Boehringer Ingelheim

Protocol for observational studies based on existing data

Document Number:	<Document Number>
BI Study No.:	0205-0538
BI Investigational Product(s):	Tiotropium bromide
Title:	Comparative effectiveness of combination therapies in COPD
Title for lay people:	Comparative effectiveness of combination therapies in COPD
Date of last version of protocol:	19 May 2017
EU PAS Register No: only applicable for PASS	*tbd*
Marketing authorization holder(s):	Boehringer Ingelheim GmbH Binger Straße 173 55216 Ingelheim am Rhein Germany
Author/Responsible Parties/BI contact person:	**Authors/Responsible parties:** Tel: Fax: **BI contact person:** Tel.: Fax: E-mail:
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Version and Date:	**Version 1.1, May 19, 2017**
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PROTOCOL ABSTRACT

Name of company: Boehringer Ingelheim			Boehringer Ingelheim
Name of product: Spiriva			
Name of active ingredient: Tiotropium bromide			
Protocol date:	**Study number:**	**Version/Revision:**	**Version/Revision date:**
19 May 2017	0205-0538	1.1	Version 1.1, May 19, 2017

Title of study:	Comparative effectiveness of combination therapies in COPD
Team member Epidemiology:	(Principal investigator)
Project team:	
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 inappropriate 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]. While most trials of the combination treatments have been conducted against the respective mono components or placebo, very few head-to-head trials versus other combinations have been performed to date. 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 [P16-05628]. Also, the ENERGITO trial reported significant improvements in lung function with a LAMA/LABA combination versus LABA/ICS in GOLD 2-3 patients after 6 weeks of treatment [P16-01440]. These trials, however, represent a limited view of the patients who could potentially use these treatments, with many exclusion criteria based on for example stage of disease, lung function and exacerbation history, as well as exclusions of many patients during the screening and run-in periods. Thus, a real-world study of patients who are representative of clinical practice is of interest. As many of these drugs have been in use in separate inhalers for many years, an observational study of their comparative effectiveness is feasible and would provide useful data on the relative benefits of these different combinations in the treatment of COPD. 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:	Primary: To assess the effectiveness of maintenance treatment of COPD with the combination of the LAMA tiotropium with a LABA compared with the combination of a LABA with ICS on the time to COPD exacerbation. Secondary: To compare the effectiveness on the rate of exacerbation and the safety on the incidence of community acquired pneumonia for LABA and tiotropium with LABA and ICS.
Study design:	A prevalent new-user cohort design will be used, with time-conditional propensity scores to match the two comparison groups.
Population:	The base cohort will consist of all patients with a diagnosis of COPD who received at least one prescription for a long-acting bronchodilator, either LABA or the LAMA tiotropium, or for an inhaled corticosteroid from 1 January 2002 until 31 December 2015. To increase the likelihood of a diagnosis of COPD, we only include patients 55 years of age or older on the date of this initial prescription and exclude all patients with a prior diagnosis of asthma. The primary study cohort will first be defined as the members of the base cohort with their first concurrent prescriptions of a LABA and tiotropium on the same date. Patients initiating a LABA and tiotropium will not include users of a LABA+ICS fixed dose combined inhaler. Patients receiving for the first time a LABA and tiotropium on the same day will be propensity score and time matched with members of the base cohort who initiate treatment with LABA and ICS on the same day, either as a fixed-dose combination or free combination. Subjects will need to have at least one year of medical history information prior to the date of combined treatment initiation (cohort entry date) to allow the identification of new use and the measurement of baseline covariates. Subjects will be followed for up to one year from the date of combined treatment initiation, or until switching to the other treatment, the date of death, 31 December 2016, or the end of coverage in the practice, whichever occurs first.
Study data source:	United Kingdom's Clinical Practice Research Datalink (CPRD) linked with the Hospital Episodes Statistics (HES) database
Expected study size:	New users of LABA and tiotropium : 3,000 New users of LABA and ICS: 3,000
Main criteria for inclusion:	- New users of long-acting bronchodilators, LABA and tiotropium on the same date or of LABA and ICS, either as a fixed-dose combination or free combination, on the same date between January 2002 and December 2015. - Diagnosis of COPD and age ≥ 55 years

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Main criteria for exclusion:	-Less than one year of medical history information prior to the date of combined treatment initiation (cohort entry) -Asthma diagnosis
Comparison groups:	Initiating LABA and tiotropium compared to initiating LABA and ICS therapy
Expected duration of exposure:	One year for the primary and secondary analyses

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1. LIST OF ABBREVIATIONS AND TERMS ---

AE	Adverse Event
BI	Boehringer Ingelheim
CI	Confidence Interval
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
ICS	Inhaled corticosteroids
IR	Incidence Rate
LABA	Long-acting beta2-agonist
N	Number
PS	Propensity score
PSTAT	Project Statistician
PY	Person-years at risk
RR	Rate Ratio
TM Epi	Team Member Epidemiology
UTS	Up-to-standard

2. RESPONSIBLE PARTIES

[redacted] (principal investigator)

Tel:
Fax:

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	June 1, 2017
End of data collection:	Not applicable. This study is an observational study based on existing data.
Study progress report(s) as referred in Article 107m(5) of Directive 2001/83/EC:	tbd
Interim report(s) of study results:	Preliminary results: 30 December 2017
Registration in the EU PAS register	tbd
Final report of study results:	May 2018

5. 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; minion et al. 2010]. Long-acting bronchodilator medications, that include long-acting beta$_2$-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].

As a result, the treatment of COPD increasingly involves using several of these drugs, with some of their combinations now formulated into single inhalers. The use of ICS has, however, increased disproportionately with respect to COPD treatment guidelines and may be inappropriate in a subset of patients, with new evidence suggesting that patients can be safely weaned off ICS.[P15-12888; P16-12287] Indeed, the large WISDOM trial observed no difference in the risk of moderate or severe exacerbations between patients who discontinued ICS and those who continued receiving ICS, while the OPTIMO study also observed no deterioration of lung function, symptoms, and exacerbation rate after withdrawal [P14-13477; P14-13078]. Moreover, discontinuation of ICS has been associated with a reduction in the risk of pneumonia [P15-13167]. While most trials of the combination treatments have been conducted against the respective mono components or placebo, few head-to-head trials versus other combinations have been performed to date. 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 [P16-05628]. Similarly, the ENERGITO trial reported significant improvements in lung function with a LABA/LAMA combination versus LABA/ICS in GOLD 2-3 patients after 6 weeks of treatment [P16-01440].

These trials, however, were limited by the fact that a majority of the patients were already using these treatments that they had to discontinue and enter a run-in period before randomisation, which does not emulate the clinical setting. Moreover, the trials represent a limited view of the patients who could potentially use these treatments, with several exclusion criteria involving for example stage of disease, lung function and exacerbation history, in addition to the exclusions of many patients during the screening and run-in periods. Thus, a real-world study of patients who are representative of clinical practice is of interest. Finally, assessing the effectiveness in terms of COPD exacerbations should be balanced against the safety of ICS with respect to pneumonia in the context of real-world clinical practice.

6. RESEARCH QUESTIONS AND OBJECTIVES

The primary objective of this study is to assess the effectiveness of maintenance treatment of COPD with the combination of a LABA and the LAMA tiotropium (LABA-TIO) compared with the combination of a LABA and an ICS (LABA-ICS) on the time to COPD exacerbation. More specifically, the patients who initiate treatment with a combination of a LABA and tiotropium at the same time, or who are on a LABA (no ICS) and who add tiotropium, or who are on tiotropium and add a LABA (no ICS), will be compared with similar patients who receive a LABA and an ICS on the time to first COPD exacerbation.

The secondary objective is to assess the comparative effectiveness on the rate of exacerbation and the comparative safety on the incidence of community acquired pneumonia.

7. RESEARCH METHODS

7.1 STUDY DESIGN

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

7.2 SETTING

The study will be conducted in a general practice setting, within the United Kingdom's Clinical Practice Research Datalink (CPRD; details in Section 7.5). It will be restricted to the practices which can be linked to the Hospital Episodes Statistics (HES) database. The maximal observation period will be from January 1995 until December 2016.

7.3 SUBJECTS

The base cohort will consist of all patients with a diagnosis of COPD from 1 January 1995 until 31 December 2015 who subsequently received at least one prescription for a long-acting bronchodilator, either LABA or tiotropium, or for an inhaled corticosteroid, alone or in combination, from 1 January 2002 until 31 December 2015. The time span for the study was selected to ensure that LABAs and tiotropium were concurrently available, in view of the differing dates of market entry for LABAs (1990s) and tiotropium (2002). To increase the likelihood of a diagnosis of COPD, we will exclude all patients less than 55 years of age on the date of their initial prescription for these drugs during this time period and exclude all patients with a previous diagnosis of asthma. Because the definition of some outcomes under study involve hospitalization, the base cohort will be restricted to the practices which can be linked to the Hospital Episodes Statistics (HES) database (please refer to section 7.5).

Study Cohort
The study cohort will be formed from the base cohort using an incident new-user cohort design with time-conditional propensity scores [P17-04653]. We will thus identify from the base cohort all subjects who, during follow-up, received for the first time prescriptions for a LABA and a tiotropium on the same day, but no inhaled corticosteroid. This can occur as the first time they received a long-acting bronchodilator, with both a LABA and tiotropium as initial treatment, or with initial treatment with a single long-acting bronchodilator followed by the addition of the other long-acting bronchodilator. We will then identify from the base cohort all subjects who, during follow-up, received for the first time prescriptions for a LABA and an ICS on the same day, as two different prescriptions or in a single inhaler, but no tiotropium. Here again, this can occur as the first time they received a LABA and ICS as initial treatment, or with initial treatment with a LABA followed by the addition of ICS or vice versa. Cohort entry will be taken as the first date that LABA and tiotropium or LABA and ICS prescriptions are given simultaneously. All subjects will require at least one year of up-to-standard (UTS) medical history prior to study cohort entry to allow a baseline period for the covariates and identification of new use. New use will thus be defined as the first simultaneous prescriptions for LABA and tiotropium or for LABA and ICS, preceded by prescriptions for only one of the two drug classes or none in the baseline year.

To form the study cohort, we will identify, for each subject initiating LABA and tiotropium (LABA-TIO) treatment, a matched LABA-ICS comparator subject using a time-conditional

propensity score-matched approach. The potential comparator subjects will be selected from the base cohort by forming time-based exposure sets defined by the calendar year of entry into the base cohort for the LABA-TIO and LABA-ICS simultaneous prescription users. To allow matching on the propensity of treatment choice, we will compute high-dimensional time-conditional propensity scores (TCPS) by identifying all available data (e.g., diagnoses, procedures, medications) in the one-year period prior to the date of cohort entry for each time-based exposure set using Cox proportional hazards regression. Then, for each LABA-TIO exposed subject, and starting chronologically with the first one, we will identify a matched comparator subject from the members of the subject's time-based exposure set. We will first match subjects on sex, previous components of the study treatment (LABA only, TIO only, ICS alone, none of these) and the presence of an acute COPD exacerbation in the year before cohort entry. The matched reference subject will then be selected as the one with the closest time-conditional propensity score in the matched set, after trimming within each exposure set, and allowing a maximum difference in scores of 0.05 for a match. In the absence of a tight propensity score match, we will take the closest and the analysis will be complemented by an adjustment for the propensity score.

After matching, the subjects in the study cohort will be followed up for up to one year from cohort entry (the date of the matched set), with follow-up ending at the earliest of the date of a switch or addition of either an ICS for the LABA-TIO group or of tiotropium to the LABA-ICS group, death, one year after cohort entry, December 31, 2016, or the end of coverage in the practice, whichever occurs first.

7.4 VARIABLES

7.4.1 EXPOSURES

The exposure measures are based on the prescription of the two long-acting bronchodilators under study, namely LABAs and tiotropium, as well as ICS. As described in the data analysis section, the as-treated analysis, which is the main analysis, will consider exposure as current use of LABA-TIO or LABA-ICS within the treated groups defined as within the 60-day period after the prescriptions' dispensing dates.

7.4.2 OUTCOME(S)

7.4.2.1 PRIMARY OUTCOME(S)

The primary outcome event is the first COPD exacerbation to occur after cohort entry. The event is defined as a hospitalization for COPD (severe exacerbation) or the prescription of an oral corticosteroid, namely prednisolone (moderate exacerbation).

7.4.2.2 SECONDARY OUTCOME(S)

The first secondary outcome is the rate of COPD exacerbations over the one-year follow-up. This outcome will be based on the number of hospitalizations and on the number of courses of treatment with an oral corticosteroid. A gap of at least 30 days between treatment courses will be required to consider the exacerbations as separate events. The second secondary outcome is the occurrence of the first hospitalization for community-acquired pneumonia (serious pneumonia). Pneumonia will be defined from the following ICD10 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

Sex, previous treatment and previous acute COPD exacerbation, as well as calendar year of cohort entry, are all matching factors and will thus inherently be accounted for.

Although we will use the high-dimensional approach to identify variables entering the time-conditional propensity score, some key covariates will be highlighted. First, we will identify key lifestyle variables available in the CPRD, known to be risk factors and potential confounders, including the body mass index (BMI), smoking status and excessive alcohol consumption. Missing data for smoking status and BMI will be entered as an additional category in the model. We will also explore the possibility of obtaining blood eosinophils measured in the year prior to cohort entry and will use this information only if complete.

Second, the occurrence of the study outcomes prior to cohort entry will be identified during the one-year baseline period and adjusted for in the analysis if found to be imbalanced between treatment groups after propensity score matching. In particular, COPD exacerbations occurring in the 30 days prior to the study cohort entry date, a marker of COPD exacerbation risk, will be identified separately from those occurring previously during the baseline year. In addition, the severe exacerbations requiring hospitalizations will be counted, while the moderate exacerbations will be identified from counts of prescriptions for oral corticosteroids.

Third, use of other respiratory drugs during the baseline period will be included as a measure of COPD severity. Thus, the number of prescriptions for short-acting beta-agonists, anticholinergics, methylxanthines and muscarinic antagonists used during the year prior to cohort entry will be identified. As well, the number of prescriptions for antibiotics for a respiratory condition will be counted. In addition, we will count the number of prescriptions for the study drugs used during the baseline period. These will be combined into a single variable because of the study design which inherently selects patients into the two study groups according to their prior LABA, TIO or ICS use. Finally, for each of the cohorts, baseline co-morbidity will be measured using diagnoses and prescriptions for various conditions observed often in patients with COPD, namely cardiovascular disease, diabetes, thyroid disease, renal failure, autoimmune disease and cancer, all in the year prior to cohort entry.

7.5 DATA SOURCES

The Clinical Practice Research Datalink (CPRD) will be used for this study. It includes computerized medical records of more than 12 million patients from more than 650 general practices in the United Kingdom. General practitioners, using standardized recording of medical information, record data on the patient's demographic characteristics, symptoms, history, medical diagnoses, and drug prescriptions, as well as details of referrals to specialists and hospitals. The completeness and validity of the recorded information on diagnoses, coded using READ codes, and drug exposures, coded using a coding system with a direct mapping to the NHS dictionary of medicines and devices, are checked on an ongoing basis by staff of the CPRD and have been shown in several studies [R11-2162; R16-2198]. In addition, the CPRD can be linked by unique identifier to the Hospital Episodes Statistics (HES) database which provides extensive information on all hospitalizations, coded using ICD-10 codes, including data on length of stay, ward types, as well as extensive disease and procedure coding, based on OPCS4 (Office of Population Censuses and Surveys Classification of Interventions and Procedures) codes. The linkage between the CPRD and the HES databases applies to over half of the practices contributing to the CPRD. The database has been used for the study of numerous diseases, including studies of COPD [R16-2197; P16-10095].

7.6 BIAS

Several potential biases inherent to any observational study need to be considered. First, confounding by indication could be an issue. Matching subjects initiating LABA-TIO with subjects initiating LABA-ICS on several marker of disease, including prior COPD exacerbations, previous treatment and on the propensity score should limit this potential bias since matched subjects will have comparable probability of using either combination. In addition to matching on the propensity score, sex, prior exacerbation, prior treatment and calendar time, several variables such as general severity of COPD, comorbidity and concomitant drug use will be in the propensity score and adjusted for in the outcome model. Second, there is the possibility of information bias due to misclassification of the outcomes or exposure. CPRD contains prescriptions written by the GP rather than filled or taken by patients. This could be a source of misclassification of exposure. Another source of information bias due that we will investigate is immeasurable time bias due to the presence of hospitalizations during follow-up, particularly during the current exposure window, where GP prescriptions are not available, so that exposure is not measurable. Finally, the linkage to HES data to identify hospitalization for COPD exacerbation and for community-acquired pneumonia should reduce the potential for misclassification of outcomes.

7.7 STUDY SIZE

In our previous study of the cardiovascular effects of long-acting bronchodilators, there were around 230,000 users of LABA or TIO between 2002 and 2012 in the CPRD, which should include around 140,000 who come from HES-linked practices [P16-10095]. From these, we expect around 4,000 who received a LABA and tiotropium on the same day, where the LABA is not combined with an inhaled corticosteroid in a single inhaler. The number of users of LABA-ICS is over 100,000, providing a large pool for matching purposes. Thus, after matching and trimming, we expect the study to include a minimum of 3,000 patients per arm, a conservative estimate. Using recent data from the FLAME trial [P16-05628], we expect that the cumulative incidence of a first COPD exacerbation, moderate or severe,

during the one-year follow-up is expected to be 50%. These sample sizes will permit to detect a 15% reduction in the risk of a first exacerbation (hazard ratio 0.85) with 99% power and a 10% reduction (hazard ratio 0.90) with 97% power. For the severe exacerbations, we expect the one-year cumulative incidence to be around 15%, which will permit to detect a 20% reduction in the risk of a first severe exacerbation (hazard ratio 0.80) with 92% power.

7.8 DATA MANAGEMENT

All data related to this study will be stored on secured and encrypted database servers of the Data Management Unit Datacentre, located in the Centre for Clinical Epidemiology, Lady Davis Institute for Medical Research of the Jewish General Hospital, Montreal. The Centre for Clinical Epidemiology is equipped with an electronic access card system which is limited to the research staff and students of the Centre. The DMU Datacentre has a unique electronic access card system which is limited to specific personnel only. The building is under 24/7 video surveillance and regular scheduled round trips by security guards are done. The DMU Datacentre is monitored and managed for data access, data integrity and backup. The DMU Datacentre uses proven technology to safeguard its data, including Cisco ASA firewalls, IDS/IPS, antivirus, anti-spyware, hard drive encrypted, user access tracking, backup of all data. Copies of backed up files are kept in a safe outside of the institution.

All statistical analyses for the study will be conducted using SAS, Version 9.4 (SAS institute, Inc., Cary, NC) and R (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). All programs written by the statistical programmer, coding of variables, outputs and protocol amendments are stored in the servers. Access to the files related to a study is password-protected on the server and accessible only to the study statisticians. For ethical and scientific reasons, data and documentation are kept for five years following the publication date.

7.9 DATA ANALYSIS

7.9.1 MAIN ANALYSIS

For the base cohort, patient characteristics at baseline will be described using standard descriptive statistics. The unmatched study cohort, which will also address the tertiary objective, will be used to provide and compare baseline patient characteristics between the two groups. These comparisons will also be provided for the matched cohort.

For the analysis of the primary objective, the matched cohort will be used to estimate the crude 1-year cumulative incidence of severe and moderate COPD exacerbations for the two combination treatment groups. The main comparative analysis will also be based on the matched cohort and a time-dependent Cox proportional hazard regression model to perform an as-treated analysis that assesses the effect of current use of LABA-TIO 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 LABA-TIO use relative to LABA-ICS use, along with 95% confidence intervals (CI). Current use will be defined as a prescription dispensed within the 60-day period of the date defined by the risk set of the Cox model. This approach allows consideration of exposure as time-dependent, accounting for the changes in exposure during the follow-up. In particular, this analysis

censors patients stopping one or both of the drugs prior to the index date. Besides the matching inherent in the design, the Cox proportional hazard regression model will be adjusted for additional confounders. This model will include patient characteristics found to be different after matching on propensity scores, as well as the decile of propensity score. Body mass index (BMI) is expected to be the only variable with missing data in the CPRD, though infrequently (less than 4% of subjects in our previous studies in COPD). Patients with missing BMI will be classified as a separate category.

The analysis of the secondary objective related to the rate of exacerbation will be based on the negative binomial regression models, which corresponds to a Poisson regression model adjusted for between-subject variation in exacerbations, with the same approach to covariate adjustment as the primary analysis. A 30-day gap between events will be used to distinguish between one continuous exacerbation and two separate events. The analysis of the secondary objective related to the risk of pneumonia will use a time-dependent Cox proportional hazard regression model with an as-treated approach, similar to that of the primary analysis.

7.10 QUALITY CONTROL

All data will be stored in the servers of the McGill Pharmacoepidemiology Research Unit located within the Center for Clinical Epidemiology. In accordance with the CPRD regulations, these data are secure within the Center which is protected by an electronic keypad entry system. All data will be kept for a period of five years after publication of the paper from this study. Documentation on the data selection, definitions and programs will be available in the Center for inspection.

Our McGill Pharmacoepidemiology Research Unit is quite familiar with the CPRD and has published over 100 scientific articles using this database since 2005.

7.11 LIMITATIONS OF THE RESEARCH METHODS

Several potential biases inherent to any observational study need to be considered. Because this is primarily a study of effectiveness, confounding by indication is among the most important potential sources of bias in the absence of randomisation. However, matching the two groups on prior COPD exacerbations, prior treatments and on the propensity score should limit this potential bias. The possibility of information bias due to misclassification of the outcomes or exposure is present. Indeed, the CPRD includes prescriptions written by the GP rather than filled or taken by patients, which could be a source of misclassification of exposure and the outcome of a moderate exacerbation defined by prescriptions. With respect to the other outcome definitions, the linkage to HES data to identify hospitalization for COPD exacerbation and for community-acquired pneumonia should also reduce the potential for misclassification of outcomes.

7.12 OTHER ASPECTS

None

8. PROTECTION OF HUMAN SUBJECTS

This study is based on existing data collected in general practices and does not require patient informed consent. All data used for this study are anonymized.

Approval of the study protocol will be obtained from the Independent Scientific Advisory Committee (ISAC) for the U.K. Medicines and Healthcare Products Regulatory Agency before coding, extraction, and processing of CPRD data. Ethics approval for this study will be obtained from the Research Ethics Committee of the Jewish General Hospital, Montreal, Canada.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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 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.

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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

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:
Combined bronchodilators in chronic obstructive pulmonary disease and the risk of adverse cardio-pulmonary events: A population-based observational study

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]	☒	☐	☐	16
1.1.2 End of data collection[2]	☒	☐	☐	16
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)	☒	☐	☐	14
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 generalised)	☒	☐	☐	16
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	15
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, randomised controlled trial, new or alternative design)	☒	☐	☐	16
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	17-18
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)	☒	☐	☐	20

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:	☒	☐	☐	16
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?	☐	☐	☒	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?				
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 categorising 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)	☒	☐	☐	19
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 action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	20

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)	☒	☐	☐	19

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)	☒	☐	☐	18
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	21

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.)	☒	☐	☐	19
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.)	☒	☐	☐	19
8.1.3 Covariates?	☒	☐	☐	19
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)	☒	☐	☐	19
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	19
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	19

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	19
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	19
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	19
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	19

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	19-20

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	20-21
10.2 Is the choice of statistical techniques described?	☒	☐	☐	20-21
10.3 Are descriptive analyses included?	☒	☐	☐	20-21
10.4 Are stratified analyses included?	☒	☐	☐	21
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	20-21
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	21

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?	☒	☐	☐	21
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	22
11.3 Are methods of quality assurance described?	☒	☐	☐	22

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	22
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	25

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)	☒	☐	☐	19-22
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	19
12.3 Does the protocol address other limitations?	☒	☐	☐	19-22

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?	☒	☐	☐	23
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	23

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?	☒	☐	☐	25

Comments:

Name of the main author of the protocol:

Date: 23/02/2017

Signature: _____

ANNEX 3: ADDITIONAL INFORMATION

Additional annexes may be included if necessary.

ANNEX 3.1: DEFINITION OF STUDY EXPOSURES

See section 7.4.1. Complete list of drug codes will be finalized and supplied to BI in the course of the study

ANNEX 3.2: DEFINITIONS OF STUDY OUTCOMES

See section 7.4.2. Complete list of READ and ICD-10 codes will be finalized and supplied to BI in the course of the study

ANNEX 3.3: DEFINITIONS OF STUDY COVARIATES

See section 7.4.3. Complete list of READ and drug codes will be finalized and supplied to BI in the course of the study

ANNEX 3.4: STATISTICAL CONSIDERATIONS

See section 7.9.