TRIAL STATISTICAL ANALYSIS PLAN

c40185913-01

BI Trial No.:	1405-0008
Title:	Safety, tolerability, pharmacokinetics, and pharmacodynamics of different oral doses of BI 1323495 bid versus placebo in patients with non-cystic fibrosis bronchiectasis (randomised, double-blind, placebo-controlled, parallel group trial) Revised protocol #02
Investigational Product(s):	BI 1323495
Responsible trial statistician(s):	[redacted] Phone. [redacted] Email:
Date of statistical analysis plan:	15 SEP 2022 SIGNED
Version:	Final

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1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Abbreviations not in Medicine Glossary are described below.

Term	Definition / description
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
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
BID	Bis in die (twice daily)
BM	Biomarker
BMI	Body Mass Index
CASA-Q	Cough And Sputum Assessment Questionnaire
Cfu	Colony forming units
CI	Confidence Interval
C_{max}	Maximum measured concentration of the analyte in plasma
CQM	Clinical Quality Monitoring
CV	Arithmetic Coefficient of Variation
DBLM	Database Lock Meeting
DILI	Drug induced liver injury
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
gCV	Geometric Coefficient of Variation
gMean	Geometric Mean
LLT	Lower Level Term
Max	Maximum
Min	Minimum
N	Number non-missing observations
NE	Neutrophil elastase
P10	10^{th} percentile
P90	90^{th} percentile

Term	Definition / description
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	PK parameter analysis set
PRO	Patient Reported Outcome
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
QOL-B	Quality of Life Questionnaire-Bronchiectasis
RAGe	Report Appendix Generator system
REP	Residual Effect Period
RPM	Report Planning Meeting
SD	Standard Deviation
SGRQ	St. George's Respiratory Questionnaire
SOC	System Organ Class
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TMF	Trial Master File
TS	Treated Set
ULN	Upper Limit of Normal
WHO-DD	World Health Organization Drug Dictionary

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, randomization.

Study data will be stored in a trial database within Medidata Rave system.

The statistical analyses will be performed within the validated working environment CARE, including SAS® (current Version 9.4, by [redacted]), 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

[redacted] Due to a limited number of patients randomized in Part A, the planned analyses described in the CTP will be limited in descriptive analyses only.

[redacted]

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoint to assess safety and tolerability of BI 1323495 is the occurrence of drug-related adverse events after 12 weeks of treatment. The timeframe for the primary endpoint is from the first drug administration until end of the REP after the last drug administration.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

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

5.2.2 Secondary endpoints

Pharmacodynamic biomarkers of target engagement:

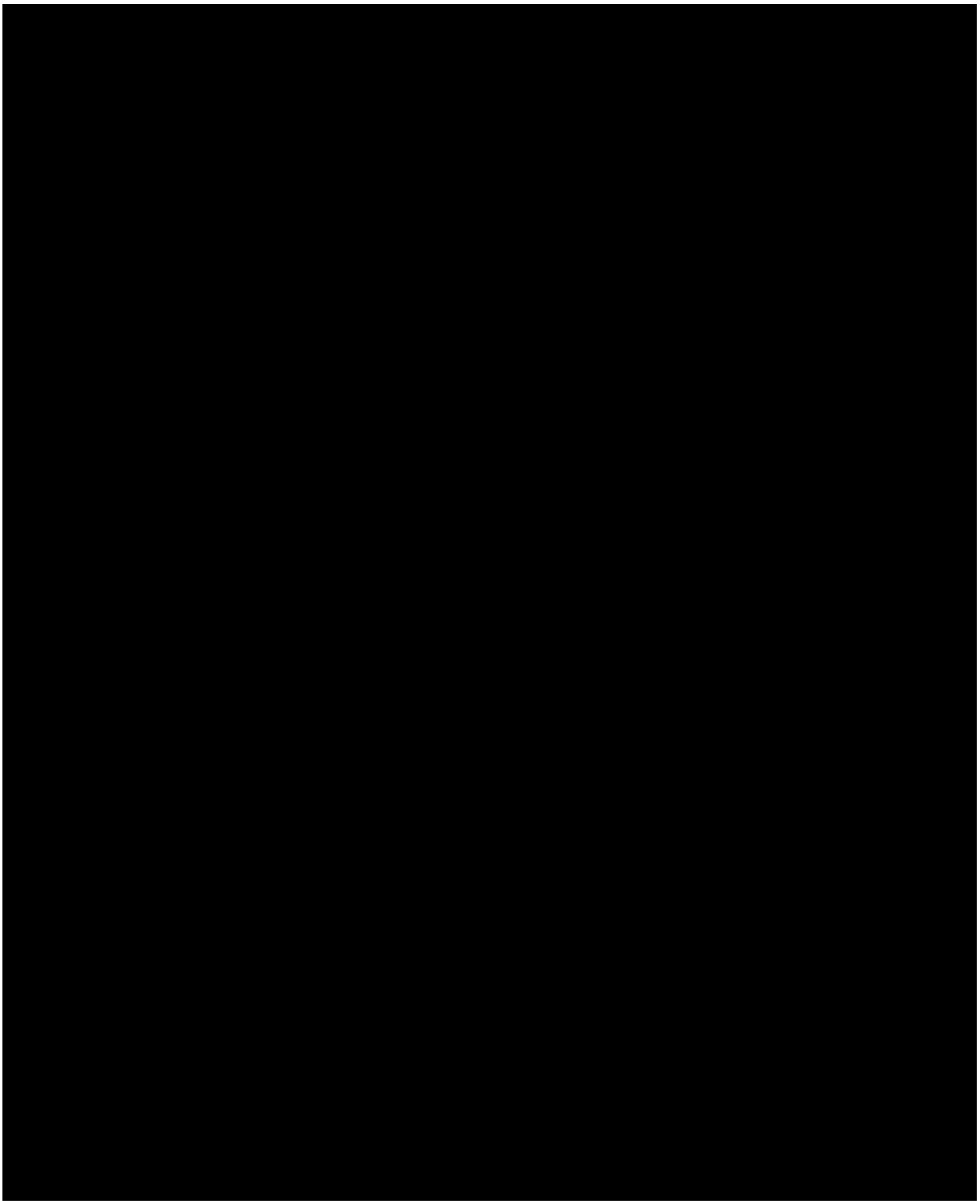
- Change from baseline to week 12 in absolute activity of neutrophil elastase (NE) [RFU] in sputum
- Change from baseline to week 12 in NE activity in whole blood after stimulation with zymosan, normalized to neutrophil counts [redacted]

Pharmacodynamic biomarkers of physiological response:

- Change from baseline to week 12 in absolute number of neutrophils [counts] in sputum For details regarding the derivation see Section 5.3.2.

Early signs of clinical efficacy:

- Change from baseline to week 12 in absolute post-bronchodilator forced expiratory volume in one second, FEV_1 [mL]



6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

For basic study information on treatments to be administered in each trial part, assignment of treatment groups, and selection of doses, cf. Section 4 of the CTP.

Placebo patients will be analysed according to their respective study part, i.e. posology. If deemed appropriate the assessment of a pooled placebo group will be added.

Analysis phases for statistical analysis of AEs, safety laboratory data, vital signs and biomarkers are defined for each patient as described in Table 6.1: 1.

Table 6.1: 1 Analysis phases for statistical analysis of AEs, and actual treatment for analysis of laboratory data and vital signs

Study analysis phase	Label	Start (included)	End (excluded)
Screening	**Screening**	Date of informed consent at 12 a.m.	Date/time of first administration of study drug
On-treatment	**Placebo bid** **Placebo qd** **BI 30mg bid** **BI 150mg qd** respectively	Date/time of first administration of study drug	12:00 a.m. on day after last administration of study drug + REP (7 days) or 12:00 a.m. on day after last contact date (whichever occurs first)
Follow-up[1]	**Follow-up**	12:00 a.m. on day after last administration of study drug + REP (7 days)	12:00 a.m. on day after last contact date

[1] This phase exists only in those patients who have last contact 7 or more days after last trial drug administration.

AE displays in CTR Section 15.3, Appendix 16.1.13.1.8.2 and Appendix 16.1.13.1.8.3 will present results for the on-treatment phase only.

Safety laboratory data, vital signs and clinical assessment data will be analysed based on dose groups (not on analysis phases defined above), with clear differentiation between baseline (refer to Section 6.7) and on-treatment measurements. Measurements will be considered on-treatment, if they were taken within the on-treatment phases as defined in Table 6.1: 1.

6.2 IMPORTANT PROTOCOL DEVIATIONS

A protocol deviation (PD) is considered “important” if it can be expected that the deviation had a distorting influence on the biomarker or clinical assessments or could affect the rights or safety of the study patients. Potentially important protocol deviations will be handled according to Boehringer Ingelheim (BI) SOP "Identify and Manage Important Protocol Deviations (iPD)" (2).

A list of potentially iPDs as well as the handling of iPDs in analysis is included in the DV domain specifications and stored within the TMF in EDMS. Note, that this is a working list and may not be finalised until database lock. During the study conduct, protocol deviations will be monitored and identified iPDs will be summarised into categories and captured in the DV domain specification. Guidance for improving / teaching the respective sites with iPD occurrences should be discussed during the study Clinical Quality Monitoring (CQM) meetings.

iPDs will be summarized and listed. Non-important Covid-19 related PDs will only be listed.

6.3 SUBJECT SETS ANALYSED

The subject sets as defined in detail in the CTP, Section 7.2 will be used. These include the Screened set (SCS), Randomized Set (RS), Treated set (TS), [redacted]

Table 6.3: 1 shows which analysis set is used for each class of assessment.

Table 6.3: 1 Subject sets for planned analyses

	Subject set			
Class of endpoint	TS	PKS	RS	SCS
Primary endpoint	X			
Secondary endpoints				
biomarker endpoints	X			
clinical assessment	X			
[redacted]	[redacted]			
[redacted]	[redacted]			
Safety parameters	X			
iPDs	X			
Compliance/exposure	X			
Demographic/baseline characteristics	X			
[redacted]		[redacted]		
Analysis sets			X	
Disposition				X

The decision on exclusion of patients from respective analysis set will be made prior to database lock at the latest and documented in the decision log.

[redacted]

6.5 POOLING OF CENTRES

No pooling of centres will be performed.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

6.6.1 Safety parameters

With regard to the safety analysis, no imputation of safety data is foreseen except for missing or incomplete AE dates. Missing or incomplete AE dates are imputed according to BI standards (5).

6.6.2 Pharmacodynamic biomarkers

No imputation will be applied to pharmacodynamic biomarkers for missing data.

Values of biomarkers will be excluded from analysis according to the following rules:

- For NE activity data from sputum samples generated from sputum processing starting ≥ 1.15 hours after completion of sputum collection
- All BM data (refer to Section 5.2.2 [redacted]) collected from the first use of restricted medications (such cases will be identified during the CQM meetings and documented as iPDs on the DV domain specifications)

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

6.6.3 Spirometry

No imputation method will be implemented for missing data.

Values of spirometry test will be excluded from analysis according to the following rules:

- All spirometry data (refer to Section 5.2.2 [redacted]) collected from the first use of restricted medications (such cases will be identified during the CQM meetings and documented as iPDs on the DV domain specifications)

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For all parameters, except for biomarkers, baseline is defined as the last non-missing value prior to first administration of the trial treatment. In case of planned multiple measurements of biomarkers within the run-in period prior to first drug administration (e.g. at Visit 2a, 2b or 3), the following will apply:

Measurements taken after first administration of trial treatment will be considered either on- or off-treatment values based on the definition in Table 6.1: 1, and will be assigned to visits for statistical analysis, if applicable, as defined below.

Analysis of AE data (including findings in 12-lead ECG assessments or physical examinations), potentially clinically significant abnormal laboratory values, concomitant medication or non-drug therapies will not be based on visits. Frequency tables for AE data will be using on-treatment data and categorized based on their occurring/starting dates. Therefore, no assignment to time windows will be necessary for such data.

Analysis day is calculated as follows:

> If assessment date and time is prior to the date and time of first study drug intake: Date of assessment – date of first study drug intake
>
> If assessment date and time is greater or equal to the date and time of first study drug intake: Date of assessment – date of first study drug intake +1 day

Analysis visit windows for other assessments during the study are given in the following tables. The date of the first drug intake will be used as study day 1 for the time windowing (including planned first drug administration visit V3 and repeated V3). If more than one value is available within one time window the one which is closest to the planned time/day is used for analysis. In case two values are equidistant from the planned time/day, then the last one will be picked.

Table 6.7: 2 Time windows for assignment of safety assessment – laboratory

Visit number (CTP)	Visit label (analysis)	Planned Day	Time window [days]		
			Window per CTP	Start (analysis)	End (analysis)
V1	**Screening**	-27	± 14	All pre-baseline measurements	
V3	**Baseline**	1	± 0	NA	Date/time of first administration of study drug
V5	**Week 2**	15	± 3	Start of on-treatment phase as defined in table 6.1.1	22
V6	**Week 4**	29	± 3	23	36
V7	**Week 6**	43	± 3	37	50
V8	**Week 8**	57	± 3	51	70
V10	**Week 12/EoT**	84	+3	71	End of on-treatment phase as defined in table 6.1.1
V11	**Follow-up**	98	± 4	All post-treatment measurements	

Table 6.7: 3 Time windows for assignment of lung function assessment (spirometry)

Visit number (CTP)	Visit label (analysis)	Planned Day	Time window [days]		
			Window per CTP	Start (analysis)	End (analysis)
V1	**Screening**	-27	± 14	All pre-baseline measurements	
V2b	**Baseline**	-2	+ 1	NA	Date/time of first administration of study drug
V5	**Week 2**	15	± 3	Start of on-treatment phase	35
V8	**Week 8**	57	± 3	36	70
V10	**Week 12/EoT**	84	+3	71	End of on-treatment phase
V11	**Follow-up**	98	± 4	All post-treatment measurements	

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI standards (6). The individual values of all patients will be listed. Listings will be sorted by treatment group, patient number and visit (if visit is applicable in the respective listing). The listings will be contained in Appendix 16.2 (SDL) of the CTR. If not stated otherwise, patients will be grouped by actual treatment received.

The following standard descriptive statistical parameters will be displayed in summary tables of continuous variables that are non-PK parameters:

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

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category, as well as the percentage (%) for each treatment group. Percentages will be rounded to one decimal place and will be based on all patients 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.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

The data will be summarized by treatment group and in total.

Demographics:

Sex, ethnicity, race, age [years], age (categories), height [cm], weight [kg] and BMI [kg/m^2], history of substance use (tobacco, nicotine, vaping products, alcohol, cannabis), UGT2B17 genotype.

BMI will be calculated as weight [kg] / $(0.01 * \text{height [cm]})^2$.

Baseline characteristics:

Pharmacogenetic results of UGT2B17 genotype will be reported as: *1/*1 or *1/*2.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive analysis by treatment group is planned for this section of the CTR.

Baseline conditions / concomitant diagnoses will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT).

Concomitant medication taken at baseline or during the treatment period will be summarized by World Health Organization-Drug Dictionary (WHO-DD) ATC3 class and PT. Previous concomitant medication, i.e. those taken and stopped prior to entering the treatment period, will be listed only.

All data will be coded using the most recent versions of WHO-DD and MedDRA dictionaries.

The relevance of the concomitant therapies to the evaluation of PD and PK will be decided no later than at the RPM.

7.3 TREATMENT COMPLIANCE

Treatment compliance will be listed and descriptive statistics for each assessment day will be displayed by treatment group. Deviations from planned intake will be addressed in the RPM (refer to Section 6.2) and relevant deviations will be described in the CTR.

Treatment compliance (yes/no) will be based on the adherence to the expected range of 80-120% for number of tablets actually taken vs. number of tablets which should have been taken as directed by the investigator, see CTP Section 4.3.

7.4 PRIMARY ENDPOINT

7.4.1 Primary analysis of the primary endpoint

The primary endpoint (cf. Section 5.1) will be derived according to BI standards (7) and (8). The proportion of patients with at least one treatment emergent drug-related AE per treatment group will be calculated. The analysis will be based on the TS and will be descriptive in nature.

7.5 SECONDARY ENDPOINTS

7.5.1 Secondary endpoints

The primary analysis of the secondary endpoints listed in Section 5.2.2. will be descriptive in nature and will be based on the TS.

For biomarkers determined on sputum the mean of all available valid samples which are within the analysis time window, will be used as Week 12/EoT value in the analyses. Actual observed values at these visits will only be listed.

Descriptive statistics of absolute values as well as changes from baseline (refer to Section 6.7) and percent changes from baseline (if applicable) will be presented by planned time point for the secondary endpoints.

For NE activity in zymosan stimulated blood, neutrophil counts measured from safety lab will be used for normalisation of NE activity when collection time points match. Otherwise, the

neutrophil count from the time point closest to sampling for NE activity assessment will be used for normalisation. The derivation detail of NE activity in whole blood is in Section 9.1

The assessment of NE activity in sputum and blood will further comprise the analysis of the % inhibition of NE activity. For each time point including baseline, % inhibition will be calculated as:

$$NE\ \%inhibition_t = \frac{NE\ activity_{baseline} - NE\ activity_t}{NE\ activity_{baseline}} \times 100$$

Descriptive statistics of maximum NE % inhibition (on patient level) will be presented by dose group. Individual line plots over time by dose group will be presented.

[redacted]

Individual NE activity data will be listed including % inhibition in sputum, % inhibition in blood, neutrophil count normalised and UGT2B17 genotype.

[redacted]

[redacted]

7.7 EXTENT OF EXPOSURE

Not all drug administrations are captured in the data base. Thus, no analysis of comprehensive exposure data is planned for the CTR. The date and time of drug administration captured in the eCRF will be listed for each patient.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

The safety data for treated patients 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.

Unless otherwise specified, 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 further details on summarization of AE data, please refer to "Analysis and presentation of adverse event data from Clinical Trials" (8) and "Handling of missing and incomplete AE dates" (7).

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

An overall summary of AEs will be presented. This overall summary will comprise summary statistics 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 (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or*
- *aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.*

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

According to ICH E3 (9), in addition to Deaths and Serious Adverse Events, 'other significant' AEs need to be listed in the CTR. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation).

The frequency of patients with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). AEs which were considered by the investigator to be drug related will be summarised separately. A listing will be provided for patients with AEs, where SAEs, drug-related AEs, AEs leading to drug withdrawal and AESIs will be presented in the listing.

The SOCs and preferred terms within SOCs will be sorted by descending frequency over all 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 SOC 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.

For support of lay summaries, the frequency of patients with drug-related SAEs will be summarized by treatment, primary SOC and preferred term.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards "Display and Analysis of Laboratory Data" (10).

Analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. The original values will be analysed if the transformation into standard unit is not possible for a parameter.

Listings of laboratory values over time and for the difference from baseline (refer to Section 6.7) will be provided. Values outside the reference range as well as possibly clinically significant values will be flagged in the listings.

Individual line plots over time by dose group will be presented.

Clinically relevant findings in laboratory data will be reported as baseline conditions (when they occurred prior to first administration of study treatment) or as AEs (when they occurred after first administration of study treatment) if judged clinically relevant by the investigator, and will be analysed as such.

7.8.3 Vital signs

Vital signs will be analysed based on treatment groups, as defined in Table 6.1: 1. Listings of each parameter over time and for the difference from baseline (refer to Section 6.7) will be provided.

7.8.4 ECG

12-lead ECG recordings will be checked by the investigator for pathological results. Clinically relevant abnormal findings for ECG will be reported either as baseline condition (when they occurred before intake of first study treatment) or will be reported as AEs (when they occurred after first administration of study treatment) and will be summarized as such.

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 first study treatment) or as AE (after first administration of study treatment) and will be summarized as such.

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-40-413:* Identify and Manage Important Protocol Deviations (iPD)", current version, Group "Clinical Operations"; IDEA for CON.
3	Jones PW. St George's Respiratory Questionnaire Manual, version 2.3 (June 2009) [R12-2870].
4	Manual Scoring Instructions for QOL-B Version 3.1 (2020), [c34996255], BIRDS
5	CASA-Q User Manual. Boehringer Ingelheim (v4.0 2015), [R18-2689]
6	*KM Asset BI-KMED-BDS-HTG-0045*: " Standards for Reporting of Clinical Trials and Project Summaries", current version, group "Clinical Trial Data Analysis"; KMED
7	*KM asset BI-KMED-BDS-HTG-0035*: "Handling of missing and incomplete AE dates", current version, group "Clinical Trial Data Analysis"; KMED
8	*KM Asset BI-KMED-BDS-HTG-0066*: " Analysis and Presentation of Adverse Event Data from Clinical Trials", current version, group "Clinical Trial Data Analysis"; KMED
9	*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
10	*KM Asset BI-KMED-BDS-HTG-0042:* "Handling, Display and Analysis of Laboratory Data", current version, group "Clinical Trial Data Analysis"; KMED
11	*KM Asset BI-KMED-TMCP-MAN-0014*: "Noncompartmental PK/PD Analyses of Clinical Studies", current version; KMED
12	*KM Asset BI-KMED-TMCP-MAN-0010*: "Description of Analytical Transfer Files, PK/PD Data files and ADA files", current version; KMED

10. HISTORY TABLE

Table 10: 1 History table

Version	Date	Author	Sections changed	Brief description of change
Final	15 SEP 2022	[redacted]	None	This is the final TSAP