Trial Statistical Analysis Plan

c13175053-01

BI Trial No.:	1237.28
Title:	A randomised, double-blind, cross-over study to evaluate the effect of 6 weeks treatment of orally inhaled tiotropium + olodaterol fixed dose combination (5/5 µg) compared with tiotropium (5 µg), both delivered by the Respimat® Inhaler, on breathlessness during the three minute Constant Speed Shuttle Test (3min CSST) in patients with Chronic Obstructive Pulmonary Disease (COPD) [OTIVATO™]
Investigational Product(s):	Tiotropium + olodaterol fixed dose combination solution for inhalation - Respimat®
Responsible trial statistician(s):	[redacted] Telephone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	21 JUL 2017 SIGNED
Version:	FINAL

1. TABLE OF CONTENTS

LIST OF TABLES

2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
ACCP	American College of Chest Physicians
AE	Adverse Event
AESI	Adverse Event of Special Interest
AMP	Auxiliary Medicinal Products
ATS	American Thoracic Society
AUC	Area under the Curve
β-HCG	Beta-Human Chorionic Gonadotropin
BAC	Benzalkonium Chloride
BDI	Baseline Dyspnea Index
BI	Boehringer Ingelheim
bid	bis in die – twice daily
BRPM	Blinded report planning meeting
f	Breathing Frequency
CA	Competent Authority
CI	Confidence Interval
CML	Local Clinical Monitor
COPD	Chronic Obstructive Pulmonary Disease
CPR	Cardiopulmonary Resuscitation
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRQ-SAS	Chronic Respiratory Questionnaire - Self Administered Standardized
CRQ-SAI	Chronic Respiratory Questionnaire - Self Administered Individualized
CSST	Constant Speed Shuttle Test
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DOMS	Delayed Onset Muscular Soreness
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ECSC	European Coal and Steel Community
EDTA	Ethylenediaminetetraacetic acid
EELV	End expiratory lung volume
EMEA	European Agency for the Evaluation of Medicinal Products
EOTERS	End of Trial
ERS	European Respiratory Society
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
FDC	Fixed Dose Combination
FEV_1	Forced Expiratory Volume in 1^{st} second

Term	Definition / description
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
Gamma-GT	Gamma-Glutamyl Transpeptidase
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HFA	Hydrofluoroalkane
hrs	Hours
IB	Investigator's Brochure
IC	Inspiratory Capacity
ICH	International Conference on Harmonisation
ICH-GCP	International Conference on Harmonization - Good Clinical Practice
ICS	Inhaled corticosteroid
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ISWT	Incremental Shuttle Walk Test
LABA	Long Acting β_2-Agonists
LAMA	Long Acting Muscarinic Antagonists
LDH	Lactate Dehydrogenase
LOCF	Last observation carried forward
MBS-S	Modified BORG Scale
MCID	Minimum clinically important difference
MDI	Metered Dose Inhaler
MDP	Multidimensional Dyspnea Profile
MedDRA	Medical Dictionary for Drug Regulatory Activities
Min	Minute
mg	milligram
mMRC	Modified Medical Research Council Dyspnea Scale
mmHg	Millimetres mercury
MMRM	Mixed Effect Repeated Measures Model
MOP	Manual of Procedures
MQRM	Medical Quality Review Meeting
mth	Month
O*C	Oracle Clinical
PDE-4	Phosphodiesterase Type 4
PFT	Pulmonary Function Test
PK	Pharmacokinetics
PPS	Per protocol set
PRN	Pro re nata – as needed
PSTAT	Project Statistician
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
qd	quaque die (once a day)
RDC	Remote Data Capture

Term	Definition / description
REML	Restricted Maximum Likelihood
REP	Residual effect period
SA	Statistical analysis
SAE	Serious Adverse Event
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SMQ	Standardised MedDRA query
SOC	System organ class
SOP	Standard Operating Procedure
SpO_2	Oxygen saturation
SQ	Sensory Quality
TCM	Trial Clinical Monitor
TDI	Transitional Dyspnea Index
TESS	Treatment emergent signs and symptoms
TLC	Total Lung Capacity
TMF	Trial Master File
TMW	Trial Medical Writer
ToC	Table of contents
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit Normal
VAS	Visual Analog Scale
V_e	Minute Ventilation
V_T	Tidal Volume
wks	Weeks
w.o.	Washout

3. INTRODUCTION

As per ICH E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size, randomization.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

[redacted]

The protocol includes the following as secondary/[redacted] endpoints.

- Change in Chronic Respiratory Questionnaire - Self Administered Individualized (CRQ-SAI) dyspnea domain score after 6 weeks of treatment.
- Change in Chronic Respiratory Questionnaire - Self Administered Standardized (CRQ-SAS) dyspnea domain score after 6 weeks of treatment.
- [redacted]

To further clarify, it is revised to:

- Change from baseline in Chronic Respiratory Questionnaire - Self Administered Individualized (CRQ-SAI) dyspnea domain score after 6 weeks of treatment.
- Change from baseline in Chronic Respiratory Questionnaire - Self Administered Standardized (CRQ-SAS) dyspnea domain score after 6 weeks of treatment.
- [redacted]

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

Primary endpoint of efficacy will be used as described in the CTP, Section 5.1.1.

5.2 SECONDARY ENDPOINTS

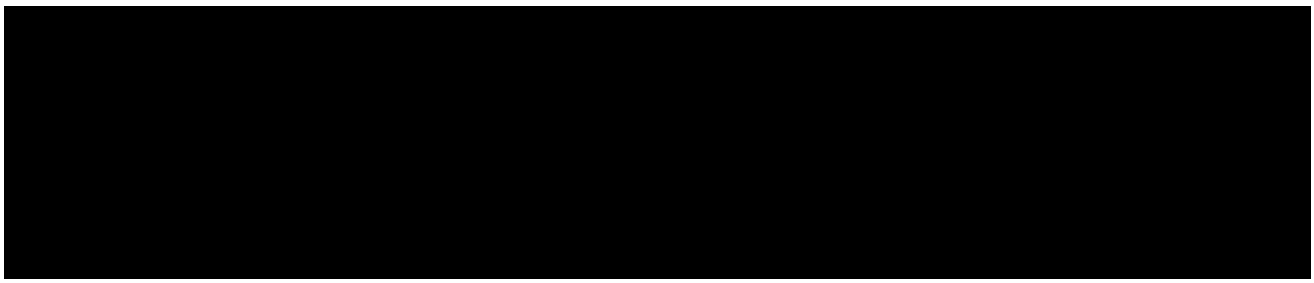
5.2.1 Key secondary endpoints

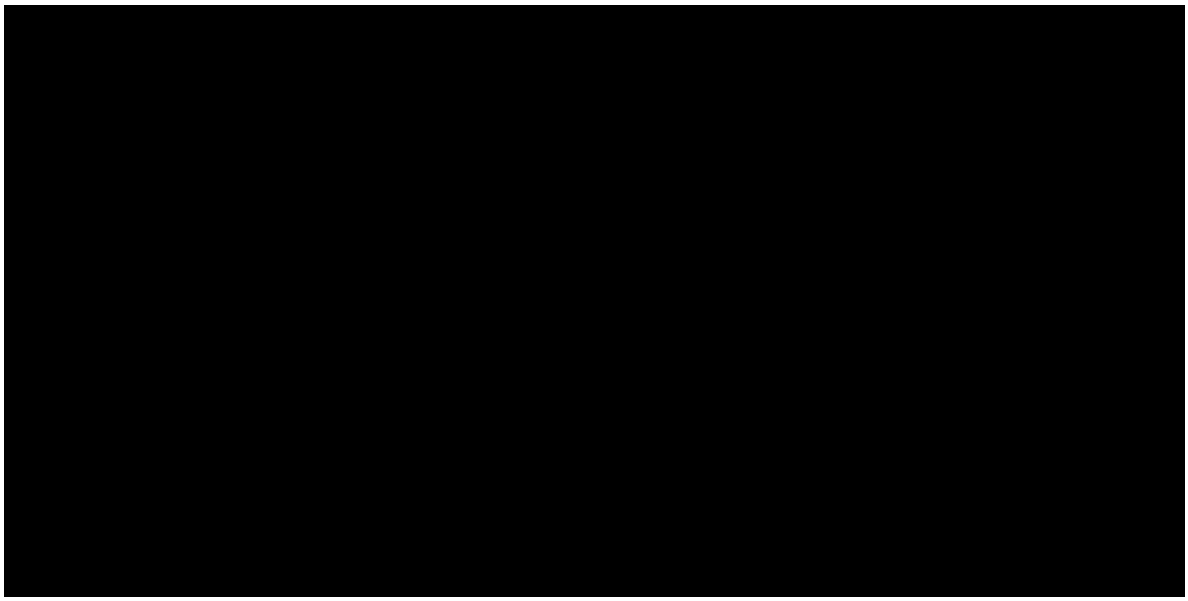
No key secondary endpoints were specified.

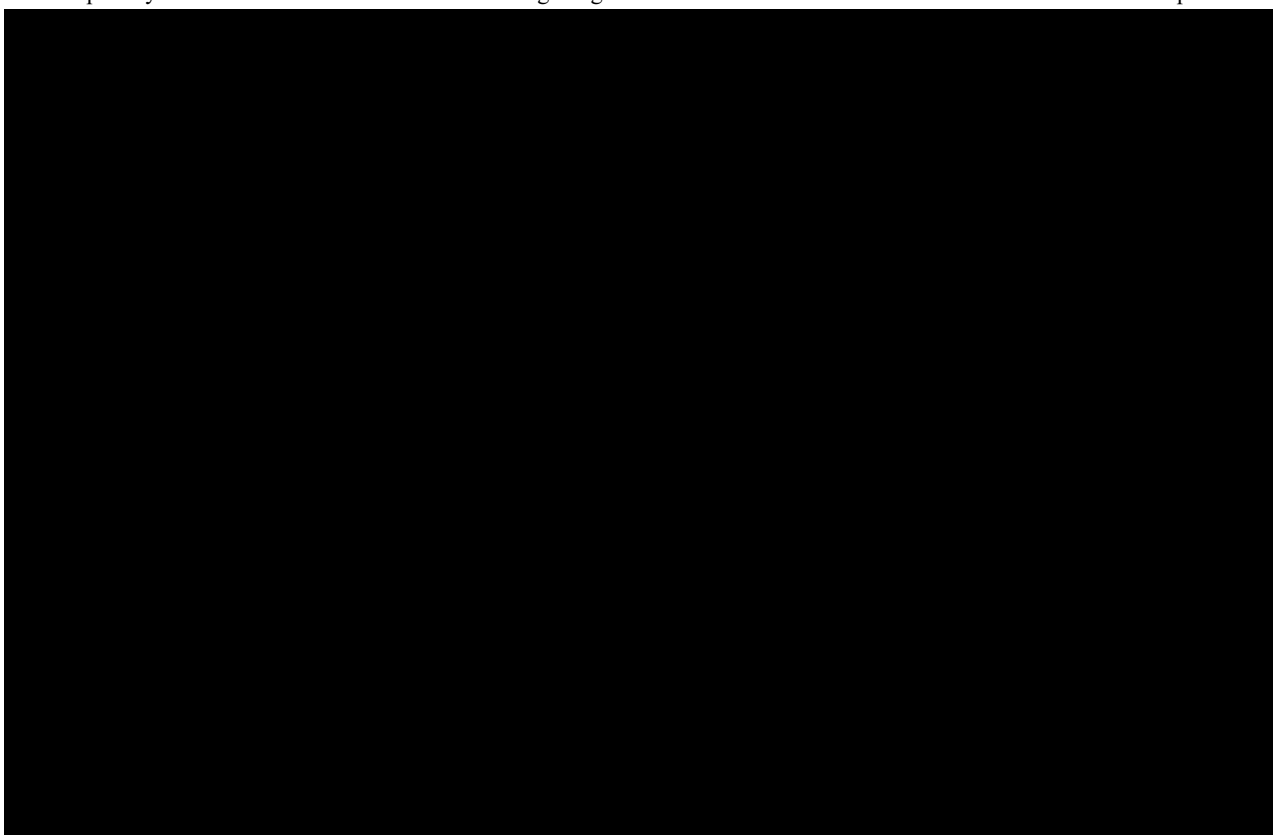
5.2.2 Secondary endpoints

Secondary endpoints of efficacy will be used as described in the CTP, Section 5.1.2.

CRQ scores are calculated according to “CRQ Package_English” (1).







6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

The doses to be administered are described in Section 4 of the CTP.

This is a crossover trial consisting of a 3 to 4-week run-in period followed by two six-week treatment periods and a three-week post-treatment period. The day after the follow-up visit will be considered the start of the post-study period in case there are any subsequent AE data we become aware of. There will be 3-week washout between treatment periods.

For the main safety analysis, data occurring during the treatment periods and within 21 days of stop of study drug for the period will be assigned to the respective treatment for that period. Data occurring before the first drug intake date is assigned to "screening". If the next treatment period starts within 21days of the end of the last period, data after the start of treatment for the next period will be assigned to the treatment for that period. Data more than 21 days after drug stop date for a period but before the start of the next period will be assigned to washout. Data more than 21 days after the end of the last treatment period and up to and including the date of the study termination will be assigned to post-treatment. Data after study termination will be assigned to post-study.

Any cases of patient being treated with the wrong study medication will be identified and summarised as an important protocol violation (PV).

- If a patient was treated with a treatment sequence different from the randomised treatment sequence throughout the on-treatment period, i.e., a patient was treated with incorrect study medication during every treatment period, this patient will be included in the treated set and will be analysed as treated for both efficacy and safety analyses, including patient disposition. Such a case will be reported as an important PV and this patient will be excluded from the per-protocol set (PPS).

- If a patient was treated with incorrect study medication throughout one treatment period only, but not both treatment periods, this patient will be included in the treated set and will be analysed as treated for safety analysis. For efficacy analysis, only efficacy data collected in the correct treatment period will be used and efficacy data collected in the other treatment period with the duplicate study medication will not be used. For patient disposition, such a patient will be analysed as randomised. Such a case will also be reported as an important PV but this patient will not be excluded from the PPS.

If a patient was treated with incorrect study medication during part of a treatment period, data of this patient will be discussed case by case at final Blinded report planning meeting (BRPM).

6.2 IMPORTANT PROTOCOL VIOLATIONS

A patient's deviation from the trial protocol is considered "relevant" if it can be expected that the deviation had a distorting influence on the assessment of the treatment effect on the primary endpoint of the trial or could affect the patient's safety/rights.

Table 6.2:1 gives the important protocol violations (IPVs) for the trial. The final decision with regards to important PVs and exclusion from the PPS will be made at the final blinded report planning meeting (BRPM) or data base lock meeting (DBLM).

In the case that a patient was randomised in both this trial and another trial or was randomised at two different sites in this trial, the patient will be indicated as having an important PV (IPV, see Table 6.2: 1-Exclusion Criterion 29). The following process will be followed with regards to the patient's data.

- All efficacy data will be excluded from the analysis and the patient will be excluded from the Full Analysis Set (FAS) (for this trial or both trials as appropriate).

- The only safety data which will be reported is exposure and serious adverse events (SAEs). These will be analysed according to the treatment which the patient actually received. If the patient was randomised twice in this study, the patient's data of periods with the same treatment will be combined (i.e. the patient is only counted once). If the patient participated in two different trials in the same project, he/she will be reported separately for each trial. As well, care will be taken with regard to the SAE narratives as to whether data for one patient number is relevant for an SAE under the other patient number.

- For disposition, demographics, baseline characteristics and important PVs, the patient will be analysed as treated. If the patient was randomised twice in this study and the treatments in periods are different, the patient will be counted under each treatment. A footnote will be included in the disposition table identifying the situation and noting that the patient is counted twice for disposition as well as demographics, baseline data and important PVs.

"Automatic" in the column "Automatic/Manual" means that the IPV can be checked automatically through the eCRF or through programming of relevant data in the database. "Automatic and Manual" and "Manual" in the column 'Automatic/Manual' means that to check the IPV, other information gained from investigator comments or CRA comments will be used.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Requirements	Excluded from	Automatic/ Manual
A		**Entrance criteria not met**			
	A1	Inclusion criteria not met	Inclusion Criteria 2-9 not met as specified in the protocol.	Exclude from PPS*: 2-9	Automatic and Manual
	A2	Exclusion criteria not met	Exclusion Criteria 1-30 not met as specified in the protocol	Exclude from PPS*: 3, 4, 8-12, 14-25, 29, 30	Automatic and Manual
B		**Informed consent**			
	B1	Informed consent not available/not done	Informed consent date missing; no signature on ICF.	All	Manual
	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 0. If date of informed consent equals to date of Visit 1, such cases will be discussed at MQRM/BRPM/DBL meetings.	None	Automatic
C		**Trial medication and randomisation**			
	C1	Incorrect trial medication taken	Not throughout study; could be at a clinic visit or between clinic visits. External vendor will check before unblinding.	PPS (decision at BRPM)	Automatic and Manual
	C2	Randomisation order not followed	Throughout the study	PPS	Automatic and Manual
	C3	Non-compliance with study medication			
	C3.1	Serious non-compliance with study medication as reported in monitoring report or manual PV spreadsheet	Decision at BRPM/MQRM.	PPS if at Visit 6 or 9	Manual
	C4	Medication code broken inappropriately	To be discussed and decided during MQRM/BRPM. Only inappropriate code breaks are IPVs (e.g. unblinding by Global Pharmacovigilance is not).	PPS	Manual

Table 6.2: 1 (continued) Important protocol violations

Category / Code		Description	Example/Comment	Excluded from	Automatic/ Manual
D		**Concomitant medication**			
	D1	Improper medication washout at baseline visit or primary endpoint visit(s)	Visit 4,6,7,9. Decision at BRPM	PPS	Automatic and Manual
	D2	Prohibited medication use during study	Check CT. Decision at BRPM.	PPS if in the week prior to Visit 4,6,7,9	Automatic and Manual
F		**Incorrect timing**			
	F3	Primary endpoint recorded outside time window			
	F3.5	Constant speed shuttle test <1 hour or >3 hours after inhalation	Only at Visits 6, 9	PPS	Automatic
Z		**Other**			
	Z1	Serious GCP non-compliance	Manual PVs reported by CML/CRA which are considered as important. Carefully reviewed, described and documented in DBL meeting minutes.	PPS	Manual
	Z2	Other PV affecting efficacy and possibly safety	Additional PV identified through monitoring which impacts the primary analysis and possibly patient's rights or safety. Carefully reviewed and documented in BRPM minutes and comment field of IPV ADS.	PPS	Automatic and Manual
	Z3	Other PV affecting safety only	Additional PV identified through monitoring which impacts patient's rights or safety. Carefully reviewed and documented in BRPM minutes and comment field of IPV ADS.	None	Automatic and Manual

KEY: CT = Concomitant Therapy, BRPM = Blinded report planning meeting, CML = Local Clinical Monitor, CRA = Clinical Research Associate, ICF = informed consent form, MQRM = Medical Quality Review Meeting, PPS = Per protocol set, DBL = Data Base Lock, ADS = Analysis Data Set

*Final decision will be discussed and determined prior to database lock.

Note: Missing visits, evaluations, and tests are considered as missing data, but not protocol deviations.

6.3 PATIENT SETS ANALYSED

The following nested patient sets are defined:

- Randomised set (RS):

This patient set includes all patients who signed informed consent form and were also randomised, regardless whether the patient was treated with study medication or not.

- Treated set (TS):

  This patient set is nested within RS and includes all patients who were dispensed study medication and were documented to have taken any dose of study medication. TS will be used for patient disposition, demographics and baseline disease characteristics, concomitant therapies, treatment compliance, treatment exposure and safety analyses (including AEs and vital signs).

- Full analysis set (FAS):

  This patient set is nested within TS and includes patients who had baseline measurement and at least one post-baseline measurement for the primary endpoint. The FAS will be used for the efficacy analyses. Assignment to the FAS will be done after implementation of any data handling rules which set measurements to missing.

- Per protocol set (PPS):

  This patient set is nested within FAS and includes only patients who had no important PVs which are specified to be excluded from the PPS (Table 6.3: 1). The final decision regarding which patients are excluded from PPS will be made at BRPM prior to data unblinding.

If the number of patients in PPS is less than 90% of the number of patients in FAS, the primary analysis for the primary endpoint will also be performed on the PPS as supportive analyses.

Table 6.3: 1 Patient sets analysed

	Patient Sets		
Class of endpoint	TS	FAS	PPS
Primary endpoint		primary analysis	supportive analysis*
Secondary endpoints		X	
Further endpoints		X	
Safety endpoints	X		
Demographic/baseline endpoints/exposure	X		

***** Performed only when the number of patients in PPS is less than 90% of the number of patients in FAS as sensitivity analysis.

[redacted]

6.5 POOLING OF CENTRES

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

6.6 HANDLING OF MISSING DATA AND OUTLIERS

As noted in the protocol, in general, missing data at a given visit will be imputed by the available data from the patient at that visit and completely missing visits will be handled through the statistical model.

Completely missing visits not due to worsening of study disease will not be imputed and will stay as missing, because such missing data are considered as randomly missing data and will be handled in the mixed model repeated measures model.

Completely missing visits due to the patient discontinuing due to worsening of study disease will be imputed with the least favourable prior visit during that period.

It could happen that a patient needed therapy for COPD symptoms at a clinic visit. This therapy was entered on the rescue medication electronic Case Report Form (eCRF). This may or may not be the rescue medication provided by Boehringer Ingelheim (BI). For purposes of the imputation rules this will be termed “rescue medication” regardless of whether or not it was BI-supplied rescue medication.

The following rules are used for exercise data:

In situations where the full 3-min of exercise was completed:

- Measurements of Borg breathing discomfort scale, [redacted] which are missing for the 3 minute time point will be imputed using the last non-missing observation during exercise (but not non-missing measurements at rest) for that visit.
- Measurements of Borg breathing discomfort scale, [redacted] which are missing for all other time points during exercise will not be imputed (i.e. left as missing).

In situations where exercise is terminated prematurely:

- Borg breathing discomfort [redacted] scores will be imputed from end-of-exercise value for all time points beyond the exercise termination (including the 3 minute time point).

[redacted]

In addition, the following rules apply:

[redacted]

- If rescue medication was used prior to exercise testing or if the time of rescue medication use is unknown, measurements taken at rest and during exercise, i.e., - Borg scale of breathing discomfort, [redacted] blood pressure, and IC will be set to missing and not imputed. If rescue medication was used during exercise testing, measurements of Borg scale of breathing discomfort [redacted] will be set to missing for those time points after the first use of rescue medication and imputed using the worst non-missing observation during exercise (but not non-missing measurements at rest) for that visit before rescue medication use.

The following rules will be used for spirometry data which were collected at Visits 4, 5, 6, 7, 8, and 9:

- Since there is only one spirometry measurement at each on-treatment clinic visit, rescue medication use on or before the spirometry measurement or rescue use with unknown time will both result in all spirometry measurements for the visit being set to missing. In these cases the entire visit will be imputed using the least favourable prior non-missing measurement from previous visits during that period.

- If the spirometry measurement for a visit is completely missing because a patient discontinued due to worsening of study disease, then all data for this visit will be imputed with the least favourable prior observation from previous visits during that period.

- Randomly missing spirometry measurements at Visits 5, 6, 8 and 9, e.g., due to a mechanical failure, will not be imputed.

Also,

[redacted]

- For endpoints with two period baselines, if one period baseline is missing, it will be imputed by the other period baseline.

- For CRQ-SAI, at visits where dyspnoea activities were selected differently than the baseline (at visit 4), those dyspnoea activity values will be set as missing values.

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates") (2).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Period baseline

The period baseline is defined as the pre-dose measurement, performed prior to dosing on the first day of each period.

Patient baseline

The patient baseline is defined as the mean of non-missing period baselines for each patient.

Study baseline

For endpoints with only one baseline measurements prior to the first treatment period, this baseline will be called study baseline.

More specifically,

Baselines for Primary Endpoint

The primary endpoint is the change from baseline in intensity of breathlessness measured using the MBS-S at the end of the 3min Constant Speed Shuttle Test (CSST) after 6 weeks of treatment.

- Period baselines are measured at the end of the 3 min CSST at visits 4 and 7

Period Baselines for Secondary Endpoints

Change from baseline in Inspiratory Capacity (IC) measured prior to exercise, after 6 weeks of treatment.

- Period baselines are measured in resting IC (Omnia) prior to exercise at visits 4 and 7

Change from baseline in IC measured at the end of exercise, after 6 weeks of treatment

- Period baselines are measured in IC at the end of exercise at visits 4 and 7

Change from baseline in 1 hour post-dose FEV_1, after 6 weeks of treatment.

- Period baselines are measured in pre-dose FEV_1 at visits 4 and 7

Change from baseline in 1 hour post-dose FVC, after 6 weeks of treatment.

- Period baselines are measured in pre-dose FVC at visits 4 and 7

Change from baseline in intensity of Breathlessness (MBS-S) at 1min, 2min, and 2.5min during the 3min CSST after 6 weeks of treatment.

- Period baselines are measured at the corresponding time point during the 3 min CSST at visits 4 and 7

Change from baseline in Chronic Respiratory Questionnaire - Self Administered Individualized (CRQ-SAI) dyspnea domain score after 6 weeks of treatment.

- Period baselines are collected at visits 4 and 7

Change from baseline in Chronic Respiratory Questionnaire - Self Administered Standardized (CRQ-SAS) dyspnea domain score after 6 weeks of treatment.

- Period baselines are collected at visits 4 and 7

[redacted]

Time windows and calculated visits

Planned and actual study day will be included in the analysis data sets. These will both be calculated relative to the beginning of the study and to the beginning of respective study periods in the crossover design as indicated in the following table (Table 6.7: 1).

Table 6.7: 1 Planned and actual study days

Visit	Relative to period start		Relative to study start	
	Planned day	Actual day	Planned day	Actual day
4	1	1	1	1
5	22	Visit 5 date - Visit 4 date + 1	22	Visit 5 date - Visit 4 date + 1
6	43	Visit 6 date - Visit 4 date + 1	43	Visit 6 date - Visit 4 date + 1
7	1	1	64	Visit 7 date - Visit 4 date + 1
8	22	Visit 8 date - Visit 7 date + 1	85	Visit 8 date - Visit 4 date + 1
9	43	Visit 9 date - Visit 7 date + 1	106	Visit 9 date - Visit 4 date + 1

7. PLANNED ANALYSIS

For End-Of-Text tables, the set of summary statistics is: N / Mean / Standard deviation (SD) / Min / Median / 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 (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Use of pulmonary medications during treatment period and testing will be summarised in the end-of-text tables in the Clinical Trial Report (CTR) and a subject data listing of all concomitant medications will be provided in Appendix 16.2.

A table of number (%) of patients with concomitant diagnoses by system organ class (SOC) and preferred term (PT) will be included along with a supporting subject data listing. Concomitant diagnoses will be coded with the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) in effect at database lock.

Descriptive statistics and frequency tables (%) will be presented for history of trial indication.

Frequency tables (%) will be presented for COPD background characteristics.

7.3 TREATMENT COMPLIANCE

Only descriptive statistics are planned for this section of the report. Only descriptive statistics, i.e. the number (%) and percent of patients with compliance in the range of 80% - 120% will be provided. (cf. Section 5.4 for calculation of treatment compliance).

7.4 PRIMARY ENDPOINTS

For the primary analysis, a mixed effect model repeated measures (MMRM) is specified in the protocol. This model will include treatment and period as fixed effects, patient as a random effect and period baseline as well as patient baseline as covariates. Compound symmetry will be used as a covariance structure for within patient variation. 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 (3). Adjusted mean values as well as treatment contrasts will be presented together with the 95% confidence intervals (CI) and p-values.

[redacted]

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 protocol.

7.5.2 Other Secondary endpoints

The MMRM described for the primary endpoint will be performed for all secondary continuous endpoints. Adjusted mean values as well as treatment contrasts will be presented together with the 95% CIs and nominal p-values. All p-values will be considered as descriptive.

[redacted]

[redacted]

7.7 EXTENT OF EXPOSURE

Extent of exposure is calculated as drug stop date minus drug start date plus one day and treatment interruptions are not taken into account in the calculation.

Extent of exposure will be summarised using descriptive statistics for the total treatment exposure in days as well as tabulation of number of patients with total exposure fall into the following categories:

- 1 day
- 2 – 21 days
- 22 – 42 days
- 43 – 63 days
- 64 - 84 days
- >=85 days.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set.

7.8.1 Adverse events

The analyses of adverse events will be descriptive in nature and will be based on BI guideline "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries" (4). All analyses of AEs will be based on the number of patients with AEs (not the number of AEs). For this purpose, AE data will be combined in a 2-step procedure into AE records.

In a first step, AE occurrences, i.e. AE entries on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)
- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

In a second step, AE episodes will be condensed into AE records provided that the episodes were reported with the same term on the respective MedDRA level and that the episodes are assigned to the same treatment. For further details on summarization of AE data, please refer to BI guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' (4).

Analyses of adverse events are based on the concept of treatment emergent adverse events. This means that all adverse events occurring between first drug intake and 21 days after last drug intake are assigned to the respective analysing treatment. All adverse events occurring before first drug intake are assigned to “screening” and all adverse events occurring after last drug intake + 21 days up to and including trial completion date are assigned to “post-treatment”. AEs more than 21 days after drug stop date for a period but before the start of the next period will be assigned to 'washout'. AEs starting after trial completing date are assigned to “post-study”. Screening, post-treatment and post-study AEs are presented in subject data listings only.

An overall summary of adverse events will be presented. A detailed description of the assignment of AE’s to treatment can be found in Section 6.1.

The frequency of patients with adverse events will be summarised by treatment, primary system organ class and preferred term. Separate tables will be provided for patients with other significant adverse events according to ICH E3 (5), for patients with adverse events leading to treatment discontinuation, for patients with adverse events leading to death, for patients with investigator determined drug-related adverse events, and for patients with serious adverse events.

According to ICH E3 (5), AEs classified as ‘other significant’ include those non-serious and non-significant adverse events with
(i) ‘action taken = discontinuation’ or ‘action taken = reduced’, or
(ii) marked haematological and other lab abnormalities or that lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator and confirmed at a BRPM.

The system organ classes will be sorted according to the standard sort order specified by EMEA, preferred terms will be sorted by frequency (within system organ class).

Standard AE analyses requested for public disclosure at CT.gov and European Union Drug Regulating Authorities Clinical Trials will also be provided in Section 16.1.9.2 of the CTR.

7.8.2 Laboratory data

Clinically significant findings in laboratory data will be reported as “baseline conditions” or “adverse events” and will be analysed accordingly.

7.8.3 Vital signs

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

7.8.4 ECG

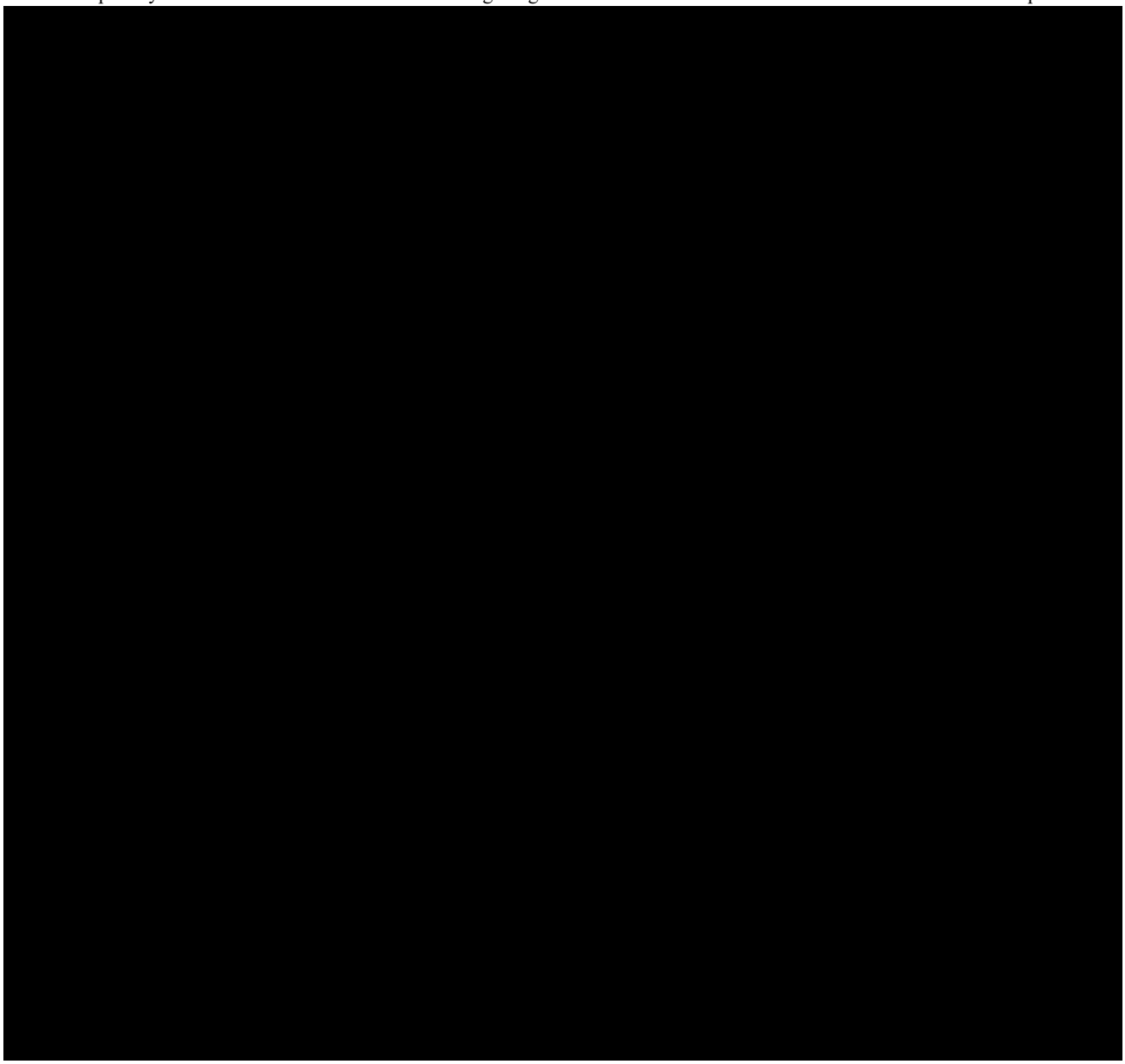
Clinically significant findings in ECG data will be reported as “baseline conditions” or “adverse events” and will be analysed accordingly.

7.8.5 Others

None.

8. REFERENCES

1	*R17-2573*: “CRQ Package_English”.
2	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON. *001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", version 5; IDEA for CON.
3	*R10-4391*: Kenward, M.G. The use of baseline covariates in crossover studies. Biostatistics 11(1),1-17 (2010)
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



10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**23-AUG-16**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct
Final	**21-JUL-17**		None	This is the final TSAP without any modification