TRIAL STATISTICAL ANALYSIS PLAN

c35537257-01

BI Trial No.:	1469-0002
Title:	A phase I open-label trial of BI 3011441 in Japanese patients with NRAS/KRAS mutation positive advanced, unresectable or metastatic refractory solid tumours Based on revised Clinical Trial Protocol (c30222580-03; Version 3.0; 19 November 2020)
Investigational Product:	BI 3011441
Responsible trial statistician:	[redacted] Telephone: [redacted], Fax: [redacted]
Date of statistical analysis plan:	23Dec2022 SIGNED
Version:	1.0

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AO	Aldehyde oxidase
aPTT	Activated partial thromboplastin
AST	Aspartate transaminase
AUC	Area under the concentration-time curve of the analyte in plasma
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
BRAF	v-Raf murine sarcoma viral oncogene homolog B
CA	Competent Authority
CK	Creatine kinase
CK-MB	Creatine kinase myocardial band
CKD-EPI	Chronic Kidney Disease Epidemiology
C_{max}	Maximum measured concentration of the analyte in plasma
[redacted]	[redacted]
CRA	Clinical Research Associate
CRC	Colorectal cancer
CREE	Enzymatic serum creatinine assay
CREJ	Non IDMS standardised Jaffe
CREJIDMS	Isotype dilution mass spectrometry standardised Jaffe
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Computed Tomography
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol

CYP	Cytochrome P450
DCR	Disease Control Rate
DILI	Drug Induced Liver Injury
DLT	Dose limiting toxicity
[redacted]	[redacted]
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
eDC	Electronic Data Capture
EGFR	Epidermal growth factor receptor
[redacted]	[redacted]
EOR	End of residual effect
EOT	End of Treatment
ERK	Extracellular signal-regulated kinases
EWOC	Escalation with overdose control
FFPE	Formalin-fixed paraffin-embedded
FMO	Flavin-containing monooxegenases
FU	Follow up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HCO_3	Bicarbonate
[redacted]	[redacted]
IB	Investigator's Brochure
IC50	Inhibitory concentration (50%)
IDMS	Isotype dilution mass spectrometry
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
KRAS	Kirsten rat sarcoma viral oncogene homologue
LVEF	Left ventricular ejection fraction
MAO	Monoamine oxidases
MAP	Mitogen-activated protein
MAPK	Mitogen-activated protein kinase

MedDRA	Medical Dictionary for Drug Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
NSCLC	Non-small cell lung cancer
OPU	Operative Unit
[redacted]	[redacted]
p.o.	per os (oral)
[redacted]	[redacted]
PFS	Progression-free survival
PK	Pharmacokinetics
PK/PD	Pharmacokinetics / Pharmacodynamics
[redacted]	[redacted]
PT	Prothrombin time
QTcF	QT interval
RAC	Accumulation Index
RAF	Rapidly Accelerated Fibrosarcoma
RAS	Rat sarcoma
RD	recommended dose
[redacted]	[redacted]
REP	Residual effect period
RPED	Retinal Pigment Epithelial Detachment
[redacted]	[redacted]
SAE	Serious adverse event
SD	Standard deviation
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
[redacted]	[redacted]
[redacted]	[redacted]
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	[redacted]
[redacted]	[redacted]

TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
WHO	World Health Organisation
β -HCG	beta human chorionic gonadotropin

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

SAS® Version 9.4 will be used for all analyses.

Pharmacokinetics (PK) parameters will be calculated using Phoenix WinNonlinTM software (version 8.1 or higher).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

This section is not applicable.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary objective of this trial is to confirm the safety and tolerability of previously identified MTD, BI 3011441 8mg (in Caucasian FIH study) as a single agent when administered orally to adult Japanese patients with NRAS/KRAS mutation positive advanced or metastatic refractory solid tumours.

In this trial, the MTD is an unknown parameter to be determined as the highest dose with less than 25% risk of the true DLT rate being equal to or above 33%. It is estimated by the Bayesian Logistic Regression Model (BLRM), which is specified in CTP Section 7 based on the frequency of patients experiencing dose limiting toxicities (DLTs) during the MTD evaluation period. The MTD is determined by the SMC. For the definition of DLTs, refer to CTP Section 5.2.6.3.

The primary endpoints in this trial are specified in CTP Section 2.1.2; they are

- MTD defined as the highest dose with less than 25% risk of the true DLT rate being equal
- or above 33% during the MTD evaluation period.
- Number of patients with DLTs in the MTD evaluation period.

5.2 SECONDARY ENDPOINTS

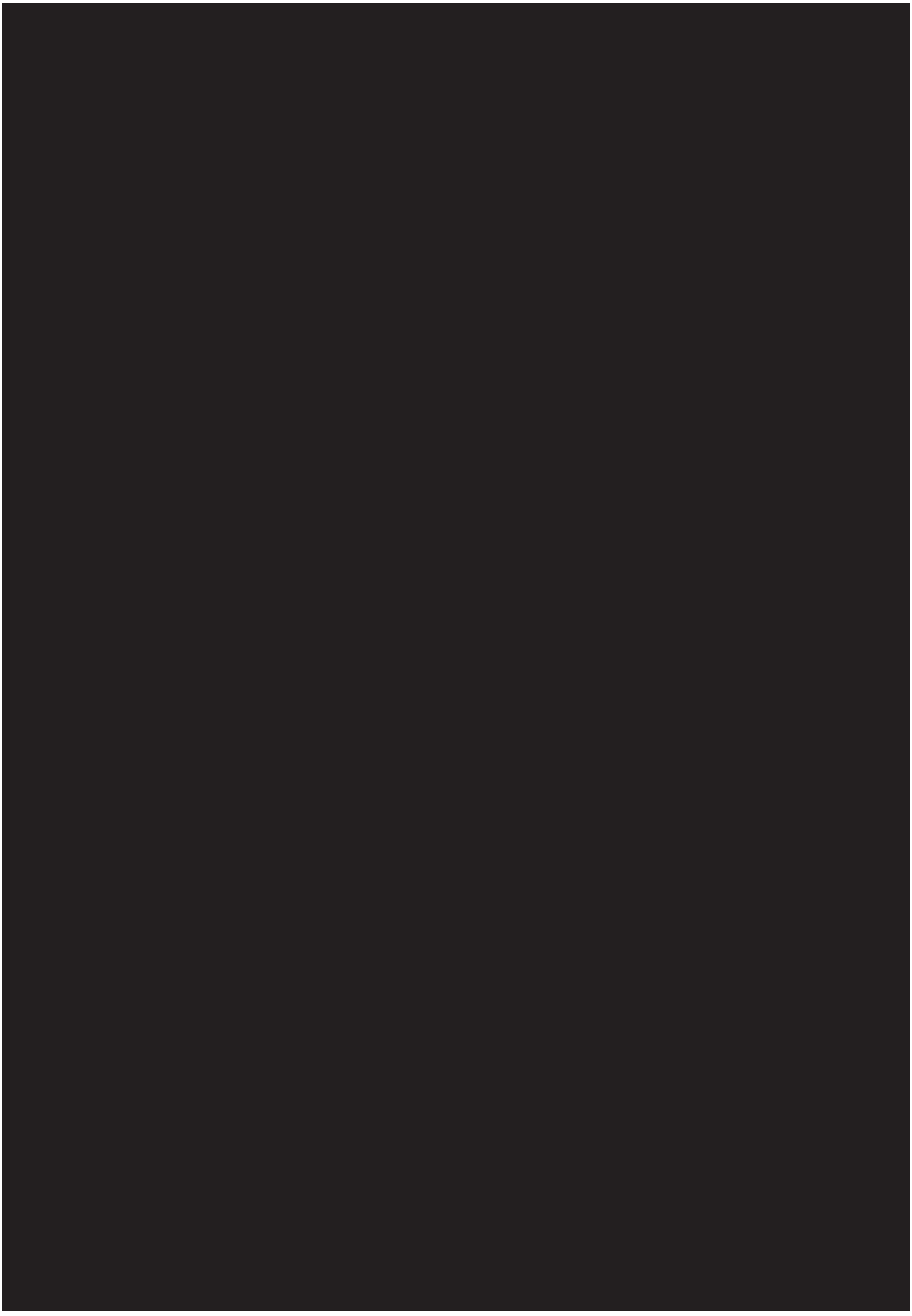
5.2.1 Key secondary endpoint

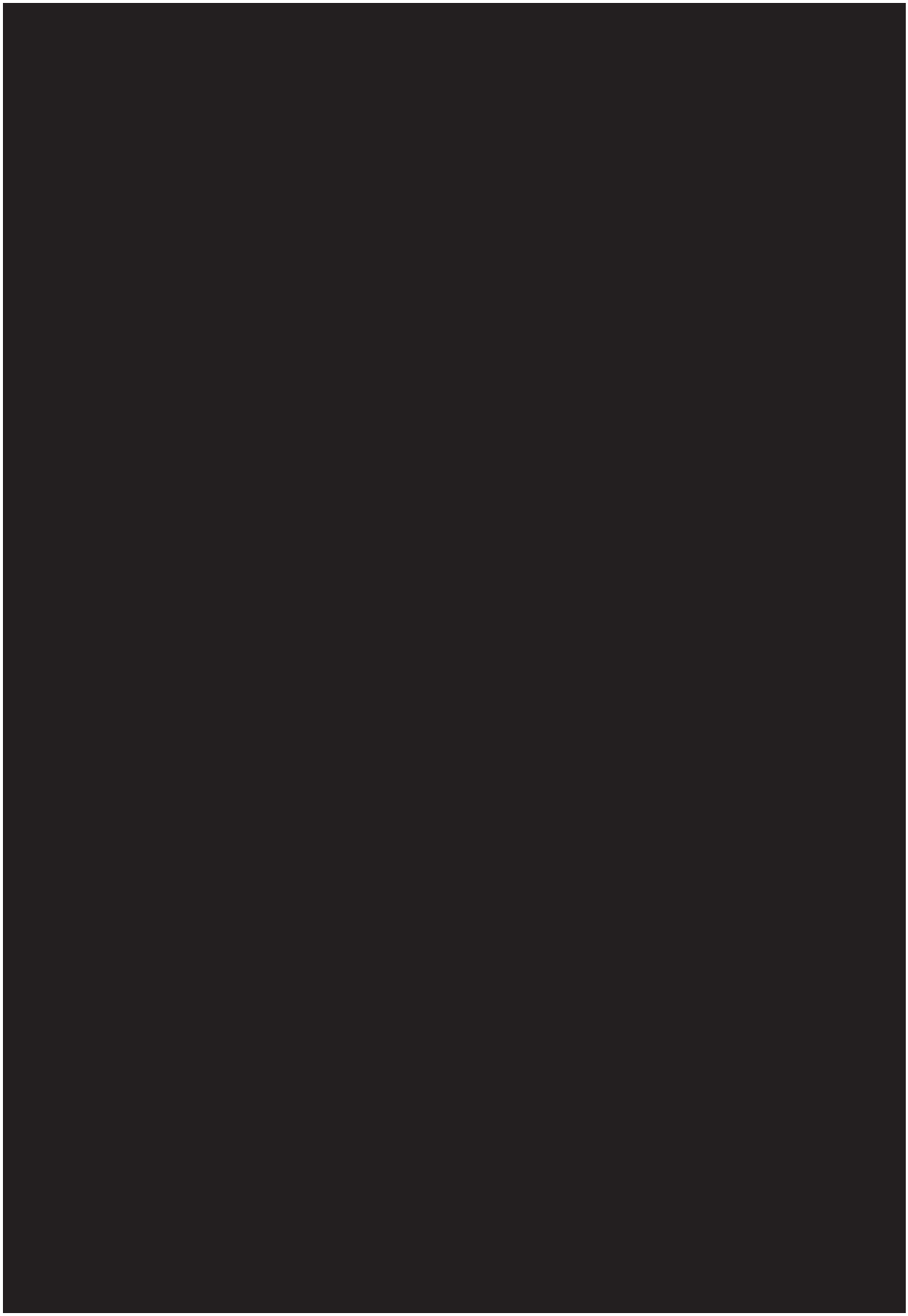
This section is not applicable as no key secondary endpoints have been specified in the protocol.

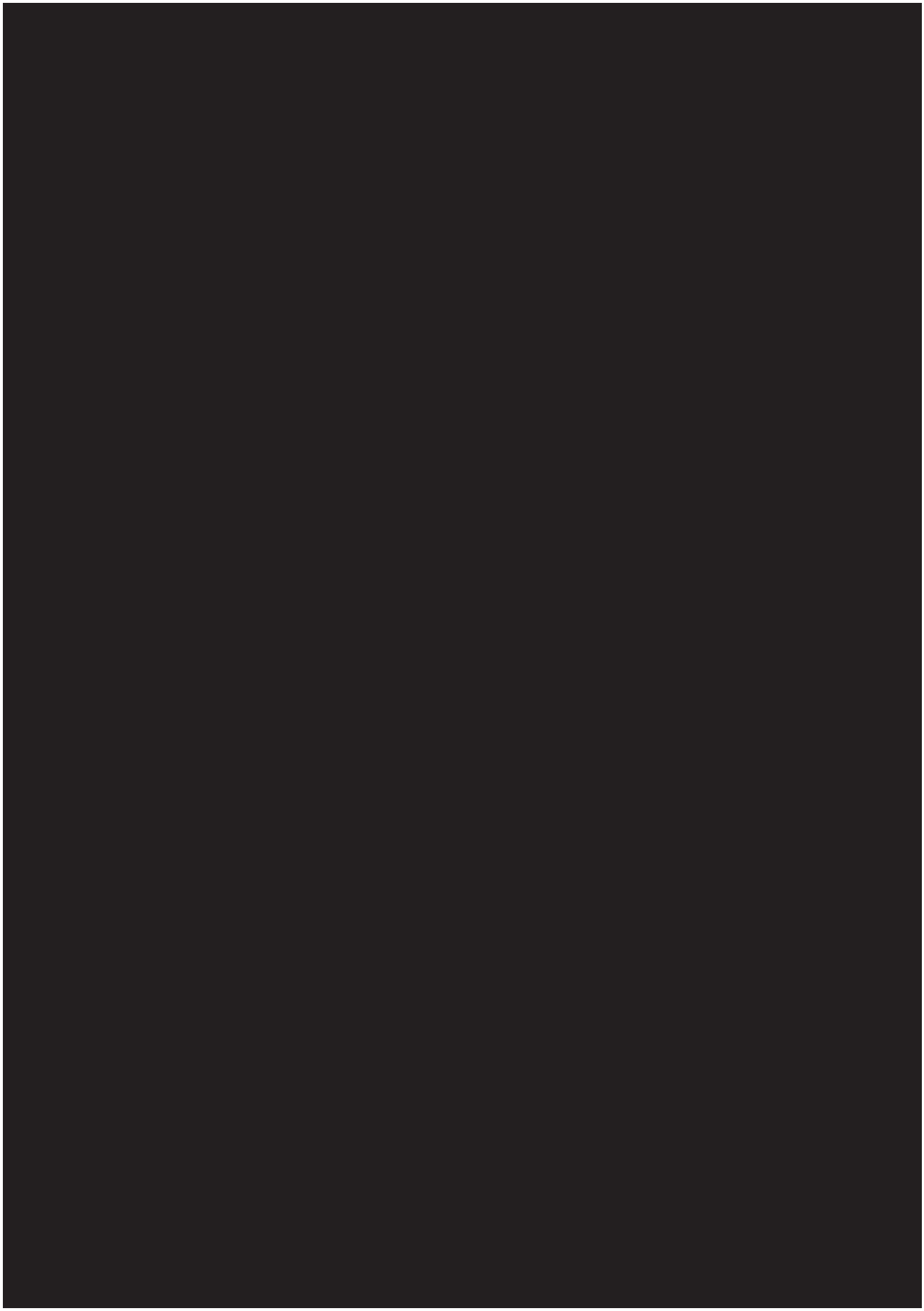
5.2.2 Secondary endpoints

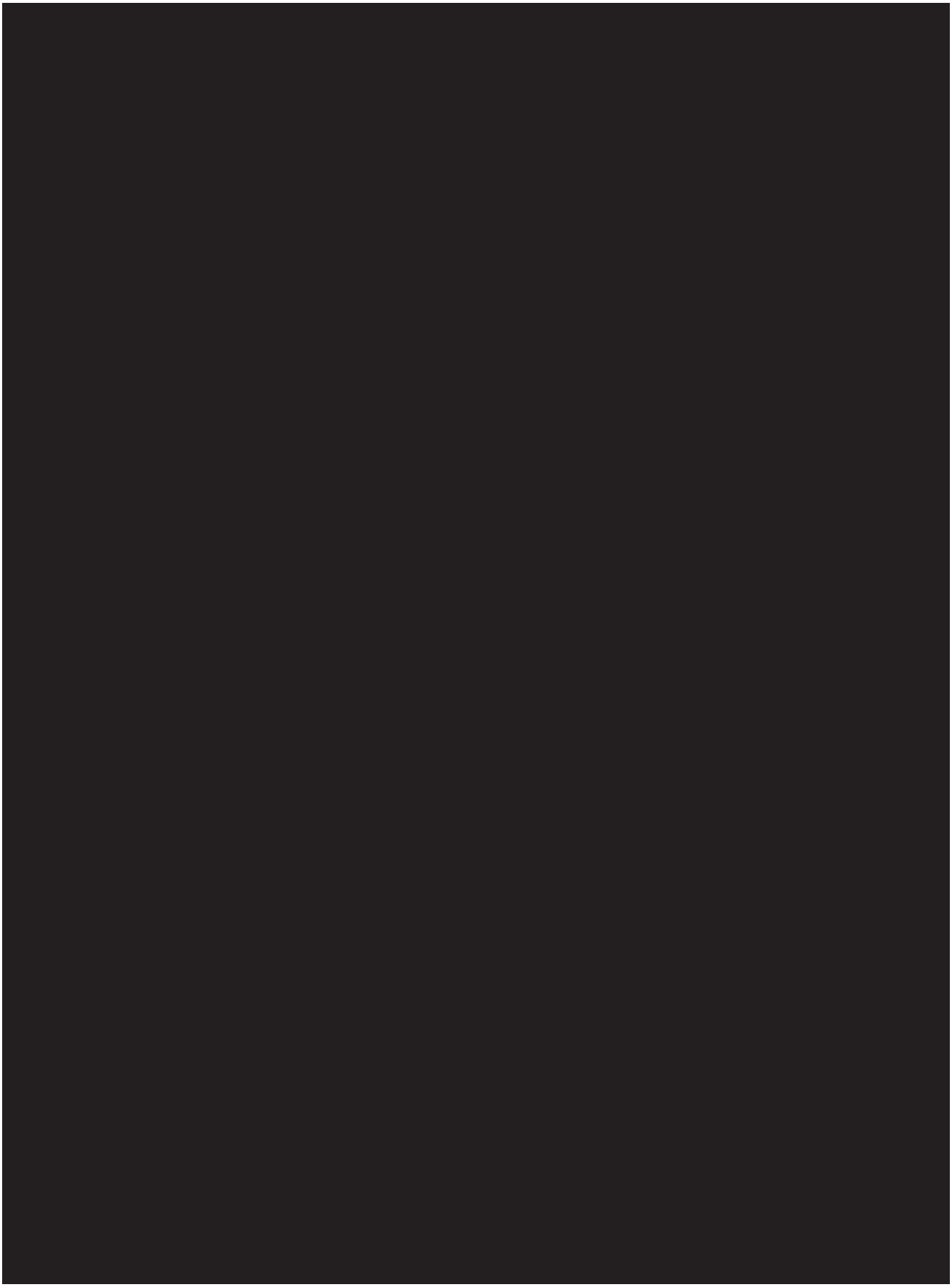
The secondary endpoints are, as specified in CTP Section 2.1.3:

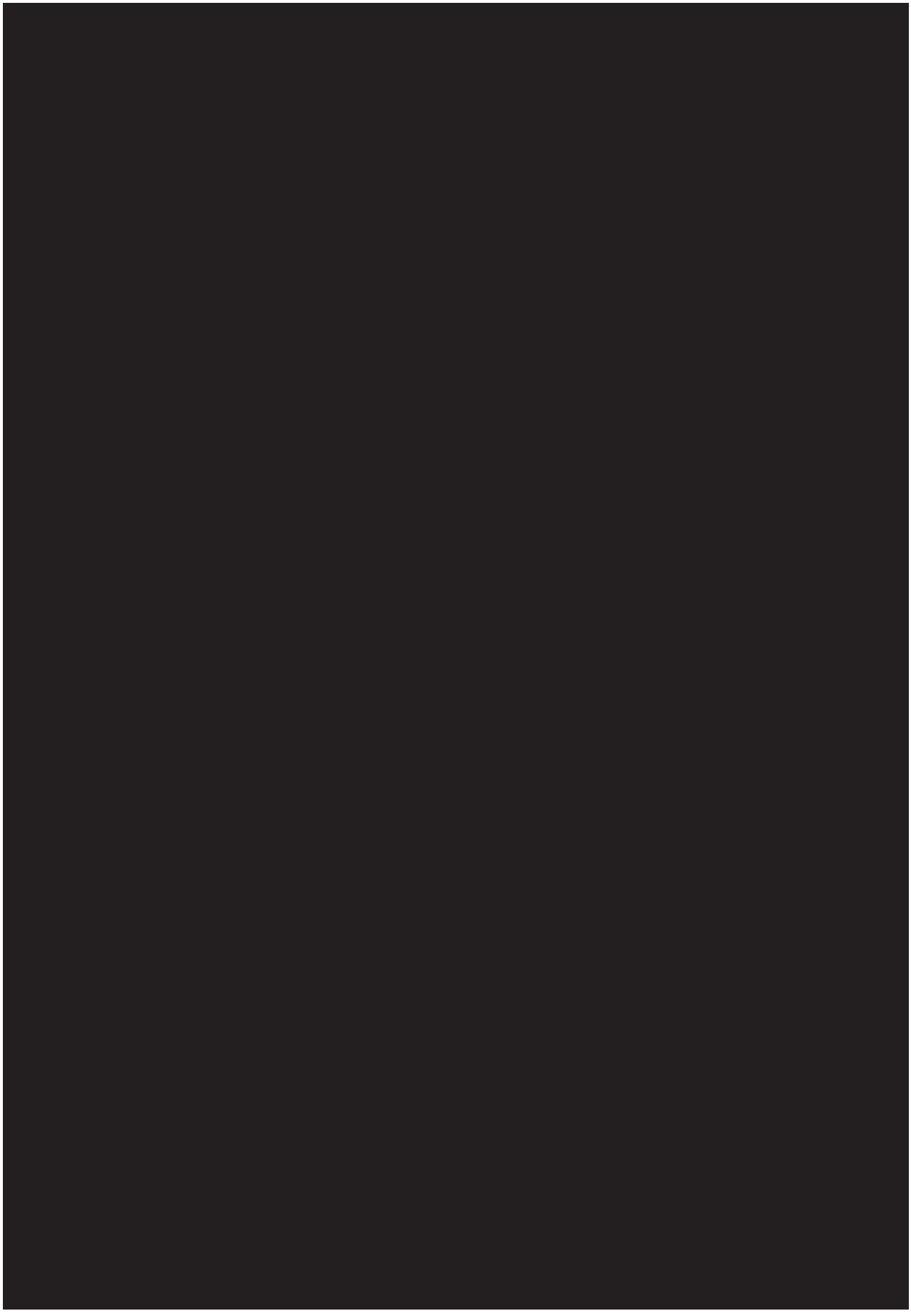
- Number of patients with DLTs during the entire on-treatment period
- Number of patients with Grade ≥3 treatment-related adverse events
- Number of patients with treatment related adverse events at each dose level
- Pharmacokinetic parameters of BI 3011441: $C_{max\ (,ss)}$, and $AUC_{0\text{-}tz(,ss)}$











[redacted]

[redacted]

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT

The trial is an open-label phase I trial with dose escalation, confirmation and expansion of BI 3011441 as monotherapy. For basic study information such as treatments to be administered, assignment of treatment groups, and selection of doses, see CTP Section 4.

For safety analyses, AEs will be classified to one of the following time periods: "Screening", "On-treatment" or "Follow-up." This will be applied for all adverse events. Detailed rule for assigning AEs to these time periods are listed below.

- If the date of informed consent ≤ AE onset date < date/time of first administration of trial treatment, then the AE is assigned to "Screening";
- If date of first administration of trial treatment ≤ AE onset date ≤ date of last administration of trial treatment + 30 days of Residual Effect Period (REP), then the AE is assigned to "On-treatment";
- If AE onset date > date of last administration of trial treatment + 30 days, then the AE is assigned to "Follow-up"

Table 6.1: 1 Definition of analysis treatment periods for safety analysis

Analysing Treatment Period	**Start Date**	**Stop Date**
Screening	Date of informed consent	Date/Time of the first administration of trial treatment
On-treatment	Date of the first administration of trial treatment	Date of the last administration of trial treatment + 30 days of REP
Follow-up	Date of the last administration of trial treatment + 31 days	Date of the last visit
MTD evaluation period*	Date of the first administration of trial treatment	Date of the first administration of trial treatment + 28 days (i.e., treatment cycle)

*The MTD evaluation period is only applied to the patients in the dose escalation part of the trial.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS.

6.3 SUBJECT SETS ANALYSED

- Screened Set:

This subject set includes all patients who have signed the informed consent. The screened set is used for patient disposition tables.

- Treated Set (TS):

This subject set includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment. The treated set is used for both efficacy analyses and safety analyses.

- MTD Set:

This subject set includes all patients evaluable for MTD in the dose escalation part of the trial, who were not replaced within the MTD evaluation period. Replaced patients will also be included (refer to CTP Section 3.3.4.1.2 for criteria for being evaluable for MTD). The MTD set will be used for Bayesian Logistic Regression Models (BLRMs).

- PK Analysis Set (PKS):

This subject set includes all patients in the treated set who provided at least one evaluable observation for at least one PK endpoint and were not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability. Analyses of PK parameters will be based on the PKS. The PKS will be used for statistical pharmacokinetic analyses.

Plasma concentrations and/or parameters of a patient will be considered as nonevaluable, if for example

1) The patient experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the patients experiencing emesis),
2) A predose concentration is >5% C_{max} value of that patient in the respective treatment period
3) Missing samples/concentration data at important phases of PK disposition curve

[redacted]

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

Every effort should be made to collect complete data at each visit for each patient. If not specified otherwise, missing data will not be imputed and remain missing. Potential outliers will be reported and analysed as observed.

Missing or incomplete AE dates are imputed according to BI standard (see "Handling of missing and incomplete AE dates") (2)

Missing data and outliers of PK data are handled according to the relevant BI standard (see BI-KMED-TMCP-MAN-0012: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics" (5) and BI-KMED-TMCP-MAN-0014 "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (6)). PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

In general, missing data not discussed in (2) and (6) will not be imputed unless required for the following analyses and definitions. Then the rules as described below apply.

Change of laboratory values from baseline

Laboratory values at baseline: For missing laboratory data at cycle 1 day 1 (before the first administration of any study medication) the data of preceding visits will be used if available.

Definition of on-treatment period and actual treatment

Date of permanent discontinuation of study medication: All reasonable efforts should be undertaken during the study to obtain the dates of permanent discontinuation of study medication. However, if the date of the very last administration is missing this will be imputed with:

- If only month and year are given, the last day of the month will be used for imputation
- If only the year is given, the 31st of December of this year will be used for imputation

If the imputed date leads to a date that is later than the date of the EOT visit, then the imputed date is the date of the EOT visit. If the imputed date leads to a date that is later than the death date, then the imputed date is the date of death.

Partial death dates

If a partial (year and month) death date is reported, the date will be imputed with the end of the month for the analysis of PFS. This is in line with the imputation of partial dates for the analysis of AEs.

Partial or missing start date of subsequent anti-cancer therapy/subsequent radiotherapy

If the day of the start date of subsequent systemic therapy/subsequent radiotherapy is missing, then the 1st of the month will be imputed unless this leads to a date before the stop date of study medication. In this case the stop date of study medication +1 day will be imputed.

If day and month, or day and month and year are missing, it will be distinguished whether the start date of subsequent systemic therapy/subsequent radiotherapy is required for censoring of PFS or for other descriptive statistics:

- For censoring of PFS: If only the year is reported, the 1st of January of this year will be imputed unless this leads to a date before the stop date of study medication. In this case the stop date of study medication +1 day will be imputed. In case of a completely missing start date of subsequent anti-cancer therapy/subsequent radiotherapy and the patient did not have any post-baseline tumour assessment or did not progress or die, the PFS of this patient will be censored at the day of first administration of study drug. Additionally, all imputed start dates of subsequent anti-cancer therapy/subsequent radiotherapy should be before death date, if available.
- For descriptive statistics: Dates will not be imputed if more than only the day of the date is missing.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Unless otherwise specified baseline is defined as the time point closest to but prior to the first administration of any study medication. If no time is specified and the date is the same as the first administration date, then it will still be considered baseline if not specified otherwise. If there is no measurement earlier than the first administration of study medication, then no baseline will be derived.

For laboratory parameters for which not only the examination date but also the sampling time was recorded, examination time should be taken into consideration when defining baseline. That is a laboratory measurement on the same date as the first administration of study treatment is considered as baseline if and only if the examination time of this laboratory measurement is before the first administration of study treatment. If any of these times is missing and the date of laboratory assessment is the same as the date of first administration of study medication, then the laboratory assessment will be considered as according to protocol, i.e., as prior to first study medication.

Study days and visits will be labelled according to the flow charts in the CTP. Study day will be calculated relative to the date of the first administration of study drug. The day prior to first

administration of study drug will be 'Day -1' and the day of first administration of study drug will be 'Day 1'; therefore 'Day 0' will not exist.

Imaging time windows:

Time windows and visits will be calculated to determine the planned day of tumour measurement and response status, based on the protocol-specified tumour imaging schedule.

For the presentation of tumour response data which will follow a calculated visit approach based on the protocol specified tumour imaging schedule: Imaging will be performed at screening and every 8 weeks after the first administration of study treatment (i.e. Week 8, 16, 24 etc.). Image data will be slotted to Week 8, 16, 24 etc. based on their relative study day (from start of treatment) and using a ±4 week window (e.g., images taken in the first 6 weeks from start of treatment will be assigned to Week 8). If two or more images for a patient are assigned to one interval then the last assessment will be used to ensure PD is not missed.

In order to identify whether consecutive imaging time points are missing for a given patient, a nominal time point (i.e. Week 8, 16, 24 etc.) will be assigned to each and every image. This is achieved by creating windows for every radiological response assessment. These windows are defined in Table 6.7: 1. If a patient does not have an image in one of the windows described above, the patient will be considered to have missed an assessment for that time point.

Table 6.7: 1 Nominal time points and windows for imaging

Nominal time point (weeks from start of study medication)	**Target day of the scan (study day)**	**Window (study day)**
8	57	1 to ≤ 85
16	113	86 to ≤ 141
24	169	142 to ≤ 197
32	225	198 to ≤ 253
40	281	254 to ≤ 309
48	337	310 to ≤ 365
56	393	366 to ≤ 421
Etc., 8 week interval	Etc.	Etc.

NOTE: The date of the first dose of study medication is Day 1

7. PLANNED ANALYSIS

Descriptive data analysis of PK endpoints and plasma concentrations will be performed by [redacted] and monitored by the [redacted] at BI and will be presented in Section 15.6 of the CTR and in Appendix 16.1.13.5.

For End-Of-Text tables, the set of summary statistics is: N / Mean / Standard deviation (StD) / Min / Median / Max. For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to Mean, StD, Min and Max .

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).

For plasma concentrations and PK parameters, the following descriptive statistics will additionally be calculated: number of observations (Nobs) / arithmetic coefficient of variation (CV) / geometric mean (gMean) / geometric coefficient of variation (gCV) / 10^{th} percentile (P10) / 1st quartile (Q1) / 3rd quartile (Q3) / 90^{th} percentile (P90).

The data format for descriptive statistics of plasma concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

Sort order for general categorical variables: if categories correspond to the collected categories on the eCRF and the table shells do not explicitly specify the ordering, the "default ordering" defined by the eCRF is to be used in such cases. If categories are derived, the ordering as specified in the table shell document should be used; in general ordinal data (e.g., categorised continuous data) are to be displayed in ascending order. Abbreviations should not be displayed without any explanations. They will be either spelled out in the table or explained in footnotes (whatever is more reasonable from the programming point of view).

If applicable, conversion from days to weeks, months and years will be as follows:

- Weeks = Days / 7
- Months = (Days * 12) / 365.25
- Years = Days / 365.25

Exclusion of PK parameters
The ADS "ADPP" (PK parameters) contains column variables APEX and APEXCO indicating inclusion/exclusion (APEX) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS will include parameters if they are not flagged for exclusion, that is APEX is equal to "Included".

Exclusion of PK concentrations

The ADS "ADPC" (PK concentrations per time-point or per time-interval) contains column variables ACEX and ACEXCO indicating inclusion/exclusion (ACEX) of a concentration and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to 'ALL CALC', the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to 'DESC STATS' the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition 'TIME VIOLATION' or 'TIME DEVIATION' the value can be used for further analyses based on actual times. If ACEXCO is set to 'HALF LIFE', the value will be excluded from half-life calculation (and, as a consequence, any calculation that relies on λz) only; the value is included for all other analyses.
Further details are given in BI-KMED-TMCP-MAN-0014 "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (6) and BI-KMEDTMCP-MAN-0010: "Description of Analytical Transfer Files and PK/PD Data Files" (7).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only standard descriptive statistics and summary tables are planned for this section of the report based on the treated set and other subject sets as appropriate. Data will be summarized by treatment group (i.e., dose cohort) and a "total" column will be included in the summary table.

Baseline demographics, oncological history, prior therapies, medical history, baseline eastern cooperative oncology group (ECOG) performance status, and baseline disease assessment are planned for this section.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report based on the treated set and other subject sets as appropriate.

Concomitant diseases will be coded similarly as AEs based on the most current Medical Dictionary for Regulatory Activities (MedDRA) version. A summary of concomitant diseases will be provided by treatment group, system organ class (SOC), and preferred term (PT).

Concomitant therapies (CTs) will be coded according to World Health Organisation Drug Dictionary (WHO DD version: latest version before Data base lock). CTs will be classified according to the Anatomical Therapeutic Chemical (ATC) classification system. The third ATC level will be used to categorise CTs by therapy type. In situations where a medical product may be used for more than one equally important indication, there are often several classification alternatives. As appropriate, patients receiving CTs with more than one possible ATC level 3 category will be counted more than once. Footnotes will clarify this possible double counting in tables.

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINT

7.4.1 Primary analysis of the primary endpoint

For the determination of the MTD, only evaluable patients for MTD in the dose escalation part will be considered (i.e., the MTD set). In this section of the report the data that led to the determination of the MTD are documented and summarised. To be specific, an overall summary of the number of patients with DLTs during the MTD evaluation period (i.e., the first treatment cycle) will be provided for each dose cohort.

The dose escalation and determination of MTD is guided by the BLRM with overdose control specified in CTP Section 7 based on the DLT data in the MTD set. Specifically, estimation of the MTD will be based on the estimation of the posterior probability of the incidence of DLT in toxicity categories during the MTD evaluation period for all evaluable patients for MTD. Tables and bar charts displaying the posterior probabilities of the true DLT rates being in either the under-toxicity interval, the target-toxicity interval or the over-toxicity interval will be produced.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Secondary endpoints

The number of patients with DLTs during the on-treatment period at each dose level will be summarized in a frequency table.

The number of patients with CTCAE Grade ≥ 3 treatment-related adverse events observed during the on-treatment period at each dose level will be summarized in a frequency table (provided tables should be refer to Section 7.8.1.2) .

The number of patients with treatment related adverse events at each dose level will be summarized in a frequency table.

The secondary PK endpoints (refer to Section 5.2.2) will be analysed descriptively. The analysis of standard PK parameters is calculated according to the relevant BI internal procedures “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (6).

7.7 EXTENT OF EXPOSURE

The total number of initiated cycles and treatment duration in days will be summarized descriptively for each dose cohort.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set. Treated patients will be analyzed according to their initial treatment.

Patients who were replaced within the MTD evaluation period will be excluded from the determination of the MTD in the dose escalation but will be considered for all other safety evaluations.

Safety data recorded during the Residual Effect Period (REP) of 30 days will be considered as on-treatment.

7.8.1 Adverse Events

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e., all adverse events occurring between start of treatment and end of the REP. All adverse events will be evaluated by initial treatment.

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 Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

7.8.1.1 Maximum tolerated dose and dose limiting toxicity
For the determination of MTD in this trial, the following will be evaluated:

- Posterior distribution is based on the number of patients with DLTs with regard to the MTD set and DLTs occurring during the MTD evaluation period (i.e., the first treatment cycle in dose escalation). The toxicity rates for the respective toxicity intervals will be evaluated.
- A table displaying DLTs by primary system organ class and preferred term will be provided by initial treatment for the MTD evaluation period for the MTD Set as well

as for the treated set. The same table will additionally be displayed for all treatment cycles of the on-treatment period for the treated set.
- The purpose of these tables is to summarize and document the data that led to the selection of MTD. A summary of the number of patients with DLT within the MTD evaluation period and for all treatment cycles of the on-treatment period will be given by initial treatment for the treated set.

7.8.1.2 Adverse events

Unless otherwise specified, 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. The analysis will be based on BI standards (3). AEs will be coded using the most recent version of MedDRA. The severity of AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

For analysis multiple AE occurrence data on the eCRF will be collapsed into an AE provided that all of the following applies:
- All AE attributes are identical (Low Level term [LLT], severity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AESI).
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake until 30 days of REP after last drug intake will be assigned to `on-treatment'. All AEs occurring before first drug intake will be assigned to 'screening' and all AEs occurring after last drug intake + 30 days will be assigned to 'follow-up' (for listings only). For details on the treatment definition, see Section 6.1.

The pre-specified Adverse events of special interest (AESIs) in this trial are DLTs and lab abnormalities in hepatic laboratory parameters. Refer to CTP Section 5.2.6.1.4 for details.

An overall summary of adverse events will be presented.

The frequency of patients with AEs will be summarized by treatment, primary system organ class (SOC) and/or preferred term (PT). The SOCs will be sorted by default alphabetically and PTs will be sorted by frequency within an SOC. Separated tables will be provided for patients with

- AEs
- Drug-related SAEs
- Drug-related AEs
- SAEs
- AESIs
- Grouped term AEs
- AEs leading to death
- AEs leading to discontinuation of trial medication

- AEs leading to dose interruption
- AEs leading to dose reduction
- DLTs during the MTD evaluation period
- DLTs during the entire treatment period

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (4).

The same on-treatment period as considered for the analysis of adverse events will be applied for laboratory values. Patients having at least one post-baseline laboratory value will be displayed in the descriptive analyses. Patients with missing CTCAE grade at baseline or no baseline value but with post-baseline values will be displayed in a new category "missing CTCAE grade at baseline" for those laboratory parameters where CTCAE grading is applicable. CTCAE grades for applicable laboratory parameters will be calculated according to CTCAE Version 5.0.

Descriptive statistics for laboratory values will be displayed using the converted values. Shift tables of change in laboratory measurements between baseline and worst value on treatment, between baseline and last value on treatment, and between worst and last value on treatment will also be presented.
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 summarized. 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.

7.8.3 Vital signs

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

Vital signs, observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.8.4 ECG

Clinically relevant abnormal findings will be reported as adverse events. Scatterplot of the BI 3011441 plasma concentration against the following individual QTcF values will be provided. Scatterplots of baseline and post QTcF against the following individual QTcF values will be provided.

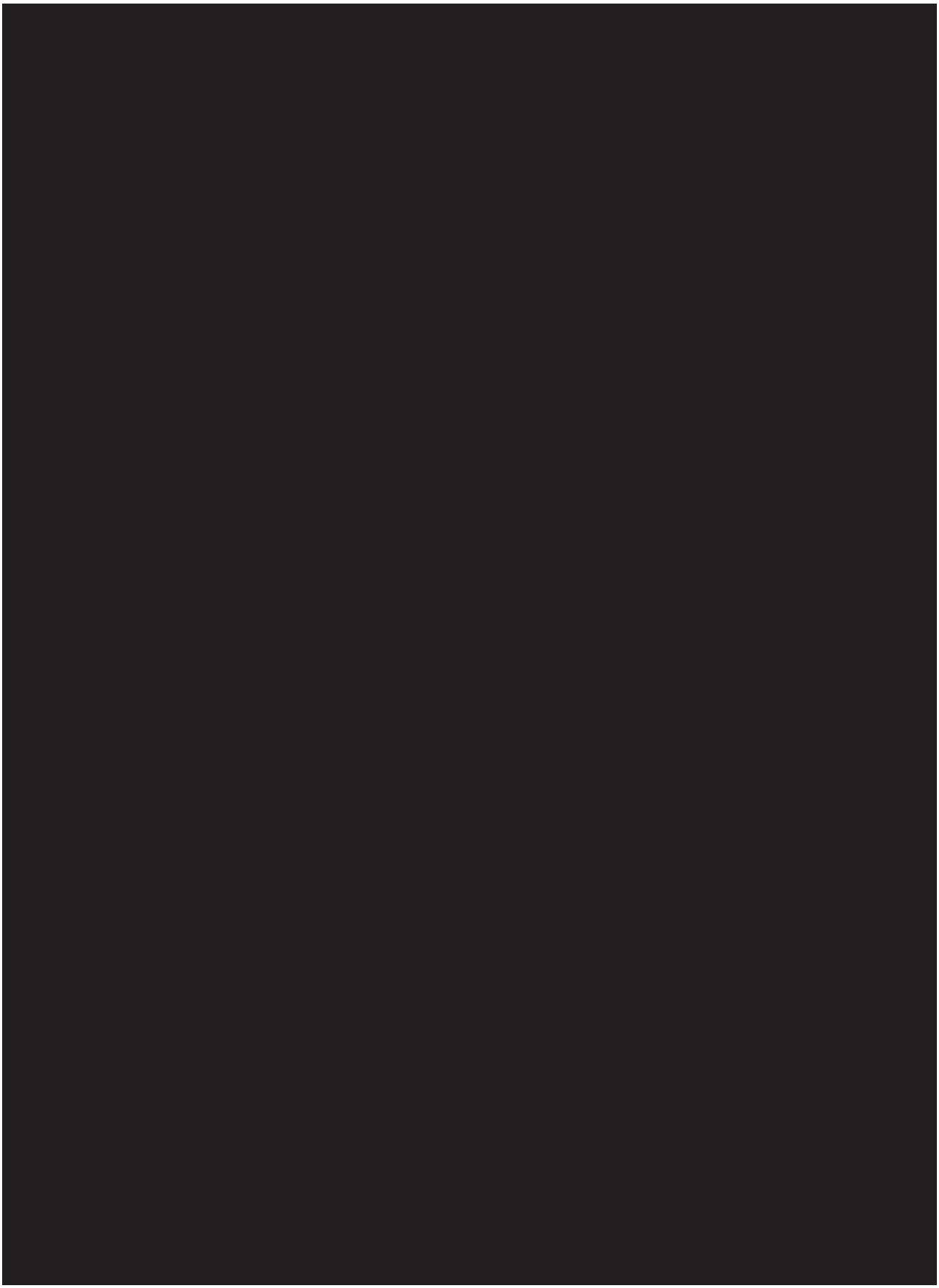
7.8.5 Others

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The treatment information will be loaded into the trial database after completion of enrolment.

9. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*BI-KMED-BDS-HTG-0035*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.
3.	*BI-KMED-BDS-HTG-0041*: “How to Guide: Analysis and Presentation of Adverse Event Data from Clinical Trials”, current version, IDEA for CON
4.	*BI-KMED-BDS-HTG-0042*: “How to Guide: Handling, Display and Analysis of Laboratory Data”, current version, IDEA for CON
5.	*BI-KMED-TMCP-MAN-0012*: “Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics”, current version; KMED.
6.	*BI-KMED-TMCP-MAN-0014*: “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies”, current version; KMED.
7.	*BI-KMED-TMCP-MAN-0010*: “Description of Analytical Transfer Files and PK/PD Data Files”, current version; KMED.



11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**23-DEC-22**	[redacted]	None	Initial TSAP

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Program [redacted]	[redacted]	10 Jan 2023 09:15 CET
Approval-Clinical Trial Leader		10 Jan 2023 09:38 CET
Approval-Medical Writer		10 Jan 2023 11:06 CET
Approval-Project Statistician		11 Jan 2023 15:15 CET
Author-Trial Clinical Pharmacokineticist		12 Jan 2023 07:16 CET
Author-Trial Statistician		13 Jan 2023 03:31 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed