TRIAL STATISTICAL ANALYSIS PLAN c24036346-02

BI Trial No.:	0205-0536
Title:	Specific Use-Result Surveillance of Spiriva Respimat in asthmatics (patients with mild to moderate persistent asthma)
Investigational Product(s):	Spiriva® 1.25 µg Respimat® 60 puffs Spiriva® 2.5 µg Respimat® 60 puffs, Tiotropium inhalation solution – Respimat Inhaler (Ba 679 BR Respimat)
Responsible trial statistician(s):	Address: Phone: , Fax:
Date of statistical analysis plan:	19 OCT 2018 SIGNED
Version:	"Final"

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ACQ	Asthma Control Questionnaire
ADS	Analysis Data Set
AE	Adverse event
BMI	Body mass index
CI	Confidence Interval
CRF	Case Report Form
EMA	European Medicines Agency
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
ICS	Inhaled Corticosteroids
LABA	Long Acting β2 Agonist
LTRA	Leukotriene Receptor Antagonist
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-interventional Study
OCS	Oral Corticosteroid
PEFR	Peak Expiratory Flow Rate
PFT	Pulmonary Function Test
PMS	Post-Marketing Surveillance
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
RMP	Risk Management Plan
SABA	Short Acting β2 Agonist
SAMA	Short Acting Muscarinic Antagonist
SD	Standard deviation
SMQ	Standardised MedDRA query
SOC	System organ class
TOC	Table of contents
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 (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 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)

The primary endpoints will be used as defined in the NIS Protocol Section 9.3.2.1.

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 9.3.2.2.

5.4 OTHER VARIABLE(S)

Demographic data and baseline characteristics:

- Sex: male, female
- Age [years]
  Age [years] = Actual age based on the first administration of Spriva Respimat

- Height [cm]
- Body mass index (BMI) [kg/m^2]
  BMI [kg/m^2] = weight [kg] / (height [m])^2

- Smoking status: Never smoked, Ex-smoker, Current smoker, Unknown
- Pack-Years

- Indication for use: Bronchial asthma, Other
- Asthma Severity: Severe persistent, Moderate persistent, Mild persistent, Intermittent, Unknown
- Duration of asthma [years]

Duration of asthma = [First administration of Spiriva Respimat – Date of indication of asthma + 1 (if negative value, then 1)] / 365.25: Day of indication is 1.

- Number of hospital admission due to asthma in the past year
- Number of urgent visit to physician due to asthma in the past year
- Medical history: Yes, No, Unknown
- Concomitant diagnosis: Yes, No, Unknown

- Previous Medication: Yes, No, Unknown
  Note: Previous medications are existing drugs, drugs which administered before initiation of the new anti-asthmatic drug, drugs of unknown starting date.

- Concomitant Medication during treatment of Spiriva Respimat: Yes, No, Unknown
  - Note: Treated during treatment period of Spriva Respimat regardless of the start and end date of the medication (except for the case that the end date of the medication and the start date of Spriva Respimat are the same)

- Concomitant therapy: Yes, No, Unknown
- Pulmonary Function Test

- Asthma control status at baseline (see the NIS Protocol Section 9.3.2.2: 1): Well-controlled, Insufficiently-controlled, Poorly-controlled, Unknown
  - Asthma symptoms (in the daytime or at night): Yes, No, Unknown
  - Use of reliever: Yes, No
  - Limitation of activities, including exercise: Yes, No, Unknown
  - PEFR (mean of the 7 days before each visit) [L/min]
- Pregnancy test: Yes, No, Unknown
- ACQ 6 score at baseline (each score and mean of 6 questions)
- Contraindication to Spiriva Respimat: Yes, No

Treatment exposure

Duration of Spiriva Respimat treatment [days] = (date of last drug intake) – (date of first drug intake) + 1 – (period of treatment interruption [days])

- Total Spiriva Respimat dose taken [µg]
- First dose of Spiriva Respimat [µg]: 2.5, 5.0, Others

Table 5.4: 1 ICS doses of ICS product

Agent	Low dose (μg/day)	Medium dose (μg/day)	High dose (μg/day)
BDP-HFA	=< 200	> 200 to 400	> 400
FP-HFA	=< 200	> 200 to 400	> 400
CIC-HFA	=< 200	> 200 to 400	> 400
FP-DPI	=< 200	> 200 to 400	> 400
MF-DPI	=< 200	> 200 to 400	> 400
BUD-DPI	=< 400	> 400 to 800	> 800
FF-DPI		100 to <200	>= 200

BDP-HFA, beclometasone dipropionate hydrofluoroalkane;
FP-HFA, fluticasone hydrofluoroalkane; CIC-HFA, ciclesonide hydrofluoroalkane;
FP-DPI, fluticasone propionate dry powder inhaler;
MF-DPI, mometasone furoate dry powder inhaler; BUD-DPI, budesonide dry powder inhaler.

Table 5.4: 2 ICS doses of ICS/LABA combination product

Agent	Low dose (μg/day)	Medium dose (μg/day)	High dose (μg/day)
FP/SM	=< 200	> 200 to 500	> 500
BUD/FM	=< 320	> 320 to 640	> 640
FP/FM	=< 200	> 200 to 500	> 500
FF/VI		100 to <200	>= 200

FP, fluticasone propionate; SM, salmeterol xinafoate; BUD, budesonide;
FM, formoterol fumarate; FF, fluticazone furate; VI, vilanterol trifenatate.

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 analyses, data up to 30 days after last treatment intake will be considered as on treatment.

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 different 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	Example/Comment	Method	Excluded from
A		**Entrance criteria not met**			
	A1.1	Patient received Spiriva Respimat treatment before registration	Refer to Previous Medication code:	Automated	Safety
	A1.2	Patients who have been enrolled this study before		Automated	Safety
B		**Contract**			
	B1	No valid site contract was available		Manual	Safety
C		**Trial medication**			
	C1	No treatment with Spiriva Respimat		Automated	Safety
D		**Missing data**			
	D1	No patient visit after registration	No visit made after the entry	Automated	Safety
	D2	No CRF after registration		Automated	Safety
	D3	No safety observation was documented after registration	No AE details	Automated	Safety
	D4	No value at baseline and/or at post treatment	None of value about asthma control status, PEFR, FEV_1, FVC and ACQ6 for effectiveness analysis, at baseline and/or at post treatment	Automated	Effectiveness
E		**Invalid registration**			
	E1	No required registration procedure was followed	See the NIS Protocol Section 9.2.2.2	Manual	Safety

6.3 SUBJECT SETS ANALYSED

The following two analysis sets are defined as in NIS Protocol Section 9.7. 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 Spiriva Respimat except for patients who had no observation documented after entry, made invalid registration or were not under the appropriate site contact.

- Effectiveness set:
  This patient set is a subset of the safety set that includes all patients in the safety set who have baseline and at least one available on-treatment asthma control status, PEFR, FEV_1, FVC or ACQ 6 score.

Table 6.3: 1 Subject sets analysed

	Subject set	
Class of endpoint	Safety Set	Effectiveness Set
Primary endpoints	X	
Secondary and further endpoints		X
Demographic and baseline characteristics	X	
Treatment exposure	X	

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

Safety:

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates").(3)

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 Spiriva Respimat.
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	0	The last observed measurement prior to administration of Spiriva Respimat	
Week 4	28	1	56
Week 12	84	57	111

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 except AE analysis 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 two 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 summarised 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)

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)

Effectiveness at each visit in each patient is determined based on the change of asthma control status from baseline. See the assessment table for effectiveness and the NIS Protocol Section 9.3.2.2: 1.

Table 7.5.2: 1 Assessment table for effectiveness

Baseline / After administration	Well controlled	Insufficiently-controlled	Poorly-controlled	Unknown / Missing
Well controlled	No change	Improvement	Improvement	Unknown
Insufficiently-controlled	Worse	Worse	Improvement	Unknown
Poorly-controlled	Worse	Worse	Worse	Unknown
Unknown / Missing	Unknown	Unknown	Unknown	Unknown

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 safety 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.

Furthermore, for analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data 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

For further details on summarization of AE data, please refer (3, 4)

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. All adverse events will be analysed up to last drug intake + 30 days. 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 will be summarised by primary system organ class and preferred term. Also, the frequency of patients with ADRs will be summarised by primary system organ class, preferred term and the time to first onset date (<29, 29 to <57, 57 to <85, >=85 days). Separate tables will be provided for patients with ADRs stratified by various patient subgroups defined in Section 6.4, for patients with serious AEs. Subgroup analysis will display the frequency of patients, percentage (%) and odds ratio with 95%CI. Logistic regression will be used for odds ratio. The ‘unknown’ and ‘missing’ categories are excluded to calculate odds ratio. Patients with ‘priority survey items’ according to the drug’s Risk Management Plan (RMP) will be summarised separately.

An ADR is defined as an AE for which either the investigator or the sponsor (or both) assess the causal relationship to Spiriva Respimat either as “Possibility high”, “Possibility low” or “Unknown”. 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).

A serious AE is defined as an AE for which either the investigator or the sponsor (or both) assess the seriousness either as “Serious”.

7.8.2 Laboratory data

Not applicable. Only clinically relevant findings reported as AE will be analysed 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

Not applicable. Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

7.8.5 Others

No plan for other safety parameters.

8. REFERENCES

1.	*Allergol Int. 2017 Apr; 66(2): 163-189.*
2.	*Annals of the Japanese Respiratory Society. 2001; 39: 1-17.*

10. HISTORY TABLE

Table 10: 1 History table

This is a revised TSAP including the following modifications to the final TSAP.

Version	**Date (DD-MMM-YY)**	**Author**	**Sections changed**	**Brief description of change**
Final	**08-AUG-18**		None	This is the final TSAP without any modification
Revised	**19-OCT-18**		2 5.4 7.8.1	'RMP' is added in list of abbreviations. Drug category name is changed from 'Theophylline' to 'Xanthine'. The definitions of 'Renal dysfunction' and 'Hepatic dysfunction' are added. The definition of 'Important identified risks' and 'Important potential risks' are revised to be aligned with the latest Japanese RMP.