Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	c02810760-01
BI Study Number:	205.525
BI Investigational Product:	Tiotropium inhalation solution – Respimat Inhaler (Ba 679 BR Respimat)
Title:	Specific Use-Result Surveillance of Spiriva Respimat in asthmatics(patients with severe persistent asthma)
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® 2.5 µg Respimat® 60 puffs (hereinafter referred to as Spiriva Respimat)
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder:	[redacted]
Joint PASS:	No
Research question and objectives:	This PMS is designed: To investigate the safety and effectiveness of Spiriva Respimat in patients with severe persistent asthma under real-world use.
Country of study:	Japan
Author:	[redacted]
Marketing authorisation	[redacted]

holder:	[redacted]
MAH contact person:	
EU-QPPV:	
Signature of EU-QPPV:	*(e-signature is on BIRDS)*
Date:	22 April 2015
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TBD = to be determined

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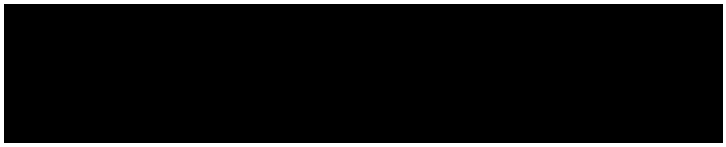
2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Confidence Interval
CRF	Case Report Form
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
EU-QPPV	European Union – Qualified Person for Pharmacovigilance
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume in one second
GCP	Good Clinical Practice
GPSP	Good Post- marketing Study Practice
FVC	Forced Vital Capacity
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISF	Investigator Site File
J-PAL	Japanese Pharmaceutical Affairs Law
J-RMP	Japan Risk Management Plan
MedDRA	Medical Dictionary for Regulatory Activities
MR	Medical Representative
NBI	Nippon Boehringer Ingelheim Co. Ltd.
OPU	Operative Unit
PEFR	Peak Expiratory Flow Rate
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
SAE	Serious Adverse Event
SPC	Summary of Product Characteristics
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan
TMM	Team Member Medicine
TMW	Trial Medical Writer
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: 15 April 2015	**Study number:** 205.525	**Version/Revision:** Ver 1.0	**Version/Revision date:** n.a.
Title of study:	Specific Use-Result Surveillance of Spiriva Respimat in asthmatics(patients with severe persistent asthma)		
Rationale and background:	The safety of Spiriva® 2.5 μg Respimat® 60 puffs (hereinafter referred to as Spiriva® Respimat®) in patients with severe 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 severe persistent asthma under real-world use.		
Study design:	Non-interventional, observational study based on new data collection		
Population:	Inclusion criteria: • Patients diagnosed with severe 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:	300 (safety set)		
Data analysis:	Descriptive		
Milestones:	Final report will be made by 1 Apr 2018 Study result in re-examination will be submitted to PMDA (Jan. 2019)		

5. AMENDMENTS AND UPDATES

There are currently no amendments to the protocol.

6. MILESTONES

Milestone	**Planned Date**
Start of data collection	1 Jun 2015
End of data collection	31 Aug 2017
Study progress report	None
<Registration in the EU PAS register>	To be registered
Final report of study results:	1 Apr 2018 (Study result in re-examination will be submitted to PMDA by Jan. 2019)

7. RATIONALE AND BACKGROUND

Tiotropium is one of the most widely used long-acting bronchodilators worldwide for the treatment of COPD, 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 the following diseases: chronic obstructive pulmonary disease (chronic bronchitis, emphysema), bronchial asthma.

Tiotropium delivered via the RESPIMAT inhaler once daily demonstrated consistent and significantly improved 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 at least a high-dose ICS+LABA or medium-dose ICS were shown to have a symptomatic benefit from taking tiotropium [U13-1598-01].

Tiotropium delivered via the RESPIMAT inhaler once daily also demonstrated acceptable long-term safety and tolerability when administered at a dose of 5 µg (Tio R5) 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 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 consistent patterns of increases in particular AEs for the tiotropium treatment groups compared to the placebo in any subgroup analysis. No deaths were reported during the entire clinical program [U13-1598-01].

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 Tio R5 as a new additional maintenance therapy in patients with asthma who remain symptomatic despite treatment with at least ICS has significance in managing lung function and symptoms of asthma patients more appropriately and may be an important paradigm shift in the treatment of asthma patients.

Result of PMDA review
PMDA judged that the 5-µg dosage form was suitable only for patients with severe persistent asthma and the 2.5-µg dosage form was suitable for patients with mild to moderate persistent asthma. But the 2.5-µg dosage form is not established for marketing and the 5-µg dosage form has no data to ensure the dose of 2.5 µg in one inhalation because Respimat inhaler can only maintain quality assurance with two inhalations at a time.
For the above reason including PMDA review, Spiriva Respimat (5-µg dosage form) for use in severe persistent asthmatics age 15 or over was approved on November 18 2014 in Japan.

PMDA instructed NBI to conduct the PMS with sever persistent ashmatics at age 15 or over as an approval condition in J-RMP.

Japanese regulation related to Post Marketing Surveillance (PMS)
This PMS study 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 study 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 4 years after approval of registration. The PMS study 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

As the submission data package for registration in Japan, we participated in two studies in adult patients with severe persistent asthma (Studies 205.416 and 205.417) and two studies (Studies 205.418 and 205.419) in adult patients with moderate persistant asthma , and we comparatively investigated the dose response between Japanese and non-Japanese by using two doses (Tio R2.5 and Tio R5). With the addition of the domestic long-term administration study in Japanese patients (Study 205.464), we investigated the validity of selecting a dose of 5 μg in Japanese asthma patients [U13-1598-01].

In the clinical trials, 212 Japanese patients with asthma received Tio R5 up to 52 weeks and some concomitant asthma therapies were allowed. However the clinical trials reflected a limited controlled experiment that might not generalize to the population, setting or condition and might not be reflected due to prohibited concomitant drugs or exclusion criteria of complicating diseases. The primary aim of clinical trials is to measure the key clinical efficacy as an end point in a limited population and clinical setting. PMS is likely to improve data monitoring and can collect post-marketing safety data in response to specific safety concerns. Even though there was no safety concern reported in patients with asthma based on the results of clinical trials, PMDA directed NBI to conduct PMS to fulfill regulatory obligations established as a condition of marketing approval.

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

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional study based on newly collected data under routine medical practice.

This PMS is designed to investigate the safety and effectiveness of Spiriva Respimat in patients with severe persistent asthma on top of at least ICS maintenance treatment under real-world use.

9.1.1 **Outcomes: effectiveness**

9.1.1.1 Primary outcome

There is no primary outcome for effectiveness as the primary objective of a PMS is evaluating safety. The primary outcome for safety is described in Section 9.1.2.1.

9.1.1.2 Secondary outcome

- Change from baseline in asthma control status at Week 52

[redacted]

9.1.1.4 Assessment of effectiveness

Asthma control status:

Asthma control status will be assessed based on the "Asthma prevention and management guideline" [! "#$"%"&%

9.1.1.4: 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

9.1.2 **Outcomes for safety**

9.1.2.1 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)

9.2 SETTING

9.2.1 **Site selection:**

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

1. Spiriva Respimat has been delivered to the site.
2. 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 Selection of population

9.2.2.1 Inclusion/Exclusion criteria:

Inclusion criteria:

- Patients diagnosed with severe persistent bronchial asthmaPatient 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]. Most severe persistent asthma is included in "Severe persistent asthma" indication in J-PI of Spiriva Respimat.

Exclusion criteria:

- Patients who have a contraindication to Spiriva Respimat defined in the package insert for Spiriva Respimat
- Patients who have been enrolled 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 variable for registration is 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 will use a signed form to confirm that patients will be registration 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 June 2015 to May 2016

9.2.3 Observations

After start of the treatment with Spiriva Respimat, each patient will be observed for 52 weeks (approximately 12 months) 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, 12 weeks and 52 weeks after the start of treatment, or at discontinuation.

9.2.5 Discontinuation of the study by the sponsor

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

1. Failure to meet expected registration overall goals or goals at a particular study site,
2. Emergence of any effectiveness/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 PMS site will be reimbursed for reasonable expenses incurred as a result of PMS termination (except in case of the third reason).

9.3 VARIABLES

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

The observation items include the following:

- Demographics
- Medical history/baseline conditions
- Previous/concomitant therapies
- Spiriva Respimat administration
- 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

- Adverse event
- Laboratory test (if corresponding AEs are reported)

Additional variable will also be included in the CRF such as cardiovascular risk factors including smoking and weight.

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.

Three case books will be used. The first book is for registry (Book 1), the second book is for baseline, 4 and 12 weeks (Book 2) and the third book is for 52 weeks (Book 3).

Data are to be transmitted immediately after being entered into the eCRF at 12 weeks and 52 weeks after the start of treatment or at discontinuation. In the case that any adverse events occur, the data should be immediately entered into eCRF and transmitted.

9.5 STUDY SIZE

It is planned to enroll 360 patients with severe persistent asthma: 360 patients will initiate the Spiriva Respimat treatment, assuming 60 patients out of 360 patients will be dropped out without any data being collected.

The planned number of patients is not driven by a formal sample size calculation but is primarily based on the availability of patients eligible for Spiriva Respimat treatment.

300 patients will be registered for this study. The frequently observed ADR (≥1.0%) in special use surveillance for Spiriva Respimat in patients with COPD was Coughing (1.2%). The frequently observed ADRs (≥1.0%) in the clinical trial in Japanese patients with asthma were asthma (1.8%), dysphonia (1.8%) and dry mouth (1.8%). In the number of cases to be surveyed, it is evaluated if there is no possibility that the trend of incidence of these main adverse events would be largely increased compared to that of COPD patients.

9.6 DATA MANAGEMENT

Data are gathered using EDC.

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. Due to the nature of the observational study, 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 Analyses of outcome events

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.

9.7.2 Safety analyses

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 Analyses of other variables

Descriptive statistics will be calculated for all outcomes.

A missing score for an item may be replaced as the mean score of the available data. In case of a missing ACQ 6 score, the missing score will not be imputed.

For other variables, missing data will not be imputed.

9.7.4 Interim analyses

Several interim analyses will be performed for the purpose of creating periodic safety update reports to the local authority (every 6 to 12 months depending on the time from the approval).

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 INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the patient's treating physician.

The rights of the investigator and of the sponsor with regard to publication of the results of this PMS are described in the contract.

9.10.1.1 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.

9.10.1.2 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.

9.10.1.3 RECORDS

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

9.10.1.3.1 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.

9.10.1.3.2 Direct access to source data and documents

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

9.10.1.4 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.

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.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a study who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including 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 Drug Reaction (ADR)
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 authorisation 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 immediately life-threatening,
- -requires in-patient hospitalization, or
- prolongation of existing hospitalization
- 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.

Every new occurrence of cancer will be is to be considered as SAE regardless of the duration between discontinuation of the study medication and the occurrence of the cancer.

Adverse Event of Special Interest (AESI)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

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 and Reporting 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 (e)CRF via EDC system from first intake of Spiriva Respimat prescribed at baseline visit and within 30 days (inclusive) after the last intake:

- all ADRs (serious and non-serious) as soon as possible,
- all AEs with fatal outcome in patients exposed to Spiriva Respimat as soon as possible,
- all AEs which are relevant for a serious ADR or an AE with fatal outcome in patients exposed to Spiriva Respimat as soon as possible

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).

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 its 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.

<u>Intensity of adverse event</u>
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
The intensity of adverse events should be classified and recorded according to the above referenced definition in the (e)CRF.

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.

The investigator will report the Pregnancy Monitoring Forms to sponsor as soon as possible via the unique entry point described in the Site Materials.

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 the 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 TIME WINDOWS

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "expected" (i.e., is a known side effect of the drug or not). Therefore a unique reference document for the evaluation of expectedness needs to be provided. For the study product, this is the current version of the Japan PI (package inserts). The current versions of these reference documents are to be provided in the Site material.

11.4 DOCUMENTATION OF ADVERSE EVENTS AND PATIENT NARRATIVES

Expedited reporting of serious adverse events (e.g., suspected unexpected serious adverse reactions (SUSARs) to health authorities) will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Site material.

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 final report will be submitted in re-examination documents. This study is planned for the publication based on the final report.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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?&"#,BCDEC$CCC

13.2 UNPUBLISHED REFERENCES

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

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
None			

ANNEX 2. ENCEPP CECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMEA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

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 page number(s) 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). Note, 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 severe persistent asthma)

Study reference number: BI Study Number: 205.525

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	10
1.1.2 End of data collection[2]	☒	☐	☐	10
1.1.3 Study progress report(s)	☒	☐	☐	10
1.1.4 Interim progress report(s)	☒	☐	☐	10
1.1.5 Registration in the EU PAS register	☒	☐	☐	10
1.1.6 Final report of study results.	☒	☐	☐	10

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**	**Page Number(s)**
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)	☒	☐	☐	11
2.1.2 The objective(s) of the study?	☒	☐	☐	13
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	16
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

none

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	14
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	14,15

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

none

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☐	☐	☒	
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	16
4.2.2 Age and sex?	☒	☐	☐	17
4.2.3 Country of origin?	☐	☐	☒	
4.2.4 Disease/indication?	☒	☐	☐	17
4.2.5 Co-morbidity?	☒	☐	☐	17
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	15

Comments:

none

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☒	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, 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?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

none

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☒	☐	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	

Comments:

none

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	17
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	17

Comments:

none

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☐	☐	☒	18
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
8.1.3 Covariates?	☐	☐	☒	
8.2 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)	☒	☐	☐	17
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	14
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	17
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	19
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	19
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

none

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	18

Comments:

none

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	19
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

none

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	19
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	18
11.3 Are methods of quality assurance described?	☒	☐	☐	20
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	20
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

none

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	20
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	
12.3 Does the protocol address other limitations?	☐	☒	☐	

Comments:

none

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	20
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	20
13.3 Have data protection requirements been described?	☐	☒	☐	

Comments:

none

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

Comments:

none

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	27
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	27

Comments:

none

Name of the main author of the protocol: [redacted]

Date: 15/Apr/2015

Signature: [redacted]

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)	52 W (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	(X)	(X)	(X)	(X)
FVC	(X)	(X)	(X)	(X)
PEFR[3]	(X)	(X)	(X)	(X)
Asthma severity	X			
Asthma Control Status	(X)	(X)	(X)	(X)
QOL (ACQ 6 score)	(X)	(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

(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 and 52 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.

APPROVAL / SIGNATURE PAGE

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Document Name: non-interventional-study-protocol

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
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Approval-Team Member Medical Affairs		23 Apr 2015 13:27 CEST
Approval-Therapeutic Area [redacted]		23 Apr 2015 13:30 CEST
Approval-EU Qualified Person Pharmacovigilance		23 Apr 2015 13:31 CEST
Approval-Project Statistician		23 Apr 2015 13:56 CEST
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Approval-[redacted] of Global Epidemiology		23 Apr 2015 18:05 CEST

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