Trial Statistical Analysis Plan

c09084743-01

BI Trial No.:	1320.17
Title:	A randomized, double-blind, placebo-controlled, parallel group, Phase I trial in healthy current smoker subjects to assess pharmacodynamic effects on segmental endotoxin induced inflammatory response and safety of 4 weeks oral administration of BI 1026706 Final Protocol (including protocol revisions 1,2, 3 and 4 (c03143538-05))
Investigational Products:	BI 1026706
Responsible trial statisticians:	[redacted] Phone: Fax: [redacted] Phone: Fax:
Date of statistical analysis plan:	23 MAR 2017 SIGNED
Version:	Final

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis data set
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine transaminase
AST	Aspartate transaminase
ANOVA	Analysis of variance
BAL	Bronchoalveolar lavage
BI	Boehringer Ingelheim
[redacted]	[redacted]
BMI	Body mass index
BP	Blood pressure
BRPM	Blinded report planning meeting
[redacted]	[redacted]
[redacted]	[redacted]
CD14-positive monocytes	cell count of monocytes, determined by flow cytometry
[redacted]	[redacted]
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DBLM	Database lock meeting
$differential_{any,\ microsc}$	differential cell count of neutrophils, eosinophils or lymphocytes, determined by cytospin microscopy
$differential_{macro,\ microsc}$	differential cell count of macrophages, determined by cytospin microscopy
$differential_{macro+mono,\ derived}$	differential cell count of macrophages plus monocytes, derived
$differential_{mono,\ microsc}$	differential cell count of monocytes, determined by cytospin microscopy
$differential_{mono,\ flow}$	differential cell count of monocytes, determined by flow cytometry
ECG	Electrocardiogram
eCRF	electronic case report form

Term	Definition / description
EMA	European Medicines Agency
EOT	End-of-trial
ES	Enrolled set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
gCV	Geometric coefficient of variation
gMean	Geometric mean
ICH	International Conference on Harmonisation
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
[redacted]	[redacted]
N	number of non-missing observations
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
O*C	Oracle Clinical
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PD	Pharmacodynamic(s)
PDS	Pharmacodynamic set
[redacted]	[redacted]
PR	Pulse rate
[redacted]	[redacted]
[redacted]	[redacted]
PV	Protocol violation
REP	Residual effect period
RS	Randomised set
SAE	Serious adverse event
SAS®	Statistical Analysis System

Term	Definition / description
SD	Standard deviation
T	Test treatment
TEAE	Treatment emergent adverse event
[redacted]	[redacted]
$total_{any,\ derived}$	total cell count of neutrophils, eosinophils or lymphocytes, derived
$total_{any,\ derived,standardised}$	total cell count of neutrophils, eosinophils or lymphocytes, derived and standardised to the retrieved BAL volume
$total\ cells_{,\ standardised}$	total cell count of all cells together standardised to the retrieved BAL volume
$total_{macro+mono,\ derived,\ standardised}$	total cell count of macrophages plus monocytes, derived and standardised to the retrieved BAL volume
$total_{mono,\ derived,\ standardised}$	total cell count of monocytes determined by flow cytometry, derived and standardised to the retrieved BAL volume
$total_{non\text{-}squamous\ cells,\ microsc}$	total cell count of non-squamous cells, determined by cytospin microscopy
TS	Treated set
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

3. INTRODUCTION

As per International Conference on Harmonisation (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, 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 the Oracle Clinical™ (O*C) system.

[redacted]

SAS® Version 9.4 will be used for all analyses [redacted].

[redacted]

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

All analyses described in the TSAP are outlined in the CTP and its amendments.

In addition to what has already been outlined in the CTP, the following changes in the analyses are introduced in this TSAP:

[redacted]

- Differential (i.e. relative) cell count of neutrophils, eosinophils, monocytes, macrophages and lymphocytes, as well as the total cell count of non-squamous cells in BAL will be determined using the method of cytospin microscopy. Since it is not possible with this method to clearly differentiate between macrophages and monocytes, the secondary and further endpoints regarding the cell type macrophages will actually present the total and differential cell count of macrophages and monocytes together and will be named as such in the analyses.

  Note, the secondary [redacted] endpoints regarding the cell type monocytes used in the analyses are based on the differential cell count determined using flow cytometry which is more accurate due to immunostaining (CD14).

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

CTP: *Total cell count of neutrophils in Bronchoalveolar Lavage (BAL) after 24 hours of the segmental endotoxin challenge.*

For detailed information regarding the determination of this primary endpoint please refer to Section 5.3 of this TSAP.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

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

5.2.2 Secondary endpoints

CTP*: Total and differential cell count of neutrophils (only differential cell count), eosinophils, monocytes, macrophages and lymphocytes in BAL after 24 hours of the segmental endotoxin challenge.*

For detailed information regarding the determination of these secondary endpoints please refer to Section 5.3 of this TSAP.

Differential (i.e. relative) cell count of neutrophils, eosinophils, monocytes, macrophages and lymphocytes will be determined using the method of cytospin microscopy. The total cell count of non-squamous cells, which will be determined in a microscopic counting chamber, is the denominator of the differential cell counts. Multiplication of the differential cell counts determined by cytospin microscopy ($differential_{any,\ microsc}$) with the total cell count of non-squamous cells ($total_{non\text{-}squamous\ cells,\ microsc}$) will result in the total cell count for the various cell types ($total_{any,\ derived}$). Furthermore the total cell count for the various cell types will be standardised to the retrieved BAL volume ($total_{any,\ derived,\ standardised}$). These differential and total cell counts for the various cell types will be analysed as primary, secondary and further endpoints:

For neutrophils, eosinophils and lymphocytes (primary, secondary and further endpoints):

$$total_{any,\ derived,\ standardised} = differential_{any,\ microsc} * total_{non\text{-}squamous\ cells,\ microsc} / \text{BAL volume}$$

The differential cell count of macrophages plus monocytes ($differential_{macro+mono,\ derived}$) will be derived as the sum of differential cell counts of monocytes ($differential_{mono,\ microsc}$) plus macrophages ($differential_{macro,\ microsc}$) from cytospin microscopy. The total cell count of macrophages plus monocytes ($total_{macro+mono,\ derived,\ standardised}$) will then be derived by multiplying the derived differential cell count with the total cell count of non-squamous cells standardised to the retrieved BAL volume. The derived differential and total cell counts of macrophages plus monocytes will be analysed as secondary [redacted] endpoints:

For macrophages plus monocytes (secondary [redacted] endpoints):

$$differential_{macro+mono,\ derived} = differential_{mono,\ microsc} + differential_{macro,\ microsc}$$

$$total_{macro+mono,\ derived,\ standardised} = differential_{macro+mono,\ derived} * total_{non\text{-}squamous\ cells,\ microsc} / \text{BAL volume}$$

The differential cell count of monocytes will in addition be determined using flow cytometry which is more accurate due to immunostaining (CD14). Thus, the differential cell counts of CD14-positive monocytes will be analysed as secondary [redacted] endpoints and will be used for derivation of the total cell counts of the monocytes ($total_{mono,\ derived}$), which will also be analysed as secondary [redacted] endpoints. This total monocyte cell count will be derived by multiplying the differential cell count of CD14-positive monocytes ($differential_{mono,\ flow}$) with the total cell count of non-squamous cells:

For monocytes (secondary [redacted] endpoints):

$$total_{mono,\ derived,\ standardised} = differential_{mono,\ flow} * total_{non\text{-}squamous\ cells,\ microsc} / \text{BAL volume}$$

In addition the total cells in BAL before segmental challenge, 24 hours after segmental endotoxin challenge and 24 hours after segmental saline challenge will be analysed. They are derived according to:

$$\text{total cells}_{,\ standardised} = total_{non\text{-}squamous\ cells,\ microsc} / \text{BAL volume}$$

The unit of the reported total cell counts for each cell type and for total cells will be 10^3/mL.

For the inferential statistical analysis of the primary and secondary endpoints, log transformed data will be used and subjects with zero values will not be considered in the inferential analysis of the respective cell type. To overcome a reduced sample size for this situation, for all cell types that have a zero cell count at Visit 7 in the LPS challenged segment, this value will be "imputed" with a small value for the ease of log transformation. To minimize the impact of such "imputation", we will use 1/10th of the roundup value of the minimal non-zero value of the total cell count observed in the data for each cell type. For the differential cell count of all cell types 0.01 will be added onto the zero values. This imputation strategy will only be applied to the data which will be inferentially analysed. The descriptive analysis will be based on the actual data.

[redacted]

Further endpoints related to safety assessment:

- *Number (%) of subjects with treatment emergent adverse events (TEAE).*
- *Number (%) of subjects with drug related AEs*

[redacted]

[redacted]

[redacted]

5.4.5 Other safety parameters

5.4.5.1 Physical examination findings

Results of physical examination will not be analysed as a specific endpoint. Clinically significant findings will be reported as baseline conditions or adverse events (AEs), cf. Section 5.3.1 of the CTP, and will be analysed as such.

5.4.5.2 Vital signs

CTP: *Systolic and diastolic blood pressure (BP) and pulse rate (PR) will be measured after the subject has rested for at least 5 minutes in a supine position.*

5.4.5.3 Safety laboratory parameters

Cf. CTP Section 5.3.3 for a definition of safety laboratory parameters assessed in this trial. Urine dipstick data will not be included in the database.

5.4.5.4 Electrocardiogram

Results from electrocardiogram (ECG) will not be analysed as a specific endpoint. Relevant ECG findings will be reported as AEs and will be analysed as such.

5.4.5.5 Pulmonary function testing

The highest FEV_1 and FVC from 3 blows as well as the time point of the first pulmonary function testing maneuver will be recorded in the eCRF.

5.4.5.6 Oxygen saturation

CTP: *Oxygen saturation will be measured by single finger pulse oximetry while conducting bronchoscopies.* However, oxygen saturation data will not be included in the database.

5.4.5.7 Adverse events

- Number (%) of subjects with serious AEs (SAEs)
- Number (%) of subjects with AEs of special interest (AESIs).
- Number (%) of subjects with other significant AEs (according to ICH E3)

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

Subjects will be treated with either

- 100 mg BI 1026706 (test treatment, T) or
- placebo (reference treatment, R),

twice daily for 28 +/- 2 days.

The following separate study analysis phases will be defined for the analyses of AEs, laboratory tests, vital signs and body weight:

- **Screening** (ranging from 0:00 h on day of informed consent until first administration of study drug)
- **On treatment** (separately for each treatment, ranging from the time of first study drug administration [redacted] 4 days after the last administration of study drug; note that 4 days after the last trial medication application are defined in CTP Section 5.3.7 as the residual effect period [REP])
- **Post-treatment** (separately for each treatment, ranging [redacted] days after the last administration of study drug, i.e. the end of the REP, to start of post-study phase)
- **Post-study** ([redacted] after the last administration of study drug or at 0:00 h on the day after the EOT visit, whichever is later)

Note that the post-treatment phase might not exist for individual subjects, e.g. if the EOT visit is [redacted] of the last administration of study drug.

Table 6.1: 1 Flow chart of study analysis phases for adverse events, laboratory tests, vital signs and body weight

Study analysis phase	Start	End
Screening	Date of informed consent	Date/time of first administration of study drug
On treatment	Date/time of first administration of study drug	Date/time of last administration of study drug + REP, [redacted] * 24 h
Post-treatment[1]	Date/time of last administration of study drug + REP ([redacted] * 24 h)	12:00 AM on day after trial completion date
Post study	Date/time of last administration of study drug + REP ([redacted] * 24 h) or 12:00 AM on day after trial completion date (whichever is later)	Not defined – a placeholder date is used, e.g. a date after database lock

[1] does not necessarily exist

Displays of AEs, laboratory tests, vital signs and body weight will be presented separately for the treatments, labelled "**BI 1026706**" and "**Placebo**".

CTR Section 15, Appendix 16.1.9.2.8.2 and Appendix 16.1.9.2.8.3 AE displays will present results for these study treatments during on-treatment phases only, labelled as indicated above. Screening, post-treatment and post-study periods will not be included in this analysis.

CTR Appendix 16.1.9.2.8.1 displays will present results for the following study analysis phases:

- Screening
- On-treatment (separately per study treatment listed above, labelled with the name of the respective study treatment)
- Post-treatment (separately per study treatment listed above, labelled "**Post-BI**" and "**Post-Placebo**")
- Post-study

In CTR Section 15 AE tables and CTR Appendix 16.1.9.2.8.1 displays, a total over both on-treatment phases (i.e., BI 1026706 plus placebo, labelled "**Total on-trt**") will be provided in addition.

In CTR Appendix 16.1.9.2.8.1 displays, a total over all study phases (labelled "**Total**") will be provided in addition.

No total columns will be provided in CTR Appendices 16.1.9.2.8.2 and 16.1.9.2.8.3.

Displays of laboratory tests, vital signs and body weight will present results by study treatment.

More details on the technical implementation of these analyses are provided in the analysis data set (ADS) Plan of this TSAP.

6.2 IMPORTANT PROTOCOL VIOLATION

Data discrepancies and deviations from the CTP will be identified for all subjects in the database (i.e., treated subjects and subjects with SAEs which the investigator considered related to the screening procedure). 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 combined blinded report planning meeting (BRPM) and database lock meeting (DBLM). At this meeting, it will be decided whether the discrepant data value can be used in analysis 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" (3).

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 (2). The following table contains the categories which are considered to be important PVs in this trial. If the data show other important PVs, this table will be supplemented accordingly by the time of the BRPM/DBLM.

Table 6.2: 1 Important protocol violations

Category /Code		Description	Identification
A		**Entrance criteria not met**	
	A1	Inclusion criteria violated	programmed
	A2	Exclusion criteria violated	programmed
B		**Informed consent**	
	B1	Informed consent not available	programmed
	B2	Informed consent too late	programmed
C		**Trial medication and randomization**	
	C1	Incorrect trial medication taken	manual
	C2	Randomisation not followed	manual
	C3	Non-compliance, which may risk the attainment of steady state reached at Visit 6 or the planned time of 14 hours between last drug administration and start of the bronchoscopy at Visit 7 is exceeded by more than 2 hours.	manual (see CTP Section 4.3) and BRPM
	C4	Medication code broken inappropriately	manual
	C5	Incorrect route of intake of trial medication	manual
D		**Concomitant medication**	
	D1	Concomitant medication with potential influence on [redacted] primary/secondary endpoints, see CTP Section 4.2.1.	BRPM
E		**Missing data (for primary and secondary endpoints)**	
	E1	Certain violations of procedures used to measure primary and secondary data	BRPM
F		**Incorrect timing**[1]	
	F1	Time difference between start of bronchoscopy at Visit 6 and 7 deviates by more than 2 hours from 24 hours.	BRPM
G		**Other trial specific important violations**	
	G1	No or improper instillation of LPS challenge at Visit 6	manual
	G2	AE in respiratory tract ongoing during bronchoscopy at Visit 6 or 7.	manual
	G3	BAL sampling at Visit 7 is not conducted in the segment with the respective challenge at Visit 6.	BRPM
	G4	[redacted]	manual

Category /Code		Description	Identification
		[redacted]	

[1] Time deviations will only be flagged as important PV, when leading to exclusion of the entire subject from an analysis set
Source: 'Protocol Violation Handling Definitions' [001-MCS-50-413_RD-01] (3)

6.3 SUBJECT SETS ANALYSED

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

The following analysis sets will be defined for this trial:

- Enrolled set (ES)
  This subject set includes all subjects who were screened for inclusion into the study, i.e., who were assigned a subject number.
  It will be used for analyses of subject disposition.

- Randomised set (RS):
  This subject set includes all randomised subjects, i.e., who were assigned a randomisation umber, whether treated or not.
  It will be used for analyses of subject disposition.

- Treated set (TS):
  This subject set includes all subjects in the RS 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.

[redacted]

[redacted]

- Pharmacodynamic set (PDS):
  This subject set includes all subjects in the TS who have evaluable cell counts measured after 24 hours of the segmental challenge in primary, secondary or further endpoints related to BAL assessment. Whether a subject has evaluable cell counts will be decided no later than in the BRPM (cf. CTP Section 7.3).

[redacted]

The discussion of all exceptional cases and problems and the decisions on the allocation of subjects to populations will be made at latest at the BRPM/DBLM.

Table 6.3: 1 Subject sets analysed

	Analysis set						
Class of endpoint	ES	RS	TS	[redacted]	[redacted]	PDS	[redacted]
Primary and secondary endpoints and further endpoints related to BAL assessment which were measured after 24 hours of the segmental challenge						X	
[redacted]							
Safety endpoints			X				
Demographic/baseline endpoints			X				
Important PVs		X					
Disposition	X	X					
[redacted]							
[redacted]							

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

The endpoints will be used as defined in the CTP, Section 7.4.

CTP: *Missing safety and pharmacodynamic data will not be imputed.*

[redacted]

[redacted]

Missing or incomplete AE dates are imputed according to BI standards (see 001-MCG-156_RD-01 (4)).

[redacted]

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

In general, baseline is defined as the last measurement before first trial mediation intake at Visit 2. This applies e.g. to laboratory data, vital signs, body weight, and pulmonary function testing, exceptions are BAL assessments [redacted]

For endpoints related to BAL assessments, baseline is defined as the measurement at Visit 6.

[redacted]

Time windows are defined in Section 6.1 of the CTP. Adherence to time windows will be checked via the consistency check listings 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" (001-MCG-159) (6).

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 (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

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 are actually 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, based on the TS.

The data will be summarised for each treatment group and in total.

7.2 CONCOMITANT DISEASES AND MEDICATION

Frequency tables are planned for this section of the CTR, based on the TS.

Concomitant diseases will be coded using the coding system of the Medical Dictionary for Drug Regulatory Activities (MedDRA). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). The coding version number will be displayed as a footnote in the respective output.

The diagnoses and medications will be listed. Subjects without any concomitant diagnoses or concomitant therapies should be marked with a "No" in the respective column.

The relevance of the concomitant therapies to the evaluation of [redacted] PD will be decided no later than at the BRPM/DBLM.

[redacted]

7.4 PRIMARY ENDPOINT

As described in CTP Section 7.3.1, the primary analysis of the primary endpoint will be an analysis of variance (ANOVA) on the log-transformed scale, based on the PDS. The ANOVA model is described in CTP Section 7.1.3.

As described in CTP Section 7.2, the primary endpoint is subject of a confirmatory statistical hypothesis test, based on the primary analysis:

H_0: geometric mean ratio, i.e. T/R, of the primary endpoint is 1.
H_a: geometric mean ratio, i.e. T/R, of the primary endpoint is not equal to 1.

H_0 will be rejected if its p-value is ≤ 0.1.

H_a is a two-sided alternative hypothesis; testing this hypothesis at the 10% significance level is equivalent to using two one-sided tests, each at the 5% significance level.

No other confirmatory statistical hypothesis tests will be conducted in this trial.

[redacted]

[redacted]

Descriptive statistics and boxplots of the primary endpoint by treatment will also be provided.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoint has been specified in the CTP.

7.5.2 Secondary endpoints

As described in CTP Section 7.3.2, secondary endpoints will be statistically assessed using the same methods as described for the primary analysis of the primary endpoint, based on the PDS.

No confirmatory statistical hypothesis tests will be conducted based on the secondary endpoints.

Descriptive statistics and boxplots of the secondary endpoints by treatment will also be provided.

[redacted]

[redacted]

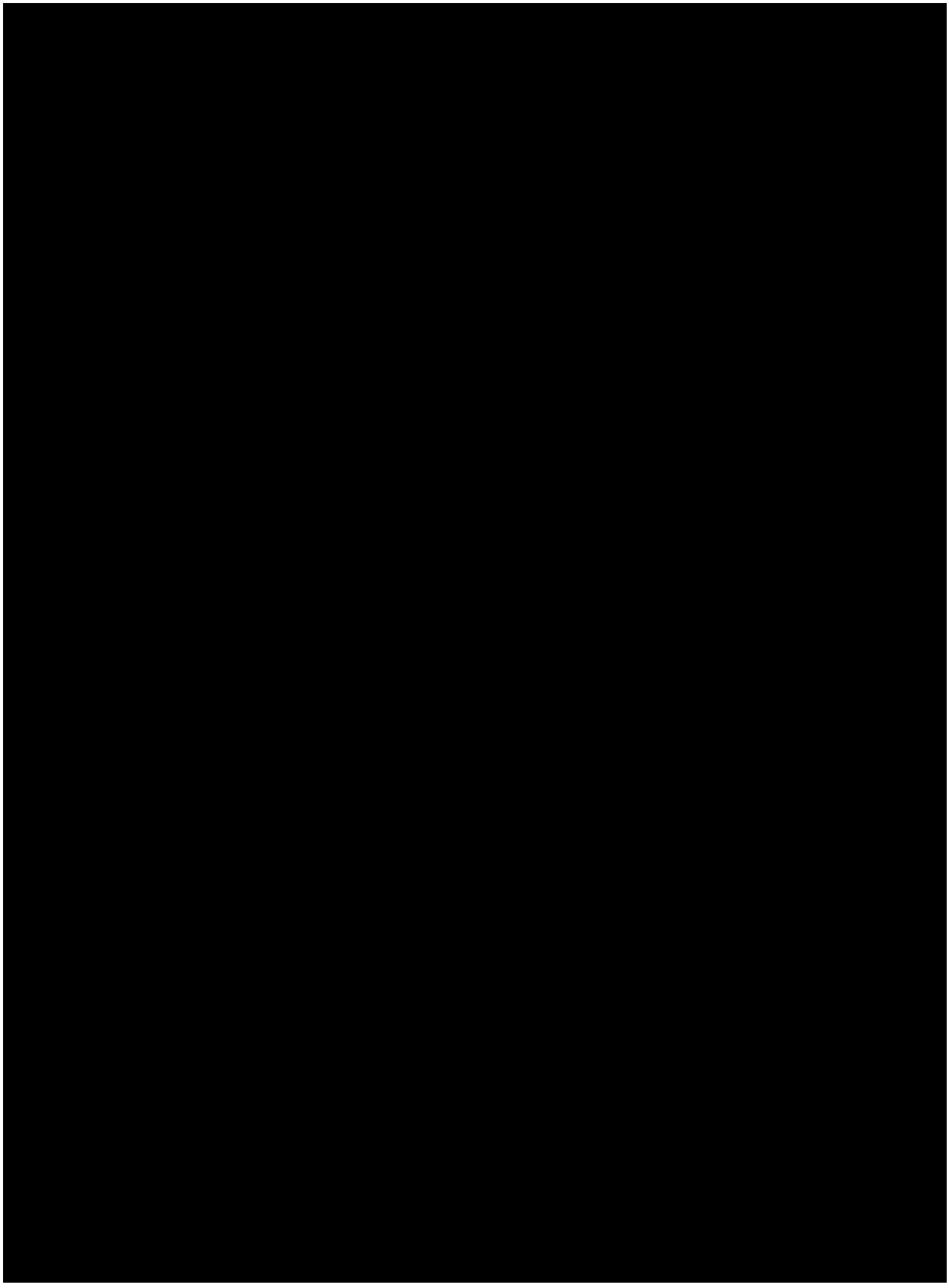
7.6.3 Endpoints related to safety assessments

These endpoints will be analysed based on the TS.

For analysis related to AEs, refer to Section 7.8.1.

CTP: *For weight the measurements per time point and the difference from baseline for the on-treatment measurements will be analyzed descriptively.*

[redacted]



[redacted]

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the TS.

If not stated otherwise, the safety results will be sorted by actual treatment.

Data of screened subjects, who withdrew after screening examination but prior to treatment, will not be included in the CTR. Exceptions are screen-failed subjects who had an SAE after the screening period, which was considered by the investigator to be related to the screening procedure. The safety data for treated subjects 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.

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 2 occurrences is given if the later 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 AE data for clinical trial reports and integrated summaries' (8) [001-MCG-156] and "Handling of missing and incomplete AE dates" (4) [001-MCG-156_RD-01].

The analysis of AEs will be based on the concept of TEAEs. That means that all AEs will be assigned to the treatment, post-treatment, screening or post-study phases 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 AESIs.

CTP: *The following are considered as AESIs:*

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- *an elevation of AST and/or ALT > 3 fold upper limit normal (ULN) combined with an elevation of total bilirubin > 2 fold ULN measured in the same blood draw sample, and/or*

- *marked peak aminotransferase (ALT and/or AST) elevations ≥10 fold ULN*

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

According to ICH E3 (9), AEs classified as 'other significant' need to be reported and will include those non-serious and non-significant AEs with
(i) 'action taken = discontinuation' or 'action taken = reduced', or
(ii) marked haematological and other lab abnormalities or AEs which lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at the BRPM.

The frequency of subjects with AEs will be summarised by treatment, primary system organ class and preferred term. This summary table will be shown based on all reported AEs. Furthermore separate tables will be presented for the frequency of subjects with procedural on-treatment AEs, the frequency of subjects with LPS related on−treatment AEs, and the frequency of subjects with non-procedural and non-LPS-related on-treatment AEs. AEs which were considered by the investigator to be related to the investigational study drug will be summarised separately. Separate tables will be provided for subjects with SAEs, subjects with AESIs and subjects with other significant AEs (according to ICH E3 (9)). AEs will also be summarised 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). The MedDRA version number will be displayed as a footnote in the respective output.

In addition, frequencies of subjects with non-serious AEs that had an incidence of > 5% (in preferred terms) for at least one treatment will be summarised by treatment, primary system organ class and preferred term.

For disclosure of AE data in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) register, additional information not included in a standard AE analysis will be performed. The following three entries will be created:

- AEs per arm for disclosure on EudraCT

- Non-serious AEs for disclosure on EudraCT

- Serious AEs for disclosure on EudraCT

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (10). If possible, analyses will be based on original values. If multiple reference ranges apply for a 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.

Descriptive statistics of laboratory values over time and for the difference from baseline (see Section 6.7, for on-treatment measurements) will be provided. Frequency tables of changes between baseline and last value on treatment with respect to the reference range will be presented.

CTP: *Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings.*

Urine dipstick data will neither be listed nor analysed.

Clinically relevant abnormal findings in laboratory data as judged by investigator will be reported as AEs (CTP Section 5.3.3) and will be analysed as part of AE analysis. Standard or project-specific rules for flagging clinically significant values will not be applied in this study.

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 difference 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

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

7.8.5 Others

7.8.5.1 Physical examination findings

Physical examination findings will be reported as relevant medical history/baseline condition (i.e., a condition already existent before intake of first 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 testing

CTP: *For the measurements obtained from the pulmonary function testing, descriptive statistics over time and for the differences from baseline will be evaluated.*

[redacted]

7.9.1 Smoking status

Smoking status at Visit 2, Visit 4 and Visit 6 will be listed, together with the stop date, if applicable, and the date and time of the last cigarette smoked prior to bronchoscopies at Visit 6 and 7 and the start date and time of the respective bronchoscopies.

[redacted]

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-50-413_RD-02:* "Important Manual Protocol Violations Spreadsheet", current version, IDEA for CON.
3	*001-MCS-50-413_RD-01*: "Protocol Violation Handling Definitions", current version, IDEA for CON.
4	*001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.
[redacted]	
6	*001-MCG-159*: "Reporting of clinical trials and project summaries", current version;
[redacted]	
8	001-MCG-156: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", Version 5; IDEA for CON.
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	*001-MCG-157*: "Display and Analysis of Laboratory Data", current version; IDEA for CON.
[redacted]	

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**23-MAR-2017**	[redacted],	None	This is the final TSAP without any modification