Trial Statistical Analysis Plan

c13209134 -01

BI Trial No.:	1237.34
Title:	Post-marketing surveillance (PMS) on long-term use of tiotropium+olodaterol fixed dose combination (Tio+Olo FDC) 5µg/5µg in patients with chronic obstructive pulmonary disease (chronic bronchitis, emphysema) in Japan. Including Protocol Amendment c02840643-02.
Investigational Product(s):	Tiotropium+olodaterol fixed dose combination solution for inhalation -RESPIMAT
Responsible trial statistician(s):	Address: Phone: , Fax:
Date of statistical analysis plan:	29 Nov 2018 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Include a list of all abbreviations used in the TSAP

Term	Definition / description
ADR	Adverse Drug Reaction
AE	Adverse event
BRPM	Blinded report planning meeting
CAT	COPD Assessment Test
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CTR	Clinical Trial Report
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
ICS	Inhaled Corticosteroid
LABA	Long Acting Beta2 Agonist
LAMA	Long Acting Muscarinic Antagonist
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MQRM	Medical Quality Review Meeting
NIS	Non-interventional Study
PGR	Patient's Global Rating
PSTAT	Project Statistician
PFT	Pulmonary Function Test
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
SA	Statistical analysis
SAE	Serious Adverse Event

Term	Definition / description
SADR	Serious Adverse Drug Reaction
SD	Standard deviation
SMQ	Standardised MedDRA query
SOC	System organ class
TCM	Trial Clinical Monitor
TESS	Treatment emergent signs and symptoms
ToC	Table of contents
TMW	Trial Medical Writer
TSAP	Trial statistical analysis plan

3. INTRODUCTION

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 post-marketing surveillance (PMS) data.

This TSAP assumes familiarity with the Non-interventional Study Protocol (NIS Protocol), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in NIS Protocol Section 9.7 “DATA ANALYSIS”. Therefore, TSAP readers may consult the NIS Protocol 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.

SAS® Version 9.4 or later will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

No change has been made in the planned analyses from the statistical methods described in the NIS Protocol.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

There is no primary endpoint for effectiveness the primary objective of the PMS study is the evaluation of safety (see the NIS Protocol Section 9.1).

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

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

5.2.2 Secondary endpoint(s)

The secondary endpoints will be used as defined in the NIS Protocol Section 9.1

5.3 FURTHER ENDPOINT(S)

The other endpoints will be used as stated in the NIS Protocol Section 9.1.

5.4 OTHER VARIABLE(S)

Demographic data and baseline characteristics:

- Gender: male, female
- Age [years]
  Age [years] = Actual age based on the first administration of Spiolto Respimat
- Age class1 [years]: <65, >=65
- Age class2 [years]: <65, 65 to <75, >=75
- Height [cm]
- Weight [kg]
- Weight class [kg]: <50, 50 to <70, >=70
- Body mass index (BMI) [kg/m^2]
  BMI [kg/m^2] = weight [kg] / (height [m])^2
- Smoking status: Never smoker, Ex-smoker, Current smoker, Unknown
- Pack-Years
  Pack-Years = packs a day * years
- Indication of study drug : Chronic obstructive pulmonary disease (COPD), Other
- Chronic obstructive pulmonary disease (chronic bronchitis, emphysema) duration [years]

- If Month of first diagnosis of COPD is missing : COPD (chronic bronchitis, emphysema) duration = ([Years of first administration of Spiolto Respimat - Years of first diagnosis of COPD])

- Severity: Mild, Moderate, Severe, Very severe
- Medical history: Yes, No, Unknown
  - Bronchial asthma: Yes, No, Unknown
  - Cardiac arrhythmia: Yes, No, Unknown
  - Ischaemic heart disease (coronary artery disease): Yes, No, Unknown
  - Cardiac failure (heart failure): Yes, No, Unknown
  - Cardiac arrest (resuscitation): Yes, No, Unknown
  - Cerebrovascular disorders, stroke: Yes, No, Unknown
  - Other cardiovascular disease: Yes, No, Unknown
  - Metabolic disorders: Yes, No, Unknown
  - Psychiatric disorders: Yes, No, Unknown
  - Renal and urinary disorders: Yes, No, Unknown
- Concomitant disease Yes, No, Unknown
  - Bronchial asthma: Yes, No, Unknown
  - Cardiac arrhythmia: Yes, No, Unknown
  - Ischaemic heart disease (coronary artery disease): Yes, No, Unknown
  - Cardiac failure (heart failure): Yes, No, Unknown
  - Cardiac arrest (resuscitation): Yes, No, Unknown
  - Cerebrovascular disorders, stroke: Yes, No, Unknown
  - Other cardiovascular disease: Yes, No, Unknown
  - Metabolic disorders: Yes, No, Unknown
  - Psychiatric disorders: Yes, No, Unknown
  - Renal and urinary disorders: Yes, No, Unknown
  - Renal function disorders: Yes, No, Unknown
  - Hepatic function disorders: Yes, No, Unknown
- COPD Assessment Test (CAT):
  - CAT score at baseline (each score and sum of 8 questions)
- Pulmonary Function Test (PFT): Baseline FEV_1 [L]
  - Baseline FEV_1 [L] post bronchodilator
  - Baseline FEV_1 [L] pre bronchodilator
  - Baseline $\%FEV_1$ [%]
  - Baseline $\%FEV_1$ [%] post bronchodilator
  - Baseline $\%FEV_1$ [%] pre bronchodilator
  - Baseline FVC [L]
  - Baseline FVC [L] post bronchodilator
  - Baseline FVC [L] pre bronchodilator
  - Baseline %FVC [%]
  - Baseline %FVC [%] post bronchodilator
  - Baseline %FVC [%] pre bronchodilator
  - Baseline EFV_1/FVC [%]
  - Baseline EFV_1/FVC [%] post bronchodilator
  - Baseline EFV_1/FVC [%] pre bronchodilator

- Note:
  "post bronchodilator"; That fall under any of the following.
  - Use of long-acting bronchodilator within 8 hours before PFT
  - Use of long-acting bronchodilator (twice daily type) within 12 hours before PFT
  - Use of long-acting bronchodilator (once daily type) within 24 hours before PFT
  "pre bronchodilator"; That fall under all of the following.
  - Not use of long-acting bronchodilator within 8 hours before PFT
  - Not use of long-acting bronchodilator (twice daily type) within 12 hours before PFT
  - Not use of long-acting bronchodilator (once daily type) within 24 hours before PFT
  note:% FEV_1 [%] = (FEV_1 [L]) / ((0.036: if male, 0.022: if female)*(height [cm]) - (0.028: if male, 0.022: if female)*age - (1.178: if male, 0.005: if female))*100
  %FVC [%] = (FVC [L]) / ((0.042: if male, 0.031: if female)*(height [cm]) - (0.024: if male, 0.019: if female)*age - (1.785: if male, 1.105: if female))*100
  (Please refer (2).)

- Pregnancy: Yes, No, Unknown
- Previous medications: Yes, No, Unknown
  Medication administered from 28 days before administration of Spiolto Respimat to 1 day before administration of Spiolto Respimat.
  - Respiratory medication: Yes, No
    note: Respiratory medication = LAMA, LABA and/or ICS
  - LAMA monotherapy: Yes, No
  - LABA monotherapy: Yes, No
  - ICS monotherapy: Yes, No
  - ICS+LABA (free combination + fixed dose combination):Yes, No
  - ICS+LAMA (free combination + fixed dose combination):Yes, No
  - LAMA+LABA (free combination + fixed dose combination):Yes, No
  - ICS+LAMA+LABA (free combination + fixed dose combination):Yes, No
    Other respiratory medication
  - Theophylline: Yes, No
  - Mucolytic: Yes, No
- Concomitant medications: Yes, No, Unknown
  - Respiratory medication: Yes, No
    note: Respiratory medication = LAMA, LABA and/or ICS
  - LAMA monotherapy: Yes, No
  - LABA monotherapy: Yes, No
  - ICS monotherapy: Yes, No
  - ICS+LABA (free combination + fixed dose combination):Yes, No
  - ICS+LAMA (free combination + fixed dose combination):Yes, No
  - LAMA+LABA (free combination + fixed dose combination):Yes, No
  - ICS+LAMA+LABA (free combination + fixed dose combination):Yes, No
    Other respiratory medication
  - Theophylline: Yes, No
  - Mucolytic: Yes, No
- Previous therapy: Yes, No, Unknown

- Concomitant therapy: Yes, No, Unknown

Treatment exposure:

- Duration of Spiolto Respimat treatment [days] = (date of last treatment intake) - (date of first intake) + 1
  If after the data lock, Spiolto Respimat is ongoing and date of last treatment intake is missing: date of last treatment intake = Latest date in book
- Duration of Spiolto Respimat treatment class [weeks]: <= 4 weeks, 4 to <= 12 weeks, 12 to <=24 weeks, 24 to <=52 weeks, > 52 weeks.
  Note: In terms of days <= 29days, 29 to <= 85days, 85 to <= 169, 169 to <= 365, >365

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

For basic information on treatment in the study, please refer to NIS Protocol Section 4. The technical specification for treatment set-up is described in the Analysis Data Set (ADS) plan.

For safety analyses, data up to 21 days after last treatment intake during observation period will be considered as on treatment for AE.

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important PVs. The final column describes which PVs will be used to exclude patients from the each patient analysis sets.

Observed PVs will be concluded as important or not important at report planning meetings before database lock at the latest.

Table 6.2:1 Important protocol violations

Category / Code		Description	Requirements	Method	Excluded from
A		**Entrance criteria not met**			
	A1	No COPD(chronic bronchitis, emphysema)		Automated	Effectiveness
	A2	Patient received Spiolto Respimat treatment before registration	See Previous Medication code:	Automated	Safety Effectiveness
	A3	Patients who have been enrolled this study before		Manual	Safety Effectiveness
	A4	Patients who are participating in a clinical trial or registry.		Manual	Safety Effectiveness
B		**Contract**			
	B1	No valid site contract was available		Manual	Safety Effectiveness
C		**Trial medication**			
	C1	No treatment with Spiolto Respimat		Automated	Safety Effectiveness
D		**Missing data**			
	D1	No patient visit after registration	See CRF “Administration status”	Automated	Safety Effectiveness
	D2	No CRF after registration		Automated	Safety Effectiveness
	D3	No Effectiveness data	No Patient's Global Rating, no Physicians' global assessment and no available change value from baseline of CAT, FEV_1 and FVC.	Automated	Effectiveness

6.3 PATIENT SETS ANALYSED

The safety set and the effectiveness set are defined as follows. The safety set will be the basis of all demographic, baseline and safety analyses. Effectiveness analysis will be on basis of the effectiveness set.

- Safety set:
  This patient set includes all patients who were documented to have taken at least one dose of Spiolto Respimat.

- Effectiveness set:
  This patient set is a subset of the safety set that not received Spiolto Respimat patients before registration, and who have change value from baseline at least one CAT, FEV1 and FVC.

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

If only year of date is non-missing, then missing date are imputed 01 JUL of reported year. Else if only year and month of date are non-missing, then missing date is imputed 15 of the reported month.

Safety:
Missing or incomplete AE dates are imputed according to BI standards (see “Handling of missing and incomplete AE dates”). (1)

Effectiveness:
Missing effectiveness data will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

With regard to effectiveness and safety endpoints, the term “baseline” refers to the last observed measurement prior to administration of Spiolto Respimat. Observation on the same day as administration of Spiolto Respimat is "baseline".

Effectiveness analyses will be performed based on calculated visits as shown in Table 6.7: 1. If two or more data points of a patient fall into the same interval, the closest value to the planned day will be selected. If there are two observations which have the same difference in days to the planned day or if there are two observations on the same day, the first value will be used.

Table 6.7:1 Baseline, time windows and calculated visits

		Time window (actual days on treatment)	
Week label	Planned days	Start	End
Baseline	1	The last observed measurement prior to or on administration of Spiolto Respimat	
Week4	29	2	57
Week12	85	58	127
Week24	169	128	267
Week52	365	268	End of study

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Q1 / Median / Q3 / Max. For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and 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 (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to 2 decimal places. The category missing will be displayed only if there are actually missing values.

In addition, individual values on demographics, safety and effectiveness will be presented in subject data listings.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

7.2 CONCOMITANT DISEASES AND MEDICATION

Concomitant diseases will be coded by the latest version of Medical Dictionary for Regulatory Activities (MedDRA). Frequency of patients will be summarized by system organ class (SOC) and preferred term (PT).
Concomitant medication will be coded by latest version of “Nihon-iyakuhinshu”.

7.3 TREATMENT COMPLIANCE

Compliance data is not collected in this study

7.4 PRIMARY ENDPOINT(S)

The analysis of the primary endpoint is described in Section 7.8.1.

7.5 SECONDARY ENDPOINT(S)

The secondary endpoints will be used as stated in the NIS Protocol Section 9.7.3.

7.5.1 Key secondary endpoint(s)

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

7.5.2 (Other) Secondary endpoint(s)

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

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

Unless otherwise specified, the analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

For further details on summarization of AE data, please refer to the guideline 'Analysis and Presentation of Adverse Event Data from Clinical Trials (1)

AE analyses will be carried out after integrating AE data from CRF and AE data from perceive system. In addition, AEs coded as “no adverse event” will not be included in the AE analyses.

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intakes till 21 days after last drug intake during observation period will be analysed. For details on the treatment definition, see Section 6.1.

An overall summary of adverse events will be presented.

The frequency of patients with AEs, ADRs, SAEs and SADRs will be summarised by primary system organ class and preferred term. Patients with 'priority survey items' according to the drug's Risk Management Plan will be summarised separately. The analysis of "priority survey items", "Important identified risks", "Important potential risks" will be conducted for AEs, ADRs.

It is created that table of patient with ADRs in each subgroup defined in Section 6.4. Not only the frequency but also the odds ratios are displayed.

In addition summaries for the time to onset of first episode for the ADRs will be tabulated, by duration (<= 4 week, 4 to <= 12 weeks, 12 to <=24 weeks, 24 to <=52 weeks, > 52), by primary system organ class and preferred term.

Adverse events leading to death and adverse events leading to discontinuation will be also summarised by treatment, primary system organ class and preferred term.

An ADR is defined as an AE for which either the investigator or the sponsor (or both) assess the causal relationship to Spiolto Respimat as "Yes". A SAE is defined as an AE for which either the investigator or the sponsor (or both) assess the seriousness either as "Serious".

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

The following AEs are detected on the basis of the Standardised MedDRA queries (SMQs) or Boehringer Ingelheim customised MedDRA query (BICMQ) (details are described in ADS plan).

Safety will be assessed by treatment exposure time adjusted incidence rate (n in 100 patient years) of ADRs.

Priority survey items

- Cardiovascular adverse events
- Anticholinergic-related adverse events
- Beta2 agonist-related events

Important identified risks

- Cardiac failure
- Atrial fibrillation and extra systoles
- Ileus, Angle closure glaucoma
- Anaphylaxis

Important potential risks

- Cardiac disorder (Myocardial ischaemia, Cardiac arrhythmia)

- Intubation and mortality related to asthma

7.8.2 Laboratory data

Only clinically relevant findings reported as AE will be analyzed as a part of AE analyses

7.8.3 Vital signs

Only clinically relevant findings reported as AE will be analysed as a part of AE analyses

7.8.4 ECG

Only clinically relevant findings reported as AE will be analyzed as a part of AE analyses

7.8.5 Others

No plan for other safety parameters.

8. REFERENCES

1	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
2	Annals of the Japanese Respiratory Society. 2001; 39: 1-17.

10. HISTORY TABLE

Table 10:1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	**29 –Nov-2018**		None	This is the final TSAP without any modification