STATISTICAL AND EPIDEMIOLOGICAL ANALYSIS PLAN (SEAP) FOR NON-INTERVENTIONAL STUDIES (NIS)

Document Number:	c40729787-01
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.
SEAP version identifier:	1.0
Date of last version of SEAP:	Not applicable
NIS Statistician [SEAP author]	The SEAP is prepared by the principal investigator, [redacted], an epidemiologist, but not a statistician.
NIS Lead [SEAP reviewer]	[redacted]
NIS Data Manager [SEAP reviewer]	[redacted]

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1. LIST OF ABBREVIATIONS

BI	Boehringer Ingelheim
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DMRP	Data management and review plan
ICS	Inhaled corticolsteroids
IQR	Interquartile range
LABA	Long-acting β2-agonists
LAMA	Long-acting muscarinic antagonists
NHI	Taiwan National Health Insurance
NIS	Non-interventional study
Olo	Olodaterol
PS	Propensity score
SEAP	Statistical and epidemiological analysis plan
Tio	Tiotropium

2. RESPONSIBLE PARTIES

NIS Statistician [SEAP author]: [redacted] the principal investigator who is an epidemiologist and not a statistician

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- BI NIS Lead [SEAP reviewer] (in all cases): [redacted]
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3. PURPOSE AND SCOPE

COPD is a leading cause of morbidity and mortality throughout the world. 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. The aim of this real world study is to assess effectiveness and safety profile between inhaled tiotropium/olodaterol (Tio/Olo) and corticolsteroids / long-acting β2-agonists (CS/LABA).

4. AMENDMENTS AND UPDATES

None

5. RESEARCH QUESTION AND OBJECTIVE

Primary objective:

- To compare time to the first moderate or severe COPD exacerbations between initiators of Tio/Olo and 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 between 1st January 2014 and 31st December 2019 apply to secondary objectives above.

6. RESEARCH METHODS

6.1 STUDY DESIGN

This study will be a non-interventional cohort study using Taiwan National Health Insurance (NHI) claims database, Taiwan Cancer Registry (TCR) and Taiwan Mortality Data. It is a secondary health data environment with relevant information on treatment and disease outcomes of COPD patients among a population of predominantly ethnic Han Chinese. As a publicly funded single payor health insurance program, a wide range health services, including hospital care, emergency visits, ambulatory clinic services, and prescription drugs are covered for virtually all Taiwan residents. The complete capture of health care encounters reimbursed by NHI among a defined group of patients has served as the basis of many longitudinal studies that evaluated safety profiles of prescribed medications.

Health data that are available for research are provided by the Health and Welfare Data Science Center (HWDSC) of the Department of Statistics, Ministry of Health and Welfare. The HWDSC staff encrypt the national ID for all individuals according to a secure encryption algorithm that is specific for each study, and the encrypted ID all individuals is used for linkage between databases. While the study will provide safety data on drugs of interest, from a regulatory perspective the source data are not auditable, nor de-identified individual level data be brought outside of HWDSC for independent verification of analysis.

Limitations of health insurance databases are well-known, as there is no information on results of clinical parameters (such as blood pressure and body mass index), clinical examinations (such as spirometry findings), or life style attributes (such as smoking). A specific items that needs to be considered for this particular study project is whether the findings are generalizable to COPD patients in China. While there is high similarity between COPD patients in Taiwan and those in China in terms of ethnicity and dietary patterns, management patterns for COPD patients, including comorbid conditions, concomitant medications, and use of traditional Chinese medication regimens, may be different.

Taking into account the strengths and potential limitations of the data source, the population-based nature and potentially large study size of patients on drugs of interest are the major reasons that this data source is a viable option for the study.

6.2 SETTING

Incident Tio/Olo combined inhaler or a ICS/LABA combined inhaler use would be identified from the Taiwan National Health Insurance (NHI) claims data through 2014 to 2019, with a 1-year look-back period to define new user.

6.3 STUDY POPULATION

Inclusion Criteria:

1. At least one prescription 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 (ICD9: 491.x, 492.x, 496; ICD10: J41.x, J42, J43.x, J44.x) at any time prior to or on the index date;

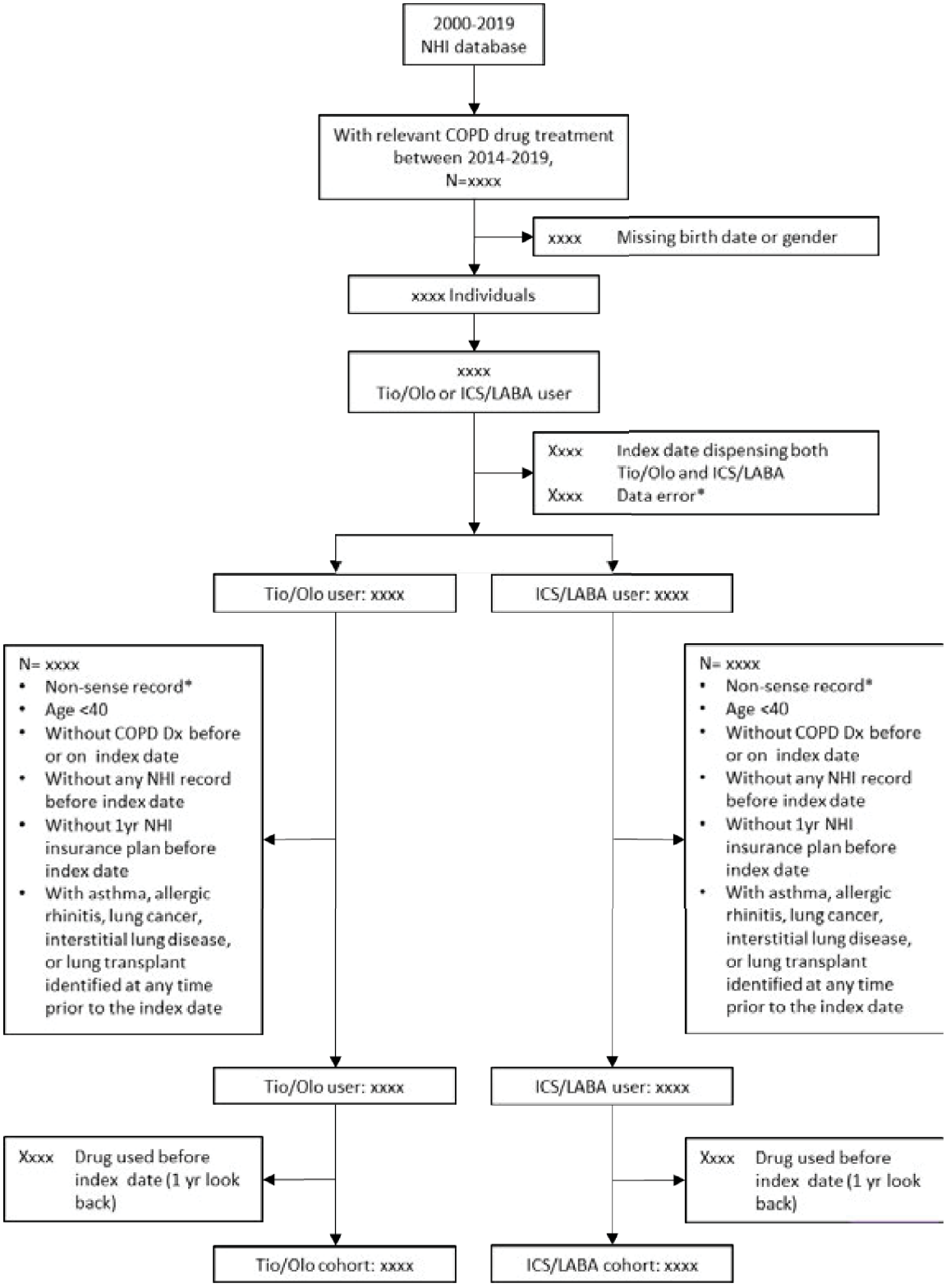
4. At least one year of continuous medical and health insurance plan prior to the index date will be required to allow for a look-back period for the covariates and identification of new use of the study drugs;
5. At least one record in the health insurance system database.

Exclusion Criteria:

1. Any use of LAMA/LABA, ICS/LABA, or ICS/LAMA/LABA in free or fixed form for one year prior to the index date (the free combination will be defined as the prescriptions of the interest products within 30 days of each other);
2. Individuals with asthma, allergic rhinitis, lung cancer, interstitial lung disease, or lung transplant identified at any time prior to the index date [redacted];

Relevant ICD codes and procedure code are provided in the Annex.

Figure 1. Patient selection flow chart



6.4 STUDY VISITS

Not applicable.

7. VARIABLES

7.1 EXPOSURES

Exposure of this study is defined as new initiation of Tio/Olo or ICS/LABA (FDC) during the study period. Detailed drug codes are provided in the Annex.

7.2 OUTCOMES

7.2.1 Primary outcomes

- **Time to the first moderate or severe COPD exacerbations after index date**

The definition of moderate or severe COPD exacerbation:

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

Detailed diagnosis codes are listed in Annex.

Tio/Olo users will be matched to the comparator through 1:1 propensity score matchingFor the analysis of the primary outcome, individuals will be followed up from the index date until the first moderate or severe COPD exacerbation. For detailed, please refer to section 10.1. As time-to-event data, the main analysis will be univariate proportional hazard regression analysis to estimate the hazard ratio (Tio/Olo vs. comparator) and its 95% confidence interval (CI). Detailed analytic approach is described in Section 10.1.

7.2.2 Secondary outcomes

Analysis of the secondary outcomes will be applied to the propensity-score matched cohorts developed for the primary outcome of interest. Detailed description of the analysis approach is described in Section 10.1

(1). Time to triple therapy escalation after index date

Triple therapy escalation, defined as any LAMA/LABA/ICS fixed dose combination or any concurrent use for 30 consecutive days of the following:

a. any LAMA/LABA fixed dose combination + any ICS single formulation
b. any LAMA single formulation + any LABA/ICS fixed dose combination
c. any LAMA single formulation + any LABA single formulation + any ICS single formulation

The event date will be the 30th day after initiation of triple therapy.

As time-to-event data, the analysis will be univariate proportional hazard regression analysis to estimate the hazard ratio (Tio/Olo vs. comparator) and its 95% CI.

(2). Incidence rate of triple therapy initiation (first event per patient)

Triple therapy escalation, defined as any LAMA/LABA/ICS fixed dose combination or any concurrent use for 30 consecutive days of the following:

a. any LAMA/LABA fixed dose combination + any ICS single formulation
b. any LAMA single formulation + any LABA/ICS fixed dose combination
c. any LAMA single formulation + any LABA single formulation + any ICS single formulation

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 IRR and their 95% CIs will be calculated using univariate negative binomial model. Incidence differences and their 95% confidence intervals will also be derived.

(3). Time to first hospitalization for community-acquired pneumonia after entry

Community-acquired pneumonia related diagnosis codes and operational definition are listed in the Annex.

As time-to-event data, the analysis will be univariate proportional hazard regression analysis to estimate the hazard ratio (Tio/Olo vs. comparator) and its 95% confidence interval (CI).

(4). Annualized rate of prescriptions of rescue medications after the index date

Rescue medications are defined as free or combination use of SABA or SAMA. Detailed drug ATC codes are listed in Annex.

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-year 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-year at risk from current use of comparator LABA/ICS during the given period)

For annualized rate and total number of prescriptions of rescue medications, the rate ratio of Tio+Olo – exposed group relative to LABA/ICS group, along with 95% CI will be derived using univariate negative binomial model.

(5). Annualized rate of moderate or severe COPD exacerbation after the index date

The definition of moderate or severe COPD exacerbation:

a. Moderate exacerbations will be defined as an outpatient visit with a diagnosis code for COPD in any field + a prescription for an oral corticosteroid or an antibiotic for respiratory infections, prescriptions within 30 days of each other were considered as continuation of the initial exacerbation.
b. Severe exacerbations will be defined as a hospitalization or emergency room visit with a primary diagnosis for COPD; hospitalizations or emergency room visits within 30 days of each other were considered as continuation of the initial exacerbation.

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-year 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-year at risk from current use of comparator LABA/ICS during the given period)

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

[redacted]

7.3 COVARIATES

Demographic characteristics and cohort entry information:

- Sex
- Age
- Calendar year of cohort entry
- Season of index date (winter, Dec-Feb; spring, Mar-May; summer, Jun-Aug; fall, Sep-Nov)

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

- Previous COPD treatments
  - LAMA monotherapy
  - LABA monotherapy
  - ICS monotherapy
  - LAMA/ICS free 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); prescriptions within 30 days of each other were considered as continuation of the initial exacerbation.
  - Hospitalizations or emergency room visits with a primary diagnosis for COPD

(Severe); hospitalizations or emergency room visits within 30 days of each other were considered as continuation of the initial exacerbation.

- Hospitalizations caused by exacerbation of heart failure in 12 months prior to index date, categorized as
  - 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.

Operational definition 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:
  - Hospitalization with a primary diagnosis for COPD
  - Hospitalization with a primary diagnosis for pneumonia
  - Second course of antibiotics for respiratory tract infections; a single course of antibiotic treatment involving multiple dispensings is defined as that involving consecutive dispensings of antibiotics with fewer than 7 days between the end of days of supply of one dispensing and the date of the next dispensing
  - Second course of systemic corticosteroids for the treatment of COPD exacerbation; a single course of systemic corticosteroids involving multiple dispensings is defined as that involving consecutive dispensings with fewer than 7 days between the end of days of supply of one dispensing and the date of the next dispensing.
  - Two diagnoses of COPD exacerbation (ICD-10: J44.1; ICD-9: 491.21) 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

Diagnosis codes and drug codes are listed in the annex.

8. DATA SOURCES

Data sources include Taiwan National Health Insurance (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.

9. DATA MANAGEMENT AND SOFTWARE/TOOLS

9.1 SOFTWARE/TOOLS

All analysis will be conducted by Taiwanese collaborators using SAS software version 9.4 (SAS Institute, Inc., Cary, NC).

9.2 HANDLING OF MISSING VALUES

As administrative data routinely submitted to the health authority, there are no missing value in the health insurance claims. Handling of apparently inconsistent is described under section 9.3. The small number of subjects with missing information on date of birth or gender will be excluded from the study and described in Figure 1.

9.3 HANDLING OF INCONSISTENCIES IN DATA AND OUTLIERS

No clinical parameter values (such as blood pressure or laboratory examination results) are available, therefore potential outliers of continuous variables are not a major concern. Apparently inconsistent data, such birth year of 1860 or Tio+Olo prescriptions during the years that it was not covered, would be identified and subjects with inconsistent data will be excluded from analysis and described in Figure 1.

10. DATA ANALYSIS

10.1 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 (PS) matching will be used to generate two comparable treatment groups. All covariates, except season of index date, will be used to estimate the propensity score with logistic regression. Patients in LABA/ICS group will be individually matched to patients in the Tio/Olo group with 1:1 ratio. A caliper of 0.06 standard deviation of logit (propensity score) will be used to define the range of estimated PS within which to select the comparator. Within that range the LABA/ICS patient with the closest estimated propensity score to the Tio/Olo patient will be selected.

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.

All the analyses for primary outcome and secondary outcomes will be performed on patients after propensity score matching. Baseline characteristic table shell are provided in Table 1. The propensity score matching will be carried out once without re-matching.

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 event would be censored:

1) disenrollment
2) the end of the study period
3) death
4) discontinuation of index drug use (a lapse of 45 days without subsequent prescription)
5) switching from Tio/Olo to ICS/LABA or from ICS/LABA to Tio/Olo
6) escalation to triple therapies (ICS/LAMA/LABA free or fix dose combination)

Note that per study protocol, switching from one ICS/LABA to another ICS/LABA is not a censoring event.

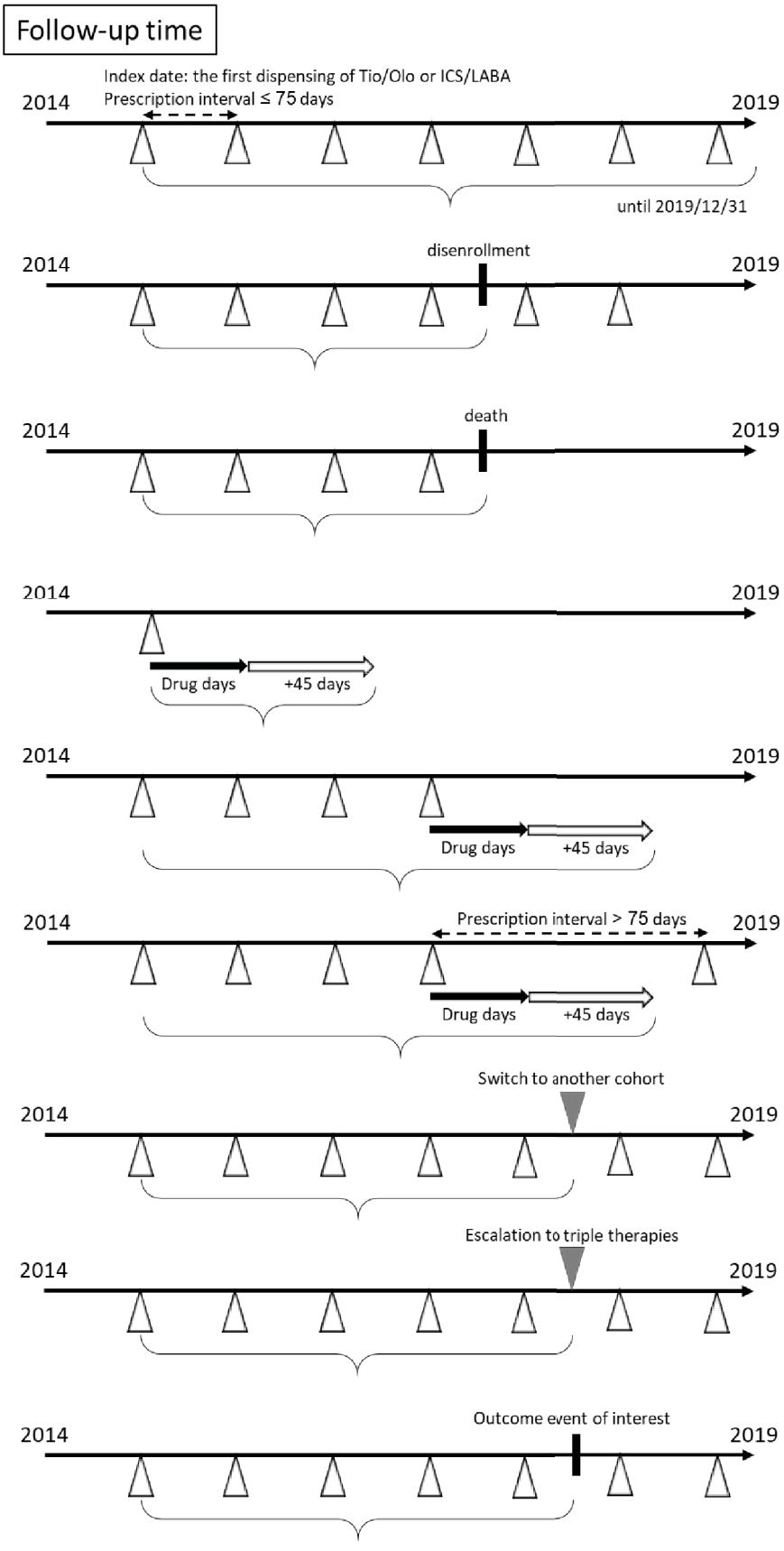
Univariate proportional hazard regression model will be used to compare the time to event between the two treatment groups. It will provide an estimate of the hazard ratio (HR) of time to the first moderate or severe COPD exacerbation associated with Tio+Olo use relative to LABA/ICS use, along with 95% CI. In the event that there are baseline covariates with unequal distribution between the treatment groups, defined as absolute standardized difference larger than 0.1, the covariate(s) will be included in a multiple regression model in addition to the exposure status (Tio/Olo or LABA/ICS).

The analysis of the secondary objectives related to time to triple therapy escalation and time to first hospitalization for community-acquired pneumonia will be univariate 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% CI will be provided. For the analysis of these time-to-event outcomes, patients will be followed until the event of interest or 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 index drug use (a lapse of 45 days without subsequent prescription)
6) switching from Tio/Olo to ICS/LABA or from ICS/LABA to Tio/Olo

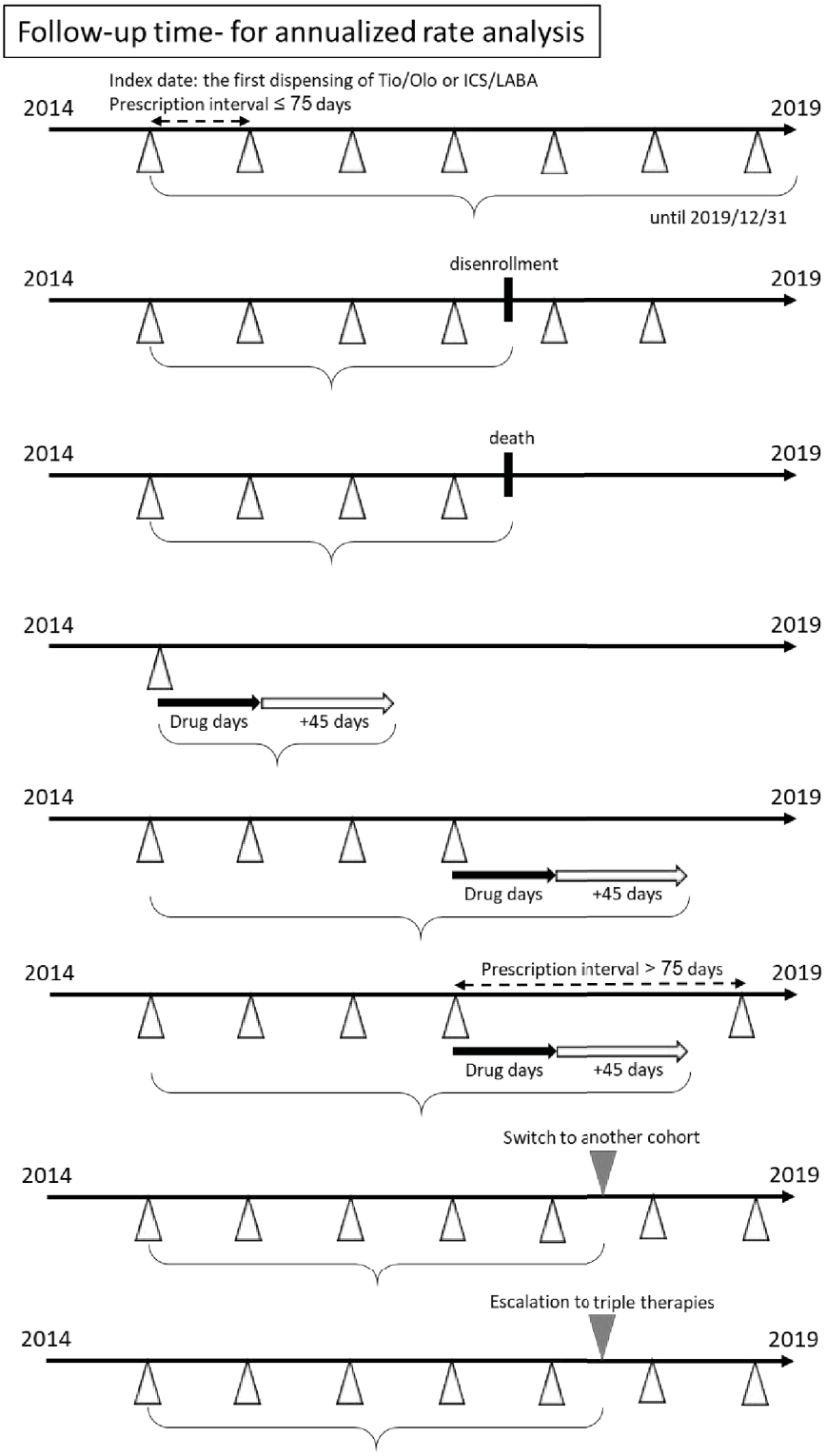
In the event that there are baseline covariates with unequal distribution between the treatment groups, defined as absolute standardized difference larger than 0.1, the covariate(s) will be included in a multiple regression model in addition to the exposure status (Tio/Olo or LABA/ICS).



The analysis of the secondary objectives related to annualized rate of prescriptions of rescue medications, the rate ratio of Tio+Olo – exposed group relative to LABA/ICS group, along with 95% CIs will be derived using univariate negative binomial model. Individuals in the study cohort will be followed from the index date until the earliest of the date of:

1) disenrollment;
2) the end of the study period;
3) death;
4) discontinuation of the index drug use (a lapse of 45 days without subsequent prescription);
5) switching from Tio/Olo to ICS/LABA or from ICS/LABA to Tio/Olo

In the event that there are baseline covariates with unequal distribution between the treatment groups, defined as absolute standardized difference larger than 0.1, the covariate(s) will be included in a multiple regression model in addition to the exposure status (Tio/Olo or LABA/ICS).



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

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-year 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-year 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% CIs will be derived using univariate negative binomial model. In the event that there are baseline covariates with unequal distribution between the treatment groups, defined as absolute standardized difference larger than 0.1, the covariate(s) will be included in a multiple regression model in addition to the exposure status (Tio/Olo or LABA/ICS).

For annualized rate of moderate or severe COPD exacerbations and annualized rate of prescriptions of rescue medications, the ratio of Tio+Olo – exposed group relative to LABA/ICS group, along with 95% CIs will be derived using negative binomial model. In the event that there are baseline covariates with unequal distribution between the treatment groups, defined as absolute standardized difference larger than 0.1, the covariate(s) will be included in a multiple regression model in addition to the exposure status (Tio/Olo or LABA/ICS).

SAS codes for negative binominal model are provided in Annex.

[redacted]

10.3 SAFETY ANALYSIS

Not applicable.

11. QUALITY CONTROL

Greater details are documented in the NIS-DMRP.

12. REFERENCES

12.1 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

12.2 UNPUBLISHED REFERENCES

None

ANNEX 1. ADDITIONAL INFORMATION

Table 1. Baseline characteristic of the study cohort

	Before propensity score match					After propensity score match				
	Tio/Olo cohort		ICS/LABA cohort		ASD	Tio/Olo cohort		ICS/LABA cohort		ASD
	N	%	N	%		N	%	N	%	
Gender										
Male										
Female										
Age										
40~54										
55~69										
70~84										
85+										
Calendar year of cohort entry										
2014										
2015										
2016										
2017										
2018										
2019										
Season of index date										
Spring (Mar-May)										
Summer (Jun-Aug)										
Fall (Sep-Nov)										
Winter (Dec-Feb)										
COPD treatments in 1 year prior to index date										
LAMA										
LABA										
ICS										
ICS+LAMA free combination										
Use of other respiratory drugs in 1 year prior to index date										
Mucolytics										
Theophylline										
Short-acting beta-agonists (SABA)										
Short-acting muscarinic antagonists (SAMA)										

	Before propensity score match					After propensity score match				
	Tio/Olo cohort		ICS/LABA cohort		ASD	Tio/Olo cohort		ICS/LABA cohort		ASD
	N	%	N	%		N	%	N	%	
Acute COPD exacerbation in 1 year prior to index date										
Moderate exacerbation										
0										
1										
>=2										
Severe exacerbation										
0										
1										
>=2										
All exacerbations (Moderate + Severe)										
0										
1										
>=2										
Acute COPD exacerbation in the 30 days prior to index date										
Moderate exacerbation										
0										
1										
>=2										
Severe exacerbation										
0										
1										
>=2										
All exacerbations (Moderate + Severe)										
0										
1										
>=2										
Hospitalizations caused by exacerbation of COPD in 1 year prior to index date										
0										
1										
>=2										
All-cause hospitalizations in 1 year prior to index date										
0										

	Before propensity score match					After propensity score match				
	Tio/Olo cohort		ICS/LABA cohort		ASD	Tio/Olo cohort		ICS/LABA cohort		ASD
	N	%	N	%		N	%	N	%	
1										
>=2										
Comorbidities:										
Cardiovascular disease										
Cerebrovascular disease										
Diabetes										
Chronic kidney disease										
Pneumonia										
Cancer										
Cirrhosis										
Charlson Comorbidity Index (CCI)										
History of medications dispensed in 1 year prior to index date										
Cardiovascular drugs:										
Antihypertensives										
Antiarrhythmics										
Nitrates										
Heart failure medications										
Lipid-lowering medications										
Blood glucose–lowering medications										
Anticoagulants and antiplatelet agents										
Antibiotics										
Antineoplastic agents										
COPD severity										
Mild										
Moderate										
Severe										
Very severe										

Table 2. Hazard ratios for COPD exacerbation, Tio/Olo users vs. ICS/LABA users

After PS match	Moderate exacerbation	Severe exacerbation	All exacerbation (Moderate + Severe)
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Tio/Olo			
ICS/LABA	Reference	Reference	Reference
	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)	Adjusted* HR (95% CI)
Tio/Olo			
ICS/LABA	Reference	Reference	Reference

* If needed, list of adjusted covariates will be listed.

Table 3. Hazard ratio for time to first triple therapy escalation, Tio/Olo users vs. ICS/LABA users

After PS match	Triple therapy escalation	
	HR (95% CI)	Adjusted* HR (95% CI)
Tio/Olo		
ICS/LABA	Reference	Reference

* If needed, list of adjusted covariates will be listed.

Table 4. Incidence rates of triple therapy initiation among the two cohorts, incidence rate ratio and incidence difference estimates

After PS match	No. with events	Person-years	Incidence Rate (95% CI)	IRR (95% CI)	Adjusted* IRR (95% CI)	Incidence difference (95% CI)
Triple therapy escalation						
Tio/Olo						
ICS/LABA				Reference	Reference	Reference

* If needed, list of adjusted covariates will be listed.

Table 5. Hazard ratio for time to first hospitalization for community-acquired pneumonia, Tio/Olo users vs. ICS/LABA users

After PS match	Hospitalization for community-acquired pneumonia	
	HR (95% CI)	Adjusted* HR (95% CI)
Tio/Olo		
ICS/LABA	Reference	Reference

* If needed, list of adjusted covariates will be listed.

Table 6. Annualized rates of prescription of rescue medications and moderate or severe COPD exacerbations

After PS match	No. of patients with events	No. of events	Person-years	Annualized rate (95CI)	Annualized rate ratio (95CI)	Adjusted* rate ratio (95CI)
Rescue medication						
Tio/Olo						
ICS/LABA					Reference	Reference
Moderate exacerbation						
Tio/Olo						
ICS/LABA					Reference	Reference
Severe exacerbation						
Tio/Olo						
ICS/LABA					Reference	Reference
All exacerbation (Moderate + Severe)						
Tio/Olo						
ICS/LABA					Reference	Reference

* If needed, list of adjusted covariates will be listed.

Appendix 1. SAS code template for negative binominal model in the analysis of the secondary outcomes of interest

The following codes are provided by Boehringer Ingelheim statistician

```
PROC GENMOD DATA=test;
CLASS treat (ref='LABA/ICS') cova_cat;
MODEL ep_count = treat cova_cat cova_con /
DIST=negbin LINK=LOGTYPE3 OFFSET=logt;
LSMEANS treat / DIFF CL;
ESTIMATE 'Treatment effect on ratio-scale' treat 1 -1 / EXP;
RUN;
```

(In the model,
treat: Tio+Olo group OR LABA/ICS group;
Cova_cat: categorical covariates;
Cova_con: continuous covariates)

For univariate analysis, Cova_cat and Cova_con are not applicable.

For calculating incidence rate ratio with 95% CI of triple therapy initiation (Tio+Olo vs. LABA/ICS),
ep_count (response): 1 (triple therapy initiation occurred per patient) or 0 (triple therapy initiation not occurred per patient);
logt: nature log of the time at risk (first event per patient)

For calculating ratio (with 95% CI) of annualized rate of moderate or severe COPD exacerbations and annualized rate of prescriptions of rescue medications (Tio+Olo vs. LABA/ICS),
ep_count (response): number of events per patient
logt: nature log of the time at risk per patient

Appendix 2. ICD-9/10-CM codes and procedure codes for identification of study cohorts

	ICD9	ICD10
For inclusion criteria		
COPD	491.x, 492.x, 496	J41.x, J42, J43.x, J44.x
For exclusion criteria		
Asthma	493.x	J45.x
Allergic rhinitis	477.x	J30.x
Lung cancer	162.x	C33.x, C34.x, C7A.090, D02.2
Interstitial lung disease	238.1, 500, 501, 502, 503, 504, 505, 506.4, 508.1, 508.8, 515, 516.x	J60, J61, J62.x, J63.x, J64, J65, J66.x, J68.4, J70.x (no 70.2), J84.1x (no J84.114), J84.2, J84.3, J84.89, J84.9, J94.1

Procedure codes	Content
68037A	Lung transplantation
68037B	Lung transplantation - Unilateral lung
68047B	Lung transplantation - bilateral sequential or en bloc double lung

Appendix 3. COPD medications

Groups	Drug name	ATC code
LAMA	Tiotropium bromide	R03BB04
	Glycopyrrolate	R03BB06
	Umeclidinium	R03BB07
LABA	Salmeterol	R03AC12
	Formoterol	R03AC13
	Procaterol	R03AC16
	Indacaterol	R03AC18
	Olodaterol	R03AC19
ICS	Beclometasone(=beclomethasone)	R03BA01
	Budesonide	R03BA02
	Fluticasone	R03BA05
	Ciclesonide	R03BA08
ICS/LABA	Salmeterol and Fluticasone	R03AK06
	Formoterol and Budesonide	R03AK07
	Formoterol and Beclometasone	R03AK08
	Vilanterol and Fluticasone furoate	R03AK10
	Formoterol and Fluticasone	R03AK11
LABA/LAMA	Vilanterol and Umeclidinium bromide	R03AL03
	Indacaterol and Glycopyrronium bromide	R03AL04
	Olodaterol and Tiotropium bromide	R03AL06
LABA/LAMA/ICS	Vilanterol, Umeclidinium bromide and Fluticasone furoate	R03AL08
	Formoterol, Glycopyrronium bromide and Beclometasone	R03AL09

Appendix 4. ICD codes and operational definition of comorbidities

	Comorbidities:	ICD codes	Operational definition
1.	Diabetes	**ICD9:** 250 **ICD10:** E10.x-E11.x	Either inpatient diagnosis or more than twice outpatient diagnosis
2.	Cardiovascular disease	**ICD9:** 250.7, 401-405, 410-414, 425-428, 429.1-429.3, 441, 442, 458 **ICD10:** E10.5x, E11.5x, I10-I13.x, I15.x, I20.x-I22.x, I24.x, I25.x, I42.x-I44, I45.xx, I46.x-I49.x, I50.xx, I51.5, I51.7, I51.9, I71.xx, I79.0, I72.x, I77.7x, I95.x	Either inpatient diagnosis or more than twice outpatient diagnosis
3.	Cerebrovascular disease	**ICD9:** 430-438 **ICD10:** I60.x-I63.x, I65.x, I66.x, G45.x, G46.x, I67.x-I69.x	Either inpatient diagnosis or more than twice outpatient diagnosis
4.	Cancer	**ICD9:** 140-199, 200-208 **ICD10:** C00-C26, C30-34, C37-39, C40-41, C43-49, C4A, C50-58, C60-69, C70-79,C7A, C7B, C80-86, C88, C90-96,	Inpatient diagnosis.
5.	Chronic kidney disease	**ICD9:** 585-587, **ICD10:** N18-19, N26.1, N26.9	Either inpatient diagnosis or more than twice outpatient diagnosis
6.	Pneumonia	**ICD9:** 480-486, 487.0 **ICD10:** J10.0, J11.0, J12-J18,	Inpatient diagnosis
7.	Cirrhosis	**ICD9:** 571.2, 571.5, 571.6 **ICD10:** K70.3x, K74.3, K74.4, K74.5, K74.6x	Either inpatient diagnosis or more than twice outpatient diagnosis

Appendix 5. Drugs of interest

Groups	ATC code
Use of other respiratory drugs	
Mucolytics	R05CB, R05CB01, R05CB02, R05CB03, R05CB04, R05CB05, R05CB06, R05CB10, R05CB11, R05CB91, R05CB92
Theophylline	R03DA04, R03DA54, R03DA74, R03DB04
SABA	R03AC02, R03AC03, R03AC04, R03AC06
SAMA	R03BB01
SABA/SAMA	R03AL01, R03AL02
Drugs for COPD exacerbation treatment	
Oral corticosteroid	H02AB01, H02AB02, H02AB04, H02AB05, H02AB06, H02AB08, H02AB10, H02BX, H02BX91
Antibiotic for COPD exacerbation	J01AA02, J01CA04, J01CR02, J01CR05, J01EE01, J01DC01, J01DC02, J01DC03, J01DC04, J01DC05, J01DC06, J01DC07, J01DC09, J01DC14, J01DD01, J01DD02, J01DD04, J01DD05, J01DD06, J01DD07, J01DD08, J01DD12, J01DD13, J01DD14, J01DD52, J01DD62, J01DE01, J01DE02, J01FA01, J01EA02, J01EA03, J01EA06, J01EA07, J01EA08, J01FA09, J01FA10, J01FA15, J01FA91, J01MA01, J01MA02, J01MA03, J01MA04, J01MA06, J01MA07, J01MA09, J01MA12, J01MA14, J01MA15
Drugs for Medication history	
● **Cardiovascular drugs**	
Anti-hypertensives	C02AA01, C02AA02, C02AA04, C02AB01, C02AB02, C02AC01, C02CA01, C02CA04, C02CA, C02CC02, C02DA01, C02DB02, C02DC01, C02DD01, C02LA01, C02LA50, C02LA51, C02LB01, C02LG02, C02N, C03AA01, C03AA03, C03AA06, C03AA07, C03AA, C03BA04, C03BA08, C03BA11, C03CA01, C03CA02, C03CA04, C03CC01, C03DA01, C03DA04, C03DB01, C03DB02, C03EA01, C03EA, C07AA01, C07AA02, C07AA03, C07AA05, C07AA06, C07AA07, C07AA12, C07AA15, C07AA19, C07AB02, C07AB03, C07AB04, C07AB05, C07AB07, C07AB09, C07AB12,

	C07AG01, C07AG02, C07BA68, C07BB02, C07CA03, C07CB03, C07DA06, C08CA01, C08CA02, C08CA03, C08CA04, C08CA05, C08CA07, C08CA08, C08CA09, C08CA12, C08CA13, C08CA15, C08DA01, C08DB01, C09AA01, C09AA02, C09AA03, C09AA04, C09AA05, C09AA06, C09AA07, C09AA08, C09AA09, C09AA16, C09BA01, C09BA02, C09BA04, C09BB04, C09BB05, C09BB, C09BB, C09CA01, C09CA02, C09CA03, C09CA04, C09CA06, C09CA07, C09CA08, C09CA09, C09DA01, C09DA03, C09DA04, C09DA06, C09DA07, C09DA08, C09DA09, C09DB01, C09DB02, C09DB04, C09DB07, C09DX01, C09DX03, C09DX04, C09XA02, C09XA52, C09XA53, C09XA54
Antiarrhythmics	C01AA04, C01AA05, C01AA07, C01AA08, C01AB01, C01AC01, C01BA01, C01BA02, C01BA03, C01BA04, C01BA08, C01BB01, C01BB02, C01BC03, C01BC04, C01BD01, C01BD07, C01CA02, C01CA04, C01CA06, C01EB10, C01EB17, C07AA01, C07AA02, C07AA03, C07AA05, C07AA07, C07AA12, C07AA15, C07AA19, C07AB02, C07AB03, C07AB04, C07AB05, C07AB07, C07AB09, C07AB12, C08DA01, C08DB01
Heart failure medications	C01AA04, C01AA05, C01AA07, C01AA08, C01AB01, C01AC01, C01CA02, C01CA07, C01CE02, C01EB09, C01EB17, C03CA02, C03CA04, C03DA04, C07AG02, C09AA01, C09AA02, C09AA03, C09AA04, C09AA05, C09AA06, C09AA07, C09AA08, C09AA09, C09AA16, C09CA01, C09CA02, C09CA03, C09CA04, C09CA06, C09CA07, C09CA08, C09CA09
Nitrates	C01DA02, C01DA05, C01DA08, C01DA14
● **Lipid-lowering medications**	
Lipid Modifying Agents, Plain	C10AA01, C10AA02, C10AA03, C10AA04, C10AA05, C10AA07, C10AA08, C10AB01, C10AB02, C10AB03, C10AB04, C10AB05, C10AB06, C10AB09, C10AC01, C10AC02, C10AC03, C10AD01, C10AD02, C10AD03, C10AD06, C10AD, C10AX02, C10AX09, C10AX13, C10AX14, C10AX

Lipid Modifying Agents, Combinations	C10BA01, C10BA02, C10BA03, C10BA05, C10BX03
● **Blood glucose-lowering medications**	
Insulins and analogues	A10AB01, A10AB03, A10AB04, A10AB05, A10AB06, A10AB30, A10AC01, A10AC03, A10AC30, A10AD01, A10AD03, A10AD04, A10AD05, A10AD06, A10AE01, A10AE04, A10AE05, A10AE06, A10AE54
Blood glucose lowering drugs, excl. insulins	A10BA02, A10BA03, A10BB01, A10BB02, A10BB03, A10BB04, A10BB05, A10BB07, A10BB08, A10BB09, A10BB12, A10BB31, A10BD02, A10BD03, A10BD05, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD13, A10BD14, A10BD, A10BD15, A10BD19, A10BD20, A10BD21, A10BD24, A10BF01, A10BF02, A10BG02, A10BG03, A10BH01, A10BH02, A10BH03, A10BH04, A10BH05, A10BJ01, A10BJ02, A10BJ03, A10BJ05, A10BJ06, A10BK01, A10BK02, A10BK03, A10BK04, A10BX01, A10BX02, A10BX03, A10BX08
● **Anticoagulants and antiplatelet agents**	
Vitamin K antagonists	B01AA02, B01AA03
Heparin group	B01AB01, B01AB04, B01AB05, B01AB06, B01AB10
Platelet aggregation inhibitors excl. heparin	B01AC04, B01AC05, B01AC06, B01AC07, B01AC09, B01AC11, B01AC13, B01AC16, B01AC17, B01AC21, B01AC22, B01AC23, B01AC24, B01AC27, B01AC30
Enzymes	B01AD01, B01AD02, B01AD04, B01AD10, B01AD11
Direct thrombin inhibitors	B01AE07
Direct factor Xa inhibitors	B01AF01, B01AF02, B01AF03
Other antithrombotic agents	B01AX05
● **Antibiotic**	

Antibacterials for systemic use	J01AA01, J01AA02, J01AA03, J01AA04, J01AA06, J01AA07, J01AA08, J01AA09, J01AA12, J01AA56, J01BA01, J01BA02, J01BA51, J01CA01, J01CA02, J01CA03, J01CA04, J01CA06, J01CA08, J01CA09, J01CA10, J01CA12, J01CA13, J01CA14, J01CA15, J01CA16, J01CA18, J01CA20, J01CA91, J01CE01, J01CE02, J01CE08, J01CE09, J01CE30, J01CF01, J01CF02, J01CF04, J01CF05, J01CG01, J01CR01, J01CR02, J01CR03, J01CR04, J01CR05, J01CR50, J01CR50, J01CR50, J01DB01, J01DB02, J01DB03, J01DB04, J01DB05, J01DB06, J01DB07, J01DB08, J01DB09, J01DC01, J01DC02, J01DC03, J01DC04, J01DC05, J01DC06, J01DC07, J01DC09, J01DC14, J01DD01, J01DD02, J01DD04, J01DD05, J01DD06, J01DD07, J01DD08, J01DD12, J01DD13, J01DD14, J01DD52, J01DD62, J01DE01, J01DE02, J01DF01, J01DH02, J01DH03, J01DH04, J01DH51, J01DI02, J01DI54, J01E, J01EA01, J01EB01, J01EB02, J01EB05, J01EB06, J01EB20, J01EC, J01EC01, J01EC02, J01EC20, J01ED01, J01ED05, J01ED20, J01EE01, J01FA01, J01EA02, J01EA03, J01EA06, J01EA07, J01EA08, J01FA09, J01FA10, J01FA15, J01FA91, J01FF01, J01FF02, J01GA01, J01GB01, J01GB03, J01GB04, J01GB05, J01GB06, J01GB07, J01GB08, J01GB09, J01GB11, J01MA01, J01MA02, J01MA03, J01MA04, J01MA06, J01MA07, J01MA09, J01MA12, J01MA14, J01MA15, J01MB01, J01MB02, J01MB03, J01MB04, J01MB08, J01RA02, J01XA01, J01XA02, J01XB, J01XB01, J01XC01, J01XD01, J01XD02, J01XD03, J01XE, J01XE01, J01XE02, J01XX01, J01XX04, J01XX05, J01XX07, J01XX08, J01XX09, J01XX91
Antimycotics for systemic use	J02AA01, J02AB01, J02AB02, J02AC01, J02AC02, J02AC03, J02AC04, J02AC05, J02AX01, J02AX04, J02AX05, J02AX06
Antimycobacterials	J04AA03, J04AB01, J04AB02, J04AB03, J04AB04, J04AB91, J04AC01, J04AC51, J04AD01, J04AK01, J04AK02, J04AK04, J04AM02, J04AM03, J04AM05, J04AM06, J04AM07, J04BA01, J04BA02

● **Antineoplastic agents**	
Alkylating agents	L01AA01, L01AA02, L01AA03, L01AA06, L01AA09, L01AB01, L01AC01, L01AC03, L01AD01, L01AD02, L01AD06, L01AX03, L01AX04
Antimetabolites	L01BA01, L01BA04, L01BA05, L01BB02, L01BB03, L01BB04, L01BB05, L01BB06, L01BC01, L01BC02, L01BC03, L01BC05, L01BC06, L01BC07, L01BC53, L01BC59
Plant alkaloids and other natural products	L01CA01,L01CA02, L01CA04, L01CB01, L01CD01, L01CD02, L01CE01, L01CE02
Cytotoxic antibiotics and related substances	L01DA01, L01DB01, L01DB02, L01DB03, L01DB04, L01DB06, L01DB07, L01DC01, L01DC03, L01DC04
Protein kinase inhibitors	L01EA01, L01EA02, L01EA03, L01EA05, L01EB01, L01EB02, L01EB03, L01EB04, L01EB07, L01EC01, L01EC02, L01ED01, L01ED02, L01ED03, L01ED04, L01ED05, L01EE01, L01EF01, L01EF02, L01EG01, L01EG02, L01EH01, L01EJ01, L01EK01, L01EL01, L01EM02, L01EX01, L01EX02, L01EX03, L01EX04, L01EX05, L01EX07, L01EX08, L01EX09, L01EX10, L01EX14
Other antineoplastic agents	L01XA01, L01XA02, L01XA03, L01XB01, L01XC02, L01XC03, L01XC06, L01XC07, L01XC08, L01XC12, L01XC13, L01XC14, L01XC15, L01XC17, L01XC18, L01XC19, L01XC21, L01XC24, L01XC26, L01XC31, L01XC32, L01XF01, L01XG01, L01XG02, L01XG03, L01XK01, L01XK04, L01XX02, L01XX05, L01XX11, L01XX23, L01XX27, L01XX35, L01XX41, L01XX52, L01XX
Hormones and related agents	L02AA01, L02AA91, L02AB01, L02AB02, L02AE01, L02AE02, L02AE03, L02AE04
Hormone antagonists and related agents	L02BA01, L02BA02, L02BB01, L02BB03, L02BB04, L02BB05, L02BG01, L02BG03, L02BG04, L02BG06, L02BX02, L02BX03

Appendix 6. Procedure codes for oxygen therapy or nebuliser therapy

Description	Procedure codes
Oxygen therapy	47054C, 54007C1, 57001B, 57002B, 57003C, 57004C, 57019C, 57020C, 57023B, 57029C
Nebuliser therapy	57021C, 57022C, 57024B

ANNEX 2. REVIEWERS AND APPROVAL SIGNATURES

The NIS SEAP 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
NIS Data Manager	X	X	X
TSTAT (for NISnd only)	X	X	X
RWE CoE	X	X	

** When BI NIS lead is not TM Epi*

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 SEAP and to all documents referenced in the study SEAP.

Position: _____ Name/Date: _____ Signature: _____

Position: _____ Name/Date: _____ Signature: _____

Position: _____ Name/Date: _____ Signature: _____

Position: _____ Name/Date: _____ Signature: _____