TRIAL STATISTICAL ANALYSIS PLAN

c26340025-01

BI Trial No.:	1399-0002
Title:	Safety, tolerability and pharmacokinetics of multiple rising inhaled doses of BI 1265162 in healthy male subjects in a randomised, double blind, placebo-controlled trial Final protocol (including protocol revision 1 (c15848749-02) and 2 (c15848749-03))
Investigational Product(s):	BI 1265162
Responsible trial statistician(s):	Phone: Fax: Phone: Fax:
Date of statistical analysis plan:	11 JAN 2019 SIGNED
Version:	"Final"

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse Event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{\tau,1}$	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 dosing interval τ
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
BMI	Body mass index
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
ECG	Electrocardiogram
FEF_{25-75}	Forced expiratory flow
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
gCV	geometric coefficient of variation
ICH	International Conference On Harmonisation
IPD	Important Protocol Deviation
MedDRA	Medical Dictionary For Regulatory Activities
NOA	Not analysed
NOR	No valid result
NOS	No sample available

Term	Definition / description
PD	Protocol Deviation
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter set
PR	Pulse rate
RAGe	Report appendix generator
RPM	Report Planning Meeting
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
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 Oracle Clinical™ 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, Certara USA Inc., Princeton, NJ, USA).

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

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

The secondary endpoint $AUC_{\tau,1}$ (as defined in the CTP) is described as $AUC_{0\text{-}12}$ in this TSAP. This is not a change in the planned analysis. Only a more precise parameter name is used.

The definition of baseline ECG is not described properly in the CTP (Section 5.2.4.1). In this TSAP, the derivation of baseline ECG values is described in more detail to clarify how data are analysed. Prior to first study drug administration, 3 triplicate ECGs (9 single ECGs) will be recorded. The mean of the first ECG measurement of each triple ECG will be analysed.

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoint is the number of subjects with drug-related AEs, 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 endpoints of this trial are AUC_{0-12} and C_{max} of BI 1265162 in plasma after the first dose, $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 1265162 in plasma after the last dose, as defined in Section 5.5.1.1 of the CTP.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

Subjects were planned to be treated either with

- multiple doses of 10, 30, 100, 300, or 600 µg of BI 1265162 (test treatments)
  or
- multiple doses of placebo (reference treatment)

The subjects will receive a single dose of BI or placebo in the morning on Day 1 and Day 8. On days 2-7 the subjects will receive the dose of BI or placebo twice daily. For the analysis, the on-treatment period will include all treatment days independent of the number of the total number of doses per day.

All placebo subjects will be analysed in one pooled placebo group (i.e. no distinction between dose groups will be made for placebo subjects).

Analysis phases for statistical analysis of AEs, safety laboratory data, vital signs, spirometry and ECG are defined for each subject as described in the table below.

Table 6.1: 1 Flow chart of analysis phases for statistical analyses of AEs, safety laboratory data, vital signs, spirometry 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,** **10 ug BI**, **30 ug BI**, **100 ug BI**, **300 ug BI**, or **600 ug BI**, respectively	Date/time of first administration of study drug	Date/time of last administration of BI 1265162 + REP or 12:00 a.m. on day after subject's trial termination date, whichever occurs earlier
Follow-up[1]	**F/U Pbo,** **F/U 10 ug BI**, **F/U 30 ug BI**, **F/U 100 ug BI**, **F/U 300 ug BI**, or **F/U 600 ug BI**, respectively	Date/time of last administration of BI 1265162 + REP	12:00 a.m. on day after subject's trial termination date

[1] Follow-up phases might not exist, e.g. if the subject's trial termination date is within 2 days after last administration of BI 1265162.

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 BI**", defined as the total over all on-treatment phases involving BI
- "**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 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

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

Consistency check listings (for identification of deviations from 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 report planning and database lock meeting (RPM/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 deviation (iPD). For definition of iPDs, and for the process of identification of these, refer to the Boehringer Ingelheim (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 RPM/DBLM minutes via an accompanying excel spreadsheet. The table below contains the categories which are considered to be iPDs in this trial. If the data show other important PDs, this table will be supplemented accordingly by the time of the RPM/DBLM.

iPDs will be summarised and listed.

Table 6.2: 1 Important protocol deviations

Category / Code		Description
A		**Entrance criteria not met**
	A1	Inclusion criteria violated
	A2	Exclusion criteria violated
B		**Informed consent**
	B1	Informed consent not available
	B2	Informed consent too late
C		**Trial medication and randomisation**
	C1	Incorrect trial medication taken
	C2	Randomisation not followed
	C3	Non-compliance
	C4	Incorrect intake of trial medication
	C5	Incorrect dose of trial medication taken
D		**Concomitant medication**
	D1	Prohibited medication use
E		**Missing data**
		None[1]
G		**Other trial specific important deviation**
	G1	Certain deviations of procedures used to measure secondary PK data

Deviations C1, C2, C5 and G1 can only be detected at the trial site.
[1] Missing visits, evaluations, and tests will be considered missing data, not protocol deviations

6.3 SUBJECT SETS ANALYSED

All entered subjects who received study medication will be included in the safety analysis and in the PK analysis depending on the availability of measurement values, and on their adherence to the CTP.

The following subject sets will be defined for statistical analysis:

- Treated set (TS):
  This subject set includes all subjects who received at least one dose of study drug. This is the full analysis set population in the sense of ICH-E9. It will be used for analysis of safety, demographic data and baseline characteristics.

- Pharmacokinetic parameter set (PKS):
  This subject set includes all subjects in the TS who provide at least one PK parameter that was not excluded because of PDs 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 subjects to analysis sets will be made at latest at the RPM/DBLM.

Table 6.3: 1 Subject sets analysed

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

6.5 POOLING OF CENTRES

This section is not applicable, because the study was performed in only one centre.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

Data of screened subjects who were withdrawn from the trial prior to first administration of any study drug will not be reported in the CTR.

Data of subjects who failed to complete all periods of the study (dropouts or withdrawals) will be reported in the CTR as far as their data are available. All withdrawals will be documented and the reason for withdrawal recorded in the CTR.

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

The only exceptions where imputation might be necessary for safety evaluation are AE dates. Missing or incomplete AE dates are imputed according to BI standards (3).

Missing data and outliers of PK data are handled according to BI standards (4).

Plasma concentration-time tables

CTP: *Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed) or BLQ (below the lower limit of quantification) will be displayed as such and not replaced by zero at any time point (this rule also applies to the lag phase, including the predose values).*

Pharmacokinetic parameters

CTP: *For tabulation and graphical displays, 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 12-lead ECG recordings at the time points specified in Table 6.7: 1.

Triple ECGs will be recorded at Visit 2 assessments and will be evaluated by a central lab. At Visit 1 and 3 only single ECGs will be recorded. This data will not be evaluated centrally. At predose (Visit 2, Day 1, planned time point -01:30, notation for data transfer -01:30, -01:25, and -01:20), three triplicate ECGs (9 single ECGs) will be recorded.

For all on-treatment assessments as well as for the 3 predose triplicates, only the first of the 3 replicate ECGs at a single assessment time will be evaluated centrally.

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

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
2	1	-01:30	Baseline
		00:10	On-treatment
		01:00	
		04:00	
		12:00	
	2	24:10	
	3	48:10	
	5	96:10	
	6	120:10	
	8	164:30	
		168:10	
		169:00	
		172:00	
		180:00	
	9	191:30	

For urine electrolytes there is a whole baseline day to have time matched baseline measurements (see Table 6.7: 2 for details).

In all other analyses the last non-missing value determined prior to the first dosing of BI 1265162 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 RPM/DBLM.

Unscheduled measurements of laboratory data, vital signs or spirometry data will be assumed to be repeat measurements of the most recent scheduled measurement (e.g. for follow-up or confirmation of a particular value). Therefore, unscheduled measurements will be assigned to the planned time point of the previous scheduled measurement.

Table 6.7: 2 Time schedule of urine electrolyte measurements

Visit	Day	**Planned time interval [hh:mm] - relative to respective drug administration (planned time at the day)**	Study phase
2	-1	-24:00 to -20:00 (08:00 to 12:00)	Baseline
		-20:00 to -16:00 (12:00 to 16:00)	
		-16:00 to -12:00 (16:00 to 20:00)	
		-12:00 to 00:00 (20:00 to 08:00 on Day 1)	
	5	96:00 to 100:00 (08:00 to 12:00)	On-treatment
		100:00 to 104:00 (12:00 to 16:00)	
		104:00 to 108:00 (16:00 to 20:00)	
		108:00 to 120:00 (20:00 to 08:00 on Day 6)	
	8	168:00 to 172:00 (08:00 to 12:00)	
		172:00 to 176:00 (12:00 to 16:00)	
		176:00 to 180:00 (16:00 to 20:00)	
		180:00 to 192:00 (20:00 to 08:00 on Day 9)	

Descriptive statistics of laboratory data will be calculated by planned time point based on the worst value of the subject at that planned time point (or assigned to that planned time point).

For vital signs and spirometry, descriptive statistics will be calculated by planned time point based on the last value of the subject at that planned time point (or assigned to that planned time point).

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

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

For PK parameters the following descriptive statistics will additionally be calculated:

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 to 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 if and only if there actually are missing values. Percentages will be based on all subjects in the respective subject 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. These will be based on the TS.

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 World Health Organisation – Drug Dictionary, version March 2018.

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

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

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

7.4 PRIMARY ENDPOINT

Refer to Section 7.8.1 for a description of the analysis of AEs, and in particular the analysis of the number of subjects 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.

Dose proportionality will be evaluated as defined in the CTP, Section 7.3.2, by use of the power model for the secondary endpoints AUC_{0-12}, C_{max}, $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 1265162 in plasma.

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. Excluded concentration itself will be listed in the CTR associated with an appropriate flag.

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).

7.7 EXTENT OF EXPOSURE

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

7.8 SAFETY ANALYSIS

All safety analyses will be performed 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 subjects 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 or on-treatment phase as defined in Section 6.1. AEs will be analysed based on actual treatments, as defined in Table 6.1: 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:
- *AST (aspartate transaminase) and/or ALT (alanine aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood 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 (8), 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 subjects with AEs will be summarised by treatment, primary SOC and preferred term. AEs which were considered by the investigator to be drug related (primary endpoint) will be summarised separately. Separate tables will also be provided for subjects with SAEs, subjects with AESIs and subjects with other significant AEs (according to ICH E3 (8)). The frequency of subjects with AEs and the frequency of subjects with AEs considered by the investigator to be drug related will also be summarised by maximum intensity, primary SOC and preferred term.

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 subjects 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 subjects 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 summarised.

For support of lay summaries, the frequency of subjects with drug-related SAEs will be summarised by treatment, primary system organ class 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" (9).

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.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7) will be provided. For urine electrolytes (including potassium-creatinine quotient and sodium-creatinine quotient), the time matched change from baseline is analysed. In addition, median urine and serum electrolytes over time will be presented graphically. The graphics will also be prepared for the ratio of sodium / potassium in urine. Frequency tables of changes between baseline and last value on treatment with respect to the reference range will be presented.

Possibly clinically significant abnormal laboratory values are only those identified either in the Investigator's comments or at the RPM/DBLM at the latest. It is the Investigator's responsibility to decide whether a lab value is clinically significant abnormal or not. Standard or project-specific rules for flagging clinically significant values in an automated manner will not be applied in this study.

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.

Exposure-response analysis

The relationship between BI 1265162 plasma concentrations and serum potassium and sodium difference from baseline (see Section 6.7) will be analysed descriptively. Scatterplots of plasma concentration versus lab parameter will be prepared by dose groups. All time points with available lab data and valid time-matched plasma drug concentrations will be included. The following time points are matched time points for serum electrolytes and drug concentration: Day 1 2:00, Day 2 23:55, Day 8 07:55 and Day 8 10:00.

For the handling of missing values, see Section 6.6. The placebo subjects will not be included in this analysis.

The relationship between the amount of BI 1265162 that is eliminated in urine during a 12h interval and urine potassium and sodium change from baseline will be analysed similarly. The following time points are matched time points for urine electrolytes and amount of eliminated BI 1265162: Day 1 08:00 to 20:00, Day 5 08:00 to 20:00, and Day 8 08:00 to 20:00.

7.8.3 Vital signs

The analyses of vital signs (blood pressure and pulse rate) 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

ECG data will be analysed based on dose groups.

Abnormal findings 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

Spirometry

CTP: *For […] spirometry, the differences from baseline will be evaluated.*

Descriptive statistics of spirometry endpoints (FEV_1, FVC and FEF_{25-75}) over time and their change from baseline will be presented. Additionally, plots over the time will be provided for spirometry data. Individual subject data and the mean per dose group will be presented.

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

Physical examinations

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	*CPMP/ICH/363/96: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9; Note For Guidance on Design, Conduct, Analysis and Evaluation of Clinical Trialss, current version*
2	*001-MCS-40-135: "Integrated Quality and Risk Management Process", 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-MCS-36-472_RD-01: "Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON*
5	*001-MCG-159: "Reporting of Clinical Trials and Project Summaries", current version; IDEA for CON*
6	*001-MCS-36-472_RD-03: "Description of Analytical Transfer Files and PK/PD Data Files", current version; IDEA for CON*
7	*001-MCG-156: "Analysis and Presentation of Adverse Event Data from Clinical Trials", current version; IDEA for CON*
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	*001-MCG-157: "Display and Analysis of Laboratory Data", current version; IDEA for CON*

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**11-JAN-18**		None	This is the final TSAP without any modification