Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document Number:	**c30708153-01**
BI Study Number:	1237.100
BI Investigational Product(s):	Spiolto® Respimat®, Spiriva® Respimat®
Title:	*Early intervention effectiveness of tiotropium / olodaterol compared to tiotropium in COPD*
Protocol version identifier:	*1.0*
Date of last version of protocol:	*27 Feb 2020*
PASS:	*No*
EU PAS register number:	*EUPAS33426*
Active substance:	*Tiotropium and Olodaterol* *Tiotropium*
Medicinal product:	*Spiolto® Respimat®; Spiriva® Respimat®*
Product reference:	*N/A*
Procedure number:	*N/A*
Joint PASS:	*No*
Research question and objectives:	*To compare the early intervention effectiveness of Tio/Olo vs. Tio among COPD patients.*
Country(-ies) of study:	*Japan*
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In case of PASS, add: **<EU-QPPV:>**	*N/A*
In case of PASS, add: <**Signature of EU-QPPV:>**	*N/A*
Date:	27 Feb 2020

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2. LIST OF ABBREVIATIONS

AMI	Acute Myocardial Infarction
[redacted]	[redacted]
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DPC	Diagnosis Procedure Combination
ENCEP	European Network of Centres for Pharmacoepidemiology and
P	Pharmacovigilance
FDC	Fixed Dose Combination
GERD	Gastroesophageal Reflux Disease
GOLD	Global Initiative for Chronic Obstructive Lung Disease
hdPS	High Dimensional Propensity Scores
HF	Heart Failure
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
ICS	Inhaled Corticosteroid
IQR	Interquartile Range
IRB	Institutional Review Board
LABA	Long-Acting Beta-Agonists
LAMA	Long-Acting Muscarinic Antagonists
MDV	Medical Data Vision
MS	Multiple Sclerosis
Olo	Olodaterol
PUD	Peptic Ulcer Disease
PVD	Peripheral Vascular Disease
PS	Propensity Score
SABA	Short-acting Beta Agonist
SAMA	Short-acting Muscarinic Antagonist
SD	Standard Deviation
Tio	Tiotropium

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Spiolto® Respimat®; Spiriva® Respimat®			
Name of active ingredient: Tiotropium / Olodaterol fixed dose combination (ATC R03AL06); Tiotropium (ATC R03BB04)			
Protocol date: 27 Feb 2020	**Study number:** 1237.100	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Title of study:	*Early intervention effectiveness of tiotropium / olodaterol compared to tiotropium in COPD*		
Rationale and background:	Chronic obstructive pulmonary disease (COPD) is a common disease with a significant morbidity and cost burden. Long-acting muscarinic antagonists (LAMA) and long-acting beta agonist (LABA) have been the first line of treatment for COPD. Recent clinical trials have suggested that a combination of LAMA and LABA is more effective in improving lung function than their mono-components alone. The combination therapy may delay the progression to uncontrolled COPD managed with triple therapy. There is, however, limited research from real world setting showing LAMA+LABA combination therapy provides more benefit than LAMA monotherapy in Japanese patients with COPD. Spiolto® Respimat®, a combination of Olodaterol (a LABA) and Tiotropium (a LAMA) (herein referred to as Tio/Olo) was approved in September 2015 in Japan. Spiriva® Respimat®, a Tiotropium (a LAMA) monotherapy (herein referred to as Tio), was approved in October 2004 in Japan. This study aims to evaluate the time to escalation to triple therapy among the Japanese COPD patients newly initiating therapy with Tio or Tio/Olo using real world data.		

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Protocol date: 27 Feb 2020	**Study number:** 1237.100	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Research question and objectives:	To compare the early intervention effectiveness of Tio/Olo vs. Tio among COPD patients. To compare the early intervention effectiveness of Tio/Olo vs. Tio among COPD patients. The primary objective of the study is to - Compare time to LAMA/LABA/ICS triple therapy initiation among initiators of Tio/Olo vs. initiators of Tio. The secondary objective of the study is to compare the following among initiators of Tio/Olo vs. initiators of Tio: - Time to First Moderate or Severe COPD Exacerbation - Number of Moderate or Severe COPD Exacerbations Further endpoints: - All-Cause Mortality, - Number of Unique Pulmonary Medication Prescriptions - Number of Hospitalizations for a Respiratory Condition - Major Cardiovascular Adverse Event (MACE) - Home oxygen therapy (HOT)		
Study design:	This will be a new-user, active comparator retrospective comparative cohort study using MDV Japan, a Japanese electronic healthcare research database. It will employ high dimensional propensity scores (hdPS) to match 1 Tiotropium initiator for each Tiotropium/ Olodaterol initiator.		

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Protocol date: 27 Feb 2020	**Study number:** 1237.100	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Population:	*The study cohort will include all patients who initiate Tiotropium/ Olodaterol (Tio/Olo) or Tiotropium (Tio) during the patient selection period (28 September 2015 to 31 December 2018). Initiation (new use) will be determined based on no prescription claims for Tio/Olo or Tio during the 180-day baseline period or during all available data prior to cohort entry date. All patients will additionally be required to have a second claim for the index medication within 60 days after cohort entry to ensure primary adherence of index therapy and regular visit to one of the MDV facilities for treatment of COPD on or any time prior to cohort entry.* *The following exclusion criteria will then be applied to generate the unmatched cohort:* ● *Aged <40 years on cohort entry.* ● *Any LAMA, LABA, or ICS maintenance therapy (alone or in combination) during the 180-day baseline period prior to cohort entry for maintenance treatment and duration >30 days, or any prescription within the 30 days prior to cohort entry.* ● *Patients without continuous enrolment (days since first inpatient/ outpatient encounter in the data) during the baseline period.* ● *No prior diagnosis of COPD [ICD-10: J41*, J43*, J44* and doubt (UTAGAIFLG) = 0 (no)]* ● *Patients without a second prescription claim of their index medication within 60 days after the cohort entry date.* ● *Diagnosis of asthma [ICD-10: J45* and doubt (UTAGAIFLG) = 0 (no)] during the baseline period.* ● *Diagnosis of lung cancer [ICD-10: C34*, D02.2, Z80.1, Z85.1 and doubt (UTALAIFLG) = 0 (no)] or lung transplant (Health claim code: 150317670, 150322510, 150322610, 150336510, 150336610, 150336710, 150399270) prior to the cohort entry date using all available data.* ● *Patients who initiate both Tio/Olo and Tio simultaneously on the cohort entry date.*		

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	● *Any use of triple therapy (LAMA + LABA + ICS) during the baseline period or between the cohort entry date and 1 day prior to the start of follow-up.* *All patients will be selected into the first treatment arm (Tio/Olo or Tio) that they qualify for and will not be allowed to re-enter the cohort by design.* *The cohort will then be used to construct two matched cohorts (not mutually exclusive) according to the: 1) basic propensity scores and 2) high dimensional propensity scores.*		

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Variables:	Exposures ● Exposure: Tiotropium/Olodaterol (Spiolto®). ● Reference: Tiotropium (Spiriva®). Primary Outcome The primary outcome of interest is time to triple therapy initiation (first event per patient) defined as any LAMA/LABA/ICS fixed dose combination or any concurrent use for 30 consecutive days of the following: ● any LAMA/LABA fixed dose combination + any ICS single formulation ● any LAMA single formulation + any LABA/ICS fixed dose combination ● any LAMA single formulation + any LABA single formulation + any ICS single formulation Secondary outcomes ● Time to First Moderate or Severe COPD Exacerbation ● Number of Moderate or Severe COPD Exacerbations Further endpoints ● All-Cause Inpatient Mortality ● Number of Unique Pulmonary Medication Prescriptions ● Number of Hospitalizations for a Respiratory Condition ● Major Cardiovascular Adverse Events (MACE) ● Home oxygen therapy (HOT) Covariates ● Demographics (last recorded): Age, Sex, Year of Cohort Entry, Hospital Size (as a proxy for urban/rural). ● Concomitant Medications (see detail below) Comorbidities/Symptoms (see detail below)		

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Data sources:	MDV is an electronic, record-based healthcare database that spans from 01 April 2008 to 31 March 2019, and contains 25.1 million observable patients from 374 medical facilities across Japan.		
Study size:	There are 1,829 new users of Tiotropium/Olodaterol and 13,132 new users of Tiotropium between 28 September 2015 and 31 October 2018 who satisfied the initial inclusion criteria of new use with at least 2 prescriptions for the index medication within 60 days, and excluding patients without a COPD diagnosis during the baseline period, age <40, diagnosis of asthma during the baseline period, no history of lung cancer or lung transplant, any LAMA, LABA, or ICS maintenance therapy within the 30 days prior to cohort entry, and without continuous enrolment (days since first inpatient/outpatient encounter in the data) during the baseline period. Based on the result of study by Hahn B et al, it is assumed that the triple therapy initiation rate during 1 year is 6% in Tio+Olo group and 10% in Tio group. In total, 1856 patients are needed to observe 141 events and to detect the difference (HR of 1.7) with 2-sided alpha of 0.05 and 90% power. After propensity score matching, it will be assessed whether sufficient number of sample size is available to detect the expected difference. If not available, the treatment difference will be explored in highly explorative manner (i.e., p-value is considered descriptively and point estimate with confidence interval is focused).		

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Data analysis:	● Descriptive analyses For demographic and lifestyle variables, the value recorded on the cohort entry date will be reported, otherwise the most recent known value will be reported. Presence of comorbidities and use of concomitant medication use will be determined based on whether they ever occurred within the 180-day baseline period preceding the index date. Differences in the confounder distributions will be inspected for successful confounder balance of measured characteristics. ● Rate of Triple Therapy Initiation Among the unmatched and matched cohorts, rates of triple therapy use for each treatment group will be reported as the number of events (first per patient) divided by the total number of person-years at risk during follow-up. Comparative rates and corresponding 95% Cis will be reported as both the rate ratio and rate difference per 1,000 person-years at risk. ● Risk of Triple Therapy Initiation Among the unmatched and matched cohorts, risk of triple therapy use for each treatment group will be reported as the number of events (first per patient) divided by the total number of patients at risk. Comparative risks and corresponding 95% CIs will be reported as both the risk ratio and risk difference per 1,000 person at risk. Comparative Effectiveness ● Hazard Ratio for Triple Therapy Use Initiation Among both the basic propensity score matched and high dimensional		

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propensity score matched cohort, Cox regression will be used to estimate the hazard ratios and 95% CI for Tiotropium/Olodaterol compared to patients treated with Tiotropium during follow-up for time-to-first triple therapy initiation using an intention-to-treat censoring approach.

Sensitivity Analyses

1. Less Stringent Qualifying Event Criterion

Instead of defining the qualifying event as two prescriptions within 60 days, patients may enter on only one prescription. While some confidence is lost in whether the patients truly took their index medications, the less stringent qualifying event criterion will allow more patients to be included, increasing statistical power. Furthermore, the possibility of immortal time bias is also mitigated, since the time between prescriptions is no longer present.

2. As-treated Censoring

The analysis will use an as-treated approach for primary, secondary and further endpoint outcomes. In addition to the censoring criteria mentioned for the intention-to-treat approach (outcome, death, or end of data), patients will also be censored after medication discontinuation or switching over to the other arm.

3. Alternative algorithm for COPD as exclusion criterion

The analysis will use a different set of diagnosis codes for COPD (J43*, J44*) to identify patients with COPD. Compared to the primary analysis, this identification approach omits the diagnostic code for chronic bronchitis (J41*), as this code is commonly used by pulmonologists when prescribing Mucolytics to patients without

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	chronic bronchitis. While some true chronic bronchitis patients may be excluded, this approach may increase specificity in identifying patients with COPD. 4. Asthma patients with doubt Asthma patients with doubt are defined as patients with a diagnosis code for asthma and without evidence of any asthma specific treatment (ie., ICS, ICS/LABA) This sensitivity analysis will include patients identified with asthma with doubt. 5. Asthma-COPD Overlap Syndrome (ACOS) sensitivity analysis Patients that have evidence of asthma during the follow-up period will have their data censored on the date of asthma diagnosis during the follow-up period. This will ensure that they contribute information during their COPD disease trajectory up until the time they develop asthma. This approach will mitigate introducing immortal time bias for those patients with ACOS during the follow-up period.		

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Milestones:	10-Sept-2019: Kickoff 16-Sept-2019: Initial Protocol Draft 18-Oct-2019: BI Review of Draft Protocol 08-Nov-2019: Revise Protocol per BI Feedback 15-Nov-2019: Protocol approval from BI 28-Feb-2020: Implement Study 14-Mar-2020: Review of preliminary results and discussion of report priorities 31-Mar-2020: Sensitivity Analysis TBD 2020: Manuscript kickoff / initial discussion with medical writing team TBD: [redacted] to provide manuscript outline with key results for medical writer 30-May-2020: Draft Study Report TBD-2020: BI Review of Study Report TBD-2020: Revise Report per BI Feedback		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
<1>	DD Month YYYY	<Text>	<Text>	<Text>
<2>	DD Month YYYY	<Text>	<Text>	<Text>
<n>	DD Month YYYY	<Text>	<Text>	<Text>

6. MILESTONES

Activities	Date	Responsible Party	Deliverable if applicable
Project Kickoff	10-Sept-2019	[redacted]/BI	
Draft Initial Protocol	16-Sept-2019	[redacted]	Protocol Draft
BI Review of Draft Protocol	18-Oct-2019	BI	
Revise Protocol per BI Feedback	08-Nov-2019*	[redacted]	Submit Protocol
Protocol approval from BI	15-Nov-2019	BI	Protocol approval
Implement Study	Feb-2020*	[redacted]	Primary Results Table, [redacted]
Review of preliminary results and discussion of report priorities	Mar-2020	[redacted]/BI	
Sensitivity Analysis	Mar-2020	[redacted]	Sensitivity Result Tables
Manuscript kickoff / initial discussion with medical writing team	TBD 2020	[redacted]/Medical Writing Team	Manuscript outline summarizing background and methods
Manuscript outline with summary of key results	TBD	[redacted]	Manuscript outline for medical writer with added result summary
Draft Study Report	TBD-2020	[redacted]	Study Report Draft
BI Review of Study Report	TBD-2020	BI	
Revise Report per BI Feedback	TBD-2020*	[redacted]	Final Report
Manuscript Review	TBD	BI-led, [redacted] supported	
**Pending time for approval and suggested changes proposed by BI. All subsequent dates are subject to shift forward if review is delayed.*			

7. RATIONALE AND BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by airway obstruction confirmed by spirometry, often including small airway obstruction, chronic bronchitis, and emphysema **(Barnes 2015)**. It is a leading cause of death in the USA, affecting 16 million Americans (National Heart Lung and Blood Institute, USA). The prevalence of COPD in Japan is about 8.6% **(Fukuchi 2004)**, costing approximately ¥805.5 billion (US$6.8 billion) per year **(Nishimura 2004)**.

No known medications can reverse COPD, but regular maintenance treatments can help manage symptoms, reduce the frequency of exacerbations, and improve health-related quality of life **(Braido 2016)**. Bronchodilators have been the cornerstone of COPD disease management and are prescribed as first-line therapy for patients with COPD. According to the 2017 GOLD guidelines, a long-acting muscarinic antagonists (LAMA) or long-acting beta agonist (LABA) is recommended as the first line treatment in GOLD B , followed by combination therapy LAMA + LABA if the COPD patients are still symptomatic in GOLD D. Several studies have found LAMA+LABA combinations to be more effective than their mono-components and without minimal increase in adverse events. In a review study, Mosely et al. reported that the combination of tiotropium and olodaterol hydrochloride is more effective at improving FEV1 than either of the two agents used alone **(Mosely 2016)**. Singh et al., in a phase III trial, found patients receiving tiotropium and olodaterol responded better than those receiving tiotropium monotherapy, and conclude that tiotropium + olodaterol should be considered as a treatment option in patients with moderate COPD who are initiating maintenance therapy **(Singh 2016)**. Other clinical trials, such as Tonado 1 and Tonado 2, have also shown that tiotropium/olodaterol fixed-dose combination (FDC) therapy provides significantly improved lung function and quality of life, compared with either therapy used individually in COPD **(Buhl 2015, Ichinose 2016)**. In addition, recent clinical trials have found tiotropium/olodaterol FDC therapy significantly improved exercise capacity, and physical activity compared with tiotropium monotherapy. **(Minakata 2019, Ichinose 2018)**

Patients with uncontrolled COPD experiencing exacerbations may escalate to triple LAMA/ LABA/ Inhaled Corticosteroids (ICS) therapy **(Vogelmeier 2017)**. According to prior COPD guidelines, ICS can be used for frequent exacerbations, but the most recent GOLD guidelines recommend that ICS only be used for Asthma-COPD-overlap patients **(Vogelmeier 2017)**. However, in the DYNAGITO study, the prevalence of LAMA/LABA/ICS (triple therapy) at baseline was 40.8% in moderate to very severe COPD patients in Japan **(Calverley 2018, Ichinose 2018)**. ICSs may lead to several minor and major complications. The side effects of ICS treatment can range from weight gain and local side effects, such as pneumonia, oral candidiasis and dysphonia, to adrenal suppression, cataracts, and osteoporosis **(Tariq 2016, Wilkie 2015)**. In addition, patients with low blood eosinophil counts may not respond to ICS **(Hizawa 2015)**.

Several clinical trials have shown that new LAMA/LABA inhalers could better manage patients, potentially reducing the use of ICS as part and parcel of maintenance therapy in COPD **(Magnussen 2014)**. However, the evidence obtained from previous clinical trials is not always reflected in clinical practice, and there is limited research from real world settings

that show LAMA+LABA combination therapy provides more benefit than LAMA monotherapy in Japanese patients with COPD. Therefore, real world evidence from Japanese COPD patients is crucial in addressing this gap in knowledge. It is also essential to understand real world treatment patterns and outcomes, in particular, escalation to triple therapy as a proxy for worsening COPD condition.

Spiolto® Respimat®, a combination of Olodaterol (a LABA) and Tiotropium (a LAMA) (herein referred to as Tio/Olo) was approved in September 2015 in Japan. Spiriva® Respimat®, a Tiotropium (a LAMA) monotherapy (herein referred to as Tio), was approved in October 2004 and widely used in Japan. Both maintenance therapies are available, but real world evidence is lacking if one therapy is superior to the other, and whether it can prolong the duration to triple therapy that includes ICS.

This study aims to evaluate the time to escalation to triple therapy among the Japanese COPD patients newly initiating therapy with Tio or Tio/Olo using real world data.

8. RESEARCH QUESTION AND OBJECTIVES

To compare the early intervention effectiveness of Tio/Olo vs. Tio among COPD patients.

The primary objective of this study is to:
- Compare time to LAMA/LABA/ICS triple therapy initiation among initiators of Tio/Olo vs. initiators of Tio.

The secondary objectives of the study are to compare the following among initiators of Tio/Olo vs. initiators of Tio:

Secondary outcomes
- Time to First Moderate or Severe COPD Exacerbation
  - Time to First Moderate COPD Exacerbation
  - Time to First Severe COPD Exacerbation
- Number of Moderate or Severe COPD Exacerbations
  - Number of Moderate COPD Exacerbations
  - Number of Severe COPD Exacerbations

Further endpoints:
- All-Cause Mortality,
- Number of Unique Pulmonary Medication Prescriptions
- Number of Hospitalizations for a Respiratory Condition
- Major Cardiovascular Adverse Events (MACE)
- Home oxygen therapy (HOT)

9. RESEARCH METHODS

9.1 STUDY DESIGN

This will be a new-user, active comparator retrospective comparative cohort study using MDV Japan, a Japanese electronic healthcare research database. It will employ high dimensional propensity scores (hdPS) to match 1 Tiotropium initiator for each Tiotropium/Olodaterol initiator.

9.2 SETTING

9.2.1 Definitions

Study Period: the entire period of time that includes the baseline period, the cohort entry date (index date), and follow-up period for the study population. The study period will be from ***01 April 2015*** (180 days prior to Spiolto approval date of 28 September 2015 in Japan) to ***31 March 2019*** (end of available data).

Patient Selection Period: the period of time for which patients are eligible to enter the cohort. The earliest date of the patient selection period is ***28 September 2015***, (the Spiolto approval date in Japan). The latest date of the patient selection period is 31 December 2018, corresponding to 90 days before the end of available data (31 March 2019), ensuring that all patients have at least 60 days after the cohort entry date to identify a second prescription for index therapy and at least 30 days to be capable of the 30-day overlap to determine the triple therapy initiation outcome.

Cohort Entry Date: Date of entry to the initial cohort of Tio/Olo vs. Tio users (*first prescription*).

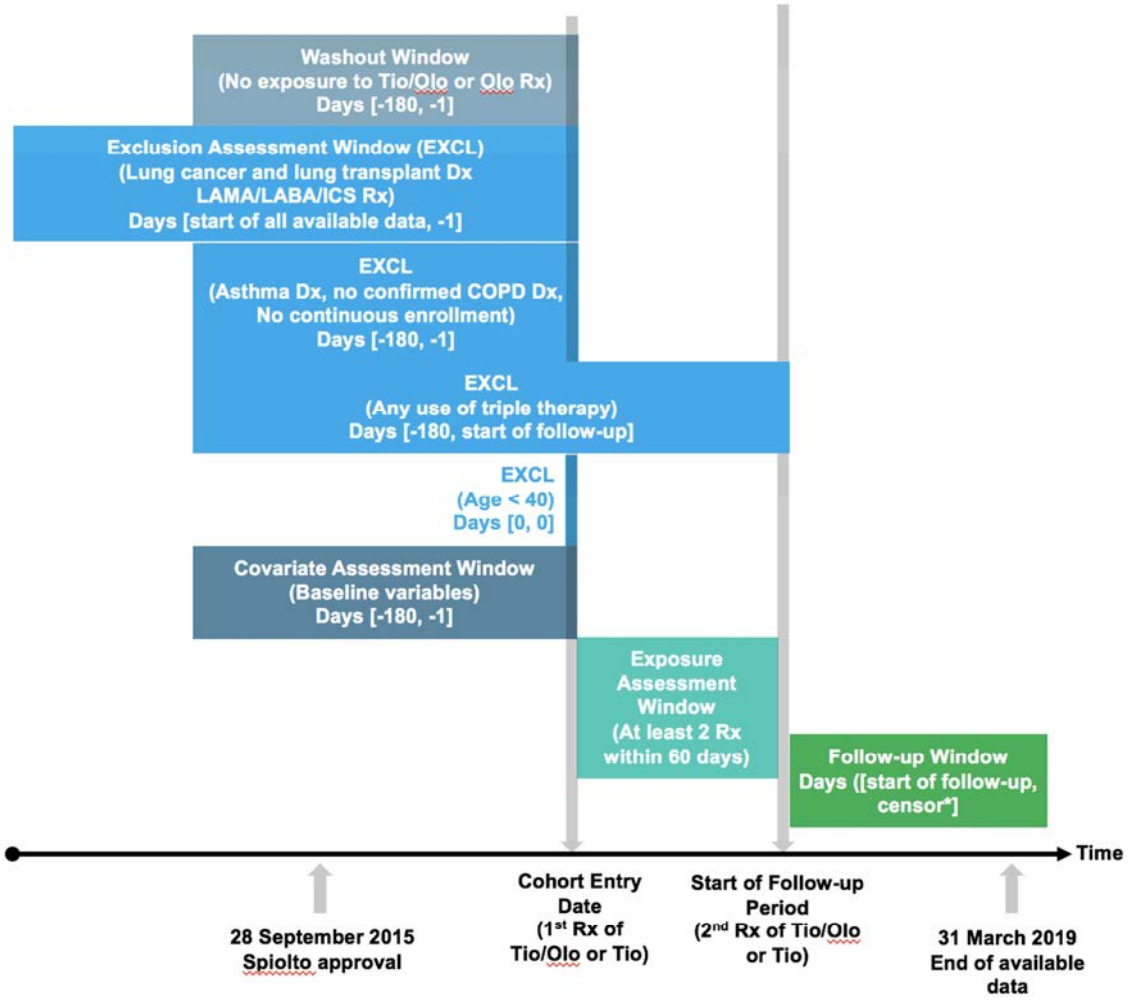
Baseline Period: the 180-day period that ends 1 day prior to the cohort entry date used to assess covariate information. The earliest start of the baseline period would be 01 April 2015, corresponding to 180 days prior to the approval date of Spiolto.

Follow-Up Period: the period starting at the second prescription for Tio/Olo or Tio within 60 days of the cohort entry date (first prescription) and ending at the earliest occurrence of the outcome (use of triple therapy), or the first occurrence of inpatient death, disenrollment, or end of the study period (31-Mar-2019). A sensitivity analysis will employ an as-treated censoring approach to further censor upon discontinuation of index therapy or initiation of the other index treatment arm. Patients may have different lengths of follow-up (i.e. variable follow-up).

Since health care is nationalized in Japan, the notion of enrollment is not applicable. Therefore, a proxy enrolment criterion defined as start of enrolment = date of first inpatient/outpatient encounter; end of enrolment = date of last inpatient/outpatient encounter will be used. “Enrolment” herein will refer to this proxy enrolment measure. For entry into the study population, patients will be required to have had at least 180 days of enrollment prior to the cohort entry date.

Data during the baseline period will be used to confirm study eligibility and classification of exposure. The follow-up period will be used for identifying the outcome. This is illustrated in Figure 1.

Figure 1 Study timeline



**Patients are allowed to enter the cohort between 28-September-2015 and 31-December-2018. The last allowable date for start of follow-up is 1-March-2019. The follow-up ends at the earliest occurrence of the outcome, or the first occurrence of inpatient death, disenrollment, or end of the study period (31-Mar-2019). A sensitivity analysis will employ an as-treated censoring approach to further censor upon discontinuation of index therapy or initiation of the other index treatment arm.*

9.2.2 Study population

The study cohort will include all patients who initiate Tiotropium/Olodaterol (Tio/Olo) or Tiotropium (Tio) during the patient selection period. Initiation (new use) will be determined based on no prescription claims for Tio/Olo or Tio during the baseline period or during all available data prior to cohort entry date. All patients will additionally be required to have a second claim for the index medication within 60 days after cohort entry to ensure primary adherence of index therapy.

The following exclusion criteria will then be applied to generate the unmatched cohort:

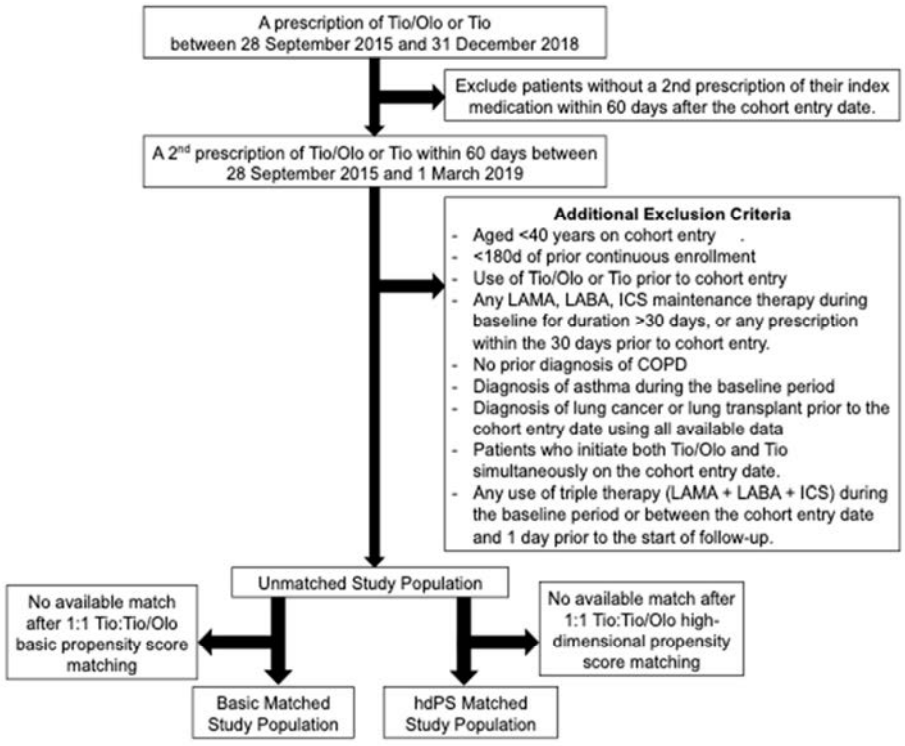
- Aged <40 years on cohort entry.

- Any LAMA, LABA, ICS maintenance therapy (alone or in combination) during the 180-day baseline period prior to cohort entry for maintenance treatment and not cough, i.e. duration >30 days, or any prescription within the 30 days prior to cohort entry.
- Patients without continuous enrolment (days since first inpatient/outpatient encounter in the data) during the baseline period.
- No prior diagnosis of COPD [ICD-10: J41*, J43*, J44* and doubt (UTAGAIFLG) = 0 (no)]
- Patients without a second prescription claim of their index medication within 60 days after the cohort entry date.
- Diagnosis of asthma [ICD-10: J45* and doubt (UTAGAIFLG) = 0 (no)] during the baseline period.
- Diagnosis of lung cancer [ICD-10: C34*, D02.2, Z80.1, Z85.1 and doubt (UTALAIFLG) = 0 (no)] or lung transplant (Health claim code: 150317670, 150322510, 150322610, 150336510, 150336610, 150336710, 150399270) prior to the cohort entry date using all available data.
- Patients who initiate both Tio/Olo and Tio simultaneously on the cohort entry date.
- Any use of triple therapy (LAMA + LABA + ICS) during the baseline period or between the cohort entry date and 1 day prior to the start of follow-up.

All patients will be selected into the first treatment arm (Tio/Olo or Tio) that they qualify for and will not be allowed to re-enter the cohort by design.

The cohort will then be used to construct two matched cohorts (not mutually exclusive) according to the: 1) basic propensity scores and 2) high dimensional propensity scores

Figure 2 Depicts the flow diagram of patients.



Basic Propensity Score Matching

Basic propensity score will be used to assess comparative effectiveness between the two exposure groups. The basic propensity score will be estimated using logistic regression with Tio/Olo treatment as the outcome and the following variables determined *a priori* as predictors:

a) predefined demographic variables (measured at time of cohort entry):
- Age
- Sex
- Calendar Year of Index
- Hospital Size (as a proxy for urban/rural)

b) all concomitant medications and comorbidities/conditions/other variables enumerated in Section 9.3.3.

The final basic propensity score will then be used to identify one initiator of *Tiotropium* for each initiator of *Tiotropium/Olodaterol* with the same propensity score (± a caliper of 5%) **(Austin 2011)**.

High Dimensional Propensity Score Matching

In addition to the basic propensity scores, high dimensional propensity score (hdPS) analysis will also be used to assess comparative effectiveness between the two exposure comparison groups. hdPS is a modification of traditional propensity scores that incorporate additional steps for empirical variable selection. Briefly, hdPS includes additional covariates by ranking a complete list of available variables of a given attribute (e.g. all ICD-10 codes) based on prevalence, recurrence, association between covariate and exposure, and association between covariate and outcome, and then including the top covariates in that list in the propensity score prediction. This technique has been shown to produce improved effect estimates compared to using all predefined covariates in the propensity score prediction (**Schneeweiss 2009**).

The set of covariates to estimate the propensity scores will include the same predefined covariates as in the basic propensity scores (categories a and b), but also an empirically chosen set of covariates (category c):

a) predefined demographic variables (measured at time of cohort entry):
- Age
- Sex
- Calendar Year of the Cohort Entry Date
- Hospital Size (as a proxy for urban/rural)

b) all concomitant medications and comorbidities/conditions/other variables enumerated in Section 9.3.3.

c) The top variables (number of variables determined by the [redacted]) chosen by the hdPS algorithm described above. The following attributes will be used to select variables eligible for hdPS analysis:
- Disease Data – ICD-10 Codes
- Inpatient ACT – Health Claim Code
- Outpatient ACT – Health Claim Code
- Lab Data – Laboratory Code

In selecting diseases eligible for hdPS, the ICD-10 code will be truncated after the dot. Importance of variables will be ordered using the bias ranking method. Health service intensity variables will also be

used. Health service intensity variables are calculated for each attribute by counting the total number of codes for each patient, counting the number of distinct codes for each patient, and creating eight binary variables representing the quartiles for both the total number of codes and number of distinct codes. Along with the binary variables created for each code, the eight binary intensity variables are used in the hdPS algorithm resulting in 2000-8000 binary variables total depending on the attributes selected.

Logistic regression conditional on the final set of covariates will be used to compute the propensity to initiate *Tiotropium/Olodaterol* versus *Tiotropium* given all the variables in a, b, and c above.
The final hdPS will then be used to identify one initiator of *Tiotropium* for each initiator of *Tiotropium/Olodaterol* with the same propensity score (± a caliper of 5%) **(Austin 2011)**.

9.3 VARIABLES

9.3.1 Exposures

- *Exposure: Tiotropium/Olodaterol (Spiolto®).*
- *Reference: Tiotropium (Spiriva®).*

Both groups will be identified according to brand name as the first of two prescriptions of the respective drug within 60 days. Given the limited information on treatment duration in the MDV data, a days supply of 14 days will be assumed for *"Spiolto Respimat 28puffs."* Otherwise, 30 days will be assumed for *"Spiriva Inhalation Capsules 18microg", "Spiriva 2.5microg Respimat 60puffs 150microg", "Spiolto Respimat 28puffs"* and *"Spiolto Respimat 60puffs"*. A grace period of 14 days between assumed end of days supply and subsequent prescription will be used as an allowable gap.

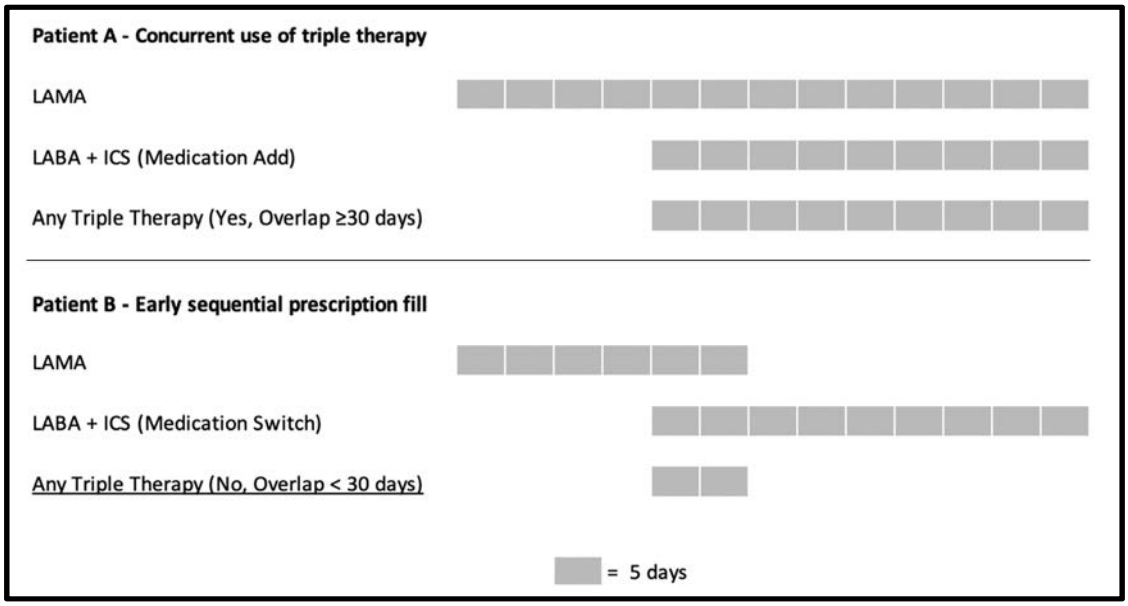
9.3.2 Outcomes

9.3.2.1 Primary outcomes

Triple Therapy Use
The primary outcome of interest is incident rate of triple therapy initiation (first event per patient) defined as any LAMA/LABA/ICS fixed dose combination or any concurrent use for 30 consecutive days of the following:
- any LAMA/LABA fixed dose combination + any ICS single formulation
- any LAMA single formulation + any LABA/ICS fixed dose combination
- any LAMA single formulation + any LABA single formulation + any ICS single formulation

MDV data has limited information on treatment duration with the days of prescription recorded as 1 day for most patients. Therefore, a days supply of 30 days will be assumed. Although we will require at least 30 days of overlap, the first date of triple therapy overlap will serve as the outcome event date, as corresponds to the initiation of triple therapy. Looking into the future to satisfy the requirement of overlap for at least 30 days has the potential to inflict immortal person-time, but is necessary to differentiate concurrent use when subsequent medication is added (see Figure 3 - example Patient A) from an early sequential prescription fill when subsequent medication is switched to (see Figure 3 - example Patient B).

Figure 3 Illustration of outcome



Censoring

Patients will be censored if they had an occurrence of any of the following: outcome (initiation of triple therapy), death, or end of data. The analysis will use an intention-to-treat censoring approach, which does not account for treatment change. A sensitivity analysis will employ an as-treated censoring approach to further censor upon discontinuation of index therapy or initiation of the other index treatment arm. Thus, events will be assigned to exposure groups according to that patient's original index medication, even if that patient discontinued or crossed over.

9.3.2.2 Secondary outcomes and further endpoints

Secondary outcomes

- Time to First Moderate or Severe COPD Exacerbation
  - Time to First Moderate COPD Exacerbation
  - Time to First Severe COPD Exacerbation
- Number of Moderate or Severe COPD Exacerbations
  - Number of Moderate COPD Exacerbations
  - Number of Severe COPD Exacerbations

Further endpoints:

- All-Cause Inpatient Mortality
- Number of Unique Pulmonary Medications
- Number of Hospitalizations for a Respiratory Condition
- Major Cardiovascular Adverse Events (MACE)
- Home oxygen therapy (HOT)

Moderate exacerbations will be defined as an outpatient visit with a diagnosis code for COPD in any field + a prescription for an oral corticosteroid or an antibiotic for respiratory infections,. Severe

exacerbations will be defined as a hospitalization with a primary diagnosis for COPD. (**Chatterjee 2012**)
Unique pulmonary medications will be defined as the following treatments: LAMA, LABA, SAMA, SABA, inhaled/oral glucocorticoids, systemic glucococorticoids, antileukotriene agents, biologics (anti-IgE, anti-IL-5, anti-Il-4), allergy medications, xanthines (theophylline), and mycolytics.

Major Cardiovascular Adverse Event (MACE) will be defined as ischemic stroke, myocardial infarction (MI), or inpatient death. Stroke will be defined as absence of a doubt flag and a disease claim for ICD-10 I60.x - Subarachnoid haemorrhage, I61.x - Intracerebral haemorrhage, I63.x - Cerebral infarction, or I67.8 - Other specified cerebrovascular diseases, a measure previously validated based on ICD-9 code equivalents to have a PPV between 85 and 98% [**Andrade 2012; Tirschwell 2002; Roumie 2008**]. MI will be defined as absence of a doubt flag and a disease claim for ICD-10 I21.x - Acute myocardial infarction or I22 - Subsequent myocardial, a measure previously validated based on ICD-9 code equivalents to have a PPV of 94% using US Medicare claims [Kiyota 2004] and 88.4% PPV using US commercial claims [Wahl 2010]. Inpatient death will be defined as either absence of a doubt flag and a disease claim or Discharge Summary Data with a death-related diagnosis (ICD-10 O96.x - Death from any obstetric cause; O97.x - Death from sequelae of obstetric causes; I46.1 - Sudden cardiac death, so described; R96 - Other sudden death, cause unknown; R98 - Unattended death; R99 - Other ill-defined and unspecified causes of mortality) or the occurrence of Discharge Summary Data with either Destination After Discharge as 8 - Completed (Death and so on.) or Discharge Summary Data with Outcome at the Time of Discharge is Death.

Home oxygen therapy (HOT) will be defined according to presence of the following:

- Health claim codes that include home/domiciliary oxygen therapy:
    - 114041610 - Add-on fee of materials for domiciliary oxygen therapy (others)
    - 114042770 - Oxygen therapy add-on fee (home-care patient home visit fee (1) 1)
    - 114043670 - Oxygen therapy add-on fee (home-care patient home visit fee (2) a)
    - 114045470 - Remote monitoring add-on fee (home oxygen therapy guidance management fee [others])
    - 114004910 - Installation type liquid oxygen reservoir add-on fee
    - 114005010 - Portable type liquid oxygen reservoir add-on fee
    - 114006110 - Oxygen tank add-on fee (others)
    - 114006210 - Oxygen enricher add-on fee
    - 114006310 - Oxygen tank add-on fee (portable oxygen tank)
    - 739210000 - Liquid oxygen/portable liquid oxygen container (LGC)
    - 739220000 - Oxygen cylinder/large size
    - 739230000 - Oxygen cylinder/small size
    - 739250000 - Liquid oxygen/portable liquid oxygen container (LGC) (remote islands and other)
    - 739260000 - Oxygen cylinder/large size (remote islands and other)
    - 739270000 - Oxygen cylinder/small size (remote islands and other)

9.3.3 Covariates

The covariates listed below consist of demographics, medications, comorbidities, and other variables that are hypothesized to confound the relationship between exposure and outcome. Covariates will be identified based on data recorded within 180 days prior to or on the index date (date of

dispensing/initiation of the exposure), unless otherwise specified. If multiple measurements are made in the baseline period, then the most recent measurement will be used.

There is an additional variable for "doubt diagnosis" related to each disease diagnosis. Only confirmed diagnoses will be used for all disease variables (this represents ~95% of all diagnoses).

Absolute and relative frequencies of each covariate will also be reported. Detailed descriptions of the listed covariates can be found in Annexes 2 and 3. The measure definitions for diagnoses are subject to modification to further incorporate disease codes/names as deemed appropriate upon further exploration of the data during study implementation.

Demographics (last recorded)

- Age
- Sex
- Year of Cohort Entry
- Hospital Size (as a proxy for urban/rural).

Concomitant Medications

- Oral/Injected Corticosteroids
- Short acting beta agonist (SABA) (number of claims)
- Short acting muscarinic antagonist (SAMA) (number of claims)
- Systemic Xanthines
- Systemic Antileukotrienes
- Interleukin Inhibitors for Asthma
- Non-steroidal Respiratory Anti-inflammatories
- Opioids/Narcotics
- Systemic Antihistamines
- Oral Antibiotics for a Respiratory Condition (number of claims)
- Cough and Cold Preparations
- Diabetes Mellitus Medications, excluding Insulin
- Insulin
- Cytostatics
- Antirheumatics, Biologic
- Antirheumatics, Non-Steroidal
- Antithrombotic Agents
- Lipid-lowering Agents
- Antihypertensives/Diuretics
- Antiepileptics/Psycholeptics/Psychoanaleptics
- Antipsoriatics
- Antivirals
- Thyroid Therapies
- Vaccinations

[Antibiotics + Respiratory diagnosis, [redacted] can try to find antibiotics specific to respiratory conditions]

Comorbidities/Symptoms

- COPD Exacerbations (number of exacerbations)
- All-Cause Hospitalization
- Hospitalization due to Respiratory Condition
- Acute Myocardial Infarction, AMI
- Angina Pectoris
- Peripheral Vascular Disease, PVD
- Heart Failure, HF

- Hypertension
- Cardiac Arrhythmias
- Cerebrovascular Disease
- Any Cancer (except nonmelanoma skin cancer)
- Allergic Rhinitis
- Chronic Sinusitis
- Bronchiectasis
- Pneumonia
- Chronic Bronchitis
- Tuberculosis
- Influenza
- Anxiety
- Dementia
- Depression
- Osteoporosis
- Acute Liver Injury or Failure
- Chronic Kidney Disease, CKD
- Peptic Ulcer Disease, PUD
- Gastroesophageal Reflux Disease, GERD
- Type 1 Diabetes Mellitus
- Type 2 Diabetes Mellitus
- Hypothyroidism
- Hyperthyroidism
- Anemia
- Rheumatoid Arthritis
- Lupus
- Inflammatory Bowel Disease, IBD
- Multiple Sclerosis, MS
- Psoriasis and Psoriatic Arthritis
- Eczema
- Blood eosinophil concentration (will be reported in the descriptive summary, but not included in the propensity score model given that this lab value is available for <10% of COPD patients in this data source).

9.4 DATA SOURCES

The proposed study will utilize data from Medical Data Vision (MDV).

MDV is an electronic, record-based healthcare database that spans from April 1, 2008 to 31 March 2019, and contains 25.1 million observable patients. It contains patient-level information on demographics, diagnoses and prescription information from 374 medical facilities across Japan. The distribution of patients in the database is similar to that of the national demographics for patients seeking healthcare, although the MDV database has more elderly and sicker patients.

The Japanese health care structure enables anyone to seek medical treatment at any facility of their choosing, including hospitals. Thus, acute hospitals in Japan consist of both primary (outpatient) and secondary (inpatient) care facilities. In fact, the MDV database is built out of more than 80% outpatient data, which allows for identification of patients who visit hospitals without severe conditions. These hospitals follow a diagnosis procedure combination (DPC) billing structure unique to Japan that enables capture of inpatient discharge summary

information (disease name, operations, adjuvant treatment, etc.), health claims for procedures (surgery information, departments, wards, etc.), and health claims for treatments (medications, medical devices, devices, etc.). A smaller subset of consenting hospitals also provide data on blood test results.

Thus, it is expected that 1) patients with COPD in these hospitals provide a good representation of the general Japanese COPD population; and 2) data from patients treated in the different hospitals cannot be linked. Due to the nature of the database, inclusion criteria to ensure that the patients are treated for COPD in the same hospitals continuously are defined as described in Section 9.2.2.

9.5 STUDY SIZE

There are 1,829 new users of *Tiotropium/Olodaterol* and 13,132 new users of *Tiotropium* between 28 Sep 2015 and 31 October 2018 who satisfied the initial inclusion criteria of new use with at least 2 prescriptions for the index medication within 60 days, and excluding patients without a COPD diagnosis during the baseline period, age <40, diagnosis of asthma during the baseline period, no history of lung cancer or lung transplant, any LAMA, LABA, or ICS maintenance therapy within the 30 days prior to cohort entry, and without continuous enrolment (days since first inpatient/outpatient encounter in the data) during the baseline period.

Based on the result of study by Hahn B et al, it is assumed that the triple therapy initiation rate during 1 year is 6% in Tio+Olo group and 10% in Tio group. In total, 1856 patients are needed to observe 141 events and to detect the difference (HR of 1.73) with 2-sided alpha of 0.05 and 90% power.

After propensity score matching, it will be assessed whether sufficient number of sample size is available to detect the expected difference. If not available, the treatment difference will be explored in highly explorative manner (i.e., p-value is considered descriptively and point estimate with confidence interval is focused).

9.6 DATA MANAGEMENT

Dataset
The Medical Data Vision dataset is comprised of administrative records of longitudinal inpatient, outpatient and drug data from multiple hospitals that have been standardized and de-identified prior to use for the analysis. The statistical analysis will be conducted using the [redacted]

COPD Maintenance Therapy Drug Duration
Given limited information on treatment duration in the MDV data, a days supply of 14 days will be assumed for “Spiolto Respimat 28puffs.” Otherwise, 30 days will be assumed for all LAMA, LABA, and ICS maintenance therapies, including “Spiriva Inhalation Capsules 18microg”, “Spiriva 2.5microg Respimat 60puffs 150microg”, “Spiriva 1.25microg Respimat 60puffs 75microg”, and “Spiolto Respimat 60puffs”. A grace period of 14 days between assumed end of days supply and subsequent prescription will be used as an allowable gap.

Handling of Missing Data
Missing data that occurs in covariates or descriptive variables will be classified as its own level (i.e. missing data indicator). In addition, a feasibility assessment before beginning the

analyses will be done, and variables with >75 % missing values will be excluded from all analyses, other than baseline characteristics. If a variable is left with only one level other than missing, the variable will be excluded completely from all analyses.

9.7 DATA ANALYSIS

9.7.1 Main analysis

For all analyses, variables will be reported as follows:

- Continuous variables (e.g., age) will be presented as means (with standard deviation, SD) and/or medians (with interquartile range, IQR), minimum, maximum.
- Categorical variables (e.g., sex) will be presented as absolute and relative frequencies.

9.7.1.1 Descriptive Analysis

All variables specified in section 9.3.3 will be reported. For demographic and lifestyle variables, the value recorded on the cohort entry date will be reported, otherwise the most recent known value will be reported. Presence of comorbidities and use of concomitant medication use will be determined based on whether they ever occurred during the baseline period prior to the cohort entry date. Differences in the confounder distributions will be inspected for successful confounder balance of measured characteristics and standardized differences will be reported.

9.7.1.2 Rates and Risks

- *Rate of Triple Therapy Initiation*

Among the unmatched and matched cohorts, rates of triple therapy use for each treatment group will be reported as the number of events (first per patient) divided by the total number of person-years at risk during follow-up. Comparative rates and corresponding 95% CIs will be reported as both the rate ratio and rate difference per 1,000 person-years at risk.

- *Risk of Triple Therapy Initiation*

Among the unmatched and matched cohorts, risk of triple therapy use for each treatment group will be reported as the number of events (first per patient) divided by the total number of patients at risk. Comparative risks and corresponding 95% CIs will be reported as both the risk ratio and risk difference per 1,000 person at risk.

9.7.1.3 Comparative Effectiveness

- *Hazard Ratio for Triple Therapy Use Initiation*

Among both the basic propensity score matched and high dimensional propensity score matched cohort, Cox regression will be used to estimate the hazard ratios and 95% CI for Tiotropium/Olodaterol compared to patients treated with Tiotropium during follow-up for time-to-first triple therapy initiation using an intention-to-treat censoring approach.

9.7.2 Subgroup analysis

Not applicable.

9.7.3 Sensitivity Analyses

1. Less Stringent Qualifying Event Criterion

Instead of defining the event to qualify patients for inclusion based on two prescriptions within 60 days, patients may enter upon only one prescription. While some confidence is lost in whether the patients truly took their index medications, the less stringent qualifying event criterion will allow more patients to be included, increasing statistical power. Furthermore, the possibility of immortal time bias is also mitigated, since the time between prescriptions is no longer present.

2. As-treated Censoring

The analysis will use an as-treated approach for primary, secondary and further endpoint outcomes. In addition to the censoring criteria mentioned for the intention-to-treat approach (outcome, death, or end of data), patients will also be censored after medication discontinuation or switching over to the other arm.

3. Alternative algorithm for COPD

The analysis will use a different set of diagnosis codes for COPD (J43*, J44*) when selecting COPD patients. Compared to the primary analysis, this algorithm omits the diagnostic code for chronic bronchitis (J41*), as this code is commonly used by pulmonologists when prescribing Mucodyne to patients who do not actually have chronic bronchitis. While some true chronic bronchitis patients may be excluded, the selection of patient will increase specificity.

4. Asthma patients with doubt
Asthma patients with doubt are defined as patients with a diagnosis code for asthma and without evidence of any asthma specific treatment (ie., ICS, ICS/LABA) This sensitivity analysis will include patients identified with asthma with doubt.

5. ACOS sensitivity analysis
Patients that have evidence of asthma during the follow-up period will have their data censored on the date of asthma diagnosis during the follow-up period. This will ensure that they contribute information during their COPD disease trajectory up until the time they develop asthma. This approach will mitigate introducing immortal time bias for those patients with ACOS during the follow-up period.

9.8 QUALITY CONTROL

The study protocol has been written following the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) [R15-4870] that provides a set of rules and principles for post-authorization studies with regard to the best practices and

transparency, thereby promoting scientific independence of such studies. The study will be registered to the ENCePP's E-register and the results will also be published on the same site.

The study protocol also follows the key elements of the Guideline for Good Pharmacoepidemiology Practices (GPP) by International Society for Pharmacoepidemiology [R11-4318], and the recent draft Guidance for Industry and FDA Staff "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets" [R15-4859]. The guidelines for good pharmacoepidemiology practices (GEP) in non-interventional studies will be respected along with any applicable local laws and regulations. This trial is not in the scope of Good Clinical Practice (GCP) studies.

[redacted] will build measures for cohort inclusion, outcomes and covariates. Some of the measure algorithms will be based on those collaboratively developed for another respiratory-related protocol with clinical input from external pulmonology experts (i.e. ICD-10 code lists for comorbidities). Regarding medications, because the health claim coding system in MDV is unique to Japan and not well documented in academic articles, queries based on generic name/brand name will be used to determine the code list for each medication measure.

All measures created, cohorts developed, statistical analyses implemented, and tables completed will undergo quality control review by at least 1 additional analyst or scientist under the supervision of the Principal Scientist. Quality controls include checks for the validity and logical content of codes and checks for missing values and variables. In order to control for potential inconsistencies and errors, all variables will be tabulated. In addition, the distribution of each variable will be examined. Extreme observations with values larger than ± 3 standard deviations (SD) will be examined as potential outliers and consequently excluded from the dataset.

This protocol will be strictly followed in the study. However, measure definitions may undergo modification if determined to be scientifically sensible. All changes to this protocol will be documented in protocol amendments.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This study will be conducted using hospital-based health insurance claims following the DPC payment system and is subject to certain limitations. One limitation is that these are based on a large, non-random convenience sample based in Japan, which may contain biases or lack generalizability to other populations. Data also come from a subset of hospitals in Japan, which would lead to failure to record events if patients visit medical centers not included in MDV's data sources **(Tanaka 2015)**. Moreover, because healthcare is nationalized in Japan, the notion of enrolment is not applicable, and all patients are assumed to be observable throughout the global date range of the data. However, if a patient's emigration or mortality is not captured, then they would remain in the study despite not truly being eligible for any events, thereby leading underestimations of the risks and rates and possible bias in the hazard ratio is these patients are differentially distributed between the exposed and unexposed groups.

Another limitation of the study is that patients on monotherapy may escalate to double therapy before receiving the triple therapy. The patients starting on double therapy do not have this option. Therefore, patients on monotherapy may take longer to get to triple therapy than the patients on double therapy.

Additionally, the MDV database also poses some limitations inherent to prescription claims data. Electronic outpatient pharmacy dispensing records are considered accurate because pharmacists fill prescriptions with little room for interpretation and are reimbursed by the government on the basis of detailed, complete, and accurate claims submitted electronically **(Stergachi 1988, Levy 2003)**. Pharmacy dispensing information is usually seen as the gold standard of drug exposure information compared to self-reported information **(West 1995)** or prescribing records in outpatient medical records **(West 1994)**. However, claims data are subject to certain limitations. The presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed, and any medications filled over-the-counter or provided as samples by the physician will not be observed in the claims data. This concern is somewhat mitigated by requiring 2 claims within 60 days for cohort entry. Finally, patients are required not to have a claim for Tiotropium/Olodaterol or Tiotropium during the baseline period, but patients may have taken maintenance therapies prior to the start of the baseline period.

MDV database only captures in-patient deaths, and mortality, one of the secondary outcomes, maybe under-reported in the data. However, the magnitude of the underestimation is unlikely to differ by exposure and comparison cohorts.

In the analytical portion of this protocol, propensity score matching will be used to ultimately derive the causal parameters of interest. Many covariates are included in the prediction model of the propensity scores, but as with all non-interventional studies, the potential for unmeasured and residual confounding cannot be ruled out.

9.10 OTHER ASPECTS

Not applicable.

9.11 SUBJECTS

9.11.1 Cases

See Section 9.2.2.

9.11.2 Controls

Not applicable.

9.12 BIAS

In principle, electronic pharmacy dispensing records are considered accurate because pharmacists fill prescriptions with little room for interpretation, and are reimbursed by insurers based on detailed, complete, and accurate claims submitted electronically **(Levy 2003; Stergachis 1988)**. Pharmacy dispensing information is usually seen as the gold standard of drug exposure information compared to self-reported information or prescribing records in medical records.
The population-based nature of the database will avoid selection bias and ensure external validity. Confounding bias through observable covariates will be controlled for by the design, which includes propensity score matching. Specifically, compared to traditional propensity

score matching, high dimensional propensity scores will be used to reduce overfitting while retaining baseline covariate balance in matched groups **(Schneeweiss 2009)**.
To minimize misclassification of the recorded patient characteristics, previously validated algorithms or code lists will be used whenever available. Code lists will be reviewed by the qualified medical reviewers prior to implementation. Basic plausibility checks will be implemented for continuous variables (e.g. age, etc.).

The covariates chosen in section 9.3.3. are hypothesized to be confounders in the relationship between exposure and outcome. The range and quantity of variables selected are aimed to make the two exposure groups more comparable so that the effect estimates may more readily have a causal interpretation.

COPD patients who start on Spiriva® Respimat® may be different than Spiolto® Respimat® initiators in the clinical course and severity of COPD. Use of propensity score matching aim to reduce bias due to confounding. The addition of covariates chosen by hdPS will further aid in reducing bias by empirically selecting for strong confounders. However, it is possible that inclusion of some variables may introduce rather than remove bias (i.e. as collider bias or M-bias). Nevertheless, such biases are demonstrated to be minor, and inclusion of variables preceding exposure are generally thought to improve rather than degrade validity **(Rassen 2011)**.

The requirement of second fill for inclusion in the study could lead to immortal time bias. However, as the follow-up will begin after the second fill rather than at the cohort entry date, this requirement is unlikely to bias the findings.

To assess the primary outcome of triple therapy among those who are not on triple therapy fixed dose combination or filling all the three medications at the same time, an algorithm will be employed to assess the concurrent use (previously described). This algorithm will require us to look into the future to determine the start of the triple therapy and may introduce bias. However, it requires an overlap of only 30 days, and it is unlikely to significantly affect the results.

The primary analysis is being conducted as an Intention to Treat (ITT) approach in which patients are analyzed according to first exposure. However, it is likely that some patients may discontinue their COPD medication or switch over to another cohort. The misclassification of exposure may bias the results. A sensitivity analysis using On Treatment approach will be conducted, which will take into account discontinuation and switching of cohort from one medication to the other.

10. PROTECTION OF HUMAN SUBJECTS

As the present study is a non-interventional retrospective cohort study, the most significant potential impact on the participants would be the potential for individual identification and loss of privacy. Patients in the MDV dataset are de-identified, such that names are not linked to patient IDs. Thus, the risks to participants are expected to be minimal.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Data is anonymized and extracted, analyzed, validated and reported in aggregate.

There is no potential that any employee of BI or agent working on behalf of BI will access individual patient data in which the patient may be identified during data compilation, data reporting or data analysis.

Based on current guidelines from the International Society for Pharmacoepidemiology [R11 4318] and the EMA [R13-1970], non-interventional studies such as the one described in this protocol, conducted using health care records, do not require expedited reporting of suspected adverse events/reactions. Specifically, as stated in section VI.C.1.2.1 of Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products, for non-interventional study designs, which are based on use of secondary data, reporting of adverse reactions is not required.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

These baseline results will be published as an abstract and/or manuscript. Conference and Journal to be decided.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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