Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	TBD
BI Study Number:	1237-0086
BI Investigational Product(s):	Tiotropium/olodaterol (Spiolto®)
Title:	Taiwan Outcomes and Real-world Treatment Options for Chronic Obstructive Pulmonary Disease (TOReTO)
Brief lay title	A study in Taiwan based on medical records that looks at the occurrence of flare-ups in patients with chronic obstructive pulmonary disease (COPD) who started LABA/LAMA or LAMA treatment
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Medicinal product:	tiotropium/olodaterol
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Procedure number:	Not applicable
Marketing authorisation holder(s):	This study is initiated, managed, and financed by: [redacted]
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Research question and objectives:	The primary objective is to understand the occurrence of COPD exacerbations in patients treated with LABA/LAMA in the routine clinical practice in Taiwan. The secondary objectives are to realize the clinical characteristics and prescription patterns for the COPD population in Taiwan.
Country(-ies) of study:	Taiwan

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Date:	25 November 2019

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2. LIST OD ABBREVIATIONS

ACOS	Asthma-COPD Overlap Syndrome
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
BI	Boehringer Ingelheim
BMI	Body Mass Index
CA	Competent Authority
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
e.g.	Exempli Gratia
etc.	ET Cetera
DVP	Data Validation Plan
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
FDC	Fixed-dose Combination
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Volume Vital Capacity
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GERD	GastroEsophageal Reflux Disease
GI	GastroIntestinal
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
GOLD	the Global Initiative for Chronic Obstructive Lung Disease
ICD	The International Classification of Diseases
ICH	The International Conference on Harmonisation
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IPPV	Intermittent Positive Pressure Ventilation
IRB	Institutional Review Board
LABA	Long-Acting Beta-Agonist
LAMA	Long-Acting Muscarinic Antagonist
MAH	Marketing Authorisation Holder
mMRC	modified Medical Research Council dyspnea scale
NIS	Non-Interventional Study
NIPPV	NonInvasive Positive Pressure Ventilator
Olo	Olodaterol
PASS	Post-Authorization Safety Study
SABA	Short-Acting Beta-Agonist
SADR	Serious Adverse Drug Reaction
SAMA	Short-Acting Muscarinic Antagonist

SOP	Standard Operating Procedure
Tio	Tiotropium
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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[redacted]	

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® (tiotropium/olodaterol)			
Name of active ingredient: tiotropium/olodaterol (ATC code: R03AL06; long-acting bronchodilators; a muscarinic receptor antagonist for tiotropium and a β adrenoreceptor agonist for olodaterol)			
Protocol date: 18 June 2019	**Study number:** 1237-0086	**Version/Revision:** 1.0	**Version/Revision date:** 25 November 2019
Title of study:	Taiwan Outcomes and Real-world Treatment Options for Chronic Obstructive Pulmonary Disease		
Rationale and background:	Recently, more and more randomized controlled trials (RCT) demonstrated effectiveness of dual bronchodilators for the treatment of chronic obstructive pulmonary disease (COPD). DYNAGITO trial[1] has provided further evidences for tiotropium + olodaterol (Tio + Olo) compared with tiotropium in reducing moderate/severe exacerbations. In the real-world setting in Taiwan, the medication environment and electronic medical charts are well-established in medical centers. Hence, retrospective analysis is fully possible. Boehringer Ingelheim (BI) Taiwan and clinical practitioners' common goal are to adopt optimal treatment for COPD patients diagnosed per GOLD guideline. So far, we can refer to some head to head studies examining the impact on lung function of various LABA/LAMA combinations; however, there is no study observing real world outcomes on prevention/risk reduction of acute exacerbations in Taiwan. The extent of outcomes from Tio + Olo (Spiolto®), other LABA/LAMA fixed-dose combinations [FDC]/free combos, or LAMA treatment of benefit for COPD patients in reducing acute exacerbation, is of great interest to explore.		
Research question and objectives:	The primary objective is to understand the occurrence of COPD exacerbations in patients treated with LABA/LAMA or LAMA in the routine clinical practice in Taiwan. The secondary objectives are to realize the clinical characteristics and prescription patterns for the COPD population in Taiwan.		
Study design:	This is a retrospective, multi-center, cohort study to collect the data on COPD patients who were administered with LABA/LAMA (FDC or free combo) or LAMA treatment for 3 months at least prior to 30 June 2018. For LABA/LAMA therapy, new initiation or switching from other therapy (i.e., single/dual/triple) are both acceptable; for LAMA		

	treatment, only new initiation will be acceptable. The data abstracted from eligible patients will be recorded only when they are available in the medical chart and will be categorized into the cohort A (patients treated with Tio + Olo), B (patients treated with other LABA/LAMA therapy), and C (LAMA therapy). The follow-up period for each patient will be from the index date* until the date of death or 1 year after the index date, whichever occurs first. Patients will be censored at the time from one LAMA/LABA or LAMA switched to another LAMA/LABA or ICS. *Index date: It is defined as the date of COPD patients in the cohort A and B stating using LABA/LAMA therapy regardless of new initiation or switching from other single/dual/triple treatment, or the date of the patients in the cohort C starting using LAMA treatment.
Population:	This study plans to review the medical chart from approximately 1,800 COPD patients receiving LABA/LAMA or LAMA treatment for 3 months at least prior to June 30 2018 in Taiwan. **Inclusion criteria** Patients who fulfil **ALL** the following criteria are included. 1. Patients who diagnosed with COPD who were prescribed with LABA/LAMA (FDC or free combo) as a new initiation or switching from other therapy (i.e., single/dual/triple), or newly receiving LAMA treatment for 3 months at least prior to 30 June 2018 2. Male or female patients ≥ 40 years of age **Exclusion criteria** Patients who meet the following criterion are not included. 1. Patients with documented diagnosis of bronchial asthma, asthma-COPD overlap syndrome (ACOS), bronchiectasis, cystic fibrosis, or lung cancer
Variables:	**Variables** • Patient demographics (date of birth, gender, race, body mass index [BMI], family history, occupation, etc.) • Diagnosis of COPD (date of diagnosis, disease severity, etc.) • Smoking status • Spirometry data (e.g., FEV_1, FVC) • COPD assessments (e.g., CAT, mMRC) • Acute exacerbations from 1 year before the index date until 1 year after the index date or the date of death (onset/stop date, etc.) • Hospitalizations due to COPD exacerbation (e.g., admission/discharge date, treatments) • Laboratory data (e.g., eosinophil counts)

	• Pharmacological/non-pharmacological treatments from 6 months before the index date to 1 year after the index date or the date of death, especially for the following: - Treatment related to COPD (start/stop dates, dosage, frequency, etc.) - Rescue treatments for COPD (antibiotics, oral corticosteroid, ventilator support, etc.) - Oxygen therapies - Surgeries for COPD therapy or improvement of lung function • Time/reasons for treatment switching (e.g., single/dual/triple therapy to LABA/LAMA prior to the index date, Tio + Olo to other therapies, single/dual escalating to dual/triple therapy) • Comorbidities (cardiovascular, cerebrovascular, respiratory, hepatic, renal, gastrointestinal, metabolic, infectious comorbidities, etc.) **Primary outcomes** • Time to the first moderate or severe COPD exacerbation **Secondary outcomes** • Annualized rate of mild/moderate/severe exacerbation • Time/reason (e.g., severe airflow limitation, diagnosis of asthma, worsening exacerbation) from LABA/LAMA escalating to LABA/LAMA/ICS or from LAMA to dual therapy • Percentage of patients receiving LABA/LAMA switched to triple therapy or LAMA switched to dual therapy • Change in pulmonary function after LABA/LAMA or LAMA initiation • Use of rescue medications
Data sources:	Source data are collected from medical charts in 12 medical hospitals in Taiwan. The case report form (CRF) will be designed for the data collection.
Study size:	Approximately 1,800 eligible COPD patients are planned to be enrolled from 12 medical hospitals in Taiwan.
Data analysis:	A Data Validation Plan (DVP) will be prepared to describe the processes for data validation. The data abstracted from the medical chart will be described with number, mean, standard deviation (SD), range, and 95% confidence intervals (95% CI) for continuous variables, and frequencies and percentages for categorical variables.

	The propensity score matching approach* will be used to balance the baseline characteristics between the study cohorts (Tio + Olo vs. other LABA/LAMA vs. LAMA therapy). These data will be compared descriptively between patients receiving different regimens (Tio + Olo vs. other LABA/LAMA vs. LAMA therapy). If the propensity score matching is done, the difference before and after matching will be considered both. The annualized rate of exacerbation with various severities will be calculated for each study group (episodes/patient-year), and the differences between the three cohorts will be compared by rate ratio. Time to the first moderate or severe COPD exacerbation or escalating to dual or triple therapy will be compared between different cohorts using Kaplan-Meier curves with the incidence and time to events, and statistical significance will be assessed using log-rank tests. Chi-square test or Fisher's exact test will be applied for categorical variables such as reasons for switching/escalating therapies, frequency, and percentage, etc. *NOTE: Variables may include but not limited to age, gender, disease duration before index date, smoking status, body mass index, COPD assessment score (e.g., CAT and mMRC), spirometry data (e.g., FEV_1), oxygen therapy, comorbidities, disease severity, previous exacerbation, previous treatments, or eosinophil counts, where appropriate.
Milestones:	Planned the start of data collection: July 2019 Planned the end of data collection: November 2019 Planned final study report: the end of January 2020

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	25 November 2019	1. Abstract 2. Section 9.2.2	Amendment	1. Revised typos from LABA/LABA to LABA/LA**M**A

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	31 July 2019
Start of data collection	01 August 2019
End of data collection	30 November 2019
Registration in the EU PAS register	31 July 2019
Final report of study results:	31 January 2020

7. RATIONALE AND BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a common, worldwide, and irreversible obstructive airway disease due to chronic inflammation in alveoli or airway. Generally, COPD manifests in males over 40 years and gradually progresses their health status even under the treatments. However, the steady increase prevalence in females or young patients is also found based on previous studies,[2,3] which implies that those already known risk factors (i.e., smoking, exposure to biomass fuel or chemical particles) should be emphasized. According to the report of World Health Organization (WHO),[4] COPD is the third leading cause of death begetting 1.7 million of death in 2016; meanwhile, it is the fifth cause of burden of disease in 2010 around the world.[5] The global prevalence of COPD cannot be estimated precisely because of the different approaches applied for calculation.[6] Averagely, the estimated global prevalence of COPD is 11.7% and the highest is observed in the America region with 15.2% compared to Europe and China with 7.4% and 6.5%, respectively.[7,8] In Taiwan, COPD is the seventh leading cause of death with the estimated prevalence of 6.1%.[9,10]

The general diagnosis of COPD includes reviewing patients' medical history, evaluating the lung function by spirometry, and emphysema using computed tomography (CT). Exacerbation/hospitalization due to exacerbation occurring ≥ 2 times/year is a predictor for a poor prognosis and increase in mortality.[11,12] Hence, how to prevent the exacerbation is at issue for the COPD management. For this purpose, pharmacological/non-pharmacological therapies are recommended based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline (version 2017)[6] for the prevention of COPD exacerbation and reduction of the symptoms. Long-acting bronchodilators are suitable for the maintenance therapies, including long-acting beta-agonists (LABA) alone, long-acting muscarinic antagonists (LAMA) alone, and the dual therapy (fixed-dose combination [FDC] or free combos).

A few studies show LABA/LAMA therapy, especially for tiotropium (Tio) plus olodaterol (Olo), is more effective on prevention of COPD exacerbation and improvement of the quality of life and lung function than monotherapy or placebo,[1,13-15] along with the comparison to other dual therapies.[16-18] In Taiwan, Tio plus Olo FDC therapy (Spiolto®) is on the market since 2016, but the clinical data reflecting the real-world setting on COPD patients treated with Tio plus Olo vis-à-vis those with other LABA/LAMA or LAMA therapy are limited. Therefore, a retrospective, cohort study is planned to collect the clinical outcome on the prevention of acute exacerbation between different therapies for COPD in Taiwan.

8. RESEARCH QUESTION AND OBJECTIVES

The primary objective is to understand the occurrence of COPD exacerbations in patients treated with LABA/LAMA or LAMA in the routine clinical practice in Taiwan.

The secondary objectives are to realize the clinical characteristics and prescription patterns for the COPD population in Taiwan.

9. RESEARCH METHODS

9.1 STUDY DESIGN

It is a retrospective, multi-center, cohort study to collect the data on COPD patients who were administered with LABA/LAMA (FDC or free combo) or LAMA therapy for 3 months at least prior to 30 June 2018. The patients using LABA/LAMA therapy will be enrolled regardless of new initiation or switched from other single/dual/triple treatment, whereas those using LAMA treatment will only be acceptable when LAMA is newly initiated. This study aims to estimate the occurrence of COPD exacerbation in the COPD population under the real-world practice in Taiwan. Additionally, the study also assesses outcomes of clinical characteristics and prescription patterns for patients using LABA/LAMA or LAMA. After Institutional Review Board's (IRB) permission, it will be carried out in around 12 medical centers in Taiwan and plans to collect the clinical data abstracted from the medical charts of approximately 1,800 eligible patients. The eligible patients will be separated into three cohorts based on the prescription for COPD on the index date. Cohort A includes the patients treated with Tio + Olo, cohort B is the patients treated with other LABA/LAMA therapy, and cohort C is the patients receiving LAMA treatment. No investigational or interventional treatment will be provided in the retrospective study.

The retrospective study will review medical charts of COPD patients with LABA/LAMA or LAMA therapy until death or 1 year after the index date, whichever occurs first. The data collection will be conducted after eligibility assessment. Medical records will be reviewed and relevant information will be abstracted for various details such as patient demographics, diagnosis of COPD, smoking status, records of exacerbations and hospitalization, examinations of lung function and laboratory, treatments related to COPD or comorbidities, reasons for treatment switching, and comorbidities.

9.2 SETTING

This study plans to retrospectively collect the data abstracted from the electronic medical charts of eligible patients from around 12 medical hospitals in Taiwan.

9.2.1 Study sites

Selected sites include around 12 medical hospitals with the highest level in Taiwan from Northern to Southern area. Further, these hospitals have adequate patient pool and sufficient clinical data for collection.

9.2.2 Study population

The data will be retrospectively abstracted from the medical chart after eligibility assessment. Eligible patients will be categorized into the cohort A (patients treated with Tio + Olo), B (patients treated with other LABA/LAMA therapy), and C (patients treated with LAMA therapy).

Inclusion criteria

Patients who fulfil **ALL** the following criteria are included.

1. Patients who diagnosed with COPD who were prescribed with LABA/LAMA (FDC or free combo) as a new initiation or switching from other therapy (i.e., single/dual/triple), or newly receiving LAMA treatment for 3 months at least prior to 30 June 2018
2. Male or female patients ≥ 40 years of age

Exclusion criteria

Patients who meet the following criterion are not included.

1. Patients with documented diagnosis of bronchial asthma, asthma-COPD overlap syndrome (ACOS), bronchiectasis, cystic fibrosis, or lung cancer

9.2.3 Study visits

The abstracted data will be recorded on the case report form (CRF). **Table 1** shows the collected data at different retrospective period of the medical chart.

Table 1 Data collection schedule

Time points / Variables	Eligibility assessment	Data collection retrospectively		
		Before the index date	Index date[#]	1-year follow-up period†
Eligibility assessments	X			
Demographics[1]			X*	
Diagnosis of COPD[2]			X*	
Smoking status[3]			X*	
Comorbidity[4, $]		X[◊]	X	X
COPD assessments[‡]				
CAT[5]		X[Δ]	X	X
mMRC[6]		X[Δ]	X	X
Examinations[‡]				
Spirometry data[7]		X[Δ]	X	X
Eosinophils		X[Δ]	X	X
Records[‡]				
Acute exacerbations[8]		X[&]	X	X
Hospital admissions[9]		X[&]	X	X
Treatments				

Time points / Variables	Eligibility assessment	Data collection retrospectively		
		Before the index date	Index date[#]	1-year follow-up period†
Related to COPD[10, $]		X[11, ◊]	X	X
Related to comorbidities[12, $]		X[◊]	X	X
Rescue treatments[13, ‡]		X[◊]	X	X
Oxygen therapy[14, $]		X[◊]	X	X
Others[15, $]		X[◊]	X	X

[#]Not later than 30 June 2018; defined as the date of COPD patients in the cohort A and B stating using LABA/LAMA therapy regardless of new initiation or switching from other single/dual/triple treatment, or the date of the patients in the cohort C starting using LAMA treatment

†Not later than 1 year after the index date

*The data nearest to the index date will be collected.

[◊]The data 6 months before the index date will be documented.

[$]The data will be collected every 6 months (allowed window: ± 1 month).

[‡]All available data on the medical chart will be recorded.

[Δ]The data nearest to the index date will be collected as the **Baseline**.

[&]The data/events ever since patients started receiving LABA/LAMA or LAMA therapy will be collected (maximum: trace back to 1 year before the index date).

1. Date of birth, gender, race, BMI, occupation, and family history
2. Date of diagnosis and disease severity (GOLD grade: GOLD 1, 2, 3, 4; GOLD group: A, B, C. or D)
3. Former, current smoker, or non-smoker
4. Cardiovascular (e.g., ischemic heart disease, heart failure, coronary artery disease, myocardial infarction), cerebrovascular (e.g., stroke), respiratory (e.g., pulmonary hypertension), hepatic (e.g., hepatitis), renal (e.g., chronic kidney disease, kidney failure), gastrointestinal (e.g., GERD, GI bleeding, gastric disease), metabolic (e.g., diabetes mellitus [T1 or T2], hypertension, obesity, hyperlipidemia), infectious (e.g., pneumonia, respiratory tract infection, influenza, tuberculosis, viral infection), osteoporosis, anxiety, and depression.
5. Score between 0 – 40 points
6. Score between 0 – 4 points
7. FEV_1 and FVC, etc.
8. The definition of an acute exacerbation is that a complex of lower respiratory events/symptoms (worsening or new onset) related to the underlying COPD, with a duration of 3 days or more, requiring a prescription of antibiotics and/or systemic steroids and/or hospitalization (ICD-9: 491.21; ICD-10: J44.1). Onset/stop date, severity (mild, moderate, severe), and leading to hospitalization/acute respiratory failure (ICD-9-518.81 or ICD-10-J96.00/J96.01/ J96.02) or not will be recorded.
9. **Hospitalizations caused by COPD exacerbation (ICD-9: 491.21; ICD-10: J44.1)** will be collected only. The information includes admission/discharge date, treatments for COPD, and reasons for switching medications.
10. Including SABA (fenoterol, salbutamol, terbutaline), SAMA (ipratropium bromide), LABA (indacaterol, olodaterol), LAMA (aclidinium bromide, glycopyrronium, tiotropium, umeclidinium), LABA + LAMA (FDC; tiotropium/olodaterol, indacaterol/glycopyrronium, vilanterol/umeclidinium), LABA + ICS (formoterol/beclomethasone, formoterol/budesonide, salmeterol/fluticasone, vilanterol/fluticasone), triple therapies (free combo or vilanterol/umeclidinium/fluticasone [FDC]), or others (theophylline, roflumilast, mucolytics, etc.). Prescription date, doses, frequency, and reasons for switching medications will be recorded.

Time points / Variables	Eligibility assessment	Data collection retrospectively		
		Before the index date	Index date[#]	1-year follow-up period†

11. If a patient receiving SABA, SAMA, LABA/ICS or a triple therapy before LABA/LAMA treatment on the index date, the relevant information on the medications, doses, frequency, the route of administration, the reasons for switching medications should be recorded.
12. Prescription date, doses, and frequency will be recorded.
13. **Therapies for the emergency/hospitalization regarding COPD (ICD-9: 491.21; ICD-10: J44.1)** will be collected, including but not limited to short-acting bronchodilators, antibiotics, oral corticosteroid (e.g., prednisone or prednisolone), ventilator support, or oxygen therapy. Prescription date, doses, frequency, and the route of administration will be recorded.
14. NIPPV or IPPV for those not for rescue use
15. Including but not limited to surgeries for COPD or improvement of lung function.

9.2.4 Study discontinuation

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

- Violation of Good Clinical Practice (GCP), the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

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

9.3 VARIABLES

9.3.1 Exposures

Not applicable.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

- Time to the first moderate or severe COPD exacerbation

9.3.2.2 Secondary outcomes

- Annualized rate of mild/moderate/severe exacerbation
- Time/reason (e.g., severe airflow limitation, diagnosis of asthma, worsening exacerbation) from LABA/LAMA escalating to LABA/LAMA/ICS or from LAMA to dual therapy

- Percentage of patients receiving LABA/LAMA switched to triple therapy or LAMA switched to dual therapy
- Change in pulmonary function after LABA/LAMA or LAMA initiation
- Use of rescue medications

[redacted]

9.3.3 Covariates

9.3.3.1 Eligibility assessments

The eligibility should be checked by investigators before the data collection (see **Section 9.2.2** in detail). The following assessments are conducted to determine the eligibility for each patient:

1. Review the medical chart to confirm if a subject with COPD were prescribed with LABA/LAMA or LAMA therapy for 3 months at least (not later than 30 June 2018). Additionally, a subject must be ≥ 40 years of age.
2. Check the medical chart to exclude the patient with bronchial asthma, ACOS, bronchiectasis, cystic fibrosis, or lung cancer

9.3.3.2 Demographics and other characteristics

1. Demographics: date of birth, gender, race, BMI, occupation, and family history
   - Family history includes asthma, COPD, bronchiectasis, and lung cancer
2. Smoking status: former, current smoker, or non-smoker
3. COPD-related history and comorbidities
   - <u>COPD-related history:</u>

     The data to be documented include date of diagnosis (ICD-9-496 or ICD-10-J44.9), disease severity on index date of starting LABA/LAMA or LAMA therapy (GOLD grade: GOLD 1, 2, 3, 4; GOLD group: A, B, C, or D), results of COPD assessments (CAT and mMRC, see the definitions in the **Section 9.3.3.4** and **9.3.3.5**), spirometry results (FEV_1 and FVC, see **Section 9.3.3.6**), and acute exacerbations (see **Section 9.3.3.3**).

     According to the COPD guideline (version 2017),[6] patients will be graded and grouped by disease severity based on the results of COPD assessments and spirometry. Detailed criteria are presented in **Figure 1**.

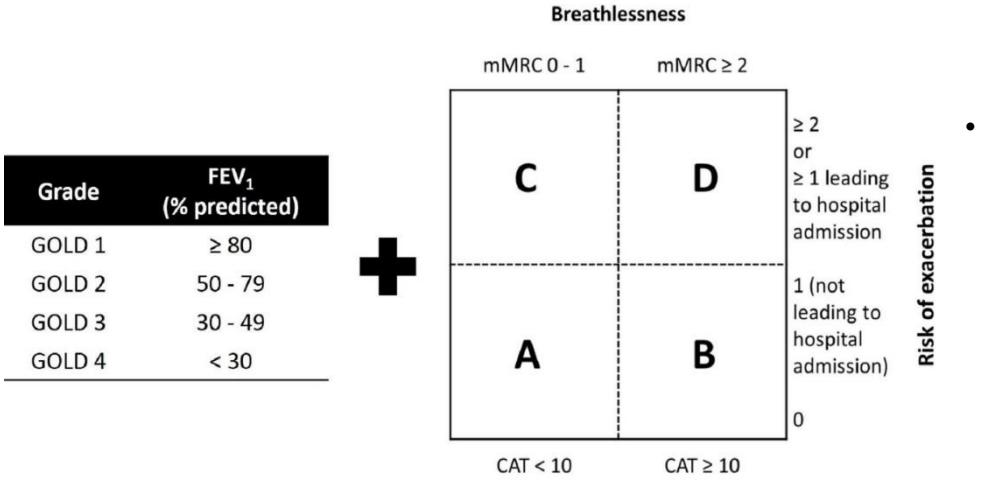

Figure 1 Disease severity of COPD

- Comorbidities of interest:

  Comorbidities regarding any medical findings from 6 months before the index date* until death or 1 year after the index date should be collected as below.

  - Cardiovascular disease: ischemic heart disease, heart failure, coronary artery disease, myocardial infarction
  - Cerebrovascular disease: stroke
  - Respiratory disease: pulmonary hypertension
  - Hepatic disease: hepatitis
  - Renal disease: chronic kidney disease, kidney failure
  - Gastrointestinal disease: gastroesophageal reflux disease (GERD), GI bleeding, gastric disease
  - Metabolic disease: diabetes mellitus [T1 or T2], hypertension, obesity, hyperlipidemia
  - Infectious disease: pneumonia, respiratory tract infection, influenza, tuberculosis, viral infection
  - Osteoporosis
  - Anxiety
  - Depression

  *Index date: It is defined as the date of COPD patients in the cohort A and B stating using LABA/LAMA therapy regardless of new initiation or switching from other single/dual/triple treatment, or the date of the patients in the cohort C starting using LAMA treatment.

4. Hospitalization records:

   These records from 1 year before the index date until death or 1 year after the index date should be collected.

The hospitalization caused by COPD exacerbation (ICD-9: 491.21; ICD-10: J44.1) should be documented on the CRF, including admission/discharge date, treatments (doses, frequency, and the route of administration), and reasons for switching medications. Other hospitalizations unrelated to COPD exacerbation will not be recorded.

5. Laboratory data: eosinophils

   The data nearest to the index date will be collected as the **Baseline** and will continue recording until death or 1 year after the index date.

   Blood eosinophil counts are used for a standard of applying ICS treatment for patients with ≥ 2% eosinophil counts.[6] Additionally, higher blood eosinophils may incur greater exacerbations in patients treated with LABA only (without ICS).[19,20] Eosinophils counts and assessment date will be recorded.

9.3.3.3 Acute exacerbation of COPD

The data from 1 year before the index date until death or 1 year after the index date should be collected.

Acute exacerbation is defined as a complex of lower respiratory events/symptoms (worsening or new onset) related to the underlying COPD, with a duration of 3 days or more, requiring a prescription of antibiotics and/or systemic steroids and/or hospitalization (should all be accompanied by code of ICD-9-491.21 or ICD-10-J44.1). Within the retrospective period, the onset/stop date of COPD exacerbation, severity* (mild, moderate, severe), and its outcome (leading to hospitalization/acute respiratory failure [ICD-9-518.81 or ICD-10-J96.00/J96.01/J96.02] or not) will be recorded. In terms of the exacerbation-related therapies, they will be recorded onto the page of "Rescue treatments" in the CRF.

*Mild exacerbation is a patient with worsening but self-managed symptoms.

Moderate exacerbation is a patient receiving an exacerbation-related prescription such as oral corticosteroid (prednisone or prednisolone) and/or antibiotic, but not requiring hospitalization.

Severe exacerbation is a patient requiring hospitalization or emergency room visit due to COPD (ICD-9-491.21 or ICD-10-J44.1).

9.3.3.4 COPD assessment test (CAT)

The data nearest to the index date will be collected as the **Baseline** and will continue recording until death or 1 year after the index date.

The COPD assessment test (CAT) is a simple, 8-item, health status instrument which provides a simple method for assessing the impact of COPD on the patient's health and the quality of life. The total CAT score ranging from 0 - 40 is calculated by summing the points for each variable. A decrease in CAT score represents an improvement in health status, whereas an increase in CAT score represents a worsening in health status.[21] The most reliable estimate of the minimum significant difference in the CAT score is 2 points.[22]

9.3.3.5 modified Medical Research Council dyspnea scale (mMRC)

The data nearest to the index date will be collected as the **Baseline** and will continue recording until death or 1 year after the index date.

mMRC is a 4-item questionnaire for measuring the severity of dyspnea of patients, and the score is correlated with health status[23] and mortality[24,25] for patients with respiratory disease. If mMRC scale of the patient is > 2, it means the patient may suffer from dyspnea.

9.3.3.6 Spirometry results

The data nearest to the index date will be collected as the **Baseline** and will continue recording until death or 1 year after the index date.

Spirometry is the most common tool to evaluate the lung function of patients with respiratory disease. Among the results of spirometry, FEV_1 and the ration of FEV_1/FVC are well-known for assisting in the diagnosis, determining disease severity, and following up the prognosis.[6,26,27] In general, patients may be suspected to have COPD based on the criteria including post-bronchodilator FEV_1 < 80% predicted and FEV_1/FVC ratio < 70% in accordance with GOLD guideline (version 2017).[6]

9.3.3.7 Treatments

Treatments for COPD will be recorded in the CRF within the retrospective duration, including medications related to COPD, rescue treatments, and oxygen therapies, etc.; of which, prescription date, doses, frequency, the route of administration, and reasons for switching medications will be recorded. Above information (except for rescue treatments) will be recorded every 6 months from 6 months before the index date until death or 1 year after the index date, whichever occurs first.

In addition, pharmacological therapies for comorbidities will also be documented and information will be recorded every 6 months from 6 months before the index date until death or 1 year after the index date, whichever occurs first.

- Related to COPD:

  <u>Medications of interest</u>

  - SABA: fenoterol, salbutamol, and terbutaline
  - SAMA: ipratropium bromide
  - LABA: indacaterol and olodaterol
  - LAMA: aclidinium bromide, glycopyrronium, and tiotropium, umeclidinium
  - LABA + LAMA: tiotropium/olodaterol, indacaterol/glycopyrronium, and vilanterol/umeclidinium (FDC)
  - LABA + ICS: formoterol/beclomethasone, formoterol/budesonide, salmeterol/fluticasone, and vilanterol/fluticasone

- Triple therapies: free combo or vilanterol/umeclidinium/fluticasone (FDC)
- Others: theophylline, roflumilast, and mucolytics, etc.

Rescue treatments

Therapies for the emergency or hospitalization regarding COPD will be collected, including but not limited to the following list:

- Short-acting bronchodilators: SABA (fenoterol, salbutamol, or terbutaline) or SAMA (ipratropium bromide)
- Antibiotics, only record those for respiratory infections
- Oral corticosteroid: prednisone or prednisolone
- Ventilator support: noninvasive (nasal/facial mask) or invasive (orotracheal tube or tracheostomy), or oxygen therapies

Others

Non-pharmacological therapies, including but not limited to the following:

- Oxygen therapy: collecting the therapy for maintenance such as noninvasive positive pressure ventilators (NIPPV) or intermittent positive pressure ventilation (IPPV)
- Surgery, especially relating to COPD or improving the lung function

• Related to comorbidities

Pharmacological therapies for comorbidities of interest (see **Section 9.3.3.2**) will be collected.

9.4 DATA SOURCES

No additional diagnostic or monitoring procedures will be applied to the patients because of a retrospective study, and this study plans to collect the data onto the designed CRF as only those are available in the medical records. The data source includes medical records in ~ 12 hospitals in Taiwan, where pulmonologists licensed with specialty care for respiratory diseases (COPD included) and critical care medicine.

Each patient is identified by a unique subject/initial number, which is only used for study purposes.

9.5 STUDY SIZE

Based on the projected market share and per physician's clinical experience, data from approximately 1,800 patients will be collected.

Among these patients, using Tio + Olo FDC versus other LABA/LAMA therapy (FDC or free combo) is assumed the ratio of 1:2 (~ 300 Tio + Olo, ~ 800 other LABA/LAMA therapy). If we assume the same annualized event rates as in the Taiwanese subgroup analysis report of DYNAGITO[1] (i.e. 0.78 per patient-year for Tio + Olo and 0.90 per patient-year for other

therapies), expecting the 95% CI for incidence rate ratio to be 0.87 (0.768, 0.978), with good precision. The following **Table 2** also shows that with smaller sample size, the precision is reduced (wider 95% CI).

Table 2 Sample size estimation

Tio + Olo		Other		Incidence rate ratio (95% CI)
True Incidence rate	Sample size	True Incidence rate	Sample size	
0.78	300	0.90	800	0.87 (0.768, 0.978)
0.78	300	0.90	300	0.87 (0.751, 1.000)
0.90	300	0.97	800	0.93 (0.829, 1.039)
0.90	300	0.97	300	0.93 (0.810, 1.062)
0.90	200	0.97	200	0.93 (0.786, 1.094)
0.90	200	0.97	100	0.93 (0.734, 1.173)

In this table, it is assumed that all patients have on average ~ 2 patient-year exposure.

9.6 DATA MANAGEMENT

The data abstracted from eligible patients in this study will be recorded on the CRF or other applicable forms. The designated personnel will capture, check, store, and analyze the data. The designated personnel will follow Boehringer Ingelheim standard operating procedures (SOPs) and their own internal SOPs.

A data validation plan (DVP) will be created to describe the process for data validation.

Data will be transferred to Boehringer Ingelheim after the closure of the study.

9.7 DATA ANALYSIS

Statistical analyses will be conducted by the designated personnel. The main analysis population will consist of all eligible patients (i.e., all patients fulfilling all inclusion criteria and no exclusion criterion).

Descriptive analyses will be performed to summarize patient baseline characteristics, the observation period, the time to exacerbation/or to escalating to triple therapy, and the rates of exacerbation, etc. Continuous variables include number, mean, median, standard deviation (SD), range (minimum and maximum value), and 95% confidence intervals (CI). Categorical variables are frequency and percentage.

Statistical analysis of all data will be performed using the latest version of SAS® statistical software (SAS Institute, Cary, NC, USA) or other commercially available standard statistical software.

All information already collected as part of the study will be retained for further analyses; however, no extra efforts will be made to obtain or record additional information regarding the patient. In general, data imputation will not be permitted for any analyses in this study.

9.7.1 Main analysis

The propensity score matching approach* will be used to balance the baseline characteristics between the study cohorts. These data will be compared descriptively between patients receiving different regimens (Tio + Olo vs. other LABA/LAMA vs. LAMA). If the propensity score matching is done, the difference before and after matching will be considered both.

For the primary outcome

Time to the first moderate or severe COPD exacerbation will be compared between different cohorts using Kaplan-Meier curves with the incidence and time to events, and statistical significance will be assessed using log-rank tests.

Time to first acute exacerbation starts from the index date to the date of the first acute exacerbation recorded on the CRF. Patients with exacerbation free at the time of escalating to ICS or no documented with exacerbations will be censored.

For secondary outcomes

- Time to escalating to dual/triple therapy will also be analysed using Kaplan-Meier curves and log-rank tests.
- The annualized rate of exacerbation with various severity will be calculated for each study group (episodes/patient-year), and the differences between the three cohorts will be compared by rate ratio.
- Results of lung function (i.e., spirometry data) and COPD assessments (i.e., CAT and mMRC) will be evaluated by the change from baseline. Pair *t*-test or other applicable statistical methods will be used for assessing the intra-group difference under a significance level of 0.05.
- Chi-square test or Fisher's exact test will be applied for categorical variables such as reasons for switching/escalating therapies, frequency, and percentage, etc.

*NOTE: Variables may include but not limited to age, gender, disease duration before index date, smoking status, body mass index, COPD assessment score (e.g., CAT and mMRC), spirometry data (e.g., FEV_1), oxygen therapy, comorbidities, disease severity, previous exacerbation, previous treatments, or eosinophil counts, where appropriate.

[redacted]

9.7.3 Handling of the missing data

No imputation will be allowed in the retrospective study to reflect the real-world data.

9.8 QUALITY CONTROL

Before the study launch, participating physicians will be trained on the protocol and study conduct procedures by Boehringer Ingelheim (or designee).

In keeping with the non-interventional design employed in this study, site interaction (e.g., direct contact between site study staff or patients) is minimized if needed.

During the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the clinical database has been declared to be complete and accurate, it will be locked. Quality control will be conducted to ensure data accuracy, completeness, and reliability. All information will be kept confidential.

Boehringer Ingelheim or designated personnel will assure database quality processes are followed including the review of the data entered into the CRFs by investigational staffs for completeness and accuracy, and in accordance with the data validation plan.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Data collection

A retrospective study is a suitable design to obtain instantly enormous information on the use of medications and their outcomes under the clinical practice. However, data integrity may be limited by data availability in the medical chart. The lack of data of interest may be one of the limitations. Considering the characteristics of COPD, the data regarding relevant assessments (CAT, mMRC, or spirometry) and medications for COPD are common tools to manage the disease progression. Sponsor, designated personnel, and sites will do their best to collect the available data of interest.

Unbalanced patients' characteristics

This study is a non-randomized retrospective study, which means the characteristics of enrolled patients may be imbalanced and influential to study endpoints. Hence, this study plans to apply propensity score matching for the study cohorts to balance the baseline characteristics. Significant difference between patients using different regimens is easier to be observed after the baseline matching.

Patient pool

The sample size of COPD patients using tiotropium/olodaterol (Spiolto®) may be less because this product is late on the market in Taiwan on April 18, 2016. To screen more possible patients, the entry criteria are non-restrictive and will permit data collection from a broad patient population.

9.10 OTHER ASPECTS

No other aspect of the research method is not covered in the previous sections.

9.10.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records and the investigator's study-related files and correspondence of this study.

9.10.2 Study records

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

- The principal investigator will sign and date the indicated places on the CRFs. These signatures will indicate that the principal investigator inspected or reviewed the data on the CRF, the data queries, and the site notifications, and agrees with the content.

9.10.2.1 Source documents

Source documents are original documents, data, and records from which the subject's CRF data are obtained from the medical chart mainly.

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 reported on the CRFs 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 CRFs, the following data need to be derived from source documents:

- Patient identification (gender, date of birth, etc.)
- Patient participation in the study (substance, study number, patient number)
- Comorbidity
- Pharmacological and non-pharmacological history (prescription date, reasons, etc.)
- Hospitalization records (start/discharge date, etc.)
- Acute exacerbation records
- COPD assessments (CAT, mMRC, etc.)

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. All persons authorized to make entries and/or corrections on the CRFs will be included on the Authority Form.

No information in source documents about the identity of the patients will be disclosed. No study document should be destroyed without prior written agreement between Boehringer Ingelheim and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify Boehringer Ingelheim in advance.

9.10.2.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g., US Food and Drug Administration [FDA]). The auditor may review all CRFs. The accuracy of the data will be verified by reviewing the documents described in the **Section 9.10.2.1**.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI Standard Operating Procedures (SOPs).

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the study report.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to the start of data collection in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) if requested by IRBs or the local regulatory organization. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Quality Medicine auditors appointed by Boehringer Ingelheim, by appropriate IRB IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this 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.

No subject names will be supplied to Boehringer Ingelheim or other responsible parties. Only the subject number and subject initials will be recorded on the CRF, and if the subject's name appears on any other document (e.g., medical chart), it must be obliterated before a copy of the document is supplied to Boehringer Ingelheim or other responsible parties. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities. All personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

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 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 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
A serious adverse event is defined as any AE which
- results in death,
- is 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.

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 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. O**nly ADRs and AEs with fatal outcomes will be collected on the CRF due to the retrospective study design.** ADR is defined as that there is an actual causal relationship with Spiolto® on the medical chart.

The following must be collected by the investigator in the (e)CRF from signing the informed consent onwards until the end of the study:

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

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 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 BI drug taken for the disease in scope of the study, 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 within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

Type of Report	Timeline
All **SADRs** associated with the Spiolto®	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to Spiolto®	immediately within 24 hours
All **non-serious ADRs** associated with the Spiolto®	7 calendar days
All **pregnancy monitoring** forms	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required

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

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® 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 rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the study report.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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13.2 UNPUBLISHED REFERENCES

None.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Please refer to the attachment.

ANNEX 3. ADDITIONAL INFORMATION

None.