Non-Interventional Study (NIS) Protocol

Document Number:	c38660249-01
BI Study Number:	1237-0110
BI Investigational Product(s):	Spiolto Respimat
Title:	Effectiveness of Maintenance Treatment with Tiotropium + Olodaterol in Comparison to Inhaled Corticosteroids + Long-acting β2 agonists in COPD patients in Taiwan: a non-interventional study based on the Taiwan National Health Insurance (NHI) data.
Brief lay title:	Effectiveness of Tiotropium + Olodaterol versus ICS+LABA among COPD patients in Taiwan
Protocol version identifier:	1.0
Date of last version of protocol:	Not applicable
PASS:	No
EU PAS register number:	Study not registered
Active substance:	Tiotropium + Olodaterol (R03AL06)
Medicinal product:	Spiolto Respimat
Product reference:	BC26735443
Procedure number:	Not applicable
Marketing authorisation holder(s):	Boehringer Ingelheim International GmbH
Joint PASS:	No
Research question and objectives:	To compare the risk of exacerbations between initiators of Tiotropium / Olodaterol (Tio/Olo) and inhaled corticolsteroids / long-acting β2-agonists (ICS/LABA) in a real world setting
Author:	[redacted]

Marketing authorisation holder(s):	Boehringer Ingelheim International GmbH
MAH contact person:	Not applicable
EU-QPPV:	Not applicable
Signature of EU-QPPV:	Not applicable
Date:	23 May 2022

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2. LIST OF ABBREVIATIONS

AE	Adverse Event
CA	Competent Authority
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
ICS	Inhaled corticolsteroids
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LABA	Long-acting β2-agonists
LAMA	Long-acting muscarinic antagonists
MAH	Marketing Authorization Holder
NHI	Taiwan National Health Insurance
NIS	Non-Interventional Study
Olo	Olodaterol
PASS	Post-Authorization Safety Study
SAE	Serious Adverse Event
Tio	Tiotropium

3. RESPONSIBLE PARTIES

Principle Investigator

[redacted]

BI NIS Lead (Scientific)

[redacted]

BI NIS Lead (Operation)

[redacted]

4. ABSTRACT

COPD is a leading cause of morbidity and mortality throughout the world. Long-acting bronchodilator medications, which include long-acting β2-agonists (LABAs) and the long-acting muscarinic antagonists (LAMAs) such as tiotropium, are the central maintenance therapy to the management of COPD, with inhaled corticosteroids (ICSs) added with increasing severity. The up-to-date GOLD guideline recommends to initiate ICS/LABA in patients with high blood eosinophils level and frequent exacerbation history[P21-01394]. However, ICS containing therapy has been widely used inappropriately in real world practice.

The role of ICS in COPD has been debated for decades and studies have been conducted to investigate the effect of ICS-containing therapy in patients with COPD. INSPIRE [P07-11820] study indicated that ICS/LABA and tiotropium showed similar effects on the reduction of exacerbations, while the risk of pneumonia was higher in the ICS/LABA group. And the FLAME [P16-05628] study showed LAMA/LABA was superior to ICS/LABA in terms of exacerbation prevention, while in some newly published data focusing on FDC triple therapy showing reversed results. .

With more and more fixed dose combination medications, i.e. LAMA/LABA, ICS/LABA/LAMA, approved and prescribed in recent years, it is of clinical interests to understand the effectiveness and safety profile of these therapies in real world settings.

The aim of this real world study is to assess effectiveness and safety profile between tiotropium/olodaterol (Tio/Olo) and ICS/LABA. The primary outcome of the study will be risk of moderate or severe COPD exacerbations. Other outcomes include time to ICS/LABA/LAMA escalation, rate of escalation to triple therapy, pneumonia and rescue medication use.

Name of company: Boehringer Ingelheim			
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Name of active ingredient: Tiotropium + Olodaterol {R03AL06}			
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Title of study:	Effectiveness of Maintenance Treatment with Tiotropium + Olodaterol in Comparison to Inhaled Corticosteroids + Long-acting β2 agonists in COPD patients in Taiwan: a non-interventional study based on the Taiwan National Health Insurance (NHI) data		
Rationale and background:	COPD is a leading cause of morbidity and mortality throughout the world. Long-acting bronchodilator medications, which include long-acting β2-agonists (LABAs) and the long-acting muscarinic antagonists (LAMAs) such as tiotropium, are the central maintenance therapy to the management of COPD, with inhaled corticosteroids (ICSs) added with increasing severity. The up-to-date GOLD guideline recommends to initiate ICS/LABA in patients with high blood eosinophils level and frequent exacerbation history[P21-01394]. However, ICS containing therapy has been widely used inappropriately in real world practice. The role of ICS in COPD has been debated for decades and studies have been conducted to investigate the effect of ICS-containing therapy in patients with COPD. INSPIRE [P07-11820] study indicated that ICS/LABA and tiotropium showed similar effects on the reduction of exacerbations, while the risk of pneumonia was higher in the ICS/LABA group. And the FLAME [P16-05628] study showed LAMA/LABA was superior to ICS/LABA in terms of exacerbation prevention, while in some newly published data focusing on FDC triple therapy showing reversed results. . With more and more fixed dose combination medications, i.e. LAMA/LABA, ICS/LABA/LAMA, approved and prescribed in recent years, it is of clinical interests to understand the effectiveness and safety profile of these therapies in real world settings. The aim of this real world study is to assess effectiveness and safety profile between tiotropium/olodaterol (Tio/Olo) and ICS/LABA. The primary outcome of the study will be time to the first moderate or severe COPD exacerbations. Other outcomes include time to ICS/LABA/LAMA		

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	escalation, rate of escalation to triple therapy, pneumonia and rescue medication use.		
Research question and objectives:	Primary objective: • To compare time to the first moderate or severe COPD exacerbations between initiators of Tiotropium / Olodaterol (Tio/Olo) and inhaled corticolsteroids / long-acting β2-agonists (ICS/LABA) after entry between 1st January 2014 and 31st December 2019 Secondary objectives: • To compare time to escalation to triple therapy between initiators of Tio/Olo and ICS/LABA; • To compare the rate of escalation to triple therapy between initiators of Tio/Olo and ICS/LABA; • To compare the time to first hospitalization for community-acquired pneumonia between initiators of Tio/Olo and ICS/LABA; • To compare the number of prescriptions of rescue medication between initiators of Tio/Olo and ICS/LABA • To compare the annualized rate of moderate or severe COPD exacerbation The study period of between 1st January 2014 and 31st December 2019 apply to secondary objectives above		
Study design:	This study will be a non-interventional cohort study based on existing data (NISed).		

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Population:	Inclusion criteria: 1. At least one prescription for Tio/Olo combined inhaler or for LABA/ICS combined inhaler between 1st January 2014 and 31st December 2019. 2. Aged ≥ 40 years on the index date 3. At least one diagnosis of COPD at any time prior to or on the index date; 4. At least one year of continuous medical and health insurance plan prior to the index date will be required to allow for a look-back period for the covariates and identification of new use of the study drugs; 5. At least one record in the health insurance system database; Exclusion criteria: 1. Any use of LAMA/LABA, ICS/LABA, or ICS/LAMA/LABA in free or fixed form for one year prior to the index date; 2. Individuals with asthma, allergic rhinitis, lung cancer, interstitial lung disease, or lung transplant identified at any time prior to the index date [redacted];		
Variables:	Exposures: Exposure of this study is defined as new initiation of Tiotropium/Olodaterol, or ICS/LABA during the study period. Outcomes: Primary outcome: • Time to the first moderate or severe COPD exacerbations after entry Secondary outcomes: • Time to triple therapy escalation after entry • Incidence rate of triple therapy initiation;		

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- Time to the first hospitalization for community-acquired pneumonia;
- Annualized rate of prescriptions of rescue medications (calculated as: annualized rate=number of prescriptions/total patient year at risk=number of prescriptions per patient year);
- Annualized rate of moderate or severe COPD exacerbation (calculated as: annualized rate=number of moderate or severe COPD exacerbations/total patient year at risk=number of exacerbations per patient year)

Covariates:

Demographic characteristics and cohort entry information:

- Sex
- Age
- Calendar year of cohort entry
- Season of index date (winter, spring, summer, fall)

Additional, the following clinical characteristics will be measured during the 1 year pre-index baseline period:

Specific previous COPD treatments

- LAMA monotherapy
- LABA monotherapy
- ICS monotherapy
- LAMA/ICS combination therapy

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Use of other respiratory drugs
- Mucolytics
- Theophylline
- Short-acting beta-agonists
- Short-acting muscarinic antagonists

- Number of previous acute COPD exacerbation (measured both 12 months and in the 30 days prior to cohort entry), categorized as 0, 1 or 2+.
  - All exacerbations (Moderate+Severe)
  - An outpatient visit with a diagnosis code for COPD in any field + a prescription for an oral corticosteroid or an antibiotic for respiratory infections (Moderate)
  - Hospitalizations or emergency room visits with a primary
  - diagnosis for COPD (Severe)

- Number of hospitalizations caused by exacerbation of COPD in 12 months prior to the index date:
  - 0;
  - 1;
  - 2+;
- Number of all-cause hospitalizations in 12 months prior to index date:
  - 0;
  - 1;
  - 2+;

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- Comorbidities:
  - Cardiovascular disease
  - Cerebrovascular disease
  - Diabetes
  - Chronic kidney disease
  - Pneumonia
  - Cancer
  - Cirrhosis
- Charlson Comorbidity Index (CCI)

- History of medications dispensed in the 12 months before or on the index date will be identified from the pharmacy dispensing history:
  - Cardiovascular drugs:
    antihypertensives
    antiarrhythmics
    nitrates
    heart failure medications
  - Lipid-lowering medications
  - Blood glucose-lowering medications
  - Anticoagulants and antiplatelet agents
  - Antibiotics
  - Antineoplastic agents

- COPD severity

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Data sources:	Data used in this study will come from the Taiwan National Health Insurance (NHI) claims data between 2014 and 2019. Data sources include Taiwan NHI, Taiwan cancer registry (TCR) and Taiwan Mortality Data. Taiwan Department of Statistics, Ministry of Health and Welfare is the unit designated by the government to manage health and social welfare statistical databases, and to develop data platform for academic research. Through the services provided by the Health and Welfare Data Science Center (HWDSC) of the Department of Statistics, researchers may access a wide range of health and welfare data, including claims, mortality (with cause of death) and Taiwan Cancer Registry (TCR). The HWDSC staff encrypt the national ID for all individuals according to a secure encryption algorithm that is not made known to the public. The encrypted ID is unique for all individuals and will be used for linkage between databases. **(a) National Health Insurance claims data** Taiwan National Health Insurance (NHI) started in 1995 and is a publicly funded single payer health insurance program for all residents. Health insurance for individuals is required by law and coverage is more than 99%. The majority of healthcare providers in Taiwan contract with the National Health Insurance Agency in Taiwan to provide a wide range of medical services. Geographic locations of health care claims are broadly classified into 6 regions in Taiwan. Salary range, which serves as the basis for enrollees' premium calculation, can serve as a proxy indicator for socioeconomic status. Bundled payment according to the Diagnosis-Related Group system only applies in limited number of disease conditions, therefore detailed drug use information during

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hospitalization is also available. An added advantage of the NHI data source is the low membership turnover rate, which is particularly important for long-term follow-up study. NHI claims were based on International Classification of Disease, ninth revision, clinical modification (ICD-9-CM) codes till the end of 2015, and then switched to International Classification of Disease, tenth revision, clinical modification (ICD-10-CM) codes after 2016. Specific NHI data column please see file "column_note_in_TW_NHI_20210824" [No document #] in the database (confidential and only can be accessed by PI)

(b) Mortality data

The household registration system in Taiwan maintain birth, marital status, and death information and is administrated by the Department of Household Registration, Ministry of the Interior. Death certificates are collected through this system and transferred to the Ministry of Housing and Works (MOHW) for coding of cause of death and maintenance of the mortality database. The cause of death was coded in the ICD-9-CM format from 1990 to 2009, and in ICD-10-CM format from 2010 to 2019. This study will use the cause of death files in years 2012-2019, primarily focusing on the date of death of study subjects.

(c) Taiwan Cancer Registry data

In Taiwan, the population-based cancer registry was founded in 1979. Since then, the registry collected basic information, referred to the "20 items short-form system," on incident cancer cases (including cancer-in-situ) within one year after the initial diagnosis from hospitals with more than 50-bed capacity throughout the country. Recorded items include date of birth, gender, time and method of diagnosis, cancer site and morphology, treatment summary and death. From 2002 onward, a "long-form" system was

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	established to collect more detailed information of cancer staging, treatment and follow-up data from hospitals with more than 500 new cancer cases diagnosed annually. The number of recorded items increased from 20 to 65 in 2002, further to 95 in 2007, and to 114 in 2011. In 2003, Cancer Control Act was introduced with all reporting hospitals mandated to submit cancer patient information to the cancer registry. To ensure quality of cancer registries and enhancing the quality of cancer registry data, Taiwan Society of Cancer Registry was established in 2006, conducting random medical record review to ensure data accuracy since 2010. TCR data from 2000 through 2018 will be used for this study.
Study size:	Based on the result of study by Wedzicha JA, et al, (where at least 25% of the patients in the Tio/Olo group have a first moderate or severe exacerbation at 127 days [95% CI, 107 to 149] and in ICS/LABA group at 87 days [95% CI, 81 to 103] (HR = 0.78, [95% CI 0.70 to 0.86])), we assume that at least 25% of patients in the ICS/LABA experienced a first moderate or severe COPD exacerbation at 103 days and the HR of Tio/Olo to LABA/ICS is 0.9. For a study duration of 6 years, a total of 4978 patients (2489 patients each arm) are needed to detect the difference between the two arms with 2-sided alpha of 0.05 and 90% power..
Data analysis:	All variables, including patient characteristics, baseline measures, and outcomes, will be analysed descriptively. All analyses will be presented for each exposure group (Tio+Olo vs LABA/ICS) overall. We will first describe formation of the study cohort. Patient characteristics at baseline in patients treated with Tio+Olo and patients treated with LABA/ICS will be described separately using standard descriptive statistics after propensity score matching. Absolute standardized differences (ASDs) will be used to compare the characteristics between the two groups after propensity score matching, in which a >0.1 ASD indicates a meaningful difference.

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For the analysis of the primary outcome, Cox proportional hazard regression model will be used to compare the outcome of interest between the two treatment groups, while accounting for the potential baseline differences between them. Other known predictors would also be included in the model as covariates. It will provide an estimate of the hazard ratio (HR) of time to the first moderate or severe COPD exacerbation associated with Tio+Olo use relative to LABA/ICS use, along with 95% confidence intervals (CI). The analysis will be on-treatment.

The analysis of the secondary objectives related to time to triple therapy escalation, time to first hospitalization for community-acquired pneumonia, will use a Cox proportional hazard regression model with an as-treated approach, similar to that of the primary analysis. The estimate of the hazard ratio (HR) of time to triple therapy escalation, hospitalization for community-acquired pneumonia associated with Tio+Olo use relative to LABA/ICS use, along with 95% confidence intervals (CI) will be provided.

Incidence rate of triple therapy initiation (first event per patient), annualized rate of moderate or severe COPD exacerbations, and annualized rate of prescriptions of rescue medications will be calculated by cohort. Incidence rate ratio (IRR) will be calculated. Incidence differences and their 95% confidence intervals will also be derived.

The incidence rate ratio (IRR) for the triple therapy initiation in the Tio+Olo - exposed group relative to that in the comparator group, along with 95% confidence intervals will be derived using negative binomial model.

For annualized rate of moderate or severe COPD exacerbation and annualized rate of prescriptions of rescue medications, ratio of Tio+Olo – exposed group relative to LABA/ICS group, along with 95% confidence intervals will be derived using negative binomial model.

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Milestones:	IRB/IEC approval: 22-Oct-2020 Feasibility assessment: 2020. Q3 EU PAS Registration: 01-Jun-2022 Full analysis: • Data Access: 15-Jun-2022 • Complete data analysis: 30-Aug-2022 Final report of study results: 15-Oct-2022 Publications timeline: • Abstract: 2023 ATS.		

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	Oct 2020 (completed)
Feasibility assessment	Oct 2020 (completed)
EU PAS Registration	01/Jun/2022
Full analysis	
Data Access	15/Jun/2022
Complete data analysis	30/Aug/2022
Final report of study results	15/Oct/2022

7. RATIONALE AND BACKGROUND

COPD is a leading cause of morbidity and mortality throughout the world. Long-acting bronchodilator medications, which include long-acting β2-agonists (LABAs) and the long-acting muscarinic antagonists (LAMAs) such as tiotropium, are the central maintenance therapy to the management of COPD, with inhaled corticosteroids (ICSs) added with increasing severity. The up-to-date GOLD guideline recommends to initiate ICS/LABA in patients with high blood eosinophils level and frequent exacerbation history[P21-01394]. However, ICS containing therapy has been widely used inappropriately in real world practice.

The role of ICS in COPD has been debated for decades and studies have been conducted to investigate the effect of ICS-containing therapy in patients with COPD. INSPIRE [P07-11820] study indicated that ICS/LABA and tiotropium showed similar effects on the reduction of exacerbations, while the risk of pneumonia was higher in the ICS/LABA group. And the FLAME [P16-05628] study showed LAMA/LABA was superior to ICS/LABA in terms of exacerbation prevention, while in some newly published data focusing on FDC triple therapy showing reversed results.

With more and more fixed dose combination medications, i.e. LAMA/LABA, ICS/LABA/LAMA, approved and prescribed in recent years, it is of clinical interests to understand the effectiveness and safety profile of these therapies in real world settings.

The aim of this real world study is to assess effectiveness and safety profile between tiotropium/olodaterol (Tio/Olo) and ICS/LABA. The primary outcome of the study will be time to first moderate or severe COPD exacerbations. Other outcomes include time to ICS/LABA/LAMA escalation, rate of escalation to triple therapy, pneumonia and rescue medication use.

8. RESEARCH QUESTION AND OBJECTIVES

Primary objective:

- To compare time to the first moderate or severe COPD exacerbations between initiators of Tio/Olo and ICS/LABA in a real world setting;

Secondary objectives:

- To compare time to escalation to triple therapy between initiators of Tio/Olo and ICS/LABA;
- To compare the rate of escalation to triple therapy between initiators of Tio/Olo and ICS/LABA;
- To compare the time to first hospitalization for community-acquired pneumonia between initiators of Tio/Olo and ICS/LABA;
- To compare the number of prescriptions of rescue medication between initiators of Tio/Olo and ICS/LABA;
- To compare the annualized rate of moderate or severe COPD exacerbation between initiators of Tio/Olo and ICS/LABA..

9. RESEARCH METHODS

9.1 STUDY DESIGN

This study will be a non-interventional cohort study based on existing data (NISed).

The aim of this real world study is to assess effectiveness and safety profile between tiotropium/olodaterol (Tio/Olo) and ICS/LABA. The primary outcome of the study will be time to the first moderate or severe COPD exacerbations. Other outcomes include time to ICS/LABA/LAMA escalation, rate of escalation to triple therapy, pneumonia and rescue medication use.

9.2 SETTING

9.2.1 Study sites

Data used in this study will come from the Taiwan National Health Insurance (NHI) claims data between 2014 and 2019.

9.2.2 Study population

Inclusion criteria:

1. At least oneprescriptions for Tio/Olo combined inhaler or a LABA/ICS combined inhaler between 1st January 2014 and 31st December 2019.
   a) The first dispensing of either Tio/Olo or LABA/ICS combined inhaler will be defined as the index date;
   b) For the main analyses, only fixed dose combination (FDC) inhalers will be included.
2. Aged ≥ 40 years on the index date [redacted]
3. At least one diagnosis of COPD at any time prior to or on the index date;
4. At least one year of continuous medical and health insurance plan prior to the index date will be required to allow for a look-back period for the covariates and identification of new use of the study drugs;
5. At least one record in the health insurance system database;

Exclusion criteria:

1. Any use of Tio/Olo, ICS/LABA, or ICS/LAMA/LABA in free or fixed form for one year prior to the index date;
2. Individuals with asthma, allergic rhinitis, lung cancer, interstitial lung disease, or lung transplant identified at any time prior to the index date [redacted];

For the analysis of the primary outcome, individuals will be followed up from the index date until the earliest of the date of: the follows, whichever first 1) moderate or severe COPD exacerbation; 2) disenrollment; 3) the end of the study period; 4) death; 5) discontinuation of the index drug use as a lapse of 1.5 months without subsequent prescription (except for switching from the index ICS/LABA to a different ICS/LABA); 6) adding ICS mono on top of Tio/Olo, or adding LAMA momo on top of the index ICS/LABA

9.2.3 Study visits

Not applicable

9.2.4 Study discontinuation

Boehringer Ingelheim reserves the right to discontinue the study at any time for the following reasons:

1. Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site, investigator or research collaborator, disturbing the appropriate conduct of the study

9.3 VARIABLES

9.3.1 Exposures

Exposure of this study is defined as new initiation of Tiotropium/Olodaterol, or ICS/LABA during the study period.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

- Outcome type: Primary
- Outcome Name:Time to the first moderate or severe COPD exacerbations after index date
- Time Frame: 2014~2019
- Safety Issue (Yes/No): No

9.3.2.2 Secondary outcomes

- Outcome type: Secondary
- Outcome Name: Time to triple therapy escalation after index date
- Time Frame: 2014~2019
- Safety Issue (Yes/No): No

- Outcome type: Secondary
- Outcome Name: Incidence rate of triple therapy initiation (first event per patient)
- Time Frame: 2014~2019
- Safety Issue (Yes/No): No

- Outcome type: Secondary
- Outcome Name: Time to the first hospitalization for community-acquired pneumonia after entry
- Time Frame: 2014~2019
- Safety Issue (Yes/No): No

- Outcome type: Secondary
- Outcome Name: Annualized rate of prescriptions of rescue medications after the index date
- Calculation: annualized rate=number of prescriptions/total patient year at risk=number of prescriptions per patient year
- Time Frame: 2014~2019
- Safety Issue (Yes/No): No

- Outcome type: Secondary
- Outcome Name: Annualized rate of moderate or severe COPD exacerbation after the index date
- Calculation: annualized rate=number of moderate or severe COPD exacerbations/total patient year at risk=number of exacerbations per patient year
- Time Frame: 2014~2019
- Safety Issue (Yes/No): No

[redacted]

9.3.3 Covariates

Demographic characteristics and cohort entry information:

- Sex

- Age
- Calendar year of cohort entry
- Season of index date (winter, spring, summer, fall)

Additional, the following clinical characteristics will be measured during the 1 year pre-index baseline period:

Previous COPD treatments
- LAMA monotherapy
- LABA monotherapy
- ICS monotherapy
- LAMA/ICS combination therapy

Use of other respiratory drugs
- Mucolytics
- Theophylline
- Short-acting beta-agonists
- Short-acting muscarinic antagonists

- Previous acute COPD exacerbation (measured both 12 months and in the 30 days prior to cohort entry), categorized as 0, 1 or 2+.
  - All exacerbations (Moderate+Severe)
  - An outpatient visit with a diagnosis code for COPD in any field + a prescription for an oral corticosteroid or an antibiotic for respiratory infections (Moderate)
  - Hospitalizations or emergency room visits with a primary diagnosis for COPD (Severe)

- Hospitalizations caused by exacerbation of COPD in 12 months prior to the index date:
  - 0;
  - 1;
  - 2+;

- all-cause hospitalizations in 12 months prior to index date:
  - 0;
  - 1;
  - 2+;

- Comorbidities:
  - Cardiovascular disease
  - Cerebrovascular disease
  - Diabetes
  - Chronic kidney disease
  - Pneumonia
  - Cancer
  - Cirrhosis

- Charlson Comorbidity Index (CCI)

- History of medications dispensed in the 12 months before or on the index date will be identified from the pharmacy dispensing history:
  - Cardiovascular drugs:
    Antihypertensives
    Antiarrhythmics
    Nitrates
    heart failure medications
  - Lipid-lowering medications
  - Blood glucose-lowering medications
  - Anticoagulants and antiplatelet agents
  - Antibiotics
  - Antineoplastic agents

- COPD severity

The definition of the severity of COPD in this study was developed based on the information in previous studies, GOLD recommendations and clinical practice in Taiwan, see below. Patients who fulfil criteria for more than one category will be classified as being in the most severe category.

Criteria of COPD severity:

- Mild:
  Naïve to COPD treatment, or at least one dispensing of the following categories of medications either alone or in combination: 1) SABA or SAMA or SABA+SAMA, 2) LAMA or LABA monotherapy, 3) theophylline or mucolytics, in the 12 months before the index date;

- Moderate:
  At least one dispensing of LAMA + LABA in the 12 months before the index date;

- Severe:
  Occurrence of at least one of the following events in the 12 months before the index date:
  - Hospitalisation for COPD
  - Recorded diagnosis of pneumonia
  - Second course of antibiotics for respiratory tract infections
  - Second course of systemic corticosteroids for the treatment of COPD exacerbation
  - Two diagnoses of COPD exacerbation without hospitalisation

- Very severe:
  Occurrence of at least one of the following events in the 12 months before the index date unless other time period is specified:
  - Dispensed oxygen therapy
  - Dispensed nebuliser therapy

9.4 DATA SOURCES

Data used in this study will come from the Taiwan National Health Insurance (NHI) claims data between 2014 and 2019.

Data sources include Taiwan NHI, Taiwan cancer registry (TCR) and Taiwan Mortality Data. Taiwan Department of Statistics, Ministry of Health and Welfare is the unit designated by the government to manage health and social welfare statistical databases, and to develop data platform for academic research. Through the services provided by the Health and Welfare Data Science Center (HWDSC) of the Department of Statistics, researchers may access a wide range of health and welfare data, including claims, mortality (with cause of death) and Taiwan Cancer Registry (TCR). The HWDSC staff encrypt the national ID for all individuals according to a secure encryption algorithm that is not made known to the public. The encrypted ID is unique for all individuals and will be used for linkage between databases.

(a) National Health Insurance claims data

Taiwan National Health Insurance (NHI) started in 1995 and is a publicly funded single payer health insurance program for all residents. Health insurance for individuals is required by law and coverage is more than 99%. The majority healthcare providers in Taiwan contract with the National Health Insurance Agency in Taiwan to provide a wide range of medical services. Geographic locations of health care claims are broadly classified into 6 regions in Taiwan. Salary range, which serves as the basis for enrollees' premium calculation, can serve as a proxy indicator for socioeconomic status. Bundled payment according to the Diagnosis-Related Group system only applies in limited number of disease conditions, therefore detailed drug use information during hospitalization is also available. An added advantage of the NHI data source is the low membership turnover rate, which is particularly important for long-term follow-up study. NHI claims were based on International Classification of Disease, ninth revision, clinical modification (ICD-9-CM) codes till the end of 2015, and then switched to International Classification of Disease, tenth revision, clinical modification (ICD-10-CM) codes after 2016. Specific NHI data column please see file "column_note_in_TW_NHI_20210824" [No document #] in the database (confidential and only can be accessed by PI).

(b) Mortality data

The household registration system in Taiwan maintain birth, marital status, and death information and is administrated by the Department of Household Registration, Ministry of the Interior. Death certificates are collected through this system and transferred to the Ministry of Housing and Works (MOHW) for coding of cause of death and maintenance of the mortality database. The cause of death was coded in the ICD-9-CM format from 1990 to 2009, and in ICD-10-CM format from 2010 to 2019. This study will use the cause of death files in years 2012-2019, primarily focusing on the date of death of study subjects.

(c) Taiwan Cancer Registry data

In Taiwan, the population-based cancer registry was founded in 1979. Since then, the registry collected basic information, referred to the "20 items short-form system," on incident cancer cases (including cancer-in-situ) within one year after the initial diagnosis from hospitals with more than 50-bed capacity throughout the country. Recorded items include date of birth, gender, time and method of diagnosis, cancer site and morphology, treatment summary and

death. From 2002 onward, a "long-form" system was established to collect more detailed information of cancer staging, treatment and follow-up data from hospitals with more than 500 new cancer cases diagnosed annually. The number of recorded items increased from 20 to 65 in 2002, further to 95 in 2007, and to 114 in 2011. In 2003, Cancer Control Act was introduced with all reporting hospitals mandated to submit cancer patient information to the cancer registry. To ensure quality of cancer registries and enhancing the quality of cancer registry data, Taiwan Society of Cancer Registry was established in 2006, conducting random medical record review to ensure data accuracy since 2010. TCR data from 2000 through 2018 will be used for this study.

9.5 STUDY SIZE

Based on the result of study by Wedzicha JA, et al, [P16-05628] (where at least 25% of the patients in the Tio/Olo group have a first moderate or severe exacerbation at 127 days [95% CI, 107 to 149] and in ICS/LABA group at 87 days [95% CI, 81 to 103] (HR = 0.78, [95% CI 0.70 to 0.86])), we assume that at least 25% of patients in the ICS/LABA experienced a first moderate or severe COPD exacerbation at 103 days and the HR of Tio/Olo to LABA/ICS is 0.9. For a study duration of 6 years, a total of 4978 patients (2489 patients each arm) are needed to detect the difference between the two arms with 2-sided alpha of 0.05 and 90% power

9.6 DATA MANAGEMENT

Full details of the data management plan are documented in a separate NIS-Data Management and Review Plan (NIS-DMRP).

9.7 DATA ANALYSIS

Full details of the statistical analysis will be documented in the SEAP, which will be finalized before the end of data collection.

9.7.1 Main analysis

All variables, including patient characteristics, baseline measures, and outcomes, will be analyzed descriptively.

- 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.

All analyses will be presented for each treatment group (Tio+Olo vs LABA/ICS) overall. We will first describe formation of the study cohort. Propensity score matching will be used to balance the baseline characteristics of patients in the two treatment groups. The covariates used to calculate the propensity score would be specified in the SEAP. All the analyses will be performed on patients after propensity score matching. Patient characteristics at baseline in patients treated with Tio+Olo and patients treated with LABA/ICS will be described separately using standard descriptive statistics after propensity score matching. Absolute standardized differences (ASDs) will be used to compare the characteristics between the two

groups after propensity score matching, in which a >0.1 ASD indicates a meaningful difference.

For the analysis of the primary outcome, individuals will be followed up from the index date until the first moderate or severe COPD exacerbation. The data after the earliest date of the following would be censored: 1) disenrollment; 2) the end of the study period; 3) death; 4) discontinuation of the index drug (except for switching from the index ICS/LABA to a different ICS/LABA); 5) escalation to triple therapies (ICS/LAMA/LABA free or fix dose combination). Cox proportional hazard regression model will be used to compare the time to event between the two treatment groups, while accounting for the potential baseline differences between them. Other known predictors will also be included in the model as covariates. It will provide an estimate of the hazard ratio (HR) of time to the first moderate or severe COPD exacerbation associated with Tio+Olo use relative to LABA/ICS use, along with 95% confidence intervals (CI). The analysis will be on-treatment.

The analysis of the secondary objectives related to time to triple therapy escalation, time to first hospitalization for community-acquired pneumonia, will use a Cox proportional hazard regression model with an as-treated approach, similar to that of the primary analysis. The estimate of hazard ratio (HR) of time to triple therapy escalation and first hospitalization for community-acquired pneumonia associated with Tio+Olo use relative to LABA/ICS use, along with 95% confidence intervals (CI) will be provided. For the analysis of these time-to-event outcomes, patients will be followed up until until the earliest of the date of the follows, whichever happened first 1) outcome event of interest; 2) disenrollment; 3) the end of the study period; 4) death; 5) discontinuation of the index drug (except for switching from the index ICS/LABA to a different ICS/LABA).

For incidence rate of triple therapy initiation (first event per patient), annualized rate of moderate or severe COPD exacerbations, and annualized number of prescriptions of rescue medications will be calculated by cohort.

For continuous and categorical variables, we will use standard descriptive statistics to describe. For incidence rates, it will be calculated for each cohort as follows:
Incidence rate among the Tio+Olo cohort = (total number of patients in the Tio+Olo cohort experiencing an event of interest for the first time during the given time period) / (total person-time at risk from current use of Tio+Olo during the given period)

Incidence rate among the comparison cohort = (total number of patients in the comparator LABA/ICS cohort experiencing an event of interest for the first time during the given time period) / (total person-time at risk from current use of comparator LABA/ICS during the given period)

The incidence rate ratio (IRR) and incidence difference for the outcome in the Tio+Olo - exposed group relative to that in the comparator group will be derived as follows:

Incidence rate ratio = incidence rate from the Tio+Olo cohort divided by the incidence rate from the matched comparator cohort.

Incidence difference = incidence rate from the Tio+Olo cohort – incidence rate from the matched comparator cohort

The IRRs will be calculated. Incidence differences and their 95% confidence intervals will also be derived.

For annualized rates, it will be calculated for each cohort as follows:
Annualized rate among the Tio+Olo cohort = (total number of events in the Tio+Olo cohort during the given time period) / (total person-time at risk from current use of Tio+Olo during the given period)

Annualized rate among the comparison cohort = (total number of events in the comparator LABA/ICS cohort during the given time period) / (total person-time at risk from current use of comparator LABA/ICS during the given period)

The incidence rate ratio (IRR) for the triple therapy initiation in the Tio+Olo - exposed group relative to that in the comparator group, along with 95% confidence intervals will be derived using negative binomial model.

For annualized rate of moderate or severe COPD exacerbations and annualized number of prescriptions of rescue medications, the ratio of Tio+Olo – exposed group relative to LABA/ICS group, along with 95% confidence intervals will be derived using negative binomial model.

[redacted]

9.7.3 Safety 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 propotol, 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.

9.8 QUALITY CONTROL

The study will strictly follow relevant BI SOPs. In addition, this study will follow key elements of the Guideline for Good Pharmacoepidemiology Practices (GPP). The statistical

analytic approach will be reviewed/repeated by a second analyst to ensure quality control. The study report will be reviewed, approved and archived per BI SOP

9.9 LIMITATIONS OF THE RESEARCH METHODS

Some important potential confounders are not available in the Taiwan NHI dataset. For example, pulmonary function data and duration of COPD may not be available in the data set. These variables will not be calculated so there might be confounding bias in the study. The definition for COPD severity was developed based on the previous evidence, treatment guideline and the clinical practice in Taiwan to reduce the bias.

COPD patients concomitant with asthma may be different from COPD patients without asthma in terms of the disease natural course, treatment regimen, and response to drugs. Therefore, COPD patients concomitant with asthma will be excluded from the primary analysis. Previous studies suggested that there might be misdiagnosis between COPD and asthma. To further exclude potential asthma patients, [redacted]

In a database study like this, we can only rely on the available information to define outcomes, exposure and covariates. There will be misclassification of study variables. In the analyses, whenever possible, validated algorithm will be used to reduce misclassifications.

9.10 OTHER ASPECTS

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 the investigator's study-related files and correspondence.

9.10.2 Study records

9.10.2.1 Source documents

Not applicable

Data are provided by Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan. Data access was only available through dedicated data analysis areas within the Ministry. Individual level data are not allowed to be brought outside of the Ministry.

9.10.2.2 Direct access to source data and documents

Not applicable.

Data are provided by Health and Welfare Data Science Center, Ministry of Health and Welfare, Taiwan. Data access was only available through dedicated data analysis areas within the Ministry. Individual level data are not allowed to be brought outside of the Ministry.

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, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant BI Standard Operating Procedures (SOPs).

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This NIS 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

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.

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.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Not applicable

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

Not applicable based on secondary use of data without any potential that any employee of BI or agent working on behalf of BI will access individually identifiable patient data.

This study is a non-interventional study based on secondary data without involving review or analysis of any individual patient level data. The data is extracted and analyzed in an aggregate manner.

11.3 REPORTING TO HEALTH AUTHORITIES

This study is a non-interventional study based on secondary data, which will not involve individual medical record review. Therefore, no AE collection of this study will be performed and reported to Chinese regulatory authorities.

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

P21-01394 Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2021 REPORT) . https://goldcopd.org/goldreports/.

P07-11820 Wedzicha JA et al. The prevention of COPD exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med.2008;177:19-26.

P16-05628 Wedzicha J A, et al. Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD. N Engl J Med, 2016, 2016(374): 2222-2234

R11-4318 Guidelines for Good Pharmacoepidemiology Practices (GPP) (revision 3: June 2015). Guidelines for Good Pharmacoepidemiology Practices (GPP) - International Society for Pharmacoepidemiology (access date: 1st March 2022) ; International Society for Pharmacoepidemiology (ISPE); 2015.

R13-1970 European Medicines Agency (EMA), Heads of Medicines Agencies (HMA); Guideline on good pharmacovigilance practices (GVP): module VI - management and reporting of adverse reactions to medicinal products (28 July 2017 EMA/873138/2011 Rev 2). Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2) (europa.eu) (access date: 1st March 2022); European Medicines Agency (EMA), Heads of Medicines Agencies (HMA); 2017.

13.2 UNPUBLISHED REFERENCES

No document # Taiwan National Health Insurance, *column_note_in_TW_NHI_20210824*. 24 Aug 2021

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
None			

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:
Effectiveness of Maintenance Treatment with Tiotropium + Olodaterol in Comparison to Inhaled Corticosteroids + Long-acting β2 agonists in COPD patients in Taiwan: a non-interventional study based on the Taiwan National Health Insurance (NHI) data.

EU PAS Register® number:
Study reference number (if applicable): 1237-0110

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

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

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.3.2
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.1
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.4
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2.2
4.2.2 Age and sex	☒	☐	☐	9.2.2
4.2.3 Country of origin	☒	☐	☐	9.4
4.2.4 Disease/indication	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Specifics will be described in SEAP.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Specifics will be described in SEAP.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.1
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☐	☒	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☐	☐	☒	

Comments:

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

Comments:

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

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BI Study Number: 1237-0110 **c38660249-01**
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Comments:

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

Date: May 23, 2022

Signature: [redacted]

001-MCS-90-118_RD-23 (2.0) / Saved on: 02 Jul 2020

ANNEX 3. ADDITIONAL INFORMATION

None

ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol must be sent for review to the following individuals **prior to approval**.

Reviewer	NIS involving BI product(s)	NIS not involving BI product(s)	
		Global NIS	Local NIS
NIS Lead	X	X	X
Global TM Epi	X	X	X
Global TMM / TMMA / TM Market Access	X	X	
Global Project Statistician	X	X	
Global TM RA	X		
Global PVWG Chair	X		
GPV SC	X	X	X
Global CTIS representative	X		
Local Medical Director	X (if local study)		X
Local Head MAcc / HEOR Director	X (if local study)		X
Global TA Head Epi*	X	X	
Global TA Head Clinical Development / Medical Affairs / Market Access*	X	X	
Global TA Head PV RM*	X		
RWE CoE	X	X	
PSTAT / PSTAT-MA (for NISnd only)	X	X	X
NIS DM	X	X	X
Local Head MA/Clinical Development			X (does not apply to NISed without chart abstraction)

* *After review by Global TM for function*

Study Title: Effectiveness of Maintenance Treatment with Tiotropium + Olodaterol in Comparison to Inhaled Corticosteroids + Long-acting β2 agonists in COPD patients in Taiwan: a non-interventional study based on the Taiwan National Health Insurance (NHI) data.

Study Number: 1237-0110

Protocol Version:1.0

I herewith certify that I agree to the content of the study protocol and to all documents referenced in the study protocol.
Note: Please insert respective signatories with regard to the SOP.

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____