Boehringer Ingelheim

TRIAL STATISTICAL ANALYSIS PLAN

Document No.:	**c44570298-01**
BI Trial No.:	**1305-0026**
Title:	Thorough QT study to evaluate the effects of BI 1015550 as single doses following oral administration on cardiac safety parameters (double-blind, randomized, placebo-controlled, five-period crossover, with open-label moxifloxacin as positive control) in healthy male and female subjects (Revised protocol including Protocol Amendment No. 3 [c41839189-04).
Investigational Product(s):	BI 1015550
Responsible trial statistician(s):	[redacted] Phone: [redacted]
Date of statistical analysis plan:	02 SEP 2024
Version:	1.0
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1. TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
BLQ	Below the Limit of Quantitation
BP	Blood Pressure
BRAVE	Boehringer Ingelheim RAVE (EDC)
CARE/RAGe	Clinical data Analysis and Reporting Environment …
Cmax	Maximum measured concentration of the analyte in plasma
CV	arithmetic coefficient of variation
ECGPCS	ECG pharmacokinetic concentration set
ECGS	ECG set
gCV	geometric coefficient of variation
gMean	geometric mean
HR	Heart rate
iPD	Important Protocol Deviation
LLOQ	Lower Limit of Quantitation
Max	maximum
Min	minimum
MMRM	mixed-effects model for repeated measurements
Moxi	Moxifloxacin
N	number non-missing observations
NOA	not analysed
Nobs	number of observations
NOP	no peak detectable
NOR	no valid result
NOS	no sample available
P1	Placebo period 1
P2	Placebo period 2
Pbo	Placebo
PKS	Pharmacokinetic parameter analysis set
PR	ECG time interval
PR	Pulse rate
Q1	1st quartile

Term	Definition / description
Q3	3rd quartile
QRS	ECG time interval
QT	ECG time interval from the start of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate, e.g. using the method of Fridericia (QTcF)
QTcF	QT interval corrected for heart rate using the method of Fridericia (QTcF)
RAVE	EDC system
REP	Residual Effect Period
RR	ECG time interval
SD	standard deviation
TS	Treated Set
WHO-DD	World Health Organisation – Drug Dictionary

3. INTRODUCTION

As per ICH E9 (CPMP/ICH/363/96) (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 as collected in the eCRF will be stored in a trial database within the [redacted]. All study data also including external data will then be uploaded to the CDR data warehouse.

The statistical analyses will be performed within the validated working environment [redacted] and a number of [redacted] for compilation/formatting of the CTR appendices).

Pharmacokinetic (PK) parameters will be calculated using [redacted] or [redacted] (or later version).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in this TSAP are in accordance with the statistical methods described in the CTP.

In the CTP Section 2.1.1, showing assay sensitivity of the trial is mentioned as secondary objective. Therefore, within this TSAP, the analysis of the secondary endpoint related to showing assay sensitivity is interpreted as secondary objective analysis, i.e. described in Section 7.5.

Further exploratory analyses related to the primary and secondary endpoint (that are not sensitivity, subgroup or supplementary analyses) as well as further endpoint analyses are interpreted as further objective analyses, i.e. described in Section 7.6.

In contrast to CTP Section 7.5.2 (“Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.”), previous and concomitant therapies will only be summarized as a total over all treatment sequences, see Section 7.1.

The investigational product BI 1015550 will be referred to as nerandomilast within the CTR. In the CTP it was still defined as BI 1015550. The TSAP will use the term nerandomilast (except for the title page) to be in accordance with the CTR. In the CTR outputs, the two doses will be referred to as “[redacted] and “[redacted], see Section 6.1.

5. ENDPOINTS(S)

No efficacy endpoints will be evaluated in this trial.

General remarks regarding ECG endpoints derived from interval measurements:
The derivation of ECG endpoints is described in Section 10.1.

Section 7.2.1.2 of the CTP:

Since it is not expected that the mean of the placebo-corrected HR change from baseline will be larger than 10 beats/min (bpm) for both doses of nerandomilast*, QTcF will be selected as the heart rate correction method for the present trial.*

Throughout this TSAP, *the term "baseline" (if not specified further)* of an ECG variable *refers to* the average of *the 3 pre-dose triplicate ECG measurements at Visits 2-6 (i.e., a separate baseline for each period will be derived from the 9 ECG recordings that comprise 4 cardiac cycles each).*

For baseline of other parameters see Section 6.7.1.

5.1 PRIMARY ENDPOINT(S)

Section 2.1.2 of the CTP:

The maximum mean difference between each single dose of either [redacted] *of* nerandomilast *and placebo in QTcF changes from baseline between 20 min to 24 hours after drug administration.*

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

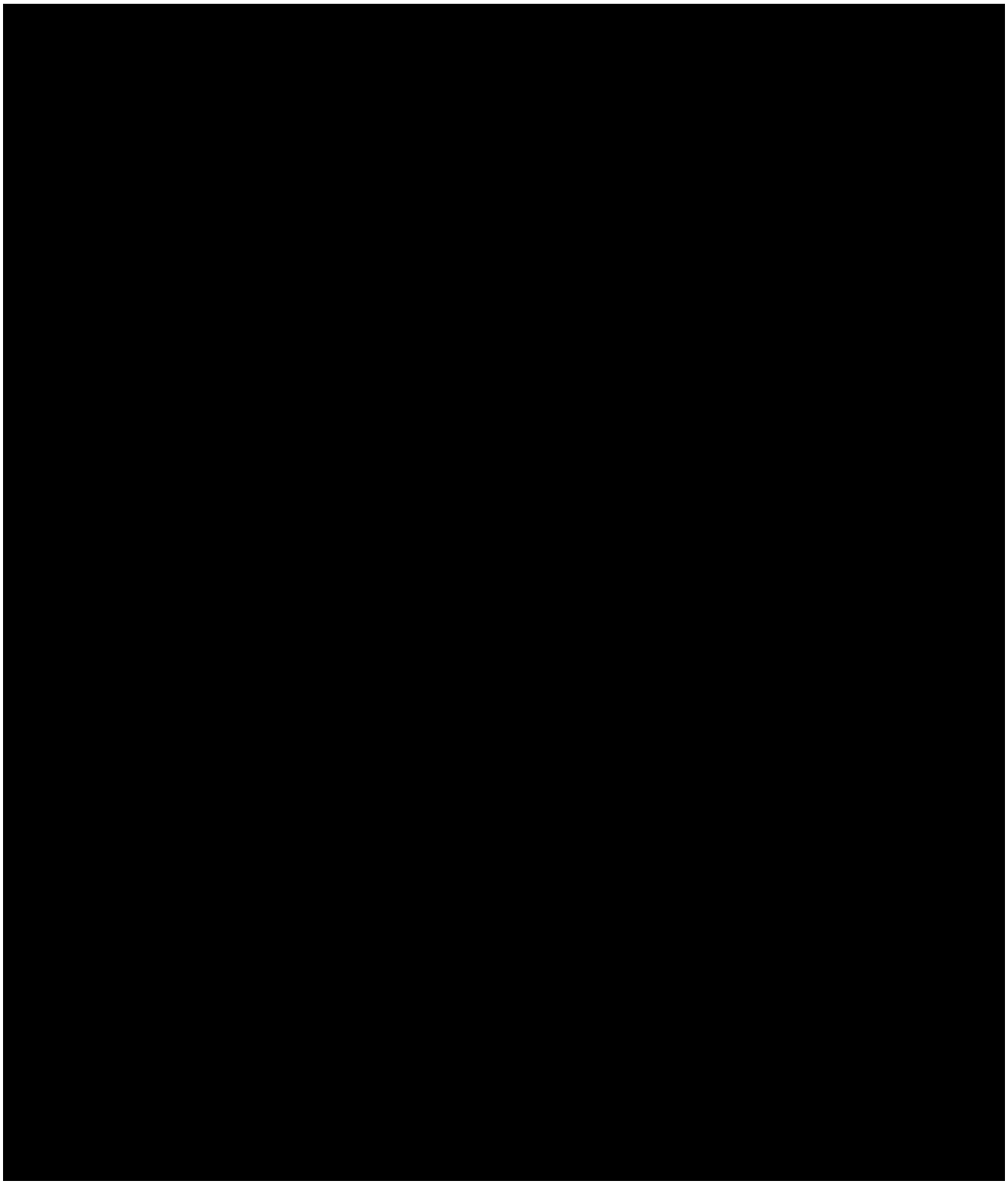
Not applicable. There are no key secondary endpoints specified in the CTP.

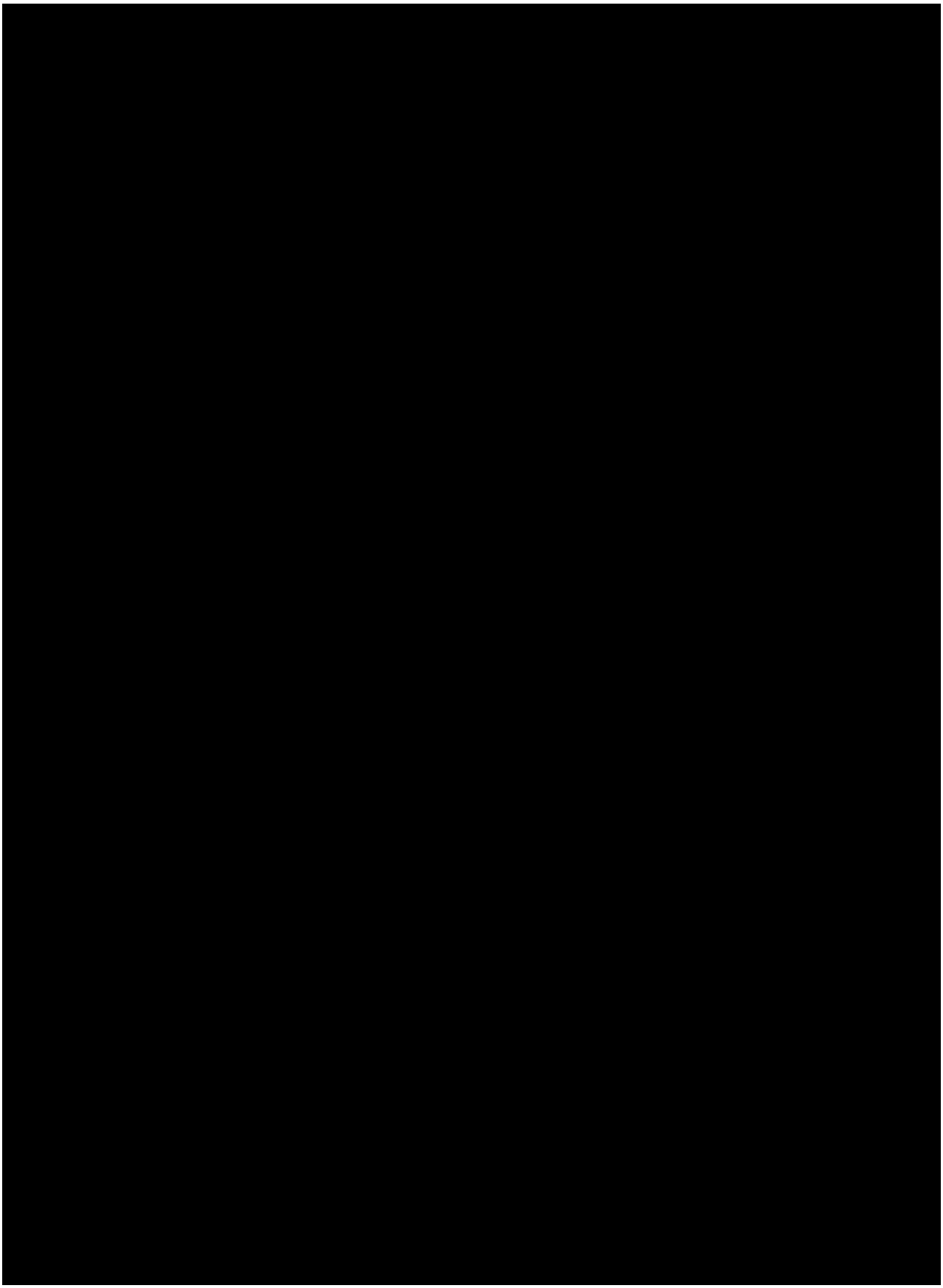
5.2.2 Secondary endpoint(s)

Section 2.1.3 of the CTP:

The maximum mean difference between moxifloxacin and placebo in QTcF changes from baseline between 20 min to 24 hours after drug administration. (The formal test for assay sensitivity will be based on the results for the pre-selected time points 2, 3, and 4 hours post dosing.)

[redacted]





6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

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

It is planned to include a total of 45 healthy male and female subjects in the trial randomly allocated to one of the 15 treatment sequences, see CTP Section 7.2.1.

CTP Section 7.2.1.1: *The trial will be performed as a randomized, double-blind, 5-period crossover of single dose treatments including* nerandomilast [redacted]*, as well as open-label moxifloxacin. The* [redacted]. The treatments will be separated by a wash-out phase of at least 7 days (cf. CTP Section 3.1).

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

Table 6.1: 1 Treatments and labels used in the analysis

Long label*	Treatment description	Short label
Placebo 1	Placebo, TABLET, FILM COATED QD ORAL, FASTED	P1
Placebo 2	Placebo, TABLET, FILM COATED QD ORAL, FASTED	P2
BI 30mg	Nerandomilast [redacted] TABLET, FILM COATED QD ORAL, FASTED	L
BI 48mg	Nerandomilast [redacted], TABLET, FILM COATED QD ORAL, FASTED	H
Moxi 400 mg	Moxifloxacin 400 mg, TABLET, FILM COATED QD ORAL 1*400 mg, FASTED	M

* without masking placebos

For analyses distinguishing between periods or treatments, the two different placebo treatment labels as in Table 6.1: 1 will be used (i.e., “Placebo 1” and “Placebo 2” or “P1” and “P2”). For analyses with regards to sequences, the short labels of Table 6.1: 1 will be used with separation of ”/” between the treatments, e.g., one sequence may be “H/M/P2/L/P1”.

Section 1.2.3 of the CTP:
The Residual Effect Period (REP) is the period after the last dose with measurable drug levels and/or pharmacodynamic (PD) effects still likely to be present. The REP of nerandomilast *is* [redacted] *The REP of moxifloxacin is 4 days.*

For Placebo, the REP is set to 7 days, i.e. equal to that of nerandomilast.

Based on this, for the statistical analysis of adverse events (AEs), the following analysis phases specified in Table 6.1: 2 will be defined for each subject.

Table 6.1: 2 Analysis phases for statistical analysis of AEs

Study analysis phase[1]	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	0:00h on date of informed consent	Date/time of first administration of study drug in period 1
On-treatment	[redacted] or **Moxi 400 mg,** respectively	Date/time of administration of study drug	Date/time of administration of study drug + REP or Date/time of administration of study drug in the next treatment period or 0:00h on day after trial termination, whatever comes first
Follow-up	[redacted] or **FUP Moxi 400 mg**, respectively	End of the respective on-treatment period, i.e. date/time of administration of respective study drug + REP	Date/time of administration of study drug in the next treatment period, if applicable, otherwise 0:00h on day after trial termination

[1] See Section 6.7 for definition of baseline, which will be used in the statistical analyses of safety laboratory data, ECG and vital signs.

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.

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). The screening and follow-up phases will not be included in this analysis.

The following totals will be provided in addition for Section 9.3 (but not in Appendix 10.5.1.8 AE tables):

- "**Total Pbo**", defined as the total over all on-treatment phases involving treatment with placebo
- "**Total BI**", defined as the total over all on-treatment phases involving treatment with nerandomilast

The treatments will be presented in Section 9.3 (AE tables) in the following sort order:

[redacted], Moxi 400 mg, Total Pbo, Total BI.

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.

Measurements will be considered on-treatment, if they were taken within the on-treatment phases as defined in Table 6.1: 2.

Statistical analyses of vital signs and laboratory data will be conducted by treatment ([redacted], Moxi 400 mg), with clear differentiation between baseline (see Section 6.7) and on-treatment measurements.

Statistical analyses of Holter ECG data will include the single periods involving BI treatment (or treatment with moxifloxacin, respectively) together with summarised Placebo and summarized BI periods (see also Section 7).

The summary of placebo and BI treatments depends on the type of ECG data. First, for quantitative ECG data the placebo periods are averaged yielding one placebo treatment ("Pbo average"); see Table 6.1: 3. Second, for categorical ECG endpoints derived from quantitative ECG endpoints the categorization is performed after averaging both placebo periods, again yielding one placebo treatment "Pbo average".

Table 6.1: 3 Single treatments with averaged placebo data used for the descriptive analyses of quantitative or derived categorical ECG data per subject

Treatment	Label	Sort order in tables	Explanation
[redacted]		1	Data from both placebo periods will be averaged. Note that for the MMRM analyses, the placebo data will not be averaged; see Section 7.4.1.
		2	
		3	
Moxi 400 mg	Moxi 400 mg	4	

Third, for qualitative endpoints not derived from continuous variables, i.e. qualitative ECG data like the morphological assessments of the extracted 10-second ECGs, pooling of placebo and BI periods, respectively, will be performed based on worst case assessments. The resulting treatments are denoted by "Total Pbo" and "Total BI"; see Table 6.1: 4.

Table 6.1: 4 Single treatments with summarized data from both placebo and from both BI periods, respectively, used for the descriptive statistics of qualitative ECG data per subject

Treatment	Label	Sort order in tables	Explanation
Placebo	**Total Pbo**	1	Worst case assessment will be used to aggregate the results from both placebo periods.
[redacted]		2	
		3	
[redacted]	Total BI	4	Worst case assessment will be used to aggregate the results from both BI periods.
Moxi 400 mg	Moxi 400 mg	5	

For more details on the technical implementation of these analyses refer to the 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 BI-VQD-12045_40-413 (3).

Important protocol deviation (iPD) categories are pre-specified in the iPD specification file (DV domain, BI-KMED-BDS-TMP-0059) (4). IPDs will be identified and the decision on exclusion of subjects from analysis sets will be made no later than in the Report Planning Meeting. These iPDs will be captured in the iPD specification file and in the decision log (001-MCS-50-415_RD-03) (5). Both documents will be stored within the TMF in EDMS. The iPDs will be summarized and listed in the CTR.

6.3 INTERCURRENT EVENTS

Not applicable.

6.4 SUBJECT SETS ANALYSED

Section 7.2.1.3 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.*
- *ECG set (ECGS): This subject set includes all subjects in the TS who have at least one on-treatment value for at least one ECG endpoint, which is not excluded due to ECG relevant iPDs. Such iPDs may be e.g., the use of pro-arrhythmic medications. Exclusion of single ECG values due to relevant iPDs is to be decided no later than in the Report Planning Meeting before data base lock and will be documented in the CTR*
- *Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was defined as a further endpoint and was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment.*
- *ECG pharmacokinetic concentration set (ECGPCS): This subject set includes all subjects from the ECGS who provide at least one pair of a valid* nerandomilast *plasma concentration and a corresponding (i.e., time-matched) ECG endpoint to be used in the exposure-response analysis. The decision whether the time differences at each PTM between the respective ECG recording and PK blood sampling are acceptable (and thus whether the pairs of values will be used) is to be made no later than at the Report Planning Meeting before data base lock. For subjects treated with* nerandomilast*, the decision about concentration value validity needs to be made within the Clinical Pharmacology Group*

The ECGS will be used for all analyses of the centrally assessed ECG data, except for the exposure-response analyses, which will be performed on the ECGPCS. The TS will be used for all other safety summaries and all safety listings. Descriptive analyses and model-based analyses of PK parameters will be based on the PKS.

The analyses with the respective used subject sets are shown in Table 6.4: 1.

Table 6.4: 1 Subject sets analysed

Class of endpoint	TS	PKS	ECGPCS	ECGS
Primary and secondary endpoints				X
Analyses of PK endpoints		X		
ECG exposure response analyses			X	
[redacted]				
Disposition	X			
Demographic/baseline parameters	X			
Important protocol deviations	X			
Exposure	X			
[redacted]				

The ECGS will be used for all analyses of the centrally assessed ECG data, except for the exposure-response analyses, which will be performed on the ECGPCS. The TS will be used for all other safety summaries and all safety listings. Descriptive analyses of PK parameters will be based on the PKS.

[redacted]

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Data of subjects who failed to complete all periods of the study (dropouts or withdrawals) will be reported in the CTR as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded in the CTR.

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

CTP Section 7.3.2: *It is not planned to impute missing values for safety parameters.*

One exception where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (see BI-KMED-BDS-HTG-0035) (6).

Missing data and outliers of PK and PD data are handled according to BI standards.

CTP Section 7.3.2: *PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.*

Drug concentration data for non-compartmental analysis identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the pre-dose values). Concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

ECG

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.

If a period baseline is missing the arithmetic mean of the remaining other period baselines will be used.

The subject baseline will be calculated based on the non-missing period baselines used in the respective comparison. Imputed period baseline values will not be used for creation of subject baselines.

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 Appendix Section 10.2.

Exposure-response analysis:

For periods of the subjects on active drug, missing plasma concentration values with ‘BLQ’ in the comment field will be replaced by 1/2* LLOQ.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

6.7.1 Baseline

If not otherwise stated, baseline is defined as the last measurement prior to drug administration in each period except for:

- Laboratory data: baseline is defined as the last measurement prior to first drug administration in the first period.
- ECG interval data: see below.

ECG interval data:

CTP Section 7.2.1.2:

Throughout this TSAP, *the term “baseline”* for ECG variables *(if not specified further) refers* to the period baseline, i.e. *to* the average of *the 3 pre-dose triplicate ECG measurements at*

Visits 2-6 (i.e., a separate baseline for each period will be derived from the 9 ECG recordings that comprise 4 cardiac cycles each).

The general term 'Change from baseline' always refers to the change from the respective period baseline. An additional 'subject baseline' is defined as the arithmetic mean of the period baselines per subject and will only be used in the context of MMRM analyses; only the baselines of the periods included in the analysis for comparing two treatments are considered; for further details see Section 7.4.1 and Section 7.5.2.

6.7.2 Time windows

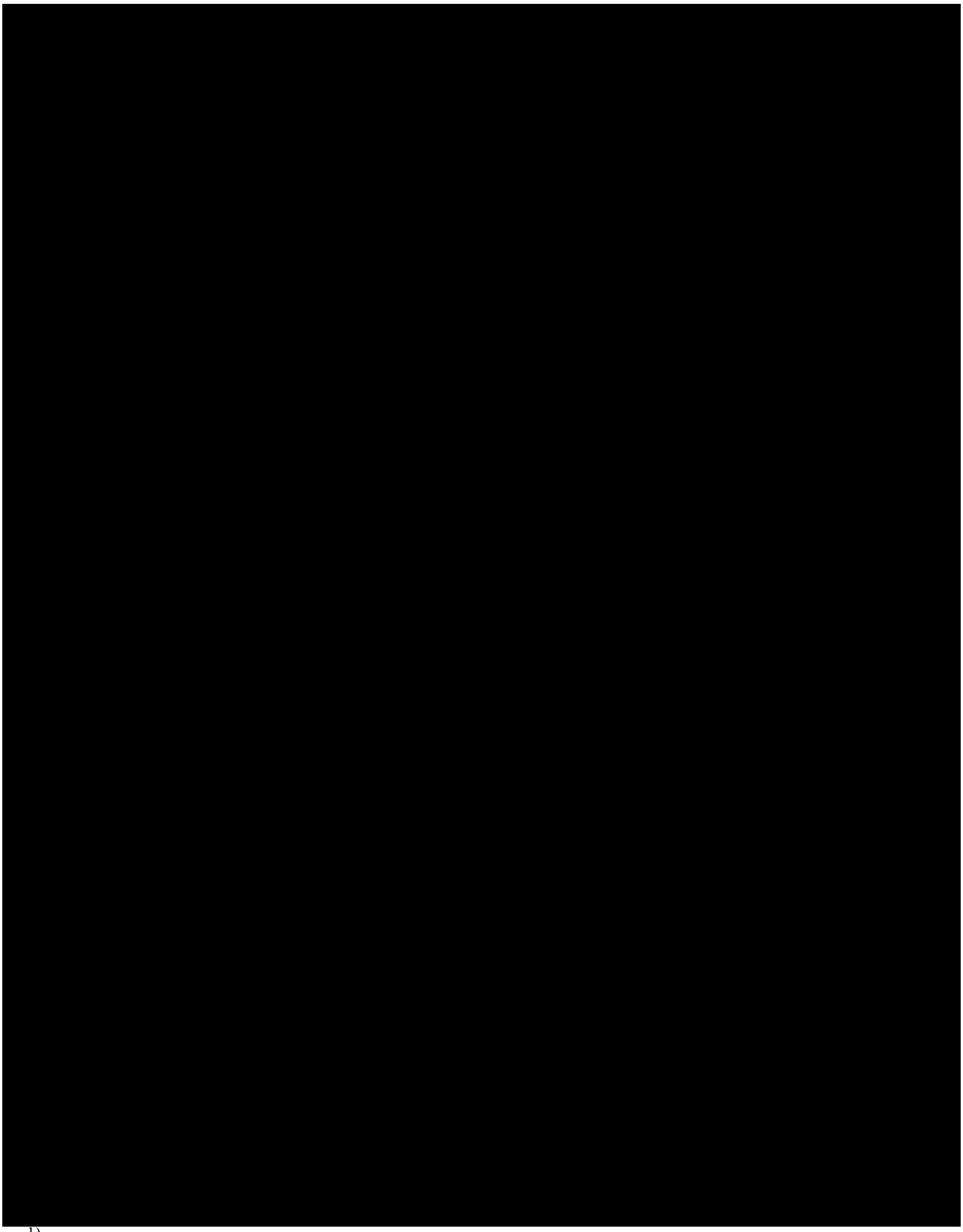
Time windows are defined in **Section 6.1 of the CTP:**
Exact times of measurements outside the permitted time windows will be documented.

- *The acceptable time windows for screening and the end of trial examination are provided in the* CTP *Flow Chart*
- *Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 h-period prior to the trial drug administration*
- *The acceptable deviation from the scheduled time for vital signs and single safety 12-lead ECGs will be ±30 min on Day 1 and 2 of each treatment period except for procedures which are to be completed within 2 h prior to drug administration as outlined in the* CTP *Flow Chart*
- *The timing of ECG extractions from 24-hour Holter recordings (see Flow Chart) is of particular importance in this clinical trial. Thus, triplicate ECG extraction from Holter ECG recordings will always precede PK sampling and measurements of vital signs if scheduled for the same time point. The acceptable time windows for ECG extractions in Holter ECG recordings (see* CTP *Section 5.2.4) are ±5 min up to 2 h after dosing and ±10 min from more than 2 h to 24 h after dosing*
- *For planned individual plasma concentration sampling times refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameter. The acceptable deviations from the nominal blood sampling times are as follows:*
    - *The pre-dose samples will be taken ≤2 h before dosing*
    - *0 to 1 h post-dose samples will be taken within ± 2 min of the planned post-dose sampling time*
    - *1.5 to 12 h post-dose samples will be taken within ± 10 min of the planned post-dose sampling time*
    - *24 h post-dose samples will be taken within ± 30 min of the planned post-dose sampling time*

- *Regarding the intended exposure-response analysis, ECG extractions and actual times of PK sampling at a planned time point need to be time-matched and should be as close as technically feasible*
- *If scheduled in the Flow Chart at the same time as a meal, blood sampling or vital signs assessment, the end of the ECGs extraction from Holter ECG recordings have to be performed first with the exception of single safety ECGs which should be printed before the actual ECG extractions. Furthermore, if several measurements including venepuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters, including ECG time intervals*
- *For a particular subject, the clock time of dosing should be similar in all [redacted] periods (±90 min). In case the time switch from normal time to daylight saving time (or vice versa) occurs throughout the trial conduct, the actual clock times will be followed (and not the clock times of first dosing).*

If a subject misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

There will be a centralised evaluation of the extractions from the Holter 12-lead ECG recordings at the time points specified in Table 6.7.2: 1 below.



[1)] Maximum acceptable time deviations for ECG triggering in Holter ECG recordings to mark the end of the extraction periods (according to CTP Section 6.1)

Three triplicate ECGs will be recorded as the baseline before the first drug administration in each period. At all other time points, 1 triplicate ECG will be recorded. The results of all triplicates will be transferred to the database. For baseline definition of an ECG variable see Section 6.7.1. At screening and end of trial examination (and further time points, see CTP flow chart), single local 12 lead ECGs (non-Holter) for safety will be recorded that will not be transferred to the central ECG lab.

Additionally, for the exposure-response analyses, acceptable maximum time deviations between timing of ECG extraction from Holter recordings and plasma concentration sampling are necessary (see the definition of the ECGPCS in Section 6.4). These are defined as specified in Table 6.7.2: 1. Pairs with time deviations exceeding those specified above will be flagged for exclusion from exposure-response analyses for discussion during RPM. The final decision if they are to be excluded is to be made during RPM. When the sampling time of the blood sample or the ECG recording is not available, the pair will also be excluded.

For all defined time windows, adherence to time windows will be checked via the consistency check listings at the RPM.

7. PLANNED ANALYSIS

Safety analysis (refer to Section 7.8) except ECG related analyses 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.

Descriptive data analysis of PK endpoints and concentrations will be performed by the [redacted] at BI and will be presented in Section 9.6 of the CTR and in Appendix 10.5.5.

ECG related analyses will be performed by the [redacted] at BI and will be presented in Section 9.3 of the CTR and in Appendix 10.6 and 10.5.1.

The format of the listings and tables will follow the BI guideline "Standards for Reporting of Clinical Trials and Project Summaries" (BI-KMED-BDS-HTG-0045) (7) with the exception of those generated for PK-calculations following BI standards for PK/PD analysis (BIKMED-TMCP-OTH-0003 (8).

The individual values of all subjects will be listed. Listings will be sorted by subject number, treatment sequence, visit and time point (if visit/ time point is applicable in the respective listing). AE listings will be sorted by assigned treatment (see Section 7.8.1 for details). The listings will be contained in Appendix 16.2 of the CTR.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables:

N	number non-missing observations
Mean	arithmetic mean
SD	standard deviation
Min	minimum
Q1	25th percentile
Median	median
Q3	75th percentile
Max	maximum

For plasma concentrations as well as for all 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

The data format for descriptive statistics of concentrations will be identical to 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.

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 (%) relative to the respective subject set (unless otherwise specified, all subjects in the respective subject set whether they have non-missing values or not). The category missing will be displayed only if there are actually missing values.

Section 7.2.1.4 of the CTP:

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

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 Report Planning Meeting) 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*

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). A predose concentration is >5% C_{max} value of that subject*
- *Missing samples/concentration data at important phases of PK disposition curve*

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. Descriptive and inferential statistics of PK parameters will be based on the PKS.

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 provided in the bioanalytical report).

Exclusion of PK parameters

The ADS "ADPP" (PK parameters) contains column variables APEXC 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 only 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 ACEXC 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.
- 'DESC STATS' the value will be excluded from descriptive evaluations per planned time point/time interval.
- '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.

If ACEXCO contains the addition 'TIME VIOLATION' or 'TIME DEVIATION' the value can be used for further analyses based on actual times. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

Further details are given in "Noncompartmental PK/PD Analyses of Clinical Studies" (BI-KMED-TMCP-MAN-0014 (9)) and "Description of Analytical Transfer Files, PK/PD Data files and ADA files" (BI-KMED-TMCP-MAN-0010 (10)).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the CTR. These will be based on the TS. The data will be summarised in total only.

7.2 CONCOMITANT DISEASES AND MEDICATION

Descriptive statistics are planned for this section of the CTR, based on the TS.

Concomitant diseases and non-drug therapies will be coded according to the most recent version of the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Concomitant medication 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.

In the remaining document 'therapy' will be used for non-drug therapies and concomitant medications.

In contrast to CTP Section 7.5.2 ("Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods."), previous and concomitant therapies will only be summarized as a total over all treatment sequences without consideration of time intervals and treatment periods.

A therapy or a disease 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 phases).

The diagnoses and therapies will be listed. Subjects without any concomitant disease or concomitant therapy should be marked with a "No" in the respective column.

The relevance of the concomitant therapies to the evaluation of PK 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 plasma concentrations of trial medication will provide additional confirmation of compliance.*

Treatment compliance will not be analyzed or listed as a specific endpoint, but judged by observed analyte concentrations. Any deviation from complete medication intake will be addressed in the RPM (see Section 6.2) and described in the CTR.

7.4 PRIMARY OBJECTIVE ANALYSIS

7.4.1 Main analysis

Primary endpoint analysis:

Section 7.2.2 of the CTP:

For the analysis of the QTcF changes from baseline at each time point between 20 min to 24 hours after dosing, a linear mixed-effects model for repeated measurements (MMRM) will be used for the primary endpoint.

The comparison between each dose of nerandomilast *and placebo will be performed pairwise, i.e., data not relevant for the comparison of interest will be excluded. Data from both placebo periods per subject will be included simultaneously in the analysis, using the same treatment code 'placebo' but differentiated by the respective period numbers. This means that the model defined below can directly be used for estimating the treatment contrast between the active drug under consideration and placebo, using the observations from both placebo periods. In the following, the 'subject baseline' is defined as the arithmetic mean of the period baselines per subject (only from the periods involved in the comparison, i.e., the period baseline of the active treatment period and those of the 2 placebo periods).*

The MMRM is based on Schall and Ring [R10-5353] (11) *and includes the fixed categorical effects of 'treatment', 'period' and 'time', the 'treatment-by-time' interaction and 'period-by-time' interactions, as well as the continuous fixed covariates 'period baseline' and 'subject*

baseline', and the 'period baseline-by-time' interaction and 'subject baseline-by-time' interaction. Subject is included as a random effect on the intercept. For the repeated effect 'time', an unstructured covariance pattern is chosen, using the blocking factor 'subject-by-period'. Note that the 'subject baseline' is included in the model to avoid cross-level bias affecting treatment comparisons; see Kenward and Roger [R10-4391] (12).

More precisely, the model is given by

$$Y_{ikm(j)} = \mu + \gamma B_{im} + \gamma' \bar{B}_i + \pi_m + \tau_j + \zeta_k + \gamma_k B_{im} + \gamma'_k \bar{B}_i + (\pi\zeta)_{mk} + (\tau\zeta)_{jk} + s_i + e_{ikm},$$

$$s_i \sim N(0, \sigma_s^2),\ (e_{i1m}, \ldots, e_{iKm}) \sim N_K\ (\mathbf{0}, \Psi),$$

where i=1,...,I indicates the subject, k=1,...,K the time point within period, m=1,...,M the period and j=1,2 the treatment,

$Y_{ikm(j)}$	*the QTcF change from period baseline for subject i receiving treatment j in period m at repeated measures time point k,*
μ	*the overall intercept,*
B_{im}	*the baseline value for subject i in period m (period baseline),*
γ	*the associated covariate effect of period baseline,*
$\bar{B}_i$	*the subject baseline value (mean of 3 period baselines) for subject i,*
γ'	*the associated covariate effect of subject baseline,*
π_m	*the effect of period m,*
τ_j	*the effect of treatment j,*
ζ_k	*the effect of time k,*
γ_k	*the interaction effect of period baseline and time,*
γ'_k	*the interaction effect of subject baseline and time,*
$(\pi\zeta)_{mk}$	*the interaction effect of period and time,*
$(\tau\zeta)_{jk}$	*the interaction effect of treatment and time,*
s_i	*the random effect of subject i on intercept, assumed mutually independent across subject,*
e_{ikm}	*the random error associated with subject i for time k and period m, assumed independent across period and subject (indices m, i), and*
Ψ	*an unstructured K-by-K covariance matrix.*

The random subject effects s_i and the random errors e_{ikm} are assumed to be independent of one another.

The primary analyses use the MMRM described above for the QTcF data from nerandomilast *and placebo treatments, based on the ECG set.*

For the pairwise comparisons between each dose of nerandomilast *and placebo, mean treatment differences in the QTcF changes from baseline at each time point will be estimated by the differences in the corresponding least-squares means. Two-sided 90% confidence intervals based on the t-distribution will also be computed for each time point.*

The repeated-measures analysis will also be applied to absolute QTcF interval. Adjusted means of 'treatment-by-time point' and two-sided 95% confidence intervals based on the t-distribution will be computed.

Section 7.1 of the CTP:

The primary objective of this clinical trial will be assessed by testing the null hypothesis for each single dose of either [redacted] *of BI 1015550 that the maximum mean difference between BI 1015550 and placebo in QTcF changes from baseline between 20 min to 24 hours is greater than or equal to 10 msec, against the alternative hypothesis that the maximum mean difference is below the threshold of 10 msec.*
The conclusion that this tQT trial is negative as per ICH E14 will be based on the rejection of this null hypothesis for each of the two doses of nerandomilast*. The one-sided tests will be performed at the 5% level, which is equivalent to the estimation of two-sided 90% confidence intervals because of the symmetry of the normal distribution. The trial will then be deemed as negative if the upper limit of the two-sided 90% confidence bound for the maximum mean difference between* nerandomilast *and placebo in QTcF changes from baseline is less than 10 msec, for both doses of* nerandomilast*.*

[redacted]

[redacted]

7.5 SECONDARY OBJECTIVE ANALYSIS

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

Assessment of assay sensitivity

Section 7.2.3 of the CTP:

The effect of moxifloxacin on the QTcF changes from baseline in comparison with placebo will be assessed using the same MMRM as applied in the primary analysis.

For this analysis, only the data from the moxifloxacin and placebo periods will be used.

For describing the time course of the effect of moxifloxacin on QTcF, 90% confidence intervals for the mean differences of the QTcF changes from baseline between moxifloxacin and placebo will be provided.

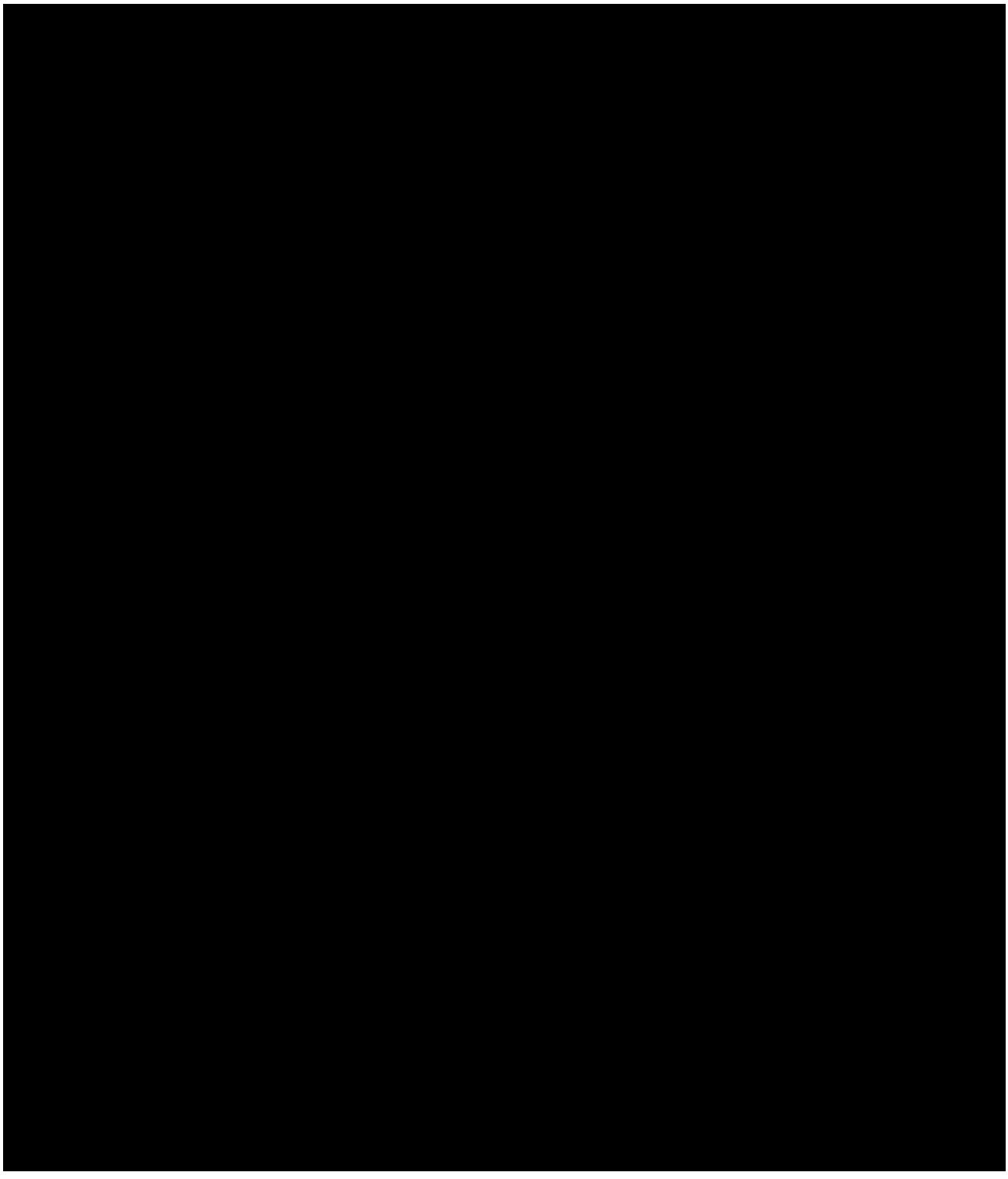
Section 7.1. of the CTP: *For the assessment of assay sensitivity of the trial, the null hypothesis that the mean difference in the QTcF changes from baseline between moxifloxacin and placebo is less than or equal to 5 msec for all of the time points 2, 3, and 4 hours after dosing will be tested at the 5 % level, against the alternative hypothesis that the mean difference is above the threshold of 5 msec for at least one of the three time points.*

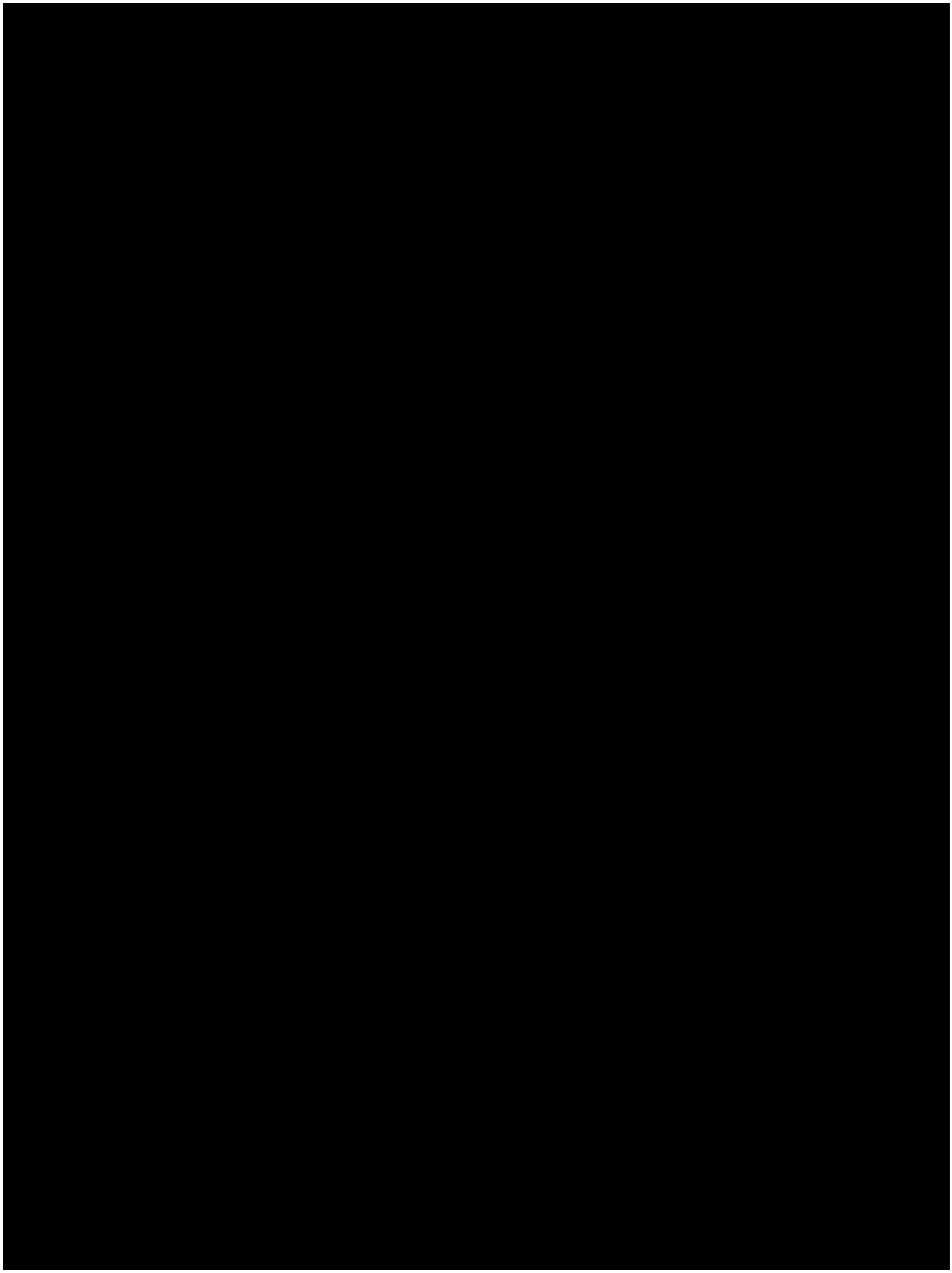
Section 7.2.3 of the CTP:

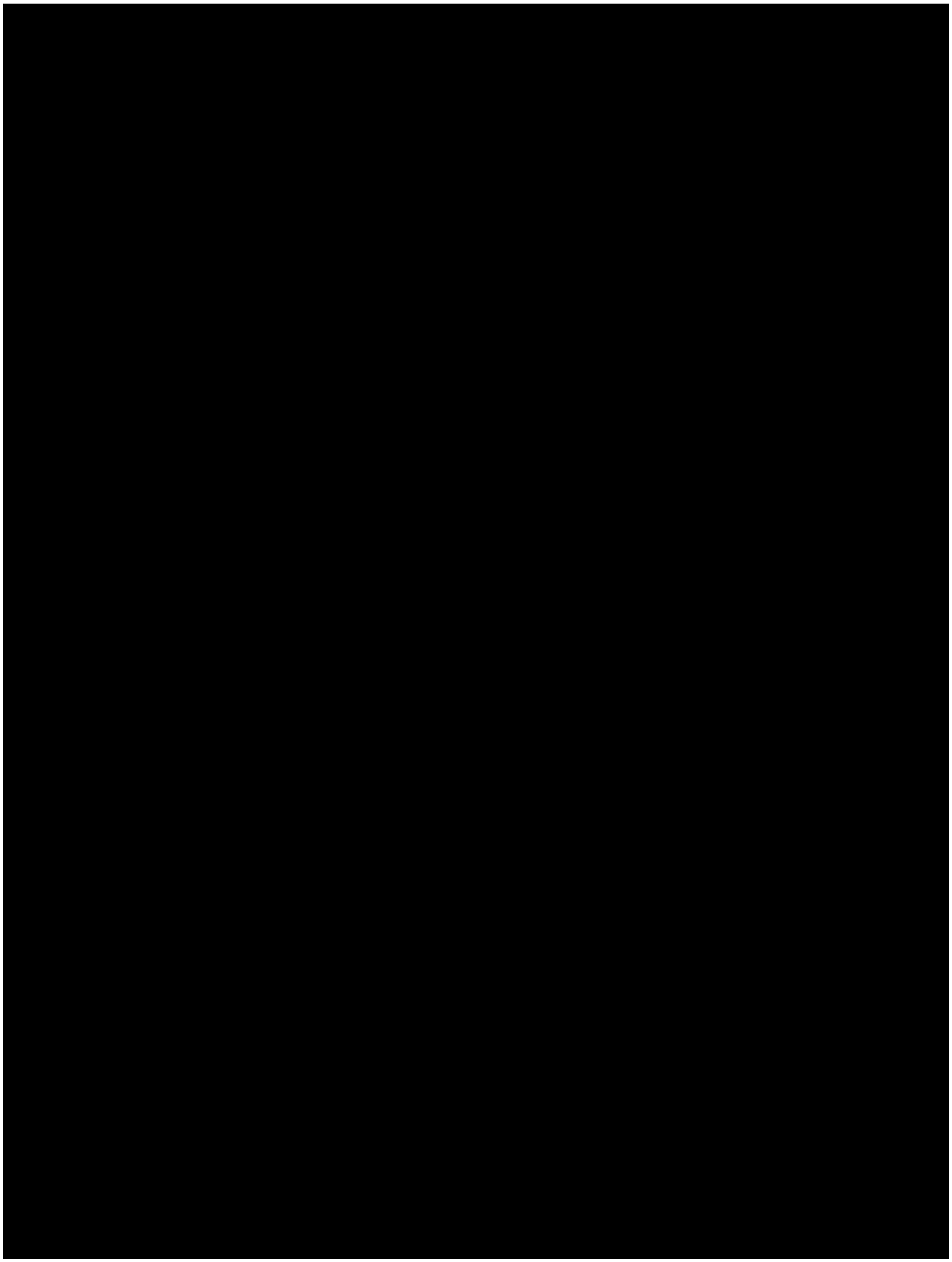
For the formal test of assay sensitivity at level α=5%, the method by Hochberg [R97-1003] (13) *will be applied. To this end, the three single hypotheses that the mean difference in the QTcF change from baseline between moxifloxacin and placebo is less than or equal to 5 msec at a given time point (out of the three time points 2, 3, and 4 hours after drug administration) will be tested based on the results of the MMRM (fitted to the data for all time points). If the largest of the three p-values is less than 5% (=α), then all single hypotheses can be rejected. If the second largest p-value is less than 2.5% (=α/2), then the corresponding null hypothesis and the one regarding the test with the lowest p-value can be rejected. If the lowest p-value is less than 1.667% (=α/3), then only the null hypothesis corresponding to this p-value can be rejected. Note that it is sufficient to reject only one of the three single null hypotheses in order*

to reject the overall null hypothesis stated in Section 7.1 (i.e., the intersection of the three single hypotheses), and hence to show assay sensitivity.

Section 7.2.3 of the CTP: *For assessing the robustness of the* used model for the main secondary endpoint, *a reduced model without the 'period-by-time' and the 'subject baseline-by-time' interactions will be fitted*.







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

For subject sets used in the safety analysis, cf. Section 6.4.

The safety data for treated subjects who failed to complete the study (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 the most recent version of MedDRA. The coding version number will be displayed as a footnote in the respective output.

Unless otherwise specified, the analyses of adverse events 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.

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: 2

For further details on summarization of AE data, please refer BI-KMED-BDS-HTG-0066 (17) and BI-KMED-BDS-HTG-0041 (18).

In addition to the presentation of AEs by treatment, both, the events in the two placebo periods, and the events of the two periods of (the different doses of) nerandomilast (see Section 6.1) will be summarized and added as totals. The interpretation of this summary for "Total BI" is "events following a dose of at least the therapeutic dose level". When comparing "Total Pbo" and "Total BI", "time under risk" is similar.

Section 5.2.6.1.4 of the CTP:
The following are considered as AESIs:

- *Potential severe DILI*

  A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

  - *An elevation of AST (aspartate aminotransferase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or*
  - *Aminotransferase (ALT, and/or AST) elevations ≥10-fold ULN*

  […]

- *Vasculitis events*

  In this CTP, vasculitis is defined as any event term included in the MedDRA SMQ Vasculitis (broad). This includes clinical and pathological features related to primary or secondary vasculitis syndromes and involving any type, size, and location of blood vessels.

  […]

- *Serious infections, opportunistic or mycobacterium tuberculosis infections.*

[…]

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

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 adverse events and for subjects with AESIs. In addition, the frequency of subjects with AEs will be summarised by treatment, worst intensity, primary SOC and preferred PT.

The system organ classes will be sorted alphabetically, PTs will be sorted by descending frequency (within SOC) over all treatment sequences.

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% (in preferred terms) for at least one treatment will be summarised by treatment, primary SOC and PT. The frequency of subjects with SAEs will also be summarised.

For disclosure of adverse events, additional information not included in a standard AE analysis will be performed. The following three entries will be created:

- Adverse Events per arm for disclosure on EudraCT
- Non-serious Adverse Events for disclosure on EudraCT
- Serious Adverse Events for disclosure on EudraCT

Other significant AEs according to ICH E3 (“Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3) (19) will be listed. The other significant AEs will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted).

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 BI-KMED-BDS-HTG-0042 (20).

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.

CTP Section 7.2.5: *Vital signs or other safety-relevant data* e.g., laboratory data *will be assessed with regard to possible on-treatment changes from baseline.*

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

Unscheduled measurements of laboratory 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. 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 follow-up time points (no on-treatment time points are included in this trial).
- last value of the subject at that planned time point (or assigned to that planned time point) for pre-treatment (e.g. baseline) time points.

Clinically relevant findings in laboratory data will be reported as baseline conditions (before first administration of a trial drug) or as AEs (during the trial), see CTP Section 7.2.5, 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 relevant abnormal or not (at the RPM at the latest).

7.8.3 Vital signs

The analyses of vital signs will be descriptive in nature. Descriptive statistics over time including change from baseline will be provided for vital signs (blood pressure and pulse rate). In the listing, the change from baseline will also be displayed. In addition, the time profiles of median and (Min, Max) will be displayed graphically by treatment.

CTP Section 7.2.5: *Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.*

Unscheduled measurements of 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. For 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 on-treatment and follow-up time points.
- last value of the subject at that planned time point (or assigned to that planned time point) for pre-treatment (e.g. baseline) time points.

If the time of measurement is missing for a scheduled post-baseline measurement (e.g. for follow-up visits) the scheduled measurement will be used in calculation of descriptive statistics (as time difference between scheduled and unscheduled cannot be assessed). If the time of measurement is missing for an unscheduled post-baseline measurement, this measurement will be listed but will be ignored for the calculation of descriptive statistics. In descriptive statistic of the Screening visit the planned time points will be used. However, if an unscheduled measurement on the same day as the screening visit exists then the unscheduled assessment will be used in descriptive statistics of Screening visit.

Clinically relevant findings will be reported as baseline conditions (before first administration of a trial drug) 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 relevant abnormal or not (at the RPM at the latest).

7.8.4 ECG

Continuous safety ECG monitoring (by investigator)

Section 7.2.5 of the CTP: *Relevant ECG findings or findings in safety laboratory data will be reported as AEs.*

Clinically relevant findings in ECG (irrespective of whether they originate from central or local evaluation) will be reported as baseline conditions (before first administration of a trial drug) or as AEs (during the trial), see Section 5.2.4.2 and 5.2.4.3 of the CTP, 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 relevant abnormal or not (at the RPM

at the latest).

CTP 5.2.4.3 Section: *All locally printed ECGs will be evaluated by the investigator or a designee. These ECGs will not be sent to the central ECG laboratory. Abnormal findings will be reported as AEs (during the trial) if assessed to be clinically relevant by the investigator. Any ECG abnormalities will be carefully monitored and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.*

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

Holter 12-lead ECG recordings

The statistical analyses of ECG endpoints selected as primary, secondary or further endpoints (see Section 5 are described in the respective sections of this TSAP (see Section 7.4, Section 7.5 and Section 7.6).

CTP Section 5.2.4.2: *Abnormalities detected during central ECG evaluation will be entered as AEs if assessed as clinically relevant based on the investigator's judgement (the investigator takes the final decision on AE documentation after having reviewed the cardiologist assessment provided by the core laboratory). […] All locally printed ECGs will be evaluated by the investigator or a designee. These ECGs will not be sent to the central ECG laboratory. Abnormal findings will be reported as AEs (during the trial) if assessed to be clinically relevant by the investigator.*

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 first administration of a trial drug) or as AE (during the trial) and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

7.9.1 Biomarker analyses

Not applicable.

7.9.2 PK / PD analyses

See Section 7.6.

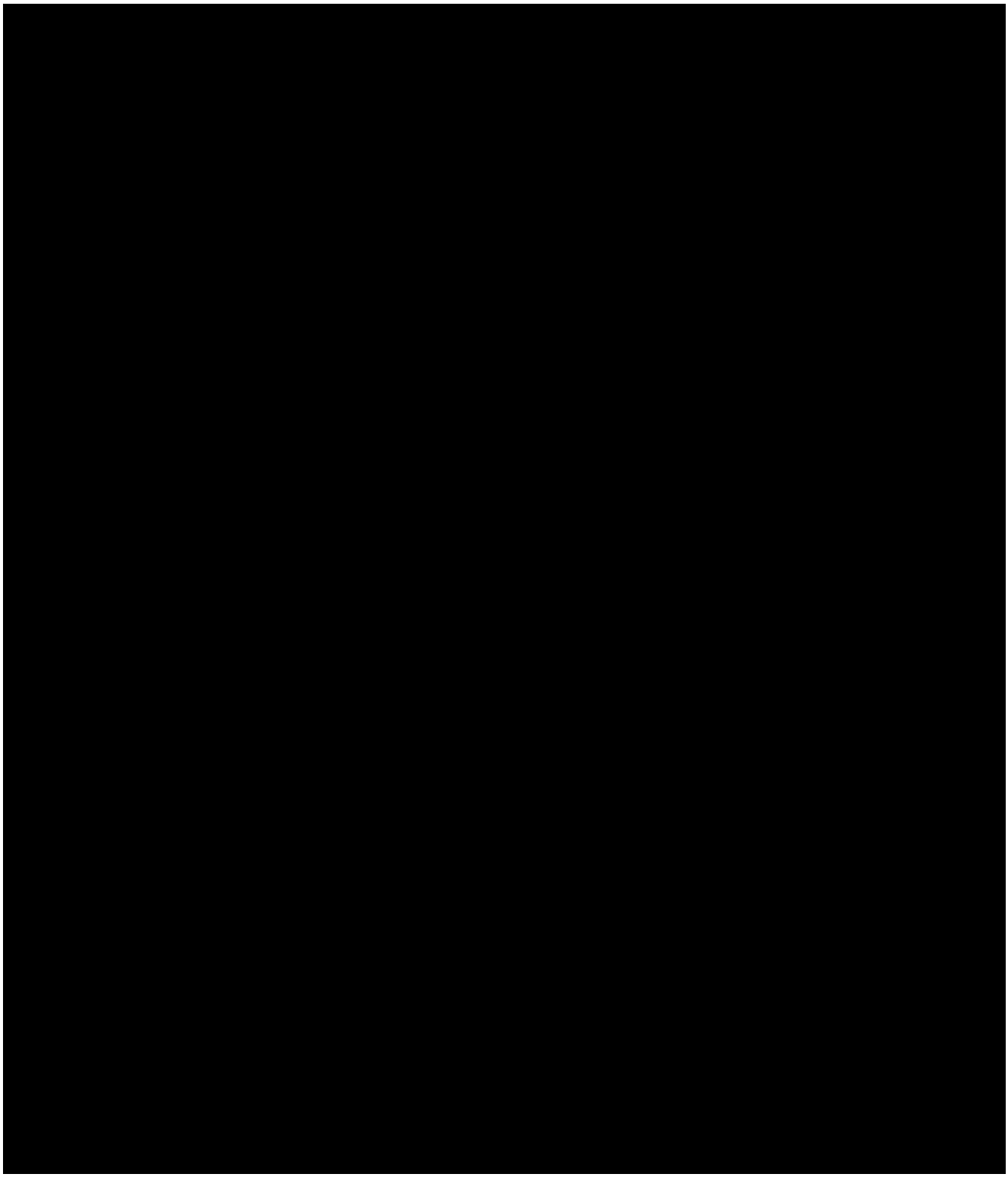
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

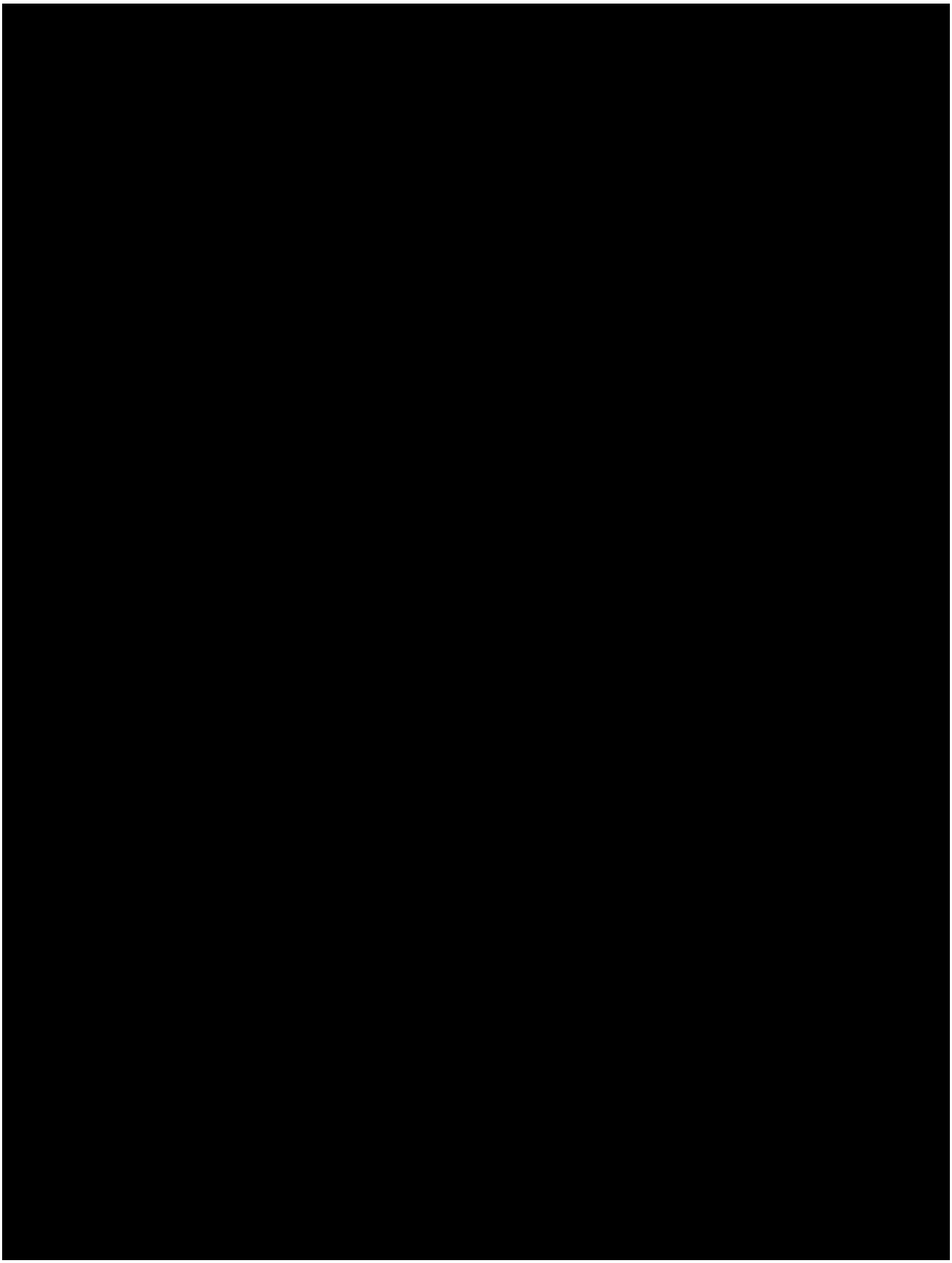
The treatment information will be released to unblind the trial database after the last patient has completed their End-of-Study/Follow-up visit and all data has been entered and cleaned as defined in the “Data Ready to be Unblinded and / or Final Trial Closure Notification” (RUN) form.

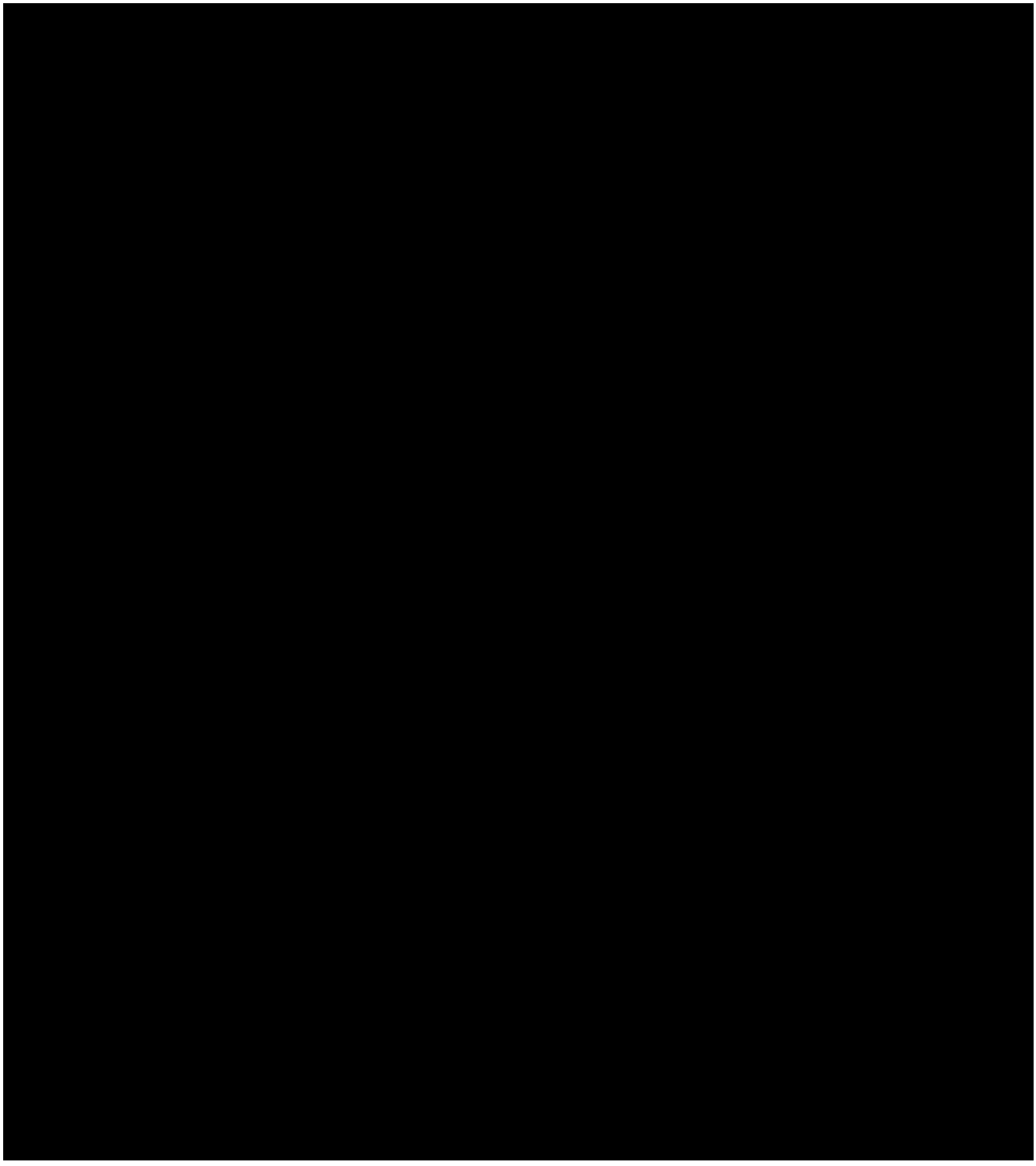
9. REFERENCES

1.	CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trials, current version
2.	Ring A, Walter B, Larbalestier A, Chanter D. An efficient crossover design for thorough QT studies. GMS Med Inform Biometr Epidemiol; 2010; 6(1) [R12-0517]
3.	BI-VQD-12045_40-413: “Identify and Manage Important Protocol Deviations (iPD)”,current version, Group “Clinical Operations”, KMED.
4.	BI-KMED-BDS-TMP-0059: “iPD specification document (sdtm-dv-domainspecification)”, template, current version, Group “Clinical Operations”, KMED.
5.	001-MCS-50-415_RD-03: “Clinical Trial Analysis Decision Log (template)”, current version, Group “Biostatistics & Data Sciences”, KMED.
6.	BI-KMED-BDS-HTG-0035: “Handling of Missing and Incomplete AE Dates”, current version, Group “Biostatistics & Data Sciences” KMED.
7.	BI-KMED-BDS-HTG-0045: “Standards for Reporting of Clinical Trials and Project Summaries”, current version, Group “Biostatistics & Data Sciences”, KMED.
8.	BI-KMED-TMCP-OTH-0003: “Graphs and Tables for Clinical Pharmacokinetics and Pharmacodynamic Noncompartmental Analyses”, current version, Group “Translational Medicine Clinical Pharmacology”, KMED.
9.	BI-KMED-TMCP-MAN-0014: “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies”, current version, Group “Translational Medicine Clinical Pharmacology”, KMED.
10.	BI-KMED-TMCP-MAN-0010: “Description of Analytical Transfer Files and PK/PD Data Files”, current version, Group “Translational Medicine Clinical Pharmacology”, KMED.
11.	Schall R, Ring A. Mixed models for data from thorough QT studies: part 1. Assessment of marginal QT prolongation. Pharmaceutical Statistics 2010 [R10-5353]
12.	Kenward MG, Roger JH. The use of baseline covariates in crossover studies. Biostatistics; 2010; 11(1); 1-17. [R10-4391]
13.	Hochberg Y. A sharper bonferroni procedure for multiple tests of significance. Biometrika; 1988; 75(4); 800-802. [R97-1003]
14.	Garnett et al. Concentration-QT relationships play a key role in the evaluation of proarrhythmic risk during regulatory review. J Clin Pharmacol; 2008; 48; 13-18. [R08-0437]

15.	Garnett et al. Scientific white paper on concentration-QTc modeling. Journal of Pharmacokinetics and Pharmacodynamics 2017 [R18-0143]
16.	BI-KMED-TMCP-HTG-0025: “Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics, current version ;, Group “Translational Medicine Clinical Pharmacology”, KMED.
17.	BI-KMED-BDS-HTG-0066: “Analysis and Presentation of AE data from clinical trials”, current version, Group “Biostatistics & Data Sciences”, KMED.
18.	BI-KMED-BDS-HTG-0041: “Analysis and Presentation of Adverse Event Data from Clinical Trials – Display Template”, current version, Group “Biostatistics & Data Sciences”, KMED.
19.	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.
20.	BI-KMED-BDS-HTG-0042: “Handling, Display and Analysis of Laboratory Data”, current version, Group “Biostatistics & Data Sciences”, KMED.







11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**02-SEP-24**	[redacted]	N/A	This is the final TSAP.