TRIAL STATISTICAL ANALYSIS PLAN

c32169102-01

BI Trial No.:	1399-0003
Title:	A randomised, double-blind, placebo-controlled and parallel group trial to evaluate efficacy and safety of twice daily inhaled doses of BI 1265162 delivered by Respimat inhaler as add-on therapy to standard of care over 4 weeks in patients with cystic fibrosis – BALANCE – CF 1 Including Protocol Amendment 1 [c23936559-02]
Investigational Product(s):	BI 1265162
Responsible trial statistician(s):	 Tel.: Fax:
Date of statistical analysis plan:	18 May 2020 SIGNED
Version:	1.0

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
AESI	Adverse event of special interest
BI	Boehringer Ingelheim
BMI	Body mass index
CASA-Q	Cough and sputum assessment questionnaire
BRPM	Blinded report planning meeting
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EudraCT	European union drug regulating authorities clinical trials
FEV_1	Forced expiratory volume in 1 second
FEV_1 % predicted	FEV_1 percent predicted
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
LCI	Lung clearance index
MBW	Multiple breath washout

Term	Definition / description
MedDRA	Medical Dictionary for Regulatory Activities
NOP	No peak detectable
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	PK analysis set
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

3. INTRODUCTION

As per 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 protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data excluding interim analysis. Another TSAP document for the interim analysis is provided separately.

This 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.

SAS® Version 9.4 will be used for all analyses. PK parameters will be calculated using Phoenix WinNonlin™ software (version Phoenix 6.3 or higher, Certara USA Inc., Princeton, NK, USA).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

The testing on the hypothesis of flat dose response curve that described in CTP will not be performed

In addition, model-based analysis of primary endpoint (trough FEV1 % predicted) and secondary endpoint (LCI),

For secondary endpoint (LCI), an analysis of covariance (ANCOVA) will be used to compare the change from baseline of LCI after 4 weeks of treatment. Other endpoints including patient reported outcomes (CASA-Q and CFQ-R) will be summarized descriptively for all dose levels.

age effect (adult versus adolescent) will be removed from the statistical model.

5. ENDPOINTS(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint to assess efficacy of BI 1265162 200 µg bid over placebo is the absolute change from baseline in percent predicted trough Forced Expiratory Volume in 1 Second (FEV_1) after 4 weeks of treatment.

Trough FEV_1 is defined as measurement performed within 30 minutes prior to dosing.

Analysis is conducted using a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM). Please refer to Section 7.4.1 for details on the MMRM model.

Tables and/or spaghetti plots will display individual trough FEV_1 % predicted values over time and the change from baseline values overtime. In addition, a waterfall plot for change from baseline at Week 4 will be presented.

Baseline trough FEV_1 % predicted is defined as the last measurement taken on day 1 before first study drug administration.

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not applicable.

5.2.2 Secondary endpoint(s)

The secondary endpoints of this trial are:

- Change from baseline in Lung Clearance Index (LCI) assessed by N_2 Multiple Breath Washout (N_2MBW) procedure after 4 weeks of treatment
- Change from baseline in Cystic Fibrosis Questionnaire Revised (CFQ-R) total score after 4 weeks of treatment
- Change from baseline in Cough and Sputum Assessment Questionnaire (CASA-Q) (4 separate sub-scores) after 4 weeks of treatment
- Percentage of patients with treatment-emergent Adverse Events (AE) up to Day 36
- $C_{t,N}$ (concentration of the analyte in plasma at time t following dose N)
- $C_{pre,N}$ (predose concentration measured for dose N)

- $AUC_{0\text{-}t,N}$ (area under the concentration-time curve of the analyte in plasma until t hours after dose N)

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

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

Patient randomisation will start with only adult patients to either 200 µg bid of BI 1265162 or placebo in a 1:1 ratio. Enrolment of adolescent patients will be based on periodic reviews of adult patient safety data. The analysis plan for periodic safety reviews of adult patients will be described separately.

As soon as 28 patients are allocated to these two treatment arms, the remaining patients will be allocated to the other doses of BI 1265162 as well as the highest dose and placebo in a 1:1:1:1:1 ratio (14 patients per treatment arm). As a result, it was planned to have patients distributed in a 2:1:1:1:2 ratio (2 for either placebo or 200 µg bid of BI 1265162 and 1 for other doses of BI 1265162) with around 20% of adolescents per group.

Patients will be analysed according to Table 6.3: 1. All planned analysis will be presented by this treatment group, unless specified otherwise. Handling of patients where treatment assignment has not been followed will be handled on a case-by-case basis, to be agreed at report planning meetings or DBL meeting (but prior to database lock).

6.3 SUBJECT SETS ANALYSED

The statistical analysis will be based on the following analysis sets.

- Enrolled set (ES): This subject set includes subjects that signed informed consent and underwent screening procedures.
- Randomized set (RS): This subject set includes all randomised subjects, whether treated or not.

- Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study drug. The treatment assignment will be determined based on the first treatment the subjects received.
- N_2 multiple breath washout set (N2MBWS): The N2MBWS includes all subjects in the treated set, who provided at least one pair (baseline and end of treatment) of evaluable measures of the N2MBW parameter.
- Pharmacokinetic set (PKS): The PK parameter analysis set (PKS) includes all subjects in the Treated Set (TS) who provide at least one PK parameter that was not excluded according to the description in Section 7.3.5 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	N2MBWS
Disposition	X				
Exposure			X		
iPDs		X			
Demographic/baseline endpoints			X		
Safety endpoints			X		
Secondary PK endpoints				X	
Efficacy endpoints based on N_2MBW measurements (LCI,					X
Efficacy endpoints from pulmonary function tests			X		
CASA-Q, CFQ-R			X		

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

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)).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

For endpoints regarding pulmonary function testing (e.g. FEV_1) in-clinic, baseline is defined as the last measurement taken on day 1 before first study drug administration.

For all other endpoints, baseline is defined as the last measurement before first study drug administration. I.e., in case the pre-dose measurement on Day 1 is missing, the measurement between Day -17 and Day -11 will be used as baseline (note. Not possible for pulmonary function testing due to different bronchodilator washout requirements).

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

7. PLANNED ANALYSIS

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 subject data listings (SDL) of the CTR.

Inferential statistical analyses of PK NCA endpoints will be presented in Section 15.5 of the CTR and in Appendix 16.1.9.3.

Descriptive data analysis of PK NCA 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 scores derived from questionnaire data, the following descriptive statistics will be calculated:

N	number of non-missing observations
Mean	arithmetic mean
SD	standard deviation

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.

7.4 PRIMARY ENDPOINT(S)

The primary endpoint to assess efficacy of BI 1265162 is the change from baseline in percent predicted trough Forced Expiratory Volume in 1 Second (FEV1) after 4 weeks of treatment. Trough FEV1 is defined as measurement performed within 30 minutes prior to dosing.

7.4.1 Primary analysis of the primary endpoint(s)

To account for the repeated nature of the data and the covariates in the nature, a restricted maximum likelihood (REML) based approach using a mixed model with repeated measurements (MMRM) will be carried out comparing the change from baseline in percent predicted trough FEV1 percent predicted at 4 weeks of treatment.

The analysis will include the fixed, categorical effects of treatment at each visit and the fixed continuous effects of baseline at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements. The model will only include data from highest dose level and placebo because of limited sample size from other dose levels.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors.

The MMRM analysis will be carried out in SAS and covariate-adjusted fixed effect estimates of average response for each dose group and the covariance matrix will be extracted from the fit.

The following SAS® code for MMRM will be used:

```
PROC MIXED DATA=alldata cl method=reml ocovtest;
      CLASS usubjid trtpso avisitn;
      MODEL ept = trtpso*avistin base*avisitn /ddfm=kr solution;
      REPEATED avisitn /subject=usubjid type UN r rcorr;
      LSMEANS trtpso*avistin / pdiff=all om cl alpha=0.05;
RUN;
```

If the model failed to converge, the following covariance structures will be tested in order: UN → AR(1).

For subgroup analysis, same MMRM model will be carried out within each subgroup.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

Not applicable.

7.5.2 Secondary endpoint(s)

7.5.2.1 Analysis of LCI

An analysis of covariance (ANCOVA) will be used to compare the change from baseline of LCI after 4 weeks of treatment with adjustment for categorical effects of treatment and the fixed continuous effect of baseline. The model will include data from highest dose level and placebo. Descriptive analysis will be performed for other dose levels.

Tables and/or spaghetti plots will display individual LCI values over time. In addition, a waterfall plot for change from baseline at Week 4 will be presented.

7.5.2.2 Safety endpoints

For analysis for AE, refer Section 7.8.1.

7.5.2.3 Pharmacokinetic endpoints

The PK analysis of secondary endpoints will be based on the PKS. For each of dose proportionality of secondary endpoints ($C_{max,N}$, $C_{pre,N}$ and $AUC_{0-t,N}$), displaying geometric means of pairwise ratios together with 95% confidence intervals will be provided by dose group. Additional PK, PKPD modelling will be defined in a separate analysis plan.

7.5.2.4 Analysis of Questionnaires (CASA-Q© and CFQ-R)

CASA-Q

The derivation of the CASA-Q domain scores will be performed according to the CASA-Q© user manual (11). All reported answers will be listed together with the derived domain scores.

Descriptive analysis will be done by treatment and domain score for baseline, Day 8, Day 29 and change from baseline.

CFQ-R

As no adolescent randomized, CFQ-R Teen/Adult version will be used.

The derivation of the CFQ-R scores will be performed according to the CFQ-R scoring instructions (12). The CFQ-R total score is the sum of each domain score. All reported answers will be listed together with the derived scores.

Descriptive analysis will be done by treatment and score for baseline, Day 29 and change from baseline and will be presented separately for total score and each domain score.

To explore the relationship between primary endpoint and CFQ-R respiratory domain score, a scatter plot of baseline CFQ-R respiratory domain score against change from baseline in FEV1 % predicted after 4 weeks of treatment.

7.7 EXTENT OF EXPOSURE

Extent of exposure to trial medication within the study will be displayed by treatment for the TS. Treatment exposure will be calculated as drug stop date - drug start date + 1 day.

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.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake till 7 days after last drug intake will be assigned to the randomised treatment. All AEs occurring before first drug intake will be assigned to ‘screening’ and all AEs occurring after last drug intake + 7 days will be assigned to ‘follow-up’ (for listings only).

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 5.2.6.1.4 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.

Adverse events ongoing at Visits 2 (baseline), 3 (week 1) and 4 (week 4) will be provided to help explaining outliers regarding efficacy.

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.

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (6). If multiple reference ranges apply for one parameter (e.g. due to different age groups), analyses will be based on normalised values, which means transforming to a standard unit and a standard reference range. If references 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. Additionally, frequency tables of changes between baseline and last values on treatment with respect to the reference ranges will be presented. Furthermore graphical representations over time will be generated for serum electrolytes.

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

Spaghetti plots will display individual potassium over time.

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 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 will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs if judged clinically relevant by the investigator.

7.8.5 Others

7.8.5.1 Physical examination

Descriptive statistics of body weight and its changes from baseline will be provided.

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.

8. REFERENCES

1	*001-MCS-40-413:* "Identify and Manage Important Protocol Deviations (iPD) ", current version, KMED
2	*BI-KMED-COPS-TMP-0001:* "iPD log", current version; KMED
3	*BI-KMED-BDS-HTG-0035:* "Handling of missing and incomplete AE dates", current version; KMED
4	*001-MCS-36-472_1*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; KMED
5	*001-MCS-36-472_RD-03:* "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON.
6	*BI-KMED-BDS-HTG-0042*: "Display and Analysis of Laboratory Data", current version, KMED
7	*BI-KMED-BDS-HTG-0045:* "Reporting of Clinical Trials and Project Summaries", current version; KMED
8	*BI position paper:* "Statistical Methods for PK", current version
9	*TDMAP:* "8-07-other-analyses-logistics-plan"
10	*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
11	CASA-Q User Manual. Boehringer Ingelheim (v4.0 2015), [R18-2689]
12	CFQ-R – General Scoring Instructions, [R18-2688]

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1.0	**18-MAY-20**		None	This is the final TSAP