# Trial Statistical Analysis Plan

**c09081010-01**

| | |
|---|---|
| **BI Trial No.:** | 205.525 |
| **Title:** | Specific Use-Result Surveillance of Spiriva Respimat in asthmatics(patients with severe persistent asthma) |
| **Investigational Product(s):** | Spiriva® 2.5 µg Respimat® 60 puffs (hereinafter referred to as Spiriva Respimat), Tiotropium inhalation solution – Respimat Inhaler (Ba 679 BR Respimat) |
| **Responsible trial statistician(s):** | [redacted]<br>Address: [redacted]<br>Phone: [redacted], Fax: [redacted] |
| **Date of statistical analysis plan:** | 1 OCT 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 |
|---|---|
| AE | Adverse event |
| CI | Confidence Interval |
| CTP | Clinical Trial Protocol |
| CTR | Clinical Trial Report |
| DM&SM | Boehringer Ingelheim Data Management and Statistics Manual |
| 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 |
| OCS | Oral Corticosteroid |
| PEFR | Peak Expiratory Flow Rate |
| PT | Preferred term |
| PV | Protocol violation |
| Q1 | Lower quartile |
| Q3 | Upper quartile |
| SA | Statistical analysis |
| SABA | Short Acting β2 Agonist |
| SAMA | Short Acting Muscarinic Antagonist |
| SD | Standard deviation |
| SMQ | Standardised MedDRA query |
| SOC | System organ class |
| TCM | Trial Clinical Monitor |
| 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 Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 9.7 “DATA ANALYSIS”. 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.

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 CTP.

# 5. ENDPOINT(S)

## 5.1 PRIMARY ENDPOINT(S)

There is no primary endpoint for efficacy, the primary objective of the PMS study is the evaluation of safety (see the CTP Section 9.1.2.1).

## 5.2 SECONDARY ENDPOINTS

The secondary endpoints will be used as stated in the CTP Section 9.1.1.2.

## 5.3 FURTHER ENDPOINTS

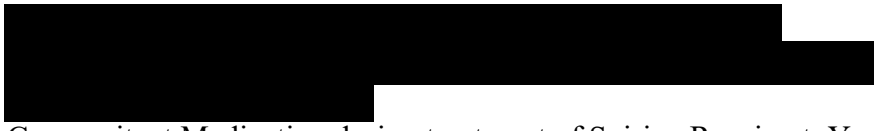
The other endpoints will be used as stated in the CTP Section 9.1.1.3.

## 5.4 OTHER VARIABLES

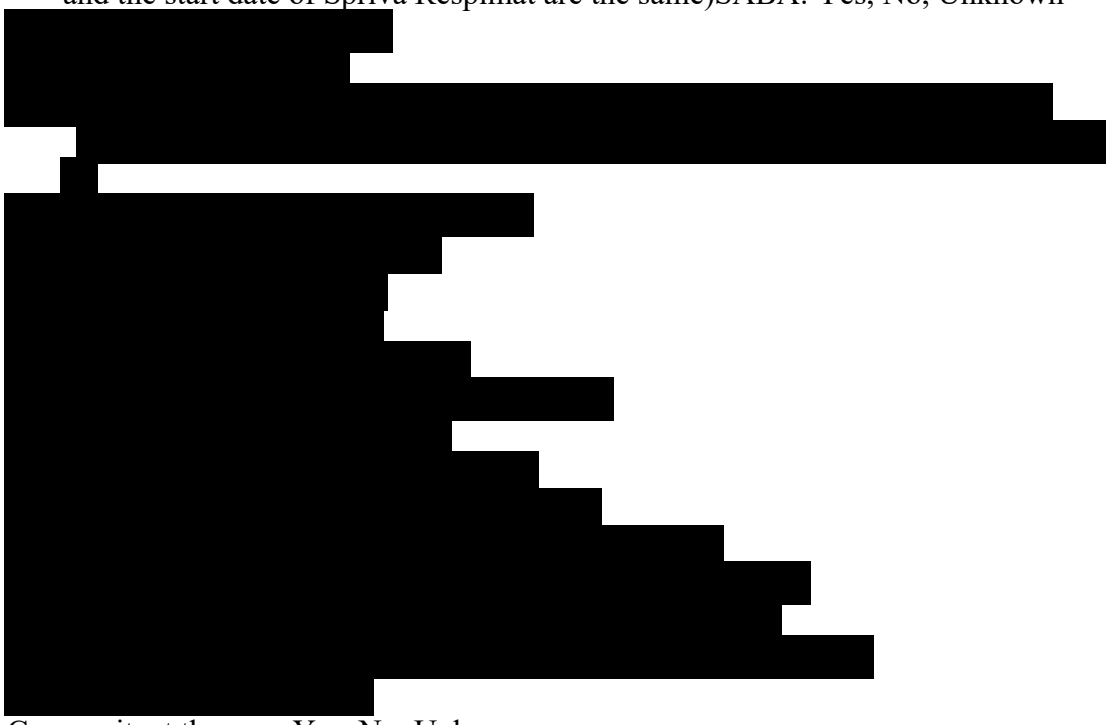
**Demographic data and baseline characteristics:**

- Sex: male, female
- Age [years]
  Age [years] = Actual age based on the first administration of Spriva Respimat
  [redacted]
- Height [cm]
- Weight [kg]
  [redacted]
- Body mass index (BMI) [$kg/m^2$]
  BMI [$kg/m^2$] = weight [kg] / (height [m])$^2$
- [redacted]
- Smoking status: Never smoked, Ex-smoker, Current smoker, Unknown
- Pack-Years
- [redacted]
- 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 (Statistics and frequency)
- Number of urgent visit to physician due to asthma in the past year (Statistics and frequency)
- 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)SABA: Yes, No, Unknown



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

- Asthma control status at baseline (see the CTP Section 9.1.1.4): 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

[redacted]

**Treatment exposure**

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

[redacted]

- Total Spiriva Respimat dose taken [ $\mu$ g]

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 TREATMENTS

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

For safety analyses and efficacy 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:225970901 | 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 efficacy analysis, at baseline and/or at post treatment | Automated | Efficacy |
| | | | | | |
| | | | | | |
| **E** | | **Invalid registration** | | | |
| | E1 | No required registration procedure was followed | See the CTP Section 9.2.2.2 | Manual | Safety |

## 6.3 PATIENT SETS ANALYSED

The following two analysis sets are defined as in CTP Section 9.7. The safety set will be the basis of all demographic, baseline and safety analyses. Efficacy analysis will be on basis of the efficacy 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.

- Efficacy 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.

[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

Safety:

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

Efficacy:

Missing efficacy data will not be imputed.

## 6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

With regard to efficacy and safety endpoints, the term "baseline" refers to the last observed measurement prior to administration of Spiriva Respimat.
Efficacy 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 | 227 |
| Week 52/EOT | 364 | 228 | 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 one decimal place. 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 ENDPOINTS

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 CTP Section 9.1.1.4. And it will be performed as well as Section 5.4. Calculate worse odds ratio in each patient characteristic (demographic and existing treatment factor).

Table 7.5: 1 Assessment table for effectiveness

| | Well controlled at baseline | Insufficiently-controlled at baseline | Poorly-controlled at baseline |
|---|---|---|---|
| Well controlled after administration | Improvement | Improvement | Improvement |
| Insufficiently-controlled after administration | Worse | Worse | Improvement |
| Poorly-controlled after administration | Worse | Worse | Worse |

[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 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. That means that all adverse events occurring between first drug intake till 30 days after last drug intake 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 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 (1 to 30, 31 to 60, 61 to 90, 91 to 180, 181 to 365, >=366 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 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”.

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).

[redacted]

### 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

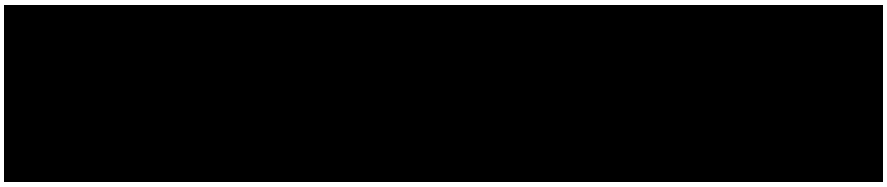
Not applicable. Only clinically relevant findings reported as AE will be analysed as a part of AE analyses.

### 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. |
| [redacted] | [redacted] |
| [redacted] | [redacted] |



# 10. HISTORY TABLE

Table 10: 1 History table

| Version | Date (DD-Mmm-YY) | Author | Sections changed | Brief description of change |
|---|---|---|---|---|
| Final | **01-Oct-2017** | [redacted] | None | This is the final TSAP without any modification |

**APPROVAL / SIGNATURE PAGE**

**Document Number: c09081010** **Technical Version Number:1.0**

**Document Name:** 8-01-tsap

**Title:** Specific Use-Result Surveillance of Spiriva Respimat in asthmatics(patients with severe persistent asthma)

**Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|
| Approval-Biostatistics | [redacted] | 01 Oct 2017 11:30 CEST |
| Approval–Clinical Monitor | | 02 Oct 2017 02:46 CEST |
| Approval-Project Statistician | | 03 Oct 2017 13:17 CEST |
| Approval-Analytical/Contributing Scientist | | 04 Oct 2017 04:50 CEST |

**(Continued) Signatures (obtained electronically)**

| Meaning of Signature | Signed by | Date Signed |
|---|---|---|