TRIAL STATISTICAL ANALYSIS PLAN c17402608-02

BI Trial No.:	1363.7
Title:	A two part phase I, multiple-dose, single- and double-blind randomised, double-dummy, placebo-controlled, four-way crossover study to assess safety and tolerability of BI 443651 via Respimat® versus placebo via Respimat® in subjects with mild asthma following methacholine challenge.
Investigational Product(s):	BI 443651
Responsible trial statistician(s):	Phone: Fax:
Date of statistical analysis plan:	23-JAN-2018 SIGNED
Version:	Version 2.0 Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis dataset
AE	Adverse event
AESI	Adverse event of special interest
AUC	Area under the curve
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
BP	Blood pressure
BRPM	Blinded report planning meeting
CARE	Clinical data analysis and reporting environment
CfB	Change from baseline
CI	Confidence interval
CML	Clinical Monitor Local
CRA	Clinical Research Assistant
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
ES	Enrolled Set
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
gCV	Geometric coefficient of variation
gMean	Geometric mean
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Term	Definition / description
IPV	Important protocol violation
KM	Kaplan-Meier
MCS	Methacholine set
MCh	Methacholine
MedDRA	Medical Dictionary for Regulatory Activities
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
P25	25th precentile
P75	75th precentile
PK	Pharmacokinetic(s)
PKS	PK analysis set
PR	Pulse rate
PV	Protocol violation
RAGe	Report appendix generator
REP	Residual effect period
RS	Randomised set
SAE	Serious adverse event
SD	Standard deviation
SDL	Subject data listing
SOP	Standard operation procedure
TS	Treated set
TSAP	Trial statistical analysis plan
VC	Variance components
WHO-DD	World Health Organisation – Drug Dictionary

3. INTRODUCTION

As per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 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 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.

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

The statistical analyses will be performed within the validated working environment CARE (Clinical data Analysis and Reporting Environment), 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 adverse event (AE) data or laboratory data; Report Appendix Generator system (RAGe) for compilation/formatting of the clinical trial report (CTR) appendices).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Descriptive statistics for primary and secondary endpoints will be based on the MCS rather than TS to be consistent with the model-based analyses.

There are no further changes in the planned analysis of the study.

5. ENDPOINTS

Figure 5.1:1 in the CTP displays all spirometry measurements during one treatment period that is during the baseline bolus challenge prior to drug administration, during drug administration and during the treatment challenge on Day 2.

In the following baseline refers to the measurement obtained from the baseline bolus Methacholine (MCh) challenge prior to administration of trial medication within each period.

5.1 PRIMARY ENDPOINT

CTP: *The primary endpoint for the study to assess safety of BI 443651 is*

- *Absolute change from baseline in maximum FEV_1 reduction following MCh challenge*

The primary endpoint will be compared to placebo for each dose level of BI 443651.

For a visualization of the endpoint refer to Figure 5.1:1, a detailed description of the primary endpoint and the primary statistical analysis is provided in Section 7 of the CTP.

5.2 SECONDARY ENDPOINTS

CTP: *The following secondary endpoints will be assessed:*

- *Relative change from baseline in FEV_1 AUC_{0-tz} following bolus MCh challenge*
- *Time to recovery of FEV_1 to within 95% of post-diluent value*

The secondary endpoints will be compared to placebo for each dose level of BI 443651.

For a visualization of the endpoints refer to Figure 5.1:1, a detailed description of the secondary endpoints including statistical analysis is provided in Section 7 of the CTP.

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.

The trial is composed of two parts: The first part (pilot study) will be a single-blind four-way crossover with dose ordered sequences. The second part (main study) will be a double-blind four-way crossover, conducted according to a William's design. In both parts of the study, BI 443651 or placebo equivalent will be administered three consecutive times, 12 hours apart, per dose level. All subjects will receive placebo, 100, 400 and 1200 µg BI 443651. Each period will be separated by a washout period of at least 14 days (and not more than 28 days). Two administrations of BI 443651 will be delivered on Day 1 (morning and evening) and a single administration on Day 2 (morning).

Table 6.1: 1 Treatments and labels used in the analysis (for both trial parts)

Treatment		**Short label**
P	Placebo, respimat, bid	Plc
A	BI 443651 Respimat, 1*100 mcg/actuation, ih, bid	BI 100
B	BI 443651 Respimat, 4*100 mcg/actuation, ih, bid	BI 400
C	BI 443651 Respimat, 4*300 mcg/actuation, ih, bid	BI 1200

Table 6.1: 2 Overview of treatments for intra-individual comparison

Test treatment (T)		**Reference treatment (R)**	
BI 100	(A)	Placebo	(P)
BI 400	(B)	Placebo	(P)
BI 1200	(C)	Placebo	(P)

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

- **Screening**: measurements planned or AEs recorded prior to first device actuation for administration of trial medication.
- **On-treatment:** measurements planned or AEs recorded between first device actuation for administration in one treatment period until first device actuation for administration of trial medication in the next treatment period or until the end of the respective residual effect period (REP) or until trial completion date (whichever occurs first) will be assigned to the preceding treatment. The REP for BI 443651 is defined as after the last trial medication application.

- **Follow-up:** measurements planned or AEs recorded between the end of REP of one treatment period and the first device actuation for treatment administration of the next treatment period or trial completion date. In case of more treatments, the follow-up will be summarized according to the previous treatment.

Table 6.1: 3 Flow chart of analysis phases for adverse events, laboratory tests, vital signs and spirometry

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

6.2 IMPORTANT PROTOCOL VIOLATIONS

Data discrepancies and deviations from the CTP will be identified for all subjects in the database (i.e. for all randomised subjects). 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 blinded report planning and database lock meeting (BRPM/DBLM). At this meeting, 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 violation (PV). For definition of important PVs, and for the process of identification of these, refer to the Boehringer Ingelheim (BI) reference document "Protocol Violation Handling Definitions" (7).

If any important PVs are identified, they are to be summarised into categories and will be captured in the BRPM/DBLM minutes via an accompanying Excel spreadsheet (8). The following Table 6.2: 1 contains the categories which are considered to be important PVs in this trial. The last column describes which iPVs will be used to exclude subjects from the different subject analysis sets by default. The final decision about exclusion from analysis sets will be made at the BRPM/DBLM. If the data show other important PVs, this table will be supplemented accordingly by the time of the BRPM/DBLM.

IPVs will be summarised and listed.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
	A1	Inclusion criteria violated*	Decision at BRPM/DBLM	None
	A2	Exclusion criteria violated*	Decision at BRPM/DBLM	None
B		**Informed consent**		
	B1	Informed consent not available*	Informed consent date missing; 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 patient signed the correct version of the ICF after Visit 1. To be discussed at BRPM/DBLM.	None
C		**Trial medication and randomisation**		
	C1	Incorrect trial medication taken*	Decision at BRPM/DBLM	None
	C2	Randomisation order not followed*		None
	C3	Non-compliance*	Decisions at BRPM/DBLM	None
	C4	Medication code broken inappropriately*	To be discussed and decided during BRPM/DBLM. Only inappropriate code breaks at IPVs (e.g., unblinding by Global Pharmacovigilance is not).	None
	C5	Incorrect intake of trial medication*	Decision at BRPM/DBLM	None
	C6	Improper washout between treatments*	Decision at BRPM/DBLM	None
D		**Concomitant medication**		
	D1	Prohibited medication use*	Decision at BRPM/DBLM	None
	D2	Mandatory medication not taken*	Decision at BRPM/DBLM	None
	D3	Improper washout of concomitant medication*	Decision at BRPM/DBLM	None
E		**Missing data**		
	E1	Certain violations of procedures used to measure primary or secondary data*	Decision at BRPM/DBLM	None
F		**Incorrect timing**		
	F1	Certain violations of time schedule used to measure primary or secondary data*	Decision at BRPM/DBLM	None

KEY: * not programmed

6.3 SUBJECT SETS ANALYSED

CTP: *The statistical analysis will be based on the following analysis sets based on the actual treatment the subject receives.*

- *Enrolled set (ES): This subject set includes subjects that signed informed consent and underwent screening procedures.*
- *Randomised set (RS): This subject set includes all randomised subjects, whether treated or not.*
- *Treated set (TS): The treated set includes all subjects who were randomised and treated with at least one dose of study drug. The treatment assignment will be determined based on the first treatment the subjects received.*
- *Methacholine set (MCS): This subject set includes all subjects in the treated set who provide at least one pair (baseline and end of treatment) of evaluable measures of spirometry parameters that were not excluded due to use of rescue medication within 3 hours after start of MCh challenge.*

Table 6.3: 1 Subject sets analysed

	Subject set			
Class of endpoint	ES	RS	TS	MCS
Disposition	X			
Exposure			X	
Important PVs		X		
Demographic data /baseline conditions			X	(X)*
Primary and secondary endpoints				
• Descriptive statistics				X
• Mixed effects model				X
Further safety parameters			X	

* An additional MCS presentation of the demographic/baseline endpoints may be provided in the EoT section, if subject numbers for MCS and treated set are clearly different.

6.5 POOLING OF CENTRES

Not applicable as this is a single centre trial.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

For evaluation of primary and secondary endpoints a measurement obtained at baseline and on-treatment per period is required. If a patient misses a visit, the missing data will not be imputed. The random intercept model will handle missing data based on a likelihood method under the "missing at random" assumptions.

Generally, it is not planned to impute missing values for further safety with the exception of missing or incomplete AE dates These will be handled according to BI standards (see SOP 001-MCG-156_RD-01 (3) for missing AE dates

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Baseline is defined as the last measurement before first study drug administration in each treatment period.

For endpoints related to methacholine challenge baseline refers to the measurement obtained from the baseline bolus MCh challenge prior to administration of trial medication within each treatment period. The post-diluent value refers to the last measurement before methacholine administration (i.e. timepoint -0:05 relative to methacholine challenge).

Measurements taken after start of administration of trial medication will be considered on-treatment values or follow-up values, based on the definition of the study analysis phases in Section 6.1.

Adherence to time windows will be checked at the BRPM/DBLM.

7. PLANNED ANALYSIS

The format of the listings and tables will follow the BI guideline "Reporting of clinical trials and project summaries" (9).

The individual values of all subjects will be listed, sorted by treatment sequence, 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.

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 endpoints related to MCh challenge, the set of summary statistics is: N / Mean / SD / Min / Q1 (1^{st} quartile) / Median / Q3 (3^{rd} quartile) / Max.

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 (WHO-DD).

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
- 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 BRPM/DBLM (cf. Section 6.2) and described in the CTR.

7.4 PRIMARY ENDPOINT

CTP: *The primary endpoint absolute change from baseline in maximum reduction in FEV1 (refer to Section 5.1.1* of the CTP*) is defined as the difference between the maximum reduction in FEV1 obtained during the treatment challenge and during the baseline challenge.*

The primary endpoint will be analyzed based on the MCS.

Descriptive statistics and boxplots of the primary endpoint by treatment (and by trial part) will be provided.

As main analysis, the following model will be applied to the main part of the trial (part II).

Statistical model

CTP: *[...] this primary endpoint will be analysed using a mixed effects model based on the MCS:*

$$y_{imj} = \mu + \pi_m + \tau_j + \gamma b_{im} + \gamma' b_i' + s_i + e_{imj},$$

where i = subject 1,..., N, m = period 1,...,4, j = treatment 1,...,4

y_{imj}	*CfB in maximum FEV_1 reduction for the i^{th} subject and the m^{th} period, receiving randomised treatment j*
μ	*overall intercept,*
π_m	*m^{th} period effect,*
τ_j	*j^{th} treatment effect,*
b_{im}	*baseline value for subject i in period m (period baseline),*
γ	*associated covariate effect of period baseline,*
b_i'	*the subject baseline value (mean of period baselines) for subject i,*
γ'	*associated covariate effect of subject baseline,*
s_i	*the random effect of subject i,*
e_{imj}	*the random error associated with subject i who received treatment j in period m.*

The treatment comparisons will be the contrast (difference) *between active dose and placebo at the endpoint visit. Adjusted means (Least Squares Means) as well as 2-sided 90% CIs will be provided.*

For the random 'subject' effect in the above model a Variance Components (VC) covariance structure will be used; in case of convergence problems refer to Additional Section 9.1. The SAS procedure MIXED will be used involving the restricted maximum likelihood estimation and the Kenward-Roger approximation for denominator degrees of freedom. This approach is described in Kenward and Roger (11).

Programming details are provided in Section 9.2.1.

7.5 SECONDARY ENDPOINTS

The secondary endpoints will be analyzed based on the MCS.

Relative change from baseline in FEV_1 $AUC_{0\text{-}tz}$ following bolus MCh challenge:

CTP: *The secondary endpoint relative change from baseline in FEV_1 $AUC_{0\text{-}tz}$ (see Section 5.1.2* of the CTP*) is defined as the ratio of FEV_1 $AUC_{0\text{-}tz}$ obtained during the treatment challenge and during the baseline challenge. During each challenge, the area above the curve of the absolute change in FEV_1 from post-diluent value will be calculated from time 0*

to tz using the trapezoidal rule (refer to 001-MCG-163). The time tz refers to the last time point before recovery of FEV_1 to within 95% of post-diluent value.

Note that in case a subject's FEV_1 does not recover to within 95% of post-diluent value the time tz refers to the last timepoint at which FEV_1 was measured for that subject in that period. Furthermore, if a subjects FEV_1 does not decrease below 95% of post-diluent value the AUC will not be defined and hence not be calculated.

Descriptive statistics and boxplots of the secondary endpoint by treatment (and by trial part) will be provided.

As main analysis, the following model will be applied to the main part of the trial (part II). The statistical model used for this secondary endpoints is comparable to the one specified for the primary endpoint, despite the fact that it is evaluated on the logarithmic scale.

Statistical model

CTP: *[…] this secondary endpoint will be analysed using a mixed effects model on the logarithmic scale based on the MCS:*

$$y_{imj} = \mu + \pi_m + \tau_j + \gamma b_{im} + \gamma' b'_i + s_i + e_{imj},$$

where i = subject 1,…, N, m = period 1,…,4, j = treatment 1,…,4

y_{imj}	*Logarithm of CfB in FEV_1 $AUC_{0\text{-}tz}$ consideration for the i^{th} subject and the m^{th} period, receiving randomised treatment j*
μ	*overall intercept,*
π_m	*m^{th} period effect,*
τ_j	*j^{th} treatment effect,*
b_{im}	*Logarithm of baseline value for subject i in period m (period baseline),*
γ	*associated covariate effect of period baseline,*
b'_i	*Logarithm of the subject baseline value (mean of period baselines) for subject i,*
γ'	*associated covariate effect of subject baseline,*
s_i	*the random effect of subject i,*
e_{imj}	*the random error associated with subject i who received treatment j in period m.*

To this end, the endpoint will be log-transformed (natural logarithm) prior to fitting the model given above. The difference between the expected means for log(Active)-log(Placebo) will be estimated by the difference in the corresponding adjusted means (Least Squares Means), and a two-sided 90% confidence interval based on the t-distribution will be computed. These quantities will then be back-transformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

For the random 'subject' effect in the above model a Variance Components (VC) covariance structure will be used; in case of convergence problems refer to Additional Section 9.1.
The SAS procedure MIXED will be used involving the restricted maximum likelihood estimation and the Kenward-Roger approximation for denominator degrees of freedom. This approach is described in Kenward and Roger (11).

Programming details are provided in Section 9.2.1.

Time to recovery of FEV_1 to within 95% of post-diluent value

CTP: *The secondary endpoint time to recovery of FEV1 within 95% of post-diluent value (see Section 5.1.2* of the CTP*) is defined as the time from maximum reduction to last time before recovery to within 95% of pre-MCh challenge during each challenge. The time obtained from the treatment challenge represents the endpoint, while the time obtained from the baseline challenge will be used for the baseline correction in the analysis.*

Descriptive statistics of the secondary endpoint by treatment (and by trial part) will be provided.

Kaplan-Meier (KM) curves will be plotted for the recovery of FEV_1 within 95% of post-diluent value by treatment irrespective of the period it is administered in, for both trial parts separately as well as combined, if applicable.

As a main analysis the following model will be applied to the main part of the trial (part II).

Statistical model

CTP: […] *this endpoint will be analysed using a Cox proportional hazards model as given below based on the MCS. The model includes the treatment effect and an effect for subject baseline. Thereby, the subject baseline is calculated as median of all period baselines per subject. Breslow's method for handling ties will be used.*

The hazard function for the i^{th} subject is assumed to be

$$\lambda_i(t) = \lambda_0(t) \cdot exp\{\beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i}\},$$

where i = 1,…, N,

$\lambda_0(t)$ is the unspecified, non-negative, baseline hazard function

- *$\beta_{1,2,3}$ are the unknown regression coefficients*
- *X_{1i} represents the treatment group*
- *X_{2i} represents the subject baseline (median of period baselines)*
- *X_{3i} represents the period*

For treatment comparisons the hazard ratios of BI 443651 vs. Placebo and asymptotic 95% Wald confidence intervals will be estimated. A hazard ratio of greater than one means that BI 443651 is not inferior to placebo.

Programming details are provided in Section 9.2.1.

7.7 EXTENT OF EXPOSURE

Treatment exposure will be listed by means of the date and time of drug administration.

7.8 SAFETY ANALYSIS

All safety analyses of further safety parameters of interest will be performed on the treated set (and will be presented for both trial parts combined).

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' (4) 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 5.3.6.1 of the CTP.

The frequency of subjects 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 will be summarised separately. Separate tables will also be provided for subjects with serious AEs (SAEs), related SAEs, subjects with AESIs and subjects with other significant AEs (according to ICH E3 (5)). 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).

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 possible, analyses will be based on normalized values. 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.

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

Treatment groups will be compared based on 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 as well as frequencies and percentages of subjects with abnormal values or clinically relevant abnormal values will be presented.

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

7.8.5 Others

7.8.5.1 Physical examination

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of study drug) or as AE and will be summarised as such. No separate listing or analysis of physical examination findings will be prepared.

7.8.5.2 Pulmonary function tests

Clinically relevant findings in spirometry data (FEV1 and FVC) will be reported as AEs and will be analysed as part of AE analysis.

Descriptive statistics will be provided for FEV1 and FVC obtained at the screening visit based on the TS.

Analyses of further endpoints and parameters of interest related to PFT are described in Section 7.6.1.

7.8.5.3 Methacholine challenge

Descriptive statistics will be provided for the methacholine concentration (PD20) obtained from the incremental challenge during screening visit based on the TS.

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 36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
3.	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
4.	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
5.	*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
6.	*001-MCG-157*: "Handling, Display and Analysis of Laboratory Data", current version; IDEA for CON.
7.	*001-MCS-50-413_RD-01:* "Protocol Violation Handling Definitions", current version, IDEA for CON
8.	*001-MCS-50-413_RD-02:* "Important Manual Protocol Violations Spreadsheet", current version, IDEA for CON
9.	*001-MCG-159:* "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON.
10.	*001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON
11.	Kenward, M.G. and Roger, J.H. (2010) The use of baseline covariates in cross-over studies. Biostatistics, 11:1-17 [R10-4391]

9. ADDITIONAL SECTIONS

9.1 STEPS IN CASE OF CONVERGENCE PROBLEMS FOR REPEATED MEASURES MODEL

In case of convergence problems one may try one (or more) of the following steps:

1) Set `SINGULAR=1E-10` as option (for `PROC MIXED`: in the model statement) – This raises the threshold at which columns are declared linearly dependent (from typically 1e-12).
2) Set `MAXITER=100` (or even higher for `PROC GLIMMIX)` and/or `MAXFUNC=200` (for `PROC GLIMMIX`, these options are available within the `NLOPTIONS` statement) – This increases the number of convergence iterations used from a default of 50.
3) Use option `SCORING=4` in the final run to request a Fisher scoring algorithm to be used for the first 4 iterations.
4) Include the additional statement in the `PROC MIXED` call:
   ```
   PERFORMANCE NOTHREAD;
   ```
   – this removes multi-threading from the calculations.
5) Provide starting values for covariance parameters using a 'parms' statement.
   Perform an initial run including the statement
   ```
   ODS OUTPUT COVPARMS=covstart;
   ```
   followed by a final run using
   ```
   PARMS / PARMSDATA=covstart;
   ```
   In the special case with the note "Convergence criteria met but final hessian is not positive definite" try instead/in addition
   ```
   PARMS / OLS;
   ```
   to request ordinary least squares starting values.
   One may also use estimates from a simpler model (e.g. using `AR(1)`) as starting values for the run with `TYPE=UN` or `UNR`

In case the VC covariance matrix does not work, also in conjunction with all steps from 1)-6) mentioned above, the following covariance structures will be chosen, in the pre-defined order:

- Unstructured covariance matrix (`type = UN`)
- Toeplitz structure with heterogeneous variances (`type = TOEPH`)
- Standard Toeplitz matrix (`type = TOEP`)
- first-order autoregressive structure (`type = AR(1)`)

9.2.1 Details for primary analyses

The following SAS code can be used to fit the model for the primary endpoint:

```
PROC MIXED data=indata METHOD=reml ORDER=formatted;
    CLASS SUBJID ATRTSL APERIOD;
    MODEL CHG = ATRTSL APERIOD BASE baseavg / SOLUTION DDFM = KR
                OUTP=pred;
    RANDOM INTERCEPT / SUBJECT = SUBJID TYPE=VC;
    LSMEANS ATRTSL / PDIFF=control('Placebo') CL ALPHA=0.1;
RUN ;
```

The following SAS code can be used to fit the model for the secondary endpoint 'FEV_1 AUC0-tz':

```
PROC MIXED data= indata METHOD=reml ORDER=formatted ;
    CLASS SUBJID ATRTSL APERIOD;
    MODEL LNRATIO = ATRTSL APERIOD  lnbase lnbaseavg / SOLUTION DDFM
                = KR OUTP=pred;
    RANDOM INTERCEPT / SUBJECT = SUBJID TYPE=VC;
    LSMEANS ATRTSL / PDIFF=control('Placebo') CL ALPHA=0.1;
RUN ;
```

The following SAS code can be used to fit the model for the secondary endpoint 'Time to recovery':

```
PROC PHREG DATA= adtte;
    CLASS ATRTSL (REF='Placebo') APERIOD;
    MODEL aval*cnsr(1) = ATRTSL APERIOD BASEAVG  / TIES=BRESLOW;
    HAZARDRATIO ATRTSL / DIFF=REF CL=WALD ALPHA=0.05;
    ODS OUTPUT HAZARDRATIOS=hazard;
RUN;
```

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**17-MAY-17**		None	This is the initial TSAP with necessary information for trial conduct
Final	**23-JAN-18**		All	This is the final TSAP.