Boehringer Ingelheim

TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**228892_990046**
BI Trial No.:	**1466-0003**
Title:	Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising subcutaneous doses and multiple subcutaneous doses over 6 weeks of BI 3006337 in healthy male Japanese subjects (single-blind, randomised within dose groups, placebo-controlled, parallel group design) (including Protocol Amendment No. 1 [c43161925-02 / VV-TMF-980521])
Investigational Product:	BI 3006337
Responsible trial statistician:	[redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	21 NOV 2024
Version:	1.0

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

See Medicine Glossary:
http://glossary

Term	Definition / description
ADA	Anti-drug Antibody
ADS	Analysis data set
ALT	Alanine Aminotransferase
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
$AUC_{0\text{-}10h}$	Area under the concentration-time curve of the analyte in serum over the time interval from 0 to 10 h
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve of the analyte in serum over the time interval from 0 extrapolated to infinity
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in serum over the dosing interval tau at steady state
[redacted]	
BMI	Body mass index
BMS	Biomarker parameter analysis set
BW	Body Weight
CI	Confidence interval
C_{max}	Maximum measured concentration of the analyte in serum
$C_{max,ss}$	Maximum measured concentration of the analyte in serum at steady state
CTP	Clinical trial protocol
CTR	Clinical trial report
[redacted]	
CV	Arithmetic Coefficient of Variation
DG	Dose group
DILI	Drug induced liver injury
ECGPCS	ECG PK concentration set
eDMS	Electronic documentation management system

Term	Definition / description
EOT	End of Trial
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
[redacted]	
LLOQ	Lower limit of quantification
LOQ	Limit of quantification
Max	Maximum
MD	Multiple dose
Min	Minimum
N	Number non-missing observations
Nobs	Number of observations
[redacted]	
P10	10^{th} percentile
[redacted]	
P90	90^{th} percentile
PKS	PK parameter analysis set
q.w.	Weekly (once a week)
Q1	1^{st} quartile
Q3	3^{rd} quartile
RAGe	Report Appendix Generator system
RPM	Report Planning Meeting
SD	Standard Deviation
SRD	Single rising dose
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
ULOQ	Upper limit of quantification
λ_z	Terminal rate constant of the analyte in plasma

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 protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This trial statistical analysis plan (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.

Study data (including data entered in the RAVE EDC system and external data provided by suppliers) will be stored in a Clinical Data Repository (CDR).

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 8.1.1 or higher, [redacted]) or SAS Version 9.4 (or later version).

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 Clinical Trial Report (CTR) appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP. The following changes will be made as compared to the CTP:

The following text from CTP Section 7.2.3 was not considered as only 3 dose groups are defined for the SRD part:
As some small doses at the beginning and/or some doses at the upper end might not contribute to the linear relationship between dose and PK, dose proportionality over the entire dose range investigated might not be shown. In that case an attempt will be made to identify a subrange of at least 3 consecutive doses where dose proportionality can be concluded.

In CTP Section 7.2.5 the following was mentioned:
Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods
In order to only display data during on treatment phases, this was changed to *Previous and concomitant therapies will be presented per treatment group* and in total.

In CTP Section 5.6.1 the formula for HOMA-beta is given as follows:
HOMA − β% = (20 ∗ FPI [mU/L]) / (FPG [mmol/L] – 3.5) ∗ 100
This formula is corrected in Section 7.6 as follows:
HOMA − β% = (20 ∗ FPI [mU/L]) / (FPG [mmol/L] – 3.5).

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

Both parts:

Section 2.1.2 of the CTP:

The primary endpoint to assess safety and tolerability of BI 3006337 is the occurrence of any treatment-emergent adverse event assessed as drug-related by the investigator. This is expressed as the percentage of subjects treated with investigational drug who experience such an event.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been defined in the CTP.

5.2.2 Secondary endpoints

Section 2.1.3 of the CTP:

The following pharmacokinetic parameters will be determined if feasible:

SRD part:

- *$AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in serum over the time interval from 0 extrapolated to infinity)*
- *C_{max} (maximum measured concentration of the analyte in serum)*

MD part (after the last dose):

- *$AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in serum over the dosing interval tau at steady state) after the last dose in Week 6*
- *$C_{max,ss}$ (maximum measured concentration of the analyte in serum at steady state) after the last dose in Week 6*

[redacted]

Both parts:

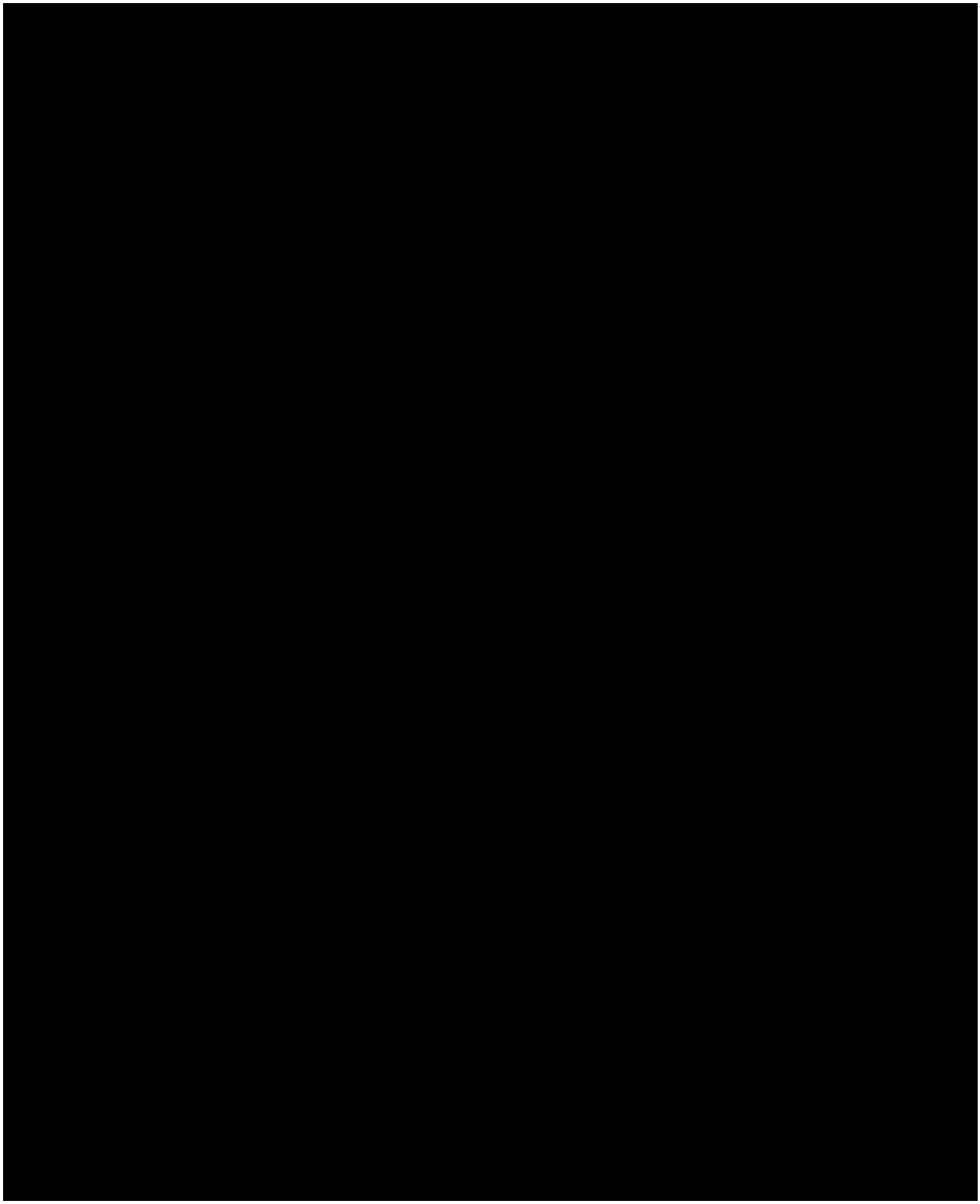
Safety and tolerability endpoints

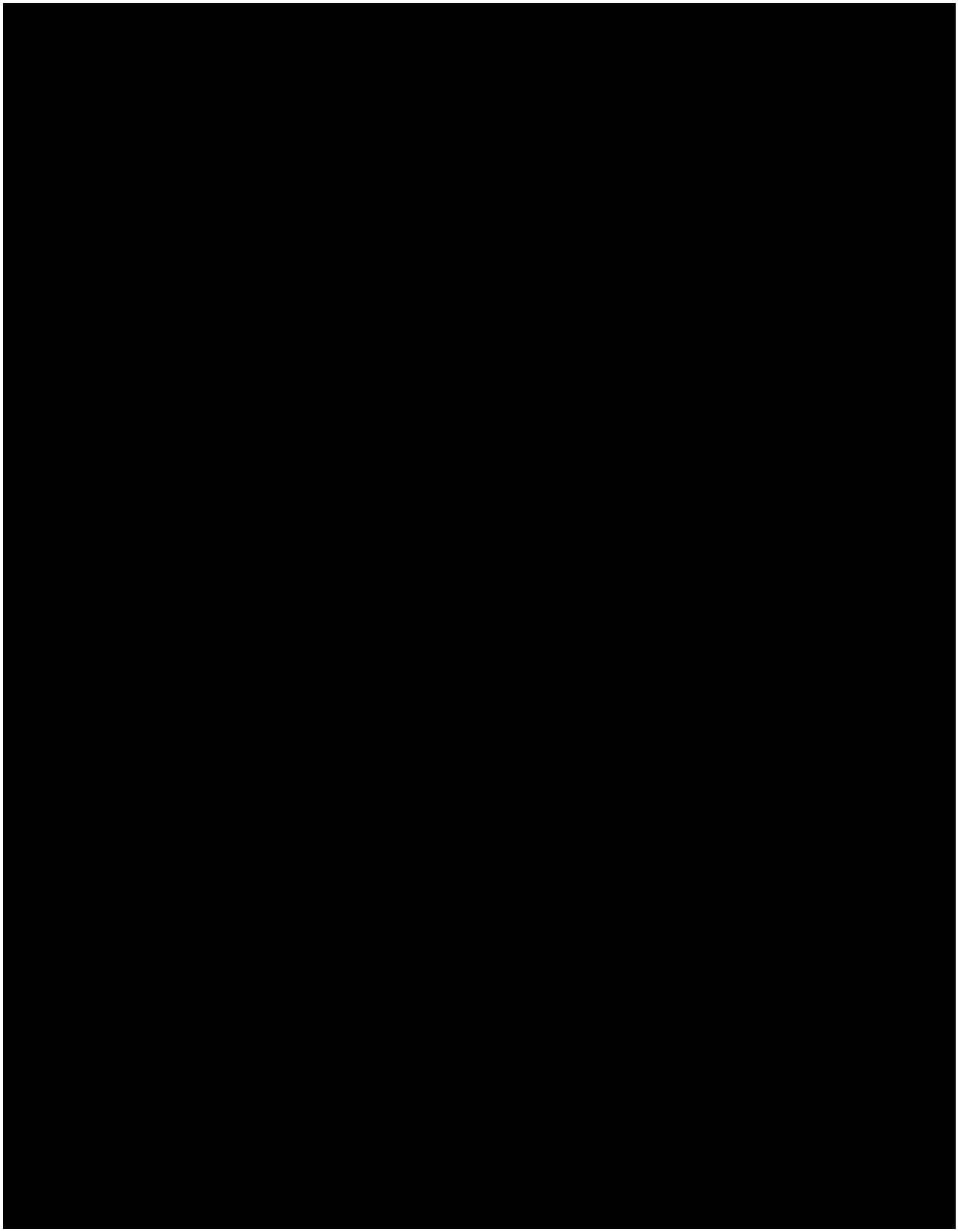
Section 2.2.2.1 of the CTP:

Safety and tolerability of BI 3006337 will be assessed based on:

- *AEs (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests*
- *12-lead ECG*
- *Vital signs (blood pressure (BP), pulse rate (PR), and intra-axillary body temperature (BT))*
- *Local tolerability assessed by investigator*
- *Columbia-Suicide Severity Rating Scale (C-SSRS) (MD part)*

[redacted]





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignment of treatment groups, selection of doses, refer to CTP Sections 3 and 4.

This single-rising dose (SRD) and multiple dose (MD) trial is designed as blinded to subject, randomised, and placebo-controlled within parallel dose groups. It is planned to include a total of 24 healthy male subjects (8 subjects per group: 6 subjects will receive BI 3006337 and 2 will receive placebo) in the single dosing part. It is planned to include a total of 12 healthy male subjects (9 subjects will receive BI 3006337 and 3 will receive placebo) in the multiple dosing part.

For details of dosage and formulation see Table 6.1: 1 and Table 6.1: 2 below.

SRD part:

Table 6.1: 1 SRD part: Treatments and labels used in the analysis

Dose group	Treatment	Short label
1-3	P Placebo, solution for injection, single dose	SRD-Placebo*
1	A BI 3006337, solution for injection, 50 mg, single dose	SRD-BI 50mg
2	B BI 3006337, solution for injection, 100 mg, single dose	SRD-BI 100mg
3	C BI 3006337, solution for injection, 150 mg, single dose	SRD-BI 150mg

* The placebo group in the safety evaluation will consist of all subjects treated with placebo for SRD part, regardless of the dose group in which they were treated.

MD part:

Table 6.1: 2 MD part: Treatments and labels used in the analysis

Dose group	Treatment	Short label
4	Q Placebo, solution for injection, 6 weeks q.w. dosing	MD-Placebo
4	D BI 3006337, solution for injection, 150 mg, 6 weeks q.w. dosing	MD-BI 150mg

Both parts:

Section 1.2.5 of the CTP:

Residual effect period (REP) is the period after the last dose with measurable drug levels and/or with still likely to be present PD effects. The estimated REP of BI 3006337 in humans is 3 weeks.

Based on this, the following study phases will be defined for the analysis of adverse events (AEs), laboratory, ECG and vital signs data:

- **Screening**
    - Ranging from 0:00 h on day of informed consent until time of first drug administration (BI or Placebo).
- **On-treatment** (labelled with short label)
    - Ranging from time of respective (first) drug administration (BI or Placebo) until 3 weeks (504 h) thereafter (SRD part) OR until 3 weeks (504 h) after last treatment administration (MD part) or until trial termination (0:00 h on the day after trial termination), whatever occurs first.
- **Follow-up** (labelled "F/U")
    - Ranging from the end of REP until trial termination (0:00 h on the day after trial termination).

Section 7.2.5 of the CTP:

Note that AEs occurring after the last per protocol contact but entered before unblinding the trial will be reported to Pharmacovigilance only and will not be captured in the trial database.

The following AE displays will be provided in the CTR:

In Section 9.3 and Appendix 10.5.1.8 (for ClinicalTrials.gov and EudraCT only) of the CTR displays, the on-treatment phase will be analysed (labelled with the short label of the study treatment as in Table 6.1: 1 and Table 6.1: 2). The screening and follow-up phases will not be included in this analysis.

In Appendix 10.5.1.8 (for ClinicalTrials.gov and EudraCT only) both trial parts will be displayed together.

For the SRD part, the following totals will be provided for Section 9.3:

- a total over all on-treatment phases involving BI 3006337 (**"BI Total"**)

In Section 9.4 and Appendix 10.6 (Listings) of the CTR displays, the screening period, as well as the follow-up phases will additionally be included and no totals will be provided.

For detailed information on the handling of the treatments refer to Technical TSAP ADS (analysis data set) plan and Analysis Data Reviewers guide.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all treated subjects. Consistency check listings (for identification of deviations of 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 Report Planning Meeting (RPM). At this meeting, all manual deviations identified at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP “Identify and Manage Important Protocol Deviations (iPD)” (2).

IPD categories will be suggested in the DV domain sheet, iPDs will be identified no later than in the RPM, and the iPD categories will be updated as needed.

If any iPDs are identified, they are to be summarised into categories and will be captured in the iPD specification file (DV domain) (3) and in the decision log (4). Both documents will be stored within the TMF in eDMS.

The iPDs will be summarized and listed in the CTR.

6.3 INTERCURRENT EVENTS

This section is not applicable.

6.4 SUBJECT SETS ANALYSED

Section 7.2.1.1 of the CTP:

Statistical analyses will be based on the following analysis sets:

- *Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug* (BI 3006337 or Placebo)*. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses.*
- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the TS who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified* below*). Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.*
- *ECG PK concentration set (ECGPCS): This subject set includes all subjects from the TS who provide at least one pair of a valid drug serum concentration and a corresponding (i.e., time-matched) ECG endpoint to be used in the exposure-response*

analyses. For placebo subjects, the serum concentration is set to zero and hence always considered as valid. The decision whether a time deviation between PK blood sampling and ECG recording is acceptable (and thus whether the pair of values will be used) is to be made no later than at the Report Planning Meeting (RPM) before database lock. The ECGPCS will be used for the exposure-response analyses.

- *Biomarker parameter analysis set (BMS): This set includes all subjects in the TS who provide at least one evaluable observation for at least one of the exploratory biomarkers without protocol deviation relevant to the evaluation of biomarkers (as specified* below*). Descriptive and model-based analysis of the biomarkers will be based on the BMS.*

The PKS will only include subjects who received at least one dose of the test product BI 3006337, placebo subjects will not be included.

All ECG analyses are performed on the TS, except for the exposure-response analyses, which are performed on the ECGPCS.

Pharmacokinetics:

Section 7.2.1.2 of the CTP:

The pharmacokinetic parameters listed in CTP *Section 2.1 and 2.2.2 for drug BI 3006337 and acetaminophen will be calculated according to the relevant BI internal procedure.*

Serum/plasma concentration data and parameters of a subject will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the RPM) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Important protocol deviations may be

- *Incorrect trial medication taken, i.e., the subject received at least one dose of trial medication the subject was not assigned to*
- *Incorrect dose of trial medication taken*
- *Use of restricted medications*

Serum/plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- *The subject 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 subjects experiencing emesis),*
- *Missing samples/concentration data at important phases of PK disposition curve.*

Serum/plasma concentration data and parameters of a subject which are flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

Biomarkers:

Section 7.2.1.3 of the CTP:

In general, biomarkers/PD endpoints of a subject will be included in the statistical analyses, if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation thereof (to be decided no later than in the RPM) or due to non-evaluability (as revealed during data analysis, based on the criteria specified below).

Relevant protocol deviations may be as listed for PK above*. Biomarker data and/or parameters of a subject may for example be considered as non-evaluable, if the time-matched blood PK sample is considered as non-evaluable.*

Exclusion of a subject's data will be documented in CTR. Biomarker data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

Table 6.4: 1 Subject sets analysed

	Subject analysis set				
Class of endpoint	TS	PKS	BMS	ECGPCS	[redacted]
Primary endpoint and further safety assessments (incl. central ECG)	X				
Analyses of PK endpoints		X			
Analyses of PD/biomarker endpoints			X		
ECG exposure response analysis				X	
[redacted]					
Disposition	X				
Demographic/baseline parameters	X				
Important protocol deviations	X				
Exposure	X				

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data and outliers will be performed as described in the CTP, Section 7.3.

It is not planned to impute missing values for safety parameters. Nevertheless, missing or incomplete AE dates are imputed according to BI standards (see "Handling of Missing and Incomplete AE Dates" (5)).

Missing data and outliers of PK and PD data are handled according to BI standards (see "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics" (6) and "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (7)).

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

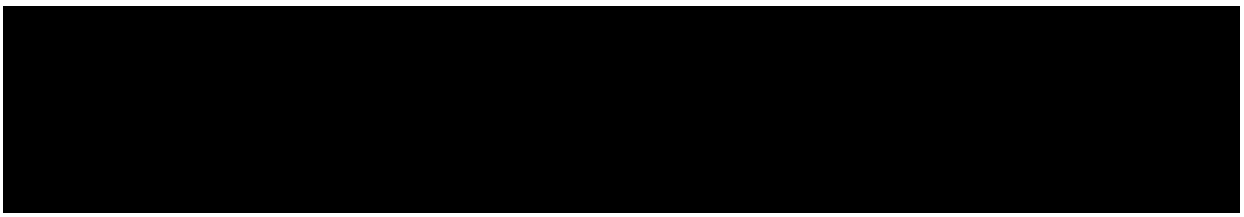
12-lead ECG and ECG-PK analysis

If single cardiac cycles of an ECG (out of the generally four) are missing, the arithmetic mean for this single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced number (1 or 2) of recordings.

For the classification of the on-treatment QTc/QT intervals into "no new onset" / "new onset" categories, the handling of missing value is described in Additional Section 10.1.3.

For subjects on active drug (e.g. post dose time points), missing serum concentration values with 'BLQ' in the comment field will be replaced by ½ LLOQ for the exposure-response analysis. For placebo subjects, the missing serum concentration values will be replaced by 0 for the exposure-response analyses.



6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In both parts, the baseline value is defined as the last measurement before first drug administration (BI 3006337 or Placebo).

Both parts:

Section 6.1 of the CTP:

The acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 30 min on Day -1 and for the first 72 h after trial drug administration, except for urine safety laboratory tests, which can be obtained in the morning of the given day. Starting from 96 h post-trial drug administration, a deviation from the scheduled time for all the planned trial activities of ± 120 min is acceptable, except for urine safety laboratory tests, which can be obtained in the morning of the given day.

[…]

For planned blood sampling times, refer to the CTP *Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for the determination of* PK *parameters.*

Adherence to time windows will be checked via the consistency check listings at the RPM.

Unscheduled measurements of laboratory data and vital signs data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement.

12-lead ECG

There will be a centralised evaluation of the 12-lead ECG recordings at the time points and for the ECG recordings specified in Table 6.7: 1 and Table 6.7: 2 below:

Table 6.7: 1 Time schedule of 12-lead ECG recordings – SRD part

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
1	-28 to -3		Screening	NA
2	-1	-26:00	Screening	Single ECG
	1	-02:00	Baseline	Single ECG
		01:00	On treatment	Single ECG
		01:30		
		02:00		
		03:00		
		07:00		
		11:00		
		15:00		
	2	23:00		
		27:00		
		31:00		
		35:00		
		39:00		
	3	47:00		
	4	72:00		
	5	96:00		
	6	120:00		
	8	168:00		
	11	240:00		
	15	336:00		
3	32 to 40		End of trial examination	NA

Table 6.7: 2 Time schedule of 12-lead ECG recordings – MD part

Visit	Day	Planned time [hh:mm] (relative to drug administration)	Study phase	Central evaluation
1	-28 to -3		Screening	NA
2	-1	-26:00	Screening	Single ECG
	1	-01:00	Baseline	Single ECG
		01:30	On treatment	Single ECG
		03:00		
		11:00		
		15:00		
	2	22:00		
		33:00		
		39:00		
	3	47:00		
	15	338:00		
	18	408:00		
	22	506:00		
	29	674:00		
	36	842:00		
	43	1007:00		
		1011:00		
		1019:00		
		1023:00		
	44	1030:00		
		1041:00		
		1047:00		
	45	1055:00		
3	64 to 74		End of trial examination	NA

At screening and end of trial examination, ECGs will be recorded and will not be transferred to the central ECG lab. At visit 2 single ECGs will be recorded. Baseline is defined as the last measurement prior to first BI/Placebo drug administration.

For the exposure response analyses, pairs of ECG variables and corresponding serum concentrations will be built using the same planned time points, e.g., the HR change from baseline and the serum concentration measured at planned time 1:00 will build one pair. Whether a time deviation between PK blood sampling time and corresponding ECG recording is too big and the pair has to be excluded from the analysis will be decided no later than at the RPM. Data exclusion due to time deviations will only be applied to subjects on active study

treatment. The acceptable maximum time deviations between ECG recordings and serum concentration sampling are proposed to be

- 15 minutes for up to 48 hours (including) after 1st dosing,
- 30 minutes for time points from more than 48 hours or later after 1st dosing,

The final decision for the handling of ECG recordings will be made in RPM.

Pairs with time deviations exceeding those specified above are supposed to be excluded from exposure-response analyses. **Section 7.2.1.1 of the CTP:** *The decision whether a time deviation between PK blood sampling and ECG recording is acceptable (and thus whether the pair of values will be used) is to be made no later than at the Report Planning Meeting (RPM) before database lock.* When the sampling time of the blood sample or the ECG recording is not available, the pair will also be excluded.

7. PLANNED ANALYSIS

If not stated otherwise, SRD part and MD part will be analysed separately. For SRD part and MD part of the trial, the same analyses will be performed if not stated otherwise.

Safety analysis (refer to Section 7.8) will be performed by [redacted] and will be presented in Sections 9.1 to 9.4 of the CTR and in Appendix 10.6 and 10.5.1.

Inferential statistical analyses of PK and PD endpoints (refer to Section 7.4, Section 7.5.2 and Section 7.6) will also be performed by [redacted] and will be presented in Section 9.5 of the CTR and in Appendix 10.5.3 for PK endpoints and in Section 9.7 and Appendix 10.5.5 for PD endpoints.

Descriptive data analysis of PK and PD endpoints [redacted] will be performed by the [redacted] at [redacted] with outsourcing to CRO ([redacted]). The results will be presented in Section 9.6 of the CTR and Appendix 10.5.5 for PK endpoints, in Section 9.7 of the CTR and Appendix 10.5.5 for PD endpoints, and in Section 9.8 of the CTR and Appendix 10.5.6 for ADA analysis.

The format of the listings and tables will follow the BI standards (see "Standards for Reporting of Clinical Trials and Project Summaries" (8)) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (9).

The individual values of all subjects will be listed, sorted by treatment group, subject number, visit and time point. The listings will be included in Appendix 10.6 of the CTR.

No formal inferential statistical interim analysis is planned.

For end-of-text tables, the set of summary statistics for non-PK parameters is:

N	number non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Median	median
Max	maximum

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

Nobs	number of observations
CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation
P10	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

The data format for descriptive statistics of concentrations will be identical to the data format of the respective concentrations. The descriptive statistics of PK and PD 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.

Tabulations of frequencies for categorical data will include all possible categories available in the CRF and will display the number of observations in a category, as well as the percentage (%). The precision for percentages should be one decimal point, unless the denominator is smaller than 100 (in all treatment columns), in which case percentages are given in integer numbers. The category 'missing' will be displayed only if there are actually missing values.

Units of variables should be given in the titles or column/row descriptors in brackets (e.g. (mg)).

Exclusion of PK and PD parameters

The ADS “ADPP” (PK parameters) and “ADYP” (PD parameters) contain column variables APEX and APEXCO indicating inclusion/exclusion (APEX) of a PK or PD parameter and an analysis flag comment (APEXCO). All analyses based on the PKS, BMS or ECGPCS, respectively, will include parameters only if they are not flagged for exclusion, that is APEX is equal to “Included”.

Exclusion of PK and PD concentrations

The ADS “ADPC” (PK concentrations per time-point or per time-interval) and “ADYC” (PD concentrations per time-point or per time-interval) contain 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 λ_z) only; the value is included for all other analyses.

Further details are given in “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (7) and “Description of Analytical Transfer Files, PK/PD Data files and ADA files” (10).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.
The data will be summarised by treatment group and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the report, based on the TS.

Concomitant diseases and non-drug therapies will be coded according to the version defined in the decision log (4) of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medications will be coded according to the most recent version of the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

Section 7.2.5 of the CTP:

Previous and concomitant therapies will be presented per treatment group and in total.

A therapy will be considered concomitant to a treatment, if it

- is ongoing at the time of study drug administration, or
- starts within the analysis phase of the respective treatment (see Section 6.1 for a definition of treatments and analysis phase).

The diagnoses, non-drug therapies and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies will be marked with a "No" in the respective column.

The relevance of the concomitant therapies to the evaluation of PK data will be decided no later than at the RPM.

7.3 TREATMENT COMPLIANCE

Section 4.3 of the CTP:

Compliance will be assured by administration of all trial medication in the trial centre under supervision of the investigating physician or a designee. The measured serum *concentrations of trial medication will provide additional confirmation of compliance.*

It is not intended to list the compliance separately. Any deviations from complete intake will be addressed in the RPM and described in the CTR.

7.4 PRIMARY OBJECTIVE ANALYSIS

Independent of the main objectives stated in the CTP, this section describes further details of the primary endpoint analyses outlined in the CTP.

7.4.1 Main analysis

Section 7.2.2 of the CTP:

The primary endpoint as specified in Section 5.1 *will be derived according to BI standards. The analysis will be based on the TS and will be descriptive in nature.*

Please refer to Section 7.8.1 for the description of the analysis of the primary endpoint.

7.5 SECONDARY OBJECTIVE ANALYSIS

Independent of the main objectives stated in the CTP, this section describes further details of the secondary endpoint analyses.

7.5.1 Key secondary objective analysis

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

7.5.2 Secondary objective analysis

Section 7.2.3 of the CTP:

Primary analyses

The secondary endpoints (refer to Section 5.2.2) will be analysed descriptively. Analyses will be performed for the parent drug.

Further exploratory analyses

In the SRD part, dose proportionality will be explored via graphical checks and if applicable via the power model stated below. The analysis will be performed for the PK endpoints $AUC_{0-\infty}$ and C_{max} as specified in Section 5.2.2.

The power model describes the functional relationship between the dose level and PK endpoint on the log scale via

$$y_{km} = \log(x_{km}) = \mu + b \cdot \log(D_k) + e_{km},$$

where

- y_{km} *logarithm of response (PK parameter) measured on subject m receiving dose k,*
- μ *the overall mean,*
- β *slope parameter of linear regression line,*
- D_k *level of dose k, k=1,…,3,*
- e_{km} *the random error associated with the m^{th} subject who was administered dose k ($e_{km} \sim N(0,\sigma^2)$ iid).*

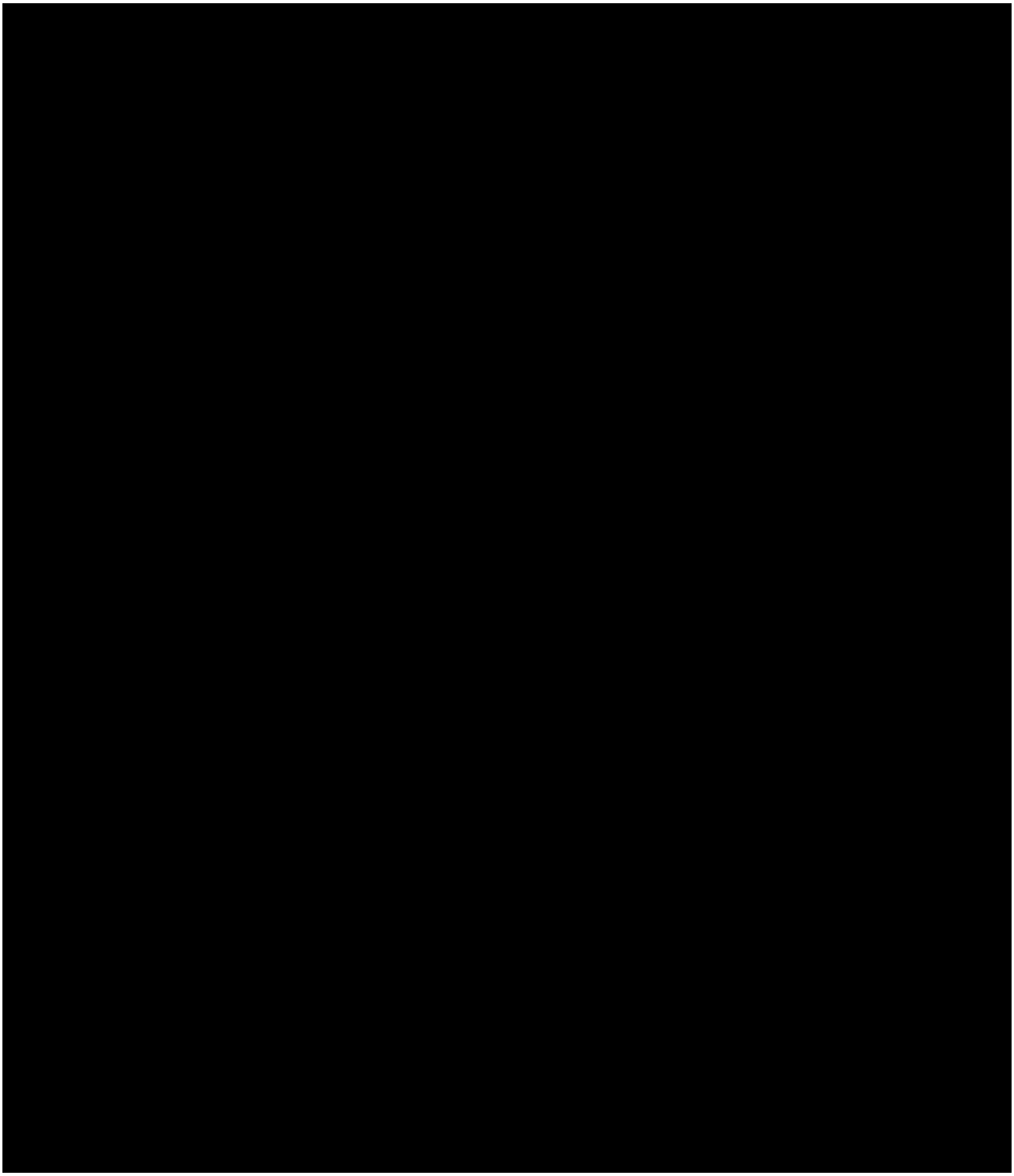
The slope parameter β together with its two-sided 90% confidence interval will be estimated. Additionally, the r-fold change $r^{(\beta-1)}$ together with its 90% CI will be derived.

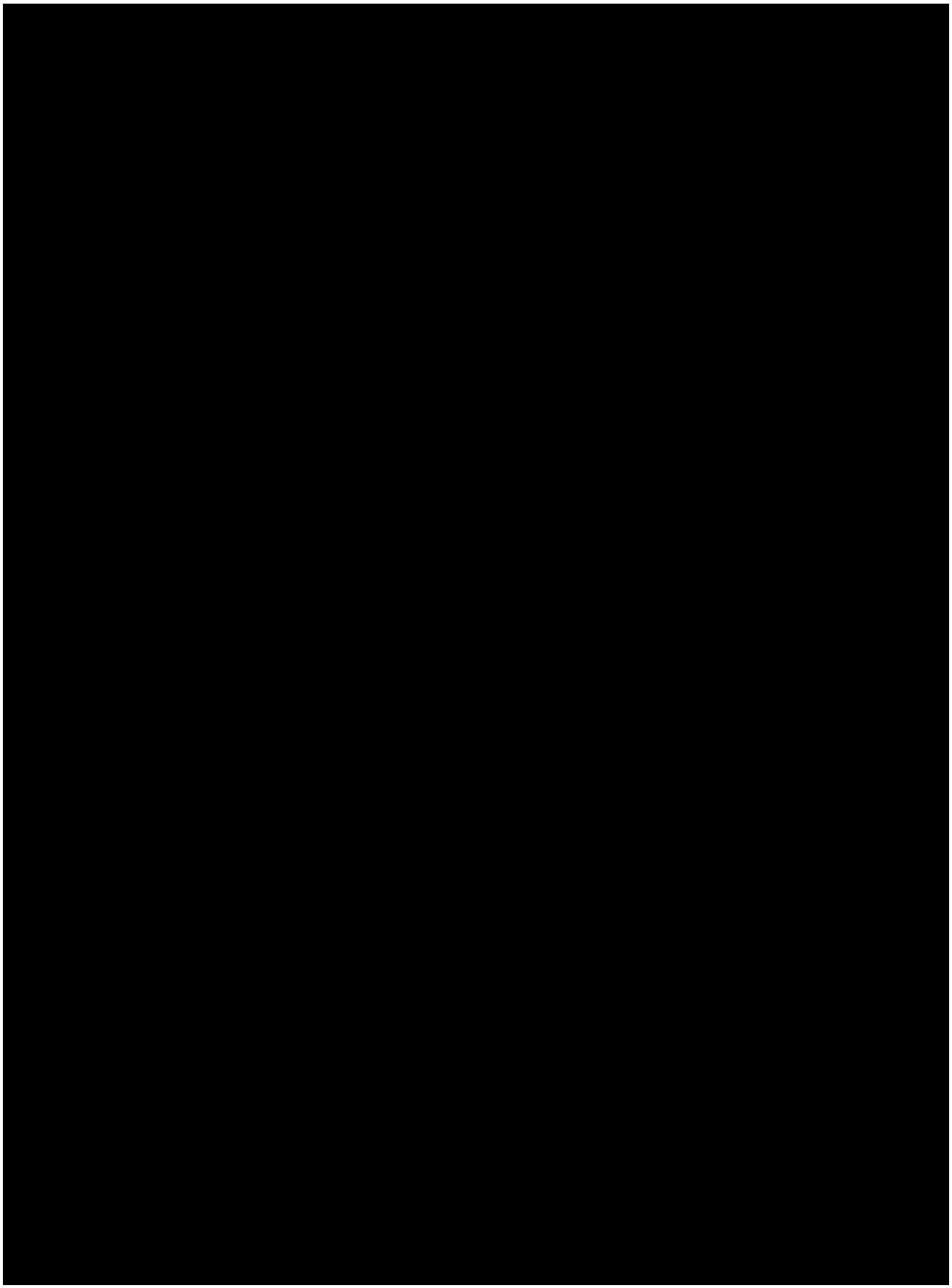
The acceptance region for (approximate) dose proportionality over a dose range will be based on the 90% CI of the deviation factor from dose proportionality, $r^{(\beta-1)}$, with r = ratio of highest dose to lowest dose of the specific dose range. Assuming maximum deviation from perfect dose proportionality to be +/- 25% or up to +/- 50%, the acceptance regions are (0.75; 1.33) and (0.5; 2.0) respectively.

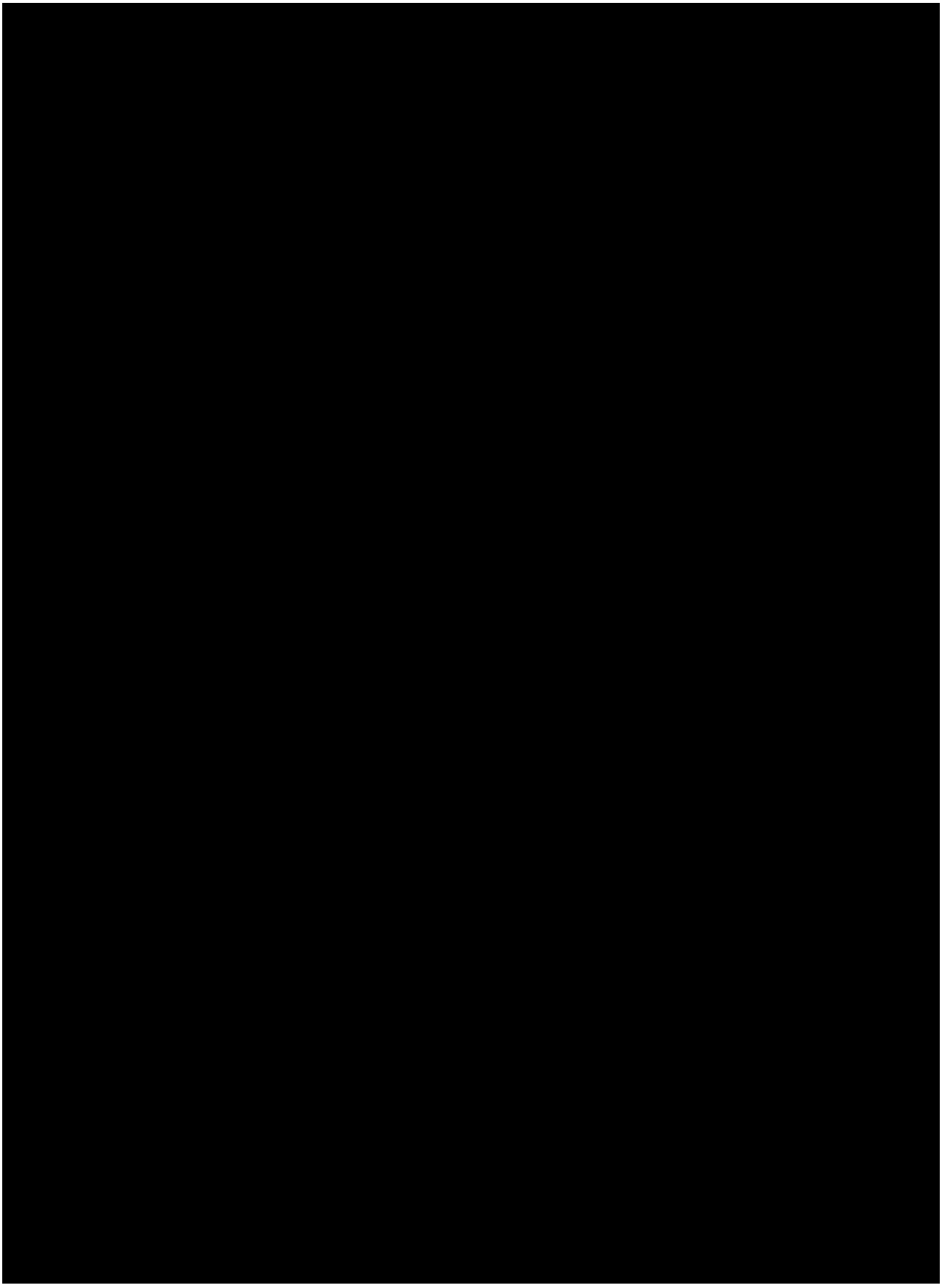
Graphical displays:

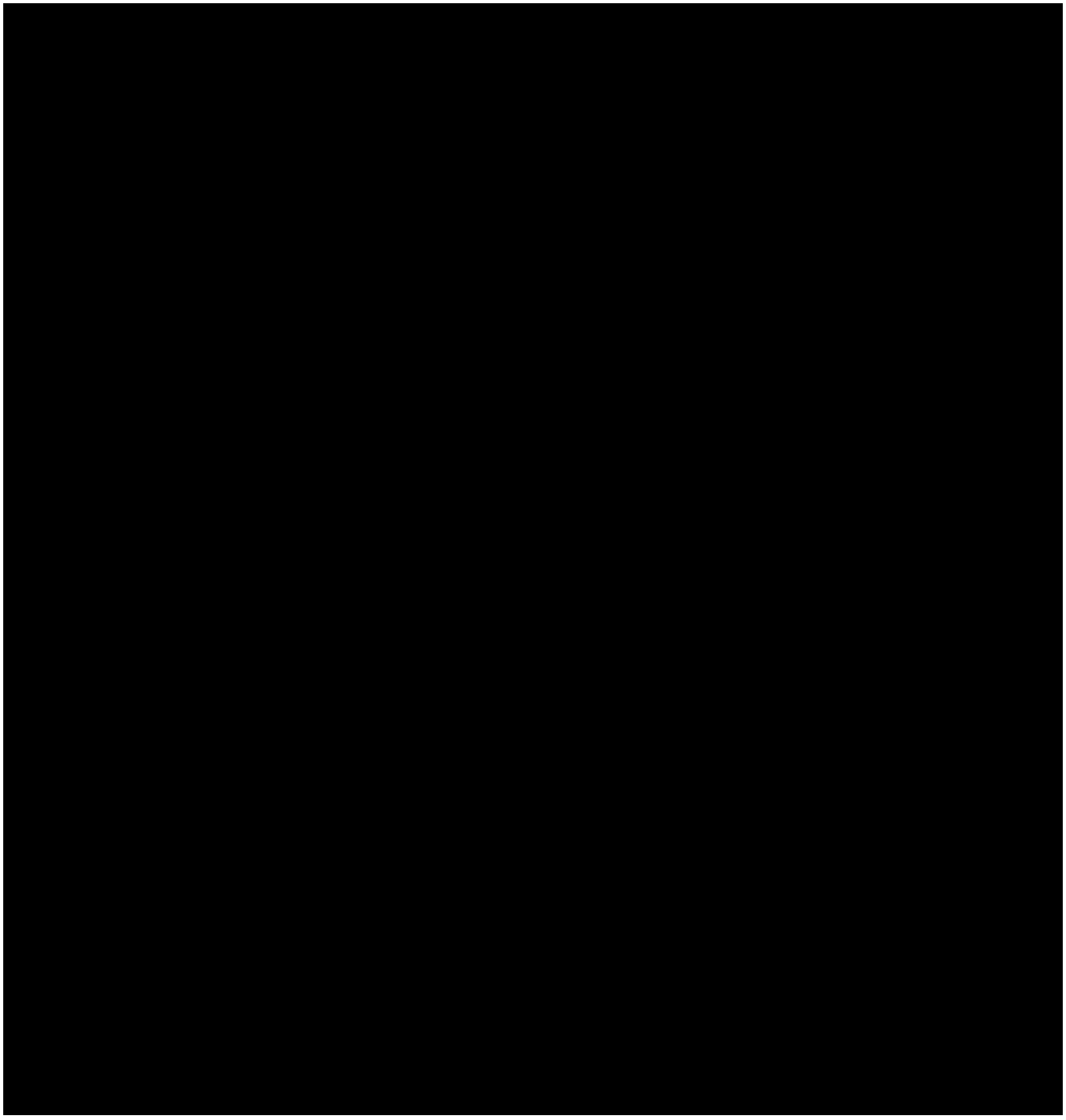
A regression plot will be provided, where the logarithm of dose is depicted versus logarithm of PK endpoint, including the estimated regression line from the power model and reference line of perfect proportionality (β=1).

Analyses of dose proportionality will be performed on the PKS using the respective CSD macros in SAS.









7.7 EXTENT OF EXPOSURE

Descriptive statistics are planned for this section of the report based on the TS. The date and time of drug administration will be listed for each subject.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS, except for the exposure-response analyses, which are based on the ECGPCS.

The safety data for treated subjects who failed to complete the trial (dropouts or withdrawals) will be reported as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded.

7.8.1 Adverse Events

AEs will be coded using MedDRA. The coding version number will be displayed as a footnote in the respective output.

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs. BI standards as presented in "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template" (11) and "Analysis and Presentation of Adverse Event data from clinical trials" (12) will be applied.

The analysis of AEs 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' phases as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 1 and Table 6.1: 2.

According to the CTP, adverse events of special interest (AESI) will be analysed:

Section 5.2.6.1.4 of the CTP:

Potential severe DILI

A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by any of the following alerts (alterations) of hepatic laboratory parameters that occur after the first dose of IMP:

1. *AST or ALT elevation ≥3 × ULN and total bilirubin ≥2 × ULN measured at the same visit, or in samples drawn within 30 days of each other, OR*
2. *AST or ALT elevation ≥3 × ULN and INR ≥1.5 × ULN measured at the same visit, or in samples drawn within 30 days of each other, OR*
3. *AST or ALT elevation ≥3 × ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%), OR*
4. *AST or ALT elevation ≥5 × ULN*

These laboratory findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without laboratory results (ALT, AST, total bilirubin) available, the Investigator should make sure that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet

the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Additionally, with subjects having a normal AST and ALT at baseline, the emergence of an isolated AST or ALT elevation between ≥3-fold and <5 × ULN requires repeat testing within 72 hours. DILI Checklist is not required unless repeat testing trigger alerts 1, 2, 3, or 4.

According to ICH E3 (13), in addition to deaths and serious AEs, 'other significant' AEs need to be listed in the CTR. These will be any non-serious AE that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

An overall summary of AEs will be presented.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug-related serious AEs, for subjects with AESIs and for subjects with AEs leading to discontinuation. In addition, the frequency of subjects with AEs will be summarised by worst intensity, treatment, primary SOC and PT.

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

For disclosure of AEs on ClinicalTrials.gov, additional information not included in a standard AE analysis will be performed, for both trial parts together. The following three entries will be created:

- Adverse Events per arm for disclosure on CTgov
- Non-serious Adverse Events (>5%) for disclosure on CTgov
- Serious Adverse Events for disclosure on CTgov

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards as presented in "Handling, Display and Analysis of Laboratory Data" (14). Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range will be flagged in the data listings.

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.

It is the investigator's responsibility to decide whether a lab value is clinically significantly abnormal or not (at the RPM at the latest).

Descriptive statistics of laboratory data including change from baseline will be calculated by planned time point based on the first value of the subject at that planned time point (or assigned to that planned time point). For baseline value, see Section 6.7.

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure, pulse rate, body temperature). In the listing the change from baseline will also be displayed. In addition, the time profiles of median (Min, Max) will be displayed graphically by treatment group.

For post-dose measurements of vital signs, descriptive statistics will be calculated by planned time point based on the first value of the subject at that planned time point (or assigned to that planned time point). For baseline value, see Section 6.7.

Clinically relevant findings 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

Continuous safety ECG monitoring (by investigator)

Clinically relevant abnormal findings will be reported as AEs.

No separate listing or analysis of continuous ECG monitoring will be prepared.

12-lead ECG

Abnormal findings will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.

All evaluations of ECG data will be based on the TS, except the exposure-response analyses, which are based on the ECGPCS.

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 10.6. For QTcB and RR, only listings will be provided. Occurrences of notable findings will be flagged.

Categorical endpoints

For the categorical endpoints, frequency tables will be provided.

For all subjects with any notable finding in ECG intervals, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 10.6), and the corresponding time profiles will be shown.

Quantitative endpoints

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the absolute values and changes from baseline over time of QTcF, HR, QT, PR and QRS. The time profiles of mean and SD for the changes from baseline on treatment will be displayed graphically by treatment.

For both parts together:

For QTcF and HR changes from baseline, the relationship to the corresponding serum concentrations will be evaluated using a random coefficient model. For subjects in the ECGPCS, all time points with available ECG endpoints and valid time-matched drug serum concentrations will be included. For the handling of missing values, see Section 6.6. The response variable will be change from baseline in QTcF (ΔQTcF). The placebo subjects will be included in the analysis, setting their serum concentrations to zero.

As a first step, it is investigated if there is a potential delayed or accelerated (e.g. due to metabolites) effect of the drug on QTcF. A general visual impression will be provided by overlaying time profiles of serum concentrations and QTcF changes from baseline (ΔQTcF). These figures will be generated for each subject (presented in the Statistical Appendix of the CTR), as well as for means per treatment group (presented in the End-of-Text part of the CTR).

The relationship between BI 3006337 serum concentrations and QTcF changes from baseline will be investigated in an exploratory manner using a random coefficient model to estimate the difference in means between BI 3006337 and placebo of QTcF change from baseline and its 90% confidence interval at clinically relevant serum concentrations, i.e. at the geometric mean of C_{max} after single dose for each dose. Additionally, the estimated overall slope with its 90% confidence interval will be provided. The used random coefficient model is based on a white paper from Garnett et. al. (15) with ΔQTcF as response variable, centered baseline QTc and serum concentration as continuous covariates, treatment, time and day as fixed categorical effects, and a random intercept and slope for each subject. Restricted maximum likelihood estimation will be performed, and the Kenward-Roger method will be applied to adjust standard errors and estimate denominator degrees of freedom. For more details refer to Section 10.1.4.

For visualization, a scatterplot of the BI 3006337 serum concentration against the following individual QTcF values will be provided: For each subject on active treatment and each time point, subtract the mean value of all individual observed ΔQTcF values from the placebo group for this time point from the individual observed ΔQTcF value for this subject and time point. This results in estimates for “individual ΔΔQTcF” values, which should only be used

for plotting purposes. The corresponding regression line and its pointwise confidence bands as well as the geometric mean of C_{max} for each dose and $C_{max,ss}$ for MD group will additionally be displayed in the plot.

The goodness of fit of the above model will be checked. The visual checks will include the inspection of concentration-QTcF quantile plots (15) and residual plots. In case of non-linearity or if there is evidence for a delayed effect, further models will be explored in order to better characterise the PK-ECG relationship.

All of the above described graphical and statistical analyses will be also performed for HR in place of QTcF.

Appropriateness of heart rate correction methods of QT interval

To evaluate the appropriateness of the heart rate correction methods, the slope of the relationship of QTcF interval versus RR interval will be estimated separately for off-drug values and active treatment, by applying the random coefficient model described in Section 10.1.2 using the QTcF and RR variable values per time point. A scatterplot of QTcF vs RR including the overall regression lines will be included in the Statistical Appendix of the CTR.

Additionally, the slope of the relationship of log-transformed QT interval versus log-transformed RR interval will be estimated separately for off-drug values and active treatment, by applying a random coefficient model per single ECG.

7.9 OTHER ANALYSIS

Physical examination
Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of trial drug) or as AEs and will be summarised as such.

No separate listing or analysis of physical examination findings will be prepared.

Local tolerability assessment
Local tolerability will be assessed as ‘swelling’, ‘induration’, ‘heat’, ‘redness’, ‘pain’, or ‘other findings’ by the investigator or authorised designee. Injection site reactions with clinically relevant findings must be recorded as AE. Clinically relevant findings of the local tolerability assessment will be reported as AEs.

A frequency table including results of local tolerability assessments will be prepared.

Suicidality assessment (C-SSRS) – MD part only
Suicidality will be assessed by administrating a questionnaire at each measuring time point indicated in the CTP Flow Chart. Results regarding C-SSRS will only be listed.

[redacted]

7.9.2 PK / PD analyses

Section 5.3.4 of the CTP:

Exposure-response relationships may be investigated graphically for selected PK parameters (e.g. $C_{max,ss}$ and $AUC_{\tau,ss}$) and selected PD, safety/tolerability endpoints including gastric emptying, nausea/vomiting, and HR. If it is considered necessary to further investigate a particular relationship, exposure-response model(s) will be developed. This pharmacometrics analysis will then not be part of the CTR but will be reported separately.

8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

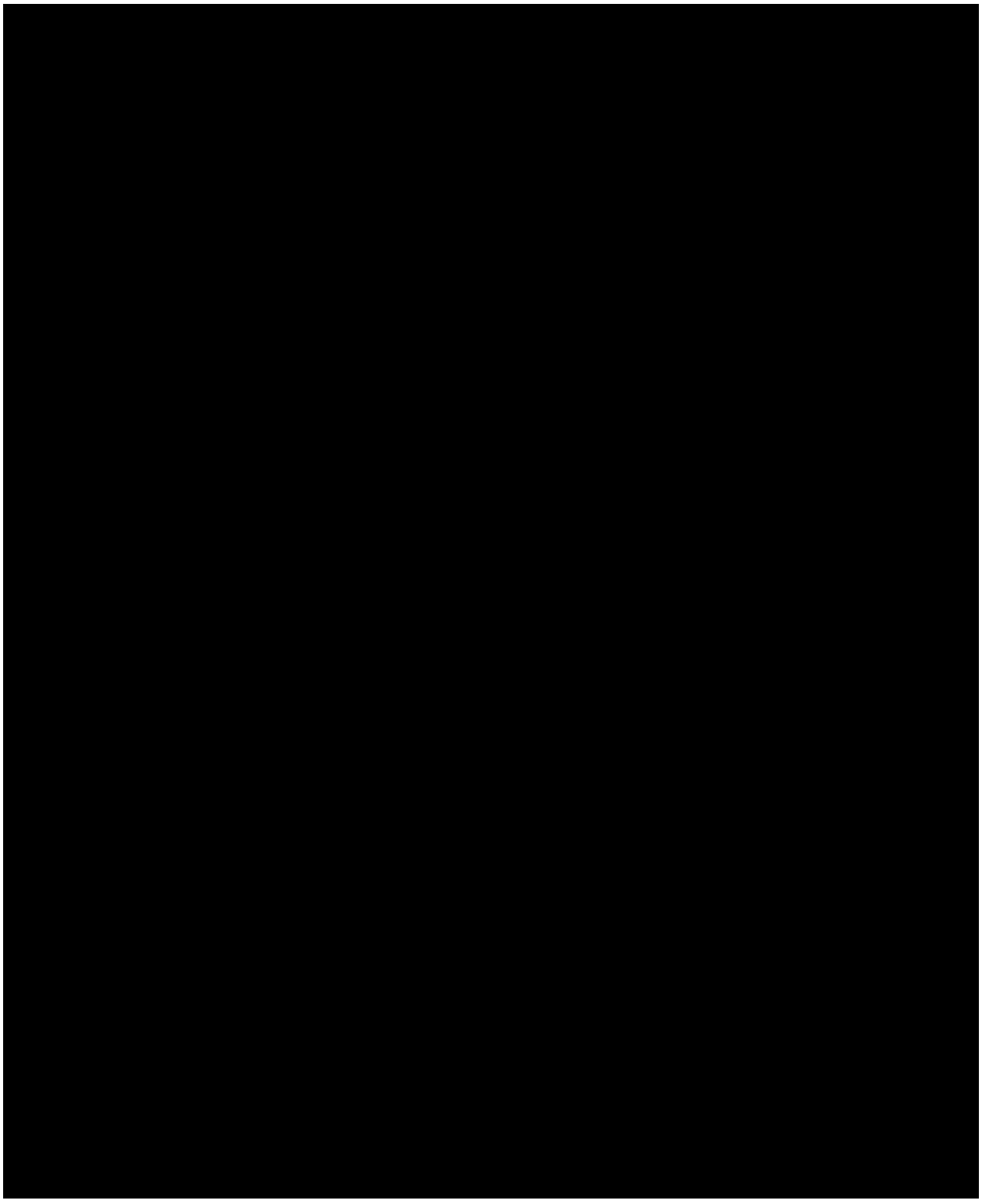
Not applicable due to open-label fashion of the trial as described in the CTP section 4.1.5.

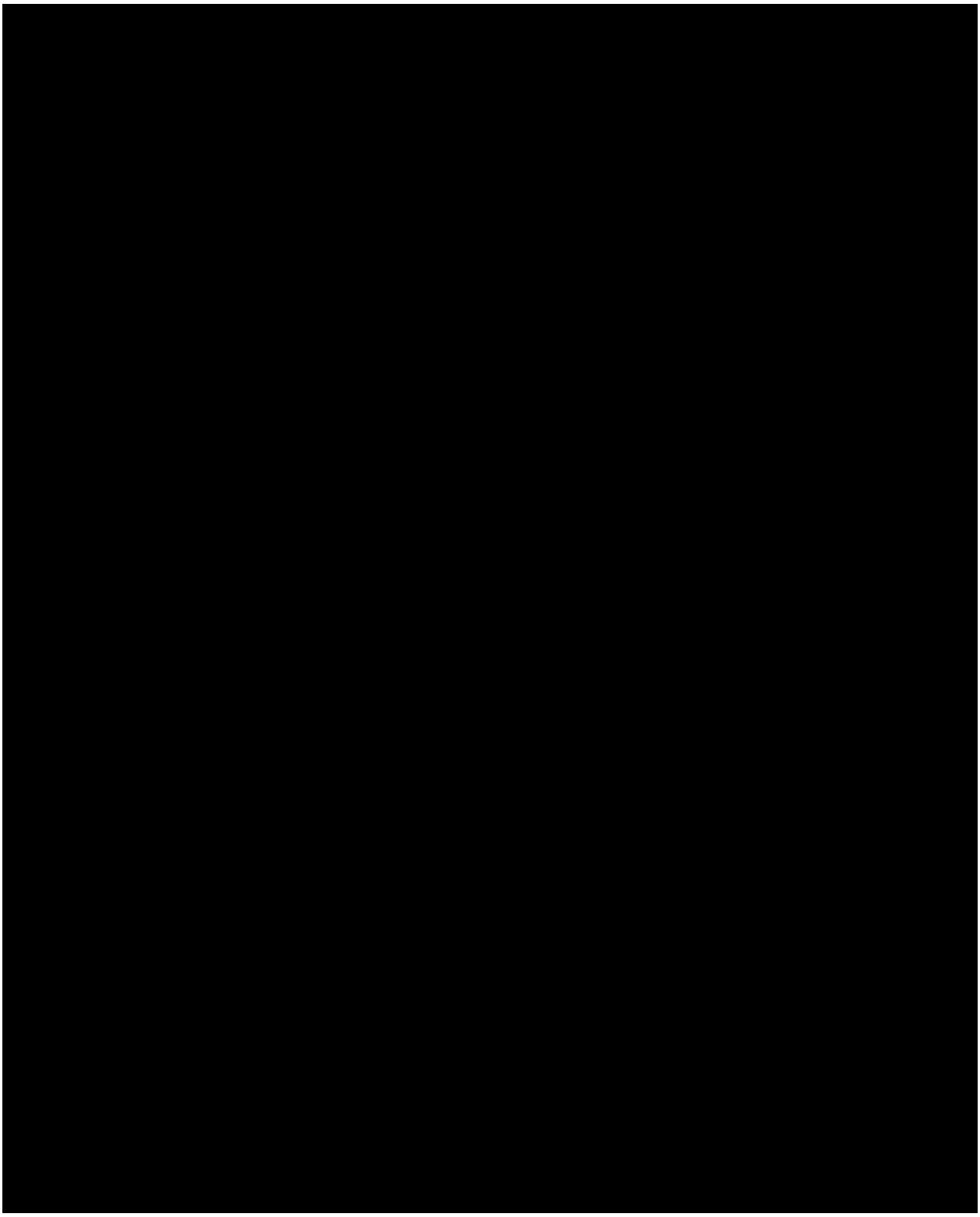
The treatment information will be loaded into the trial database after trial initiation.

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-VQD-12045_40-413:* "Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations", KMED.
3.	*BI-KMED-BDS-TMP-0059*: "iPD specification document (sdtm-dv-domain-specification)", template, current version, Group "Clinical Operations", KMED.
4.	*001-MCS-50-415_RD-03*: "Clinical Trial Analysis Decision Log (template)", current version, Group "Biostatistics & Data Sciences", KMED.
5.	*BI-KMED-BDS-HTG-0035*: "Handling of Missing and Incomplete AE Dates", current version, Group "Biostatistics & Data Sciences", KMED.
6.	*BI-KMED-TMCP-HTG-0025*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
7.	*BI-KMED-TMCP-MAN-0014*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
8.	*BI-KMED-BDS-HTG-0045*: "Standards for Reporting of Clinical Trials and Project Summaries", current version, Group "Biostatistics & Data Sciences", KMED.
9.	*BI-KMED-TMCP-OTH-0003*: "Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
10.	*BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files, PK/PD Data files and ADA files", current version, Group "Translational Medicine Clinical Pharmacology", KMED.
11.	*BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template", current version, Group "Biostatistics & Data Sciences", KMED.
12.	*BI-KMED-BDS-HTG-0066*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version, Group "Biostatistics & Data Sciences", KMED.
13.	*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.

14.	*BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version, Group "Biostatistics & Data Sciences", KMED.
15.	*R18-0143:* Garnett C, Bonate PL, Dang Q, Ferber G, Huang D, Liu J, et al; Scientific white paper on concentration-QTc modeling. J Pharmacokin Pharmacodyn (2017)





11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**21-NOV-24**	[redacted]	None	This is the final TSAP.