Non-Interventional Study (NIS) Protocol

Document Number:	c38644780-01
BI Study Number:	1237-0109
BI Investigational Product(s):	Spiolto Respimat
Title:	Safety profile of Tiotropium + Olodaterol used as maintenance treatment in COPD patients in Taiwan: a non-interventional study based on the Taiwan National Health Insurance (NHI) data
Brief lay title:	Safety of Tiotropium + Olodaterol in COPD patients in Taiwan: a non-interventional study based on the Taiwan National Health Insurance (NHI) data
Protocol version identifier:	1.0
Date of last version of protocol:	Not applicable
PASS:	Yes
EU PAS register number:	Study not registered
Active substance:	Tiotropium + Olodaterol (R03AL06)
Medicinal product:	Spiolto Respimat
Product reference:	BC26735443
Procedure number:	Not applicable
Marketing authorization holder(s):	Boehringer Ingelheim International GmbH
Joint PASS:	No
Research question and objectives:	To estimate the incidence of safety outcomes in patients with COPD who initiated Tiotropium / Olodaterol (Tio/Olo)
Country(-ies) of study:	TCM (The Chinese Market)

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Marketing authorization holder(s):	Boehringer Ingelheim International GmbH
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Signature of EU-QPPV:	
Date:	11 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
NHIRD	Taiwan National Health Insurance Research Database
NIS	Non-Interventional Study
Olo	Olodaterol
PASS	Post-Authorization Safety Study
SAE	Serious Adverse Event
Tio	Tiotropium

3. RESPONSIBLE PARTIES

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4. ABSTRACT

According to requirement by local regulatory authority, the safety information of newly approved drugs is to be collected to provide supplementary data to those identified in randomized clinical studies within 5 years period after approval. This is a non-interventional study based on existing data. It will provide the safety information of Spiolto (tiotropium+olodaterol) in Chinese patients with chronic obstructive pulmonary disease (COPD) in routine clinical practice in Taiwan.

Data used in this study will come from the Taiwan National Health Insurance (NHI) claims data between 2014 and 2019. There will be around 4,000 patients using Tiotropium/ Olodaterol (Tio+Olo) in the Taiwan National Health Insurance Research Database (NHIRD) that can be enrolled in this study. The primary outcome of this study will be incidence of adverse events in patients with COPD treated with Tio+Olo. Other outcomes include the baseline characteristics of patients who initiated Tio+Olo and comparing the baseline characteristics of patients who initiated Tio+Olo with those treated with other LAMA/LABAs in the Taiwan NHIRD database.

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Name of finished medicinal product: Spiolto Respimat			
Name of active ingredient: Tiotropium + Olodaterol {R03AL06}			
Protocol date: 11 May 2022	**Study number:** 1237.0109	**Version/Revision:** 1.0	**Version/Revision date:** NA
Title of study:	Safety profile of Tiotropium + Olodaterol used as maintenance treatment in COPD patients in Taiwan: a non-interventional study based on the Taiwan National Health Insurance (NHI) data		
Rationale and background:	According to requirement by local regulatory authority, the safety information of newly approved drugs is to be collected to provide supplementary data to those identified in randomized clinical studies within 5 years period after approval. This is a non-interventional study based on existing data. It will provide the safety information of Spiolto (tiotropium+olodaterol) in Chinese patients with chronic obstructive pulmonary disease (COPD) in routine clinical practice in Taiwan. COPD is a leading cause of morbidity and mortality throughout the world and now is the third leading cause of mortality in China. The prevalence of COPD in China was 13.7% in population who were ≥40 years old [R22-0908]. Spiriva Respimat® (tiotropium 5µg qd) has been approved worldwide for over one decade and provides improvements on lung function and symptoms, and prevents exacerbations for patients with COPD [P13-11053]. Olodaterol, a long acting β2–agonist, in the completed global clinical development for COPD, has shown a 24-hour duration of action profile, rapid onset of action, and an optimized inhaled LABA profile. Also, olodaterol at doses of 5µg once daily is safe and well tolerated [P05-10481]. The combination of tiotropium and olodaterol in a single Respimat®		

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	Inhaler device provides a rational target for optimizing bronchodilator treatment of COPD, the safety and efficacy profile of which has been demonstrated in large clinical development program with no concerns of any new safety issues comparing with placebo and its mono-components [P15-03344, P18-02990].China participated Tio+Olo Respimat® inhaler pivotal trials. In Chinese patients, the safety finding is in line with those in total trial population and the efficacy is similar to that in all trial population [c03489048-01]. In conclusion, the safety and efficacy profile of tiotropium + olodaterol (Tio+Olo) 5/5µg delivered via the RESPIMAT inhaler has been demonstrated in entire completed global clinical program (Tio+Olo) with no concerns of any new safety issues and well-tolerated.		
Research question and objectives:	Primary objective: • To estimate the incidence rate of safety outcomes in Chinese patients with COPD who initiated Tio/Olo between 1st January 2014 and 31st December 2019; Secondary objective: • To compare the baseline characteristics of patients between those treated with Tio/Olo and those with other LAMA/LABAs FDC (Vilanterol/Umeclidinium; INDACATEROL/ GLYCOPYRRONIUM) or (LABA: Salmeterol; Formoterol; Procaterol; Indacaterol; Olodaterol, LAMA: Tiotropium bromide; Glycopyrrolate; Umeclidinium) free combination;		
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 (fixed dose combination (FDC) or free combination) as a new initiation between 1st January 2014 and 31st December 2019. 2. Aged ≥ 40 years on the index date (The first dispensing of Tio/Olo combined inhaler will be defined as the index date); 3. At least one diagnosis of COPD (ICD9: 491.x, 492.x, 496; ICD10: J41.x, J42, J43.x, J44.x) 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 in free or fixed form within 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. Another cohort of patients using other LAMA/LABA (FDC or free combination) will also be enrolled to collect the information of baseline characteristics to be compared with those of patients treated with Tio+Olo. The Inclusion/Exclusion criteria are similar with those of Tio+Olo, which include: Inclusion criteria: 1. At least one prescription for LAMA+LABA (FDC or free combination) other than Tio/Olo as a new initiation between 1st		

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	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 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.		
Variables:	Exposures: Exposure of this study is defined as new initiation of Tiotropium/Olodaterol during the study period between 1st January 2014 and 31st December 2019. Outcomes: Primary outcome: • Incidence rate of adverse events in patients with COPD treated with Tio+Olo Secondary outcomes: • To describe the baseline characteristics of patients who initiated Tio+Olo;		

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	• To compare the baseline characteristics of patients who initiated Tio+Olo with those treated with other LAMA/LABAs in the Taiwan NHIRD database; Covariates: Including sex, age, calendar year of cohort entry, season of index date (winter, spring, summer, fall) Additional characteristics will be defined during the 1 year pre-index baseline period: specific previous COPD treatments, previous COPD exacerbation, hospitalizations caused by exacerbation of heart failure, all-cause hospitalizations, comorbidities, Charlson Comorbidity Index (CCI), history of medications dispensed.		
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.		

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(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 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

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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.

Study size:

There will be around 4,000 patients using Tio+Olo in the Taiwan NHIRD that can be enrolled in this study.

The following table provides an estimation and 95% CI for incidence rate of each AE among new users of Spiolto® Respimat® for the study

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duration of 6 years.

Adverse events	Incidence rates per 100 patient years	N	95% CI	
			Lower	Upper
Pneumonia	4.69	4000	4.308	5.083
COPD exacerbation	55.42	4000	54.092	56.758
Arrhythmia	1.82	4000	1.583	2.067
Supraventricular tachycardia	1.16	4000	0.975	1.358

Data analysis:

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

We will first describe formation of the study cohort. Patient characteristics at baseline will be described using standard descriptive statistics. For the analysis of primary outcome, the incidence rates of AEs during entire follow-up period will be calculated based on the following formula:

(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)

Absolute standardized differences (ASDs) will be used to compare the

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	baseline characteristics between the two groups, in which a >0.1 ASD indicates a meaningful difference. As an objective of the study was to compare the clinical attributes of patients in each study group. The standardized difference will be used as a parameter to quantify the between-group differences for each clinical attribute. This metric is commonly used in studies utilizing secondary health data, in which a standardized difference of larger than 0.1 indicates a meaningful difference with respect to the clinical attribute between the two study groups.		
Milestones:	Feasibility assessment: 2020. Q3 EU PAS Registration: 01-Jun-2022 Full analysis: • Touching the data: 15-Jun-2022 • Study result: 30-Jul-2022 Publication's timeline: Abstract: 2023 ATS		

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	Oct 2020 (completed)
Feasibility assessment	Qct 2020 (completed)
EU PAS Registration	01/Jun/2022
Full analysis	
Accessing the data	15/Jun/2022
Complete data analysis	30/June/2022
Final report of study results:	15/Oct/2022

7. RATIONALE AND BACKGROUND

According to requirement by local regulatory authority, the safety information of newly approved drugs is to be collected to provide supplementary data to those identified in randomized clinical studies within 5 years period after approval.

This is a non-interventional study based on existing data. It will provide the safety information of Spiolto (tiotropium+olodaterol) in Chinese patients with chronic obstructive pulmonary disease (COPD) in routine clinical practice in Taiwan.

COPD is a leading cause of morbidity and mortality throughout the world and now is the third leading cause of mortality in China. The prevalence of COPD in China was 13.7% in population who were ≥40 years old [R22-0908].

Spiriva Respimat® (tiotropium 5µg qd) has been approved worldwide for over one decade and provides improvements on lung function and symptoms, and prevents exacerbations for patients with COPD [P13-11053]. Olodaterol, a long acting β2–agonist, in the completed global clinical development for COPD, has shown a 24-hour duration of action profile, rapid onset of action, and an optimized inhaled LABA profile.

Also, olodaterol at doses of 5µg once daily is safe and well tolerated [P05-10481].

The combination of tiotropium and olodaterol in a single Respimat® Inhaler device provides a rational target for optimizing bronchodilator treatment of COPD, the safety and efficacy profile of which has been demonstrated in large clinical development program with no concerns of any new safety issues comparing with placebo and its mono-components [P15-03344, P18-02990]. China participated Tio+Olo Respimat® inhaler pivotal trials. In Chinese patients, the safety finding is in line with those in total trial population and the efficacy is similar to that in all trial population [c03489048-01].

In conclusion, the safety and efficacy profile of tiotropium + olodaterol (Tio+Olo) 5/5µg delivered via the RESPIMAT inhaler has been demonstrated in entire completed global clinical program (Tio+Olo) with no concerns of any new safety issues and well-tolerated.

8. RESEARCH QUESTION AND OBJECTIVES

Primary objective:

- To estimate the incidence rate of safety outcomes in Chinese patients with COPD who initiated Tio/Olo;

Secondary objective:

- To compare the baseline characteristics of patients between those treated with Tio/Olo and those with other LAMA/LABAs;

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 the safety profile of tiotropium/olodaterol (Tio/Olo). The primary outcome of this study will be the incidence rate of adverse events in patients with COPD treated with Tio+Olo. Other outcomes include the baseline characteristics of patients who initiated Tio+Olo and comparing the baseline characteristics of patients who initiated Tio+Olo with those treated with other LAMA/LABAs in the Taiwan NHIRD database.

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 one prescription for Tio+Olo (FDC or free combination) as a new initiation 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 Tio+Olo in free or fixed form within 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;

Another cohort of patients using other LAMA/LABAs (FDC or free combination) will also be enrolled to collect the information of baseline characteristics to be compared with those of patients treated with Tio+Olo. The Inclusion/Exclusion criteria are similar with those of Tio+Olo, which include:

Inclusion criteria:

1. At least one prescription for LAMA+LABA (FDC or free combination) other than Tio/Olo as a new initiation 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 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.

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: 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 Tio/Olo during the study period between 1st January 2014 and 31st December 2019. The duration of exposure is defined as the period between the index date and the end of follow-up which is described in section 9.7.1.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

- Outcome type: Primary
- Outcome Name: Incidence rate of adverse events in patients with COPD treated with Tio+Olo
- Time Frame: 2014~2019
- Safety Issue (Yes/No): Yes

9.3.2.2 Secondary outcomes

- Outcome type: Secondary
- Outcome Name: Baseline characteristics of patients who initiated Tio+Olo or other LAMA/LABA
- Time Frame: 2014~2019
- Safety Issue (Yes/No): No

9.3.2.3 Further outcomes

None

9.3.3 Covariates

Covariates:

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

Additional characteristics will be defined during the 1 year pre-index baseline period:

- Specific previous COPD treatments
  - LAMA monotherapy
  - LABA monotherapy
  - ICS monotherapy
  - LAMA/ICS combination therapy
  - LAMA+LABA free combinations
- 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 index date:
  - 0;
  - 1;
  - >=2;
- All-cause hospitalizations in 12 months prior to index date;
- 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

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 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 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

There will be around 4,000 patients using Tio+Olo in the Taiwan NHIRD that can be enrolled in this study.

Assuming that observed incidence rates of each AE from Ferguson paper could be replicated, and 4000 patients were enrolled in the study in a uniform distribution from 0 to 6 years. The estimation and 95% CI for incidence rate of each AE among new users of Spiolto® Respimat® for the study duration of 6 years were calculated based on Poisson distribution and provided as the following table.

Table 1 Incidence rate of AEs

Adverse events	Incidence rate per 100 patient years	N	95% CI	
			Lower	Upper
Pneumonia	4.69	4000	4.308	5.083
COPD exacerbation	55.42	4000	54.092	56.758
Arrhythmia	1.82	4000	1.583	2.067
Supraventricular tachycardia	1.16	4000	0.975	1.358

Incidence rate of AEs from Ref: G.T. Ferguson, et al., Respiratory Medicine 143 (2018) 67–73.

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 analysed 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.

We will first describe formation of the study cohort. Patient characteristics at baseline will be described using standard descriptive statistics. Absolute standardized differences (ASDs) will be used to compare the characteristics between the two groups, in which a >0.1 ASD indicates a meaningful difference.

As an objective of the study was to compare the clinical attributes of patients in each study group. The standardized difference will be used as a parameter to quantify the between-group differences for each clinical attribute. This is metric is commonly used in studies utilizing secondary health data, in which a standardized difference of larger than 0.1 indicates a meaningful difference with respect to the clinical attribute between the two study groups.

For the analysis of primary outcome, the incidence rates of AEs during entire follow-up period will be calculated based on the following formula:

(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)

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 occurs first 1) disenrollment; 2) the end of the study period; 3) death; 4) discontinuation of the index drug; 5) adding ICS mono on top of Tio/Olo.

9.7.2 Further analysis

One sensitivity analysis will exclude patients with adverse events happened 30 days prior to index date.

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 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.

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) and the Guideline for Good Pharmacovigilance Practices (GVP).

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.

Greater details are documented in the NIS-DMRP.

9.9 LIMITATIONS OF THE RESEARCH METHODS

In this study, we will describe the incidence rate of AEs among patients who initiate Spiolto. Patients taking Spiolto might be different from patients taking only

maintenance therapies (so-called channelling) in terms of their baseline characteristics, which makes it difficult to interpret the results. To help put the results into perspective, we will compare the baseline characteristics between patients who initiated Spiolto and patients treated with other LAMA/LABAs to understand the potential channelling.

In a database study like this, we can only rely on the available information to define outcomes, exposure and covariates. Misclassification may happen during this process.

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 were 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 were 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. This study was classified as a post authorization safety study, and the study report would be reported to health authorities as drug intensive monitoring according to local regulation.

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

R22-0908 Wang C, Xu J, Yang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study) a national cross-sectional study. Lancet, 2018, 391(10131): 1706-1717.

P13-11053 Torchio, Roberto. (2013). Tiotropium Respimat inhaler and the risk of death in COPD.. New England Journal of Medicine. 369. 1491.

P05-10481 Hochrainer D, Hölz H, Kreher C, Scaffidi L, Spallek M, Wachtel H. Comparison of the aerosol velocity and spray duration of Respimat Soft Mist inhaler and pressurized metered dose inhalers. J Aerosol Med. 2005 Fall;18(3):273-82. doi: 10.1089/jam.2005.18.273. PMID: 16181002.

P15-03344 Buhl R, Maltais F, Abrahams R, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4) [published correction appears in Eur Respir J. 2015 Jun;45(6):1763]. Eur Respir J. 2015;45(4):969-979. doi:10.1183/09031936.00136014

P18-02990 Calverley PMA, Anzueto AR, Carter K, Grönke L, Hallmann C, Jenkins C, Wedzicha J, Rabe KF. Tiotropium and olodaterol in the prevention of chronic obstructive pulmonary disease exacerbations (DYNAGITO): a double-blind, randomized, parallel-group, active-controlled trial. Lancet Respir Med. 2018 May;6(5):337-344. doi: 10.1016/S2213-2600(18)30102-4. Epub 2018 Apr 5. PMID: 29605624.

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

c03489048-01 China Clinical Overview. 7 Apr 2015

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:
Safety profile of Tiotropium + Olodaterol used as maintenance treatment 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): 1237-0109

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®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Milestone is updated in protocol.

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 generalized)	☒	☐	☐	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)	☒	☐	☐	9.7.3/11

Comments:

3.5 Secondary data for observational study

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	☒	☐	☐	9.7.1
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 categorizing 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 categorized according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorized 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?	☒	☐	☐	9.2.2

Comments:

5.4 There is only one dosage of Spiolto and exposure duration in observational studies is uncertain

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)	☐	☒	☐	

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

The Outcome and Analysis sections will be complemented with 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)	☐	☒	☐	
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)	☐	☒	☐	

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)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
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:

9.3 Details 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?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2

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:

11.1 Details will be described in DMRP.

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?	☐	☒	☐	
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).	☐	☐	☒	
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:

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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)?	☐	☐	☒	
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

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

Date: May 11, 2022

Signature: [redacted]

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: Safety profile of Tiotropium + Olodaterol used as maintenance treatment in COPD patients in Taiwan: a non-interventional study based on the Taiwan National Health Insurance (NHI) data

Study Number: 1237-0109

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**:** _____