Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document Number:	**c30699487-01**
BI Study No.:	1237-0094
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, Long-acting β2 Agonists and Long-acting Muscarinic Antagonists in COPD Patients
Title for lay people:	Comparative Effectiveness and Safety of Tiotropium and Olodaterol in comparison to Triple Therapy
Date of last version of protocol:	NA
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Author/Responsible Parties/BI contact person:	Authors/Responsible parties: Tel.: Mobil: Fax: Email:
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Signature of EU-QPPV: **only applicable for PASS**	Not applicable

Version: 1.0	**Date : 12 Dec 2019**

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ABSTRACT

Name of company: Boehringer Ingelheim			Boehringer Ingelheim
Name of product: Spiolto			
Name of active ingredient: Tiotropium bromide + Olodaterol			
Protocol date:	**Study number:**	**Version/Revision:**	**Version/Revision date:**
12 December 2019	1237-0094	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, Long-acting β2 Agonists and Long-acting Muscarinic Antagonists in COPD Patients
Team member Epidemiology:	and
Project team:	(Principal Investigator)

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12 December 2019	1237-0094	1.0	NA

Rationale and background:	The treatment of COPD involves multiple therapies, including long-acting β2 agonists (LABA) (with and without inhaled corticosteroids (ICS) and long-acting muscarinic antagonists (LAMA), with combinations of these drugs now formulated into single inhalers. There are recommendations to restrict triple therapy use further, to only patients who are likely to respond to ICS (such as those with asthma-COPD overlap or patients with high risk of exacerbations and elevated blood eosinophils [P15-08642, P07-11503, R19-3048]. There is an increasing body of evidence suggesting that ICS are particularly effective at reducing the incidence of COPD exacerbations in patients only with a very high blood eosinophil concentration, but not in normal levels [P18-09975]. Hence there is a clear need for better evidence on specific patient populations upon which to base treatment recommendations. This non-interventional study aims to assess the comparative effectiveness of combination Tiotropium and Olodaterol (Tio+Olo) (FDC) compared to combination LAMA/LABA and ICS (fixed or open), and to explore whether this varies across COPD sub populations defined by exacerbation risk. The intended audiences are payers and prescribers. The results from the study will be published in the scientific literature.

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Name of active ingredient: Tiotropium bromide + Olodaterol			
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12 December 2019	1237-0094	1.0	NA

Research question 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 ICS/LABA/LAMA. All analyses will be repeated 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 (with exacerbation history defined as either 1+ hospitalization or 2+ exacerbations in emergency department or outpatients settings [R05-1384]), and (2) circulating eosinophils (cut-off B-Eos 300 cells/uL [P18-09975]) Both overall and among those without a history of exacerbation. The primary objective is to compare the effectiveness of maintenance therapy initiation with the combination treatment Tiotropium and Olodaterol (Tio+Olo) compared with any LABA/LAMA/ICS combination in COPD as the time to the first COPD exacerbation. The secondary objective is to assess the association between maintenance therapy initiation with the combination treatment (Tio+Olo vs any LABA/LAMA/ICS combination in COPD and time to community acquired pneumonia. Additionally, we will assess differences between Tio+Olo vs any LABA/LAMA/ICS in healthcare utilization and all-cause and COPD-specific cost overall and by care setting.
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 consist of all patients in the HIRD with a diagnosis of COPD who received Tio+Olo or combination LABA/LAMA/ICS treatment from 1 January 2013 until 31 March 2019 (or the most recent date available at the time of cohort extraction). To increase the likelihood of a diagnosis of COPD and decrease the likelihood of including misdiagnosed asthma patients, we will only include patients 40 years of age or older on the index date and exclude all patients with a diagnosis of asthma within the year prior to the index date or lung cancer, interstitial lung disease, or lung transplantation at any time prior to the index date. Patients will have at least one year of medical history information prior to the cohort entry date to allow the identification of new use and the measurement of baseline covariates. Patients will be followed until switching to the other treatment, other changes in therapy, discontinuation of COPD treatment, the end of the individual's health plan eligibility, 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: 5,458 New users of LABA/LAMA/ICS: 42,361 With eosinophil result data: New users of Tio+Olo: 2,198 New users of LABA/LAMA/ICS: 15,712
Main criteria for inclusion:	- New users of Tio+Olo on the same date or of LABA, LAMA and ICS, either as a fixed-dose combination (LABA/LAMA/ICS) or free combination (LABA/ICS + LAMA, etc), on the same date between January 2013 and March 2019. - Diagnosis of COPD prior to first maintenance inhaler and age ≥ 40 years at index date

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Main criteria for exclusion:	-Less than one year of medical history information prior to the date of combined treatment initiation (index date) -Lung cancer, interstitial lung disease, or lung transplantation at any time prior to the index date -Asthma diagnosis within one year prior to the index date
Comparison groups:	Initiating Tio+Olo compared to initiating LABA/LAMA/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.

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1. LIST OF ABBREVIATIONS AND TERMS

AE	Adverse Event
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
EMA	European Medicines Agency
FDC	Fixed Dose Combination
GVP	Guideline on Good Pharmacovigilance Practices
HIPAA	Health Insurance Portability and Accountability Act
HIRD	HealthCore Integrated Research Database
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
PHI	Protected Health Information
PS	Propensity score
PSTAT	Project Statistician
PY	Person-years at risk
RR	Rate Ratio
TIO+OLO	Tiotropium+Olodaterol

TM Epi	Team Member Epidemiology
cells/µL	Microliter
US	United States
UTS	Up-to-standard

2. RESPONSIBLE PARTIES

(Principal Investigator)

Tel:

3. AMENDMENTS AND UPDATES

There are currently no amendments to the protocol.

4. MILESTONES

Milestone	**Planned date**
Start of data collection: Data extraction and coding	August 1, 2019
End of data collection:	Not applicable. This study is an observational study based on existing data.
Study progress report(s) as referred in Article 107 m(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)

5. RATIONALE AND BACKGROUND

The treatment of COPD involves multiple therapies, including Long-acting β2 agonists (LABA) (with and without inhaled corticosteroids (ICS) and long-acting muscarinic antagonists (LAMA), with combinations of these drugs now formulated into single inhalers.

Several trials compared a single-inhaler triple therapy with an ICS/LABA and a LAMA respectively and found greater benefit with triple FDC [P19-08111]. However, they represent a limited view of the patients who could potentially use these treatments so that a real-world study of patients who are representative of clinical practice is of interest.

There are recommendations to restrict triple therapy use further, to only patients who are likely to respond to ICS (such as those with asthma-COPD overlap or elevated blood eosinophils [P15-08642). There is an increasing body of evidence suggesting that ICS are particularly effective at reducing the incidence of COPD exacerbations in patients only with a very high blood eosinophil concentration, but not in normal levels [P18-09975]. Hence there is a clear need for better evidence on specific patient populations upon which to base treatment recommendations.

This non-interventional study aims to assess the comparative effectiveness of combination Tiotropium and Olodaterol (Tio+Olo) (FDC) compared to combination LAMA/LABA and ICS (fixed or open) This study will provide useful data on the relative benefits of different combinations in treating COPD patients The intended audiences are payers and prescribers. The results from the study will be published in the scientific literature.

6. 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 ICS/LABA/LAMA. All analyses will be conducted for the total population, as well as in sub-groups of patients under (1) high- or low risk of exacerbation based on previous history of exacerbations in the year preceding cohort entry (cut-off: 0-1 vs 2+ exacerbations [P07-11503], (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 objectives:
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/LAMA/ICS combination in COPD as the time to the first COPD exacerbation.

Secondary objective:
The secondary objective is to assess the association between maintenance therapy initiation with the combination treatment (Tio+Olo vs any LABA/LAMA/ICS combination in COPD and time to community acquired pneumonia.

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

7. RESEARCH METHODS

7.1 STUDY DESIGN

Population-based incident new-user cohort design.

7.2 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 7.5). 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).

7.3 SUBJECTS

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

Inclusion Criteria:

1. At least one prescription for Tio+Olo or a LABA/LAMA/ICS combination between 1 January 2013 and 31 March 2019.
    a. For Tio+Olo users, the first dispensing of Tio+Olo will be defined as the index date.
    b. LABA/LAMA/ICS use can occur either in free or fixed combinations. The first date when all three medications are used based on either concurrent or overlapping dispensings in the pharmacy claims data will be defined as the index date.
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 ICS for the Tio+Olo 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.

7.4 VARIABLES

7.4.1 Exposures

The exposure measures are based on pharmacy dispensings of the study medications, namely Tio+Olo and LABA/LAMA/ICS combination therapy. As described in the data analysis section, the as-treated analysis, which is the main analysis, will consider continuing exposure of the initial treatment of Tio+Olo or LABA/LAMA/ICS within the treated groups defined by 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 7.9.2). Codes used to identify study medications are included in Annex 3.1.

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, applies to Tio+Olo only)
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.

7.4.2 Outcome(s)

7.4.2.1 Primary outcome(S)

The primary outcome event for effectiveness is the first COPD exacerbation to occur 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
  - Dispensing of an antibiotic and an oral corticosteroid on the same day

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 with the prescription of an antibiotic and/or 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.

7.4.2.2 Secondary outcome(s)

The secondary outcome is the occurrence of the 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].

7.4.3 Covariates

Patient characteristics at baseline will be assessed for Tio+Olo and LABA/LAMA/ICS user 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
  - LABA/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 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 will include patients with high or low circulating eosinophils (B-Eos 300 cells/uL [P18-09975] 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. However, number of patients with baseline exacerbations and data available on B-Eos is very low (see section 7.7) and therefore analysis would not be meaningful and will not be performed.

7.5 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 enrolment, 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]

7.6 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 [R19-3031].

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.

7.7 STUDY SIZE

Preliminary patient counts in the HIRD are shown here:

	Tio+Olo		ICS/LABA/LAMA	
	N	**%**	**N**	**%**
New users	8,233	100.0	82,534	100.0
At least 12 months of pre-index eligibility	6,263	76.1	50,153	60.8
Age 40 +	6,126	97.8	48,267	96.2
At least 1 diagnosis of COPD	5,469	89.3	42,227	87.5
At least 1 eosinophil % result prior to the index date	2,207	40.4	15,699	37.2
Eosinophil result (N, % of those with a result)				
0-2%	1,059	48.0	7,488	47.7
2-4%	745	33.8	5,136	32.7
4%+	403	18.3	3,075	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	9,516	27.3
≥300 cells/uL	481	10.5	3,481	10.0
Unknown	2,739	59.5	21,813	62.7
Eosinophil result, patients with high exacerbation history (1 + inpatient or 2 + outpatien t events at baseline, N, %)			vents	
<300 cells/uL	226	26.0	1,888	25.5
≥300 cells/uL	105	12.1	707	9.5
Unknown	537	61.9	4,822	65.0

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 and analyses that are stratified based on the presence of claims-based indicators of exacerbation are expected to have adequate power. Analyses limited to individuals with specific eosinophils will be more limited. Given low expected sample size, stratification by eosinophil analysis within individuals with exacerbations at baseline will not be performed by Eosinophil categories.

7.8 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.

7.9 DATA ANALYSIS

7.9.1 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 ug/mL
- Circulating eosinophils: B-Eos 300 ug/mL+
- History of exacerbation: 0 inpatient and 0-1 outpatient events & circulating eosinophils: B-Eos < 300 ug/mL
- History of exacerbation: 0 inpatient and 0-1 outpatient events & circulating eosinophils: B-Eos 300 ug/mL +

We will first describe formation of the study cohort. Patient characteristics at baseline in patients treated with Tio+Olo and patients treated with LABA/LAMA/ICS will be described 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 LABA-LAMA-ICS combination versus the Tio+Olo 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 LABA-LAMA-ICS use relative to Tio+Olo 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. This approach allows consideration of exposure as time-dependent, accounting for the changes in exposure during the follow-up. In particular, this analysis excludes patients stopping one or more of the drugs prior to the index date.

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 risk of pneumonia will also use a time-dependent Cox proportional hazard regression model with an as-treated approach, similar to that of the primary analysis.

In addition, we will repeat the primary effectiveness analysis on the time to exacerbation separately for moderate and severe exacerbations.

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.

7.10 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.

7.11 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.

7.12 OTHER ASPECTS

None

8. 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.

9. 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.

10. PLANS FOR DISSEMINATION AND COMMUNICATION OF 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.

11. REFERENCES

11.1 PUBLISHED REFERENCES

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11.2 UNPUBLISHED REFERENCES

None

12. FUNDING

There are no additional sources of funding.

13. 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, Long-acting β2 agonists and long-acting muscarinic antagonists in COPD patients

Study reference number:
205.526

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]	☒	☐	☐	15
1.1.2 End of data collection[2]	☒	☐	☐	15
1.1.3 Study progress report(s)	☒	☐	☐	15
1.1.4 Interim progress report(s)	☒	☐	☐	15
1.1.5 Registration in the EU PAS register	☒	☐	☐	
1.1.6 Final report of study results.	☐	☐	☒	15
	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1Does 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)	☒	☐	☐	17
2.1.2 The objective(s) of the study?	☒	☐	☐	17
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	17
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

[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.

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)	☒	☐	☐	18
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	18
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)	☒	☐	☐	25-27

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1Is the source population described?	☒	☐	☐	18, 22
4.2Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	18
4.2.2 Age and sex?	☒	☐	☐	18
4.2.3 Country of origin?	☒	☐	☐	18
4.2.4 Disease/indication?	☒	☐	☐	18, 22
4.2.5 Co-morbidity?	☒	☐	☐	18, 20-21
4.2.6 Seasonality?	☒	☐	☐	20
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	18

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)	☒	☐	☐	19
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before	☒	☐	☐	19, 22

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
the outcome occurred, use of validation sub-study)				
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	19
5.4 Is exposure classified based on biological mechanism of 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?	☒	☐	☐	19-20
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)	☒	☐	☐	19-20, 22

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)	☒	☐	☐	20-21
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	22

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:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	22
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.)	☒	☐	☐	22
8.1.3 Covariates?	☒	☐	☐	22
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	22
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	22
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	22
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	22
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	22
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	22
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?	☒	☐	☐	22-23

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	25-27
10.2 Is the choice of statistical techniques described?	☒	☐	☐	25-27
10.3 Are descriptive analyses included?	☒	☐	☐	25
10.4 Are stratified analyses included?	☒	☐	☐	25-27
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	25-27
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	25-27

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
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	24
11.3 Are methods of quality assurance described?	☒	☐	☐	24
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	24
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	27

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)	☒	☐	☐	22, 28
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of	☒	☐	☐	22-23

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
follow-up in a cohort study, patient recruitment)				
12.3 Does the protocol address other limitations?	☒	☐	☐	22, 28

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?	☒	☐	☐	28-29
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	24

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?	☒	☐	☐	14

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?	☒	☐	☐	29

Comments:

Name of the main author of the protocol:
Date: 16 August 2019

Signature: _____

ANNEX 3:ADDITIONAL INFORMATION

Additional annexes may be included if necessary.

ANNEX 3.1: DEFINITION OF STUDY EXPOSURES

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

Medication	HCPCS	GPI
Indacaterol/glycopyrronium		44209902600110
Vilanterol/umeclidinium		4420990295X
Olodaterol/tiotropium		4420990292X
LABA-LAMA-ICS		
Fluticasone furoate/umeclidinium/vilanterol		44209903408020

ANNEX 3.2: DEFINITIONS OF STUDY OUTCOMES

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
COPD	491	J41				
	491	J41.0				
	491.1	J41.1				
	491.2	J41.8				
	491.21	J42				
	491.22	J43				
	491.8	J43.0				
	491.9	J43.1				
	492	J43.2				
	492	J43.8				
	492.8	J43.9				
	496	J44				
		J44.0				
		J44.1				
		J44.9				
Pneumonia	480	J10.00				
	480.1	J10.01				
	480.2	J10.08				
	480.3	J11.00				

	480.8	J11.08				
	480.9	J12.0				
	481	J12.1				
	482	J12.2				
	482.1	J12.3				
	482.2	J12.81				
	482.3	J12.89				
	482.31	J12.9				
	482.32	J13				
	482.39	J14				
	482.4	J15.0				
	482.41	J15.3				
	482.42	J15.4				
	482.49	J15.5				
	482.81	J15.6				
	482.82	J15.7				
	482.83	J15.8				
	482.84	J15.9				
	482.89	J16.0				
	482.9	J16.8				
	483	J17				
	483.1	J18.0				
	483.8	J18.1				
	484.1	J18.2				
	484.3	J18.8				
	484.5	J18.9				
	484.6	J69.0				
	484.7	J85.1				
	484.8	J95.4				
	485	J95.89				
	486					
	997.31					

	997.32					

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

ANNEX 3.3: DEFINITIONS OF STUDY COVARIATES

Complete list of ICD-9-CM, ICD-10, CPT, HCPCS, and GPI codes.

Medication	HCPCS	GPI
Short-acting beta-agonists		
Levalbuterol	J7617,J7607,J7612, J7614,J7615	4420104510X 4420104550X
Albuterol	J7602, J7603, J7609-J7611, J7613, J7616, J7620, J7625, Q4093, Q4094	4420101000X 4420101010X
Terbutaline	J3105,J7680,J7681	442010602X
Isoproterenol	J7657 J7658 J7659 J7660	44201040X
Methylxanthines		
Aminophylline		4430001000x 4430001010x
Theophylline (SR)	J2810	4430004000x 499100240X 4499100220X 4499100242X 4499100250X 44992203X 44993003X 44993204X 44999003X 44999602X 4499220310X 4499960270X 4499220315X

Medication	HCPCS	GPI
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

Medication	HCPCS	GPI
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	J45.31				
	493.12	J45.32				
	493.2	J45.4				
	493.2	J45.40				
	493.21	J45.41				
	493.22	J45.42				
	493.8	J45.5				
	493.81	J45.50				
	493.82	J45.51				

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
	493.9	J45.52				
	493.9	J45.9				
	493.91	J45.90				
	493.92	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	S2060 S2061	00580 32850 - 32856 33935 33933

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
				0BYD0Z2		
				0BYF0Z0		
				0BYF0Z1		
				0BYF0Z2		
				0BYG0Z0		
				0BYG0Z1		
				0BYG0Z2		
				0BYH0Z0		
				0BYH0Z1		
				0BYH0Z2		
				0BYJ0Z0		
				0BYJ0Z1		
				0BYJ0Z2		
				0BYK0Z0		
				0BYK0Z1		
				0BYK0Z2		
				0BYL0Z0		
				0BYL0Z1		
				0BYL0Z2		
				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;	I20.%-I25.%%% I47.%, I48.%%; I49.%% I44.%%; I45.%% I50.%% I11.%; I13.%; O10.1%; O10.3%	37.7x–37.8x, 37.94–37.99			

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
	443.xx 272.x 393-398; 421.x; 422.xx; 746.0x-746.7	I70.%%%; I71.%%; I72.%; I73.%% E78.%% I05.%- I09.%%; I33.%-I39; Q22.%, Q23.%				
Diabetes	250	E10.10				
	250.01	E10.11				
	250.02	E10.21				
	250.03	E10.29				
	250.1	E10.311				
	250.11	E10.319				
	250.12	E10.36				
	250.13	E10.37X1				
	250.2	E10.37X2				
	250.21	E10.37X3				
	250.22	E10.37X9				
	250.23	E10.39				
	250.3	E10.40				
	250.31	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				

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
	250.53	E10.65				
	250.6	E10.69				
	250.61	E10.10				
	250.62	E10.11				
	250.63	E10.21				
	250.7	E10.29				
	250.71	E10.311				
	250.72	E10.319				
	250.73	E10.36				
	250.8	E10.37X1				
	250.81	E10.37X2				
	250.82	E10.37X3				
	250.83	E10.37X9				
	250.9	E10.39				
	250.91	E10.40				
	250.92	E10.51				
	250.93	E10.618				
		E10.620				
		E10.621				
		E10.622				
		E10.628				
		E10.630				
		E10.638				
		E10.641				
		E10.649				
		E10.65				
		E10.69				
		E10.10				
		E10.11				
		E10.21				
Thyroid	226, 240.0,	D09.3, D34,				

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
disease	240.9, 241.0, 241.1, 241.9, 242*, 243, 244*, 245*, 246*, 790.94	D44.0, E01.1,E01.2, E01.8, E02, E03*, E04*, E05*, E06*, E07*, E01.0 E89.0				
Renal failure	403	I12.0				
	403.01	I12.9				
	403.1	N18.1				
	403.11	N18.2				
	403.9	N18.3				
	403.91	N18.4				
	585.1	N18.5				
	585.2	N18.6				
	585.3	N18.9				
	585.4	N17.0				
	585.5	N17.1				
	585.6	N17.2				
	585.9	N17.8				
	586	N17.9				
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				

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
	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	M34.89				
	715.96	M34.9				
	719.42	M35.00				
	719.44	M35.01				
	719.45	M35.02				
	719.47	M35.03				
	719.49	M35.04				
	720	M35.09				
	721.9	M33.90				

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
	725	M35.9				
	729.1	M00.9				
	729.5	M11.9				
	795.79	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				

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
		R76.11				
		R76.12				
		R76.8				
		R76.9				
Obesity	278	E65				
	278.01	E66.01				
	278.02	E66.2				
	278.03	E66.3				
	278.1	E66.9				
	278.2	E67.0				
	278.3	E67.1				
	278.4	E67.3				
	278.8	E67.8				
	V85.30	Z68.30				
	V85.31	Z68.31				
	V85.32	Z68.32				
	V85.33	Z68.33				
	V85.34	Z68.34				
	V85.35	Z68.35				
	V85.36	Z68.36				
	V85.37	Z68.37				
	V85.38	Z68.38				
	V85.39	Z68.39				
Alcohol use disorder	303	F10.159	94.46	HZ2ZZZZ		
	303.01	F10.180	94.53	HZ30ZZZ		
	303.02	F10.181	94.61	HZ31ZZZ		
	303.03	F10.188	94.62	HZ32ZZZ		
	303.9	F10.20	94.63	HZ33ZZ		

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
				Z		
	303.91	F10.21	94.67	HZ34ZZZ		
	303.92	F10.229	94.68	HZ35ZZZ		
	303.93	F10.259	94.69	HZ36ZZZ		
		F10.27		HZ37ZZZ		
		F10.280		HZ38ZZZ		
		F10.281		HZ39ZZZ		
		F10.288		HZ3BZZZ		
		F10.959		HZ40ZZZ		
		F10.980		HZ41ZZZ		
		F10.99		HZ42ZZZ		
		Z65.8		HZ43ZZZ		
				HZ44ZZZ		
				HZ45ZZZ		
				HZ46ZZZ		
				HZ47ZZZ		
				HZ48ZZZ		
				HZ49ZZZ		
				HZ4BZZZ		

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
				HZ93ZZZ		
				HZ96ZZZ		
Tobacco use or cessation counselling	305.1* 649.0* 989.84 V15.82	Z72.0 F17.21 F17.210 F17.211 F17.218 F17.219 Z71.6			C9801 C9802 G0375 G0376 G0436 G0437 G8453 G8455 G8456 G8692 G9276 G9458 G9497 G9642 G9792 G9906 G9908 S9075 S9453 G9902 G9907 G9909	99406 99407
Cancer (excluding basal cell carcinoma)	140.xx – 195.xx	C00%-C76%,				
	200.xx – 208.xx	C81%-C96%				
	196.xx - 199.xx	C77%-C80%				
	EXCLUDING:	EXCLUDING:				
	173.01	C44.01				
	173.11	C44.111				

Condition	ICD9	ICD10	ICD9 proc	ICD10 proc	HCPCS	CPT
	173.21	C44.1121				
	173.31	C44.119				
	173.41	C44.91				
	173.51	C44.311				
	173.61	C44.319				
	173.71	C44.310				
	173.81	C44.510				
	173.91	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 7.9

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Other		17 Dec 2019 13:14 CET
Approval-Therapeutic Area Safety Evaluation		18 Dec 2019 08:50 CET
Approval-Epidemiology of Global		07 Jan 2020 20:03 CET
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Approval-Team Member Medicine		16 Jan 2020 15:26 CET

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