

Trial Statistical Analysis Plan

c13382205-03

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|---|--|
| BI Trial No.: | 1363.2 |
| Title: | A Phase Ib, multicentre, double blind, randomized, two-part study, first part multiple rising dose and second part two-way cross-over, to assess safety, tolerability, efficacy and pharmacokinetics of BI 443651 compared to placebo via Respimat® in healthy volunteers and CF subjects including Protocol Amendment 7 (c09013915 -08) |
| Investigational Product: | BI 443651 |
| Responsible trial statistician(s): | Phone: Fax: |
| Date of statistical analysis plan: | 18SEP2018 REVISED |
| Version: | Revised 3.0 |
| Page 1 of 38 | |
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2. LIST OF ABBREVIATIONS

| Term | Definition / description |
|----------------------|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| BI | Boehringer Ingelheim |
| BLQ | Below the lower limit of quantification |
| BMI | Body mass index |
| CARE | Clinical data analysis and reporting environment |
| CF | Cystic fibrosis |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| CV | Arithmetic coefficient of variation |
| DBLM | Database lock meeting |
| DNA | Deoxyribonucleic acid |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EMA | European Medicines Agency |
| EudraCT | European union drug regulating authorities clinical trials |
| FEF ₂₅₋₇₅ | Forced expiratory flow |
| FEV ₁ | Forced expiratory volume in 1 second |
| FEV _{1pp} | FEV ₁ percent predicted |
| FRC | Functional residual capacity |
| FVC | Forced vital capacity |
| gCV | Geometric coefficient of variation |
| gMean | Geometric mean |
| HR | Heart rate |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IPD | Important protocol deviation |

| Term | Definition / description |
|--------|--|
| MedDRA | Medical Dictionary for Regulatory Activities |
| NOA | Not analysed |
| NOP | No peak detectable |
| NOR | No valid result |
| NOS | No sample available |
| PD | Pharmacodynamic(s) |
| PEF | Peak expiratory flow |
| PFT | Pulmonary function testing |
| PK | Pharmacokinetic(s) |
| PKS | PK analysis set |
| QTcB | QT interval corrected for heart rate using the method of Bazett (QTcB) |
| QTcF | QT interval corrected for heart rate using the method of Fridericia (QTcF) |
| RAGe | Report appendix generator |
| RPM | Report planning meeting |
| RS | Randomised set |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SDL | Subject data listing |
| TEAE | Treatment emergent adverse event |
| TS | Treated set |
| TSAP | Trial statistical analysis plan |
| ULN | Upper limit of normal range |

3. INTRODUCTION

As per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 ([10](#)), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the revised Clinical Trial Protocol (CTP), 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 revised CTP. 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.

Within the earlier version 2.0 of the TSAP, the planned analyses for the healthy volunteer (HV) cohort has been specified. All descriptions and planned analyses for this trial part are based on CTP Version 6.0 (20 April 2017) even though part 1 was conducted according to CTP Version 3.0 (01 December 2016) which was applicable when recruitment for part 1 started. Planned analyses for CF subjects were described as detailed as possible in version 2.0 of the TSAP. At the time of recruitment of the first CF subjects for part 2 of the study, CTP Version 7.0 (06 September 2017) was applicable and the CTP was amended to Version 8.0 (09 November 2017) during conduct of part 2. Within the current revised version of the TSAP the planned analyses for the CF subjects were updated or added based on CTP Version 8.0. For further details refer to [Section 4](#).

Study data will be stored in a trial database within the Oracle ClinicalTM system.

The statistical analyses will be performed within the validated working environment CARE (Clinical data Analysis and Reporting Environment), including SASTM (current Version 9.4, by SAS Institute Inc., Cary, NC, USA), and a number of SASTM-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).

Non-compartmental pharmacokinetic (PK) parameters will be calculated using WinNonlinTM software (professional Network version 5.2, Pharsight Corporation, Mountain View, CA 94041-1530, USA). Population PK, PK/PD analysis will be conducted with appropriate software, which will be documented in the population PK, PK/PD report.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Changes implemented within TSAP Version 2.0:

CTP Version 6.0 (dated 20 April 2017) was the basis for planned analyses of HV part (trial part 1). The corresponding amendment implemented the following changes which also affect the planned analysis of the study:

- The COPD cohort was not performed. All planned analyses will be based on healthy volunteers and CF subjects only.
- After completion of part 1 with healthy volunteers (HV) the final unblinded analysis of this data will be performed to enhance further project planning. Logistical details are described in a separate Logistics Plan [\(9\)](#). Data obtained from part 1 will be cleaned and an interim database lock will be made before unblinding and finalization of the outputs. A final TSAP for the analyses of HV was provided before interim database lock.

For PK parameters assessed on Day 7 of part 1 for HV it was not clear at the time of analysis whether steady state had been reached. Therefore, for the purpose of the final analysis and reporting the parameters $C_{\max,ss}$ and $AUC_{\tau,ss}$ at Day 7, which are defined as secondary endpoints for HV, will now be referred to as $C_{\max,13}$ and $AUC_{\tau,13}$.

Changes implemented within this TSAP Version 3.0:

Since planned analyses for CF subjects were not completely described in TSAP version 2.0, all details on planned analyses for CF subjects are described in this revised TSAP prior to final database lock at the end of the trial.

CTP Version 7.0 (dated 06 September 2017) was applicable at the time of first recruitment of CF subjects in part 2 of the trial. It implemented changes to facilitate trial logistics which did not affect the planned analyses of the trial.

The Final Version 8.0 of the CTP (dated 09 November 2017) implemented the following changes which also affect the planned analysis of the study part 2 with CF subjects:

- Planned times for pre-dose assessments on Days 1, 7 were changed as listed below:

| Study day | Planned time according to | |
|-----------|---------------------------|----------|
| | CTP V7.0 | CTP V8.0 |
| Day 1 | -2:00 | -1:00 |
| | -1:00 | -0:30 |
| Day 7 | 142:00 | 143:00 |
| | 143:00 | 143:30 |

Pre-dose measurements collected according to planned times of CTP Version 7.0 will be set to the corresponding planned time of CTP Version 8.0 for analyses.

Further changes/clarifications to the planned analyses of CF subjects (not based on a CTP amendment):

- In addition to the further safety endpoints regarding PFT, FEV₁/FVC ratio will be evaluated as further safety endpoint similar to FEV₁ and FVC.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint to assess safety and tolerability of BI 443651 is the frequency (in percent) of subjects with treatment-emergent adverse events (TEAE) over the treatment period. The primary endpoint will be reported separately for HV and CF subjects.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

No applicable.

5.2.2 Secondary endpoints

The following pharmacokinetic parameters of BI 443651 will be determined after first dose (morning of Day 1) in HV in Part 1:

- C_{\max} (maximum measured concentration of the analyte in plasma after first dose)
- AUC_{0-12} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 12 h after first dose)

The following pharmacokinetic parameters of BI 443651 will be determined after last dose (13th dose, morning of Day 7) in HV in Part 1:

- $C_{\max,13}$ (maximum measured concentration of the analyte in plasma over the time interval from 0 to 12 h after the 13th dose)
- $AUC_{\tau,13}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 12 h after the 13th dose)

5.3.2 Safety endpoints

The following endpoints are further safety criteria of interest:

- Related AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)
- Pulmonary function tests (FEV₁, FVC, FEV₁/FVC ratio (CF subjects only), FEF₂₅₋₇₅)

12-lead ECG endpoints

For the definition of baseline and a summary of time points please refer to [Section 6.7](#).

Quantitative ECG endpoints:

The following quantitative ECG endpoints will be determined for the ECG variables RR, PR, QRS, QT, HR, QTcF and QTcB derived as described in [Section 9.1](#):

- absolute values (per time point)
- changes from baseline (per time point)
- percent changes from baseline (per time point; only for HR, PR, QRS)

Categorical ECG endpoints

The following categorical ECG endpoints will be determined based on the quantitative ECG endpoints:

- New onset (meaning that this or a higher category was not present at baseline) of maximum QTcF interval > 450 to 480 msec, > 480 to 500 msec, or > 500 msec on treatment. For assignment of a particular subject to one of the above categories, all time points on-treatment will be considered. If baseline is missing, but the maximum absolute QT(c) interval falls in a category other than normal (i.e. when QTcF > 450 msec), then this is categorized as a new onset in the respective category. If baseline is missing, but the maximum absolute QT(c) interval is normal, then it is categorized as 'No new onset'.
- Maximum change from baseline in QT interval of ≤ 60 msec, or > 60 msec on treatment
- Maximum change from baseline in QTcF interval of ≤ 30 msec, > 30 to ≤ 60 msec, or > 60 msec on treatment

The occurrence of any of the following will be viewed as "notable findings":

- New onset (not present at baseline) of uncorrected QT interval > 500 msec at any time on treatment
If baseline is missing, any occurrence of QT interval > 500 msec at any time on treatment will be a notable finding
- New onset of QTcF interval > 500 msec at any time on treatment
If baseline is missing, any occurrence of QTcF interval > 500 msec at any time on treatment will be a notable finding
- Increase in QTcF interval from baseline by > 60 msec at any time on treatment
- Increase in HR from baseline by $\geq 25\%$, when corresponding on-treatment value of HR is > 100 beats/min, or decrease in HR by $\geq 25\%$, when corresponding on-treatment value of HR is < 50 beats/min, at any time on treatment
- Increase in the PR interval from baseline by $\geq 25\%$, when corresponding on-treatment value of PR interval is > 200 msec, at any time on treatment
- Increase in the QRS complex from baseline by $\geq 10\%$, when corresponding on-treatment value of QRS complex is > 110 msec, at any time on treatment

Findings from the morphologic analyses of the ECGs (done for CF subjects in Part 2) will be determined and categorized based on SDTM terminology.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered please refer to Section 4 of the CTP.

The trial is composed of two parts, a multiple rising-dose (MRD) and a cross-over part. Both parts are randomised, placebo-controlled and double-blind.

During the MRD part, healthy volunteers (40 subjects planned to be included) will be treated with doses of 100, 400, 1200 and 1800 µg b.i.d. of BI 443651 or placebo.

For the cross-over part, a total of 24 subjects with CF will be included in the study. Each subject will receive both placebo and active drug at the dose level 600 µg b.i.d. of BI 443651.

Measurements (such as ECG, spirometry, vital signs, or laboratory parameters) or adverse events (AE) will be assigned to treatments and study periods by applying the following rules:

- **Screening:** measurements made or AEs which started prior to first administration of trial medication.
- **On-treatment:** measurements made or AEs which started between first administration of trial medication in a treatment period and first administration of trial medication in the next treatment period or end of REP will be assigned to the preceding treatment. The REP for BI 443651 is defined as 30 days after the last trial medication application.
- **Follow-up:** measurements made or AEs which started between the end of REP and first administration of trial medication in the next treatment period or trial termination date. In case of 2 or more treatments, the follow-up will be summarized according to the previous treatment.

Table 6.1: 1 Flow chart of analysis phases for adverse events, laboratory tests, vital signs and spirometry for healthy volunteers

| Study analysis phase | Start | End |
|--|--|---|
| Screening | Date of informed consent | Date/time of first device actuation for administration of BI 443651 or placebo |
| On treatment | Date/time of first device actuation for administration of BI 443651 or placebo | 0:00 AM on day after end of REP or 0:00 AM on day after trial termination date Whatever comes first |
| Follow-up (not identical to time points acc. To CTP) | 0:00 AM on day after end of REP | trial completion date |

Table 6.1: 2 Flow chart of analysis phases for adverse events, laboratory tests, vital signs, ECG and spirometry for CF subjects

| Study analysis phase* | Start | End |
|---------------------------|---|---|
| Screening | Date of informed consent | Date/time of first device actuation for administration of BI 443651 or placebo (first treatment period) |
| On treatment (period 1/2) | Date/time of first device actuation for administration of BI 443651 or placebo (in the actual treatment period) | 0:00 AM on day after end of REP or 0:00 AM on day after trial termination date or date/time of first drug intake in the next treatment period whatever comes first |
| Follow-up | 0:00 AM on day after end of REP | 0:00 AM on day after trial termination date or date/time of first drug intake in the next trial period |

*In case measurements (baseline or on-treatment) scheduled for period 2 were obtained within the on-treatment phase of treatment period 1 deviations in the assignment to study phases or possible exclusions will be discussed in the BRPM.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Data discrepancies and deviations from the CTP will be identified for all subjects entered and randomized who did not fail during screening.

Consistency check listings (for identification of deviations of time windows) and a list of protocol deviations (e.g. deviations in drug administration, in blood sampling times, etc.) will be provided to be discussed at the Medical Quality Review Meetings (MQRM) and Blinded Report Planning Meetings (BRPMs). At these meetings, all manual deviations identified at the sites by the CRAs and deviations too complex to program will be reviewed by the trial team to decide which are considered important. For definition of important protocol deviations (iPD), and for the process of identification of these, refer to the Boehringer Ingelheim (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" ([1](#)).

If any iPDs are identified, they are to be summarised into categories and will be captured in the MQRM/BRPM minutes via an accompanying Excel spreadsheet ([2](#)). The following tables contain the categories which are considered to be iPDs in this trial, separately for healthy volunteers and CF subjects. The column "Excluded from" specifies a general rule when an iPD results in exclusion from analysis datasets, but the final decision with regard to iPDs and exclusion from analysis datasets should be made at the BRPM or Database Lock Meeting (DBLM). If the data show other iPDs, these tables will be supplemented accordingly by the time of the DBLM at the latest.

Table 6.2: 1 Important protocol deviations for healthy volunteers

| Category / Code | Description | Example/Comments | Excluded from |
|-----------------|---|---|---------------|
| A | Entrance criteria not met | | |
| A1 | Inclusion criteria not met | | None |
| A2 | Exclusion criteria not met | | None |
| B | Informed consent | | |
| B1 | Informed consent not available/not done | Missing informed consent (ICF); no signature on ICF | All |
| B2 | Informed consent too late | Date of informed consent was after the date of any study-related procedure, or a subject signed the correct version of the ICF after Visit 1. To be discussed at MQR/BRPM/DBL meetings. | None |
| C | Trial medication and randomization | | |
| C1 | Incorrect trial medication taken * | Medication kit assigned not matching treatment subject was randomized to and/or not matching IVRS assignment | None |
| C2 | Randomisation order not followed* | | None |
| C3 | Non-compliance | Compliance <80% or >120% Decisions at MQR/BRPM. | None |
| C4 | Medication code broken inappropriately * | To be discussed and decided during MQR/BRPM. Only inappropriate code breaks at iPDs (e.g., unblinding by Global Pharmacovigilance is not). | None |
| C5 | Incorrect intake of trial medication | | None |
| | | | |

Table 6.2: 1 Important protocol deviations for healthy volunteers (cont.)

| Category / Code | Description | Example/Comments | Excluded from |
|-----------------|---|---|---------------|
| D | Concomitant medication | | |
| D1 | Prohibited medication use * | Decision at MQR/BRPM | None |
| D3 | Improper medication washout at baseline visit or primary endpoint visit(s) * | Decisions at MQR/BRPM. | None |
| E | Missing data (for primary and secondary endpoints)¹ | | |
| E1 | Certain deviations of procedures used to measure primary or secondary data | Decision at MQR/BRPM | None |
| F | Incorrect timing² | | |
| F1 | Certain deviations of time schedule used to measure primary or secondary data | Incorrect timing for PK sampling * Decision at MQR/BRPM | None |
| G | Other trial specific important deviations | | |
| G1 | Incorrect intake of meal* | | None |
| G2 | protocol deviations affecting safety and rights. * | Manual deviations reported by CML/CRA which are considered as important. Carefully reviewed, described and documented in DBL meeting minutes. | None |

*not programmed

¹ Missing visits, evaluations, and tests will be considered missing data, not protocol violations

² Time deviations will only be flagged as iPD, when leading to exclusion of the entire subject from an analysis set

Table 6.2: 2 Important protocol deviations for CF subjects

| Category / Code | Description | Example/Comments | Excluded from |
|-----------------|--|---|---------------|
| A | Entrance criteria not met | | |
| A1 | Inclusion criteria not met | | |
| A1.1 | Age limitation not met or women with childbearing potential (with no confirmed menstrual period prior to dosing) | IN3, IN4 | None |
| A1.2 | CF diagnosis not met | IN2 | None |
| A1.3 | Pre-bronchodilator parameter at screening not met. | IN6 | None |
| A1.5 | Ability to perform technically acceptable pulmonary function tests not given | IN8 | None |
| A1.6 | Other reason | IN5, IN7 | None |
| A2 | Exclusion criteria not met | | |
| A2.1 | Co-morbidity conditions not met | EX1, EX2 | None |
| A2.2 | Cardiovascular related conditions not met | EX4, EX5, EX13, EX14 | None |
| A2.3 | Safety lab not met | EX11 | None |
| A2.4 | Substance abuse | EX19, EX20, EX21 | None |
| A2.5 | Use of restricted medication | EX15, EX16, EX17 | None |
| A2.6 | Other reasons | EX3, EX6, EX7, EX8, EX9, EX10, EX18, EX22, EX23, EX24, EX25, EX26, EX27, EX28, EX29 | None |
| B | Informed consent | | |
| B1 | Informed consent not available/not done | Missing informed consent; no signature on ICF | All |
| B2 | Informed consent too late | Date of informed consent was after the date of any study-related procedure, or a subject signed the correct version of the ICF after Visit 1. To be discussed at MQR/BRPM/DBL meetings. | None |
| C | Trial medication and randomization | | |
| C1 | Incorrect trial medication taken * | Medication kit assigned not matching treatment subject was randomized to and/or not matching IVRS assignment | None |
| C2 | Randomisation order not followed | | None |

Table 6.2: 2 Important protocol deviations for CF subjects (cont.)

| Category / Code | Description | Example/Comment | Excluded from |
|-----------------|---|--|---------------|
| C3 | Non-compliance | Compliance <80% or >120% Decisions at MQRM/BRPM. | None |
| C4 | Medication code broken inappropriately * | To be discussed and decided during MQRM/BRPM. Only inappropriate code breaks at iPDs (e.g., unblinding by Global Pharmacovigilance is not). | None |
| C5 | Incorrect intake of trial medication | | None |
| C6 | Improper washout between treatments | | None |
| D | Concomitant medication | | |
| D1 | Prohibited medication use * | Decision at MQRM/BRPM | None |
| D3 | Improper medication washout at baseline visit or primary endpoint visit(s) * | Decisions at MQRM/BRPM. | None |
| D4 | Improper use of rescue medication | Decisions at MQRM/BRPM. | None |
| E | Missing data¹ | | |
| E1 | Certain deviations of procedures used to measure primary, secondary or efficacy data | Decision at MQRM/BRPM | None |
| F | Incorrect timing² | | |
| F1 | Certain deviations of time schedule used to measure primary, secondary or efficacy data | Incorrect timing for PK sampling * Decision at MQRM/BRPM | None |
| G | Other trial specific important deviations | | |
| G1 | Incorrect intake of meal | | None |
| G2 | protocol deviations affecting efficacy, safety and rights. * | Manual protocol deviations reported by CML/CRA which are considered as important. Carefully reviewed, described and documented in DBL meeting minutes. | None |

*not programmed

¹ Missing visits, evaluations, and tests will be considered missing data, not protocol deviations

² Time deviations will only be flagged as iPD, when leading to exclusion of the entire subject from an analysis set

6.3 PATIENT SETS ANALYSED

The statistical analysis will be based on the following analysis set:

- Enrolled set (ES): all subjects who signed informed consent and underwent screening procedures
- Randomized set (RS): all randomised subjects, whether treated or not
- Treated set (TS): all subjects who were randomized and treated with at least one dose of study drug (active or placebo). The treatment assignment (for CF part: within each treatment period) will be determined based on the first treatment the subjects received.
- Pharmacokinetic set (PKS): all HVs in the TS who provide at least one PK parameter that was not excluded according to the description in Section 7.3.2 of the CTP. 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.

Table 6.3: 1 Analysis Sets

| | | Analysis Set | | | | |
|--------------------------------|--|--------------|----|----|-----|--|
| Class of endpoint | | ES | RS | TS | PKS | |
| Disposition | | X | | | | |
| Exposure | | | | X | | |
| iPDs | | | X | | | |
| Demographic/baseline endpoints | | | | X | | |
| Safety endpoints | | | | X | | |
| Secondary PK endpoints | | | | | X | |
| Further PK endpoints | | | | | X | |
| | | | | | | |
| | | | | | | |

6.5 POOLING OF CENTRES

For HV there is only one centre.

For CF subjects all planned analyses will be performed across all centres.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Generally, it is not planned to impute missing values for safety or efficacy evaluations with the exception of missing or incomplete AE dates and missing data of PK data. These will be handled according to BI standards (see SOP 001-MCG-156_RD-01 for missing AE dates ([3](#)) and SOP 001-MCS-36-472 for missing PK data ([4](#))).

Plasma 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 to the lag phase, including the predose values).

For the non-compartmental analysis of pharmacokinetic parameters, 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.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For endpoints regarding pulmonary function testing (e.g. FEV₁) in-clinic, baseline is defined as the last measurement taken on Day 1 before first study drug administration within each treatment period.

For pulmonary function testing using the home spirometer, baseline is defined as the last measurement taken between Day -7 and -3 before first study drug administration within each treatment period.

For ECG endpoints, baseline is defined as the mean of the last triplicate measurement taken on Day 1 before first study drug administration within each treatment period.

For all other endpoints, baseline is defined as the last measurement before first study drug administration within each trial period. I.e., in case the pre-dose measurement on Day 1 is missing, the measurement between Day -7 and Day -3 will be used as baseline.

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked at the MQRM.

There will be a centralised evaluation of all 12-lead ECG recordings at the time points identified in Tables 6.7:1 and 6.7:2 for HV and CF subjects, respectively.

Table 6.7: 1 12-lead ECG recordings for HV

| Visit | Day | Planned time [hh:mm] (relative to drug administration) | Approximate clock time [hh:mm] of actual day | Study phase | Triplicate ECG ¹ |
|-------|-----------|--|--|--------------|-----------------------------|
| 1 | -21 to -1 | | | Screening | |
| 2 | -3 to -1 | | | | |
| | 1 | -01:00 | 07:00 | Baseline | X |
| | | 00:45 | 08:45 | On-treatment | X |
| | | 02:00 | 10:00 | | X |
| | | 04:00 | 12:00 | | X |
| | | 11:00 | 19:00 | | X |
| | 2 | 23:00 | 07:00 | | X |
| | 4 | 71:00 | 07:00 | | |
| | 7 | 143:00 | 07:00 | | X |
| | | 144:45 | 08:45 | | X |
| | | 146:00 | 10:00 | | X |
| | | 148:00 | 12:00 | | X |
| | | 155:00 | 19:00 | | X |
| | 8 | 167:00 | 07:00 | | X |
| | 16 | 360:00 | 08:00 | | |
| | 23 | 528:00 | 08:00 | | |
| | 30 | 696:00 | 08:00 | | |
| 4 | 37-44 | 9999:00 | 08:00 | e.o.s. | |

Note: Times are based on Flow Chart I – Healthy Volunteers of CTP Version 3.0 (01 December 2016)

¹ Triplicate ECGs on Day 1, 2, 7 and 8 will be evaluated centrally.

Table 6.7: 2 12-lead ECG recordings for CF subjects

| Per iod | Visi t | Day | Planned time [hh:mm] (relative to drug administration) CTP Version 8.0(7.0) | According to CTP, Version 7.0 Approxima te clock time [hh:mm] of actual day | Accordin g to CTP, Version 8.0 Approxi mate clock time [hh:mm] of actual day | Study phase | Triplic ate ECG |
|------------|-----------|-----------|---|---|---|----------------------------|-----------------------|
| | 1 | -21 to -3 | | | | Screen ing | |
| 1/2 | 2/3 | 1 | -1:00(-02:00) | 06:00 | 7:00 | Period Baseli ne 1/2 | X |
| | | | 00:30 | 08:30 | 08:30 | On- treatm ent 1/2 | |
| | | | 04:00 | 12:00 | | | |
| | | | 11:00 | 19:00 | | | |
| | | 7 | 143:00(142:00) | 06:00 | 7:00 | | |
| | | 11 | 239:00 | 07:00 | | | |
| | | 14 | 311:00(310:00) | 06:00 | 7:00 | | |
| | | 23 | 528:00 | 08:00 | | | |
| | | 30 | 696:00 | 08:00 | 8:00 | | |
| | | 37 | 864:00 | 08:00 | | | |
| | 4 | 44-51 | 9999:00 | 08:00 | 8:00 | e.o.s. | |

Note: at the end of Visit 2 (period 1), subjects will washout for at least 30 days prior to crossing-over and commencing Day 1 of Visit 3 (period 2). At the end of Visit 3 (period 2), subjects will continue to the end of study visit (Visit 4).

Note: Times are based on Flow Chart II – CF subjects of CTP Version 7.0 (06 September 2017) and Version 8.0 (09 November 2017); all ECGs (single and triplicate) will be evaluated centrally

7. PLANNED ANALYSIS

This version of the TSAP describes analyses for HV and CF subjects.

Generally, HV and CF subjects will be evaluated separately. For safety analyses a total active treatment column will be displayed, if applicable.

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" ([7](#)).

The individual values of all subjects will be listed, sorted by treatment group, subject number and visit (if visit is applicable in the respective listing). AE listings will be sorted by assigned treatment (see [Section 7.8.1](#) below for details). The listings will be contained in Appendix 16.2 (SDL) of the CTR.

Inferential statistical analyses of PK endpoints 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 presented in Section 15.6 of the CTR.

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

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

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

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group. Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values. Percentages will be based on all subjects in the respective analysis set whether they have non-missing values or not.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

Only frequency tables are planned for this section of the CTR.

A medication will be considered concomitant to a treatment, if

- it is ongoing at the time of administration of the respective treatment or
- it starts within the on-treatment phase of the respective treatment (see [Section 6.1](#)).

7.3 TREATMENT COMPLIANCE

Treatment compliance will not be analysed as a specific endpoint. Any deviations from complete intake will be addressed in the MQRM/BRPM (cf. [Section 6.2](#)) and described in the CTR.

7.4 PRIMARY ENDPOINT

Refer to [Section 7.8.1](#) for a description of the analysis of AEs, and in particular the analysis of the frequency of subjects with TEAEs, which is the primary endpoint of this trial.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

Not applicable.

7.5.2 Secondary endpoints

According to CTP Version 8.0 secondary endpoints are only defined for HV and not for CF subjects.

The analysis of secondary endpoints will be based on the PKS.

Dose proportionality of secondary endpoints (AUC_{0-12} , C_{max} , $AUC_{\tau,13}$, $C_{max,13}$ for HV) over the entire dose range will be evaluated as defined in the CTP, Section 7.3.2, by use of the power

model for healthy volunteers. For each of the secondary endpoints tables displaying geometric means of pairwise ratios together with 95% confidence intervals will be provided by dose group. A summary of results of the power model as described in the CTP, Section 7.3.2 will be displayed by a table. The relationship between the dose and the respective PK parameters will additionally be visualized graphically.

7.6.1 Safety endpoints

Further safety endpoints will be analysed as described in [Section 7.8](#) of this TSAP.

7.7 EXTENT OF EXPOSURE

Treatment exposure will be listed by means of the date and time of drug administration. Additionally, tables displaying descriptive statistics for treatment exposure (number of doses and total dose administered) will be given separately for HV and CF subjects.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

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. All analyses of AEs 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 electronic case report form (eCRF) will be collapsed into one event provided that all of the following applies:

- All AE attributes are identical (lower level term, intensity, action taken, therapy required, seriousness, reason for seriousness, relationship, outcome, AE of special interest (AESI))
- The occurrences were time-overlapping or time-adjacent (time-adjacency of two occurrences is given if the second occurrence started at most 1 hour after the first occurrence ended)

For further details on summarization of AE data, please refer to 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' ([5](#)) and "Handling of missing and incomplete AE dates" ([3](#)).

The analysis of AEs will be based on the concept of treatment emergent AEs, i.e. all AEs will be assigned to the treatment phase, screening phase or follow-up phase as defined in [Section 6.1](#).

An overall summary of AEs will be presented. This overall summary will comprise summary statistics for the class of other significant AEs according to ICH E3 and for the class of adverse events of special interest (AESI). For the definition of AESI please refer to Section 5.3.10.1 of the CTP.

The frequency of subjects with AEs will be summarised by treatment (dose), primary system organ class and preferred term. AEs which were considered by the investigator to be drug related will be summarised separately. Separate tables will also be provided for subjects with serious AEs (SAEs), subjects with AESIs and subjects with other significant AEs (according to ICH E3). AEs will also be summarized by maximum intensity.

The system organ classes will be sorted according to the standard sort order specified by the European Medicines Agency (EMA), preferred terms will be sorted by total frequency (within system organ class).

A further table will present AEs by preferred term, dose group and intensity, sorted by descending relative frequency in any dose group.

For disclosure of AE data on ClinicalTrials.gov, the frequency of subjects with non-serious AEs occurring with an incidence of greater than 5 % (in preferred terms) will be summarised by treatment, primary system organ class and preferred term. The frequency of subjects with SAEs will also be summarised.

For disclosure of AE data in the European union drug regulating authorities clinical trials (EudraCT) register, the frequency of AEs, the frequency of non-serious AEs with an incidence of greater than 5 % (in preferred terms) and the frequency of SAEs will be summarised.

Tables prepared for public disclosure (ClinicalTrial.gov and EudraCT) will include subjects of both trial parts combined (HV and CF subjects).

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (6). If possible, analyses for HV will be based on original values. If multiple reference ranges apply for one parameter (e.g. due to different age groups) for HV, analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. Analyses for CF subjects will be based on normalized values. If reference ranges are not available, analyses will be based on original values.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done over comparing laboratory data to their reference ranges. Values outside the reference range will be highlighted in the listings.

Dose groups will be compared with descriptive statistics of laboratory values over time and by analysing differences from baseline (see [Section 6.7](#) for definition of baseline). Additionally, frequency tables of changes between baseline and last values on treatment with respect to the reference ranges will be presented. For electrolytes, descriptive statistics of values over time and differences from baseline will be provided comparing all active doses versus placebo for HV. Furthermore graphical representations over time will be generated for serum electrolytes for HV and CF subjects and for urine electrolytes for HV subjects.

Clinically relevant findings in laboratory data will be reported as AEs and will be analysed as part of AE analysis.

7.8.3 Vital signs

The analyses of vital signs will be descriptive in nature. Descriptive statistics of vital signs over time and for the changes from baseline (see [Section 6.7](#)) will be provided.

Clinically relevant findings in vital signs data will be reported as AEs and will be analysed as part of AE analysis.

7.8.4 ECG

Abnormal findings in 12-lead ECG or continuous ECG monitoring will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator.

The evaluation of 12-lead ECG data will be based on the TS.

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 of quantitative ECG recordings, a separate listing will be created as end-of-text display (same display as in Appendix 16.2), and the corresponding time profiles will be shown. Comments regarding the ECGs will be listed.

Analysis of central tendency

For quantitative ECG endpoints (RR, PR, QRS, QT, HR, QTcF and QTcB) descriptive statistics for absolute values and absolute changes from baseline will be provided for HV and CF subjects.

For QTcF, QT and HR of HV, a repeated measurements analysis of the changes from baseline with baseline as a covariate will be performed. The model will include the fixed effects “base”, “dose group”, “base*time” interaction, and “dose group*time” interaction. The covariance model for the repeated effect “time” will be unstructured. For each dose group and each time point, the contrast of the means for “treatment-placebo” will be estimated by the difference in the corresponding adjusted means (Least Squares Means); two-sided 90% CIs based on the t-distribution will also be computed. For each of the above ECG variables, the time profiles of the mean differences to placebo in the changes from baseline and the corresponding 90% CIs will be presented in a figure.

For QTcF, QT and HR of CF subjects, a repeated measurements analysis of the changes from baseline with subject and period baseline as covariates will be performed, if feasible, for time-points defined in CTP Version 8.0:

The model will include the fixed effects “base 1” as the subject baseline (i.e. the arithmetic mean of the respective period baselines per subject), “base2” as the period baseline, “treatment”, “time”, “Period”, “base1*time” and “base2*time” interaction, “period*time” interaction, and “treatment*time” interaction. Subject is included as a random effect on the intercept. The covariance model for the repeated effect “time” will be unstructured, using the blocking factor ‘subject-by-period’. For each time point, the contrast of the means for “treatment-placebo” will be estimated by the difference in the corresponding adjusted means (Least Squares Means); two-sided 90% CIs based on the t-distribution will also be computed. For each of the above ECG variables, the time profiles of the mean differences to placebo in the changes from baseline and the corresponding 90% CIs will be presented in a figure.

Categorical Endpoints

For the categorical endpoints, frequency tables will be provided.

Categorical endpoints will also include morphological findings that might be attributable to treatment. In particular, new onsets of findings not present at baseline will be explored. A morphological finding observed on treatment that was not reported at baseline will be categorized as a ‘new onset’ of this finding.

For subjects with notable findings, the individual time courses of RR, PR, QRS, QT, HR, QTcF and QTcB of these subjects will be presented in figures.

7.8.5 Others

7.8.5.1 Spirometry

For HV and CF subjects descriptive statistics of spirometry endpoints (FEV₁, FVC, FEV₁/FVC (CF subjects only) and FEF₂₅₋₇₅) over time and their change from baseline will be presented for data obtained in-clinic and with the home spirometer separately (see [Section 6.7](#) for definition of baseline). Time courses of individual subject data and median of FEV₁ and

changes from baseline per dose group will additionally presented graphically separately for data obtained in-clinic and with the home spirometer.

Furthermore, the changes from pre-dose values up to two hours post-dose on Days 1, 7 and 14 will be analysed descriptively.

Clinically relevant findings in spirometry data will be reported as AEs and will be analysed as part of AE analysis.

7.8.5.2 Physical examination

Descriptive statistics of body weight obtained e.o.s and its changes from baseline (see [Section 6.7](#)) will be provided for CF subjects.

Other 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.

| | | | | |
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8. REFERENCES

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|----|--|
| 1 | <i>001-MCS-40-413</i> : "Identify and Manage Important Protocol Deviations (iPD) ", current version, BIRDS |
| 2 | <i>BI-KMED-COPS-TMP-0001</i> : "iPD log", current version; KMED |
| 3 | <i>001-MCG-156_RD-01</i> : "Handling of missing and incomplete AE dates", current version; BIRDS |
| 4 | <i>001-MCS-36-472_1</i> : "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; BIRDS |
| 5 | <i>001-MCG-156</i> : "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; BIRDS |
| 6 | <i>001-MCG-157</i> : "Display and Analysis of Laboratory Data", current version, BIRDS |
| 7 | <i>001-MCG-159</i> : "Reporting of Clinical Trials and Project Summaries", current version; BIRDS. |
| 8 | <i>BI position paper</i> : "Statistical Methods for PK", current version |
| 9 | <i>TDMAP</i> : "8-07-other-HV-analyses-logistics-plan" |
| 10 | <i>CPMP/ICH/363/96</i> : "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trials, current version |
| 11 | CASA-Q User Manual. Boehringer Ingelheim (v4.0 2015), [R18-2689] |
| 12 | CFQ-R – General Scoring Instructions, [R18-2688] |

9.1 DETAILED DESCRIPTION OF ENDPOINTS FOR ECG

RR, PR, QRS and QT baseline and on-treatment measurements (see [Table 6.7: 1+2](#)) are included in the centralised ECG evaluation. For CF subjects also recordings at screening and end of study are included in addition.

For each single ECG with centralised evaluation, measurements of QT, PR, QRS and preceding RR intervals of four cardiac cycles will be determined and stored in the database as raw data.

QTcF, HR and QTcB will be calculated based on the derivation rules as follows:

From the four cardiac cycles of a single ECG, the HR (measured in beats/min) will be calculated as

$$HR [bpm] = \frac{60\,000}{\overline{RR}}$$

where \overline{RR} is the mean of the four RR intervals (measured in msec).

Similarly, the QT interval corrected for HR according to Fridericia's formula (QTcF) for a single ECG will be derived as

$$QTcF [ms] = \sqrt[3]{\frac{1000}{\overline{RR}}} \overline{QT},$$

where \overline{QT} is the mean of the four QT intervals and \overline{RR} is the mean of the corresponding preceding RR intervals of the four cardiac cycles for this ECG.

Likewise, the HR-corrected QT interval according to Bazett's formula (QTcB) for a single ECG is given by

$$QTcB [ms] = \sqrt{\frac{1000}{\overline{RR}}} \overline{QT}.$$

The PR and QRS values for a single ECG are derived as the means of the PR and QRS values, respectively, of the four cardiac cycles for this ECG.

In case of triple ECGs at a time point, the respective ECG variable will be averaged over the triple ECG measurements at this time point (arithmetic mean). Note that in case of missing values the averaging is simply done for the available values.

10. HISTORY TABLE

Table 10: 1 History table

| Version | Date (DD-MMM-YY) | Author | Sections changed | Brief description of change |
|-----------------------------|---------------------|--------|---------------------|--|
| Initial Version (1.0) | 09-Jan-17 | | None | This is the initial TSAP |
| Final 2.0 | 04-Jul-17 | | All | This is the final TSAP (for HV analyses) |
| Revised 3.0 | 18-Sep-18 | | All | This is the final revised TSAP (for HV analyses and CF subject analyses) |