TRIAL STATISTICAL ANALYSIS PLAN

c21926247-02

BI Trial No.:	1305-0012
Title:	Safety, tolerability, and pharmacokinetics of multiple rising oral doses of BI 1015550 in patients with idiopathic pulmonary fibrosis (IPF) on no background anti-fibrotic therapy Including protocol amendments 1, 2, 3, and 4 [c17703547-05]
Investigational Product(s):	BI 1015550
Responsible trial statistician(s):	Phone: Fax:
Date of statistical analysis plan:	05 SEP 2019 SIGNED
Version:	"Final"

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
ANCOVA	Analysis of covariance
$AUC_{\tau,1}$	Area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
BMI	Body Mass Index
BMS	Biomarker set
BRPM	Blinded Report Planning Meeting
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state over a uniform dosing interval τ
CARE	Clinical data analysis and reporting environment
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DLCO	Diffusion capacity of the lung for carbon monoxide
ES	Entered set
FAS	Full Analysis Set
FEV1	Forced expiratory volume in one second
FVC	Forced Vital Capacity
Hb	haemoglobin
ICH	International Conference On Harmonisation
IPF	Idiopathic Pulmonary Fibrosis
IPD	Important Protocol Deviation
MedDRA	Medical Dictionary For Regulatory Activities
MQRM	Medical Quality Review Meeting
NOA	Not analysed
NOR	No valid result
NOS	No sample available
PK	Pharmacokinetics

Term	Definition / description
RAGe	Report appendix generator
SAE	Serious adverse event
SD	Standard Deviation
SOC	Standard of care
TEAE	Treatment Emergent Adverse Event
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal range

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

This TSAP assumes familiarity with the CTP and its 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 RAVE EDC system.

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).

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

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The initial core TSAP is based on the final CTP whereas the final core TSAP is based on the revised CTP. Compared to the initial TSAP, the analyses are described in more detail in the final TSAP. Further, the analyses are adapted to be consistent with the revised CTP and the current BI analysis standards (e.g., analysis of central ECG data is adapted).

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

The third stopping criteria of the trial (refer to CTP Section 3.3.4.2) was met after 15 patients were treated in the 18 mg BI 1015550 dose group. The predicted gMean for free $AUC_{0\text{-}24,ss}$ was above the threshold. Therefore, the dose was not escalated to the 24 mg and the trial was stopped.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoint is the number (%) of patients with drug-related AEs on-treatment, as defined in Section 5.2.1 of the CTP.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

Not applicable.

5.2.2 Secondary endpoints

Secondary PK endpoints are defined as in Section 5.5.1 of the CTP.

Secondary endpoints of this trial are $AUC_{\tau,1}$ and C_{max} of BI 1015550 in plasma after the first dose on Day 1 and $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 1015550 in plasma after the last dose on Day 14.

5.3.3 Further safety criteria

Further safety criteria will be used as defined in Section 5.2.1 of the CTP:

CTP:

- *TEAEs (including clinically relevant findings from the physical examination)*
- *Safety laboratory tests (including testing for fecal occult blood and fecal calprotectin and urinanalysis for hematuria)*
- *12-lead ECG*
- *Vital signs (blood pressure, pulse rate, respiratory rate, oral body temperature and body weight)*
- *Suicidality monitoring*

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 QTcF, QT, HR, PR, QRS, RR and QTcB derived as described in Additional Section 9.1:

- absolute values (per time point)
- changes from baseline (per time point)

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 patient to one of the above categories, all time points on-treatment (refer to Table 6.7: 1) will be considered. If baseline is missing, but the maximum absolute QTcF 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 QTcF interval is normal, then it is categorized as "No new onset".
- Maximum change from baseline in QT interval ≤ 60 msec, or > 60 msec on treatment
- Maximum change from baseline in QTcF interval ≤ 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 ≥ 25%, when corresponding on-treatment value of HR is > 100 beats/min, or decrease in HR by ≥ 25%, when corresponding on-treatment value of HR is < 50 beats/min, at any time on treatment
- Increase in PR from baseline by ≥ 25%, when corresponding on-treatment value of PR is > 200 msec
- Increase in QRS from baseline by ≥ 10%, when corresponding on-treatment value of QRS complex is > 110 msec

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered, assignments of dose groups, and selection of doses, cf. Section 4 of the CTP.

Patients with IPF will be assigned to two sequential dose groups: DG 1A with 18 mg of BI 1015550 and DG 1B with 12 mg or 24 mg of BI 1015550. Each dose group is planned to comprise 9 patients (6 on active drug and 3 on placebo). An additional 6 patients (4 on active, 2 on placebo) will be entered in dose group 1A.

The trial was stopped after 15 patients were treated in DG 1A (18 mg dose group). The following descriptions in this core TSAP are based on this decision.

Patients were planned to be treated for 14 days as follows:

- multiple doses of 18 mg of BI 1015550 (test treatment)
  or
- multiple doses of placebo (reference treatment).

In case of no safety concerns, the treatment duration will be extended to 4 weeks for patients who are included in the trial based on CTP Amendment 3. Patients who enter the trial before approval of this Amendment (Global amendment 3) are allowed to be treated up to 12 weeks.

For statistical analysis of AEs, safety laboratory data, vital signs and ECG, the following analysis phases are defined for each patient:

Table 6.1: 1 Flow chart of analysis phases for statistical analyses of AEs, safety laboratory data, vital signs and ECG

Study analysis phase	Label	Start (inclusive)	End (exclusive)
Screening	**Screening**	Date of informed consent	Date/time of first administration of study drug
On-treatment	**Pbo**, **18 mg BI**, respectively	Date/time of first administration of study drug	12:00 a.m. on the day after last administration of study drug + REP (7 * 24 h) or 12:00 a.m. on day after patient's trial termination date, whichever occurs earlier
Follow-up[1]	**F/U Pbo**, **F/U 18 mg BI**, respectively	12:00 a.m. on the day after last administration of study drug + REP (7 * 24 h)	12:00 a.m. on day after patient's trial termination date

[1] Follow-up phases might not exist, e.g. if the patient's trial termination date is within 7 days after last administration of BI 1015550.

CTR Section 15, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE displays will present results for the on-treatment phase only.

In CTR Section 15 AE tables (but not in Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 AE tables), the following totals will be provided in addition:

- "**Total on-trt**", defined as the total over all on-treatment phases, including placebo

CTR Appendix 16.1.13.1.8.1 displays will present results for the screening, on-treatment phases and follow-up phases.

Additionally to the totals defined above, the following total will be provided in CTR Section 16.1.13.1.8.1 AE tables:

- "**Total**", defined as the total over all study phases (screening + on-treatment + follow-up)

More details on the technical implementation of these analyses are provided in the ADS Plan of this TSAP.

6.2 IMPORTANT PROTOCOL DEVIATIONS

Consistency check listings (for identification of violations 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 MQRMs, at the Trial Oversight Meeting prior to DBL or at the BRPM. At these meetings, it will be decided whether a discrepant data value can be used in analyses or whether it must be corrected in the clinical database. Each protocol deviation must be assessed to determine whether it is an important protocol deviation (IPD). For definition of IPDs, and for the process of identification of these, refer to the BI SOP "Integrated Quality and Risk Management Process" (2).

If any IPDs are identified, they are to be summarised into categories and will be captured in the MQRM minutes or the TOM minutes and additionally via an accompanying Excel spreadsheet. The following table contains the categories which are considered to be IPDs in this trial. If the data show other IPDs, this table will be supplemented accordingly by the time of the MQRMs/BRPM.

Not all IPDs will per default lead to exclusion from analysis sets. IPDs leading to exclusion from analysis sets are indicated as such in the table below.

IPDs will be summarised and listed.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Example/Comments	Excluded from	
A		**Entrance criteria not met**			
	A1.3	"A clinical diagnosis based on ATS/ERS/JRS/ALAT 2011 guideline (P11-07084) within the previous 5 years" not confirmed	Inclusion criterion 3	To be decided at MQRM/BRPM.	#
	A2	Exclusion criteria met	Exclusion criteria not met as specified in the protocol	To be decided at MQRM/BRPM	
B		**Informed consent**			
	B1	Informed consent not available	Informed consent date missing	All	
	B2	Informed consent too late	Informed consent date <*actual consent date*> was after Visit 1 date <*actual Visit 1 date*>.	To be decided at MQRM/BRPM.	
C		**Trial medication and randomisation**			
	C1	Incorrect trial medication taken	Medication kit assigned not matching treatment patient was randomized to and/or not matching IVRS assignment	None	
	C2	Randomisation order not followed	Patient received trial medication from medication kit assigned to another patient	None	
	C3.1	Wrong dosage schedule	Tablets (BI 1015550 or matching placebo) taken once daily instead of bid and/or incorrect daily dose taken (more or less than required number of tablets (based on dose level assigned))	None	
	C3.2	Non-compliance	Compliance <80% or >120% from Day 1 until Day 14	To be decided at MQRM/BRPM.	
	C4	Medication code broken inappropriately	Medication code broken inappropriately - reason for medication code break	To be decided at MQRM/BRPM.	
	C5	Incorrect intake of trial medication	Refer to CTP, Section 4.1.4.3.	To be decided at MQRM/BRPM.	#
D		**Concomitant medication**			
	D2	Prohibited medication use	See the list of restricted medication in CTP, Table 4.2.2.1: 1 and Table 4.2.2.1: 2.	To be decided at MQRM/BRPM.	#
E		**Missing data**			
	E1	Certain violations of procedures used to measure primary or secondary data	E.g., violation of the sampling procedures for PK blood described in CTP, Section 5.5.2.1	To be decided at MQRM/BRPM.	
	E2	Certain violations of procedures used to measure PD data	E.g., violation of the sampling procedures for PD data (target engagement biomarkers) as described in CTP, Section 5.6.1	To be decided at MQRM/BRPM.	#
F		**Incorrect timing**			
	F1	Certain violations of time schedule used to measure primary or secondary data	Incorrect timing for PK sampling	To be decided at MQRM/BRPM	#
G		Other trial specific important violations			
	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 MQRM/BRPM minutes.	None	#

Protocol deviation will be detected manually (all other protocol deviations will be programmed).

6.3 PATIENT SETS ANALYSED

The following patient sets will be defined for statistical analysis:

- Entered set (ES):
  This patient set includes all patients who signed informed consent.
  It will be used for analyses of protocol deviations.

- Randomised set (RS):
  This patient set includes all entered and randomised patients. It will be used for analyses of patient disposition.

- Treated set (TS):
  This patient set includes all patients who received at least one dose of study drug. It will be used for analysis of safety, demographic data and baseline characteristics as well as the analysis of ECG.

- Pharmacokinetic parameter set (PKS):
  This patient set includes all patients in the TS who provide at least one PK parameter that was not excluded because of protocol deviations relevant to the statistical evaluation of PK endpoints as defined in Section 7.3 of the CTP.

The discussion of all exceptional cases and problems and the decisions on the allocation of patients to analysis sets will be made at latest at the MQRMs/BRPMs.

Table 6.3: 1 Patient sets analysed

	Patient set				
Class of endpoint	ES	RS	TS	PKS	
Disposition	X				
Exposure			X		
IPDs	X				
Demographic/baseline endpoints			X		
Primary endpoint			X		
Other safety parameters			X		
ECG endpoints			X		
Secondary PK endpoints				X	

6.5 POOLING OF CENTRES

It was planned that 24 patients (9 plus 6 additional patients in dose group 1A and 9 patients in DG 1B) in up to 20 centres across 9 countries in Europe will be entered in this trial, i.e., a small number of patients entered per centre can be expected. The third stopping criteria of the trial (refer to CTP Section 3.3.4.2) was met after 15 patients were treated in the 18 mg BI 1015550 dose group. Given the low number of patients per centre and the primarily descriptive nature of statistical analysis, separate analyses by centre are not meaningful and not desirable. All patients from all centres will be pooled for statistical analysis.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Withdrawals

CTP: *If a patient is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the clinical trial report (CTR). At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. These discontinuations will be discussed in the CTR.*

6.6.3 Safety data

CTP: *With respect to safety evaluations, it is not planned to impute missing values.*

One exception where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (see (3)).

No imputation will be done for ECG endpoints. If replicate ECG recordings are missing, the arithmetic means per time point will be computed with the reduced (1 or 2) number of recordings. If single cardiac cycles (also denoted as beats or waveforms) are missing, the arithmetic mean per single ECG will be computed with the reduced (1, 2 or 3) number of cardiac cycles.

6.6.4 PK data

For patients on active drug, missing plasma concentration values with 'BLQ' in the comment field will be handled according to BI standards [001-MCS-36-472_RD-01] (4).

Missing data and outliers of PK data are handled according to BI standards (see 001-MCS-36-472_RD-01). **CTP**: *Drug concentration data identified with no sample available (NOS), no valid result (NOR), not analysed (NOA), or below the lower limit of quantification (BLQ) will be displayed as such and not replaced by zero at any time point (this rule also applies to the lag phase, including the pre-dose values).*

CTP: *For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ will be set to zero. All other BLQ 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

There will be a centralised evaluation of all 12-lead ECG recordings at the time points specified in the table below.

Table 6.7: 1 Time schedule of 12-lead ECG recordings with centralised evaluation

Visit	Day	Planned time [hh:mm] (relative to respective drug administration)	Study phase
3	1	-02:00	Baseline
		01:00	On-treatment
		02:00	
		04:00	
		06:00	
		08:00	
		12:00	
	2	23:30	
8	14	311:30	
		313:00	
		314:00	
		316:00	
		318:00	
		320:00	
		324:00	

Triple ECGs (3 single ECGs recorded within 180 sec) will be recorded on all post-baseline time points with centralised ECG evaluation (as listed in the table above). At baseline three triplicates will be performed, i.e. 9 ECGs will be recorded at site, but of these three triplicates only the first will be evaluated centrally. For all on-treatment assessments, only the first of the three replicate ECG at a single assessment time will be evaluated.

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

In all other analyses (except for analyses of ECG variables), the last non-missing value determined prior to the first dosing of BI 1015550 will be defined as baseline.

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

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (5).

The individual values of all patients will be listed. Listings will generally be sorted by dose group, patient 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.

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
P10	10^{th} percentile
Q1	1^{st} quartile
Q3	3^{rd} quartile
P90	90^{th} percentile

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. Percentages will be rounded to one decimal place. The category missing will be displayed if and only if there actually are missing values. Percentages will be based on all patients in the respective patient 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 CTR.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded according to the most recent version of MedDRA. Concomitant medication will be coded according to the most recent version of the World Health Organisation – Drug Dictionary.

Only descriptive statistics 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 first administration of the respective treatment or
- starts within the analysis phase of the respective treatment (see Section 6.1 for a definition of treatments and analysis phases).

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of 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 patients with drug related AEs, which is the primary endpoint of this trial.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

Not applicable.

7.5.2 Secondary endpoints

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

Attainment of steady state for BI 1015550 and for BI 764333 will be explored using a nonlinear mixed effects model as described in Section 7.3.2 of the CTP.

Graphs will be prepared, showing individual time-courses, the nonlinear fitted curve and the (geometric) mean over time

Exclusion of PK parameters

The ADS ADPP contains column variables APEXC and APEXCO indicating inclusion/exclusion (APEXC) of a PK parameter and an analysis flag comment (APEXCO). All analyses based on the PKS are based on PK parameter values which are not flagged for exclusion, i.e. with APEXC equal to "Included".

Exclusion of plasma concentrations

The ADS ADPC (PK concentrations per time-point or per time-interval) contains column variables ACEXC or ACEXCO indicating inclusion/exclusion (ACEXC) of a concentration

and an analysis flag comment (ACEXCO). Exclusion of a concentration depends on the analysis flag comment ACEXCO. For example, if ACEXCO is set to "ALL CALC", the value will be excluded for all types of analyses based on concentrations. If ACEXCO is set to "DESC STATS" the value will be excluded from descriptive evaluations per planned time point/time interval. If ACEXCO contains the addition "TIME VIOLATION" or "TIME DEVIATION", the value can be used for further analyses based on actual times. If ACEXCO is set to "HALF LIFE", the value will be excluded from half-life calculation only; the value is included for all other analyses.

Further details are given in "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies" (4) and "Description of Analytical Transfer Files and PK/PD Data Files" (6).

7.6.2 Safety parameters

Safety and tolerability will be analysed as described in Section 7.8 of this TSAP.

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analysis will be based on the TS.

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 patients with AEs and not on the number of AEs.

For analysis, multiple AE occurrence data on the 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, 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 "Analysis and Presentation of Adverse Event Data from Clinical Trials" (7) and "Handling of missing and incomplete AE dates" (3).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs will be assigned to the screening, on-treatment 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 (8) and for the class of AESIs.

CTP: *The following are considered as AESIs:*

- *Hepatic injury:*
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - *an elevation of AST and/or ALT ≥3fold ULN combined with an elevation of total bilirubin ≥2fold ULN measured in the same blood sample, and/or*
  - *aminotransferase (ALT, and/or AST) elevations ≥10fold ULN.*

The investigator had to classify on the eCRF whether an observed AE was an AESI or not.

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

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

In addition, AEs related to “Diarrhoea and GI hypermotility” will be summarised in a separate table. The AEs will be identified with the following preferred terms: Diarrhoea”, “Frequent bowel movements” and “Faeces soft”.

The system organ classes and preferred terms within system organ classes will be sorted by descending frequency overall treatment groups.

For disclosure of AE data on ClinicalTrials.gov, the frequency of patients 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 patients with SAEs will also be summarised.

For disclosure of AE data in the 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 summarized.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Handling, Display and Analysis of Laboratory Data" (9).

The analysis will be based on normalised values, which means transforming to a standard unit and a standard reference range.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be provided.

Laboratory values will be compared to their reference ranges; a shift table will be provided for the number of patients within and outside the reference range at baseline and at the last measurement on treatment. This analysis will be based on standardized laboratory values and reference ranges as provided by the local laboratory of each site.

Potentially clinically significant abnormalities will be identified based on BI standard rules which are based on normalized converted lab values, i.e. using SI units. These rules will be listed in the SDL appendix of the CTR. Frequency tables will summarize the number of patients with potentially clinically significant abnormalities. Patients having an abnormal lab value at baseline will be presented separately.

All individual laboratory data will be listed. Values outside the reference range will be flagged. In addition, potentially clinically significant values will be flagged in the listing.

Clinically relevant findings in laboratory data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.3 Vital signs

The analyses of vital signs (blood pressure, pulse rate, respiratory rate, oral body temperature and body weight) will be descriptive in nature. Descriptive statistics of vital signs over time and for the difference from baseline (see Section 6.7) will be provided.

Clinically relevant findings in vital signs data will be reported as baseline conditions (at screening) or as AEs (during the trial) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.4 ECG

12-lead ECG

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

All evaluation of ECG data 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 (as defined in Section 5.3.3) will be flagged.

For QTcB and RR, only listings will be provided.

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

Comments regarding the ECGs will be listed.

Categorical Endpoints

For the categorical endpoints, frequency tables will be provided.

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

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 group for QTcF, HR; PR and QRS. No plots are planned for QT.

7.8.5 Others

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.

Data of suicidal risk assessments will only be listed.

8. REFERENCES

1 *CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trials, current version

2 *001-MCS-40-135: "Integrated Quality and Risk Management Process", current version; IDEA for CON*

3 *KM Asset BI-KMED-BDS-HTG-0035*: "Handling of missing and incomplete AE dates", current version; KMED

4 *001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON

5 *KM Asset: BI-KMED-BDS-HTG-0045:* "Reporting of Clinical Trials and Project Summaries", current version; KMED

6 *001-MCS-36-472_RD-03*: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON

7 *KM Asset BI-KMED-BDS-HTG-0041*: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; KMED

8 *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

9 *KMAsset BI-KMED-BDS-HTG-0042*: "Handling, Display and Analysis of Laboratory Data", current version; KMED

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**26-FEB-18**		None	This is the initial TSAP with necessary information for trial conduct
Final	**05-SEP-2019**		-	This is the final TSAP The analysis was adapted to the current CTP version.