# TRIAL STATISTICAL ANALYSIS PLAN

**c22177016-01**

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| **BI Trial No.:** | 1408.1 |
| **Title:** | Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of BI 705564 (single-blind, partially randomised, placebo-controlled parallel group design) and food effect on a tablet formulation of BI 705564 (open-label, randomised, single-dose, two-period, two-sequence crossover design) in healthy male subjects<br>Including Protocol Amendment 1, 2, 3 and 4 [c13141675-05] |
| **Investigational Product:** | BI 705564 |
| **Responsible trial statisticians:** | Phone:<br>Fax:<br><br>Phone:<br>Fax: |
| **Date of statistical analysis plan:** | 16 MAR 2018 SIGNED |
| **Version:** | Final |

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# 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 |
| $AUC_{0-tz}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point |
| $AUC_{0-\infty}$ | Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity |
| BB | Bioavailability/Bioequivalence, inter-individual comparison |
| BI | Boehringer Ingelheim |
| BWC | Bioavailability/Bioequivalence, Within-Subject Design, Time-Controlled |
| CI | Confidence Interval |
| $C_{max}$ | Maximum measured concentration of the analyte in plasma |
| CRF | Case Report Form |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| CV | Arithmetic Coefficient of Variation |
| DB | Dose Proportionality, Between-Subject Design |
| DBLM | Database Lock Meeting |
| ECG | Electrocardiogram |
| ECGPCS | ECG Pharmacokinetic Concentration Set |
| FE | Food Effect |
| gCV | Geometric Coefficient of Variation |
| gMean | Geometric Mean |
| ICH | International Conference On Harmonisation |
| LLT | Lower Level Term |
| Max | Maximum |

| Term | Definition / description |
|---|---|
| MedDRA | Medical Dictionary For Regulatory Activities |
| Min | Minimum |
| O*C | Oracle Clinical |
| PK | Pharmacokinetic(s) |
| PKS | PK parameter analysis set |
| PT | Preferred Term |
| PV | Protocol Violation |
| R | Reference Treatment |
| RAGe | Report Appendix Generator system |
| REP | Residual Effect Period |
| RPM | Report Planning Meeting |
| SAS® | Statistical Analysis System |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SRD | Single rising dose |
| T | Test treatment |
| $t_{max}$ | Time from dosing to maximum measured concentration of the analyte in plasma |
| 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 |

# 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 ClinicalTM (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 AE data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the CTR appendices).

# 4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses as planned in the CTP will be performed and are described in more detail in this TSAP.

# 5. ENDPOINTS

## 5.1 PRIMARY ENDPOINTS

**Section 5.2.1 of the CTP:**

***Single rising dose parts under fasting and fed conditions***

*Primary endpoint to assess safety and tolerability of BI 705564 is the number [N (%)] of subjects with drug-related adverse events (adverse reactions).*

**Section 5.5.1.1 of the CTP:**

***Food effect part***

*The following primary endpoints will be determined for BI 705564:*

- *$AUC_{0\text{-}tz}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point)*
- *$C_{max}$ (maximum measured concentration of the analyte in plasma)*

## 5.2 SECONDARY ENDPOINTS

### 5.2.1 Key secondary endpoints

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

### 5.2.2 Secondary endpoints

**Section 5.5.1.2 of the CTP:**

***Single rising dose parts under fasting and fed conditions***

*The following secondary endpoints will be determined for BI 705564:*

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

***Food effect part***

*The following secondary endpoints will be determined for BI 705564:*

- *$AUC_{0\text{-}\infty}$*

**Safety:**

Further criteria of interest:

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Continuous ECG monitoring (SRD parts under fasting and fed conditions only)
- Vital signs (blood pressure, pulse rate)

For detailed information (formula) please refer to Section 7.8.

# 6. GENERAL ANALYSIS DEFINITIONS

## 6.1 TREATMENTS

It is planned that in total 92 volunteers participate in this study.
48 healthy male subjects will enter the SRD part under fasting conditions (8 per dose group, 6 on active and 2 on placebo), 12 healthy males will enter the FE part (one dose group, all on active) and 32 healthy males will enter the SRD part under fed conditions (8 per dose group, 6 on active and 2 on placebo) of the study.

It is possible that the same subject participate in the SRD part as well as in the FE part. If this is the case, the information from the prior participation will be used for total baseline characteristics. Subjects participating in both parts will be identified in the RPM/DBLM.

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

Table 6.1: 1 Labels for treatments for use in the CTR (SRD part under fasting and fed conditions)

| **Treatment** | | **Short label** |
|---|---|---|
| P/Q | Placebo PfOS / tablet, qd, fasted | Placebo fast |
| V | Placebo, tablet, qd, fed | Placebo fed |
| P/Q/V* | Placebo PfOS / tablet fasted or fed | Placebo total |
| A | BI 705564, 0.25 mg/mL solution, 1 mg, po, qd | BI 1mg fast |
| B | BI 705564, 0.25 mg/mL solution, 3 mg, po, qd | BI 3mg fast |
| C | BI 705564, 10 mg tablet, fasted qd | BI 10mg fast |
| D | BI 705564, 2*10 mg tablet, fasted qd | BI 20mg fast |
| E | BI 705564, 4*10 mg tablet, fasted qd | BI 40mg fast |
| F | BI 705564, 8*10 mg tablet, fasted qd | BI 80mg fast |
| G | BI 705564, 2* 10 mg tablet, fed qd | BI 20mg fed |
| H | BI 705564, 4* 10 mg tablet, fed qd | BI 40mg fed |
| L | BI 705564, 8* 10 mg tablet, fed qd | BI 80mg fed |
| M | BI 705564, 6*10mg + 100mg tablets, fed qd | BI 160mg fed |

*: The placebo total group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated and regardless of whether they participated in the single rising dose part under fed or under fasting conditions.

Table 6.1: 2 Labels for treatments for use in the CTR (FE part)

| Treatment | | Short label |
|---|---|---|
| R | BI 705564, 10 mg tablet, fasted qd | BI 10mg fast |
| S | BI 705564, 10 mg tablet, fed qd | BI 10mg fed |

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 first administration time of study drug)
- **On treatment**
  (SRD parts under fasting and fed conditions: separately for each treatment, ranging from administration time of study drug until 0:00 h on the day after trial termination date;
  FE part: separately for each treatment, ranging from administration time of study drug until administration time of next study drug dose or 0:00 h on the day after 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 above, including “Placebo total”.

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

**A)** Section 15.3 (separately for combined SRD parts and FE part) and Appendix 16.1.13.1.8 (for ClinicalTrials.gov (separately for combined SRD parts and FE part) and EudraCT (all parts 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 on treatment phases included in this analysis ("Total on treatment") (Section 15.3 only)
- SRD parts: a total over all BI-treated phases under fasting conditions (“BI fast total”)
- SRD parts: a total over all BI treated phases under fed conditions (“BI fed total”)
- SRD parts: a total over all BI-treated phases (“BI total”)

**B)** Section 15.4 and Appendix 16.1.13.1.8 (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 16.1.13.1.8 AE tables (separately for combined SRD parts and FE part), the following totals will be provided in addition:

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

Tables of vital signs, ECG and laboratory values will present results by the above mentioned on treatment phase, including “Placebo 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.

If any important PVs are identified, they are to be summarized 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 protocol violations 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 | Concomitant medication with the potential to affect the assessment of the trial medication |
| **E** | | **Missing data** |
| | E1 | Certain violations of procedures used to measure primary or secondary data |
| **F** | | **Incorrect timing**[1] |
| | F1 | Certain violations of time schedule used to measure primary or 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)

## 6.3 SUBJECT SETS ANALYSED

- Treated set (TS):
  This subject set includes all subjects 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 analyses. (The ECG analyses are performed on the TS, except for the exposure-response analyses, which are performed on the ECGPCS defined below.)

**Section 7.3.1 of the CTP:** *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 violation 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.*

*Relevant protocol violations 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).*
- *The subject experiences emesis at any time during the labelled dosing interval.*
- *A pre-dose concentration is >5% of the $C_{max}$ value of that subject.*
- *Missing samples/concentration data at important phases of PK disposition curve.*

- PK parameter analysis set (PKS):
  The PK parameter analysis set (PKS) includes all subjects from the TS receiving BI 705564 who provide at least one primary or secondary PK parameter (AUC or $C_{max}$) that was not excluded according to the description above.
  Thus, a subject will be included in the PKS, even if he contributes only one PK parameter value for one period to the statistical assessment (FE part).

It is used for assessment of dose proportionality (SRD parts under fasting and fed conditions) and for assessment of the food effect (FE part and each dose level that was tested under both fasting and fed conditions).

The descriptive analysis of PK concentrations will be based on the ADS ADPC as described at the beginning of Section 7.

Table 6.3: 1 Subject sets analysed

| | Analysis set | | |
|---|---|---|---|
| Class of endpoint | TS | PKS | ECGPCS |
| Primary and further safety endpoints (incl. ECG) | X | | |
| ECG endpoints and plasma concentrations used in exposure-response analysis | | | X |
| Primary and Secondary PK endpoints | | X | |
| Demographic/baseline endpoints | X | | |
| Important PVs/Disposition | X | | |
| Disposition | X | | |

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

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

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

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

For the classification of the on-treatment QTc/QT intervals into “no new onset” / “new onset” categories, a missing value is obtained only in case that
(i) all on-treatment values are missing and
(ii) the baseline value is less than or equal to 500 msec, or missing.
If condition (i) is fulfilled but the baseline value is greater than 500 msec, this case will be categorized as “no new onset”. If baseline is missing and the maximum on treatment QTc interval is greater than 450 msec (or 500 msec for QT interval, respectively), this is classified as a “new onset” in the respective category. If baseline is missing and the maximum QTc interval is less than or equal to 450 msec (or 500 msec for QT interval, respectively), this will be categorized as “no new onset”. If baseline is missing, a QTc/QT interval > 500 msec at any time on treatment will be a notable finding. In case of a missing qualitative ECG finding at baseline, a finding observed on treatment will be categorized as “new onset”.

For placebo subjects the missing plasma concentration values will be replaced by 0 for the exposure response analysis.

## 6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For laboratory parameters, the baseline value is defined as the last measurement before first trial drug administration in the first treatment period.

For vital signs and PK parameters, the baseline value is defined as the last measurement before trial drug administration in each treatment period.

**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 end of trial examination are given in* CTP *Flow Chart 1 and* CTP *Flow Chart 3 for the single rising dose part under fasting and fed conditions, respectively, and* CTP *Flow Chart 2 for the food effect part.*

*Study measurements and assessments scheduled to occur ‘before’ trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration (including blank values for PK and biomarkers).*

*Starting from 72 h post administration a deviation from the scheduled time for PK and biomarker sampling of ±70 min is acceptable. The biomarker samples planned time Day 6 (single rising dose parts) may be taken on day 5 (up to 26 h earlier).*

*The acceptable deviation from the scheduled time for vital signs, ECG and laboratory tests will be ± 15 minutes for the first 4 hours after trial drug administration and ± 30 minutes 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 parts under fasting and fed conditions, there will be a centralised evaluation of the 12-lead ECG recordings at the time points and for the ECG recordings specified in the Table 6.7: 1 below:

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

| Visit | Day | Planned time [hh:mm] (relative to drug administration) | Study phase | Central evaluation |
|---|---|---|---|---|
| 1 | -21 to -1 | | Screening | NA |
| 2 | 1 | -02:00 | Baseline | triplicate ECG |
| | | 00:30 | On treatment | first of three replicate ECG |
| | | 01:00 | | first of three replicate ECG |
| | | 01:30 | | first of three replicate ECG |
| | | 02:00 | | first of three replicate ECG |
| | | 03:00 | | first of three replicate ECG |
| | | 04:00 | | first of three replicate ECG |
| | | 06:00 | | first of three replicate ECG |
| | | 08:00 | | first of three replicate ECG |
| | | 12:00 | | first of three replicate ECG |
| | 2 | 24:00 | | first of three replicate ECG |
| | 3 | 48:00 | | first of three replicate ECG |
| | 4 | 72:00 | | first of three replicate ECG |
| 4 | 11 to 15 | | End of trial examination | NA |

Triple ECGs will be recorded (three single ECGs within 180 sec) at all time points in Visit 2. At Visits 1 and 4, single ECGs will be recorded.

**Section 5.2.4.1 of the CTP:** *With the exception of the first triple ECG (used as baseline before the first drug administration), only the first of the three replicate ECGs at a single assessment time will be evaluated.*

The baseline value of an ECG variable is defined as the mean of the 3 triplicate ECG measurements prior to drug administration.

For the exposure response analyses, pairs of ECG measurements and corresponding plasma concentrations will be built using the same time points, e.g. HR change from baseline and

plasma sample taken at planned time 0:30 will build one pair. Whether a time deviation between PK blood sampling time and corresponding ECG recording is too big and the pair has to be excluded will be decided no later than at the RPM. This critical time deviation depends on the PK properties. When plasma concentrations are expected to change only little around a given time point, the time deviation between ECG recording and PK blood sampling can be bigger.

For the FE part, no centralised evaluation of all 12-lead ECG recordings is planned.

# 7. PLANNED ANALYSIS

The combined SRD parts and FE part will be evaluated separately.

In the combined SRD parts, the placebo group under fasting (labelled "Placebo fast") and the placebo group under fed conditions (labelled "Placebo fed") will be compared, as well as the combined placebo group (labelled "Placebo total") to all active treatment groups.

Safety analysis (refer to Section 7.8) will be performed by and will be presented in Sections 15.1 to 15.4 of the CTR and in Appendix 16.2 and 16.1.13.1.

Inferential statistical analyses of PK endpoints (refer to Sections 7.4 and 7.5.2) will also be performed by and will be presented in Section 15.5 of the CTR and in Appendix 16.1.13.3.

Descriptive data analysis of PK parameters and concentrations will be performed by BI and will be presented in Section 15.6 of the CTR.

Descriptive data analysis of PD endpoints will be performed by department Translational Medicine and Clin. Pharmacology at BI 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.

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

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 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/sequence. 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 analysis data set (ADS) ADPP (PK parameters) 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 (and, as a consequence, any calculation that relies on $\lambda_z$) 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.

The data will be summarised by treatment group and in total (combined SRD parts).
The data of the FE part will be summarised by treatment sequence and in total.

For public disclosure, both trial parts will be combined. In case that a subject participate in both trial parts, the information from the prior participation will be used for total baseline characteristics.

## 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

**Section 4.3 of the 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 ENDPOINTS

Safety evaluation – combined SRD parts under fasting and fed conditions

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 705564.

Investigation of relative bioavailability (food effect evaluation) – FE part

Relative bioavailability is to be determined on the basis of the primary and secondary PK parameters ($AUC_{0-tz}$, $C_{max}$ and $AUC_{0-\infty}$). Those parameters will be ln-transformed (natural logarithm) prior to fitting the model.

**Primary analysis**

**Section 7.1.3 of the CTP:** *The statistical model used for the analysis of primary* ($AUC_{0-tz}$ and $C_{max}$) *and […] secondary* ($AUC_{0-\infty}$) *endpoints 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. 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 (*$AUC_{0\text{-}tz}$, $C_{max}$, $AUC_{0\text{-}\infty}$*) measured on subject m in sequence i receiving treatment k in period j,*

$\mu$ *the overall mean,*

$\zeta_i$ *the ith sequence effect, i = 1, 2*

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

$\pi_j$ *the jth period effect, j = 1, 2*

$\tau_k$ *the kth treatment effect, k = 1, 2*

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

The difference between the expected means for test treatments (tablets under fed conditions, T) and reference treatment (tablets under fasting conditions, R) ln(T)-ln(R), 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.

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

## 7.5 SECONDARY ENDPOINTS

### 7.5.1 Key secondary endpoints

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

### 7.5.2 Secondary endpoints

Assessment of dose proportionality - SRD parts under fasting and fed conditions

**Section 7.3.2 of the CTP:** *Two separate analyses will be performed, one for the doses under fasting conditions, and one for the doses under fed conditions.*

Dose proportionality of the PK endpoints $AUC_{0-\infty}$ and $C_{max}$ in plasma of BI 705564 will be explored using the power model that describes the functional relationship between dose and PK endpoints. The basic model consists of a regression model applied to ln-transformed data. The corresponding ANCOVA (Analysis of Covariance) model includes the logarithm of the dose as a covariate.

The model is described by the following equation:

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

where

| | |
|---|---|
| $Y_{ij}$ | logarithm of the pharmacokinetic endpoint for subject j at dose level i; j = 1, 2, …, N, |
| $\alpha$ | intercept parameter; |
| $\beta$ | slope parameter; |
| $X_i$ | logarithm of dose i; |
| $\varepsilon_{ij}$ | random error associated with subject j at dose level i (assumed to be independent and identically normally distributed). |

**Section 7.3.2 of the CTP:** *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* ln-*transformed pharmacokinetic endpoint and the* ln-*transformed dose will be checked.*

*If dose proportionality over the entire dose range 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.

To support the analyses of dose proportionality, a regression plot will be performed, where the logarithm of dose is depicted versus logarithm of PK endpoint, including the estimated regression line from the power model and reference line of perfect proportionality ($\beta=1$).

A joint analysis (fasting and fed conditions) of dose proportionality will not be performed.

Investigation of relative bioavailability (food effect evaluation) – FE part

Refer to TSAP Section 7.4 for a description of the analysis of food effect for the secondary endpoint $AUC_{0-\infty}$.

Safety

Refer to TSAP Section 7.8 for a description of the analysis of safety and tolerability of BI 705564.

## 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 treatment group (combined SRD parts) or by actual treatment (FE part).

In the combined SRD parts, the placebo group under fasting (labelled “Placebo fast”) and the placebo group under fed conditions (labelled “Placebo fed”) will be analysed separately and compared, as well as the combined placebo group (labelled “Placebo total”) to all active treatment groups.

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 with the most recent version of MedDRA.

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] (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 one hour after end of the first occurrence)

For further details on summarization of AE data, please refer to [001-MCG-156] (9).

**Section 5.2.2.1 of the CTP:** *The following are considered as AESI in this trial:*

- *Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:*
  - *An elevation of AST and/or ALT ≥3-fold 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.

**Section 5.2.2.2 of the CTP:** *The REP for BI 705564, 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 AEs (including AESIs) will be presented.

The frequency of subjects with AEs will be summarized 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 (within system organ class). 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).

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 CRF 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

**Continuous safety ECG monitoring (by investigator) – (SRD parts only)**

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 (SRD parts + FE part)**

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

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

The following ECG analyses will only be performed in the SRD parts:

Listing of individual data

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

Comments regarding the ECGs will be listed.

Categorical endpoints

For the categorical endpoints, frequency tables will be provided.

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

Quantitative endpoints:

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

For QTcF and HR changes from baseline the relationship to the corresponding plasma concentration is evaluated using an exposure response model.

This model will be evaluated separately for doses under fasting conditions and doses under fed conditions.

For the following analyses, all time points with available ECG endpoints and time-matched plasma concentrations of all dose groups will be included. For the handling of missing values see Section 6.6.

The response variable will be the change from baseline in QTcF (ΔQTcF). The placebo subjects will be included in the analysis, setting their plasma concentrations to zero.

As a first step, it is investigated if there is a potential delayed or accelerated (e.g. metabolites) effect of the drug on QTcF. A general visual impression is provided by overlaying time profiles of plasma concentrations and QTcF changes from baseline (ΔQTcF). All figures will

be generated for each subject (presented in statistical Appendix of the CTR), as well as for means per active treatment (presented in the End-of-Text tables of the CTR).

The relationship between BI 705564 plasma concentrations and QTcF changes from baseline will be investigated in an exploratory manner using a random coefficient model approach to estimate the difference in means between BI 705564 and placebo in QTcF change from baseline and its 90% confidence interval at the geometric mean of the $C_{max}$ for each dose. Additionally, the estimated slope with its 90% confidence interval will be provided. The used random coefficient model is based on Garnett et al. 2016 (12) with ΔQTcF as response variable, centered baseline QTc and plasma concentration as continuous covariates, treatment and time as fixed categorical effects, and a random intercept and slope for each subject. For more details refer to Section 9.3.

For visualization, the BI 705564 plasma concentration against the response will be plotted as well as the (fixed effect) regression line, its 90% confidence interval and the geometric mean of $C_{max}$ for each dose. For each subject and each time point, subtract the mean value of all individual observed ΔQTc values from the placebo group for this time point from the individual observed ΔQTc value for this subject and time point. This results in estimates for "individual ΔΔQTc" values. These estimates will only be used for plotting purposes.

To check model assumptions, the conditional residuals will be plotted and presented in the statistical Appendix. In case of non-linearity or if there is evidence for a delayed effect, further models will be explored that better characterise the PK/ECG relationship (log(concentration), effect compartment, non-linear model etc.).

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

Appropriateness of heart rate correction methods of QT interval

To evaluate the appropriateness of the correction methods, the slope of the relationship of QTcF interval versus RR interval (values log-transformed using the natural logarithm) will be estimated by applying the random coefficient model described in Section 9.3 using all time points. A scatterplot of QTcF vs RR including the estimated regression line will be included in the statistical Appendix of the CTR. The resulting (fixed effect) slope together with two-sided 95% confidence intervals will be included in this plot.

### 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.

# 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”, current version; 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. | Garnett C, Needleman K, Liu J, Brundage R, Wang Y; Operational characteristics of linear concentration-QT models for assessing QTc interval in the thorough QT and phase I clinical studies. Clin Pharmacol Ther 100 (2), 170 - 178 (2016) |

# 10. HISTORY TABLE

Table 10: 1 History table

| Version | Date (DD-MMM-YY) | Author | Sections changed | Brief description of change |
|---|---|---|---|---|
| Final | 16-MAR-18 | | None | This is the final TSAP without any modification |