assignment of efficacy observations to visits will be based on the non-imputed (observed) data. Visits which were not assigned a value based on the time windows above, will have values imputed using the BOCF/LOCF of NRI approaches defined in Section 6.6.

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

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

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

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” (4).

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

The precision for percentages should be one decimal point. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

Demographic data and baseline characteristics will be summarised by treatment arm and overall. For some continuous variables, the following categories will be defined and presented according to the number and percentage of patients in each category (Table 7.1: 1):

Table 7.1: 1 Categories for summary of continuous variables

Variable	Categories	Additional information
Age	Age class 1 (Section 6.4) Age class 2 (Section 6.4)	
Weight	Refer to Section 6.4	
Ideal Weight	Use categories for Weight (Section 6.4)	
BMI	< 20 kg/m^2 20 to <25 kg/m^2 25 to < 30 kg/m^2 ≥ 30 kg/m^2	
Time since first diagnosis of CD	≤ 5 years > 5 years	If only a partial date is available, then the following rules apply for imputation. If only the year is present, select the earliest of June 15th of the provided year and informed consent date. If only year and month is provided, select the earliest of the 15th of the provided year and month and informed consent date
SES-CD	Moderate (≤15) Severe (> 15)	

The following demographics and baseline characteristics will be tabulated:

Demographic characteristics:

- Sex
- Ethnicity
- Race
- Country
- Age (continuous, category)
- Tobacco use
- Weight (continuous, category)
- Ideal weight (continuous, category)
- Height
- Body Mass Index

Baseline characteristics:

- SES-CD score (continuous, category)
- CDEIS score
- Time since diagnosis (continuous, category)
- Disease pattern
- CDAI total score
- CDAI components (SF, AP, GWB, Extra manifestations, etc)
- C-reactive proteine (CRP)
- Elevated CRP (> 5mg/L)
- Fecal calprotection
- Elevated fecal calprotectin(>250 ug/g)
- Elevated CRP and elevated fecal calprotectin
- Presence of ulcerations overall and by segment

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.

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 CD will be displayed by each medication and the reason for discontinuation. Additionally, a tabulation of historical medications by category (Biologics/TNF antagonists, Immunomodulators, Systemic Corticosteroids, Crohn's Disease specific antibiotics, and 5-ASA) will be produced, as will a summary of the number of previous biologic/TNF antagonists.

The frequency and percentage of patients with background medication for Crohn's Disease will be displayed by defined categories and preferred name. Categories will be as described in Table 4.2.2.1: 1 in the CTP: Oral 5-ASA, Immunomodulators, Systemic corticosteroids, and CD specific antibiotics. A detailed summary of background corticosteroid dose (prednisone equivalent) at baseline use will also be included.

A medication will be considered concomitant to study treatment if it is ongoing at the time of first administration of BI 706321/Placebo or ustekinumab or starts within the study period (cf. Section 6.1).

The frequency and percentage of patients having a concomitant non-drug therapy will be tabulated by the preferred term of the therapy. Tabulations will be produced for therapies up to the end treatment period and up to the end of the treatment_+ follow-up period.

A medication or 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 time of first administration of BI 706321/Placebo or ustekinumab.

Concomitant medication use (excluding 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:

- Baseline: starting prior medication taken any time prior to Day 1 (the day of start of trial treatment) and continuing into the treatment period
- Medications introduced during the induction period (cf. Section 6.1)
- Medications introduced during the whole study period (induction or follow-up period).

Background medication (eCRF) for Crohn's Disease will be analysed in the same way and presented separately.

7.3 TREATMENT COMPLIANCE

Treatment compliance will be summarized based on the FAS. Only descriptive statistics are planned for this section of the CTR.

Compliance with BI 706321/placebo

The number and percentage of patients with treatment compliance during the induction period by treatment group and overall will be categorized based on the CRF question:

- Study medication taken according to protocol (Yes, No)

Refer to Section 4.3 of the CTP. A CRF response of "Yes" indicates that, based on tablet counts, the number of tablets actually taken is between 80 -120% of the number of tablets that should have been taken as directed by the investigator. Responses will be tabulated by visit. Reasons for not having taken study medication according to the protocol will be listed.

Compliance with ustekinumab

Treatment compliance of ustekinumab will be summarised by the number and percentage of patients who received ustkinumab at each visit (Day 1 and Weeks 8, 16, 24, 32, 40).

7.4 PRIMARY ENDPOINT(S)

7.4.1 Primary analysis of the primary endpoint(s)

CTP Section 7.1: *This is an exploratory trial. No confirmatory testing is performed and hence no null and alternative hypotheses are defined.*

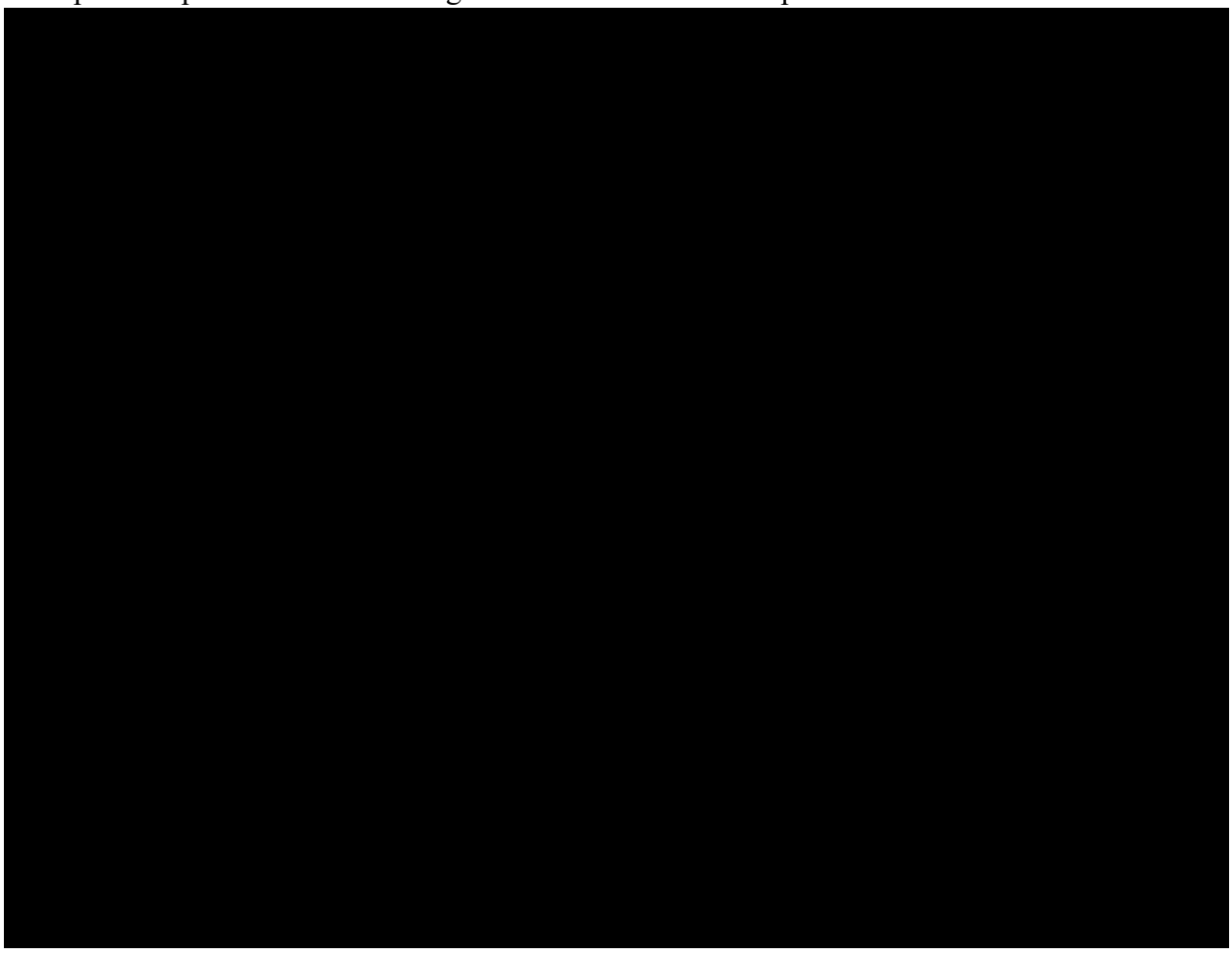
CTP Section 7.2.2: *The primary analysis is a restricted maximum likelihood (REML) based analysis of covariance (ANCOVA) comparing the absolute change from baseline in SES-CD scores at Week 12. Baseline will be the based on screening endoscopic assessment (See Flow Chart). For the ANCOVA model, absolute change in SES-CD score will be the dependent variable, treatment group and baseline corticosteroid use (yes/no) will be fixed effects and baseline SES-CD score will be continuous covariate. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard errors. Adjusted means for each group and mean difference between treatment groups will be presented along with confidence intervals (95%).*

To assess the homogeneity of the treatment effect on the primary endpoint across the levels of baseline corticosteroid use, the same ANCOVA model will be fitted, but also including the treatment by baseline corticosteroid use interaction. A descriptive p-value of treatment effect homogeneity will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable.
Refer to subgroup analyses within Section 7.4.2 for more details.

The FAS using the BOCF/LOCF approach will be used for the analysis of the primary endpoint, absolute change from baseline in SES-CD score at Week 12. This means that if a patient discontinues after 6 weeks (42 days) of study treatment and has an SES-CD assessment during the Visit 7/Week 8 visit window (cf. Table 6.7: 1), that the change in SES-CD score at Week 8 will be carried forward to the Week 12 time point and used in the primary analysis. If there is no post-baseline endoscopic assessment then the baseline value will be carried forward (BOCF). This analysis is consistent with the Treatment Policy strategy for handling of intercurrent events (discontinuation of BI 706321/Placebo during the first 12 weeks) described in Section 7.2.1 of the CTP.

Descriptive statistics (unadjusted) for SES-CD and change from baseline up to Week 12 will also be tabulated for the LOCF and OC approaches described in Section 6.6.

Graphical representations of change in SES-CD will also be presented.



7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

7.5.1.1 Primary analysis of the key secondary endpoint(s)

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

[redacted]

7.5.2 (Other) Secondary endpoint(s)

CTP Section 7.2.3: *Percent change from baseline from baseline to Week 12 in SES-CD score will be analysed in the same manner as the primary endpoint.*

Unadjusted absolute rate difference between treatment groups will be calculated simply as the difference in the observed proportion of patients who achieve binary response and remission endpoints. The influence of stratification factors (baseline corticosteroid use or other potential prognostic factors) and/or baseline SES-CD will also be explored. These analyses will be specified in the TSAP.

Consistent with a composite strategy for handling of interrcurrent events and potential missing data, Non Response Imuptation (NRI) will be applied to clinical and endoscopic response and remission endpoints, that is imputing as failure to achieve a response.

For binary secondary endpoints, unadjusted absolute risk differences between the two treatment groups will be provided for each time point separately and for proportions of patients achieving the endpoint at both Week 12 and Week 48. In addition, 95% confidence intervals will be displayed. The method to provide confidence intervals for single proportions will be based on the Wilson method (5). The method to provide confidence intervals for the unadjusted risk differences will be derived from the Newcombe method (6).

To explore the influence of baseline covariates adjusted risk differences a logistic regression model will be utilized and weighted risk differences and 95% confidence intervals will be calculated using the methodology described by Ge et. al. (7). The logistic model will include treatment group and baseline corticosteroid use (yes/no) as fixed effects and baseline SES-CD score will be continuous covariate. In case 0 events are observed in one of the dose groups, a penalized regression based on the Firth's bias reduction method (8,9) will be used.

Additionally, selected subgroups will be explored and unadjusted absolute risk differences at Week 12 between the two treatment groups will be provided along with 95% confidence intervals.

The table below outlines the planned analyses for the secondary endpoints, including the patient set, imputation method, and subgroups.

Endpoint(s) **Analyses**		**Details**
Percent change in SES-CD from baseline at Week 12		
ANCOVA: as in primary analysis of the primary endpoint with sensitivity analyses for baseline SES-CD	FAS	LOCF
Descriptive statistics by treatment group and visit	FAS	LOCF,OC
Endoscopic response at Week 12*		
Endoscopic remission at Week 12*		

Biological remission at Week 12 Clinical response at Week 12* Clinical remission at Week 12*			
Unadjusted risk differences and 95% confidence intervals	FAS	NRI	*Inc. subgroups (NRI)
Logistic regression with baseline corticosteroid use and SES-CD as covariates	FAS	NRI	
Endoscopic response at Week 48 Endoscopic remission at Week 48 Clinical remission at Week 48 Biological remission at Week 48			
Unadjusted risk differences and 95% confidence intervals	FAS	NRI	

[redacted]

7.7 EXTENT OF EXPOSURE

Treatment duration (as described in Section 5.4) will be summarised for BI 706321/placebo and for ustekinumab. Descriptive statistics (N, Mean, SD, Min, Median, Max) for each will be tabulated. Frequencies and percentages of patients will also be tabulated for defined exposure categories in a cumulative fashion. Exposure categories for each are defined below.

Cumulative exposure categories to be displayed:

BI 706321/placebo	Ustkinumab
>0 days	>0 days
>=28 days	>=56 days
>=42 days	>=112 days
>=56 days	>=168 days
>=70 days	>=224 days
	>=280 days

7.8 SAFETY ANALYSIS

From CTP Section 7.2.5:

All treated patients (i.e. the TS) will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

All safety analyses will be performed following BI standards. No hypothesis testing is planned. The primary safety analysis will be based on data through the first 12 weeks of treatment at the time of the database snapshot after the last patient last visit for the primary endpoint, which is consistent with the timing of the primary efficacy analysis per CTP. Further analysis, once the trial is complete and has final database lock, will also be done which will include all safety data up to end of the Follow-up period will be produced.

7.8.1 Adverse Events

From CTP Section 7.2.5:

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All AEs with an onset between start of BI 706321/placebo + ustekinumab and end of the REP, a period of 16 days after the

last dose of trial medication (BI 706321/placebo), will be assigned to the Induction period for evaluation. Additionally, AEs with an onset between start of BI 706321/placebo + ustekinumab and (e)EOS will be assigned to the Induction + Follow-up period. AEs with onset before the first intake of any trial medication will be assigned to the Screening period.

...

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring only during the Induction period or the Induction+Follow-up period as defined above will be considered 'treatment-emergent' during the respective period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at database lock. Summaries will be presented by treatment for all AEs and the defined AESIs.

For the Induction period, all AEs occurring between the first intake of BI 70631/placebo and the last intake of BI 70631/placebo + REP will be assigned to the on-treatment period.

For the Induction + Follow-up period, all AEs occurring between the first intake of BI 70631/placebo and the (e)EOS will be assigned to the on-treatment period. The REP will be applied in cases where the (e)EOS is less than 16 days after the patient discontinues BI 706321/placebo.

According to ICH E3 (10), in addition to Deaths and serious adverse events, 'other significant' AEs need to be listed in the clinical trial report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of adverse events will be presented that will include the number of patients in the trial along with the frequency and percentage of patients with:

- Any AE
- Severe AE
- Investigator defined drug-related AEs
    - BI 706321
    - Ustekinumab
- AEs leading to discontinuation
    - BI 706321
    - Ustekinumab
- AEs of special interest (refer to Section 5.2.6.1.4 of the CTP)
- Serious AEs:
    - Death
    - Life threatening
    - Disability or permanent damage
    - Hospitalization (initial or prolonged)
    - Congenital Anomaly or Birth Defect
    - Other

- Other significant AEs (according to ICH E3)

The frequency of patients with AEs will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for patients with any AE, SAEs, AEs leading to treatment discontinuation (separately for BI 705321/placebo, ustekinumab), AEs by severity, related AEs (separately for BI 705321/placebo, ustekinumab) serious and related AEs, and AEs of special interest.

The system organ classes will be sorted by frequency, PTs will be sorted by frequency (within SOC).

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 system organ class and preferred term. The frequency of patients with SAEs and drug related SAEs will also be summarised.

For disclosure of AE data in the EudraCT registry, the frequency of serious drug-related AEs by treatment, primary SOC and PT will be tabulated.

Items for these registries will be included in Appendix 16.1.13.1.

7.8.2 Laboratory data

From CTP Section 7.2.5:

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (11). Refer to Section 6.6 for rules for handling laboratory data and Section 6.7 for the assignment of time windows for visits. Note that data from the central laboratory will be used for all displays described below, unless otherwise specified.

Treatment periods for laboratory analyses are defined as follows:

- **Induction period:** All samples collected between the first intake of BI 70631/placebo and the last intake of BI 70631/placebo + REP will be assigned to the on-treatment period.

- **For the Induction + Follow-up period:** All samples collected between the first intake of BI 70631/placebo and the (e)EoS will be assigned will be assigned to the on-treatment period. The REP will be applied in cases where the (e)EoS is less than 16 days after the patient discontinues BI 706321/placebo

For continuous safety laboratory parameters, converted values (original values that are converted to standard units, if different) will used and differences to baseline will be calculated. Only patients with at least one available post-baseline value will be included in the analysis of an individual laboratory parameter. Parameters collected only at screening will not be included in tables. All individual laboratory data will be listed. Values outside the reference range will be flagged.

Descriptive statistics of converted laboratory values over time and for the difference from baseline will be and provided by visit, 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; shift tables will be provided for the number of patients below, normal, and high values at baseline versus the category for the minimum, maximum and last measurement on treatment. Additionally, a frequency table of patients with low, normal, and high laboratory values by treatment and visit will be presented.

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on converted lab values. These rules will be listed in the Subject Data Listing appendix of the CTR. Frequency tables will summarize the number of patients with potentially clinically significant abnormalities. Two tabulations will be presented; one that excludes patients having a potential clinically significant abnormal lab value at baseline and one that includes all patients. A separate listing will present all patient's lab values for the parameter where at least one lab value with clinically significant abnormality within the group.

The frequency of patients with AST or ALT elevations ≥ 3xULN along with total bilirubin ≥ 1.5xULN, 2xULN within a 30 day period will be produced. Those with total bilirubin >-2xULN will also be categorized by those having ALP<2xULN and ALP≥2xULN. 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 standardised laboratory values. Frequencies of patients with > 3xULN, 5xULN, 10xULN, and 20xULN for ALT and AST separately will be presented as well. A graphical analysis of the ALT and total bilirubin during the on-treatment period will also be performed; the so called eDISH plot. In the graph, for each subject, the peak total bilirubin is presented as a fold increase over the ULN against the peak ALT as a fold increase over the ULN, on a log10 scale. The measurements displayed 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).

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate, body temperature, body weight, and respiratory rate) will be descriptive in nature.

Descriptive statistics of vital signs over time (by visit) and for the difference from baseline will be provided by treatment and will include the last value during on-treatment period, the

minimum value during on-treatment period, and the maximum value during on-treatment period for a) the induction period and b) the induction+follow-up period.

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

7.8.4 ECG

The analysis if the centrally read ECG data will be based on the ECGs. Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator. The analyses of ECG quantitative endpoints will be descriptive in nature.

ECG data will be summarized descriptively by visit (only for the quantitative endpoints) and dose group and listed. Occurrences of values above thresholds (see Section 5.3) will be flagged in the listings. For QTcB and RR, only listings will be provided.

Categorical endpoints

For the categorical endpoints (see Section 5.3), frequency tables will be provided.

Categorical endpoints will also include morphological findings that might be attributable to treatment during the induction period. In particular, new onsets of findings not present at baseline will be explored. A morphological finding observed on treatment that was not reported at baseline will be categorized as a ‘new onset’ of this finding.

For all patients with any notable finding in ECG intervals, a separate listing will be created as end-of-text display, and the corresponding time profiles over the induction + follow-up period will be shown.

Quantitative endpoints

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the pre-dose absolute values and changes from baseline over time of QTcF, HR, QT, PR and QRS by visit and dose group for the inducuction + follow-up period. For each endpoint (QTcF, HR, QT, PR and QRS) the time profiles of mean and associated SD for the changes from baseline through the last ECG measurement will be displayed graphically for each dose group.

A scatterplot of QTcF at baseline and the maximum change from baseline (based on all on treatment values during the induction period, independent of whether these were selected for analysis based on time windows described in Section 6.7) will be produced. The plot will include diagonal reference lines at absolute QTcF being equal to 450 msec, 480 msec and 500 msec (thus, the occurrence of new onsets of high categories for absolute values can be directly seen), as well as horizontal reference lines at 30 msec and at 60 msec for the maximum QTcF change from baseline.

Frequency tables will be provided for the categorical variables described which are determined from the quantitative ECG variables.

7.8.5 Others

Not applicable

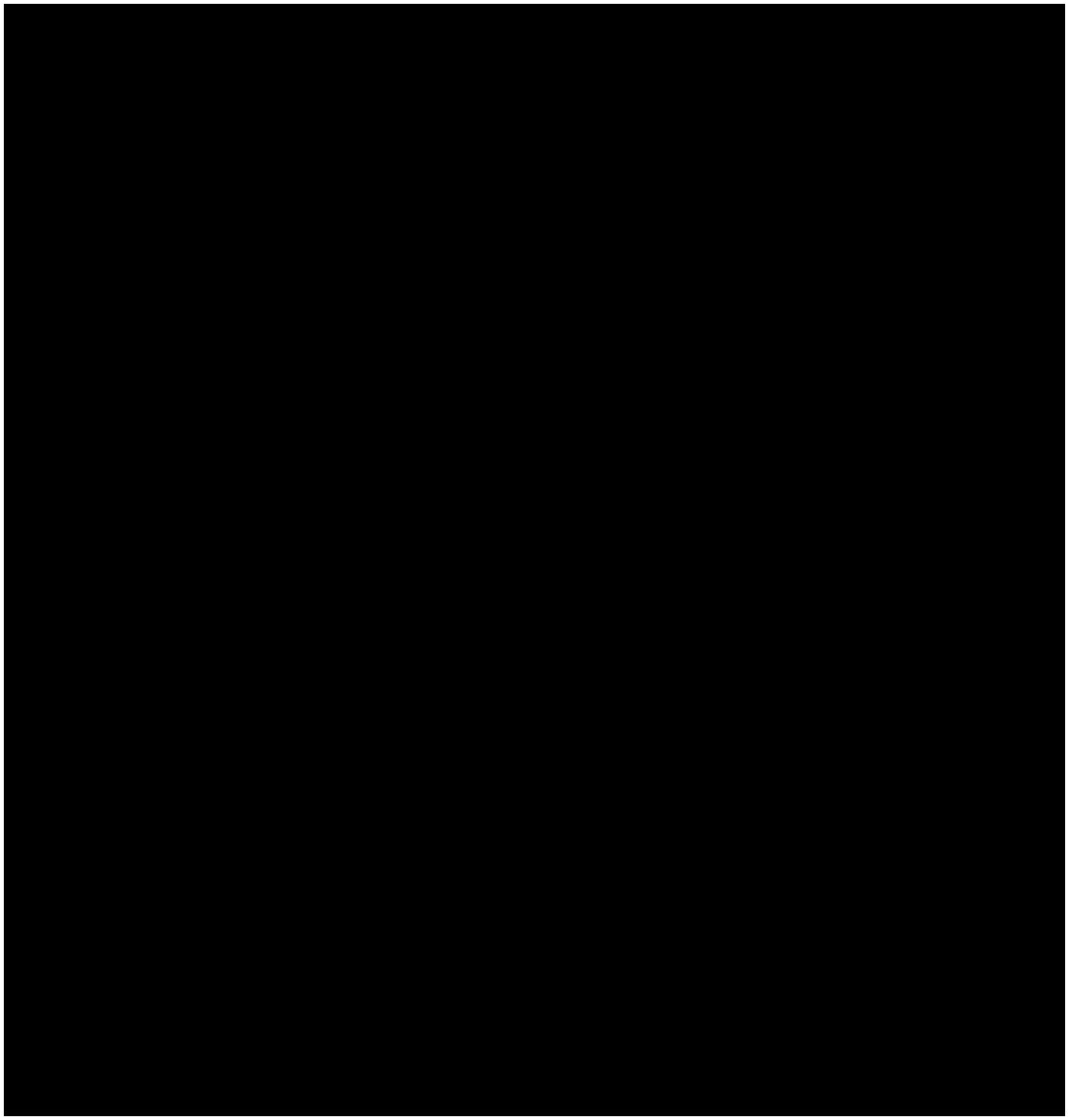
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

From CTP Section 4.1.5: 1:

Unblinded descriptive analyses will be performed at different time points during the trial conduct. The release of treatment codes at the individual time points will be documented accordingly.

9. REFERENCES

1.	*BI-KMED-TMCP-HTG-0025:* "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, Group "Biostatistics & Data Sciences", current version; KMED.
2.	*BI-VQD-12045_40-413:* Identify and Manage Important Protocol Deviations (iPD)", current version; KMED
3.	*KM Asset BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
4.	*KM Asset BI-KMED-BDS-HTG-0045:* "Standards for Reporting of Clinical Trials and Project Summaries", current version; KMED
5.	*Brown LD, Cai TT, DasGupta A.* Confidence intervals for a binomial proportion and asymptotic expansions. Ann Stat 30 (1), 160 – 201 (2002). [R12-3710]
6.	*Newcombe RG.* Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med 17, 873 – 890 (1998). [R08- 4386]
7.	*Ge M, Durham LK, Meyer RD, Xie W, Thomas N, Covariate-adjusted difference in proportions from clinical trials using logistic regression and weighted risk difference. Drug Inf J; 2011; 45; 481-493 [R16-5360]*
8.	*Heinze G, Schemper M.* A solution to the problem of separation in logistic regression. Statistics in Medicine 21: 2409-2419 (2002).
9.	*Firth D*. Bias reduction of maximum likelihood estimates. *Biometrika* 80, 27–38 (1993).
10.	*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, EMA webpage.
11.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON
12.	Lemmens, H.J.M., Brodsky, J.B. & Bernstein, D.P. Estimating Ideal Body Weight – A New Formula. *OBES SURG* **15,** 1082–1083 (2005).



10.2 DETAILED DESCRIPTION OF CDAI DERIVATION

The CDAI is derived based on eight components: number of liquid stools, extent of abdominal pain, general well-being, occurrence of extraintestinal symptoms, need for antidiarrheal drugs, presence of abdominal masses, haematocrit, and body weight.

a) From the diary, the average of the daily number of liquid or soft stools over the 7 days prior to the visit is calculated as sum of number of liquid or soft stools per day divided by the number of reported days. The average score is taken, multiplied by 7 and multiplied by 2.
Bowel preparation day(s), day of ileocolonoscopy, and day after ileocolonoscopy will not be used in the calculation of the 7 day totals if these procedures occur within the 7 days preceding the visit date. In these cases the window preceding the visit day may extend from 7 up to 11 days.

b) From the diary, the average of the daily abdominal pain rating over the 7 days prior to the visit is calculated as sum of abdominal pain rating (0=none, 1=mild, 2= moderate, 3=severe) per day divided by the number of reported days. The average score is taken, multiplied by 7 and multiplied by 5.
Bowel preparation day(s), day of ileocolonoscopy, and day after ileocolonoscopy will not be used in the calculation of the 7 day totals if these procedures occur within the 7 days preceding the visit date. In these cases the window preceding the visit day may extend from 7 up to 11 days

c) From the diary, the average of the daily general well-being rating over the 7 days prior to the visit is calculated as sum of the general well-being rating (0=generally well, 1= slightly under par, 2=poor, 3= very poor, 4= terrible) per day divided by the number of reported day. The average score is taken, multiplied by 7 and multiplied by 7.
Bowel preparation day(s), day of ileocolonoscopy, and day after ileocolonoscopy will not be used in the calculation of the 7 day totals if these procedures occur within the 7 days preceding the visit date. In these cases the window preceding the visit day may extend from 7 up to 11 days

d) From the investigator physical assessment, the number complications (arthritis or arthralgia, iritis or uveitis, erythema nodosum, pyroderma gangrenosum or aphthous stomatitis, anal fissure, fistula or perianal abscess, other bowel-related fistula, and fever over 37.8 degree C (100 F)) is multiplied by 20.

e) Use of medication taken for diarrhoea (0=no, 1=yes) is multiplied by 30.

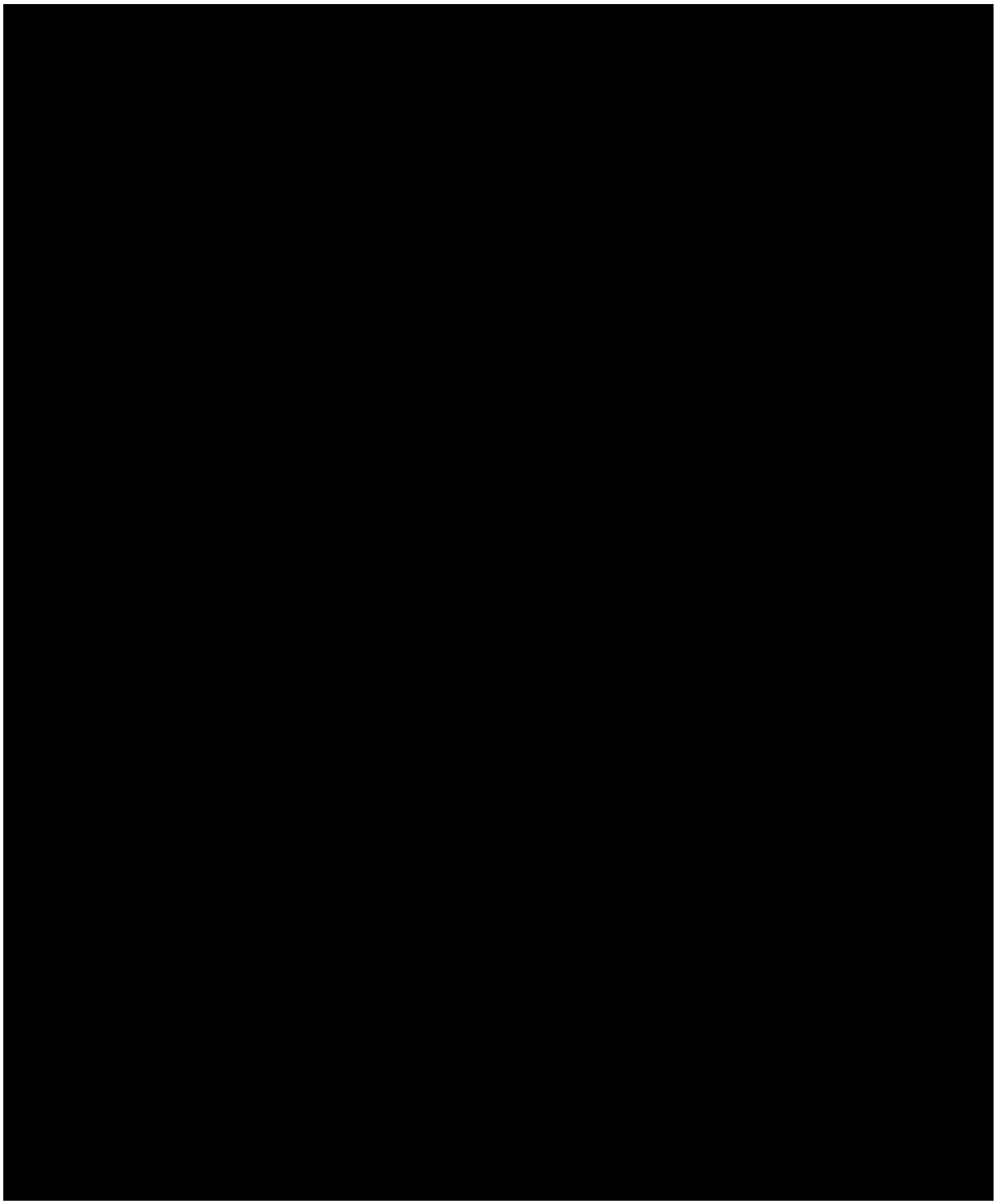
f) Abdominal mass (0=no, 2 questionable, 5= definite) is multiplied by 10.

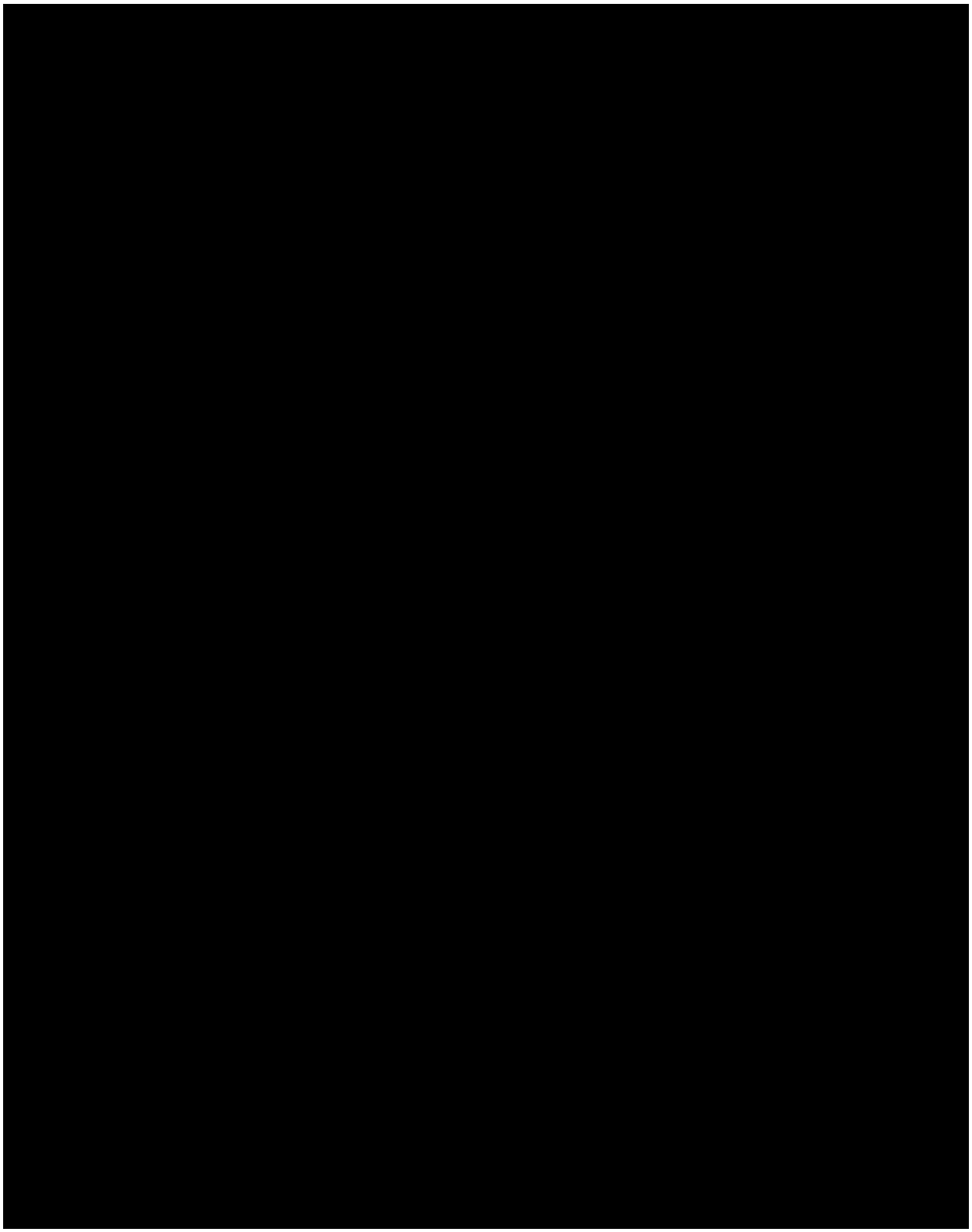
g) Haematocrit (males: maximum of ((47-HCT (%))*6 and 0), females: maximum of ((42-HCT (%))*6 and 0). HCT should be rounded to an integer number.

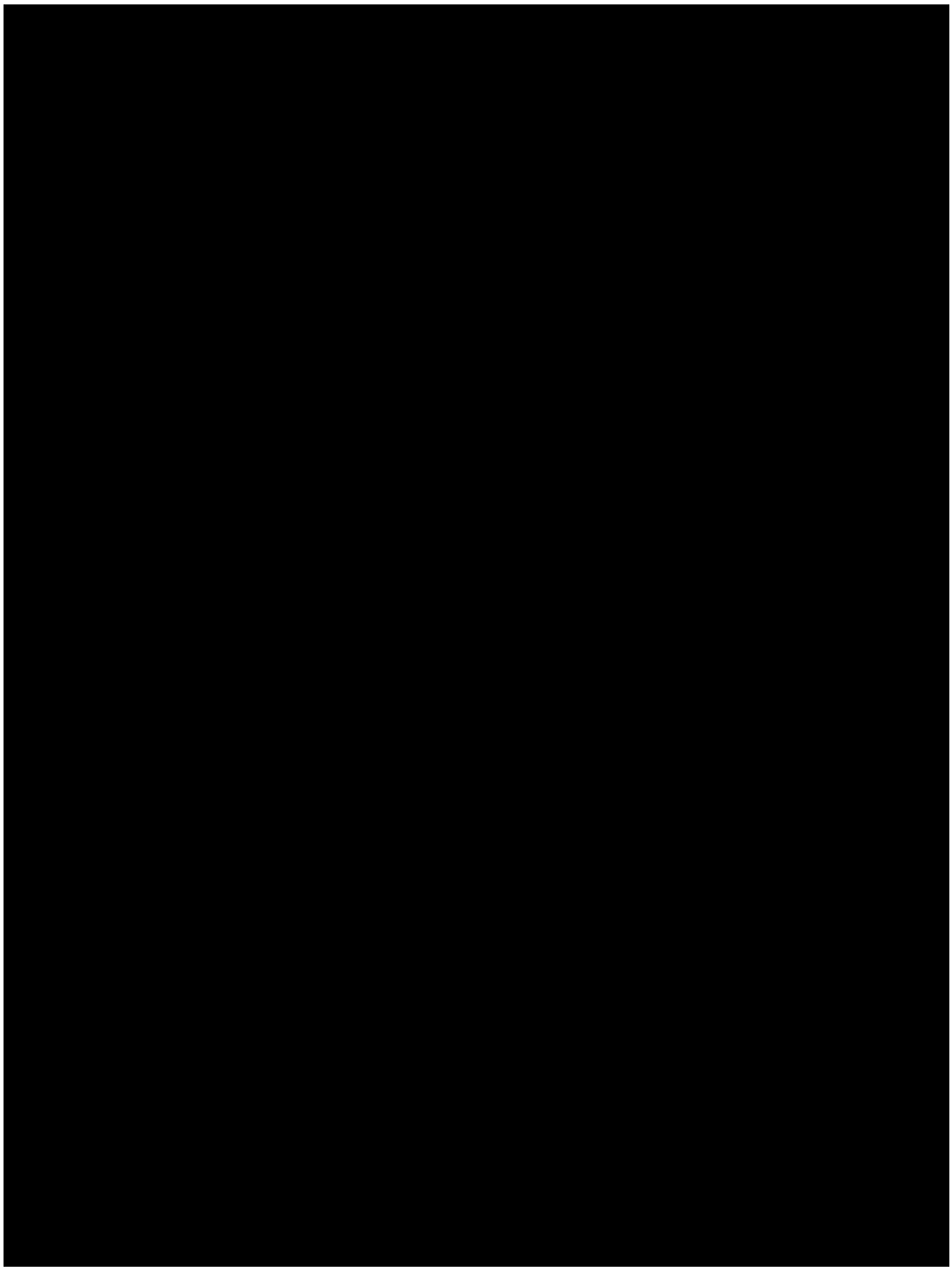
h) Body weight (1-(current weight kg/standard ideal body weight)) multiplied by 100. Ideal body weight is calculated as 22 x H^2, where H is the patient height in meters (12). For the calculation, body weight is rounded to 3 decimal places. If the calculated value is less than -10 then the value is set to -10.

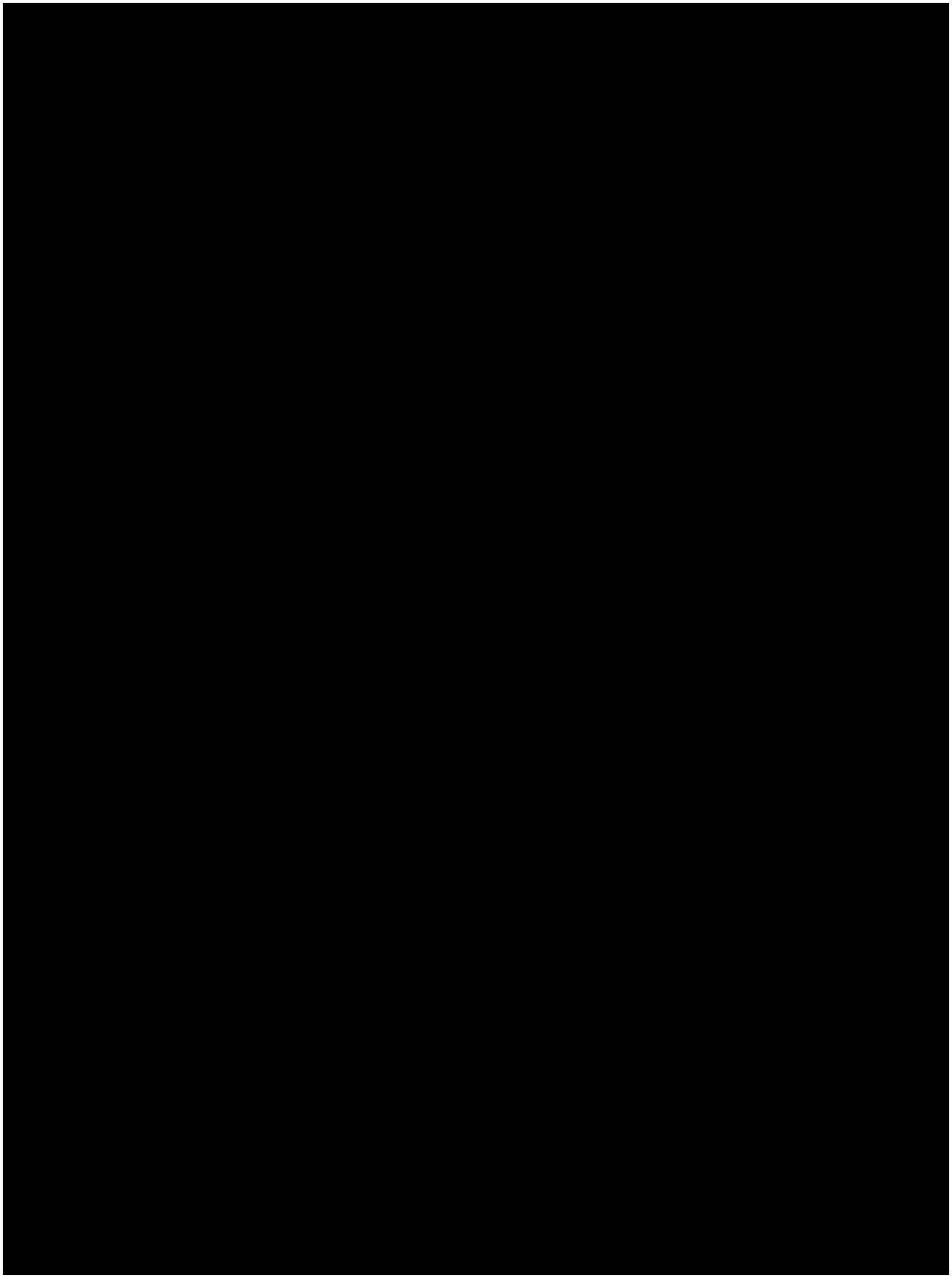
The expected range of the scores is 0 to ~600.The CDAI is derived as the sum over the eight scores. In case of a negative score the score will be set to zero.

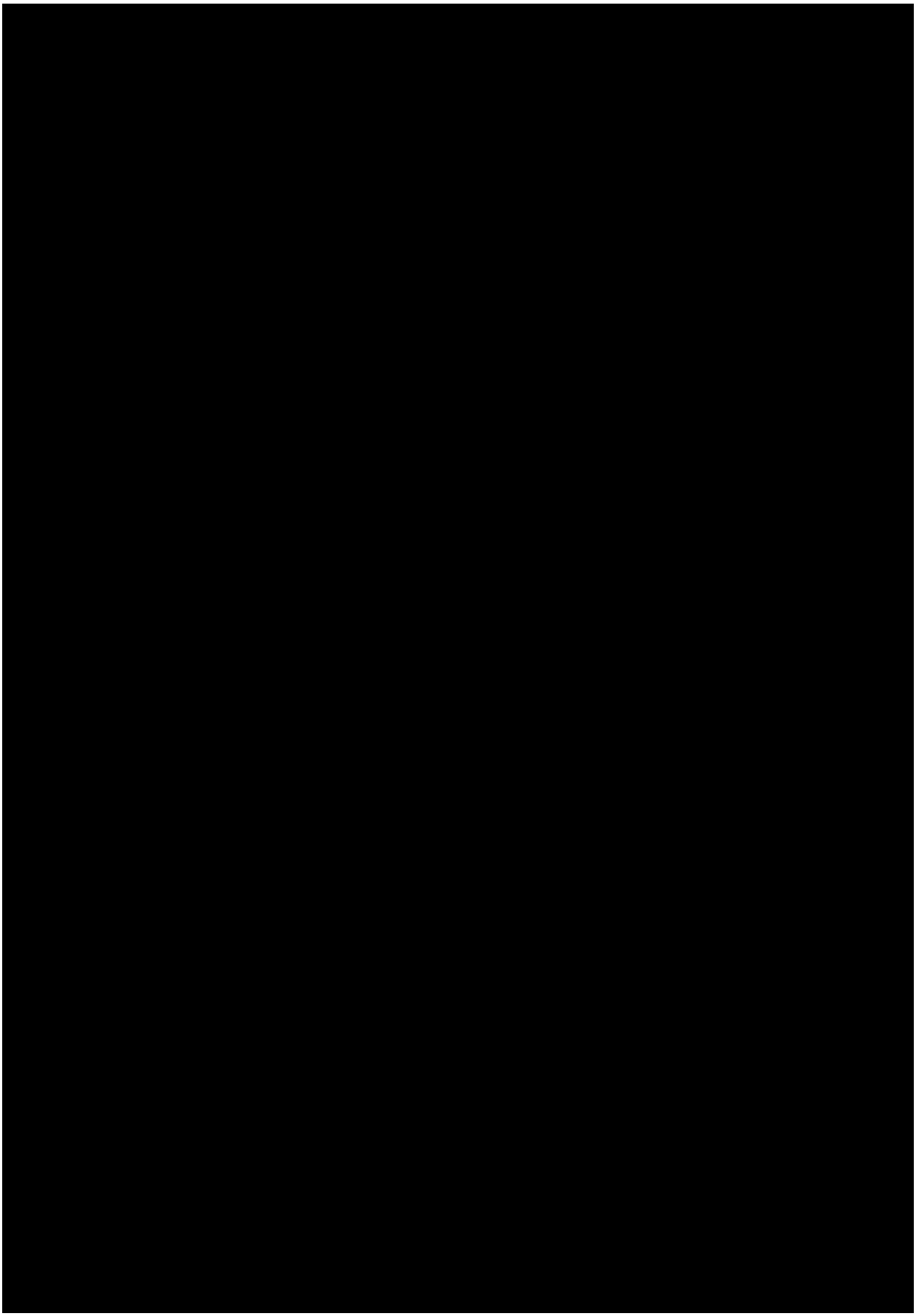
Refer to Section 6.6.2 for handling of missing data.

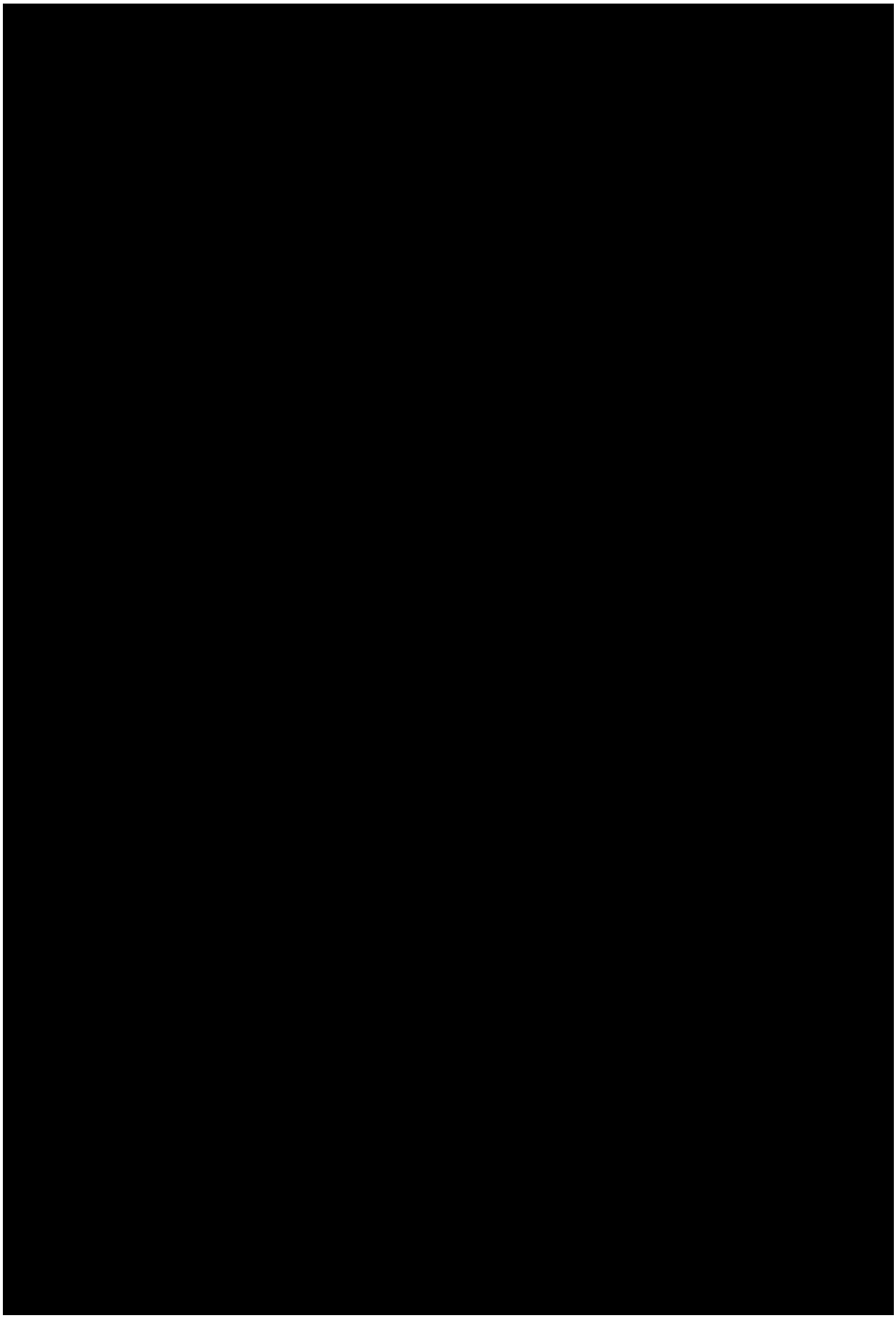


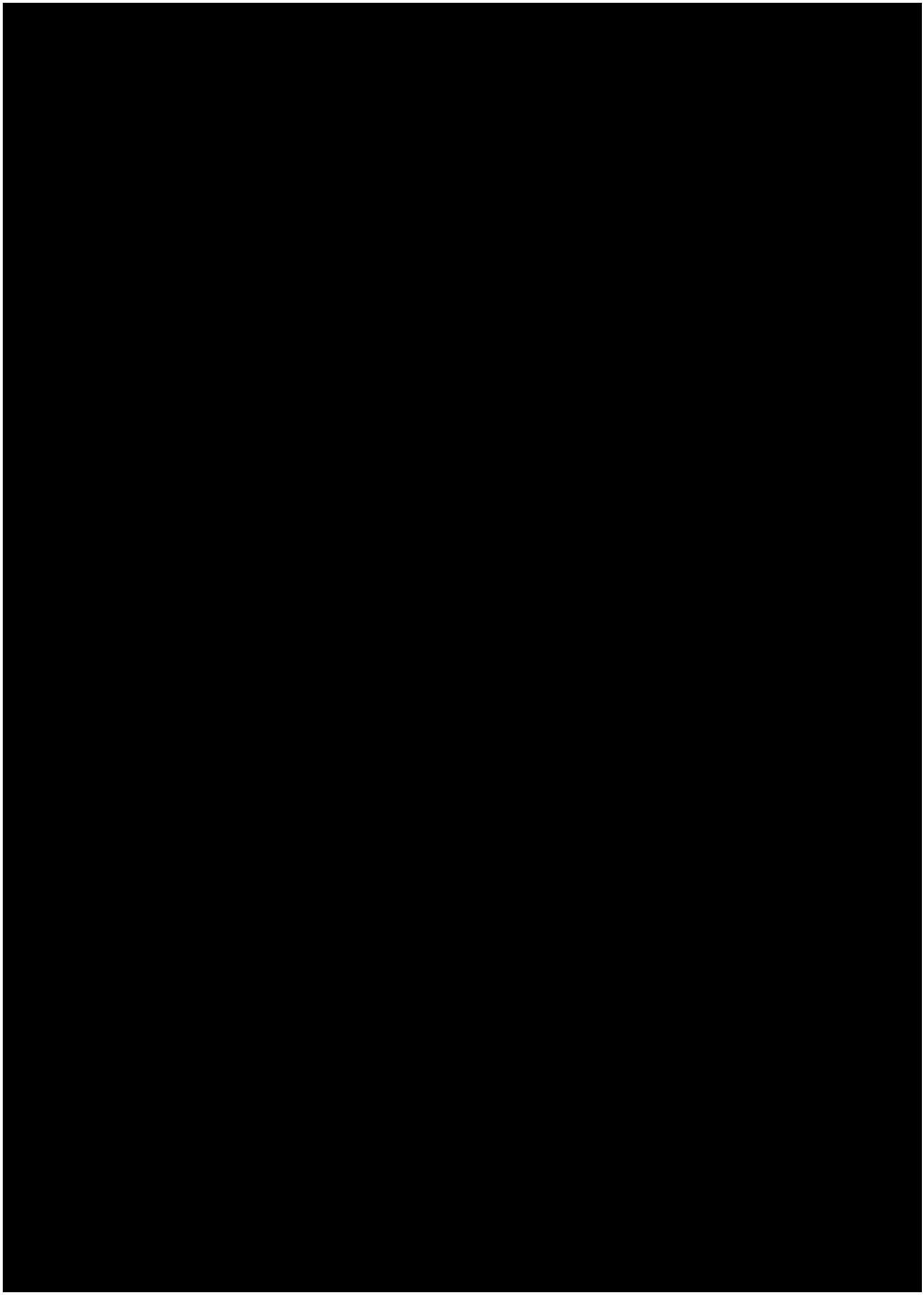












11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**29-NOV-2022**	[redacted]	None	This is the initial TSAP to be approved prior to any release of treatment information.
2	**02-AUG-2024**	[redacted]	4,5, 6, 7	Updated to reflect complete analysis of the trial and decisions made since the first version