TRIAL STATISTICAL ANALYSIS PLAN

c16606849 -01

BI Trial No.:	1407.1
Title:	A partially randomised, single-blind, placebo-controlled trial to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of BI 730357 administered as oral solution and tablets to healthy subjects, and a randomized, open-label, single-dose, three-way cross-over bioavailability comparison of BI 730357 as tablet versus oral solution and tablet with and without food "Including Protocol Amendment 1, 2, and 3 [c11248385-04]"
Investigational Product:	BI 730357
Responsible trial statisticians:	[redacted] Phone: [redacted] Fax: [redacted] Phone: [redacted] Fax:
Date of statistical analysis plan:	22 SEP 2017 SIGNED
Version:	Final

Proprietary confidential information
© 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved.
This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission.

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

1. TABLE OF CONTENTS

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

LIST OF TABLES

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis Dataset
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
BA	Bioavailability
BI	Boehringer Ingelheim
BLQ	Below The Lower Limit Of Quantification
BMI	Body Mass Index
BWC	Bioavailability/Bioequivalence, Within-Subject Design, Time-Controlled
BWU	Bioavailability/Bioequivalence, Within-Subject Design, Time-Uncontrolled
CARE	Clinical Data Analysis and Reporting Environment
CI	Confidence Interval
Cmax	Maximum measured concentration of the analyte in plasma
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic Coefficient of Variation
DB	Dose Proportionality, Between-Subject Design
DBLM	Database Lock Meeting
DG	Dose Group
ECG	Electrocardiogram
ECGPKS	ECG PK Set
eCRF	Electronic Case Report Form
EudraCT	European Union Drug Regulating Authorities Clinical Trials
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
HR	Heart Rate

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Term	Definition / description
ICH	International Conference On Harmonisation
[redacted]	[redacted]
LLT	Lower Level Term
Max	Maximum
mRNA	Messenger Ribonucleic Acid
Mean	Arithmetic Mean
MedDRA	Medical Dictionary For Regulatory Activities
Min	Minimum
N	Number non-missing Observations
NC	Not Calculated
NOA	Not Analysed
NOP	No Peak Detectable
NOR	No Valid Result
NOS	No Sample Available
O*C	Oracle Clinical
PD	Pharmacodynamic(s)
PDS	Pharmacodynamic Set
PfOS	Powder For Oral Solution
PK	Pharmacokinetic(s)
PKS	PK Parameter Analysis Set
po	per oral
POC	Percent Of Control
PR	Pulse Rate
PT	Preferred Term
PV	Protocol Violation
qd	Quaque Die, Once Daily
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference Treatment
RAGe	Report Appendix Generator system
REP	Residual Effect Period

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Term	Definition / description
RPM	Report Planning Meeting
RS	Randomised Set
SAS®	Statistical Analysis System
SD	Standard Deviation
SOC	System Organ Class
SP	Sampling Point
SRD	Single Rising Dose
T	Treatment
T1/T2	Test treatment 1/2
Tb	Tablet
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary
XPKISTAT	Library of SAS® Macros for PK analysis

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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, randomisation.

Study data will be stored in a trial database within the Oracle Clinical™ (O*C) system.

Pharmacokinetic (PK) parameters will be calculated using Phoenix WinNonlin™ software (version 6.3, Certara USA Inc., Princeton, NJ, USA).

The statistical analyses will be performed within the validated working environment CARE, including SAS™ (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SAS™-based tools (e.g., macros for the analyses of adverse event (AE) data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the clinical trial report (CTR) appendices).

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Analysis of dose proportionality will only be performed on the fasted dose groups receiving tablets because it is known from previous studies that Pharmacokinetics differ considerably for administration of Powder for Oral Solution (PfOS).

All other analyses as planned in the revised trial protocol (based on all amendments) will be performed and are described in more detail in this TSAP.

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

CTP: *Primary endpoint to assess safety and tolerability of BI 730357 is the number [N (%)] of subjects with adverse reactions.*

Please note that adverse reactions are defined and analysed as drug-related AEs.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

As no key secondary endpoints have been specified in the CTP, this section is not applicable.

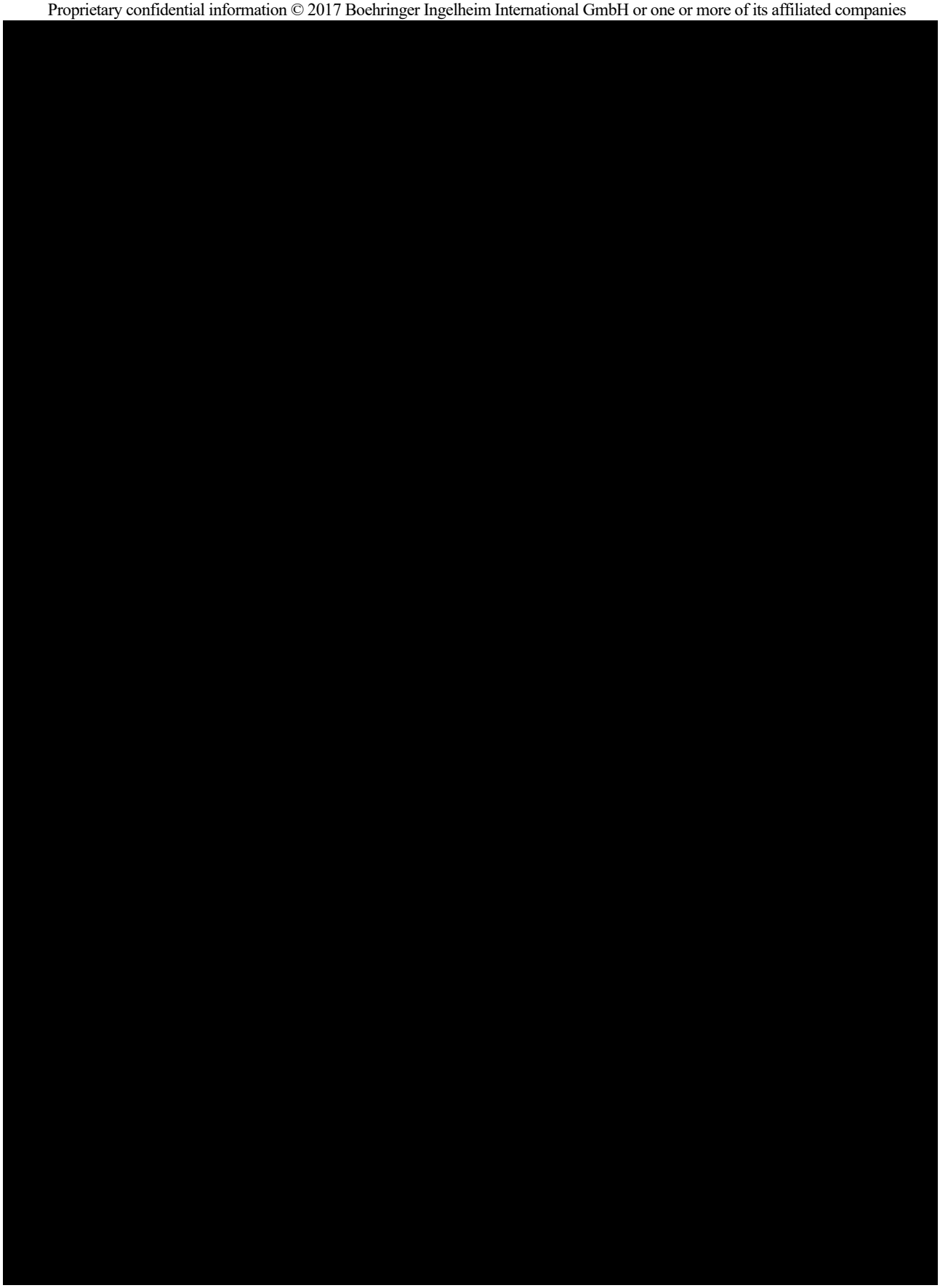
5.2.2 Secondary endpoints

For the single rising dose (SRD) and the bioavailability (BA) part the secondary PK parameters are:

CTP:

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

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies



Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

SRD part:
In total, it was planned to include 72 healthy male volunteers in the SRD part of this trial. Each of the 10 sequential groups includes 8 subjects (6 active, 2 placebo) and is divided into two cohorts. The first cohort will be treated in a fixed sequence and the second cohort will be randomised.

In dose groups (DG) 1-7 and 10 each subject will receive one oral dose of BI 730357 or Placebo respectively at Visit 2, Day 1.
In DG 8 (400 mg/placebo with continental breakfast; Visit 2, Day 1) and DG 9 (400 mg/placebo with high-fat breakfast; Visit 3, Day 1) the same subjects will be included and treated with the same treatments (i.e. always with active or with placebo) for an intra-individual comparison of the two different diets (after washout period of at least 14 days).

BA part:
In total, it was planned to include 12 healthy male volunteers in the BA part of this trial. Each subject will receive BI 730357 as tablet (Tb) in a fasting state (reference treatment R), as oral solution (PfOS) in a fasting state (test treatment T1) and as tablet after a standardised high fat breakfast (test treatment T2) in an open label, randomised manner.

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

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 6.1: 1 Labels for treatments for use in the CTR (SRD Part)

Dose group	Treatment		Short label
1-10	M/N/U/V	Placebo solution / tablet, po, qd	Placebo total
1-7	M/N	Placebo solution / tablet, po, qd	Placebo fast
8	U	Placebo tablet, po, qd, fed continental	Placebo fed1
9-10	V	Placebo tablet, po, qd, fed high-fat	Placebo fed2
8-10	UV*	Placebo tablet, po, qd, fed continental/high-fat	Placebo fed
1	A	BI 730357, 1 mg/mL solution, 2 mg, po, qd	2mg PfOS fast
2	B	BI 730357, 1 mg/mL solution, 8 mg, po, qd	8mg PfOS fast
3	C	BI 730357, tablet, 25 mg, qd	25mg Tb fast
4	D	BI 730357, tablet, 50 mg , qd	50mg Tb fast
5	E	BI 730357, tablet, 2*50 mg, qd	100mg Tb fast
6	F	BI 730357, tablet, 4*50 mg, qd	200mg Tb fast
7	G	BI 730357, tablet, 8*50 mg, qd	400mg Tb fast
8	S	BI 730357, tablet, 8*50 mg, qd, fed continental	400mg Tb fed1
9	T	BI 730357, tablet, 8*50 mg, qd, fed high-fat	400mg Tb fed2
8-9	ST*	BI 730357, tablet, 8*50 mg, qd, fed continental/high-fat	400mg Tb fed
10	K	BI 730357, tablet, 16*50 mg, qd, fed high-fat	800mg Tb fed2

fed1 means intake of standard continental breakfast prior to drug administration
fed2 means intake of standard high-fat breakfast prior to drug administration
fed means intake of either standard continental or standard high-fat breakfast prior to drug administration
*: Placebo fed / 400mg Tb fed will be included in the same analyses in which within the BA part only the total group would be displayed, otherwise Placebo fed / 400mg Tb fed will be split into fed1 for subjects with continental breakfast and fed2 for subjects with high-fat breakfast

CTP: *The placebo control group in the safety evaluation will consist of all placebo treated subject, regardless of the dose group in which they were treated.*

This is applicable to the placebo control groups total, fast, fed1, fed2 and fed.

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 6.1: 2 Labels for treatments for use in the CTR (BA Part)

Treatment		**Short label**
X (R)	BI 730357, tablet, 25 mg, fasted, qd	25mg Tb fast
Y (T2)	BI 730357, tablet, 25 mg, fed high-fat, qd	25mg Tb fed2
Z (T1)	BI 730357, 10 mg/mL solution, 25 mg, fasted, po, qd	25mg PfOS fast

Table 6.1: 3 Overview of treatments for intra-individual comparison

Study part	**Test treatment (T)**		**Reference treatment (R)**	
SRD	400mg Tb fed2		400mg Tb fed1	
BA	25mg PfOS fast	(T1)	25mg Tb fast	(R)
	25mg Tb fed2	(T2)	25mg Tb fast	(R)

The following separate study phases will be defined for the analyses of AEs:

- **Screening** (ranging from 0:00 h on day of informed consent until administration time of study drug)
- **On-treatment**
  (SRD part:
  DGs 1-7, 10: ranging from administration time of study drug until end of trial-termination date
  DG 8 and 9: separately for each treatment, ranging from administration time of study drug until administration time of next study drug dose or end of trial-termination date
  BA part:
  separately for each treatment, ranging from administration time of study drug until administration time of next study drug dose or end of trial-termination date)

Please note that all AEs reported between start of trial drug administration and the last per-protocol contact will be considered on treatment (i.e. no follow-up period is considered in this trial).

Displays of AEs will be presented separately for the treatments described in Table 6.1: 1 and Table 6.1: 2. In the SRD part, the subjects in DG 8 and 9 will be handled separately, but counted only once in total.

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Two types of AE displays will be provided in the report:

A) Section 15.3 (separate for SRD and BA part) and Appendix 16.1.9.2.8 (for ClinicalTrials.gov (separate for SRD and BA part) and EudraCT (SRD and BA part combined)) of the CTR displays:

In these displays, the on-treatment phase will be analysed (labelled with the name of the study treatment (short label)). Screening will not be included in this analysis.
The following totals will be provided in addition:

- a total over all BI-treated phases included in this analysis, DG A-G, S, T, ST and K ("Total BI")
- a total over all on-treatment phases included in this analysis ("Total on-treatment")

  (Section 15.3 only)

B) Section 15.4 and Appendix 16.1.9.2.8 (except for ClinicalTrials.gov and EudraCT) of the CTR displays:

- Screening
- On-treatment (labelled with the name of the study treatment (short label))

In Section 16.1.9.2.8 AE tables (separate for SRD and BA part), the following totals will be provided in addition:

- a total over all study phases ("Total")

For detailed information on the handling of the treatments in the O*C views refer to Technical TSAP ADS (analysis data set) plan.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Data discrepancies and deviations from the CTP will be identified for all randomised subjects. Listings of protocol deviations and of unresolved discrepancies will be provided to be discussed at the combined report planning and database lock meeting (RPM/DBLM), e.g. deviations in drug administration, in blood sampling etc. At this meeting, it will be decided whether the discrepant data can be used as they are or whether the data have to be corrected in the clinical database.

Each protocol deviation must be assessed to determine whether it is an important protocol violation. A protocol violation (PV) is important if it affects the rights or safety of the study subjects or if it can potentially influence the primary outcome measure(s) for the respective subjects in a way that is neither negligible nor in accordance with the study objectives. This last category of important PV forms the basis for the decision of whether a subject does or does not belong to an analysis set. PVs that do not influence the subject's rights and safety or the evaluability of the subjects for the main study objectives are called non-important PVs. These are only considered when checking the trial quality in general.

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

If any important PVs are identified, they are to be summarised into categories and will be captured in the RPM/DBLM minutes via an accompanying Excel spreadsheet [001-MCS-50-413_RD-02] (2). The following table contains the categories which are considered to be important PVs in this trial. If the data show other important PVs, this table will be supplemented accordingly by the time of the RPM/DBLM.

Table 6.2: 1 Important protocol violations

Category /Code		Description
A		**Entrance criteria not met**
	A1	Inclusion criteria violated
	A2	Exclusion criteria violated
B		**Informed consent**
	B1	Informed consent not available
	B2	Informed consent too late
C		**Trial medication and randomisation**
	C1	Incorrect trial medication taken
	C2	Randomisation not followed
	C3	Non-compliance
	C4	Incorrect intake of trial medication
	C5	Improper washout between treatments
D		**Concomitant medication**
	D1	Prohibited medication use
	D2	Mandatory medication not taken
	D3	Improper washout of concomitant medication
E		**Missing data**
	E1	Certain violations of procedures used to measure secondary data
F		**Incorrect timing**[1]
	F1	Certain violations of time schedule used to measure secondary data
G		**Other trial specific important violations**
	G1	Incorrect intake of meal before administration of treatment
	G2	PVs affecting safety and rights

[1] Time deviations will only be flagged as important PV, when leading to exclusion of the entire subject from an analysis set
Source: 'Protocol Violation Handling Definitions' [001-MCS-50-413_RD-01] (3)

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

6.3 SUBJECT SETS ANALYSED

- Randomised set (RS):
  This subject set includes all randomised subjects, whether treated or not.

- Treated set (TS):
  This subject set includes all subjects from the RS who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.
  This is the full analysis set population in the sense of ICH-E9 (1). It is used for safety analysis.

CTP: *Pharmacokinetic parameters of a subject will be included in the analysis unless the subject has an important protocol violation relevant for the evaluation. Whether a protocol violation is important will be decided no later than in the Report Planning Meeting.*

Reasons for exclusion of single pharmacokinetic parameters may be:

- *The subject experiences emesis at or before two times median t_{max}. Median t_{max} is to be determined for the test product excluding the subjects experiencing emesis.*
- *The subject experiences emesis at any time during the labelled dosing interval.*
- *Time deviations*
- *Use of restricted medications*

The subject set for the evaluation of PK endpoints (PKS) will include all treated subjects that provide at least one observation for at least one secondary *endpoint without important protocol violations with respect to the statistical evaluation of PK endpoints. It will also be decided in the Report Planning Meeting which subjects are to be included in the PKS.*

Excluded subjects will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

- PK parameter analysis set (PKS):
  This subject set includes all evaluable subjects from the TS of the SRD part or BA part who were treated with BI 730357 and who provide at least one secondary PK endpoint ($AUC_{0-\infty}$ or C_{max}) that was not excluded according to the description above.

  In the SRD part, it is used for assessment of dose proportionality under fasting conditions and for intra-individual comparison of fed conditions
  In the BA part, it is used for assessment of the bioavailability and food effect.

- Pharmacodynamic set (PDS):
  This subject set includes all evaluable subjects from the TS of the SRD part who provide at least one evaluable observation for one of the exploratory biomarkers and without important protocol violations relevant to the evaluation of PD.
  It is used for the PD (biomarker) analysis (SRD part).

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- ECG PK Set (ECGPKS):
  This subject set includes all subjects from the TS of the SRD part who provide at least one pair of a valid drug plasma concentration and a corresponding (i.e. time-matched) ECG endpoint to be used in the exposure-response analysis. Note that the placebo subjects will be included, with zero plasma concentrations.

Table 6.3: 1 Subject sets analysed

	Analysis set				
Class of endpoint	RS	TS	PKS	PDS	ECGPKS
Primary and further safety endpoints		X			
Secondary and further PK endpoints			X		
PD endpoints				X	
Demographic/baseline endpoints		X			
Important PVs/Disposition	X				
PK-ECG exposure-response					X

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable, because the study was performed in only one centre.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Handling of missing data and outliers will be performed as described in the CTP, Section 7.4.

The only exception where imputation might be necessary for safety evaluation is AE dates. Missing or incomplete AE dates are imputed according to BI standards (see 001-MCG-156_RD-01 (4)).

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Missing plasma concentrations and pharmacokinetic parameters

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01) (5).

Plasma concentration-time profiles and descriptive statistics of concentration data

CTP: *Drug concentration data 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 predose values).*

Pharmacokinetic parameters and their descriptive statistics

CTP: *For the non-compartmental analysis, 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.*

Missing pharmacodynamic parameters

Pharmacodynamic parameters and their descriptive statistics

Missing PD values will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline value is defined as the last measurement before trial drug administration in each treatment period.

CTP: *Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and end of trial examination are given in the Flow Chart.*

The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 15 min for the first 6 h after trial drug administration and ± 30 min thereafter. Starting from 72 h post administration a deviation from the scheduled time for vital signs, ECG and laboratory tests of ±70 min is acceptable.

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

For the SRD part, there will be a centralised evaluation of all 12-lead ECG recordings at the time points specified in the Table 6.7: 1 below:

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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**
2/3*	1	-02:00	Baseline
		00:30	On-treatment
		01:00	
		02:00	
		03:00	
		04:00	
		05:00	
		06:00	
		08:00	
		10:00	
		12:00	
	2	24:00	
		34:00	
	3	48:00	

*Visit 3 only applicable for subjects in DG 8 and 9.

Triple ECGs (3 single ECGs of 10 sec duration each, recorded within 180 sec) will be recorded at the baseline before the first drug administration and at all time points on-treatment.

The baseline value of an ECG variable is defined as the mean of the triple ECG measurements prior to drug administration.

CTP: *With the exception of the first triple ECG (used as baseline before the first drug administration), only the first of the three replicate ECG at a single assessment time will be evaluated.*

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

7. PLANNED ANALYSIS

The SRD and BA part will be evaluated separately.

Safety analysis (refer to Section 7.8) will be performed by M.A.R.C.O. GmbH & CO. KG and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2.

Inferential statistical analyses of PK endpoints (refer to Section 7.5.2) as well as the PK-ECG analysis will also be performed by M.A.R.C.O. GmbH & CO. KG and will be presented in Section 15.5 of the CTR and in Appendix 16.1.9.3.

Descriptive data analysis of PK endpoints will be performed by Translational Medicine and Clin. Pharmacology at BI and will be presented in Section 15.6 of the CTR.

Descriptive data analysis of PD endpoints (refer to Section 7.6) will be performed by M.A.R.C.O GmbH & Co. KG and will be presented in Section 15.7 of the CTR.

The format of the listings and tables will follow the standards defined in the BI corporate guideline “Reporting of clinical trials and project summaries” [001-MCG-159] (6) with the exception of those generated for PK calculations.

The individual values of all subjects will be listed, sorted by treatment group (SRD part) or by treatment sequence (BA part), subject number, visit, study day and actual treatment (BA part, if appropriate). The listings will be included in Appendix 16.2 of the CTR.

DG 8 (400 mg/placebo with continental breakfast) and DG 9 (400 mg/placebo with high-fat breakfast) will be listed and tabulated as if they consist of different individuals, but will be counted only once to get subjects in total.

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 as well as for all PK parameters, the following descriptive statistics will additionally be calculated:

CV	arithmetic coefficient of variation
gMean	geometric mean
gCV	geometric coefficient of variation

The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of PK parameters will be calculated using the individual values with the number of decimal places as provided by the

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 and will display the number of observations in a category, as well as the percentage (%) for each treatment group. Percentages will be rounded to one decimal place and will be based on 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.

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

Exclusion of PK parameters

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

Exclusion of PK concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) 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 only; the value is included for all other analyses.

Further details are given in 001-MCS-36-472_RD-01 “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies” (5) and 001-MCS-36-472_RD-03 “Description of Analytical Transfer Files and PK/PD Data Files” (7).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report, based on the TS.

In the SRD part, the data will be summarised by treatment group (joined DG 8 and DG 9) and in total.

In the BA part, the data will be summarised in total only.

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Concomitant diseases will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies 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/DBLM.

7.3 TREATMENT COMPLIANCE

CTP: *Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations and/or urinary excretion 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/DBLM (cf. TSAP Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINT

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 730357.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Secondary endpoints

Assessment of dose proportionality (SRD part, tablet application under fasting conditions)

Dose proportionality of the PK endpoints $AUC_{0-\infty}$ and C_{max} in plasma of BI 730357 tablets under fasting conditions (dose groups C, D, E, F, and G) will be explored as a secondary analysis using the power model that describes the functional relationship between dose and PK endpoints. The basic model consists of a regression model applied to log-transformed data under fasting conditions. The corresponding ANCOVA (Analysis of Covariance) model includes the logarithm of the dose as a covariate.

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

The model is described by the following equation:

CTP:

$$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$$

where

Y_{ij}	*logarithm of the pharmacokinetic endpoint for subject j at dose level i; where i = 1, 2, ...,5 j = 1, 2, ..., 6,*
α	*intercept parameter;*
β	*slope parameter;*
X_i	*logarithm of dose i;*
ε_{ij}	*random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).*

This equation can be fit as a linear regression model. Based on the estimate for slope parameter (β), a 2-sided 95% CI for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked.

If dose proportionality over the entire dose range under fasting conditions investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed.

This analysis will be accomplished by using the XPKISTAT macro (design DB), based on the PKS.

Intra-individual comparison of fed conditions (SRD part, DG 8 and 9 only)

The intra-individual comparison of fed conditions is primarily to be determined on the basis of the parameters $AUC_{0-\infty}$ and C_{max}. Those parameters will be ln-transformed (natural logarithm) prior to fitting the model.

The statistical model used for the analysis of $AUC_{0-\infty}$ and C_{max} will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: ‘subjects’ and ‘treatment’. The effect ‘subjects’ will be considered as random, whereas the ‘treatment’ effect will be considered as fixed. The model is described by the following equation

$$y_{km} = \mu + s_m + \tau_k + e_{km},$$

where

y_{km}	logarithm of response measured on subject m receiving treatment k,
μ	the overall mean,
s_m	the effect associated with the m^{th} subject, m =1, 2, ..., n

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

τ_k the k^{th} treatment effect, k = 1, 2

e_{km} the random error associated with the m^{th} subject who received treatment k.

The difference between the expected means for test treatment (400mg high-fat breakfast) and reference treatment (400mg continental breakfast), ln(400mg high-fat breakfast)-ln(400mg continental breakfast), will be estimated by the difference in the corresponding Least Square Means (point estimate). Two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the ratio between response under test and response under reference.

The analysis will be accomplished by using the XPKISTAT macro, based on PKS (design BWU).

Investigation of relative bioavailability (BA part)

CTP: *Relative bioavailability is primarily to be determined on the basis of the parameters $AUC_{0-\infty}$ and C_{max}* […]. *Those parameters will be ln-transformed (natural logarithm) prior to fitting the model.*

The statistical model used for the analysis of $AUC_{0-\infty}$ and C_{max} will be an ANOVA (analysis of variance) model on the logarithmic scale. This model will include effects accounting for the following sources of variation: 'sequence', 'subjects within sequences', 'period' and 'treatment'. The effect 'subjects within sequences' will be considered as random, whereas the other effects will be considered as fixed. For tests on subject, period, and treatment effects, the denominator sum of squares will be the sum of squares for error; while for tests on sequence effects, the denominator will be the sum of squares for subjects. The model is described by the following equation

$$y_{ijkm} = \mu + \zeta_i + s_{im} + \pi_j + \tau_k + e_{ijkm},$$

where

y_{ijkm} *logarithm of response measured on subject m in sequence i receiving treatment k in period j,*

μ *the overall mean,*

ζ_i *the i^{th} sequence effect, i = 1, 2, …, 6*

s_{im} *the effect associated with the m^{th} subject in the i^{th} sequence, m =1, 2, …, n_i*

π_j *the j^{th} period effect, j = 1, 2, 3*

τ_k *the k^{th} treatment effect, k = 1, 2* (Note: Separate models will be used to assess the difference between R and T1 and R and T2.)

e_{ijkm} *the random error associated with the m^{th} subject in sequence i who received treatment k in period j.*

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

The difference between the expected means for test treatments and reference treatment log(T_i)-log(R), i=1,2, will be estimated by the difference in the corresponding Least Square Means (point estimate) and two-sided 90% confidence intervals based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to give the point estimator (geometric mean) and interval estimates for the ratio between response under test and response under reference.

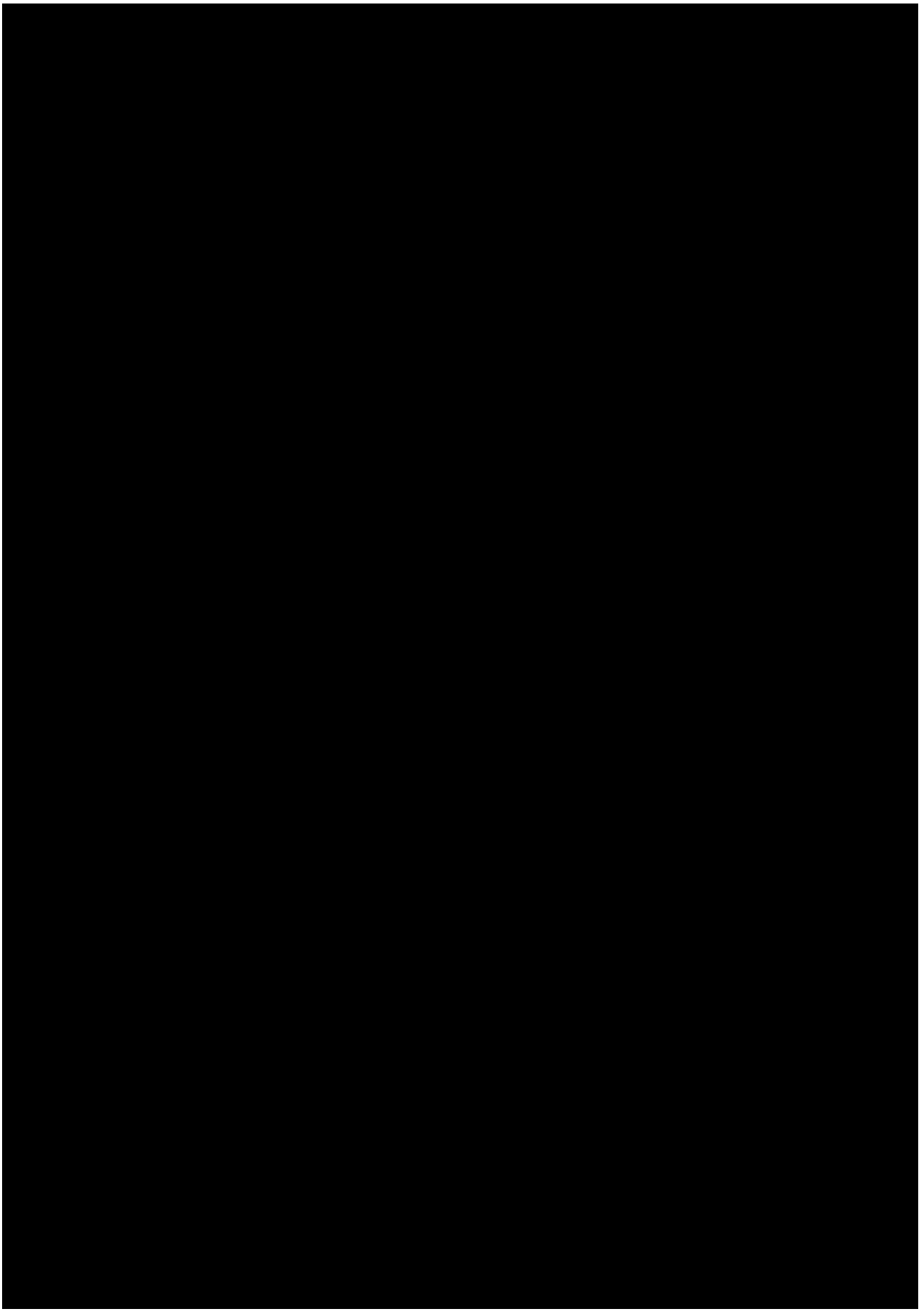
Pairwise comparisons will be done for:

- *Oral solution (PfOS) fasted (Test 1/T1) vs tablet fasted (Reference)*
- *Tablet fed (Test 2/T2) vs tablet fasted (Reference)*

The analysis will be accomplished by using the XPKISTAT macro, based on PKS (design BWC).

In addition, a sensitivity analysis will be performed by fitting the model described above, but using all effects as fixed. This analysis will be done using PROC GLM.

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies



Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

If not stated otherwise, the safety results will be sorted by actual treatment, applicable to SRD part and to BA part.

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

The analyses of AEs will be descriptive in nature and will be based on BI standards as presented in the corporate guideline: "Analysis and presentation of adverse event data from clinical trials" [001-MCG-156], version 6 (9).

The standard AE analyses will be based on the number of subjects with AEs (and not on the number of AEs).

For analysis multiple AE occurrence data on the CRF will be collapsed into an AE provided that all of the following applies:

- All AE attributes are identical (lower level term (LLT), intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest)
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started within the same hour)

For further details on summarization of AE data, please refer to (4, 9).

CTP: *The following are considered as* adverse event of special interest (*AESI*) *in this trial:*

- *Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:*

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- *an elevation of AST and/or ALT ≥3-fold* upper limit of normal (*ULN*) *combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, and/or*
- *marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN*

The analysis of adverse events will be based on the concept of treatment emergent adverse events.

CTP: *The* residual effect period (*REP*) *for BI 730357, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known for this first-in-human trial. Therefore, all AEs reported until the end of trial examination (last per protocol contact) will be considered on treatment […].*

According to ICH E3 (10), AEs classified as 'other significant' needs to be reported and will include those non-serious and non-significant adverse events with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting.

An overall summary of adverse events will be presented.

The frequency of subjects with adverse events will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for subjects with other significant AEs according to ICH E3 (10), for subjects with serious AEs, for subjects with drug-related AEs, for subjects with drug related serious adverse events and for subjects with AESIs.

The SOC and PTs will be sorted by frequency. The MedDRA version number will be displayed as a footnote in the respective output.

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% for at least one treatment will be summarised by treatment, primary SOC and PT.

For disclosure of adverse events on EudraCT 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

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [001-MCG-157] (11).

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Laboratory data will be analysed qualitatively via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the data listings.

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments on the electronic case report form (eCRF) or at the RPM/DBLM at the latest. It is the investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Standard or project-specific rules for flagging clinically significant values will not be applied in this study.

7.8.3 Vital signs

Descriptive statistics over time including change from baseline will be performed for vital signs (blood pressure and pulse rate).

7.8.4 ECG

The ECG analyses will only be performed in the SRD part.

Continuous safety ECG monitoring (by investigator)

Clinically relevant abnormal findings will be reported as adverse events.

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 evaluation of ECG data except of exposure response analysis will be based on the TS. The exposure-response analysis will then be done on the ECGPK set.

Listing of individual data

For all quantitative endpoints, listings of individual data will be shown in Appendix 16.2. Occurrences of notable findings will be flagged.

For all subjects with any notable finding in quantitative ECG recordings, a separate listing will be created as end-of-text display (based on the same display template as in Appendix 16.2), and the corresponding time profiles will be shown.

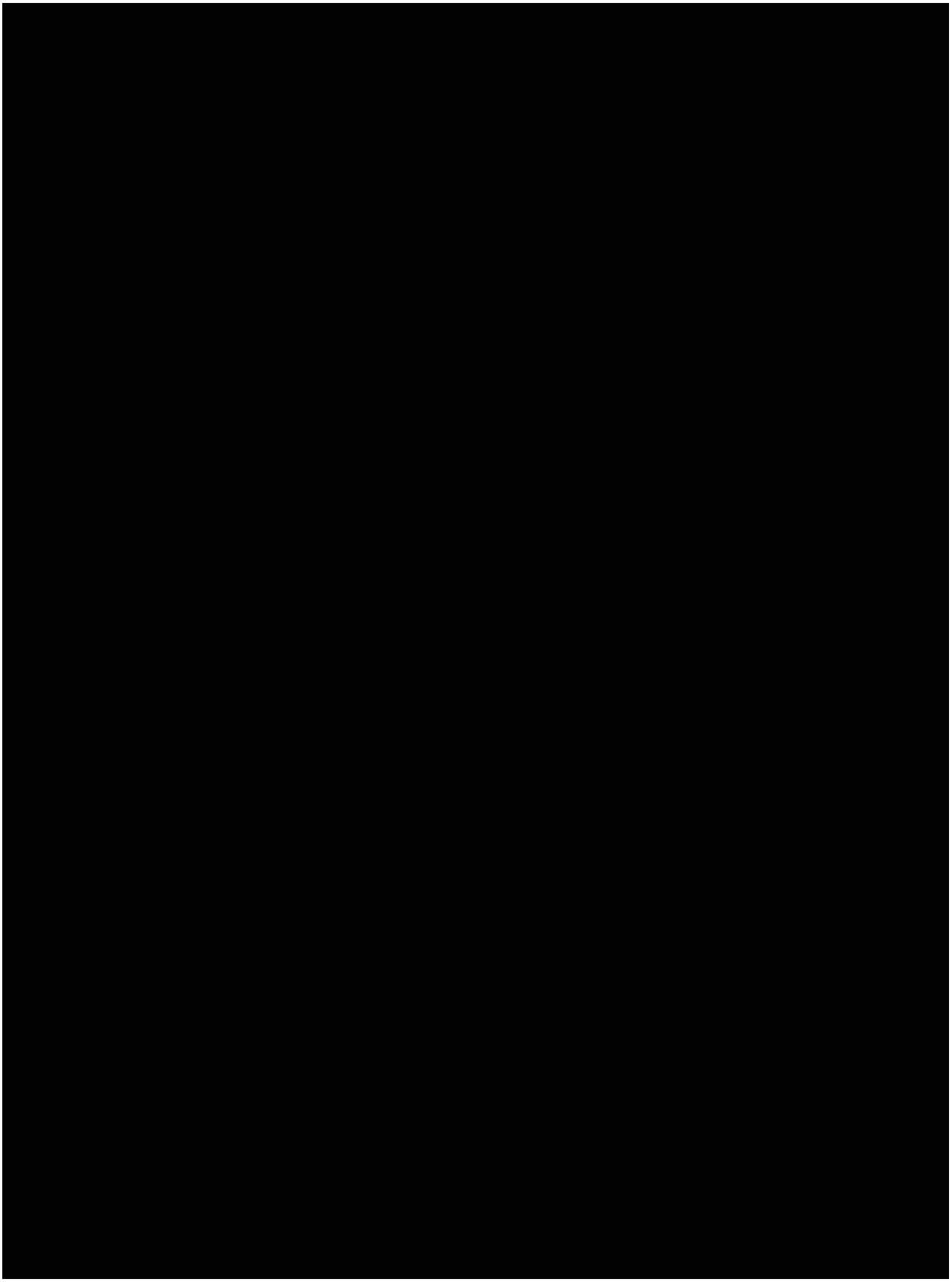
Comments regarding the ECGs will be listed.

Analysis of central tendency

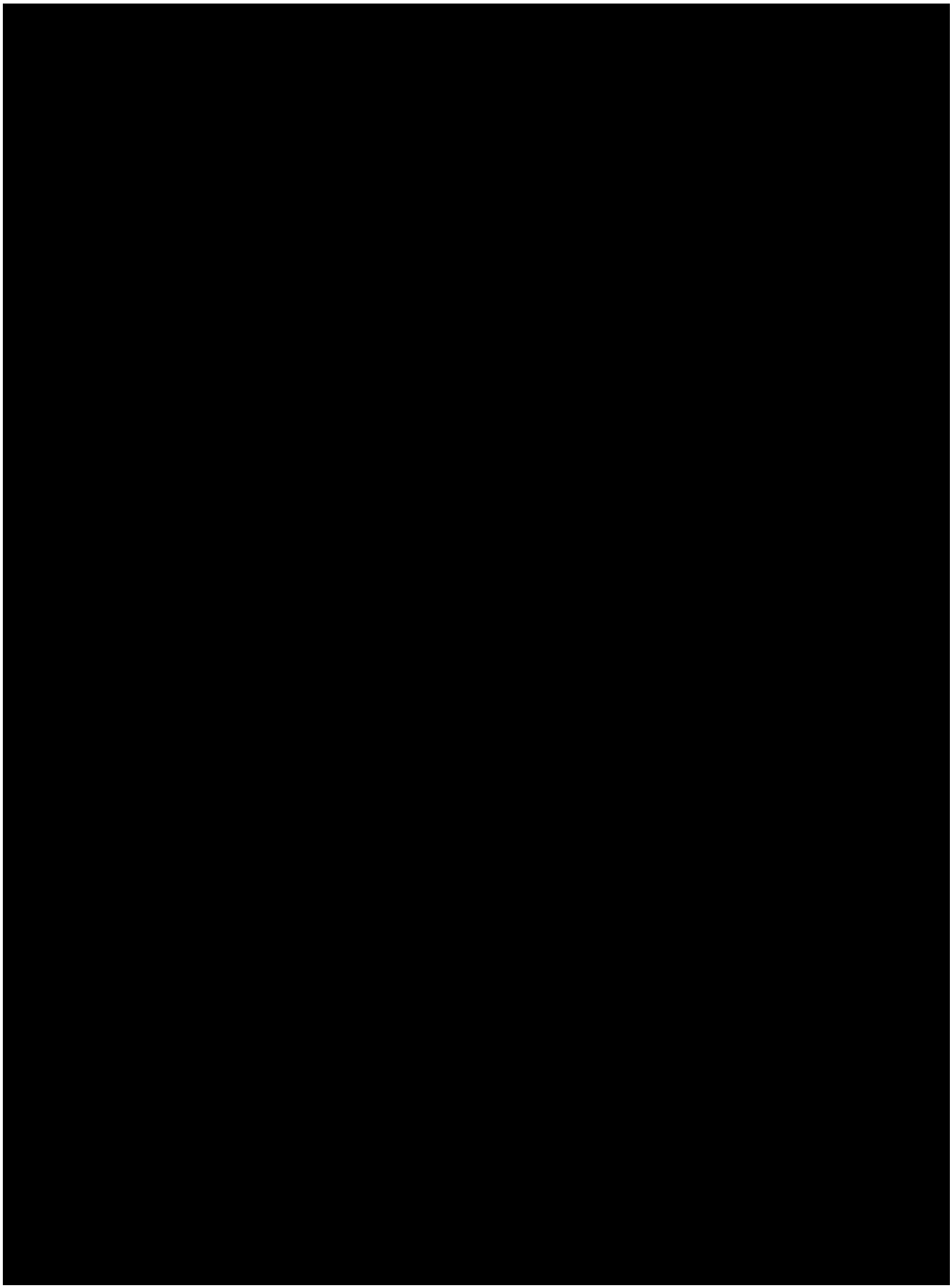
Descriptive statistics (SRD part):

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Descriptive statistics (N, mean, SD, min, median, max) will be provided for the changes from baseline over time in all ECG variables.



Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies



Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

7.8.5 Others

Physical examination

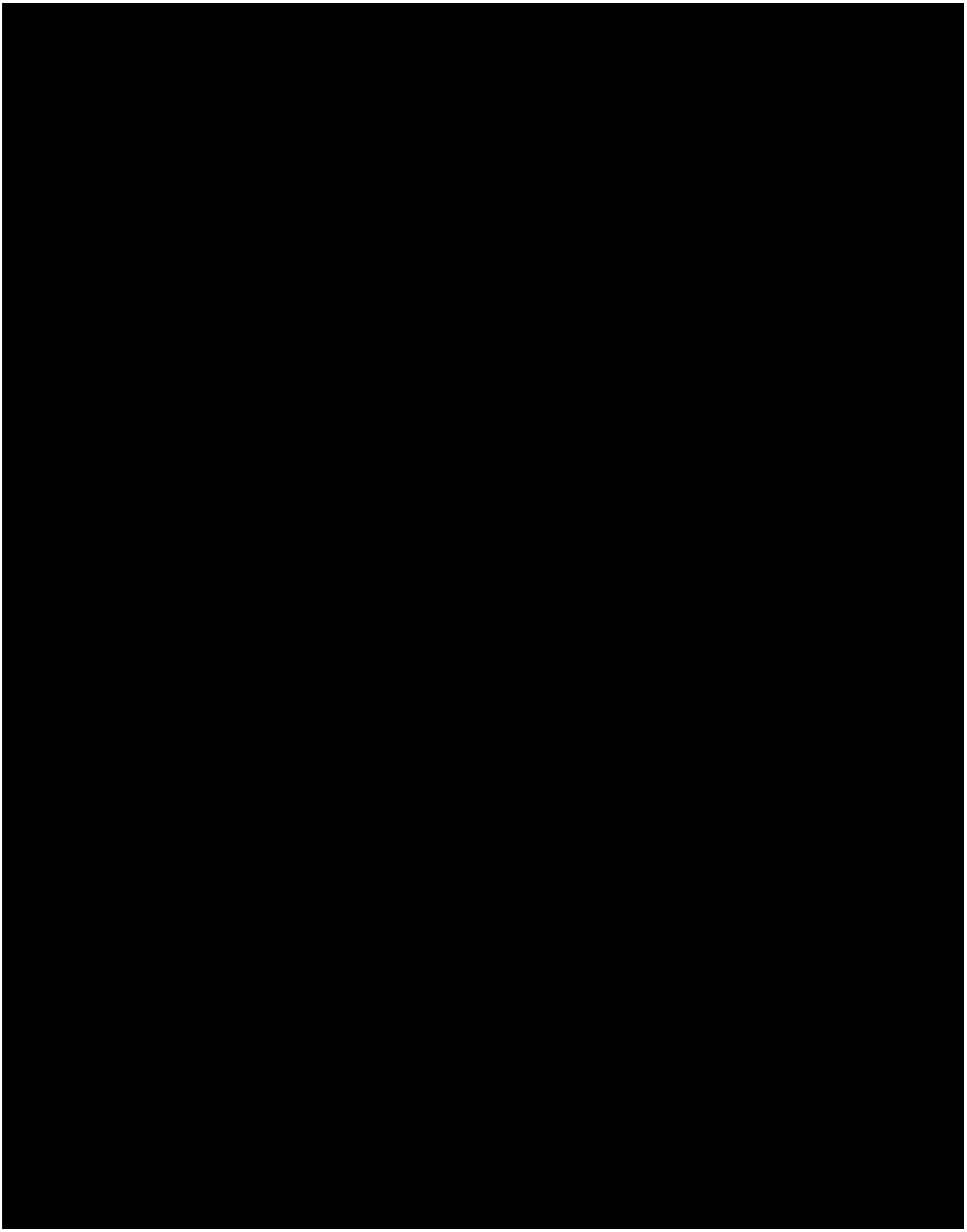
Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

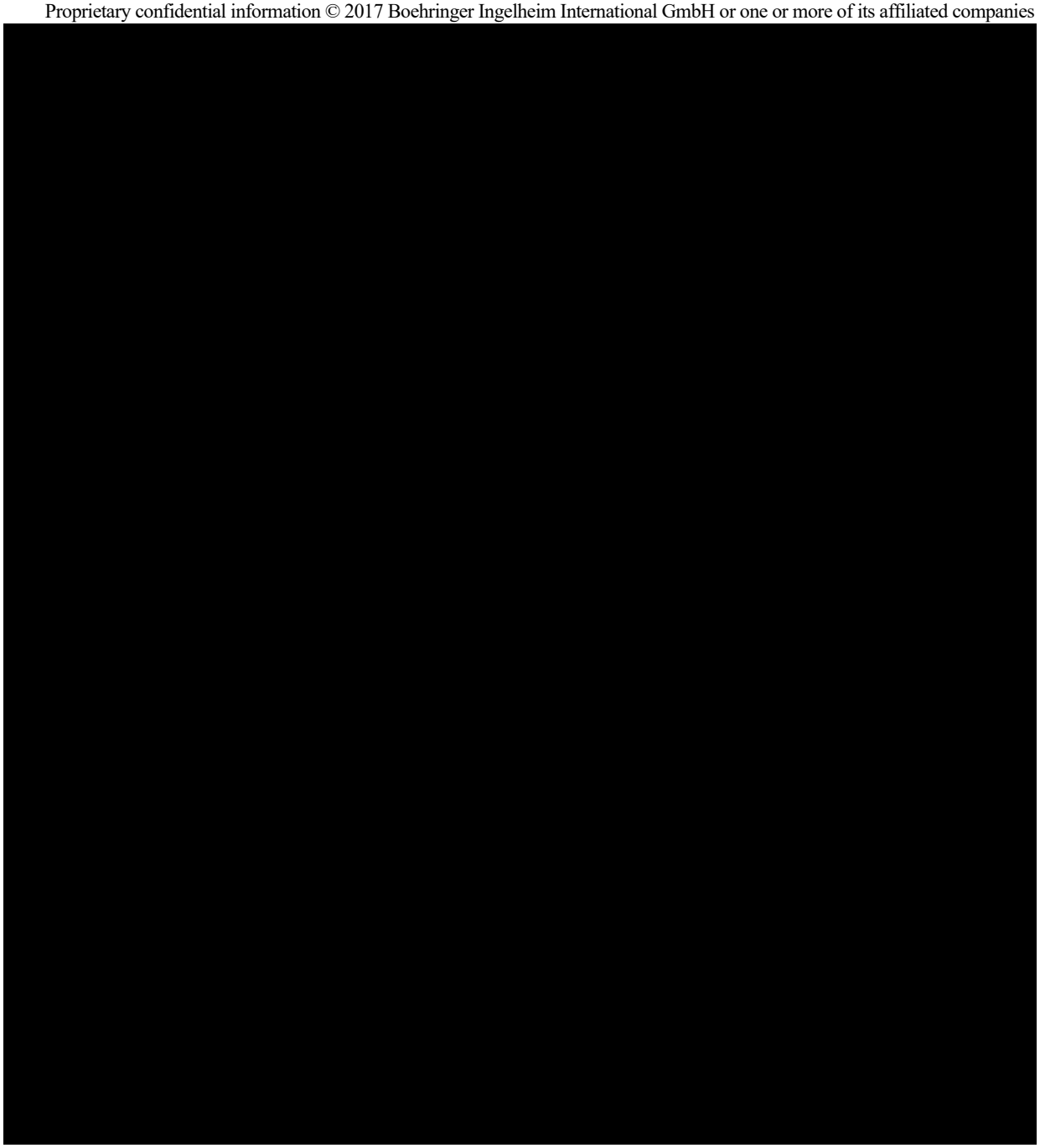
8. REFERENCES

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.	*001-MCS-50-413_RD-02:* “Important Manual Protocol Violations Spreadsheet”, current version, IDEA for CON.
3.	*001-MCS-50-413_RD-01*: “Protocol Violation Handling Definitions”, current version, IDEA for CON.
4.	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
5.	*001-MCS-36-472_RD-01*: “Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies”, current version; IDEA for CON.
6.	*001-MCG-159*: “Reporting of clinical trials and project summaries”, current version; IDEA for CON.
7.	*001-MCS-36-472_RD-03:* “Description of Analytical Transfer Files and PK/PD Data Files”, current version; IDEA for CON.
8.	*001-MCS 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
9.	*001-MCG-156*: “Analysis and presentation of adverse event data from clinical trials”, Version 6; IDEA for CON.
10.	*CPMP/ICH/137/95*: “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version
11.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
12.	*R08-0437:* Garnett, Christine E. et al.: “Concentration-QT relationships play a key role in the evaluation of proarrhythmic risk during regulatory review”, J Clin Pharmacol 48, 13 - 18 (2008))

Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies



Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies



Proprietary confidential information © 2017 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	22-SEP-2017	[redacted]	None	This is the final TSAP