Boehringer Ingelheim

Protocol for observational studies based on existing data

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BI Investigational Product(s):	Tiotropium bromide + Olodaterol
Title:	Effectiveness and Safety of Maintenance Treatment with Combination of Tiotropium and Olodaterol in Comparison to Maintenance Treatment with a Combination of Inhaled Corticosteroids and Long-acting β2 agonists in COPD patients
Title for lay people:	Comparative Effectiveness and Safety of Tiotropium and Olodaterol in Comparison to LABA/ICS
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Author/Responsible Parties/BI contact person:	Tel.: Mobil: Email:
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Version and Date:	**1.0, 19th February 2020**
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Name of product: Stiolto/Spiolto			
Name of active ingredient: Tiotropium bromide + Olodaterol			
Protocol date:	**Study number:**	**Version/Revision:**	**Version/Revision date:**
19 February 2020	1237-0093	1.0	NA

Title of study:	Effectiveness and Safety of Maintenance Treatment with Combination of Tiotropium and Olodaterol in Comparison to Maintenance Treatment with a Combination of Inhaled Corticosteroids and Long-acting β2 agonists in COPD patients
Team member Epidemiology:	(Principal Investigator)
Project team:	

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Rationale and background:	The treatment of COPD increasingly involves multiple therapies, including long-acting bronchodilators (LAMAs and LABAs) and inhaled corticosteroids (ICS), with combinations of these drugs now formulated into single inhalers. The use of ICS has increased disproportionately with respect to COPD treatment guidelines and may be appropriate only in a subset of these users [P15-12888; P16-12287]. New evidence suggests that patients can be safely weaned off ICS, including the WISDOM trial that observed no difference in the risk of moderate or severe exacerbations between patients who discontinued ICS and those who continued receiving ICS [P14-13477]. Moreover, discontinuation of ICS has been associated with a reduction in the risk of pneumonia [P15-13167]. The recent FLAME randomized trial reported that patients receiving the LABA/LAMA combination had fewer exacerbations than those receiving the LABA/ICS combination over a one-year follow-up period. The ENERGITO study showed significant improvements in lung function with the LAMA/LABA FDC Tio+Olo versus LABA/ICS. Although, a recent population-based observational study showed no difference in exacerbation risk for COPD patients with B-Eosinophils below 4% if treated either with LAMA or LABA/ICS [P18-09975], this data have yet to be confirmed in population based studies in real world conditions. Given high-cost adverse events associated with long-term use of ICS and inconsistent evidence concerning whether there is a clinically relevant benefit of ICS combination therapy in terms of disease control, it is important to assess differences between subsets of COPD patients in terms of the effectiveness and cost of LABA/ICS combination therapies versus other non-ICS options, such as Tiotropium+Olodaterol (Tio+Olo). The proposed study will investigate the comparative effectiveness of Tiotropium and Olodaterol (Tio+Olo) vs any LABA /ICS combination in COPD, describe differences in healthcare utilization, and compare cost effectiveness. Whether associations with time to exacerbation, community acquired pneumonia, escalation to triple therapy, and adverse outcome are modified by exacerbation risk (measured based on individual history and eosinophil levels) will also be assessed. The intended audience is the scientific community, patients, payers and prescribers. The results from the study will be published in the scientific literature.

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Research question and objectives:	The primary objective is to compare the effectiveness of maintenance therapy initiation with the combination treatment Tiotropium and Olodaterol (Olo+Tio) compared with LABA/ICS combination in COPD as the time to the first COPD exacerbation. Secondary objectives are to compare patients treated with Tio+Olo and patients treated with LABA/ ICS combination: (1) Time to community acquired pneumonia, (2) time to escalation to triple therapy (3) time to an adverse outcome including exacerbation, escalation to triple therapy, or pneumonia, and (4) healthcare utilization outcomes and an analysis of all-cause and COPD-specific cost overall and by care setting. Additionally, the study will investigate the effect modification of circulating eosinophil levels and exacerbation history on the safety and effectiveness of Tio+Olo compared with any LABA/ICS. Analyses will be repeated in sub-groups of patients under high or low risk of exacerbation based on previous history of exacerbations in the year preceding cohort entry (with exacerbation history defined as either 1+ hospitalization or 2+ exacerbations in emergency department or outpatients settings [R05-1384]), as well as based on circulating eosinophils (cut-off: B-Eos 300cells/uL [P18-09975]) overall and among those without a history of exacerbation.
Study design:	A incident new-user cohort design will be used, with confounding controlled via fine stratification and reweighting of time-conditional propensity scores

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Population:	The cohort will include all patients with a diagnosis of COPD who received at least one dispensing of a long-acting bronchodilator, Tio+Olo, LABA or for an inhaled corticosteroid from 1 January 2013 until 31 March 2019 (or the most recent date available at the time of cohort extraction). Only fixed-dose combinations products will be included in the main analyses. To increase the likelihood of a diagnosis of COPD, we only include patients 40 years of age or older at initiation of study treatment (i.e., the index date) and exclude all patients with a diagnosis of asthma within the baseline year or lung cancer, interstitial lung disease, or lung transplantation at any time prior to the index date. Patients will need to have at least one year of medical and pharmacy health plan eligibility prior to the date of Tio+Olo or LABA/ICS initiation (index date) to allow the identification of new use and the measurement of baseline covariates. Patients will be followed until switching to the other treatment, the end of the individual's health plan eligibility, escalation of therapy, discontinuation of COPD treatment, or the end of the study period, whichever occurs first. Main analyses will be limited to the first year following the index date. Additional restriction to individuals who have laboratory test result data showing eosinophil levels will occur for relevant sensitivity analyses.
Study data source:	The HealthCore Integrated Research Database^{SM} (HIRD)
Expected study size:	Overall: New users of Tio+Olo: 5,469 New users of LABA/ICS: 53,432 With eosinophil result data: New users of Tio+Olo: 2,207 New users of LABA/ICS: 19,407

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Main criteria for inclusion:	- New users of Tio+Olo or LABA/ICS in a fixed dose combination between January 2013 and March 2019. - Diagnosis of COPD and age ≥ 40 years
Main criteria for exclusion:	-Less than one year of medical history information prior to the index date -Asthma diagnosis within one year prior to the index date -Lung cancer, interstitial lung disease, or lung transplantation at any time prior to the index date -Use of triple therapy (LABA/LAMA/ICS) prior to the index date
Comparison groups:	Initiating Tio+Olo compared to initiating LABA/ICS therapy
Expected duration of exposure:	Analyses will be limited to one year following the index date for the primary and secondary analyses. Sensitivity analyses will use all available exposure data.

2. LIST OF ABBREVIATIONS AND TERMS

BI	Boehringer Ingelheim
BMI	Body Mass Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
DSAs	Data Sharing Agreements
ED	Emergency Department
FDC	Fixed Dose Combination
FTCO	First Treatment Carry-On Analysis
HIPAA	Health Insurance Portability and Accountability Act
HIRD	HealthCore Integrated Research Database
HR	Hazard Ratio
ICD-9	International Classification of Disease, Version 9
ICD-10	International Classification of Disease, Version 10
ICS	Inhaled Corticosteroids
IR	Incidence Rate
IRB	Institutional Review Board
ITT	Intention to Treat
LABA	Long-acting Beta2-agonist
LAMA	Long-acting Muscarinic Antagonists
N	Number
NDI	National Death Index
PHI	Protected Health Information
PS	Propensity Score
RR	Rate Ratio
SOPs	Standard Operating Procedures
cells/µL	Microliter
US	United States

3. RESPONSIBLE PARTIES

(Principal Investigator)

Tel:

4. AMENDMENTS AND UPDATES

There are currently no amendments to the protocol.

5. MILESTONES

Milestone	Planned date
Start of data collection: Data extraction and coding	August 1, 2019
End of data collection:	March 31, 2019*
Study progress report(s) as referred in Article 107m(5) of Directive 2001/83/EC:	Not applicable
Interim report(s) of study results:	Not applicable
Registration in the EU PAS register	Not applicable
Final report of study results:	April 2020 (Preliminary results: 19 December 2019)

* This is an observational study based on existing data collected in the form of administrative claims. The date listed reflects the expected end of data availability at the start of analysis.

6. RATIONALE AND BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality throughout the world [P07-11503]. It has recently risen to become the third leading cause of death in the US [R13-1383]. Long-acting bronchodilator medications, that include long-acting beta2-agonists (LABAs) and the long-acting muscarinic antagonists (LAMAs) such as the anticholinergic tiotropium, have become central maintenance therapy to the management of COPD, with inhaled corticosteroids (ICS) added with increasing severity [P07-11503].

The treatment of COPD increasingly involves multiple therapies including long-acting bronchodilators (LAMAs and LABAs) and inhaled corticosteroids (ICS) with combinations of these drugs now formulated into single inhalers. Optimal treatment choice appears to be influenced by a variety of factors including exacerbation risk. Although the use of ICS has increased disproportionately with respect to COPD treatment guidelines, it may be appropriate only in a subset of these users [P15-12888; P16-12287]. For example, the recent FLAME randomized trial reported that patients receiving the LABA/LAMA combination had fewer exacerbations than those receiving the LABA/ICS combination over a one-year follow-

up period. In the WISDOM trial, in patients on triple therapy the risk of moderate or severe exacerbations was similar among those who discontinued and those who continued ICS. The ENERGITO study showed significant improvements in lung function with the LAMA/LABA FDC Tio+Olo versus LABA/ICS. Further, pneumonia associated with long-term ICS use increases the risk of hospitalization, and is associated with substantial increases in cost [P07-09514; R18-2874].

Although, a recent population-based observational study showed no difference in exacerbation risk for COPD patients with B-Eosinophils below 300 cells/uL) if treated either with LAMA or LABA/ICS [P18-09975], this data have yet to be confirmed in population based studies in real world conditions. Given high-cost adverse events associated with long-term use of ICS and inconsistent evidence concerning whether there is a clinically relevant benefit of ICS combination therapy in terms of disease control, it is important to assess differences between subsets of COPD patients in terms of the effectiveness and cost of LABA/ICS combination therapies versus other non-ICS options, such as Tiotropium+Olodaterol (Tio+Olo).

The proposed study will investigate the comparative effectiveness of Tio+Olo vs any LABA /ICS combination in COPD, describe differences in healthcare utilization, and compare cost effectiveness. Whether associations with time to exacerbation, community acquired pneumonia, escalation to triple therapy, and adverse outcome are modified by exacerbation risk (measured based on individual history and eosinophil levels) will also be assessed.

7. RESEARCH QUESTIONS AND OBJECTIVES

The goal of this study is to investigate the risk of COPD exacerbations, community acquired pneumonia, and health care utilization in patients treated with Tio+Olo in comparison to patients treated with LABA/ICS combination therapy. All analyses will be conducted for the total population, as well as in sub-groups of patients under high- or low risk of exacerbation based on (1) previous history of exacerbations in the year preceding cohort entry (cut-off: 0-1 vs 2+ exacerbations [R05-1384], (2) circulating eosinophils (cut-off B-Eos 300 cells/uL [P18-09975]), and (3) as an exploratory analysis, a combination of exacerbation history and circulating eosinophils.

Primary objective:
The primary objective is to compare the effectiveness of new use of maintenance therapy initiation with the combination treatment Tiotropium and Olodaterol (Tio+Olo) compared with new use of LABA/ICS combination in COPD as the time to the first COPD exacerbation.

Secondary objectives:
Secondary objectives are to compare patients treated with Tio+Olo and patients treated with LABA/ICS combination therapy with respect to:
Time to first community acquired pneumonia,
Time to escalation to triple therapy, and

Time to an adverse outcome including exacerbation, pneumonia, or escalation to triple therapy

Exploratory objective:
To assess differences between Tio+Olo vs any LABA/ICS combination in all-cause and COPD-specific healthcare utilization and cost overall and by care setting

8. RESEARCH METHODS

8.1 STUDY DESIGN

Population-based propensity score-matched new-user cohort study.

8.2 SETTING

The study will be conducted using administrative healthcare claims and laboratory result data captured in the HealthCore Integrated Research Database (HIRD; details in Section 8.5). The observation period will be from January 2013 until the most recent date available at the time that the cohort is extracted (estimated March 2019).

8.3 PATIENTS

The study cohort will be formed based on the following entry criteria.

Inclusion Criteria:

1. At least one prescription for Tio+Olo combined inhaler or a LABA/ICS combined inhaler between 1 January 2013 and 31 March 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. Sensitivity analyses will also accept free combinations of LABA/ICS.
2. At least one diagnosis of COPD at any time prior to the index date.
3. At least one year of continuous medical and pharmacy health plan eligibility prior to the index date will be required to allow a baseline period for the covariates and identification of new use of the study drugs.

Exclusion Criteria:

1. To increase the likelihood of a true diagnosis of COPD, we will exclude:
    a) All patients less than 40 years of age on the index date, and
    b) All patients with a diagnosis of asthma in the year prior to the index date
2. To limit the population to those without severe lung compromise outside of COPD, we will exclude individuals with lung cancer, interstitial lung disease, or lung transplant identified at any time prior to the index date
3. To restrict the cohort to new users of Tio+Olo or LABA/ICS, we will exclude any individual with use of either Tio+Olo, LABA/ICS, or LABA/LAMA/ICS

combination therapy in free or fixed form for at least one year prior to the index date.

Outpatient laboratory data is available for a subset of patients. Some analyses will be further restricted to the subset of the population with at least one laboratory result showing circulating eosinophil levels within six months before the index date.

Individuals in the study cohort will be followed from the index date until the earliest of the date of a switch in treatment, addition of either an ICS for the Tio+Olo group or of LAMA to the LABA/ICS group, discontinuation of COPD treatment, the end of the study period, or the end of continuous health plan eligibility. Main analyses will be further limited to the first year after cohort entry, with sensitivity analyses considering all available data.

8.4 VARIABLES

8.4.1 Exposures

The exposure measures are based on pharmacy dispensings of the two long-acting bronchodilators under study, namely fixed-dose combination of Tio+Olo and a fixed-dose combination of LABA and ICS, over one year of follow-up. As described in the data analysis section, the as-treated analysis, which is the main analysis, will consider exposure as current use of Tio+Olo or LABA/ICS within the treated groups defined as within the days supply recorded at the time of pharmacy dispensing, allowing for a gap between dispensings of up to 15 days. This gap is allowed in consideration of plausible delays in obtaining medication refills and continued use beyond the days supplied where medication has been missed due to imperfect adherence, and will be varied in sensitivity analyses (see Section 8.9.2). The treatment segment ends at the earliest of the following events:

1. Fifteen days after the end of the observed days supply for the medication received on the index date without a subsequent dispensing of COPD medication (i.e., discontinuation)
2. Initiation of triple therapy (i.e., addition of ICS to Tio+Olo or a LAMA to LABA/ICS (i.e., treatment escalation)
3. Any other change in use of study medication by active ingredient, inclusive of a change to a different combination therapy, change from a fixed form to a free form combination therapy, or a change from combination therapy to monotherapy (i.e., switch)

Changes in dose for medications started on the index date will not impact the end of the treatment segment. Codes used to identify study medications are included in Annex 3.1.

8.4.2 Outcome(s)

8.4.2.1 Primary outcome(s)

The primary outcome event for effectiveness is time to first COPD exacerbation after cohort entry. The event is defined as follows:

- Severe exacerbation:

  - Hospitalization with a principal discharge diagnosis of COPD.
- Moderate exacerbation:
  - An ED visit with a discharge diagnosis of COPD, and/or
  - An antibiotic for a respiratory condition dispensed the same day as an oral corticosteroid

Time to the first COPD exacerbation will be measured from cohort entry until the occurrence of a hospitalization for COPD (severe exacerbation) or ED visit for COPD or prescription of an antibiotic and an oral corticosteroid on the same day (moderate exacerbation). Severe and moderate exacerbations will be considered as a composite for main analyses. Sensitivity analyses will stratify by exacerbation severity.
Although there is precedent for defining moderate exacerbation based on use of antibiotics for a respiratory infection without requiring concomitant oral corticosteroids, we have chosen a more restrictive definition of exacerbation. Because diagnoses listed on outpatient claims often correspond to a patient's past medical history in addition to acute problems, we expect limited ability to capture the indication for which antibiotics are prescribed. As such, including antibiotics alone as a case definition for exacerbation would introduce potentially substantial misclassification of outcome where antibiotics were truly given for non-respiratory infections. Given that our analyses will yield estimates on a ratio measure, non-differentially reduced sensitivity is a less important threat to validity than reduction of outcome specificity, which produces an expectation of bias towards the null hypothesis. In order to test our assumptions that the sensitivity of our outcome definition is not differential between the Tio+Olo and LABA/ICS groups, we would produce counts of patients with antibiotics alone during follow-up, and determine whether the proportion of potential exacerbations that we excluded through this design decision is comparable across groups.

8.4.2.2 Secondary outcome(s)

The first secondary outcome is time to first hospitalization for community-acquired pneumonia (serious pneumonia). Pneumonia will be defined using ICD-9-CM diagnoses 481.x-486.x; 487.0, 507.x, 507.0, 507.1, 507.8, 510.0, 510.9, 511.0, 513.0, 514.x, 517.1, 519.8, 530.84, and ICD-10 diagnosis codes J10.0; J11.0; J12-J18; J22; J69; J85.0; J85.1; J86. This definition has been used successfully in COPD [P07-09514; P16-10095].

The second secondary outcome is time to a pharmacy dispensing indicating escalation to triple therapy, (i.e., addition of ICS to Tio+Olo or a LAMA to LABA/ICS).

The third secondary outcome is time to an adverse outcome including exacerbation, hospitalization for pneumonia, and escalation to triple therapy, defined as time from cohort entry until the earliest primary or secondary outcome as defined above (See Section 8.4.2.1, 8.4.2.2).

8.4.4 Covariates

Patient characteristics at baseline will be assessed for Tio+Olo and LABA/ICS users overall and stratified by history of exacerbation, circulating eosinophils, subgroups defined by both exacerbation and eosinophil levels.

We will identify and describe the following demographic characteristics as of the index date:

- Sex
- Age (years, as both a categorical and a continuous variable)
- Calendar year of cohort entry
- Season of index date (winter, spring, summer, fall)
- US census region of residence
- Insurance type (e.g., Commercial, Medicare)

Additional characteristics will be defined during the 12-month pre-index baseline period:

- Number of previous COPD treatments
- Specific previous COPD treatments
    - LAMA monotherapy
    - LABA monotherapy
    - ICS monotherapy
    - LAMA/ICS combination therapy
- Previous acute COPD exacerbation (measured both overall and in the 30 days prior to cohort entry), categorized as 0, 1, or 2+.
    - All exacerbations (Moderate+Severe)
    - ED visits or dispensings of inhaled corticosteroids/antibiotics (Moderate)
    - Hospitalizations (Severe)
- Use of other respiratory drugs in the 12-month pre-index period::

  - Short-acting beta-agonists
  - Anticholinergics
  - Methylxanthines
  - Muscarinic antagonists
  - Short-acting muscarinic antagonists
- Use of antibiotics commonly prescribed for a respiratory condition (e.g., azithromycin)

Chronic comorbidities will be defined using diagnoses identified during all available data prior to the index date, and will include:

- Cardiovascular disease
- Charlson comorbidity index
- Diabetes
- Thyroid disease
- Renal failure
- Autoimmune disease
- Pneumonia
- Obesity*
- Alcohol use disorder*
- Tobacco use or cessation counselling*
- Cancer (excluding basal cell carcinoma)

*We anticipate limited capture of lifestyle variables known to be risk factors and potential confounders, including obesity, smoking status and excessive alcohol consumption. Although we will describe them as identified in the HIRD, bias analyses to examine the extent to which residual confounding may impact results are also planned.
Additionally to the covariates defined above, we will use the high-dimensional approach to identify variables entering a time-conditional propensity score.

Sub-populations with high or low risk of exacerbations will be defined as based on circulating eosinophils (cut-off of B-Eos 300 cells/uL) as identified based on the laboratory result value that is closest but prior to the index date (within 6 months). Additional stratification will include previous history of exacerbations in the year preceding cohort entry (with exacerbation history defined as either 1+ hospitalization or 2+ exacerbations in emergency department or outpatients settings), and among those without a history of exacerbation at baseline, based on circulating eosinophil results as noted above. We will not present results stratified by circulating eosinophil levels among those with baseline exacerbations due to low counts observed when assessing study feasibility (see Section 8.7).

8.5 DATA SOURCES

This study will be conducted using the HIRD, a large administrative healthcare database maintained by HealthCore for use in health outcomes and pharmacoepidemiologic research. The HIRD includes longitudinal medical and pharmacy claims data from health plan

members across the United States (US). Member enrollment, medical care (professional and facility claims), outpatient prescription drug use, outpatient laboratory test result data, and health care utilization may be tracked for health plan members in the database dating back to January 2006, and with diagnoses recorded in International Classification of Disease, Version 10 (ICD-10) since October, 2015. Laboratory result data are additionally available for those tests that have been performed using two large, national reference laboratories (Quest and LabCorp) [R14-4278]. The database has been used for the study of numerous diseases, including studies of COPD [R19-2324; R19-2321; R19-2323; R19-2322; P15-11025; P14-12233].

8.6 BIAS

Several potential biases are inherent to any observational study in the HIRD. In the absence of randomization, confounding by indication could be an issue. Controlling by propensity score should limit this bias, but can control only for measured covariates and may produce estimates that are impacted by residual confounding. This is of particular importance in the case of lifestyle factors that are less critical to insurance billing and thus poorly captured in claims data. Quantitative bias analyses can formally describe the extent to which these issues are present, but bias analysis parameters are informed by literature and clinical expert opinion. As such, the accuracy of bias corrected analyses is limited by the accuracy of the assumptions that inform them.

Second, there is the possibility of information bias due to misclassification of the outcomes or exposure or missing data, especially, differential missingness of some data (e.g. eosinophils, which may only be measured in sicker patients). The prescriptions dispensed by a pharmacy but not taken by patients could lead to misclassification of exposure. Pharmacy dispensing data does bring us one step closer to patient use than physician prescribing given that the patient has taken the effort to obtain the medication as instructed, however, information such as indication can only be inferred based on diagnostic patterns.

8.7 STUDY SIZE

Preliminary counts of FDC Tio+Olo and ICS/LABA users in the HIRD are shown here:

	Tio+Olo		ICS/LABA	
	N	%	N	%
New users	8,233	100.0	341,352	100.0
At least 12 months of pre-index eligibility	6,263	76.1	187,093	54.8
Age 40+	6,126	97.8	136,310	72.9
At least 1 diagnosis of COPD	5,469	89.3	53,432	39.2
At least 1 eosinophil % result prior to the index date	2,207	40.4	19,407	36.3
Eosinophil result (N, % of those with a result)				
0-2%	1,059	48.0	8,907	45.9
2-4%	745	33.8	6,698	34.5

4%+	403	18.3	3,802	19.6
Eosinophil result, patients with low exacerbation history(0 inpatient and 0-1 outpatient events at baseline, N, %)				
<300 cells/uL	1,381	30.0	12,351	27.1
≥300 cells/uL	481	10.5	4,437	9.7
Unknown	2,739	59.5	28,733	63.1
Eosinophil result, patients with high exacerbation history (1+ inpatient or 2+ outpatient events at baseline, N, %)				
<300 cells/uL	226	26.0	1,820	23.0
≥300 cells/uL	105	12.1	670	8.5
Unknown	537	61.9	5,421	68.5

In a recent analysis of the risk of exacerbations based on Clinical Practice Research Datalink (CPRD), a total of 2,000 patients per cohort detected a 15% difference in risk of a first exacerbation (hazard ratio 0.85) with over 90% power. As such, overall analyses are expected to have adequate power. Analyses that are stratified based on the presence of claims-based indicators of exacerbation and/or limited to individuals with specific eosinophils levels will be more limited. Given low expected sample size, stratification by eosinophil results within individuals with exacerbations at baseline will not be performed.

8.8 DATA MANAGEMENT

All statistical analysis for the study will be conducted using SAS version 9.4 or higher (SAS Institute, Cary, NC). All sensitive data pertaining to the study will be stored on secured servers with access only permitted by approved study team members.

A number of Information Security policies are enforced, audited, and in place at HealthCore, including complex password requirements and encryption systems. Security mechanisms and policies are in place HealthCore's facilities are standard corporate office space. Office space is segregated and managed by monitored electronic access. HealthCore areas which contain project and study-related documents are only access by HealthCore associates or contract personnel. All non-HealthCore associates must be accompanied by an associate at all times in order to enter these areas. All study related files are kept in locked cabinets and work areas. There are no visible labels or client listings viewable by any visitor or passerby. All passwords and user authentication mechanisms are forced changed at regular intervals and there is automatic locking of workstations after a short period of time (< 15 minutes).

Data Center space is permitted on an as required basis and monitored by electronic access. HealthCore maintains a cumulative record that indicates, for any point in time, the names of authorized personnel, their titles, and a description of their access privileges to the Data Center. Data access is restricted, monitored, logged, and audited. HealthCore’s computer

networks have been designed to separate patient or physician identified data from de-identified or masked data. Network security, firewalls, and password permissions control which HealthCore personnel have access to patient or physician identifiers. Unless the study protocol calls for patient or physician authorization or a waiver of authorization as granted by an IRB, no research analyst will have access to patient or physician identifiers within HealthCore's computer systems. All research analysis databases have been de-identified. HealthCore's Data Center is also physically secured by a controlled access facility, with only authorized personnel having access to network servers, tape libraries and other media that contains patient identifiers.

Research analysis files used by HealthCore do not contain patient or physician identifiers unless necessary to perform such research; if such is the case, access will be made after receipt of the patient's or physician's authorization or IRB waiver of such authorization has been granted. It is also HealthCore policy to provide for secure storage of study materials, including data, reports, and other files after the study is completed, with a destroy date assigned based on study requirements. HealthCore reviews data requirements for each study to assure that only the minimum of patient or physician information is obtained to answer the research question(s). For those studies where direct patient identifiers are needed for additional data collection such as medical chart abstracts, access to information will be limited to the greatest possible extent within the research team. Both structural and contractual safeguards reinforce policies to minimize the risk of breaching patient or physician privacy. The structural safeguards include a clearly defined data flow process. This process minimizes the risk of individual identifiers being improperly used or disclosed. The contractual safeguards include contractual binding to confidentiality of individuals involved in the research.

8.9 DATA ANALYSIS

8.9.1 Main analysis

All analyses will be presented for each group (Tio+Olo vs LABA/LAMA/ICS) overall and stratified as follows:

- History of exacerbation: 0 inpatient and 0-1 outpatient events
- History of exacerbation: 1+ inpatient or 2+ outpatient events
- Circulating eosinophils: B-Eos <300 cells/µL
- Circulating eosinophils: B-Eos 300 cells/µL+
- History of exacerbation: 0 inpatient and 0-1 outpatient events & circulating eosinophils: B-Eos <300 cells/uL
- History of exacerbation: 0 inpatient and 0-1 outpatient events & circulating eosinophils: B-Eos 300 cells/uL+

We will first describe formation of the study cohort. Patient characteristics at baseline in patients treated with Tio+Olo and patients treated with LABA/ICS will be described separately using standard descriptive statistics. Because eosinophil levels may vary based on exacerbation, we will also provide a count and percentage of the number of individuals whose eosinophil results were recorded within 30 days of an exacerbation event.

High-dimensional propensity scores including both pre-specified and data-derived variables will then be calculated. We will use fine stratification and reweighting of the exposure propensity score to control for measured covariates [R19-3030]. Balance of patient characteristics between the cohorts will be described before and after propensity score application and compared using standardized differences (in the crude population and the reweighted pseudo-population). Standardized differences greater than 0.10 (10%) will be taken to indicate imbalance and further refinement approaches will be applied.

For the analysis of the primary objective, a Cox proportional hazard regression model will be used to perform an as-treated analysis that assesses the effect of current use of Tio+Olo combination versus the LABA/ICS combination on the risk of a first COPD exacerbation. It will provide an estimate of the hazard ratio (HR) of a COPD exacerbation associated with Tio+Olo use relative to LABA/ICS use, along with 95% confidence intervals (CI). Current use will be defined based on the days supply during the period of overlap, allowing a grace period of 15 days following the end of days supply to account for intermittent use.

Stratified analyses will use the same approach. Because not all individuals will have available laboratory result data available, fine stratification and reweighting by propensity score will be repeated within the subset of the cohort with available results to create weighted populations suitable for these stratified analyses. Potential effect modification by B-Eosinophils and/or exacerbation history will be studied by comparing models with and without interaction terms and through qualitative consideration of differences in stratum-specific estimates.

The analysis of the secondary objectives related to the risk of pneumonia, treatment escalation, and an adverse outcome will use a Cox proportional hazard regression model with an as-treated approach, similar to that of the primary analysis.

In terms of healthcare utilization, we will present continuous and categorical variables using standard descriptive statistics to describe total visits and total costs related to inpatient, outpatient, office visit, and emergency care as well as total pharmacy dispensings, distinct medications used, and pharmacy costs. Utilization and costs will be stratified to facilitate comparison between Tio+Olo and LABA/ICS, and presented by individual setting and as a composite. All-cause and COPD-specific data will be shown.

8.10 QUALITY CONTROL

HealthCore operates observational research studies with the goal that the services provided to our clients are of high quality. To support this imperative we believe it is critical 1) to have dedicated training and quality resources and 2) that all talking points and major processes to be implemented with the study be approved by Boehringer Ingelheim in advance.

HealthCore's quality control program is centralized within the Regulatory Compliance Office. The Regulatory Compliance Office Manager is responsible for quality control and reports directly to the Vice President of Operations of HealthCore on all quality matters. HealthCore's quality system is organized around the Quality Manual, the quality checks within the project life cycle, and Standard Operating Procedures (SOPs). HealthCore has procedures for retention of protected health information (PHI) and project data. The study will be tracked at various levels to help ensure that all aspects including project delivery, infrastructure, quality processes, resource management, and financial issues are addressed. To help ensure the highest level of quality on every project, HealthCore has established several layers of quality assurance throughout the project lifecycle.

Role Based Control Checks: Each member of the team is responsible to perform thorough quality control checks on their work. In addition, the PI and Research Project Manager are also accountable for quality of all deliverables.

Quality Check Points: Centralized "checkpoints" have been implemented during the data management cycle to help ensure accurate translation of programming requests.

Quality Assurance Standards: Standard review procedures have been developed and are applied throughout the project lifecycle.

Automation: HealthCore has developed standard definitions of many variables and disease states and developed programs to apply these standards as needed on projects. These standards help ensure consistency, repeatability and accuracy for each project.

8.11 LIMITATIONS OF THE RESEARCH METHODS

Several potential biases are inherent to any observational study in the HIRD. In the absence of randomization, confounding by indication could be an issue. Controlling for propensity to add the second treatment should limit this bias, but can control only for measured covariates

and may produce estimates that are impacted by residual confounding. This is of particular importance in the case of lifestyle factors that are less critical to insurance billing and thus poorly captured in claims data. Quantitative bias analyses can formally describe the extent to which these issues are present, but bias analysis parameters are informed by literature and clinical expert opinion. As such, the accuracy of bias corrected analyses is limited by the accuracy of the assumptions that inform them.

Second, there is the possibility of information bias due to misclassification of the outcomes or exposure or missing data, especially, differential missingness of some data (e.g. eosinophils, which may only be measured in sicker patients). The prescriptions dispensed by a pharmacy but not taken by patients could lead to misclassification of exposure. Pharmacy dispensing data does bring us one step closer to patient use than physician prescribing given that the patient has taken the effort to obtain the medication as instructed, however, information such as indication can only be inferred based on diagnostic patterns.

8.12 OTHER ASPECTS

None

9. PROTECTION OF HUMAN SUBJECTS

HealthCore maintains Data Sharing Agreements (DSAs) and Business Associate Agreements with covered entities that provide protected health information (PHI) incorporated into the HealthCore Integrated Research Database (HIRD). HealthCore's access, use, and disclosure of PHI are in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule [45 CFR Part 160 and Subparts A and E of Part 164]. HealthCore does not access, use, or disclose PHI other than as permitted by HIPAA and its Business Associate Agreements. When using PHI for research, this typically means we will use PHI to create limited data sets for research, or when that is not feasible we may obtain a specific waiver of the HIPAA authorization requirements from an Institutional Review Board (IRB). HealthCore also takes into consideration other federal and state laws and regulations that might limit use of certain types of data more than HIPAA, including those laws related to identifiable records related to substance abuse and human immunodeficiency virus.
The current study is designed as an analysis based on medical and pharmacy claims data from a large insured population in the United States (US). There is no active enrollment or active follow-up of study subjects, and no data will be collected directly from individuals.
At no time during the conduct of this study will HealthCore provide patient or provider identifying information to Boehringer Ingelheim All data and/or results will be in an aggregated and de-identified format. Data variables with values ≤10 will be reported only as "≤10." Boehringer Ingelheim will not attempt to re-identify any results provided for the study.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Data is anonymized and extracted, analyzed, validated and reported in aggregate.
There is no potential that any employee of BI or agent working on behalf of BI will access individual patient data in which the patient may be identified during data compilation, data reporting or data analysis.

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

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

We plan to publish the study in a peer-reviewed medical journal.
Authorship and publication will follow the corresponding BI SOP 001-MCS-00-002 and guidelines of good scientific practice.

12. REFERENCES

12.1 PUBLISHED REFERENCES

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P14-13078 Rossi A, Guerriero M, Corrado A. Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO). Respir Res 2014;15:77.

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P15-11025 Trudo F, Kern DM, Davis JR. Comparative effectiveness of budesonide/formoterol combination and tiotropium bromide among COPD patients new to these controller treatments. Int J Chron Obstruct Pulmon Dis. 2015;10:2055–2066.

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R05-1384 Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017.

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R19-3030 Desai, R.J., et al., A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent. Epidemiology, 2017. 28(2): 249-257.

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12.2 UNPUBLISHED REFERENCES

None

13. FUNDING

There are no additional sources of funding.

14. ANNEX

ANNEX 1: LIST OF STAND-ALONE DOCUMENTS

Documents listed in Annex 1 can be maintained separately from the study protocol. They should be clearly identifiable and provided on request. Write "None" if there is no document or list documents in a table as indicated below.

Number	Document reference number	Date	Title
1	None	None	None

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

Study title:
Safety and Effectiveness of Maintenance Treatment with Combination of Tiotropium and Olodaterol in Comparison to Maintenance Treatment with a Combination of Inhaled Corticosteroids and Long-acting β2 Agonists in COPD Patients

Study reference number:
1237-0093

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	13
1.1.2 End of data collection[2]	☒	☐	☐	13
1.1.3 Study progress report(s)	☒	☐	☐	13
1.1.4 Interim progress report(s)	☒	☐	☐	13
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	13

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	15
2.1.2 The objective(s) of the study?	☒	☐	☐	15
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	15
2.1.4 Which formal 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**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	☒	☐	☐	16
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	16
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	25-26

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	16
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	16
4.2.2 Age and sex?	☒	☐	☐	16
4.2.3 Country of origin?	☒	☐	☐	16
4.2.4 Disease/indication?	☒	☐	☐	16
4.2.5 Co-morbidity?	☐	☐	☒	16
4.2.6 Seasonality?	☐	☐	☒	19
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	16

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorizing exposure)	☒	☐	☐	17
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	17, 20-21
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	17
5.4 Is exposure classified based on biological mechanism of	☐	☐	☒	

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
action and taking into account the pharmacokinetics and pharmacodynamics of the drug?				
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	17-18
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	18, 20-21

Comments:

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	19-20
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	20

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				20
8.1.1 Exposure? (E.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	20
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	20
8.1.3 Covariates?	☒	☐	☐	
8.2 Does the protocol describe the information available from the data source(s) on:				

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	20
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	20
8.2.3 Covariates? (E.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	20
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	20
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	20
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	20
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	21-22

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	23-26
10.2 Is the choice of statistical techniques described?	☒	☐	☐	23-26
10.3 Are descriptive analyses included?	☒	☐	☐	23
10.4 Are stratified analyses included?	☒	☐	☐	23-26
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	23-26
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	23-26

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	22-23
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	22-23
11.3 Are methods of quality assurance described?	☒	☐	☐	26
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	22-23
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	26

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☐	☒	
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	20-21, 27
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	21-22
12.3 Does the protocol address other limitations?	☒	☐	☐	20-21, 27

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	28
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	22

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
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?	☒	☐	☐	30

Comments:

Name of the main author of the protocol:
Date: DDMMYYYY

Signature: _____

ANNEX 3: ADDITIONAL INFORMATION

Additional annexes may be included if necessary.

ANNEX 3.1: DEFINITION OF STUDY EXPOSURES

See section 8.4.1. Complete list of drug codes will be added to this document after review and approval.

Medication	HCPCS	GPI
LABA (single)		
Indacaterol		44201042X
Salmeterol		4420105810X
Formoterol	J7605, J7606, J7640, Q4099	44201027X 44201012102520
Olodaterol		44201052X
LAMA (single)		
Tiotropium		44100080X
Aclidinium		44100007X
Glycopyrronium	J7642, J7643	44100020X
Umeclidinium		44100090X
Revefenacin		44100075002020
ICS (single)		4440X 4220X
Fluticasone	J7641	44400033X
Budesonide	J7626, J7627, J7633, J7634	44400015X
Beclomethasone	J7622	42200010x 44400010x
Mometasone		42200045101820 44400036X
Flunisolide	J7641	44400030X
Ciclesonide		4440001700x
Dexamethasone		4440002010x
Triamcinolone	J7683, J7684	4440004020x

LABA/LAMA		
Formoterol/glycopyrronium		44209902543220
Indacaterol/glycopyrronium		44209902600110
Vilanterol/umeclidinium		4420990295X
Olodaterol/tiotropium		4420990292X
LABA-ICS		
Fluticasone furoate/salmeterol		4420990270X
Fluticasone furoate/vilanterol		4420990275X
Mometasone/formoterol		4420990290X
Budesonide/formoterol		4420990241X

ANNEX 3.2: DEFINITIONS OF STUDY OUTCOMES

See section 8.4.2. Complete list of codes will be added to this document after review and approval.

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
COPD	491 491 491.1 491.2 491.21 491.22 491.8 491.9 492 492 492.8 496	J41 J41.0 J41.1 J41.8 J42 J43 J43.0 J43.1 J43.2 J43.8 J43.9 J44 J44.0				

		J44.1 J44.9				
Pneumonia	480 480.1 480.2 480.3 480.8 480.9 481 482 482.1 482.2 482.3 482.31 482.32 482.39 482.4 482.41 482.42 482.49 482.81 482.82 482.83 482.84 482.89 482.9 483 483.1 483.8 484.1 484.3 484.5	J10.00 J10.01 J10.08 J11.00 J11.08 J12.0 J12.1 J12.2 J12.3 J12.81 J12.89 J12.9 J13 J14 J15.0 J15.1 J15.20 J15.211 J15.212 J15.29 J15.3 J15.4 J15.5 J15.6 J15.7 J15.8 J15.9 J16.0 J16.8 J17				

	484.6 484.7 484.8 485 486 997.31 997.32	J18.0 J18.1 J18.2 J18.8 J18.9 J69.0 J85.1 J95.4 J95.89				

Medication	HCPCS	GPI
Prednisolone	J2650, J7510, J7512	22100040X 22109902201810 22100045X

ANNEX 3.3: DEFINITIONS OF STUDY COVARIATES

See section 8.4.3.Complete list of codes will be added to this document after review and approval.

Medication	HCPCS	GPI
Short-acting beta-agonists		
Levalbuterol	J7617J7607J7612, J7614,J7615	4420104510X 4420104550X
Albuterol	J7602, J7603, J7609-J7611, J7613, J7616, J7620, J7625, Q4093, Q4094	4420101000X 4420101010X
Terbutaline	J3105J7680,J7681	442010602X
Isoproterenol	J7657 J7658 J7659	44201040X

	J7660	
Methylxanthines		
Aminophylline		4430001000x 4430001010x
Theophylline (SR)	J2810	4430004000x 499100240X 4499100220X 4499100242X 4499100250X 44992203X 44993003X 44993204X 44999003X 44999602X 4499220310X 4499960270X 4499220315X
SAMA (Short-acting muscarinic antagonists)		
Ipratropium bromide	J7644, J7655	4230X 44100030X
Antibiotics for a respiratory condition		
Aamikacin	J0278	07000010x
Amoxicillin/potassium clavulanate		0199000220x
Amoxicillin		01200010x
Ampicillin	J0290	01200020x
Ampicillin-sulbactam	J0295	0199000225x
Azithromycin	J0456	03400010x
Aztreonam	S0073	16000005x
Cefaclor		02200040x
Cefdinir		02300040x
Cefepime	J0692	02400040x
Cefixime		02300060x
Cefotaxime	J0698	02300075x
Cefpodoxime		02300065x
Cefprozil		02200062x
Ceftazidime	J0713, J0714	02300080x
Ceftriaxone	J0696	02300090x

Cefuroxime	J0697	02200065x
Ciprofloxacin	J0744	05000020x
Clarithromycin		03500010x
Doxycycline		04000020x
Ertapenem	J1335	16150030x
Erythromycin	J1364	0310x
Gemifloxacin		05000083x
Imipenem	J0743	16159902x
Levofloxacin	J1956	05000034x
Linezolid	J2020	16230040x
Meropenem	J2185	16150050x
Moxifloxacin	J2280	05000037x
Penicillin G benzathine	J0561, J0558	01990002x, 01100020x
Penicillin VK		01100040x
Piperacillin	S0081	01400040x
Piperacillin-tazobactam	J2543	019900027x
Procaine penicillin	J0558, J2510	
Ticarcillin		01400050x
Ticarcillin-clavulanate	S0040	019900023x
Trimethoprim-sulfamethoxazole	S0039	169900023x
Vancomycin	J3370	16000060102x

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
Asthma	493	J45				
	493	J45.2				
	493	J45.20				
	493.01	J45.21				
	493.02	J45.22				
	493.1	J45.3				
	493.1	J45.30				

	493.11 493.12 493.2 493.2 493.21 493.22 493.8 493.81 493.82 493.9 493.9 493.91 493.92	J45.31 J45.32 J45.4 J45.40 J45.41 J45.42 J45.5 J45.50 J45.51 J45.52 J45.9 J45.90 J45.901 J45.902 J45.909 J45.99 J45.990 J45.991 J45.998				
Lung cancer	162 231.2 197.0 176.4 235.7 V10.11	C33 C34.00 C34.10 C34.2 C34.30 C34.80 C34.90 C46.50 C78.00 D02.20 D38.1 Z85.118				
Interstitial lung disease	516.6* 516.34	J84.115 J84.83 J84.841				

		J84.842 J84.843 J84.848				
Lung transplant			33.50 33.51 33.52	0BYC0Z0 0BYC0Z1 0BYC0Z2 0BYD0Z0 0BYD0Z1 0BYD0Z2 0BYF0Z0 0BYF0Z1 0BYF0Z2 0BYG0Z0 0BYG0Z1 0BYG0Z2 0BYH0Z0 0BYH0Z1 0BYH0Z2 0BYJ0Z0 0BYJ0Z1 0BYJ0Z2 0BYK0Z0 0BYK0Z1 0BYK0Z2 0BYL0Z0 0BYL0Z1 0BYL0Z2	S2060 S2061	00580 32850 - 32856 33935 33933

				0BYM0Z0 0BYM0Z1 0BYM0Z2		
Cardiovascular disease	410.xx-414.xx 427.xx; 785.0; 785.1 426.xx 428.xx 401.xx–405.xx 440.xx; 441.xx; 442.xx; 443.xx 272.x 393-398; 421.x; 422.xx; 746.0x-746.7	I20.%-I25.%%% I47.%, I48.%%; I49.%% I44.%%; I45.%% I50.%% I11.%; I13.%; O10.1%; O10.3% I70.%%%; I71.%%; I72.%; I73.%% E78.%% I05.%-I09.%%; I33.%-I39; Q22.%, Q23.%	37.7x–37.8x, 37.94–37.99			
Diabetes	250 250.01 250.02 250.03 250.1 250.11 250.12 250.13 250.2 250.21 250.22 250.23 250.3 250.31	E10.10 E10.11 E10.21 E10.29 E10.311 E10.319 E10.36 E10.37X1 E10.37X2 E10.37X3 E10.37X9 E10.39 E10.40 E10.51				

	250.32	E10.618				
	250.33	E10.620				
	250.4	E10.621				
	250.41	E10.622				
	250.42	E10.628				
	250.43	E10.630				
	250.5	E10.638				
	250.51	E10.641				
	250.52	E10.649				
	250.53	E10.65				
	250.6	E10.69				
	250.61	E10.8				
	250.62	E10.9				
	250.63	E11.00				
	250.7	E11.01				
	250.71	E11.10				
	250.72	E11.11				
	250.73	E11.21				
	250.8	E11.29				
	250.81	E11.311				
	250.82	E11.319				
	250.83	E11.36				
	250.9	E11.39				
	250.91	E11.40				
	250.92	E11.51				
	250.93	E11.618				
		E11.620				
		E11.621				
		E11.622				
		E11.628				
		E11.630				
		E11.638				

		E11.641 E11.649 E11.65 E11.69 E11.8 E11.9 E13.10				
Thyroid disease	226, 240.0, 240.9, 241.0, 241.1, 241.9, 242*, 243, 244*, 245*, 246*, 790.94	D09.3, D34, D44.0, E01.1,E01.2, E01.8, E02, E03*, E04*, E05*, E06*, E07*, E01.0 E89.0				
Renal failure	403 403.01 403.1 403.11 403.9 403.91 585.1 585.2 585.3 585.4 585.5 585.6 585.9 586 584.5 584.6 584.7 584.8	I12.0 I12.9 N18.1 N18.2 N18.3 N18.4 N18.5 N18.6 N18.9 N17.0 N17.1 N17.2 N17.8 N17.9				

	584.9					
Autoimmune disease	135	D86.9				
	274.9	M10.9				
	275.49	E83.59				
	279.49	D89.89				
	283	D59.0				
	443	D59.1				
	448.9	I73.00				
	530.5	I73.01				
	555.9	I78.9				
	571.42	K22.4				
	571.6	K50.90				
	576.1	K75.4				
	579	K74.3				
	696	K74.4				
	696.1	K74.5				
	710	K83.0				
	710.1	K90.0				
	710.2	L40.50				
	710.3	L40.54				
	710.9	L40.59				
	711.9	L40.0				
	712.19	L40.1				
	714	L40.2				
	714.3	L40.8				
	715.09	M32.10				
	715.11	M34.0				
	715.12	M34.1				
	715.13	M34.2				
	715.14	M34.81				
	715.15	M34.82				
	715.17	M34.83				

	715.18 715.96 719.42 719.44 719.45 719.47 719.49 720 721.9 725 729.1 729.5 795.79	M34.89 M34.9 M35.00 M35.01 M35.02 M35.03 M35.04 M35.09 M33.90 M35.9 M00.9 M11.9 M06.9 M08.00 M15.0 M19.019 M19.029 M19.039 M19.049 M16.0 M16.10 M16.11 M16.12 M19.079 M19.91 M17.9 M25.529 M79.643 M79.646 M25.559 M25.579 M25.50 M45.9 M47.819 M35.3 M60.9 M79.1 M79.609 R76.0 R76.11 R76.12 R76.8 R76.9				

Obesity	278 278.01 278.02 278.03 278.1 278.2 278.3 278.4 278.8 V85.30 V85.31 V85.32 V85.33 V85.34 V85.35 V85.36 V85.37 V85.38 V85.39 V85.41 V85.42 V85.43 V85.44 V85.45	E65 E66.01 E66.2 E66.3 E66.9 E67.0 E67.1 E67.3 E67.8 Z68.30 Z68.31 Z68.32 Z68.33 Z68.34 Z68.35 Z68.36 Z68.37 Z68.38 Z68.39 Z68.41 Z68.42 Z68.43 Z68.44 Z68.45				
Alcohol use disorder	303 303.01 303.02 303.03 303.9 303.91 303.92 303.93	F10.159 F10.180 F10.181 F10.188 F10.20 F10.21 F10.229 F10.259	94.46 94.53 94.61 94.62 94.63 94.67 94.68 94.69	HZ2ZZZZ HZ30ZZZ HZ31ZZZ HZ32ZZZ HZ33ZZZ HZ34ZZ		

		F10.27 F10.280 F10.281 F10.288 F10.959 F10.980 F10.99 Z65.8		Z HZ35ZZ Z HZ36ZZ Z HZ37ZZ Z HZ38ZZ Z HZ39ZZ Z HZ3BZZ Z HZ40ZZ Z HZ41ZZ Z HZ42ZZ Z HZ43ZZ Z HZ44ZZ Z HZ45ZZ Z HZ46ZZ Z HZ47ZZ Z HZ48ZZ Z HZ49ZZ Z HZ4BZZ Z HZ93ZZ Z HZ96ZZ Z		
Tobacco use or cessation counselling	305.1* 649.0* 989.84 V15.82	Z72.0 F17.21 F17.210 F17.211 F17.218			C9801 C9802 G0375 G0376 G0436	99406 99407

		F17.219 Z71.6			G0437 G8453 G8455 G8456 G8692 G9276 G9458 G9497 G9642 G9792 G9906 G9908 S9075 S9453 G9902 G9907 G9909	
Cancer (excluding basal cell carcinoma)	140.xx – 195.xx 200.xx – 208.xx 196.xx - 199.xx EXCLUDING: 173.01 173.11 173.21 173.31 173.41 173.51 173.61 173.71 173.81 173.91	C00%-C76%, C81%-C96% C77%-C80%EXCLUDING: C44.01 C44.111 C44.1121 C44.119 C44.91 C44.311 C44.319 C44.310 C44.510 C44.511 C44.519 C44.41 C44.81 C44.211 C44.212 C44.219 C44.611 C44.612				

		C44.619 C44.711 C44.712 C44.719				

ANNEX 3.4: STATISTICAL CONSIDERATIONS

See section 8.9.

APPROVAL / SIGNATURE PAGE

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Title: Effectiveness and Safety of Maintenance Treatment with Combination of Tiotropium and Olodaterol in Comparison to Maintenance Treatment with a Combination of Inhaled Corticosteroids and Long-acting β2 agonists in COPD patients

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader		19 Feb 2020 10:55 CET
Approval- of Global Epidemiology		19 Feb 2020 11:29 CET
Approval- Safety Evaluation Therapeutic Area		19 Feb 2020 14:55 CET
Approval-Team Member Medicine		02 Mar 2020 09:18 CET
Approval-Team Member Medicine		02 Mar 2020 09:48 CET

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