Trial Statistical Analysis Plan

c08927535-01

BI Trial No.:	1237.33
Title:	A randomised, double-blinded, active-controlled 2-way cross over trial to assess the effects of 6 weeks treatment of once daily orally inhaled tiotropium + olodaterol fixed dose combination delivered by RESPIMAT Inhaler compared with tiotropium delivered by RESPIMAT Inhaler on lung hyperinflation, exercise capacity and physical activity in Japanese patients with Chronic Obstructive Pulmonary Disease (COPD)
Investigational Product(s):	Japanese Physical Activity Study [VESUTO™]
Responsible trial statistician(s):	[redacted] [redacted]. Address: [redacted] Phone: [redacted] Fax: [redacted]
Date of statistical analysis plan:	10 APR 2017
Version:	Final

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2. LIST OF ABBREVIATIONS

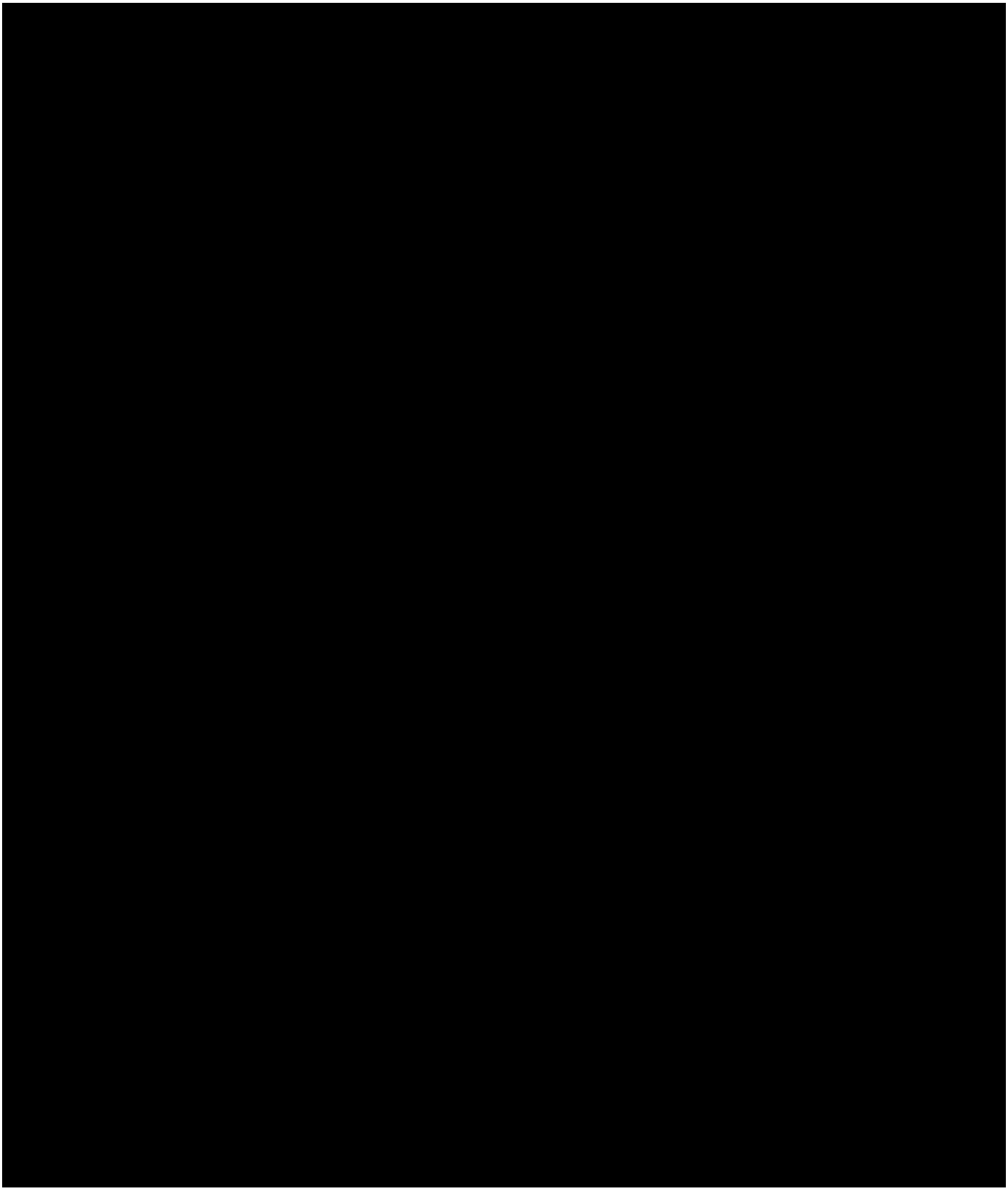
Term	Definition / description
AE	Adverse event
BRPM	Blinded report planning meeting
[redacted]	[redacted]
CRF	Case Report Form
COPD	Chronic Obstructive Pulmonary Disease
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
[redacted]	[redacted]
ECG	Electrocardiogram
FAS	Full analysis set
[redacted]	[redacted]
IC	Inspiratory capacity
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
METs	Metabolic equivalents
MQRM	Medical Quality Review Meeting
[redacted]	[redacted]
PPS	Per protocol set
PT	Preferred term
PV	Protocol violation
RS	Randomised set
SAE	serious adverse event
[redacted]	[redacted]
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
SD	Standard deviation
SOC	System organ class
TS	Treated set
TSAP	Trial statistical analysis plan

3. INTRODUCTION

As per International Council for Harmonisation (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 Trial statistical analysis plan (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.



5. ENDPOINTS

5.1 PRIMARY ENDPOINT

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

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoint

This section is not applicable since there are no key secondary endpoints specified in the CTP.

5.2.2 Secondary endpoints

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

[redacted]

5.4 OTHER VARIABLES

Treatment compliance

- Percent compliance
- Percent missing compliance

Treatment compliance will be based on data from the patient diary. The patients will report whether they took study medication for each day during the treatment period. For each patient, percent compliance will be calculated as the number of times they reported taking study medication divided by the number of times a non-missing response was given (excluding clinic visit days for both numerator and denominator) times 100. The percent of missing compliance data will also be calculated as the number of occasions of missing compliance data divided by the expected number of non-clinic occasions times 100. In case there are multiple records with the same diary date, the responses will be compared within that date. If all of the responses are identical (yes, no, or missing) to a common value, then that common value will be used. If not all of the responses are identical, then the response will be set to missing. Two examples are given in Table 5.4: 1.

Table 5.4: 1 Examples for duplicate compliance data

		Date	Study drug Taken
Case 1	Original data	25Sep2014	Yes
		25Sep2014	Yes
	Collapsed data	25Sep2014	Yes
Case 2	Original data	15Jan2015	No
		15Jan2015	Yes
	Collapsed data	15Jan2015	.

Due to the nature of how compliance data is collected, the value for percent treatment compliance can never be more than 100%. This is because yes/no responses for taking study medication are collected rather than the number of doses taken. The ranges on the compliance table will be <80% and 80% - 100%.

Safety

- pulse rate and blood pressure in conjunction with Pulmonary function testing

- pulse rate and SpO2 in conjunction with 6MWT
- For vital signs in conjunction with spirometry, frequency tables will be presented with the number and percentage of patients with marked changes in vital signs (decrease, increase) at any time and for each time point separately by treatment. Marked changes are defined in Table 5.4: 2.

Table 5.4: 2 Definition of marked changes in vital signs in conjunction with spirometry

Variable	Criteria
Systolic blood pressure increase	value > 150 mmHg and an increase >= 25 mmHg above baseline
Systolic blood pressure decrease	value < 100 mmHg and a decrease >10 mmHg below baseline
Diastolic blood pressure increase	value > 90 mmHg and an increase > 10 mmHg above baseline
Diastolic blood pressure decrease	value < 60 mmHg and a decrease > 10 mmHg below baseline
Pulse rate increase	> 100 bpm and an increase > 10 bpm above baseline
Pulse rate decrease	< 60 bpm and a decrease > 10 bpm below baseline

- all adverse events (AEs), including any clinically relevant changes/abnormalities in physical examination, vital signs, laboratory values, and electrocardiogram (ECG)

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 two-week screening 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. In this study, there will be no 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 that 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 21 days 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. In this trial, next treatment will be started after end of treatment of first period as soon as possible because there is no washout period as planned. 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 "important" 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 lists the important PVs for this trial. Some of the important PVs can be checked automatically through the electronic case report form or through programming of relevant data in the database; others will need information gained from investigator comments or site monitoring reports and will need a decision at a Medical Quality Review Meeting (MQRM) or BRPM or through team review of the manual PV log.

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 27). 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 and both treatments are the same, the patient's data 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 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.

The final decision with regards to important PVs and exclusion from the PPS will be made at the final BRPM or database lock meeting before unblinding.

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from	Automatic/ Manual
A		**Entrance criteria not met**			
	A1	**Inclusion criteria violated**	Inclusion Criteria 2,3,4,5,6,7,8 not met	Exclude from PPS: 2,3,4,5,6,7,8	Criteria 3 ,5 and 6 are Automatic. Otherwise Manual.
	A2	**Exclusion criteria violated**	Exclusion Criteria 2-14,16-29 not met	Exclude from PPS: 3,9-14,17-20,23,27,28 Keep in PPS: 2,4-8,15, 16, 21, 22, 24-26,29	Manual
B		**Informed consent**			
	B1	**Informed consent not available/not done**			
	B1.1	Informed consent to study 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 a patient signed the correct version of the ICF after Visit 0, such cases will be discussed at MQRM/BRPM/DBL meetings.	None	Automatic

ICF = Informed Consent Form
DBL = Database Lock
BRPM = Blinded report planning meeting
MQRM = Medical Quality Review Meeting
PPS = Per protocol set

Table 6.2: 1 (cont'd) Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from	Automatic/ Manual
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 and incorrect trial medication taken**	Throughout the study	PPS	Automatic and Manual
	C3	**Non-compliance with study medication**			
	C3.2	Serious non-compliance with study medication as reported in monitoring report or manual PV spreadsheet	Decision at BRPM/MQRM.	PPS if at Visit 3 or 4	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
D		**Concomitant medication**			
	D1	**Improper medication washout at baseline visit or primary endpoint visit(s)**	Visit 2, 3 or 4. Refer to Table 4.2.2.1: 1 in CTP. Decision at BRPM	PPS	Manual
	D2	**Prohibited medication use during study**	Check CT. Decision at BRPM.	PPS if in the week prior to Visit 3 or Visit 4	Manual
F		**Incorrect timing**			
	F3	**Primary endpoint recorded outside time window**			
	F3.6	PFT measurement at 60 minutes planned time taken <30 minutes or > 3 hours after dosing	Visit 3 or 4	PPS	Automatic

CT = Concomitant Therapy
BRPM = Blinded report planning meeting
MQRM = Medical Quality Review Meeting
PPS = Per protocol set

Table 6.2: 1 (cont'd) Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from	Automatic/ Manual
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	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	Manual
	Z4	**Missing value of all primary and secondary endpoints**	Patients who had baseline measurement and at least one post-baseline measurement for the primary endpoint or a secondary endpoint will be included FAS. Patient who does not have above measurement is IPV.	FAS	Automatic

CML = Local Clinical Monitor
CRA = Clinical Research Associate
Note: Missing visits, evaluations, and tests are considered as missing data, but not protocol deviations.
DBL = Data Base Lock
ADS = Analysis Data Set

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 or a secondary 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 PPS will be used for sensitivity analysis if PPS less than 90% of FAS.

  The final decision regarding which patients are excluded from PPS will be made at BRPM prior to data unblinding.

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		

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

6.4 SUBGROUPS

No subgroups are defined and no subgroup analyses are planned.

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

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/weeks due to the patient discontinuing due to worsening of study disease will be imputed with the baseline value.

It could happen that a patient needed therapy for COPD symptoms at a clinic visit. This therapy was entered on the rescue medication of 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.

For spirometry data, the records which are flagged as "unacceptable" by the vendor (ERT) will be administratively set to missing and treated as randomly missing data for imputation purpose.

The following rules are used for exercise data:

- [redacted]
- Measurements of oxygen saturation, blood pressure and heart rate which are missing during recovery will not be imputed.
- [redacted]

The following rules will be used for spirometry data which were collected at Visits 2, 3 and 4:

- 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 with baseline.

- If spirometry measurements for an entire visit are completely missing because a patient discontinued due to worsening of study disease, then all data for this visit will be imputed with baseline.

- Randomly missing spirometry measurements will not be imputed.

Missing safety data will not be imputed with the exception of missing or incomplete AE dates which will be imputed according to BI guideline 'Handling of missing and incomplete AE dates' (1).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Measurements collected at Visit 2 will be used as baseline with the exception of the activity endpoints which are averaged over 2 weeks. For endpoints of physical activity monitoring, baseline will be the average value in two weeks prior the day before first administration (Visit 2) except for Day -2 and Day -1. These will be defined as "Study baseline" which will be common baseline for both period 1 and period 2.

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 Planned and actual study days, and time windows

	Relative to period start		Relative to study start	
Visit	Planned day	Actual day	Planned day	Actual day
2	1	1	1	1
3	43	Visit 3 date – Visit 2 date + 1	43	Visit 3 date – Visit 2 date + 1
4	43	Visit 4 date – Visit 3 date + 1	85	Visit 4 date – Visit 2 date + 1
5	3	Visit 5 date – Visit 4 date + 1	106	Visit 5 date – Visit 2 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 for the treated set 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. Summary statistics will be given for percent compliance along with the number (%) of patients with compliance in the categories <80%, 80% - 100% (cf. Section 5.4 for calculation of treatment compliance).

7.4 PRIMARY ENDPOINT

The primary analysis for Inspiratory capacity (IC) will be conducted using mixed effect repeated measurement including treatment and period as categorical fixed effects, study baseline as a covariate and patient as a random effect treatment. 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 (2). Adjusted mean values as well as treatment contrasts will be presented together with the 95% confidence intervals and p-values.

If the number of patients in PPS is less than 90% of the number of patients in FAS, the primary analyses will also be performed on PPS. These will be supportive analyses to assess the robustness of the primary analysis using FAS.

Descriptive statistics by treatment will be displayed.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoint

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

7.5.2 Secondary endpoints

The analysis will be performed as defined in the CTP, Section 7.3.2.

Descriptive statistics by treatment will be displayed.

Additional analysis are described follows.

7.5.2.1 Average number of step per day (step/day) in the 2 weeks prior to Week 6

[redacted]

7.5.2.2 Average daily duration (minute) of ≥4 metabolic equivalents (METs) in the 2 weeks prior to Week 6

[redacted]

7.5.2.3 Average daily duration (minute) of ≥3 METs in the 2 weeks prior to Week 6

[redacted]

7.5.2.4 Average daily duration (minute) of ≥2 METs in the 2 weeks prior to Week 6

[redacted]

7.5.2.5 Average daily active strength (METs·minute) of ≥3 METs in the 2 weeks prior to Week 6

[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 AEs will be descriptive in nature and will be based on BI guideline 'Handling and summarisation of AE data for CTRs and integrated summaries' (3). All analyses of AE will be based on the number of patients with AEs and NOT on the number of AEs. For this purpose, AE data will be combined in a 2-step procedure into AE records.

In the first step, AE occurrences, i.e. AE entries collected in the eCRF, 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 are 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 the 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 summarisation of AE data, please refer

to BI guideline 'Handling and summarisation of AE data for CTRs and integrated summaries' (3).

Analyses of AEs are based on the concept of treatment emergent adverse events. This means that all AEs occurring between first drug intake and 21 days after last drug intake are assigned to the respective analysing treatment. All AEs occurring before first drug intake are assigned to ‘screening’ and all AEs 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 completion date are assigned to ‘post-study’. Screening, post-treatment and post-study AEs are presented in subject data listings only. For details on the treatment definition, see Section 6.1.

An overall summary of AEs will be presented.

The frequency of patients with AEs will be summarised by treatment, primary SOC and PT. Separate tables will be provided for patients with other significant adverse s according to ICH E3 (4), for patients with AEs leading to treatment discontinuation, for patients with AEs leading to death, for patients with investigator determined drug-related adverse events, and for patients with SAEs.

According to ICH E3 (4), 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 the European Medicines Agency, PTs will be sorted by frequency (within SOC).

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

This section is not applicable.

8. REFERENCES

1	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
2	*R10-4391*: Kenward, M.G. The use of baseline covariates in crossover studies. Biostatistics 11(1),1-17 (2010)
3	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", version 5; IDEA for CON.
4	*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. ADDITIONAL SECTIONS

PROGRAMMING CODE FOR INFERENTIAL ANALYSIS

- SAS codes for primary analysis:

```
PROC MIXED data=indata order=internal method=reml cl covtest;
     CLASS trtgrp period usubjid;
     MODEL ept = trtgrp period eptbase / ddfm=kr solution;
     repeated period / type=cs subject=usubjid r rcorr;
     LSMEANS trtgrp / pdiff cl;
RUN;
```

The endpoint is denoted by `ept`, `eptbase` denotes the baseline value of the endpoint, `trtgrp` denotes treatment, `period` denotes the treatment period, and `usubjid` denotes patient number.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	10-APR-2017	[redacted]	None	This is the final TSAP without any modification.