BI Study Number:	1237-0109
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
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This page has been added to the Statistical and Epidemiological Analysis Plan (SEAP) to reflect the requirements by ClinicalTrials.gov. This information is not part of the standard document.

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

Document Number:	c40431892 -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
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

AE	Adverse Event
BI	Boehringer Ingelheim
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
DMRP	Data management and review plan
FDC	Fixed dose combination
ICS	Inhaled corticolsteroids
IQR	Interquartile range
LABA	Long-acting β2-agonists
LAMA	Long-acting muscarinic antagonists
NHI	Taiwan National Health Insurance
NHIRD	Taiwan National Health Insurance Research Database
NIS	Non-interventional study
Olo	Olodaterol
SAE	Serious Adverse Event
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

SEAP reviewers are:

- BI NIS Lead [SEAP reviewer] (in all cases): [redacted]
- NIS Data Manager [SEAP reviewer] (in all cases): [redacted]@!20210208
- RWE CoE [SEAP reviewer] (for all globally initiated studies and for local studies) involving BI products and Global NIS not involving BI products: [redacted]
- TSTAT (for NISnd only): NA
- TM Epi [SEAP reviewer] (When BI NIS lead is not TM Epi; in all cases): [redacted]

3. PURPOSE AND SCOPE

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.

4. AMENDMENTS AND UPDATES

None

5. RESEARCH QUESTION AND OBJECTIVE

Primary objective:
- To estimate the incidence rate of safety outcomes in 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;

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

Data used in this study will come from the Taiwan National Health Insurance (NHI) claims data. Cohort for incident Tio/Olo combined inhaler use would be identified from 2014 through 2019, with a 1-year look-back period to define new user. Cohort for other incident LAMA/LABAs combined inhaler use would be identified from 2014 through 2019, and also with a 1-year look-back period to define new user.

6.3 STUDY POPULATION

For incident Tio/Olo combined inhaler cohort

- **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 (the free combination will be defined as the prescriptions of the two compounds on the same day);
  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. (the free combination will be defined as the prescriptions of the two compounds within 30 days);
  2. Individuals with asthma, allergic rhinitis, lung cancer, interstitial lung disease, or lung transplant identified at any time prior to the index date.

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

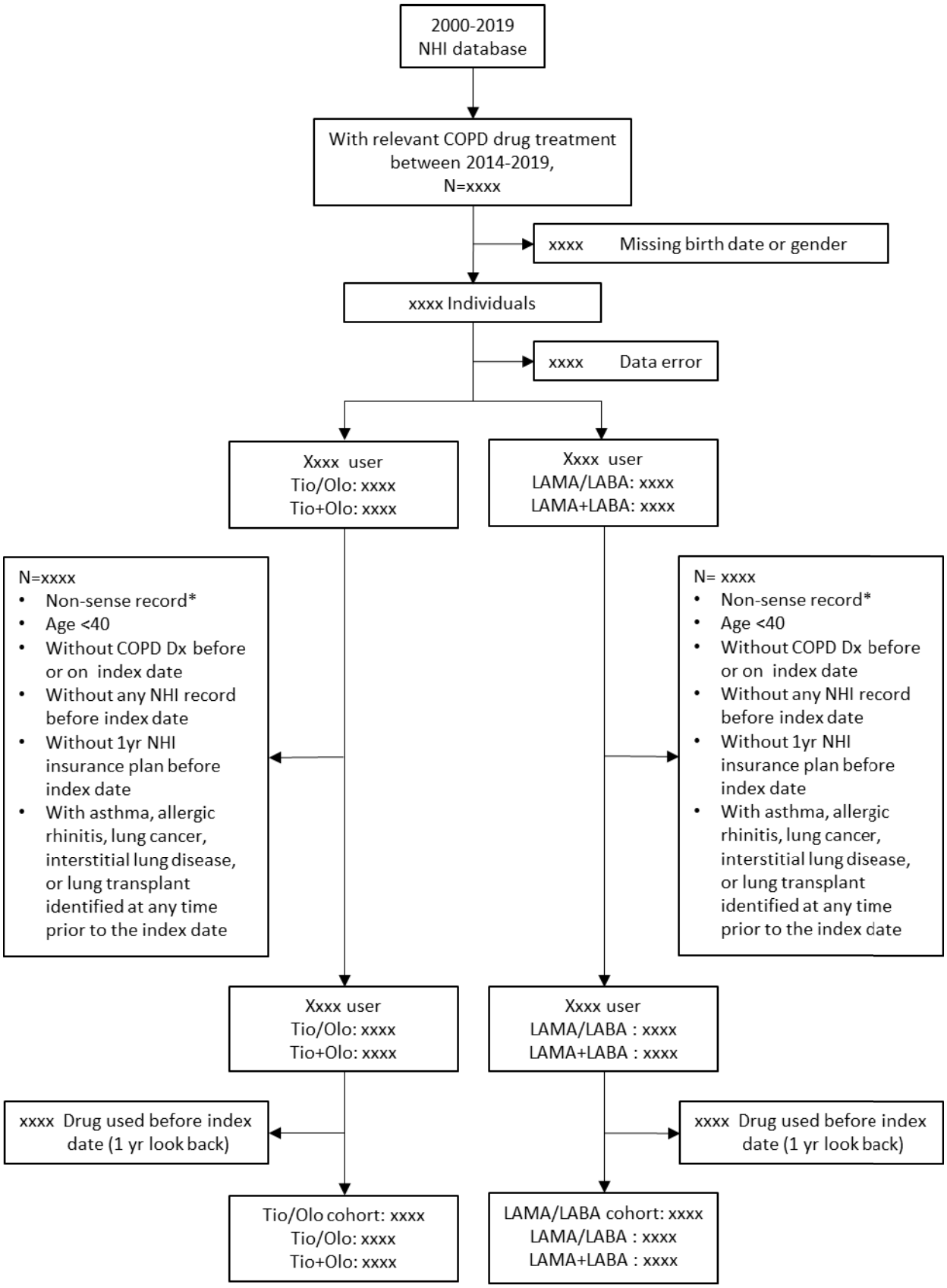
For other incident LAMA/LABAs combined inhaler cohort

- **Inclusion criteria:**
  1. At least one prescription for LAMA+LABA FDC (Vilanterol/Umeclidinium; Indacaterol /Glycopyrronium) or free combination (LABA: Salmeterol; Formoterol; Procaterol; Indacaterol; Olodaterol, LAMA: Tiotropium bromide; Glycopyrrolate; Umeclidinium) other than Tio/Olo as a new initiation between 1st January 2014 and 31st December 2019 (the free combination will be defined as the prescriptions of the two compounds on the same day);
  2. Aged ⩾ 40 years on the index date (The first dispensing of LAMA+LABA combined inhaler will be defined as 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 (the free combination will be defined as the prescriptions of the two compounds within 30 days);
  2. Individuals with asthma, allergic rhinitis, lung cancer, interstitial lung disease, or lung transplant identified at any time prior to the index date.

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 other LAMA/LABA inhaler (FDC or free combination) during the study period. The free form will be defined as the prescriptions of the two compounds on the same day. Drug codes of interest are provided in the Annex.

7.2 OUTCOMES

7.2.1 Primary outcomes

- **Incidence rate of adverse events in patients with COPD treated with Tio+Olo**

  List of adverse events:

  For acute, potentially recurrent events, including COPD exacerbations listed below, all subjects will be evaluated, regardless of whether such events occurred during the one-year baseline period.

  - Respiratory tract disorders
    1. Nasopharyngitis
    2. Pneumonia
    3. COPD exacerbation
  - Gastrointestinal disorders
    1. Constipation
    2. Diarrhoea
  - Urinary disorders
    1. Urinary retention
    2. Urinary tract infection
  - Immune system
    1. Urticaria

2. Rash

For chronic conditions listed below, subjects who had diagnosis of the condition during the one-year baseline period will be excluded from the incidence of adverse event analysis.

- Cardiovascular disorders
  1. Arrhythmia
  2. Myocardial ischemia
  3. Supraventricular tachycardia

- Ophthalmic disorders
  1. Glaucoma

- Serious Adverse Event (SAE)

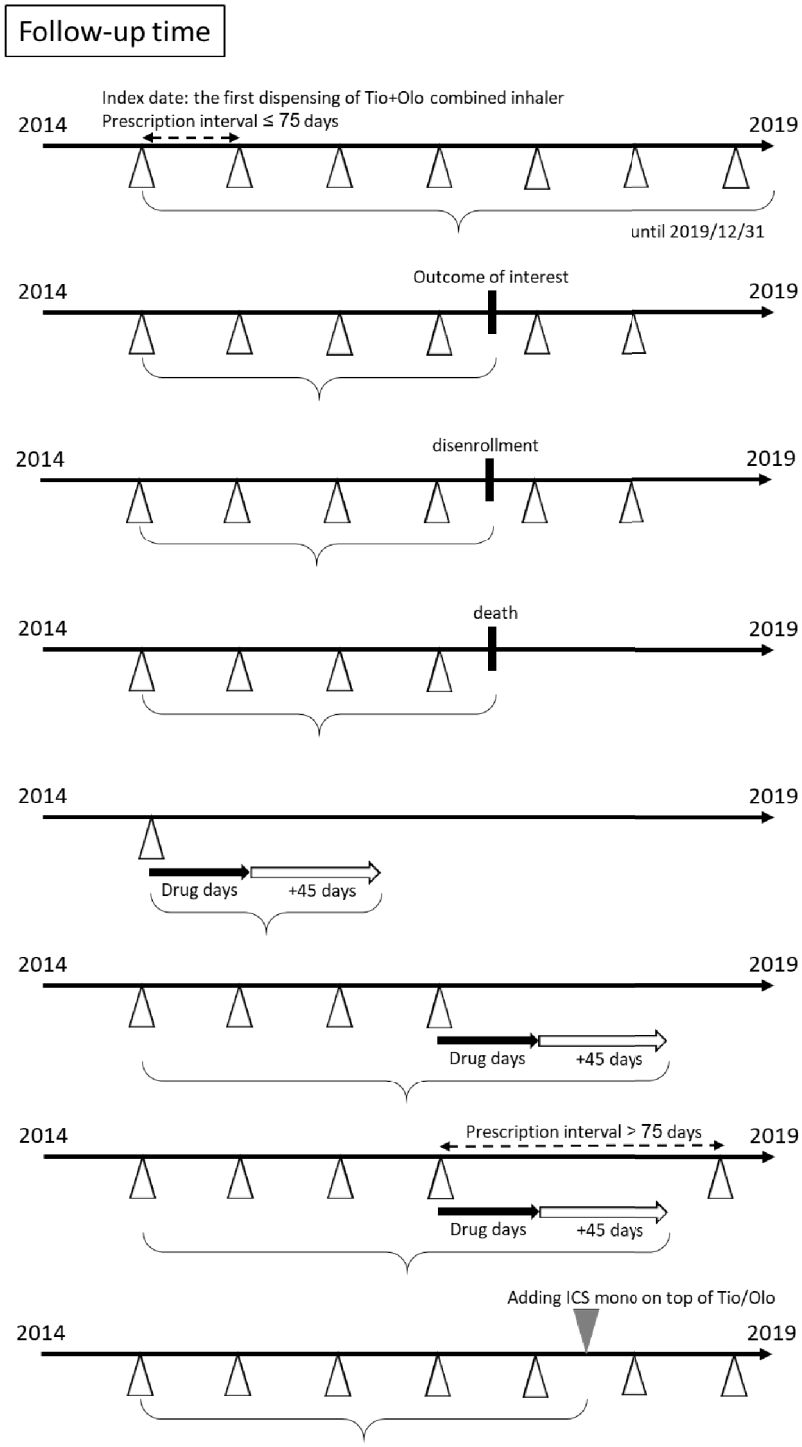
  1. Nonfatal myocardial infarction
  2. Nonfatal stroke (hemorrhagic stroke, ischemic stroke and acute cerebrovascular disease)

Lastly, all-cause mortality, a serious adverse event, will be evaluated.

Relevant ICD codes and operational definition are provided in the Annex.

For the analysis of the primary outcome, individuals will be followed up from the index date until the earliest of the following

1) Outcome of interest
2) disenrollment;
3) the end of the study period;
4) death;
5) discontinuation of the index drug use as a lapse of 45 days without subsequent prescription;
6) adding ICS mono on top of Tio/Olo.



7.2.2 Secondary outcomes

These are not "outcomes" that occurred after the index date in most studies. These are analysis of baseline characteristics of patients who initiated Tio+Olo or other LAMA/LABA.

Basic characteristics:

- 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:

- Specific previous COPD treatments
  - LAMA monotherapy
  - LABA monotherapy
  - ICS monotherapy
  - LAMA/ICS combination therapy on the same day
  - LAMA+LABA free combinations and fixed dose combination

- 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 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

Relevant ICD codes, drugs ATC codes and operational definition are provided in the Annex.

[redacted]

7.3 COVARIATES

Covariates are the same as that listed under 7.2.2.

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.

The ICD-9-CM coding system was used until the end of 2015 and the use of ICD-10-CM codes started on January 1, 2016.

9. DATA MANAGEMENT AND SOFTWARE/TOOLS

9.1 SOFTWARE/TOOLS

All analysis will be conducted by SAS software version 9.4 ([redacted]).

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 data 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.

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.

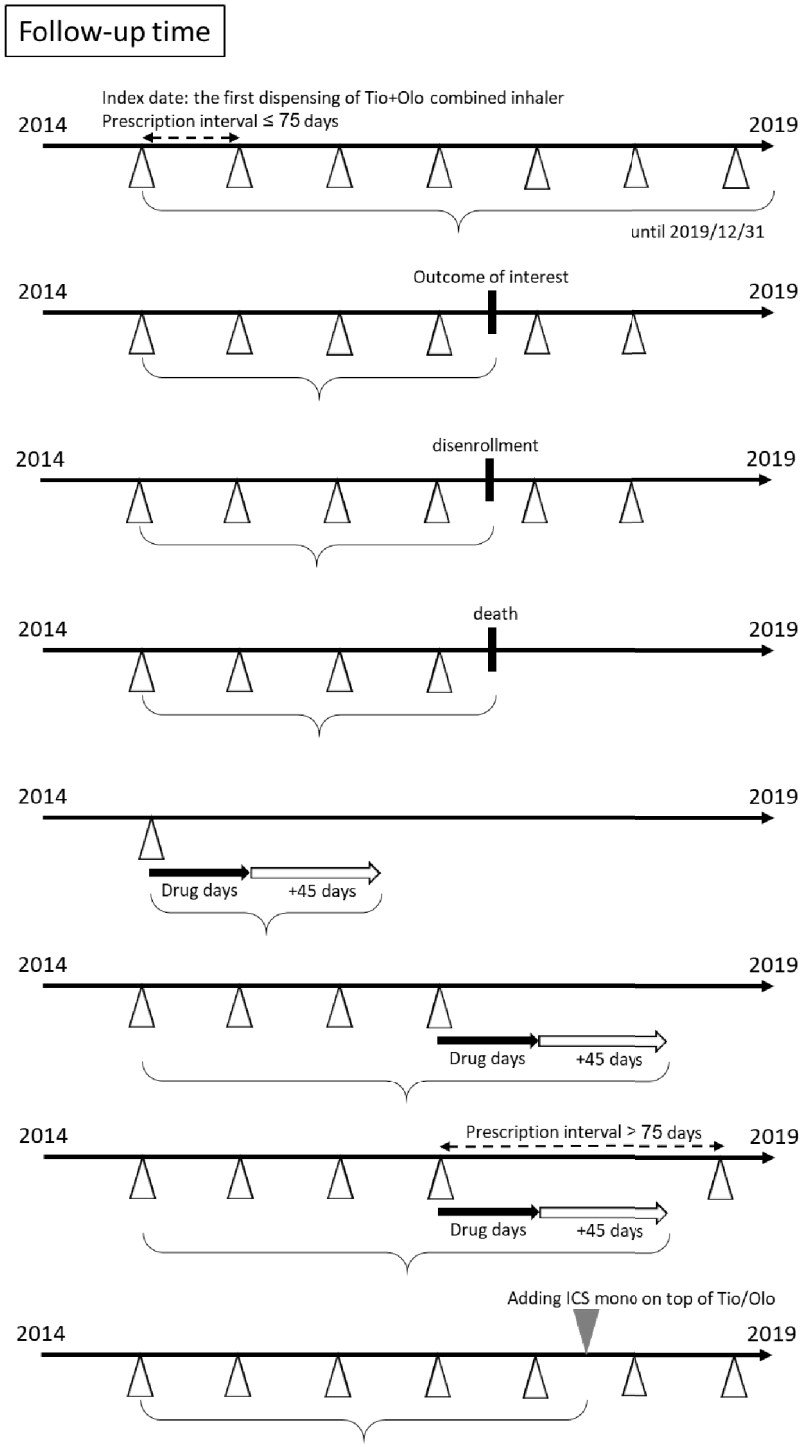
For the analysis of primary outcome, the incidence rates of AEs during entire follow-up period will be calculated based on the following formula:

(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)

Number of at-risk patients will be defined for specific adverse outcome of interest, taking into account whether it is a chronic condition for which patients with a prevalent condition are not considered at risk.

For the analysis of the primary outcome, individuals will be followed up from the index date until the earliest of the following

1) Outcome of interest
2) disenrollment;
3) the end of the study period;
4) death;
5) discontinuation of the index drug use as a lapse of 45 days without subsequent prescription;
6) adding ICS mono on top of Tio/Olo.



[redacted]

10.3 SAFETY ANALYSIS

Not applicable.

11. 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.

12. REFERENCES

12.1 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.

P11-13226 Verhamme KM, Afonso AS, van Noord C, Haag MD, Koudstaal PJ, Brusselle GG, et al. Tiotropium Handihaler and the risk of cardio- or cerebrovascular events and mortality in patients with COPD. Pulm Pharmacol Ther. 2012 Feb;25(1):19-26.

R08-1492 Soriano JB, Maier WC, Visick G, Pride NB. Validation of general practitioner-diagnosed COPD in the UK General Practice Research Database. Eur J Epidemiol. 2001;17(12):1075-80.

P07-09136 Curkendall SM, Lanes S, de Luise C, et al. Chronic obstructive pulmonary disease severity and cardiovascular outcomes. Eur J Epidemiol. 2006;21(11):803-13.

P19-08890 Moretz C, Bengtson LG, Sharpsten L, et al. Evaluation of rescue medication use and medication adherence receiving umeclidinium/vilanterol versus tiotropium bromide/olodaterol. Int J Chron Obstruct Pulmon Dis. 2019 Sep 4;14:2047-2060.

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

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.

12.2 UNPUBLISHED REFERENCES

None

ANNEX 1. ADDITIONAL INFORMATION

Table 1. Demographic and cohort entry of the Tio/Olo cohort and LAMA/LABA cohort

	Tio/Olo cohort N=xxxx		LAMA/LABA cohort N=xxxx	
	N	%	N	%
Gender				
Male				
Female				
Age				
Mean, SD				
40~59				
60~79				
80+				
Calendar year of cohort entry				
2014				
2015				
2016				
2017				
2018				
2019				
Season of cohort entry date				
Spring (Mar-May)				
Summer (Jun-Aug)				
Fall (Sep-Nov)				
Winter (Dec-Feb)				

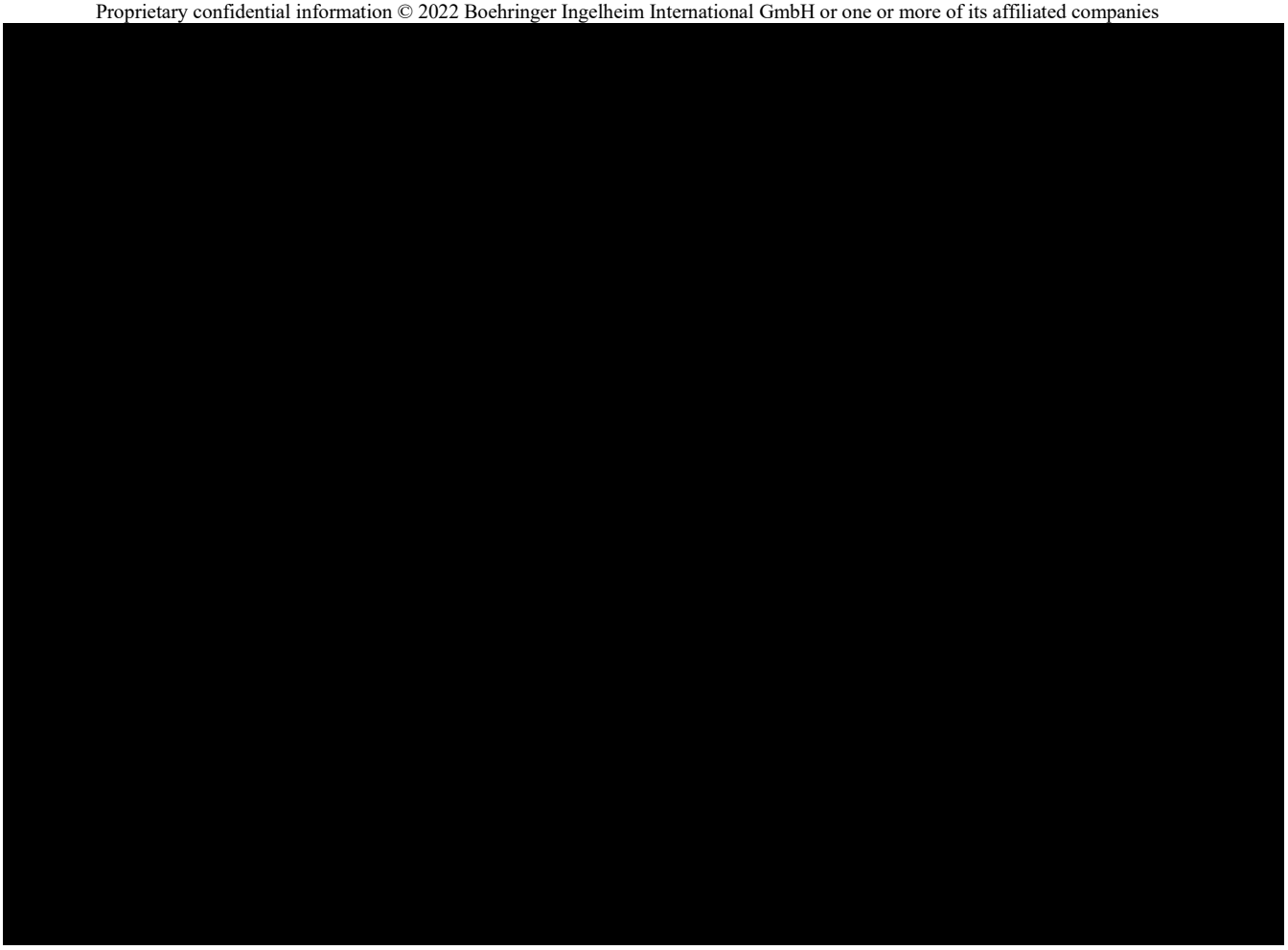
Table 2. Incidence rate of adverse events in patients with COPD treated with Tio+Olo

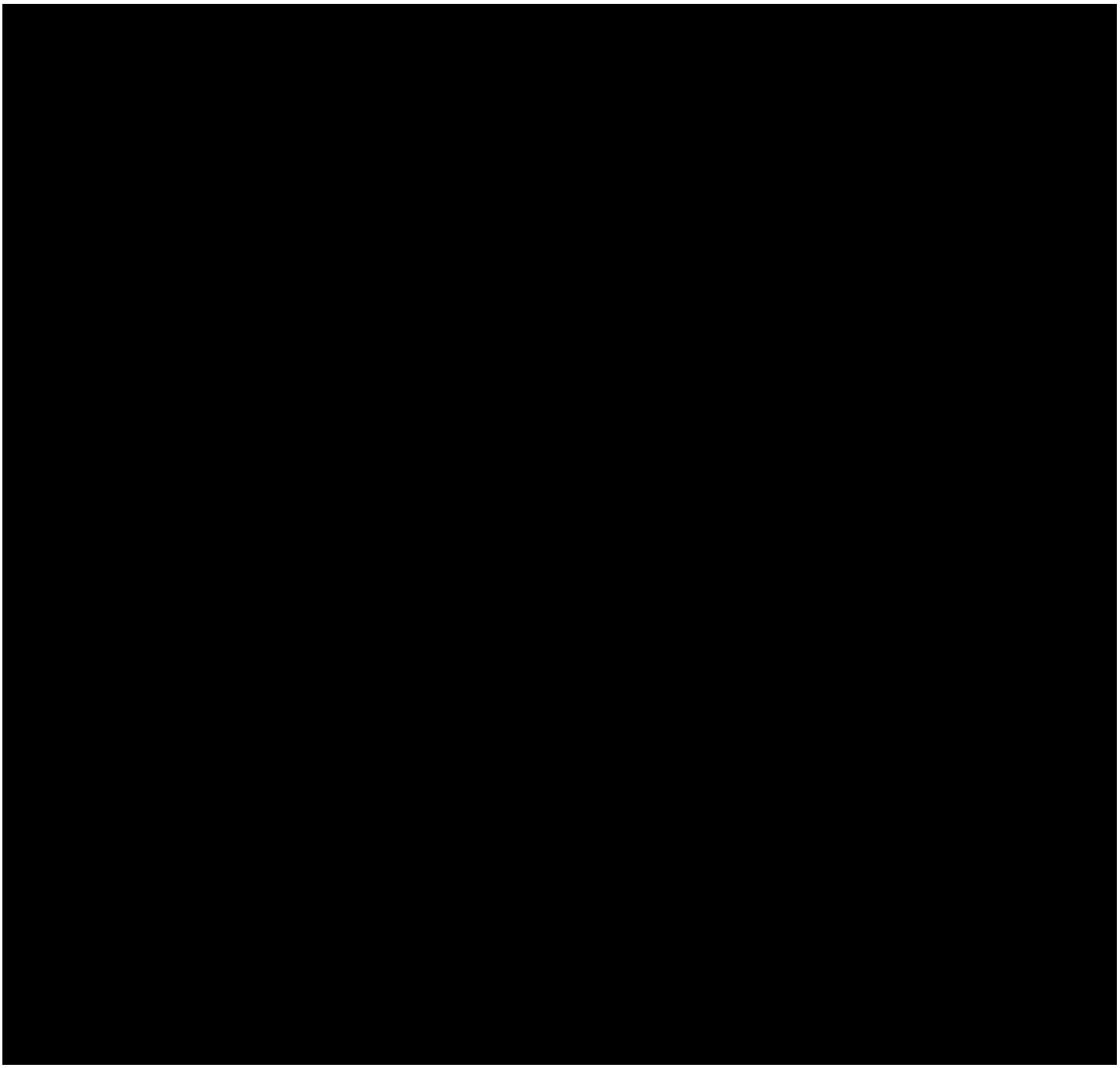
Adverse event	No. of events	Person-Years	Incidence rate (per 100 000 person year)	95% CI
Potentially recurrent events				
Nasopharyngitis				
Pneumonia				
Moderate COPD exacerbation				
Severe COPD exacerbation				
Constipation				
Diarrhoea				
Urinary retention				
Urinary tract infection				
Urticaria				
Rash				
Incident events (no occurrence of corresponding codes during the 1-year baseline period)				
Arrhythmia				
Myocardial ischemia				
Supraventricular tachycardia				
Glaucoma				
Nonfatal myocardial infarction				
Nonfatal hemorrhagic stroke				
Nonfatal ischemic stroke				
Nonfatal Acute, but ill-defined, cerebrovascular disease				
Death				

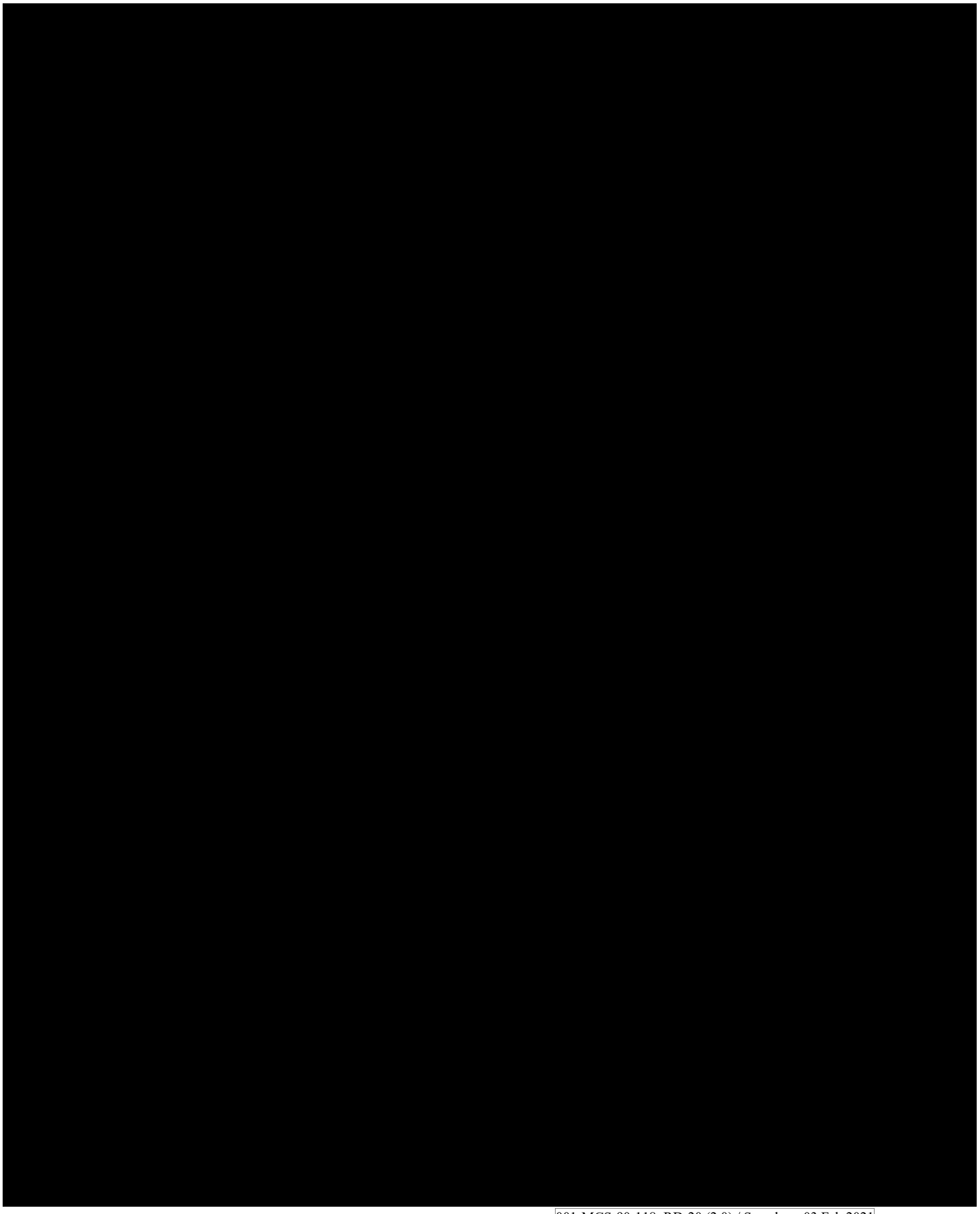
Table 3. Secondary outcome (baseline comparison between two study groups)

	Tio/Olo cohort N=xxxx		LAMA/LABA cohort N=xxxx		Standardized difference
	N	%	N	%	
COPD treatments in 1 year prior to index date					
LAMA					
LABA					
ICS					
ICS+LABA free combination					
ICS+LAMA free combination					
LAMA+LABA free combination					
ICS+LAMA+LABA free combination					
ICS/LABA FDC					
LAMA/LABA FDC					
ICS/LAMA/LABA FDC					
Use of other respiratory drugs in 1 year prior to index date					
Mucolytics					
Theophylline					
Short-acting beta-agonists (SABA)					
Short-acting muscarinic antagonists (SAMA)					
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					

	Tio/Olo cohort N=xxxx		LAMA/LABA cohort N=xxxx		Standardized difference
	N	%	N	%	
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					
1					
>=2					
Comorbidities:					
Cardiovascular disease					
Cerebrovascular disease					
Diabetes					
Chronic kidney disease					
Pneumonia					
Cancer					
Cirrhosis					
Charlson Comorbidity Index (CCI) (mean, SD)					
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					







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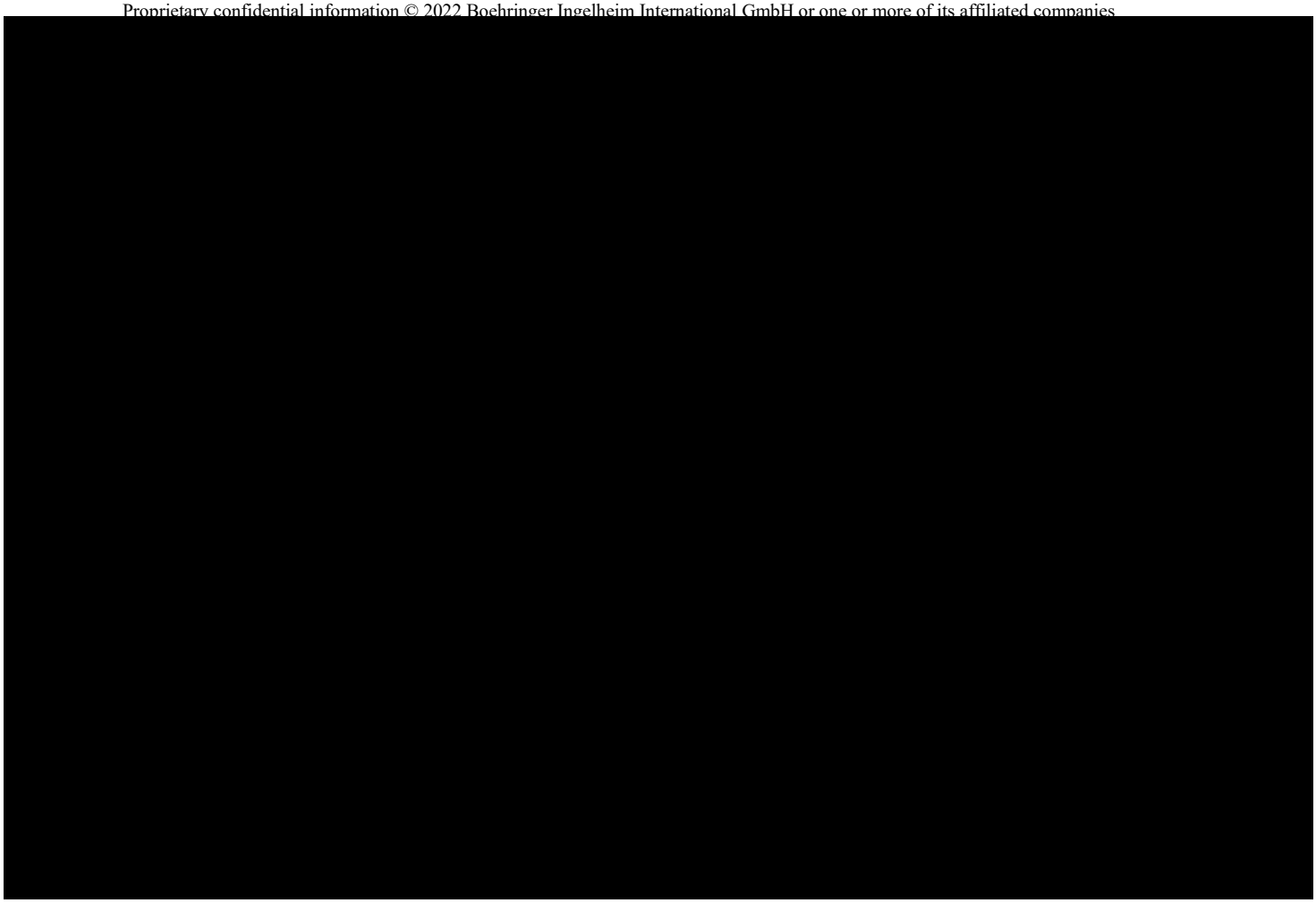

Appendix 1. Relevant ICD-9/10-CM code and procedure code

	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 2. List of COPD medication

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 3. ICD codes and operational definition of adverse events

	Adverse events	ICD codes	Operational definition
1	Nasopharyngitis	**ICD9:** 472.2, 460 **ICD10:** J31.1, J00	Inpatient or outpatient (including ER visit) diagnosis.
2	Pneumonia	**ICD9:** 480-486, 487.0 **ICD10:** J10.0, J11.0, J12-J18,	1. Primary inpatient diagnosis 2. Inpatient diagnosis.
3	Moderate COPD exacerbation	**ICD9:** 491.x, 492.x, 496 **ICD10:** J41.x, J42, J43.x, J44.x	Outpatient diagnosis plus a prescription for oral corticosteroid or antibiotic for respiratory infection
4	Severe COPD exacerbation	**ICD9:** 491.x, 492.x, 496 **ICD10:** J41.x, J42, J43.x, J44.x	Inpatient or ER visits with a primary diagnosis.
5	Arrhythmia	**ICD9:** 427.x **ICD10:** I47.x, I48.x, I49.x	Inpatient or outpatient (including ER visit) diagnosis.
6	Myocardial ischemia	**ICD9:** 410.x, 411.x, 413.x **ICD10:** I20.x, I21.x, I22.x, I23.x, I24.x	Inpatient or outpatient (including ER visit) diagnosis.
7	Supraventricular tachycardia	**ICD9:** 427.0 **ICD10:** I47.1	Inpatient or outpatient (including ER visit) diagnosis.
8	Constipation	**ICD9:** 564.0, 564.00, 564.09 **ICD10:** K59.0, K59.00, K59.09	Inpatient or outpatient (including ER visit) diagnosis.
9	Diarrhoea	**ICD9:** 787.91 **ICD10:** R19.7	Inpatient or outpatient (including ER visit) diagnosis.
10	Urinary retention	**ICD9:** 788.2, 788.20, 788.29 **ICD10:** R33.x	Inpatient or outpatient (including ER visit) diagnosis.
11	Urinary tract infection	**ICD9:** 590, 595, 601, 604 **ICD10:** N10, N12, N15.1, N30.0, N30.8, N30.9, N41.0, N41.2, N41.3, N39.0	1. Primary inpatient diagnosis 2. Inpatient diagnosis. 3. Either inpatient diagnosis or at least 2 outpatients (including ER visit) diagnosis; diagnostic interval within 30 days.
12	Urticaria	**ICD9:** 708.x **ICD10:** L50.x	Inpatient or outpatient (including ER visit) diagnosis.
13	Rash	**ICD9:** 782.1 **ICD10:** R21	Inpatient or outpatient (including ER visit) diagnosis.

14	Glaucoma	**ICD9:** 365.x **ICD10:** H40.x	Inpatient or outpatient (including ER visit) diagnosis from ophthalmologist.
15	Nonfatal myocardial infarction	**ICD9:** 410.x, 411.x **ICD10:** I21.x, I22.x, I23.x	1. Primary inpatient diagnosis + hospital discharge without death certificates 2. Inpatient diagnosis + hospital discharge without death certificates
16	Nonfatal hemorrhagic stroke	**ICD9:** 430, 431, 432.x **ICD10:** I60.x, I61.x, I62.x	1. Primary inpatient diagnosis + hospital discharge without death certificates 2. Inpatient diagnosis + hospital discharge without death certificates
17	Nonfatal ischemic stroke	**ICD9:** 433.x, 434.x **ICD10:** I63.x, I66.x	1. Primary inpatient diagnosis + hospital discharge without death certificates 2. Inpatient diagnosis + hospital discharge without death certificates
18	Nonfatal acute cerebrovascular disease	**ICD9:** 436 **ICD10:** I67.8	1. Primary inpatient diagnosis + hospital discharge without death certificates 2. Inpatient diagnosis + hospital discharge without death certificates
19	Fatal events		All cause of death

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

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: 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 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**:** _____