Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	c14514897-01
BI Study Number:	0205-0536
BI Investigational Product(s):	Tiotropium inhalation solution – Respimat Inhaler (Ba 679 BR Respimat)
Title:	Specific Use-Result Surveillance of Spiriva Respimat in asthmatics (patients with mild to moderate persistent asthma)
Brief lay title	Specific Use-result Surveillance of Spiriva Respimat® in mild to moderate persistent asthmatic patients
Protocol version identifier:	1.0
Date of last version of protocol:	Not applicable
PASS:	Yes
EU PAS register number:	To be registered
Active substance:	R03BB04 : Tiotropium
Medicinal product:	Spiriva® 1.25 µg Respimat® 60 puffs Spiriva® 2.5 µg Respimat® 60 puffs
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	
Joint PASS:	No
Research question and objectives:	This PMS is designed: To investigate the safety and effectiveness of Spiriva Respimat in patients with mild to moderate persistent asthma under real-world use.
Country(-ies) of study:	Japan
Author:	

Marketing authorisation holder(s):	
MAH contact person:	
EU-QPPV:	
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically
Date:	16 January 2017

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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
CA	Competent Authority
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU-QPPV	European Union – Qualified Person for Pharmacovigilance
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GPSP	Good Post- marketing Study Practice
GVP	Good Pharmacovigilance Practices
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
J-PAL	Japanese Pharmaceutical Affairs Law
J-RMP	Japan Risk Management Plan
J-PSR	Japanese Periodic Safety Report
MedDRA	Medical Dictionary for Regulatory Activities
MAH	Marketing Authorisation Holder
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
SAE	Serious Adverse Event
TSAP	Trial Statistical Analysis Plan

3. RESPONSIBLE PARTIES

Sponsor

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiriva Respimat			
Name of active ingredient: Tiotropium bromide			
Protocol date: 16 January 2017	**Study number:** 0205-0536	**Version/Revision:** 1.0	**Version/Revision date:** NA
Title of study:	Specific Use-Result Surveillance of Spiriva Respimat in asthmatics (patients with mild to moderate persistent asthma)		
Rationale and background:	The safety of Spiriva® 1.25 µg Respimat® 60 puffs and Spiriva® 2.5 µg Respimat® 60 puffs (hereinafter referred to as Spiriva Respimat) in patients with mild to moderate persistent asthma under the real-world use was not confirmed in clinical trials.		
Research question and objectives:	This PMS is designed; To investigate the safety and effectiveness of Spiriva Respimat in patients with mild to moderate persistent asthma under real-world use.		
Study design:	Non-interventional, observational study based on new data collection		
Population:	Inclusion criteria: • Patients diagnosed with mild to moderate persistent bronchial asthma • Patient aged ≥ 15 years old • Patients who are naive to Spiriva Respimat and receive Spiriva Respimat for the first time for the treatment of bronchial asthma on top of at least ICS treatment.		
Variables:	Demographics Medical history/baseline conditions Previous/concomitant therapies Pulmonary function test (peak expiratory flow rate, forced expiratory volume in 1 second, forced vital capacity), if available Asthma severity and asthma control status, if available ACQ 6 score, if available Spiriva Respimat administration Adverse event Safety laboratory test (if corresponding AEs are reported)		
Data sources:	Patients data will be gathered by electronic Case Report Form on EDC		
Study size:	150 (safety set)		
Data analysis:	Descriptive		
Milestones:	Final report will be prepared by 31 July 2019		

5. AMENDMENTS AND UPDATES

None

Number	Date	Section of study protocol	Amendment or update	Reason
-	-	-	-	-

6. MILESTONES

Milestone	Planned Date
Start of data collection	01 July 2017
End of data collection	31 December 2018
Study progress report	None
Study interim report 1	08 January 2018 (J-PSR)
Study interim report 2	08 January 2019 (J-PSR)
Study interim report 3	17 February 2019 (re-examination report for Spiriva Respimat in asthmatics)
Registration in the EU PAS register	To be registered
Final report of study results:	31 July 2019

7. RATIONALE AND BACKGROUND

Tiotropium is one of the most widely used long-acting bronchodilators worldwide for the treatment of COPD (including chronic bronchitis and emphysema), and now, after systematic clinical investigation, it is proposed to be designated for relief of various symptoms associated with the obstructive impairment of airways due to bronchial asthma.

Tiotropium delivered via the Respimat® inhaler once daily demonstrated consistent and significant improvement in lung function parameters in the Phase III trials despite the fact that the requirement for stable asthma maintenance therapy at baseline and throughout the treatment period might impose limitations on the effect size that can be achieved with an additional treatment. In addition to the improvements in lung function, patients who remained symptomatic despite treatment with high-dose ICS+LABA or medium-dose ICS were shown to have a symptomatic benefit from taking tiotropium.

Tiotropium delivered via the Respimat® inhaler once daily also demonstrated long-term safety and tolerability compared with that of placebo when administered at a daily dose of 2.5 and 5 μg to adult patients with asthma. Exposure to tiotropium in the clinical program covered more than 1000 patient-years in more than 2200 patients. The overall frequencies of AEs, drug-related AEs, and SAEs were similar across all treatment dose groups in trials with the same duration and patient population. In general, no specific concerns with regard to abnormal vital signs were raised for patients who took tiotropium. There were no patterns of increased particular AEs for the tiotropium treatment groups compared with that of placebo in any subgroup analysis. No deaths were reported during the entire clinical program. According to the current guidelines for the treatment of asthma, although various treatment options are available for long-term asthma management including ICS as the first-line therapy and other additional therapies depending on asthma severity (e.g., LABA, leukotriene receptor antagonist, theophyllines, antihistamines, oral steroids, anti-IgE), improvement of symptoms is insufficient in many patients (i.e., uncontrolled and/or at potential risk of asthma exacerbation), and there is a growing medical need for additional therapeutic options for the treatment of asthma. Responding to the medical needs, inhaled administration of anticholinergic bronchodilator tiotropium is a new additional maintenance therapy in patients with asthma who remain symptomatic despite treatment with at least ICS. Treatment with tiotropium improves lung function and symptoms of asthma patients more appropriately and may be an important paradigm shift in the treatment of asthma patients.

Japanese regulation related to Post Marketing Surveillance (PMS)
This PMS is planned according to the Japanese Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical. The law requires in principle that data on the safety and effectiveness of all launched products to be accumulated under real-world clinical practice. The data collected in the PMS are required to be submitted to the Pharmaceuticals and Medical Devices Agency (PMDA), the local regulatory agency in Japan, according to the process of re-examination which will take place 10 years after approval of registration. The PMS is a part of the local Risk Management Plan in Japan (J-RMP) to be submitted to PMDA at New Drug Application.

8. RESEARCH QUESTION AND OBJECTIVES

The objective of this PMS is to investigate the safety and effectiveness of Spiriva Respimat in patients with mild to moderate persistent asthma under real-world use.

9. RESEARCH METHODS

9.1 STUDY DESIGN

Non-interventional observational study based on newly collected data under real-world use.

9.2 SETTING

9.2.1 Study sites

will nominate the candidate sites which satisfied the following criteria and ask the nominated sites to participate in the study.

- Spiriva Respimat has been delivered to the site.
- The observation of peak expiratory flow meter is done as part of the usual medical practice.

Planned number of sites: Approximately 25 Sites
A medical representative will explain the objectives, subjects and methods of the surveillance to the investigator at the site and exchange a written contract with the head of the site (e.g., hospital director).

9.2.2 Study population

9.2.2.1 Inclusion/Exclusion criteria

Inclusion criteria:

- Patients diagnosed with mild to moderate persistent bronchial asthma
- Patient aged ≥ 15 years
- Patients who are naive to Spiriva Respimat and receive Spiriva Respimat for the first time for treatment of bronchial asthma on top of at least ICS treatment.

*:Asthma severity is defined by “Table 6 Classification of asthma severity based on the present treatment (adult)” of “Japanese Guideline for Adult Asthma 2014”[P14-15105].

Exclusion criteria:

- Patients who have a contraindication to Spiriva Respimat defined in the package insert for Spiriva Respimat
- Patients who have been enrolled in this study before.

9.2.2.2 Patient registration method

The registration method will be a continuous investigation system. Patients who begin treatment with Spiriva Respimat after the conclusion of the contract will be registered by

entering necessary information in the EDC within 14 days whenever possible from the day of treatment initiation (inclusive).

The necessary variables for registration are gender, date of birth, start date of administration and the reason for use. And ICS treatment as of inclusion criteria will be checked in the EDC system.
Patient registration will be stopped when the target number of the study is reached. After the end of the registration period, investigators use a signed form to confirm that patients have been registered continuously at the site. A log of all patients included into the study will be maintained at the site.

9.2.2.3 Registration period

From July 2017 to June 2018

9.2.3 Study visits

After start of the treatment with Spiriva Respimat, each patient will be observed for 12 weeks or at premature discontinuation from the PMS. Observations are made at the following time points: before first administration of Spiriva Respimat (this visit is defined as baseline), 4 weeks and 12 weeks after the start of treatment, or at discontinuation.

9.2.4 Study discontinuation

reserves the right to discontinue the PMS overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the PMS.
3. Violation of Good Post-marketing Study Practice (GPSP) or the contract of a study site or investigator, thereby disturbing the appropriate conduct of the PMS.

The investigator / the study site will be reimbursed for reasonable expenses incurred in case of PMS termination (except in case of the third reason).

9.3 VARIABLES

9.3.1 Exposures

This PMS is conducted under real-world use of Spiriva® 1.25 µg Respimat® 60 puffs and Spiriva® 2.5 µg Respimat® 60 puffs following the labeling (Japanese package insert).

9.3.2 Outcomes

9.3.2.1 Primary outcome

The primary Outcome is the absolute and relative (%) frequency of patients with suspected adverse drug reactions (ADRs).

Safety will be assessed by use of the following other parameters of interest:
- Adverse events irrespective of seriousness
- Laboratory tests (if corresponding AEs are reported)

There is no primary outcome for effectiveness as the primary objective of a PMS is evaluating safety.

9.3.2.2 Secondary outcome

- Change from baseline in asthma control status at Week 12

Asthma control status:
Asthma control status will be assessed based on the "Asthma prevention and management guideline" [P14-15105]

9.3.2.2: 1 Asthma control status Table

Patients control status	Well-controlled	Insufficiently-controlled	Poorly-controlled
	Meet all the criteria	Meet 1 or 2 criteria	Meet all of 3 Criteria
Asthma symptoms (in the daytime or at night)	None	Once or more a week	Once or more a week
Use of reliever	None	Once or more a week	Once or more a week
Limitation of activities, including exercise	None	Restricted	Restricted

9.3.3 Covariates

The investigator will enter the following patient data into the eCRF for registration.

- Patient's ID, gender, date of birth, start date of administration, indication, asthma severity

Demographics
At baseline:
Patient background including weight, height and smoking history
Medical history/baseline conditions
(Ischaemic heart disease, Cardiac failure, Myocardial infarction, Angina pectoris, Cardiac arrhythmia, Renal failure)
Previous /concomitant therapies
Pulmonary function test (PEFR (peak expiratory flow rate), FEV1 (forced expiratory volume in 1 second), FVC (forced vital capacity), if available
Asthma severity and asthma control status, if available [P14-15105]
ACQ 6 score, if available
Spiriva Respimat® administration, dose

At week4:
Concomitant therapies
Pulmonary function test (PEFR, FEV1, FVC), if available
Asthma severity and asthma control status, if available [P14-15105]
ACQ 6 score, if available
Spiriva Respimat® administration, dose, particularly any changed in dose with details provided

At week12:
Concomitant therapies
Pulmonary function test (PEFR, FEV1, FVC), if available
Asthma severity and asthma control status, if available [P14-15105]
ACQ 6 score, if available
Spiriva Respimat® administration, dose, particularly any changed in dose with details provided

Observation period and follow-up period by 30 days:
Adverse events
Priority survey items:
Cardiovascular adverse events
Anticholinergic-related adverse events
Asthma related death/hospitalization/intubation
Safety laboratory test (if corresponding AEs are reported)

See ANNEX 3 for more details.

9.4 DATA SOURCES

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via the Electronic Data Capture (EDC) system.

One case book is used. Book 1 is for baseline, Week 4 and Week 12.

Data is to be transmitted immediately after being entered into the eCRF at 12 weeks after the start of treatment or at discontinuation. When any adverse events occur, the data should be immediately entered into eCRF and transmitted.

9.5 STUDY SIZE

It is planned to enroll 180 patients with mild to moderate persistent asthma to ensure the number of 150 patients as safety analysis set at least.

150 (safety set)
150 patients will be set as a safety analysis set. The main ADR (about 2.0%) in clinical trials were asthma (1.8%), dysphonia (1.8%) and dry mouth (1.8%). With 150 patients, the incidence of the main adverse events would be evaluated.

9.6 DATA MANAGEMENT

Data is gathered by the EDC system provided by external vendor below.

Table 9.6: 1

	Contract research organizations 1	Contract research organizations 2
Name		

9.7 DATA ANALYSIS

This is a non-interventional, observational study to collect new real-world data (i.e., data under routine medical practice) on safety and effectiveness of Spiriva Respimat treatment in patients. Analyses are descriptive in nature including means, standard deviation, Q1, medians,

Q3, frequency and percentages. For safety outcomes, incidence rates with corresponding 95% confidence interavals will also be calculated. No confirmatory statistical testing is foreseen in this study.

Per local regulation, any patient who meets one of the following criteria is treated as ineligible for all analyses:

- No safety observation was documented after registration
- No required registration procedure was followed
- No valid site contract was available

9.7.1 Main analysis

The analysis of outcome events will include all patients registered in the study and receiving the Spiriva Respimat treatment. All outcome events are based on reported AE data which will be handled according to BI standards.

The safety analysis will include all patients registered in the study and receiving the Spiriva Respimat treatment. In general, safety analyses will be descriptive in nature, will be based on BI standards, and will focus on ADRs related to the Spiriva Respimat treatment.

AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be based on the concept of treatment emergent AEs. To this end, all AEs occurring between the first intake of Spiriva Respimat prescribed at baseline visit and within 30 days (inclusive) after the last intake will be considered ‘treatment emergent’. An AE is considered to be ADR if either the physician who has reported the AE or the sponsor assesses its causal relationship as ‘related’.

The frequency of AEs/ADRs will be tabulated by system organ class and preferred term for overall and for subgroups based on the important baseline characteristics.

No imputation is planned for missing AE data except for missing onset dates which will be handled according to BI standard.

9.7.3 Interim analyses

Several interim analyses will be performed for the purpose of creating periodic safety update reports to the local authority (see 6. MILESTONES).

9.8 QUALITY CONTROL

All processes are conducted according to GPSP SOPs and GPSP working instruction. Appropriate records and documents are stored based on the GPSP SOPs and these processes are checked by internal self-check.

9.9 LIMITATIONS OF THE RESEARCH METHODS

No randomized assignment of patients to the survey is implicated. This may induce selection bias. The site will be nominated by the availability of conducting the study with a peak flow meter, and might have a more intensive observation compared with the non-selected site.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

This PMS is to be conducted in accordance with both the in-house PMS SOP and working instructions which are in compliance with GPSP. This study should be conducted in compliance with SOP 001-MCS-90-118.

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, via EDC.

9.10.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For eCRFs all data must be derived from source documents.

9.10.2.2 Direct access to source data and documents

Direct access to source data and documents for PMS is not allowed in Japan.

9.10.3 Completion of study

When the study is completed, the investigator should inform the head of the study site of the completion in writing, and the head of the study site should promptly inform the IRB and sponsor of the completion in writing.

10. PROTECTION OF HUMAN SUBJECTS

There is no regulation or requirement for ensuring the well-being and rights of participants in a non-interventional observational study.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

The review by IRB is not mandatory for conducting PMS in Japanese GPSP. The sponsor will enter into a contract with a representative (e.g., head of hospital) in accordance with GPSP. Written informed consent prior to patient participation in the trial is not a regulatory or legal requirement in accordance with GPSP.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this PMS is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Data generated as a result of the PMS needs to be available for inspection on request by the regulatory authorities.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions (see 001-MCS-05-501-RD-01 for collection requirements) and of any new information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted.

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or

development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

An AE which possibly leads to disability will be reported as an SAE.

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the eCRF. When any adverse events occur, the data should be immediately entered into eCRF and transmitted. :

- all adverse drug reaction (ADRs) (serious and non-serious),
- all AEs with fatal outcome,

All ADRs, including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced

- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken Spiriva Respimat, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well as soon as possible.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than Spiriva Respimat, according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The progress reports and final reports will be submitted to PMDA in Japan PSR (Periodic safety report). And also the interim report for this PMS is included in re-examination documents.
This study is planned for the publication based on the final report.

13. REFERENCES

13.1 PUBLISHED REFERENCES

P14-15105 Ohta K, Ichinose M, Japanese Guideline for Adult Asthma 2014, Allergology Int, 2014,63:293-333

13.2 UNPUBLISHED REFERENCES

U13-1598-01 2.5 Clinical Overview, Spiriva Respimat, addition of asthma indication, 25 July 2013

001-MCS-05-501-RD-01 "Individual Case Safety Report (ICSR) collection, processing and reporting by Source", version 4.0, date 03 Oct 2016

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Specific Use-Result Surveillance of Spiriva Respimat in asthmatics (patients with mild to moderate persistent asthma)

Study reference number:
BI Study Number: 0205-0536

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

none

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

none

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☐	☐	☒	
4.2 Is the planned study population defined in terms of:	☒	☐	☐	6
4.2.1 Study time period?	☒	☐	☐	9.3
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	9.3

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.4 Disease/indication? 4.2.5 Duration of follow-up?	☒	☐	☐	9.3
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

none

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

none

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

none

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☐	☐	☒	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☐	☒	
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

none

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

none

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
9.1.3 Covariates?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.3
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.7
	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates?				
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

none

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☐	☐	☒	
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

none

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.10
11.2 Are methods of quality assurance described?	☒	☐	☐	9.10
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.10

Comments:

none

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☐	☒	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	

Comments:

none

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

none

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

none

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

none

Name of the main author of the protocol: ___ _____

Date: 16/Dec/2016

Signature: ____

ANNEX 3. FLOW CHART OF VARIABLES

1. Observation period

Item \ Time	Observation period[1]		
	Before first administration of Spiriva Respimat	4W	12W (or at discontinuation)
Patient registration	X[2]		
Patient demographics	X		
Administration of Spiriva Respimat	X (to be recorded throughout the observation period)		
Medical history/baseline conditions	X		
Previous/concomitant therapies	X (to be recorded throughout the observation period)		
Pulmonary function test FEV_1 FVC PEFR[3]	 (X) (X) (X)	 (X) (X) (X)	 (X) (X) (X)
Asthma severity	X		
Asthma Control Status	(X)	(X)	(X)
QOL (ACQ 6 score)	(X)	(X)	(X)
Adverse events	X (to be recorded throughout the observation period)		
Laboratory tests[4] associated with AE	(X)		
EDC transmitted time[5]	X		

(X): If applicable

1: Time points during the observation period are approximate. Collected data should be reported as of the closest available visit.
2: Patients administered Spiriva Respimat will be registered within 14 days from whenever the day of first administration is possible.
3: PEFR is defined as the mean of the PEFR values of the 7 days before each visit.
4: When laboratory related AE is reported, Laboratory tests associated with AE are reported.
5: eCRF (electronic case report form): Data are to be transmitted immediately after being entered into the eCRF at 12 weeks after the start of treatment or at discontinuation. In case of occurrence of any adverse events, the data should be immediately entered into the eCRF and transmitted.