Trial Statistical Analysis Plan

c16258258-02

BI Trial No.:	1237.30
Title:	An open-label trial to assess pharmacokinetics and safety of tiotropium + olodaterol fixed-dose combination (5 µg/ 5 µg) delivered by the RESPIMAT inhaler after single and multiple dose treatment in Chinese patients with Chronic Obstructive Pulmonary Disease (COPD) Including Protocol Amendment 2 [c07779972-03]
Investigational Product:	Tiotropium + olodaterol fixed-dose combination solution for inhalation - RESPIMAT
Responsible trial statistician:	[redacted] Phone: [redacted], Fax: [redacted]
Date of statistical analysis plan:	30 JUN 2017 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADS	Analysis data set
AE	Adverse event
BAC	Benzalkonium chloride
BI	Boehringer Ingelheim
bpm	beats per minute
COPD	Chronic Obstructive Pulmonary Disease
CTP	Clinical Trial Protocol
DBL	Database lock
ECG	Electrocardiogram
ECSC	European Community for Steel and Coal
EDTA	Ethylene diaminete taacetic acid
EX	Exclusion criterion
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
ms	milliseconds
O*C	Oracle Clinical
PK	Pharmacokinetics
PR interval	The ECG interval from the start of the P wave to the start of the QRS complex
PT	Preferred term
PV	Protocol violation
QRS complex	Combination of Q wave, R wave, and S wave
QT interval	The ECG interval from the start of the QRS complex to the end of the T wave

Term	Definition / description
QTc interval	QT interval, heart rate corrected
QTcF interval	QT interval, corrected according to Fridericias formula
RPM	Report planning meeting
RR interval	The ECG interval from the peak of the R wave to the peak of the subsequent R wave
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
TSAP	Trial statistical analysis plan

3. INTRODUCTION

As per International Conference on 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, randomisation.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

There has been no change in the planned analyses from the statistical methods described in the CTP.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

No efficacy endpoint is defined for this trial. The objective of this trial is to assess the pharmacokinetics (PK) and safety of tiotropium + olodaterol fixed dose combination (5 µg/ 5 µg). The primary endpoints are specified as defined in the CTP, Sections 5.1.1.

5.2 SECONDARY ENDPOINTS

The secondary endpoints are specified as defined in the CTP, Sections 5.1.2.

[redacted]

5.4 OTHER VARIABLES

Demographic data:

- Gender: Male, Female
- Age [years]
- Race
- Height [cm]
- Weight [kg]
- Body mass index [kg/m^2]
- Smoking status: Never smoked, Ex-smoker, Currently smokes
- Smoking history [pack years]

History of trial indication:

- Trial diagnosis duration [days]

Treatment compliance:

Compliance [%] = (number of actual administered days) / (date of last trial drug administration – date of first trial drug administration + 1) × 100

Treatment exposure:

Extent of exposure [days] = date of last trial drug administration – date of first trial drug administration + 1 day

Pharmacokinetic:

The derivation of standard pharmacokinetic parameters will be performed according to 001-MCS-36-472 (1).

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Analysing treatments will be used for safety analysis. Date from the first trial drug intake up to 21 days after the last trial drug intake will be considered as on-treatment.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Table 6.2: 1 gives the important protocol violations (PVs) for this trial. Patients with important PVs relevant to the evaluation of PK will be excluded from PK analysis. If data shows other important PVs, this table will be supplemented accordingly at the Database lock (DBL) meeting at latest.

Table 6.2: 1 Important protocol violations

Category / Code		Description	Comment/Example	Excluded from
A		**Entrance criteria not met**		
	A1	**Respiratory conditions**		
	A1.1	Without diagnosis of COPD	IN 2 not met Detected manually	None
	A1.2	Age<40	IN 3 not met Detected manually	None
	A1.3	Never smoke or ex-smokers with a smoking history of less than 10 packs year	IN 4 not met Detected automatically	None
	A1.4	Patients are not capable to enter the trial	IN 5 not met Detected manually	None
	A1.5	Patients are unable to inhale medication	IN 6 not met Detected manually	None
	A1.6	Women of childbearing potential but are unable to use effective methods in birth control	IN 7 not met or EX 23 met Detected manually	None
	A2	**Exclusion criteria met**		
	A2.1	With significant disease other than COPD	EX1 Detected manually	None
	A2.2	With clinically relevant abnormal baseline haematology, blood chemistry, or urinalysis	EX2 Detected manually Detected automatically for SGOT, SGPT, bilirubin, creatinine	None
	A2.3	With asthma	EX3 Detected manually	None
	A2.4	Patients are under conditions specified in exclusion criteria 4-14	EX4-14 Detected manually	None
	A2.5	Have undergone thoracotomy with pulmonary resection	EX15 Detected manually	None
	A2.6	Treated with any oral β-adrenergics	EX16 Detected manually	None
	A2.7	Treated with oral corticosteroid medication at unstable dose	EX17 Detected manually	None
	A2.8	Regularly use daytime oxygen therapy	EX18 Detected manually	None
	A2.9	Completed a pulmonary rehabilitation program in the six weeks prior to visit 1 or currently in the program	EX19 Detected manually	None
	A2.10	Insufficient wash-out period	EX20 Detected manually	None

Category / Code		Description	Comment/Example	Excluded from
	A2.11	Hypersensitivity toβ-adrenergics and/or anticholinergic drugs, BAC, EDTA or any other component of the RESPIMAT inhalation solution	EX21 Detected manually	None
	A2.12	Pregnant or nursing women	EX22 Detected manually	None
	A2.13	Patients who were in this study or are currently participating another study	EX24 Detected manually	None
	A2.14	Patients who are unable to comply with pulmonary medication restrictions prior to allocation	EX25 Detected manually	None
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing. No signature on ICF Detected automatically/manually	All
	B2	Informed consent too late	Date of informed consent was after the date of any study-related procedure. If date of informed consent equals to date of Visit 1, such cases will be discussed at MQRM/RPM/DBL meetings. Detected automatically/manually	None
C		**Trial medication and randomisation**		
	C1	Study medication taken >2 weeks longer than planned	Study medication was documented to be taken for >5 weeks Detected automatically	case by case discussio n before DBL if fraudulent data detected
	C2	Serious non-compliance as reported in monitoring report	Detected manually	None
D		**Concomitant Medication**		
	D1	Prohibited medication use during study	Review concomitant therapies Detected manually.	None
E		**Incorrect timing**		
	E1	Incorrect timing – visit	Only for PK endpoints Detected manually	PK set
	E2	Incorrect timing – examination	Only for PK endpoints Detected manually	PK set

KEY: EX = exclusion criterion, SGOT = serum glutamic oxaloacetic transaminase, SGPT = serum glutamic pyruvic transaminase, BAC = benzalkonium chloride, EDTA = ethylene diaminete taacetic acid, ICF = informed consent form, MQRM = medical quality review meeting, RPM = report planning meeting

6.3 PATIENT SETS ANALYSED

- Treated set:
  This patient set includes all patients who were dispensed study medication and were documented to have taken at least one dose of investigational treatment.

- PK set:
  This patient set includes all patients in the treated set with at least one evaluable PK parameter in the treatment period. The patients with important PVs related to PK will be excluded from PK set.

6.4 SUBGROUPS

No subgroup is defined in this trial.

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

Missing safety data will not be imputed with the exception of missing adverse event (AE) dates which will be imputed according to Boehringer Ingelheim (BI) standards (see "Handling of missing and incomplete AE dates"). (2)

Missing data and outliers of PK data are handled according to 001-MCS-36-472, RD-01 (1) (6).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The definition of baseline values is described in the CTP, Section 7.1 'STATISTICAL DESIGN – MODEL'.

7. PLANNED ANALYSIS

Non-pharmacokinetic variables:

For End-Of-Text tables, the set of summary statistics is: N / Mean / SD / Minimum / Median / 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 (%) (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.

Pharmacokinetic variables:

For all pharmacokinetic tables, the set of descriptive statistics is: N (number of subjects with nonmissing values) / Mean / geometric mean (gMean) / SD / coefficient of variation (CV) / geometric coefficient of variation (gCV) / Min / 10th percentile (P10) / Q1 (lower quartile) / Median / Q3 (upper quartile) / 90th percentile (P90) / Max.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. COPD background characteristics will be listed only.

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded similarly as the AEs based on the most recent version of Medical Dictionary for Regulatory Activities (MedDRA). Concomitant medications will be coded according to the most recent version of World Health Organization Drug Dictionary.

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

7.3 TREATMENT COMPLIANCE

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

7.4 PRIMARY ENDPOINTS

No efficacy endpoint is defined in this trial.

Primary pharmacokinetic endpoints will be analysed as described in Sections 7.9.

7.5 SECONDARY ENDPOINTS

See Section 7.8 for safety analyses which are the secondary objectives of this trial.

[redacted]

7.7 EXTENT OF EXPOSURE

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

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 standards (see 'Handling and summarisation of adverse event data for clinical trial reports and integrated summaries') (3). All analyses of AEs will be based on the number of patients with AEs (not the number of AEs).

For analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the Case Report Form, 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

For further details on summarization of AE data, please refer the BI guidelines. (2), (3).

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake till 21 days after last drug intake will be assigned to the treatment. All AEs occurring before first drug intake will be assigned to 'screening' and all AEs occurring after last drug intake + 21 days will be assigned to 'follow-up' (for listings only).

According to ICH E3 (4), AEs classified as 'other significant' needs 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 lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical Quality Review Meeting (MQRM).

An overall summary of AEs will be presented.

The frequency of patients with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for patients with other significant AEs according to ICH E3 (4), for patients with AEs leading to death, for patients with AEs leading to treatment discontinuation, for patients with AEs of special interest, for patients with serious AEs, for patients with related serious AEs, and for patients with drug-related AEs. The frequency of patients with AEs will also be summarised by intensity, treatment, primary SOC and PT.

The SOCs will be sorted according to the standard sort order specified by European Medicines Agency. PTs will be sorted by frequency (within SOC).

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards (5).

7.8.3 Vital signs

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

7.8.4 ECG

Not applicable as ECG measurement data are not collected in this study.

7.8.5 Others

Not applicable since no other endpoint was planned.

7.9 PK ANALYSIS

The analysis of standard PK parameters will be performed according to 001-MCS-36-472 RD-01 (6), and also as described in CTP Section 7.3.

8. REFERENCES

1	*001-MCS-36-472*: "Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics", current version; IDEA for CON.
2	*001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", version 1.0; IDEA for CON.
3	*001-MCG-156*: “Handling and summarization of adverse event data for clinical trial reports and integrated summaries”, version 5.0; 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.
5	*001-MCG-157*: “Display and Analysis of Laboratory Data”, current version, IDEA for CON.
6	*001-MCS-36-472 RD-01*: “Noncompartmental Pharmacokinetic / Pharmacodynamic Analyses of Clinical Studies”, current version; IDEA for CON.

9. ADDITIONAL SECTIONS

Not applicable as no additional information is needed.

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
Initial	**01-Mar-2017**	[redacted]	None	This is the initial TSAP with necessary information for trial conduct
Final	**30-Jun-2017**	[redacted]	None	This is the final TSAP