Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c02840643-02**
BI Study Number:	1237.34
BI Investigational Product(s):	Tiotropium+olodaterol fixed dose combination solution for inhalation -RESPIMAT
Title:	Post-marketing surveillance (PMS) on long-term use of tiotropium+olodaterol fixed dose combination (Tio+Olo FDC) 5µg/5µg in patients with chronic obstructive pulmonary disease (chronic bronchitis, emphysema) in Japan
Protocol version identifier:	Ver 2.0
Date of last version of protocol:	15 November 2015
PASS:	Yes
EU PAS register number:	NA
Active substance:	Tiotropium:R03BB04 Olodaterol:R03AC19
Medicinal product:	Spiolto RESPIMAT 28 puffs (Tio+Olo FDC solution for inhalation-RESPIMAT)
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	.
Joint PASS:	No
Research question and objectives:	The study objective is to assess the long-term safety and effectiveness of Tio+Olo FDC 5µg/5µg in patients with chronic obstructive pulmonary disease (chronic bronchitis, emphysema) in real-world setting.
Country(-ies) of study:	Japan
Author:	(Trial Clinical Monitor, Patient Safety 3 ,

Marketing authorisation holder(s):	
In case of PASS, add: **MAH contact person:**	
In case of PASS, add: **<EU-QPPV:>**	
In case of PASS, add: **<Signature of EU-QPPV:>**	*e-signature is on BIRDS*
Date:	10 MAY 2016

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
CAT	COPD Assessment Test
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU-QPPV	European Union – Qualified Person for Pharmacovigilance
FDC	Fix Dose Combination
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GPSP	Good Post- marketing Study Practice
ICS	Inhaled Corticosteroid
IRB	Institutional Review Board
J-PAL	Japanese Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices
J-RMP	Japan Risk Management Plan
LABA	Long Acting Beta2 Agonist
LAMA	Long Acting Muscarinic Antagonist
MedDRA	Medical Dictionary for Drug Regulatory Activities
PMDA	Pharmaceuticals and Medical Devices Agency
PMS	Post Marketing Surveillance
SAE	Serious Adverse Event

3. RESPONSIBLE PARTIES

Contact details and the list of all investigators will be kept in a stand-alone document. This document will be managed in the PMS tracking system which manage the contracts with site and investigators name.

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto Respimat 28 puffs/ Spiolto Respimat 60 puffs			
Name of active ingredient: Tiotropium + olodaterol fixed-dose combination solution for inhalation - RESPIMAT			
Protocol date: 15 November 2015	**Study number:** 1237.34	**Version/Revision:** Ver 2.0	**Version/Revision date:** 10 MAY 2016
Title of study:	Post Marketing Surveillance (PMS) on long-term use of tiotropium+olodaterol fixed dose combination (Tio+Olo FDC) 5µg /5µg in patients with chronic obstructive pulmonary disease (chronic bronchitis, emphysema) in Japan		
Rationale and background:	The number of patients exposed to Tio+Olo FDC 5µg /5µg is limited in clinical trials. In addition, the clinical trial setting had some limitations compared to the real-world setting, such as inclusion/exclusion criteria defined patient's background and restriction of concomitant medications. In addition it is important to understand treatment patterns in routine clinical practice.		
Research question and objectives:	The study objective is to assess the long-term safety and effectiveness of Tio+Olo FDC 5µg/5µg in patients with chronic obstructive pulmonary disease (chronic bronchitis, emphysema) in real-world setting.		
Study design:	Observational study based on newly collected data for 52 weeks.		
Population:	- Inclusion criteria · Patients who have been diagnosed with chronic obstructive pulmonary disease (chronic bronchitis, emphysema) by physician and need to be treated co-administration of a long-acting inhalational anticholinergic and a long-acting inhalational β2-agonist to relief of various symptoms associated with the obstructive impairment of airways. · Patients who are prescribed Tio+Olo FDC 5µg /5µg for the first time - Exclusion criteria · Patients who have already been registered in this study once (re-entry of patients is not allowed) · Patients who are participating in a clinical trial or registry. · Patients who have a contraindication to Tio+Olo FDC 5µg /5µg		

	defined in the package insert for Tio+Olo FDC 5µg /5µg.
Variables:	Baseline characteristics Demographics Duration from indication COPD status (severity (i.e. GOLD stage)) Tio+Olo FDC 5µg /5µg administration status Medical history/ baseline conditions Previous /concomitant therapies Concomitant/ past medications (start/stop date, dosage, unknown) Chronic obstructive pulmonary disease (chronic bronchitis, emphysema) medications (ICS, LABA, LAMA, other, unknown) other medications (start/stop date, dosage, unknown) CAT (COPD Assessment Test) FVC and FEV_1 (if the data is available at sites with information of pulmonary medication (i.e. pre-dose or post-dose)) Pregnancy
Data sources:	Patients' data will be collected by electronic Case Report Form (eCRF) on EDC system
Study size:	1000 (safety set)
Data analysis:	Analyses are descriptive in nature. AEs are described with their incidence and incidence rate per treatment time. Subgroup analyses are performed for suitable sized samples with regard to patient characteristics and AE groups of medical interest. Due to the nature of the observational study, no confirmatory statistical testing is foreseen in this study.
Milestones:	Study Report planned to be archived in 3Q 2019 Study result based on study report is submitted in the re-examination document to PMDA in 4Q 2023.

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
2.0	10 MAY 2016	Abstract	Change the indication	To comply with J-PI
		Milestones	Change the study period	Delay of EDC system setup
		Physicians' global assessment	Add "(compared to the day before initiation of Tio+Olo FDC 5µg /5µg)"	To make the rule clearer
		Data management	Change name of CRO	CRO changed their name
		9.1 STUDY DESIGN	Updated	Added visits based on the requirement from PMDA.

6. MILESTONES

Milestone	**Planned Date**
Start of data collection	23 August 2016 (Launch of the investigated product: 3 December 2015)
End of data collection	30 November 2018
Registration in the EU PAS register	To be registered
Final report of study results:	July 2019

7. RATIONALE AND BACKGROUND

This PMS study is planned according to the requirement by the Pharmaceutical Affairs Law in Japan (J-PAL). 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 8 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.

The results of clinical trials and PMS studies related to Tio mono or Tio+Olo FDC are summarised below.

Clinical trials evaluating Tio mono until re-examination:
Until now, there were five clinical trials [P05-08673][U03-3113][U03-3144][U08-3718][P09-15298] in Japanese patients with COPD for Tio HandiHaler and Tio Respimat as indicated in Table 7: 1.

Table7: 1 Study list of Tiotropium mono until re-examination

Study type [reference], BI study number	Treatment period	Number of Japanese patients (safety set)
Phase II, dose finding study [P05-08673], 205.139	Single dose	HandiHaler, 27
Phase III, DBT [U03-3113], 205.226	4 weeks	HandiHaler, 67
Phase III for long term administration, open trial for safety [U03-3144], 205.227	1 year	HandiHaler, 110
Phase IIIb, UPLIFT trial [U08-3718], 205.235	4 years	HandiHaler, 100
Phase II, crossover trial for equivalence between HandiHaler and Respimat [P09-15298], 205.291	4 weeks	HandiHaler, 81 Respimat, 76

A total of 385 Japanese patients received Tio in these clinical trials. Even though there were no reports of safety concern to Tio in patients with COPD based on the results of clinical trials, PMDA directed to conduct PMS to fulfil regulatory obligations established as a condition of marketing approval. Therefore two PMS studies [U09-1849-01] [U09-2234-01] for Tio HandiHaler and 1 PMS study [U12-2679-01] for Tio Respimat were conducted. A total of 4130 patients received Tio in these PMS studies.

Clinical trials evaluating Tio+Olo FDC:
A total of 238 Japanese patients were treated with Tio+Olo FDC (5µg/ 5µg; the planned registered dose) up to 52 weeks in 3 phase III trials for Tio+Olo FDC program [U13-1759-01][U13-1760-01] [U13-1762-01]. Clinical trials of Tio+Olo FDC also include 149 Japanese patients receiving Olo mono 5µg and 76 Japanese patients receiving Tio mono 5µg.

There were no safety concerns of Tio+Olo FDC, Olo mono and Tio mono in these clinical trials in Japanese patients compared to the respective global safety experience. However, clinical trials have limitations in comparison to real-world clinical practice due to the restriction of concomitant drugs and the exclusion of complicating severe diseases. In addition, no safety experience beyond 1-year of exposure is currently available from clinical trials with Tio+Olo FDC
Therefore, PMDA directed to conduct PMS to collect mainly safety data from real-world clinical practice to fulfil regulatory obligations established as a condition of marketing approval.

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 8 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

This PMS study is one of the action plans of collecting post-marketing safety information focused on the following risks and information of Tio+Olo FDC 5µg/5µg in the J-RMP.

- Important identified risks: Cardiac failure, atrial fibrillation and extrasystoles, Ileus, Angle closure glaucoma, Anaphylaxis
- Important potential risks: Cardiac disorder (Myocardial ischaemia, Cardiac arrhythmia), Intubation and mortality related to asthma
- Important missing information: none specified

The study objective is to assess the long-term safety and effectiveness of Tio+Olo FDC 5µg/5µg in patients with chronic obstructive pulmonary disease (chronic bronchitis, emphysema) in real-world setting.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is an observational study based on newly collect real-world data (i.e., data under real-world practice) to evaluate safety and effectiveness of Tio+Olo FDC 5µg/5µg in patients with chronic obstructive pulmonary disease (chronic bronchitis, emphysema).

The study will be initiated after marketing of Tio+Olo FDC 5µg/5µg in Japan. The study will consist of a baseline visit and further visits in a 52-week follow-up for patients who have initiated the Tio+Olo FDC 5µg/5µg treatment.

As this is an observational study, no specific treatment is mandated or withheld from the patients. The choice of maintenance treatment for chronic obstructive pulmonary disease (chronic bronchitis, emphysema) must be according to regular medical practice and at discretion of physician (i.e., no randomised assignment of patient to treatment [Tio+Olo FDC or other treatment] is performed). In total, approximately 1100 patients are planned to be registered at approximately 200 study sites in the study.

Patients participating in the subsequent follow-up will undergo regular observations. These observations should be reported after 4, 12, 24 and 52 weeks since the initiation of Tio+Olo FDC 5µg/5µg as long as they continue to receive the treatment. Patients will not be followed any longer once they are reported to have discontinued the Tio+Olo FDC 5µg/5µg treatment. Patients who experience adverse events will be followed up until detailed information on the outcome of the adverse event is collected.

The primary outcome of this study is the incidence and exposure-time adjusted incidence rate of adverse drug reactions (ADRs).

The secondary outcome of this study is:

- COPD assessment test (CAT) at 12 weeks.

9.2 SETTING

9.2.1 Site selection:

Tio+Olo FDC 5µg/5µg has been delivered to the sites and PMS Director who is assigned on Good Post- marketing Study Practice (GPSP) will decide sites to participate in the study based on the site selection checklist.

Planned number of site: Approximately 200 Sites

A medical representative will explain the objective and design of this study to investigators at each study site and exchange a written contract with the head of the study site (e.g., hospital director).

9.2.2 Selection of population

9.2.2.1 Inclusion/ exclusion criteria

Patients who fulfil the following criteria will be included.

- Patients who have been diagnosed with chronic obstructive pulmonary disease (chronic bronchitis, emphysema) by physician and need to be treated co-administration of a long-acting inhalational anticholinergic and a long-acting inhalational β2-agonist to relief of various symptoms associated with the obstructive impairment of airways
- Patients who are prescribed Tio+Olo FDC 5µg/5µg for the first time

Patients who present the following criteria will be excluded.

- Patients who have been registered once in this study (i.e., re-entry of patients is not allowed).
- Patients who are participating or registry in a clinical trial.
- Patients who have a contraindication to Tio+Olo FDC 5µg/5µg defined in the package insert for Tio+Olo FDC 5µg/5µg.

9.2.2.2 Registration period

From August 2016 to August 2017

9.2.2.3 Patient registration method

Patients will neither be selected randomly nor assigned to treatment randomly. At each study site, patients who are judged by investigator eligible to the study will be consecutively registered. Investigators register patients sequentially who are prescribed Tio+Olo FDC

5µg/5µg treatment according to regular medical practice to reach the number of contract with site.

Patients will be registered by entering necessary information into the EDC immediately or within 14 days whenever possible from the day of treatment initiation (inclusive). The necessary information for registration is gender, date of birth, start date of administration and the reason for use.
Investigators will use a signed form to confirm that the patients will be registered continuously at the site.

End of registration
Patient registration will be stopped when the target number of study is reached. A log of all patients included into the survey will be maintained at the sites.

9.2.3 Discontinuation of the study by the sponsor

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

1. Failure to meet expected enrolment overall goals or goals at a particular study site,
2. Emergence of any efficacy/safety information that could significantly affect continuation of the study or any other administrative reasons.
3. Violation of GPSP, the NIS protocol, or the contract by study site or investigator, disturbing the appropriate conduct of the study.

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

9.2.4 Priority survey items

The following outcomes of interest are set with particular priority as priority survey items.
- Cardiovascular adverse events
- Anticholinergic-related adverse events
- Beta2 agonist-related events

9.3 VARIABLES

9.3.1 Exposure

Exposure to Tio+Olo FDC 5µg/5µg is estimated as time from the day Tio+Olo FDC 5µg/5µg is initiated until the day the drug is last administrated on a patient-level (or the final contact with the patient during the regular observation period).

9.3.2 Outcomes

The following events are considered important outcomes.

Safety:

Safety will be assessed with the incidence (n and % in treatment group) and treatment exposure time adjusted incidence rate (n in 100 patient years) of AEs in patients treated with Tio+Olo FDC (treatment emergent). Results will be stratified by different treatment types prior to baseline and age as a general risk factor.

- Adverse Drug Reactions (ADRs) (primary outcome) : related AEs as judged by the investigator or sponsor with a suspected causal relationship with the Tio+Olo FDC 5µg/5µg treatment
- AEs leading to death
- AEs leading to discontinuation of the Tio+Olo FDC 5µg/5µg treatment)
- Serious Adverse Events(SAEs)
- Priority survey items: Cardiovascular adverse events, Anticholinergic-related adverse events, Beta2 agonist-related adverse events

Section 11 covers how to assess and report AEs including the definitions.

Additional subgroup analyses/ safety outcomes might be included based on new information that could become available during the course of the study.

Effectiveness:

Patient's global rating (PGR)

Patients will be asked to rate their health (respiratory condition) at 4 weeks, 12 weeks, 24 weeks and 52 weeks (compared to the day before they commenced treatment with study drug) on the following 7-point scale.

1	2	3	4	5	6	7
very much better	much better	a little better	no change	a little worse	much worse	very much worse

COPD Assessment Test (CAT)

See ANNEX 3

Physicians' global assessment

Effectiveness of the Tio+Olo FDC 5µg/5µg treatment will be comprehensively assessed (compared to the day before initiation of the Tio+Olo FDC 5µg/5µg) according to the following scale based on the observed symptoms and results of pulmonary function test.

1. Improved, 2.Unchanged, 3.Deteriorated, 4. Not assessable

FVC and FEV_1

If the data is available at sites with information of pulmonary medication (i.e. pre-dose or post-dose)

See ANNEX 2 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.

In EDC system, two casebooks will be set up; Book 1 includes baseline, 4 weeks, and 12 weeks. Book 2 includes 24 weeks and 52 weeks.

The data are to be transmitted immediately after being entered into EDC at 12 weeks (Book 1) and 52 weeks (Book 2) after the start of treatment or at discontinuation.
For any adverse events, the data should be immediately entered into EDC and transmitted.

9.5 STUDY SIZE

Study size is 1000 patients with chronic obstructive pulmonary disease (chronic bronchitis, emphysema) analysed (safety analysis set). As approximately 10 % of the patients are assumed to drop out without any data (just registered), therefore, 1100 patients is planned to be registered.

This is a descriptive study and no confirmatory tests are planned.

The proportion of overall patients with serious cardiovascular events was 2.6% in Tio+Olo FDC 5µg/5µg group in the pooled data of trials 1237.5, 1237.6 and 1237.22. With 1000 patients, the 95% confidence interval of serious cardiovascular events could be estimated with a width of 2.0% to 2.8% (Wilson interval) if the proportion of patients with serious cardiovascular events is between 2.6% and 5.2%.

If the true proportion of patients with serious cardiovascular events is assumed to be 2-fold (i.e., 5.2%), the sample size of 873 is required to have 98% power for rejecting the null hypothesis of incidence=2.6% by using one sample chi-square test with a 0.05 two-sided significance level.

9.6 DATA MANAGEMENT

Patients' data will be gathered by EDC system provided by external vendor below.

	Contract 1	Contract 2
Company Name		
Outsourced work	EDC system setting Patient registration Clinical Data Management	Document management of contract with site.

9.7 DATA ANALYSIS

This is an observational study to collect real-world data (i.e., data under routine medical practice) on safety and effectiveness of Tio+Olo FDC 5µg/5µg treatment. Analyses are descriptive in nature, including confidence intervals. Due to the nature of the observational study, no confirmatory statistical testing is foreseen in this study. Subgroup analyses are also performed if sample size allows.

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 Tio+Olo FDC 5µg/5µg treatment. All outcome events are based on reported AE data which will be handled according to BI standards (see the section below).

9.7.2 Analyses of Safety

The safety analysis will include all patients registered in the study and receiving the Tio+Olo FDC 5µg/5µg treatment except for patients who meet the ineligible criteria (see section9.7). In general, safety analyses will be descriptive in nature, be based on BI standards, and focus on AEs related to the Tio+Olo FDC 5µg/5µg treatment.

AEs will be coded using the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) and will be based on the concept of treatment emergent AEs. To this end, all AEs occurring between the initiation of Tio+Olo FDC 5µg/5µg prescribed at baseline visit and 21 days (inclusive) after the last administration will be considered 'treatment emergent'. An AE is considered to be an ADR if either the physician/investigator who has reported the AE or the sponsor assesses its causal relationship as 'related'.

The incidence (n and % in treatment group) and treatment exposure time adjusted incidence rate (n in 100 patient years) of AEs in patients treated with Tio-Olo FDC (treatment emergent including 21 days after discontinuation of Tio+Olo FDC medication) will be tabulated by MedDRA SOC and PT for overall and for subgroups based on the important baseline characteristics, if sample size allows (see9.3.3)

9.7.3 Analyses of effectiveness

For patients' global rating and physicians' global assessment, the frequency of patients with each score will be tabulated.

For CAT, descriptive statistics will be calculated for the total score and the score of each individual component and the changes from scores at week 12 before first administration.

9.7.4 Interim analyses

Several interim analyses (AEs' tabulate) will be performed for the purpose of submission of periodic safety update reports to PMDA in project (status update of using Spiolto not only with this trial but all usage, every 6 month in two years after approval and every 12 months afterward. The submission date is 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

The general objective of this observational study is to obtain an estimate of the effect of a drug exposure on the occurrence of the events of interest in the population of the study. Due to the nature of a single cohort observational study, however, there are issues that may impose threats in particular on the validity of the assessment based on the study data, such as selection bias, loss to follow up, channeling bias and information and recall bias, and these issues should be fully taken into account as limitations of this study design when, conducting, analyzing and interpreting the study. In addition interpretation of results may be challenging due to the lack of a comparator.

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 study are described in the contract. As a general rule, no PMS study results should be published prior to finalization of the Study Report.

9.10.1.1 Study approval, patient information, and informed consent

The review by IRB is not mandatory for conducting PMS study according to GPSP. The sponsor will enter into a contract with a study site representative (e.g. head of hospital) in accordance with GPSP. Informed consent prior to patient participation in the study 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 SOP and working instructions which are in compliance with GPSP.

9.10.1.3 Records

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

9.10.1.4 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 study site. For the CRFs, all of the data must be derived from source documents.

9.10.1.5 Direct access to source data and documents

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

9.10.1.6 Statement of confidentiality

Individual patient's medical information obtained as a result of this PMS study 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 this PMS study need to be submitted on request by the regulatory authorities.

10. PROTECTION OF HUMAN SUBJECTS

There is no need for a clinical trial type insurance of well-being and rights of participants because this is a non-interventional study and there is no risk of an experimental treatment. There is no regulation or requirement for ensuring the well-being and rights of participants.

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 unfavorable 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) is 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 authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious Adverse Event (SAE) - 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 judgment 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 hospitalization but might jeopardize 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 hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.
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11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT 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 authorization. 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 Tio+Olo FDC 5µg/5µg prescribed at baseline visit and within 21 days (inclusive) after the last intake:
- all AEs (serious and non-serious) as soon as possible,
- all AEs with fatal outcome in patients exposed to Spiolto Respimat as soon as possible,
- all AEs which are relevant for a serious ADR or an AE with fatal outcome in patients exposed to Spiolto 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 characterized 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 reintroduced
- **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; 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.

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

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 Spiolto 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 Spiolto 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 the 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 final report will be submitted in re-examination documents.

13. REFERENCES

13.1 PUBLISHED REFERENCES

P05-08673 Hirata K, Kurihara N, Irino T, Yoshikawa J.Dose ranging study of a new long-acting bronchodilator tiotropium in single administration, double blind, 4-treatment and 4-period crossover design in patients with chronic obstructive pulmonary disease (COPD).Original in Japanese. J Clin Ther Med 20(9),925-939(2004).

P09-15298 Ichinose M, Fujimoto T, Fukuchi Y Tiotropium 5 mcg via Respimat and 18 mcg via HandiHaler; efficacy and safety in Japanese COPD patients. Respir Med 104 (2), 228 - 236 (2010)

P11-06784 Fukuchi Y, Fernandez L, Kuo HP, Mahayiddin A, Celli B, Decramer M, Kesten S, Liu D, Tashkin DEfficacy of tiotropium in COPD patients from Asia: a subgroup analysis from the UPLIFT trial.Respirology 16 (5), 825 - 835 (2011).

P11-08788 Antoniu SA. Effects of inhaled therapies on health-related quality of life in stable chronic obstructive pulmonary disease. Expert Rev Pharmacoeconomics Outcomes Res 2010;10(2):155-162.

R13-0957 CAT: COPD assessment test (healthcare professional user guide), expert guidance on frequently asked questions (issue 3: February 2012). http://www.catestonline.org/images/UserGuides/CATHCPUser%20guideEn.pdf (access date: 28 February 2013) ; GlaxoSmithKline; 2012.

13.2 UNPUBLISHED REFERENCES

U03-3113 , A Multiple Dose Comparison of 18 µg, 36 µg of Ba679BR (Tiotropium) Inhalation Capsules and Oxitropium Metered Dose Inhaler (2 puffs of 100µg) in a 4-week, Double-Blind, Double-Dummy, Safety and Efficacy Study in Patients with Chronic Obstructive Pulmonary Disease (COPD).205.226, 12 May 2003

U03-3144 , A Multiple Dose Comparison of Tiotropium 18µg Inhalation Capsules and Oxitropium MDI (2 puffs of 100µg) in a One-year, Open-Label, Safety and Efficacy Study in Patients with COPD, 205.227, 11 June 2003

U08-3718 UPLIFT®: Understanding Potential Long-term Impacts on Function with Tiotropium / A randomized, double-blind, placebo-controlled, parallel group trial assessing the rate of decline of lung function with tiotropium 18 mcg inhalation capsule once daily in patients with chronic obstructive pulmonary disease (COPD), 205.235, 28 October 2008

U09-1849-01 , Drug Use Results Survey of Tiotropium bromide. 205.314 20 November 2009

U09-2234-01 , Special Survey Long-term Treatment of Tiotropium. 205.315 30 October 2009.

U12-2679-01	Post Marketing Surveillance on Long-Term Drug Use of Spiriva 2.5 µg Respimat® 60 puffs in Patients with Chronic Obstructive Pulmonary Disease. 205.463 18 December 2012
U13-1759-01	A randomised, double-blind, parallel group study to assess the efficacy and safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg / 5 µg;5 µg /5 µg) (delivered by the Respimat® Inhaler) compared with the individual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat® Inhaler) in patients with Chronic Obstructive Pulmonary Disease (COPD) [TOnado™ 1]. 1237.5, 10 April 2014. (c01735218-02)
U13-1760-01	, A randomised, double-blind, parallel group study to assess the efficacyand safety of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed dose combination (2.5 µg / 5 µg;5 µg /5 µg) (delivered by the Respimat® Inhaler) compared with theindividual components (2.5 µg and 5 µg tiotropium, 5 µg olodaterol) (delivered by the Respimat® Inhaler) in patients with ChronicObstructive Pulmonary Disease (COPD) [TOnado™ 2]. 1237.6, 10 April 2014. (c01735249-02)
U13-1762-01	, A randomised, double-blind, parallel-group study to assess the safetyand efficacy of 52 weeks of once daily treatment of orally inhaled tiotropium + olodaterol fixed-dose combination (2.5 µg/ 5 µg, 5 µg/5 µg) and olodaterol (5 µg) delivered by the Respimat® inhaler in Japanese patients with Chronic Obstructive Pulmonary Disease(COPD). 1237.22, 03 April 2014. (c02099166-02)

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
None	None		

ANNEX 2. FLOW CHART OF VARIABLES

Item \ Time	Observation period					
	Before first administration of Tio+Olo FDC 5µg/5µg		4W	12W (or at discontinuation)	24W	52W (or at discontinuation)
Patient registration	X					
Patients visit date		X	X	X	X	X
Patient demographics		X				
COPD Characteristics		X				
Administration of Tio+Olo FDC 5µg/5µg		X (to be recorded throughout the observation period)				
Medical history/baseline conditions		X				
Previous/concomitant therapies		X (to be recorded throughout the observation period)				
Prescribed medication for chronic obstructive pulmonary disease (chronic bronchitis, emphysema) treatment		X (to be recorded throughout the observation period)				
Concomitant medications		X (to be recorded throughout the observation period)				
CAT		X	X	X	X	X
Patient's global rating (PGR)			X	X	X	X
Physician's global assessment			X	X	X	X
FVC and FEV_1*		(X)	(X)	(X)	(X)	(X)
Adverse events		X (to be recorded throughout the observation period)				
Laboratory tests associated with AE		X				
EDC transfer time	X[a]	X (Book 1)			X (Book 2)	

a: At patient registration: Patient's ID, gender, date of birth, start date of administration, indication and registration group will be entered into eCRF and transmitted.
*if the data is available at sites with information of pulmonary medication (i.e. pre-dose or post-dose)

ANNEX 3. COPD ASSESMENT TEST (CAT)

The COPD Assessment Test™ (CAT)

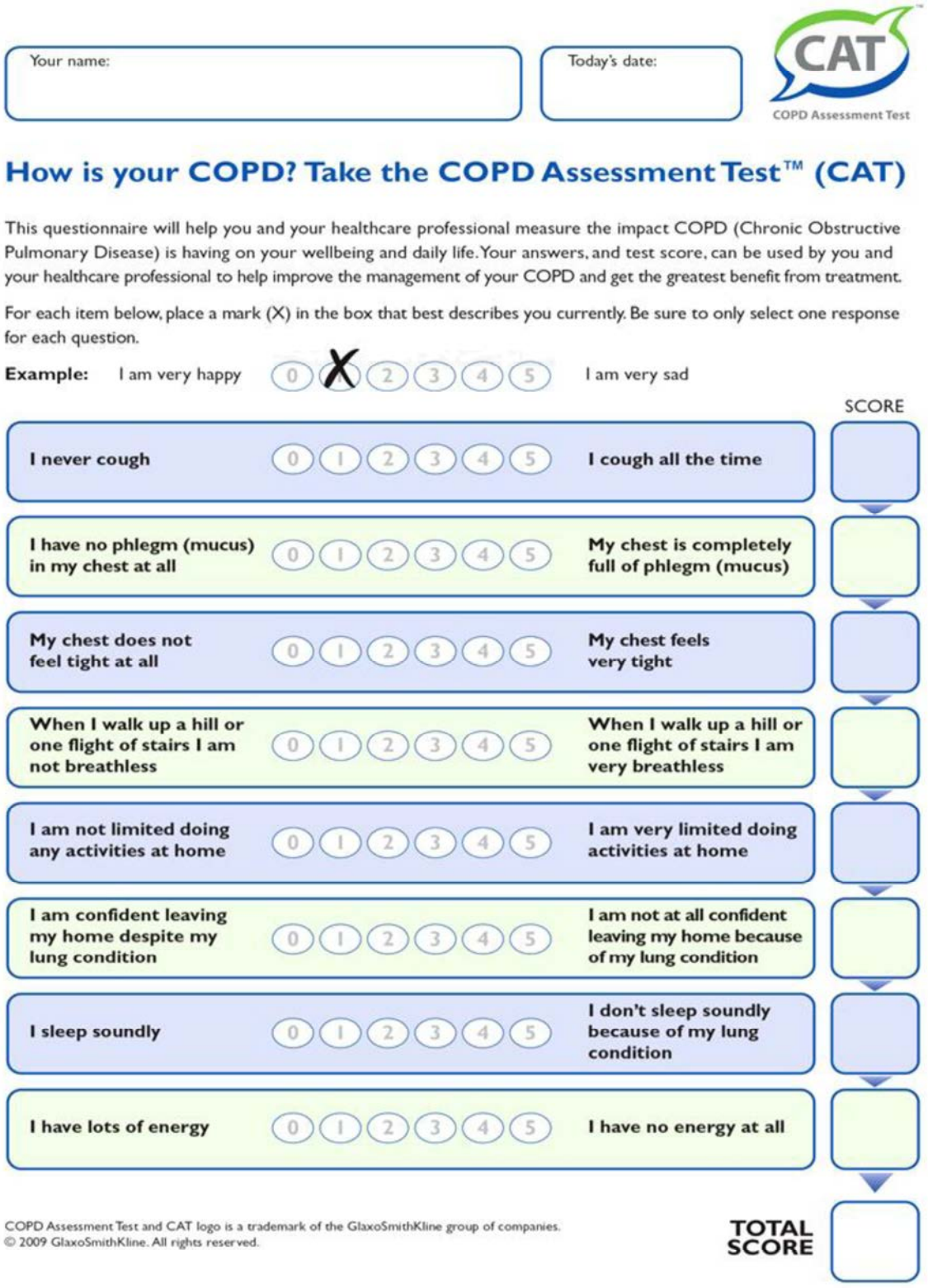
The COPD Assessment Test™ (CAT) is a short 8-item questionnaire for assessment and monitoring of COPD health status in routine practice. Its scale is 0-40 (high score = poor health). The CAT questionnaire has the advantage of a reduced number of items and could be used to assess the effects of inhaled therapies [P11-08788]. The CAT is attached following

The CAT will be performed at Visit 1 and each subsequent clinic visits until the last study treatment visit. The questionnaire will be paper based.

The test will be performed according to the "HEALTHCARE PROFESSIONAL USER GUIDE; CAT™; COPD Assessment Test; Expert guidance on frequently asked questions; Issue 3; February 2012" [R13-0957]. The CAT translated Japanese version will be used.

Site staff will check the answered CAT questionnaire for completeness. Site staff must not exercise any influence on the patient what to answer.

The patient's answers on the CAT questionnaire will be transcribed in the eCRF. The CAT score is the sum of the values corresponding to the answers to the eight questions.



Your name:

Today's date:

CAT
COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 X 2 3 4 5 I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	

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TOTAL SCORE

APPROVAL / SIGNATURE PAGE

Document Number: c02840643 **Technical Version Number:2.0**

Document Name: non-interventional-study-protocol-1237-34

Title: Post-marketing surveillance (PMS) on long-term use of tiotropium+olodaterol fixed dose combination (Tio+Olo FDC) 5µg/5µg in patients with chronic obstructive pulmonary disease (chronic bronchitis, emphysema) in Japan

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor		07:29 CEST
Approval-Medical		07:38 CEST
Approval- Pharmacovigilance		07:54 CEST
Approval- Safety Evaluation Therapeutic Area		08:41 CEST
Author-Trial Statistician		09:02 CEST
Approval-EU Qualified Person Pharmacovigilance		11:54 CEST
Approval-Team Member Medicine		13:43 CEST
Approval-Therapeutic Area		17:09 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed