Boehringer Ingelheim

Protocol for observational studies based on existing data

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Additional Information

Research question and objectives:	This study aims to characterise the use of single-agent olodaterol and single-agent indacaterol, the only marketed long-acting beta2-agonist (LABAs) authorised for chronic obstructive pulmonary disease (COPD), but not for asthma, in clinical practice. Study objectives are as follows: Primary objectives: • Quantify the frequency of off-label use of olodaterol among new users of these medications (i.e., the proportion of new users who do not have COPD) • Describe the baseline characteristics of new users of olodaterol Secondary objective: • Quantify the frequency of off-label use of indacaterol (a LABA approved for COPD but not for asthma) among new users of these medications (i.e., the proportion of new users who do not have COPD), in order to put into perspective the results for olodaterol initiators • Describe the baseline characteristics of new users of indacaterol
Country(-ies) of study:	The Netherlands, Denmark, and France
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

AMI	Acute Myocardial Infarction
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
BMI	Body Mass Index
CAT	COPD Assessment Test
COPD	Chronic Obstructive Pulmonary Disease
DAMD	Danish General Practice Database
DDD	Defined Daily Dose
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FEV_1	Forced Expiratory Volume in 1 Second
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner or General Practice
ICD	International Classification of Diseases
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICD-10-CM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification
ICD-9	International Classification of Diseases, 9th Revision
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICPC	International Classification of Primary Care
ICS	Inhaled Glucocorticosteroid
LABA	Long-Acting Beta2-Agonist
LAMA	Long-Acting Muscarinic Antagonist
LPD	Longitudinal Patient Database
mMRC	Modified British Medical Research Council Questionnaire
NCSP	Nordic Medico-Statistical Committee Classification of Surgical Procedures
NPR	National Patient Register (Sweden)
PASS	Post-Authorisation Safety Study

PHARMO	Institute for Drug Outcomes Research (the Netherlands); also short for the PHARMO Database Network
PHARMO-GP	a data subset of PHARMO Database Network with information from GPs
PPV	Positive Predictive Value
PRO	Patient-Reported Outcome
RWE	Real-World Evidence
SABA	Short-Acting Beta2-Agonist
SAMA	Short-Acting Muscarinic Antagonist
SD	Standard Deviation
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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The following institutions will implement the study and have reviewed the study protocol:

PHARMO Institute, the Netherlands
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IMS Health Information Solutions, France

4. ABSTRACT

Name of company: Boehringer Ingelheim GmbH			
Name of finished medicinal product: Striverdi, Respimat			
Name of active ingredient: Olodaterol			
Protocol date: 14 Oct 2014	**Study number:** 1222.53	**Version/Revision:** 3.0	**Version/Revision date:** 03 Aug 2016
Title of study:	Drug Utilisation Study for Olodaterol		
Rationale and background:	Boehringer Ingelheim GmbH (BI) developed olodaterol, an inhaled long-acting beta2-agonist (LABA), for the indication of chronic obstructive pulmonary disease (COPD). LABAs are used in COPD to relieve bronchial constriction and, consequently, to improve symptoms. Because the use of LABAs has been associated with increased morbidity and mortality in patients with asthma, within the "Decentralised Procedure for Striverdi Respimat" the health authorities of the European Union/European Economic Area Member States requested the conduct of a post-approval drug utilisation study to assess potential off-label use of olodaterol in asthma and to characterise the use of olodaterol in clinical practice.		
Research question and objectives:	This study aims to characterise the use of single-agent olodaterol and single-agent indacaterol, the only marketed LABAs authorised for COPD, but not for asthma, in clinical practice. Study objectives are as follows: Primary objectives: • Quantify the frequency of off-label use of olodaterol among new users of these medications (i.e., the proportion of new users who do not have COPD) • Describe the baseline characteristics of new users of olodaterol Secondary objective: • Quantify the frequency of off-label use of indacaterol (a LABA approved for COPD but not for asthma) among new users of these medications (i.e., the proportion of new users who do not have COPD), in order to put into perspective the results for olodaterol initiators • Describe the baseline characteristics of new users of indacaterol		
Study design:	This is a cross-sectional study using information collected in health care databases among new users of olodaterol or indacaterol in the Netherlands, Denmark, and France.		

Name of company: Boehringer Ingelheim GmbH			
Name of finished medicinal product: Striverdi, Respimat			
Name of active ingredient: Olodaterol			
Protocol date: 14 Oct 2014	**Study number:** 1222.53	**Version/Revision:** 3.0	**Version/Revision date:** 03 Aug 2016
Population:	The source population is all subjects enrolled in the selected study databases at the date olodaterol became available in each database's country. The study groups are those subjects from the source population who receive a first dispensing for single-agent formulations of olodaterol for the primary objective or indacaterol for the secondary objective and have at least 12 months of continuous enrolment in the study databases.		
Variables:	Indication and potential off-label use of olodaterol and indacaterol; characterisation of new users of olodaterol and indacaterol by demographic variables, medical history, and use of other medications.		
Data sources:	The study is planned to be conducted in the following databases: the PHARMO Database Network in the Netherlands, the National Registers in Denmark, and the IMS Health Information Solutions (IMS) Real-World Evidence (RWE) Longitudinal Patient Database (LPD) in France. A description of each database is provided in Section 9.4. The study will be conducted by using data on drug prescriptions/dispensings and disease occurrence routinely collected on an ongoing basis for large, population-based, automated health care databases in the Netherlands, Denmark, and France.		
Study size:	No sample size calculations have been done given that there will be no hypothesis testing. During 2014 and 2015, about 2,000 patients used olodaterol in the three data sources.		
Data analysis:	Number and proportion of new users by indication and potential off-label use. Number and proportion of new users according to medical history and use of comedications.		
Milestones:	Start of data collection (start of data extraction): • For interim report: planned Q1 2017 • For final report: planned Q1 2018 End of data collection (date final analytic file is available): • For interim report: planned Q3 2017 • For final report: planned Q3 2018 Interim reports of study results: planned Q3 2017 Final report of study results: planned Q3 2018		

5. AMENDMENTS AND UPDATES

Version 2.0 includes clarification to the milestone table and revision of the primary and secondary study objectives in the context of regulatory review of the protocol.

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	30 Sep 2014	6	Update of milestones	Delay in finalisation of protocol to respond to regulatory authority review
2	30 Sep 2014	8	Research objectives	Modified in response to regulatory authority review
3	30 Sep 2014	9.3.4	Clarification of primary outcomes	Modified in response to regulatory authority review
4	25 Jul 2016	6	Updated and clarified milestones	According to EMA guidance for post-authorisation studies definitions
5	25 Jul 2016	Across the protocol	Changed ICD-9 for ICPC codes	PHARMO uses ICPC codes; none of the other databases included use ICD-9 codes
6	25 Jul 2016	9.1	Clarified study design	To better describe study periods and differentiate from study milestones
7	25 Jul 2016	9.3.2	Defined period named as “ever before”	To clarify definition in each database
8	25 Jul 2016	9.3.3	Updated COPD severity definition	To better align with COPD guidelines recommendations
9	25 Jul 2016	9.4.1	Updated information on the PHARMO databases	Research partners updated description of PHARMO databases according to the latest available information
10	25 Jul 2016	9.4.2	Deleted Danish General Practice Database (DAMD) data source; updated description of Danish databases	DAMD is no longer available for research. Research partners updated description of Danish databases according to the latest available information

Number	Date	Section of Study Protocol	Amendment or Update	Reason
11	25 Jul 2016	9.4.3	Deleted Swedish National Registers	Due to limited uptake.
12	25 Jul 2016	9.4.3	Added French IMS RWE LPD	Due to the limited uptake in Sweden the French database was evaluated for feasibility
13	25 Jul 2016	9.4.4	Updated summary of study databases	To match with updates in the description of the databases performed in Sections 9.4.1 through 9.4.3
14	25 Jul 2016	9.5	Added data on the number of olodaterol users in each data source	Olodaterol was not launched at the time of the initial protocol
15	25 Jul 2016	9.7	Added estimation of 95% confidence intervals	To specify that the 95% confidence intervals of the prevalence proportion of off-label use will be estimated
16	25 Jul 2016	Annexes	Deleted Annex 5	The annex included information on a PHARMO database that is already included under Section 9.4.1.

6. MILESTONES

Milestone	**Planned Date** [1]
Start of data collection (date from which data extraction starts):	For the interim report: Q1 2017[2] For the final study report: Q1 2018[3]
End of data collection (the date from which the analytical data set is completely available):	For the interim report: Q3 2017 For the final study report: Q3 2018
Interim report(s) of cumulative study results:	Q3 2017
Registration in the EU PAS Register:	After regulatory endorsement of the amended protocol
Final report of study results from all databases:	Q3 2018

EU PAS Register = European Union electronic register of post-authorisation studies; Q1 = first quarter; Q2 = second quarter; Q3 = third quarter; Q4 = fourth quarter.

1 Preliminary; dependent on market uptake of olodaterol and contracts with MAH and research partners.

2 Data will be extracted during Q1 2017 and will include data from launch (January 2014) up to Q3 or Q4 2015 in Denmark, from launch (March 2014) up to Q4 2015 in the Netherlands, and from launch (October 2015) up to Q4 2016 in France.

3 Data will be extracted during Q1 2018 and will include data from launch in each country and up to Q3 or Q4 2016 in Denmark, up to Q4 2016 in the Netherlands, and up to Q4 2017 in France.

7. RATIONALE AND BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a serious, chronic disease that affects millions of people worldwide. [P13-02399] COPD typically involves persistent limitation of airflow, a progressive course, and chronically enhanced inflammatory response of the airways to airborne particulates and gases. [P13-02399]

Worldwide, the estimated number of patients with COPD is 63.6 million. [R09-2531] In 2004, the World Health Organization estimated that the European region had approximately 11.3 million patients with prevalent, symptomatic COPD. [R09-2531] A systematic review and meta-analysis of 67 studies conducted in 28 countries between 1990 and 2004 showed that the prevalence of COPD is higher in subjects over 40 years of age than those under 40. The pooled prevalences were 3.1% in subjects under 40 years of age and 9.9% in those 40 years old or older, 8.2% for ages 40-64, and 14.2% for ages 65 years or older. [R06-4117] The health, social, and economic burdens of COPD are predicted to increase in the next several decades because of continuing exposure to tobacco smoke and other risk factors and because of the increasing age of the general populations in many countries. [P13-02399]

Inhaled long-acting beta2-agonist (LABA) drugs are used in COPD and in asthma. At present, the approved indication for the five major LABAs in COPD—formoterol, salmeterol, indacaterol, olodaterol, and vilanterol (only approved in fixed-dose combination with fluticasone furoate or with umeclidinium bromide)—is maintenance or long-term use. Formoterol, salmeterol, and vilanterol are also approved for use in asthma; for this condition, simultaneous use with corticosteroids is strongly recommended.

Olodaterol and indacaterol are the only marketed LABAs authorised for the treatment of adult patients with COPD, but not for patients with asthma, in clinical practice.

Within the Decentralised Procedure for Striverdi Respimat, the health authorities of the European Union/European Economic Area Member States requested the conduct of a post-approval drug utilisation study to assess the potential off-label use of olodaterol in asthma patients and to characterise the use of olodaterol in clinical practice.

This protocol is a core protocol describing the study design, methods, and analysis for implementing the study in three European health care databases in the Netherlands, Denmark, and France. This core protocol will need to be adapted to the specifics of each database regarding the type and availability of the recorded information and the coding systems used to record diagnoses and medications.

8. RESEARCH QUESTION AND OBJECTIVES

This study aims to assess the use of single-agent olodaterol in clinical practice. The single agent indacaterol, the only other marketed LABA authorised in clinical practice for COPD but not for asthma, will also be assessed. Study objectives are as follows:

Primary objectives:

- Quantify the frequency of off-label use of olodaterol among new users of these medications (i.e., the proportion of new users who do not have COPD)
- Describe the baseline characteristics of new users of olodaterol

Secondary objectives:

- Quantify the frequency of off-label use of indacaterol (a LABA approved for COPD but not for asthma) among new users of these medications (i.e., the proportion of new users who do not have COPD), in order to put into perspective the results for olodaterol initiators
- Describe the baseline characteristics of new users of indacaterol

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a cross-sectional study using information collected in health care database(s) among new users of olodaterol or indacaterol in the Netherlands, Denmark, and France. The study period will be approximately 3 consecutive years, with two reports of study results, an interim report in Q3 2017 and a final report of cumulative study results in Q3 2018. Evaluation of off-label use and characterisation of new users will be conducted based on all available information in each data source prior to and up to 30 days after the **index date**, defined as the date an eligible patient receives the first dispensing of olodaterol or indacaterol during the study period (Figure 1). Demographic and comorbid information will be assessed using all available information in the database prior to the index date (as far back in time as records in the data source are available—i.e., 01 Jan 1994 in Denmark, 1998 in PHARMO, 1994 for GP panel and 2007 for pulmonologist panel in IMS RWE LPD); medication use, severity of COPD, and resource utilisation will be assessed for the 1-year period prior to the index date.

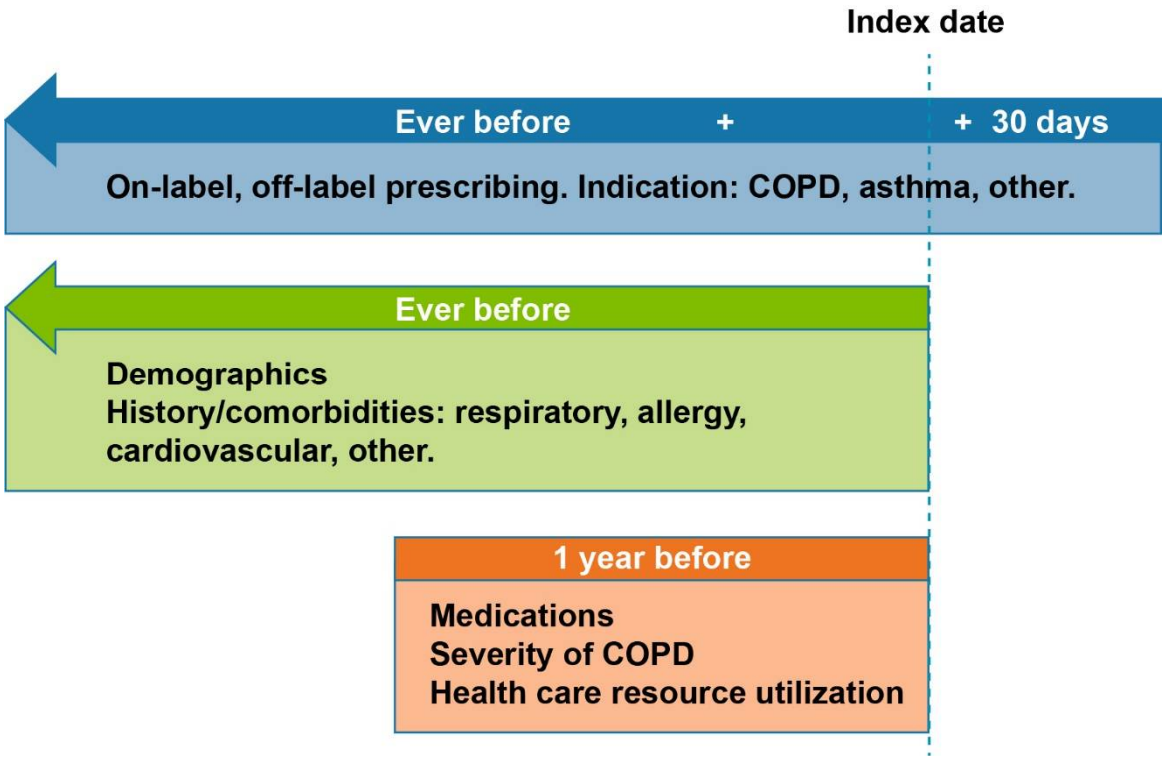


Figure 1 Study Overview

9.2 SETTING

The study is planned to be conducted in the following databases: the PHARMO Database Network in the Netherlands, the National Registers in Denmark, and the Real-World Evidence (RWE) Longitudinal Patient Database (LPD) in France. The type of data available

in each database is summarised in Table 1. A detailed description of each study database is provided in Sections 9.4.1, 9.4.2, and 9.4.3.

Table 1 Selected characteristics of the study databases

Type of Data	PHARMO, the Netherlands	National Registers, Denmark	IMS RWE LPD, France
Hospital inpatient discharge diagnoses	Yes	Yes	No
Hospital inpatient procedures	Yes, mainly for surgical procedures	Yes	No
Hospital/clinics outpatient diagnoses	No	Yes	No
General practitioner diagnoses	Yes, in data subset PHARMO-GP[1]	No	Yes (a panel of 1,200 general practitioners)[2]
Specialist diagnoses	Yes, those in the hospital (no outpatient hospital or non-hospital clinics) or as communicated to and recorded by the GP in PHARMO-GP	Yes, those in the hospital and hospital outpatient clinics (not outside the hospital)	Yes (a panel of 40 pulmonologists)[3]
Pharmacy-dispensed medications	Yes	Yes	No
Prescribed medications	Yes in data subset PHARMO-GP[1]	No	Yes

GP = General Practitioner; IMS = IMS Health Information Solutions; PHARMO = PHARMO Database Network; RWE LPD = Real-World Evidence Longitudinal Patient Database.

1 PHARMO-GP includes approximately 1 million patients.

2 The GP panel covers a population of approximately 1.8 million active patients.

3 The pulmonologist panel covers a population of approximately 55,000 active patients.

In each country, new users of olodaterol and indacaterol will be identified in the databases, which record information on the medications prescribed by the physicians or dispensed in the pharmacies. New users will be characterised in terms of past medical history and use of medications. Past medical history will be evaluated using the primary care, hospitalisation, and prescription databases, which provide information on outpatient diagnoses, hospital and outpatient discharge diagnoses and procedures, and use of medications that may be used as surrogates for disease. Use of other medications will also be evaluated using the recorded information on prescriptions/dispensings. Off-label prescribing will be evaluated based on the past medical history.

The coding of diagnoses and procedures varies across databases (Table 2).

Table 2 Types of diagnosis, procedures, and medication codes in the study databases

Type of Code	PHARMO, The Netherlands	National Registers, Denmark	IMS RWE LPD, France
Diagnoses	Hospital: ICD-10 Primary health care: ICPC[1]	ICD-10	Local in-house thesaurus that can be mapped to ICD-10
Procedures	CBV	NCSP version 1.16, 2012	Local in-house thesaurus that can be mapped to ICD-10
Medications	ATC	ATC	Claude Bernard/ EphMRA mapped to ATC

ATC = Anatomical Therapeutic Chemical; CBV = Dutch Hospital Data Foundation–owned registration system for procedures, which links to the Dutch Healthcare Authority (NZa) declaration codes and the Dutch Classification of Procedures; EphMRA = European Pharmaceutical Market Research Association; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICPC = International Classification of Primary Care; IMS = IMS Health Information Solutions; NCSP = *Nordic Medico-Statistical Committee's Classification of Surgical Procedures*; PHARMO = PHARMO Database Network; RWE LPD = Real-World Evidence Longitudinal Patient Database.

1 Available for PHARMO-GP, a data subset of PHARMO with information from GPs.

9.2.1 Source population

The study source population includes all subjects enrolled in the selected study databases at the date both olodaterol and indacaterol are available in each database's country.

9.2.2 Study period

The study period will start on the date of olodaterol launch in each country and end on the latest date the data are available at the time of each data extraction for the interim and final study reports. For each patient, the observation period will start at the index date and look retrospectively for historical data and prospectively for up to 30 days after the index date (Figure 1). The index date is defined as the date of the first recorded dispensing of olodaterol or indacaterol during the study period in each database. Anticipated study periods for each data source at the time of each data extraction are shown in Table 3.

Table 3 Estimated Study Period in Each Study Data Source

Event	PHARMO, the Netherlands	National Registries, Denmark	IMS RWE LPD, France
Olodaterol launch in country[1]	March 2014	January 2014	October 2015
Interim report data extraction	Q1 2017	Q1 2017	Q1 2017
Anticipated study period included in interim report[2]	March 2014 – Q4 2015	January 2014 – Q4 2015	October 2015 – Q4 2016
Final report data extraction	Q1 2018	Q1 2018	Q1 2018
Anticipated study period for final report	March 2014 – Q4 2016	January 2014 Q4 2016	October 2015 – Q4 2017

IMS = IMS Health Information Solutions; PHARMO = PHARMO Database Network; Q1 = first quarter of calendar year; Q4 = fourth quarter of calendar year; RWE LPD = Real-World Evidence Longitudinal Patient Database.

1. Provided by Boehringer Ingelheim International GmbH.
2. Study periods of observation are estimated based on the following lag times in each data source: PHARMO, approximately 6 to 18 months, Danish registries, approximately 6 to 12 months; IMS RWE LPD, 2 to 7 months.

9.2.3 Study groups

9.2.3.1 Inclusion criteria

Study groups are those subjects from the source population who (1) receive a first prescription/dispensing for single-agent formulations of olodaterol or indacaterol during the study period (no prescriptions/dispensings ever before) and (2) have at least 12 months of continuous enrolment in the study databases preceding the index date. Two study groups will be created: (1) a group of new users of olodaterol and (2) a group of new users of indacaterol.

New users of olodaterol are defined as patients who, with at least 12 months of continuous enrolment before the index date, have their first record of a dispensing for olodaterol. Similarly, new users of indacaterol have their first record of a dispensing for indacaterol in the database (after at least 12 months of continuous enrolment). Patients who receive a prescription/dispensing for olodaterol or indacaterol before they meet the criteria of 12 months of continuous enrolment in the database are not eligible to enter the corresponding study groups (olodaterol or indacaterol). This will allow evaluation of the medical history and prior use of medications of included patients.

Each group of new users of olodaterol and new users of indacaterol will be divided into two subgroups: (1) LABA naïve in the short term (3 months) and (2) switchers from another LABA. Patients who are LABA naïve in the short term are defined as any new users of olodaterol or indacaterol who did not receive any prescription/dispensing for LABAs with duration of use that ended within 3 months before the index date. Switchers are defined as any new user of olodaterol or indacaterol who received a dispensing for a different LABA within the 3 months before the index date. Within the olodaterol group and within the indacaterol group, LABA-naïve patients and switchers will be described and compared.

9.2.3.2 Exclusion criteria

Because the study aims to assess the use of olodaterol and indacaterol in regular clinical practice, no exclusions regarding age, sex, or comorbidity will be defined. However, individuals with missing or implausible values for age or sex will be excluded.

9.3 VARIABLES

9.3.1 Exposures

New users of olodaterol and indacaterol will be identified at the first record of a prescription/dispensing for the relevant medication code specific to each database. New users are defined in Section 9.2.3.

The ATC code for indacaterol is R03AC18, classified as a selective beta2-adrenoreceptor agonist in the category of inhalant adrenergics. Indacaterol is available as inhalation powder with a defined daily dose (DDD) of 0.15 mg. The ATC code for olodaterol is R03AC19.

9.3.2 Indication and potential off-label prescribing

The indication for the prescribing of medications is not recorded in the PHARMO databases and Danish National Registries; indication is available but may be incomplete in the IMS Health Information Solutions (IMS) database. Therefore, when indication is not available, the indication of treatment and potential off-label use of olodaterol and indacaterol will be inferred from the diagnosis codes recorded at any time before the index date (as far back in time as records in the data source are available—i.e., 01 Jan 1994 in Denmark, 1998 in PHARMO, 1994 for GP panel and 2007 for pulmonologist panel in IMS RWE LPD) or up to 30 days after the index date and from the clinical review of information in computerised patient profiles; see Section 9.3.2.3). Potential off-label use will be evaluated separately by the following groups formed by age at the index date:

- 0 to 17 years (all paediatric use is off-label)
- 18 to 29 years
- 30 to 39 years
- 40 to 49 years
- 50 to 59 years
- 60 to 69 years
- 70 to 79 years
- 80 years and older

9.3.2.1 On-label prescribing: indication of COPD

The indication of COPD is defined as a recorded diagnosis of COPD, chronic bronchitis, or emphysema recorded in the database at any time before the index date or up to 30 days after the index date. Because COPD can occur in association with asthma, patients with a recorded

diagnosis for both COPD and asthma will be considered on-label. [R14-0350] [R07-2620] [R08-1492]

For this study, classification of COPD status will be based on age, general practice diagnoses, pulmonologist diagnoses, drug prescriptions/dispensings, hospital outpatient clinic diagnoses, and inpatient discharge diagnoses, depending on data availability in each data source. No validation data are available for COPD diagnoses recorded in PHARMO and IMS RWE LPD. In Denmark, validation has been performed for COPD diagnoses ascertained via hospital (inpatient and outpatient) diagnoses. ICD diagnoses codes for COPD have shown a good positive predictive value (PPV). In the Danish National Registers, the PPV for the hospital discharge diagnosis of COPD (ICD-10 code J44) has been reported to be 92%. [R14-0359]

The ICD-10 and ICPC codes to identify the diagnosis of COPD are detailed in Table 4. Diagnosis codes include COPD, chronic bronchitis, and emphysema.

Table 4 ICD-10 and ICPC diagnoses and codes to identify patients with COPD

ICD-10 Code Description	ICD-10 Code	ICPC Code
Chronic bronchitis	J41-J42	R78, R91
Emphysema	J43	—
Other COPD	J44	R95[1]
COPD with acute lower respiratory infection	J44.0	—
COPD with acute exacerbation, unspecified	J44.1	—
Other specified COPD	J44.8	—
COPD, unspecified	J44.9	—

COPD = Chronic Obstructive Pulmonary Disease; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICPC = *International Classification of Primary Care*.

1. Data sources use different coding systems with different degrees of granularity; thus, COPD diagnosis and subclassification will be adapted to each database.

9.3.2.2 Off-label prescribing

Patients without a recorded diagnosis of COPD at any time before or up to 30 days after the index date or patients with a recorded diagnosis of asthma in the absence of a diagnosis for COPD will be considered off-label users. Patients aged 17 years or younger will be considered off-label users. The off-label prescribing of olodaterol and indacaterol for the treatment of asthma is of special interest because this class of medication is often used in asthma but olodaterol and indacaterol have not been developed or approved for asthma or for patients aged less than 18 years.

Few studies have examined the validity of ICD codes for identifying patients with asthma. The PPV of asthma diagnoses recorded in the Danish National Patient Registry among

children aged 6-14 years was estimated at 85% (95% confidence interval, 80%-89%). [R16-2628] [R16-2629] In a validation study conducted in Sweden, a country with a national health records system similar to that of Denmark, the PPV for the diagnosis of asthma (ICD-10 code J45) associated with visits to outpatient specialty clinics and inpatient stays and recorded in the National Patient Registry among patients 18 to 45 years of age treated with asthma medications was 89% (95% confidence interval, 83%-93%). [R14-0349] The proportion of subjects misclassified as COPD was 1.6%. In another study conducted in the RAMQ Medical Services database of the province of Quebec in Canada, the PPV for having one or more recorded diagnoses of asthma (ICD-9 493) over a 1-year period in patients aged 16 to 44 years was 75% when the diagnosis was recorded by respiratory physicians and 67% when it was recorded by family physicians. The PPV increased to 77% for respiratory physicians and to 78% for family physicians when two or more recorded diagnoses of asthma were required. [R14-0352] Another study conducted in children under 4 years of age using data from the Rochester Epidemiology Project database showed that the overall agreement of ICD-9 code 493 for asthma (corresponding to the ICD-10 code J45) and information from the medical chart was 81.6%. [R14-0351]

The ICD-10 and ICPC codes to identify patients with asthma are detailed in Table 5.

Table 5 ICD-10 and ICPC diagnoses and codes to identify patients with asthma

ICD-10 Code Description	ICD-10 Code	ICPC Code
Asthma	J45	R96
Predominantly allergic asthma	J45.0	R96.02[1]
Non-allergic asthma	J45.1	
Mixed asthma	J45.8	—
Asthma, unspecified	J45.9	—
Chronic obstructive asthma	—	—
Other forms of asthma	—	—
Status asthmaticus	J46	—

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICPC = *International Classification of Primary Care*.

1. Data sources use different coding systems with different degrees of granularity; thus, asthma diagnosis and subclassification will be adapted to each database.

9.3.2.3 Review of patient profiles and medical records

The prescribed indication for olodaterol and indacaterol and the potential for off-label prescribing of these medications will be further evaluated through the clinical review of patient profiles of a random sample of about 100 new users of each medication prior to and up to 30 days after the first exposure to the respective drug. Patient profiles are chronological listings of the routinely recorded codes that represent clinical events recorded in the study databases for individual patients. These listings include general practitioner diagnoses (if available, depending on the data source), outpatient and hospital discharge diagnoses and procedures, and dispensings of medications. The clinical review of patient profiles will

provide more accurate information for evaluation of the indication and potential off-label use of olodaterol and indacaterol than use of codes alone. This information will be useful for developing clinical algorithms that can be applied to the evaluation of all new users of olodaterol and indacaterol.

The random sampling of patient profiles for review will be stratified by age (18-39 years, ≥ 40 years) and sex because PPVs are expected to vary by prevalence of COPD, which in turn varies by age and sex.

9.3.2.4 Classification of patients

According to the presence of a recorded diagnosis of COPD and/or asthma, adult new users of olodaterol and new users of indacaterol will be classified into the following categories: (1) on-label prescribing (indication of COPD), (2) off-label prescribing for asthma, and (3) off-label prescribing with no evidence of COPD or asthma (Table 6).

Table 6 Classification of patients according to indication or off-label prescribing of olodaterol and indacaterol

Recorded diagnosis[1]	On-Label Prescribing: Indication of COPD	Off-Label Prescribing for Asthma	Potential Off-Label Prescribing Other than Asthma
COPD	Yes		
COPD and asthma	Yes		
Asthma		Yes	
No COPD, no asthma			Yes

COPD = Chronic Obstructive Pulmonary Disease.

1 Diagnosis recorded at any time before the index date or at the index date and up to 30 days after the index date.

9.3.3 Characterisation of new users of olodaterol and indacaterol

New users of olodaterol and new users of indacaterol will be characterised at the index date according to demographic variables, available data on lifestyle habits, comorbidity, and use of medications. Comorbidity will be ascertained through diagnosis codes and procedures recorded at any time before the index date. Use of medications will be ascertained for the 12 months before the index date.

In the following sections, we list the variables that will be used to characterise new users of olodaterol and new users of indacaterol. The variables will be assessed according to the availability of information in each study database (see Table 9 in Section 9.4.4 for availability of variables of interest). Some of the variables (e.g., lifestyle habits or socioeconomic indicators) may be partially or completely unavailable in the study databases. We provide ICD-10 and ICPC codes for diagnoses and procedures and ATC codes for medications.

9.3.3.1 Demographics and lifestyle habits at the index date, where available

- Age
- Sex
- Calendar year
- Body mass index
- Smoking status
- Alcohol consumption
- Socioeconomic indicators or proxies (e.g., deprivation index, education level, postal code)

9.3.3.2 Respiratory comorbidity and allergies

- Time since first diagnosis of COPD
- Respiratory conditions recorded at any time before the index date (Table 7)

Time between the first recorded diagnosis of COPD in the database and the index date will be ascertained for new users of olodaterol and indacaterol.

Table 7 Respiratory comorbidity and allergies

Disease Description[1]	**ICD-10**[2]	**ICPC**
COPD	J41-J44	R95
Chronic bronchitis	J41-J42	R78, R91
Emphysema	J43	—
Other COPD	J44	—
Asthma	J45, J46	R96
Pneumonia	J09-J18	R81
Allergic rhinitis	J30	R97
Bronchiectasis	J47	—
Lung diseases due to external agents	J60-J69	—

COPD = Chronic Obstructive Pulmonary Disease; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICPC = *Internation Classification of Primary Care*.

[1] Other respiratory comorbidities of interest may be described depending on data availability.

[2] The use of ICD-10 code J40 "Bronchitis, not specified as acute or chronic" will be assessed in the data source–specific definitions.

9.3.3.3 Severity of COPD

While the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines published prior to 2011 classified COPD severity based only on percent predicted FEV_1, current guidelines recommend that physicians evaluate the severity of COPD and its impact

on the health of patients by the combination of (1) the current level of symptoms, (2) the severity of the spirometric abnormality, and (3) the risk of exacerbations. [P16-00121] The presence of comorbidities also determines the severity of COPD and is a predictor of morbidity and mortality. According to these parameters, severity of COPD is classified in four severity groups as illustrated in Figure 2.

Risk GOLD classification of airflow limitation				**Risk** Exacerbation history
4 3	**C**	**D**	**≥ 2 without hospitali-sation or ≥ 1 hospitalisa-tion**	
2 1	**A**	**B**	**≤ 1 without hospitalisa-tion and no hospitali-sations**	
	mMRC 0-1 CAT < 10	**mMRC ≥ 2 CAT ≥ 10**		

COPD Severity Categories

Severity Category	Characteristics	Spirometric Classification	Exacerbations per Year	mMRC	CAT
A	Low risk, fewer symptoms	GOLD 1-2 (mild-moderate)	≤ 1 without hospitalisation and no hospitalisations	0-1	< 10
B	Low risk, more symptoms			≥ 2	≥ 10
C	High risk, fewer symptoms	GOLD 3-4 (severe-very severe)	≥ 2 without hospitalisation or ≥1 hospitalisation	0-1	< 10
D	High risk, more symptoms			≥ 2	≥ 10

CAT = COPD Assessment Test; COPD = Chronic Obstructive Pulmonary Disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = Modified British Medical Research Council Questionnaire.
Source: Adapted from GOLD, 2016. [P16-00121]

Figure 2 Association between symptoms, spirometric classification, and future risk of exacerbations according to the Global Initiative for Obstructive Lung Disease

Some of the parameters to evaluate the severity of COPD are not available or are only partially recorded in automated health databases. These parameters include the level of symptoms of COPD and the results from spirometric tests. Therefore, severity of COPD in studies conducted in health databases is usually evaluated by other parameters that serve as proxies of severity. [R08-1492] [R09-0579] [R13-1392] [P09-04948] [P11-13226]

A summary of the evaluation of severity of COPD in health database studies is presented in Annex 3. In a study conducted in the General Practice Research Database (now known as the Clinical Practice Research Datalink) from the United Kingdom, the definition of severity was based on the intensity of use of bronchodilators and the use of oxygen therapy or nebulised therapy. [R08-1492] A modification of this definition of severity was used in a recent study conducted in the Integrated Primary Care Information Project database in the Netherlands. [P11-13226] If spirometry was available (30% of patients), severity of COPD was determined according to the GOLD guidelines. In all other patients, the definition used in that study included hospitalisations for COPD, the use of antibiotics for the treatment of respiratory tract infections, and the use of systemic glucocorticosteroids for the treatment of COPD exacerbations. The classification of severity based on these factors had a PPV of 82%

when compared with results from spirometry. In another study conducted in the Saskatchewan Health databases in Canada, determinants of COPD severity were the presence of emphysema, the use of nebuliser therapy, the use of oxygen therapy, the use of inhaled and/or systemic glucocorticosteroids, the intensity of bronchodilator use, pneumonia, and prior COPD exacerbation. [R09-0579] These factors were associated with increased cardiovascular morbidity and mortality.

9.3.3.4 Definition of COPD severity

Severity of COPD will be evaluated among new users of olodaterol and indacaterol that have a recorded diagnosis of COPD before the index date. In the current study, severity of COPD will be evaluated at the index date by a modified version of the algorithm developed by Verhamme and colleagues [P11-13226] and taking into account the updated GOLD recommendations (see Table 8). [P16-00121] Definitions shown in Table 8 will be adapted to the characteristics and data availability in each data source. For example, hospitalisation data are not available in IMS RWE LPD, and information on the dispensing of oxygen therapy is not available in PHARMO. Details on the operational definitions will be provided in the statistical epidemiological analysis plan.

Table 8 Definition criteria of COPD severity (to be adapted to available data in each data source)

Severity of COPD	**Definition**
Mild	Less than two prescriptions/dispensings of the same COPD drug class with a maximum interval of 6 months in the 12 months before the index date
Moderate	Regular bronchodilator treatment, defined as having at least two prescriptions/dispensings of the same COPD drug class with a maximum interval of 6 months in the 12 months before the index date[1,2]
Severe	Occurrence of at least one of the following events in the year before the index date: • Hospitalisation for COPD[2] • Recorded diagnosis of pneumonia[2] • Second course of antibiotics for respiratory tract infections[2] • Second course of systemic corticosteroids for the treatment of COPD exacerbation[2] • Two diagnoses of COPD exacerbation without hospitalisation
Very severe	Occurrence of at least one of the following events in the year before the index date unless other time period is specified: • Dispensed oxygen therapy[1,2] • Dispensed nebuliser therapy[1,2] • Diagnosis of emphysema at any time before the index date[2]

COPD = Chronic Obstructive Pulmonary Disease.

Sources: modified from Verhamme et al., 2012 [P11-13226]; Soriano et al., 2001 [R08-1492]; Curkendall et al., 2006 [P07-09136]; and GOLD, 2016 [P16-00121].

1 Severity criteria also included in definition from Soriano et al., 2001. [R08-1492]

2 Severity criteria also included in definition from Curkendall et al., 2006. [P07-09136]

Prescription of antibiotics and oral corticosteroids and hospitalisations for COPD have been used by other authors as markers of severity of COPD exacerbations. [P12-09396] [P12-09395] [P12-14293]

Indicators of severity presented in Table 8 will be mutually exclusive, and patients that fulfil criteria for more than one category will be classified as being in the more severe category. The proposed operational definitions to be applied when assessing the severity of COPD are as follows:

- Same-class bronchodilators. The following bronchodilators classes will be considered (see Annex Table 4:2):
    1. Bronchodilators: inhaled short-acting muscarinic antagonists (SAMAs), inhaled long-acting muscarinic antagonists (LAMAs), inhaled short-acting beta2-agonists (SABAs), inhaled LABAs, and fixed combinations of SABAs and SAMAs
    2. Inhaled glucocorticosteroids (ICSs): ICS alone, fixed combinations of SABAs and ICSs, and fixed combinations of LABAs and ICSs
    3. Systemic glucocorticosteroids
    4. Systemic beta2-agonists
    5. Xanthines
    6. Roflumilast
- Hospitalisation for COPD
    - Primary or secondary hospital discharge diagnosis for COPD
    - ICD-10 codes: J41-J44
- Recorded diagnosis of pneumonia
    - Primary or secondary hospital discharge diagnosis for pneumonia or outpatient diagnosis for pneumonia
    - ICD-10 codes J09-J18; ICPC codes: R81
- Second course of antibiotics for respiratory tract infections
    - A course with antibiotic is defined as that involving consecutive prescriptions/dispensings of antibiotics with less than 7 days between the end of days of supply of one prescription/dispensing and the date of the next prescription/dispensing
    - ATC codes for antibiotics: J01 (antibacterials for systemic use)
- Second course of systemic glucocorticosteroids for the treatment of COPD exacerbation

  - A course with systemic corticosteroids is defined as that involving consecutive prescriptions/dispensings with less than 7 days between the end of days of supply of one prescription/dispensing and the date of the next prescription/dispensing
  - ATC codes for systemic glucocorticosteroids: H02AB
- Two diagnoses of COPD exacerbation without hospitalisation
- Oxygen therapy, ATC code: V03AN01
- Nebuliser therapy (to be identified in each database using national drug codes)
- Emphysema
  - Primary or secondary hospital outpatient or inpatient discharge diagnosis of emphysema at any time before the index date
  - ICD-10 code: J43; ICPC code: not available

9.3.3.5 Other comorbidity and conditions

The following comorbidities and conditions recorded at any time before the index date will be evaluated: cardiovascular diseases, hyperlipidaemia, diabetes mellitus, renal disease, anaemias, peptic ulcer disease, liver disease, osteoporosis, rheumatoid arthritis, systemic connective tissue diseases, malignancy, depressive disorders, and pregnancy. Specific diseases and conditions and ICD-10 and ICPC codes are provided in Annex 4, Annex Table 4:1.

9.3.3.6 Comedications

The following comedications dispensed within 12 months before the index date will be evaluated: respiratory medications, cardiovascular medications, antithrombotic agents, systemic antibacterials, iron preparations, proton pump inhibitors, drugs used in diabetes, drugs for musculoskeletal system conditions, antidepressants, antineoplastic agents, immunosuppressants, antivirals for systemic use, hormone-replacement therapy, and drugs used in nicotine dependence.

Specific medication and ATC codes are provided in Annex Table 4:2.

9.3.3.7 Health care resource utilisation

Health care resource utilisation will be evaluated for the **12 months before the index date**. Data on prescriptions will be used when no data on dispensings are available. Availability of hospitalisation data will vary by data source.

- Total number of dispensings; all medications included in Annex Table 4:2
- Total number of dispensings for respiratory medications; all medications included in the section on respiratory medications in Annex Table 4:2
- Total number of dispensings for systemic glucocorticosteroids; ATC code H02AB
- Total number of dispensings for LABAs; ATC codes R03AC012 (salmeterol) and R03AC013 (formoterol)

- Total number of hospitalisations; number of hospitalisations for any cause
- Total number of hospitalisations for COPD; number of hospitalisations with a primary discharge code for COPD; ICD-10 codes J41-J44
- Total number of hospitalisations for asthma; number of hospitalisations with a primary discharge code for asthma; ICD-10 codes J45, J46

9.3.4 Outcomes

9.3.4.1 Primary outcome

The primary outcome is the prevalence of off-label prescribing among new users of olodaterol.

9.3.4.2 Secondary outcomes

The secondary outcome is the prevalence of off-label prescribing among new users of indacaterol.

9.3.4.3 Further outcomes

Not applicable.

9.3.5 Covariates

Not applicable.

9.4 DATA SOURCES

The study will be conducted in the following databases:

- PHARMO Database Network
- National Registers in Denmark
- IMS RWE LPD in France

A description of each database is provided in the following sections. The study will be conducted by using data on drug prescription/dispensings and disease occurrence routinely collected on an ongoing basis for large population-based automated health care databases in the Netherlands, Denmark, and France (see Table 1 for characteristics of these databases). New users will be characterised in terms of past medical history and use of medications. An overview of the information on diagnosis and procedure codes by data source is shown in Table 2.

9.4.1 PHARMO Database Network

9.4.1.1 Database characteristics

The PHARMO Database Network in the Netherlands is a population-based network of health care databases that combines data from different health care settings, including general

practice, in- and outpatient pharmacy, clinical laboratory, hospitals, cancer registry, pathology registry, and perinatal registry. Data sources are linked on a patient level through validated algorithms. Detailed information on the methodology and the validation of the record linkage method used can be found elsewhere. [P14-01899] [R16 2062]

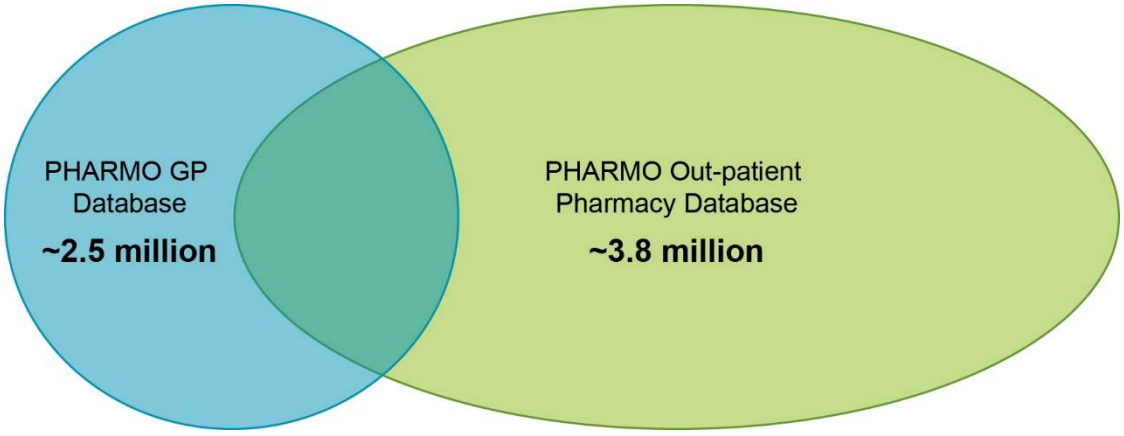
The longitudinal nature of the PHARMO Database Network enables follow-up of more than 4 million residents of a well-defined population in the Netherlands (25% of that country's population) for an average of 10 years. Data collection period, catchment area, and overlap between data sources differ. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status, and mortality. Other information available is dependent on the data source.

To address the objectives of the present study, the following PHARMO databases will be used:

- Out-patient Pharmacy Database
- General Practitioner (GP) Database
- Hospitalisation Database

The patients covered in each database are not necessarily included in all of the databases, as some of the geographical areas overlap partially, but if they are in more than one database, they can be linked to construct the medical history as shown in Figure 3. Thus, high-quality research can be conducted with ascertainment of patient demographics, drug dispensings, hospital morbidity, clinical laboratory results, and date of death.

The Out-patient Pharmacy Database (dispensings), covering 3.8 million individuals, can use a validated algorithm to identify patients with COPD, asthma, or other respiratory conditions. All patients are linked with the Hospitalisation Database. Approximately 15% of patients can be linked to GP data for severity indicators as recorded by the GP.



GP = general practitioner.

Figure 3 Schematic overview of overlap example among databases included in the PHARMO Database Network

The GP Database, covering 2.5 million individuals, has information as recorded by the GP, including forced expiratory volume in 1 second (FEV_1) and spirometry data. Approximately

half of the population in the GP Database can be linked to both dispensing (outpatient pharmacy) and hospitalisation data.

9.4.2 Denmark

The Danish health care system provides universal coverage to all Danish residents (5.6 million inhabitants). Health care coverage includes visits to GPs and specialists, hospital admissions, and outpatient visits. The costs of medicines are partially covered by the Danish health system. The centralised Civil Registration System in Denmark allows for personal identification of each person in the entire Danish population and for the possibility of linkage to all Danish registries, including the Danish National Patient Registry, Danish National Health Services Prescription Database, and the Danish Registry of Causes of Death. Data collected in these registries are available for research purposes.

For 1980-2008, the National Patient Registry counted 236,494 patients with a first hospital contact for COPD. [R12-3324] From the National Health Service, for persons aged 45 to 84 years, the prevalence of COPD was estimated at 12%, using a sample of 299,000 residents of two counties. [R12-3265]

9.4.3 France

The French IMS RWE LPD is an anonymised medical records database. The primary care panel was launched in 1994 and currently includes 1,200 primary care physicians covering 1.8 million patients. The database is representative of primary care physicians and the general population according to age and sex distribution. Furthermore, the primary care physicians are representative with regards to geographical location. The data contain events that physicians record during routine clinical practice, e.g., diagnoses, prescriptions, measurements, tests, and referrals. Medical diagnoses and symptoms are coded and mapped to ICD-10 codes, and the ATC coding system is used for therapies.

The database is not used for payment purposes, and the recorded prescriptions cover both reimbursed and unreimbursed medications. An associated diagnosis, but not necessarily the clinical indication, is always recorded with an issued prescription.

The Longitudinal Patient Database includes the following raw data:

- Demographic information (age, sex)
- Medical history (event dates, diagnoses, risk factors, referrals to specialists)
- Therapeutic history (generic and brand name, date and duration of prescription, dosage)
- Additional information (test results, immunisations, height, weight, blood pressure)

The IMS RWE panel of participating medical doctors is selected from a large number of French physicians who use the Cegedim management software for their daily practice. These office-based, active physicians have agreed to upload to Cegedim servers anonymous and coded excerpts from medical files of patients who have come to see them. The data collected are gathered for each patient within the same doctor's office, thus providing longitudinal data on the same patients. The representativeness of the panel of physicians is checked using three

criteria known to influence prescribing: age, sex, and geographic area of coverage. However, there are limitations in this database, such as no availability of information on hospitalisations, deaths, or date transferred out of the system.

9.4.4 Summary of study databases

Table 9 shows and compares the characteristics of the study databases.

Table 9 Overview of the study databases

Data Element	PHARMO, the Netherlands	National Registers, Denmark	IMS RWE LPD, France
Database type	Patient-centric data obtained from community pharmacies and with variable linkage rates to other health care files	National health record and prescription databases linked through the unique civil personal registration number	Primary health care electronic medical record database
Database population	3.8 million	Denmark	1.8 million for GP panel 50,000 for pulmonologist panel
Country population[1]	16,900,726	5,659,715	66,352,469
Approximate proportion of the country's population covered by the database	25%	100%	4%
Representative-ness of patients and practices	Known to be representative [P93-73309] [P14-01899]	Complete, given that the total population of the country is included	GPs of the panel are representative according to sex, age, and geographic location Patients are representative of those who visit office-based GPs
Data on medications	Outpatient pharmacy–dispensed prescriptions and GP prescriptions	Outpatient pharmacy–dispensed prescriptions	Physician prescriptions
Dose	Yes	Formulation strength	Prescribed dose
Duration	Yes	Based on prescriptions	Based on prescriptions
Drug dictionary codes/therapeutic classification	ATC	ATC	ATC

Table 9 (cont'd) Overview of the study databases

Data Element	PHARMO, the Netherlands	National Registers, Denmark	IMS RWE LPD, France
Indacaterol prescriptions or dispensings	12,867 (2014-2015)	7,165 DDD (2014-2015	GP panel 2015: 9,493 Pulmonologist panel 2015: 1,437
Number of users of indacaterol	2,044 (1,518 new users) (2014-2015)	22,487 (2014-2015)	GP panel 2015: 3,654 Pulmonologist panel 2015: 1,073
Clinical indication	For approximately 15% of the 3.8 million PHARMO patients (included in outpatient database), via linkage to GP files and proximity of clinical diagnoses; for all patients in GP Database	Not recorded but may be surmised based on proxies (i.e., prescribed medication and hospital discharge diagnosis history)	Associated with new courses of medications, but completeness is variable
Prescriber characteristics	GP vs. specialist	GP vs. specialist	GP vs. specialist
Outpatient diagnosis	For all PHARMO patients (included in outpatient databases): main diagnoses in ICPC codes for all admissions for > 24 hours and admissions for < 24 hours for which a bed is required; for subcohort of GP Database patients with linkage to outpatient pharmacy database	Hospital specialist clinic outpatient diagnoses	General practitioner diagnoses
Hospital diagnosis	Main hospital diagnostic/surgical procedures	Yes	No

Table 9 (cont'd) Overview of the study databases

Data Element	PHARMO, the Netherlands	National Registers, Denmark	IMS RWE LPD, France
Procedure codes	Available for approximately 1 million of pharmacy file patients; GP laboratory tests for all patients in GP Database	Yes, NCSP version 1.16:2012	Yes, ICD-10
Pulmonary function testing	Yes, if recorded	From hospital clinics	From pulmonologist and also from primary care when recorded
Information on death	Fact and date of death, Mortality Register	Date of death: the Civil Registration System Cause of death: Danish Registry of Causes of Death	No
Access to medical records	Variable	Possible, additional approval required	No
Lifestyle risk factors (smoking status, BMI, alcohol intake)	Yes, if recorded by GPs	In general, no; only some risk factors are available if recorded for inpatients (BMI and alcohol only from diagnosis codes, smoking not available, SES proxies available)	Yes, if recorded by GPs
Data availability	1998	Since 1994 (ICD-10)	GPs since 1994 Pulmonologists since 2007
Updates	Pharmacy data: 2 months All other data and linked database, annual; available following Q4	Biannual	Monthly

Table 9 (cont'd) Overview of the study databases

Data Element	PHARMO, the Netherlands	National Registers, Denmark	IMS RWE LPD, France
Approximate time lag	6-18 months	6-12 months	2-7 months
Data transfer	Review by the independent compliance committee STIZON/ PHARMO Institute This committee consists of representatives of the individual data suppliers and is chaired by a privacy expert	No, requires collaboration with local investigator	No, requires collaboration with local investigator
Approval process	Data application and ethics committee approval required	Data application approval by the Danish Data Protection Agency required. Ethics committee approval required if access to medical records is needed	No data application or ethics committee approval required The Longitudinal Patient Database global process (formerly BKL Consultant, Thalès) was authorised by the CNIL in December 1993 (Receipt 271.306) and renewed on 20 June 2002 (Receipt 271.306 version 2) and 25 January 2011 (Receipt 271.306 version 3)

ATC = Anatomical Therapeutic Chemical; BMI = Body Mass Index; CNIL = French data protection authority; DDD = Defined Daily Dose; GP = General Practitioner; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICPC = International Classification of Primary Care; IMS = IMS Health Information Solutions; NCSP = *Nordic Medico-Statistical Committee's Classification of Surgical Procedures*; PHARMO = PHARMO Database Network; Q4 = fourth quarter of calendar year; RWE LPD = Real-World Evidence Longitudinal Patient Database; SES = socioeconomic status.

1 Eurostat. 2015 Available at: website: epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&init=1&language=en&pcode=tps00001&plugin=1. Accessed February 9, 2016.

9.5 STUDY SIZE

No formal sample size calculations have been done given that there will be no hypothesis testing. Table 10 shows the confidence intervals around estimated prevalence of comorbidity and comedications under various exposure group size scenarios.

Table 10 Confidence intervals around selected estimated prevalences for varying numbers of patients

Number of Patients	95% Confidence Intervals for Various Prevalences of Diseases (%)				
	1%	2%	5%	7%	10%
300	0.2-2.9	0.7-4.3	2.8-8.1	4.4-10.5	6.8-14.0
800	0.4-2.0	1.1-3.2	3.6-6.7	5.3-9.0	8.0-12.3
2,000	0.6-1.5	1.4-2.7	4.1-6.0	5.9-8.2	8.7-11.4
5,000	0.7-1.3	1.6-2.4	4.4-5.6	6.3-7.7	9.2-10.9

Note: This table was prepared with the use of Episheet—spreadsheets for the analysis of epidemiologic data. [R13-1396]

Olodaterol was launched in the Netherlands in February 2014, in Denmark in March 2014, and in France in November 2015. The number of users of olodaterol was obtained by searching for ATC code R03AC19 in publicly available resources or directly from the data source custodians.

Table 11 presents a summary of the available number of users of olodaterol during 2014 and 2015 in the data sources of interest.

Table 11 Summary table of olodaterol users in the Netherlands, Denmark, and France; 2014-2015

Country and Database	Number of Unique Users		
	2014	2015	Total Available in Database as of December 2015
The Netherlands (PHARMO)	326	394	720
Demark (National Database of Reimbursed Prescriptions)	643	1,102	> 1,102
France (IMS RWE LPD)	0	95 in the GP panel 69 in the pulmonologist panel	164

GP = General Practitioner; IMS = IMS Health Information Solutions; PHARMO = PHARMO Database Network; RWE LPD = Real-World Evidence Longitudinal Patient Database;

9.6 DATA MANAGEMENT

Routine procedures include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all

programs. Each database research partner will maintain any patient-identifying information securely onsite according to internal standard operating procedures.

Each collaborating data source has been reviewed and qualified by the RTI Health Solutions Office of Quality Assurance. Each research team will follow its own established procedures and generate appropriate result tables. All summary tables of results, and no individual patient identifiers, will be provided to RTI Health Solutions, which will compile the results and develop the report. RTI Health Solutions will follow quality-control procedures regarding transfer of data.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed. Standard procedures will be in place at each location handling the data to restore files in the event of a hardware or software failure.

The extent of missing data will be evaluated and described. Due to the nature of this study, no imputation of missing data is planned.

For requests to access to data for audit purposes, only aggregated data from all research centres will be available at the coordinating centre. The audit trail will consist of a detailed description of the methods to extract and process the electronic health records or claims data, as applicable. Access to raw data at each database research centre will require the data requestor to obtain a licence or apply for approval at a research committee and to fulfil the conditions required under the governance rules of each database research centre.

9.7 DATA ANALYSIS

All analyses will be conducted separately in each study database and will be further analysed separately by new users of olodaterol and by new users of indacaterol, further stratified by treatment-naïve subjects and switchers. In the French IMS RWE LPD, data will be analysed separately for the panel of general practitioners and for the panel of pulmonologists. Analysis for each report (i.e., interim and final) will include data on all patients starting treatment with olodaterol or indacaterol from the start of such treatment up to the latest available data. Statistical analyses will be descriptive in nature. Descriptive statistics will include the absolute and relative number of subjects, mean, median, standard deviation, and range for continuous variables. Statistical inference will not be performed (e.g., no *P* values will be generated). Where appropriate, two-sided 95% confidence intervals will be presented.

9.7.1 Main analysis

9.7.2 Indication and potential off-label prescribing

The main analysis will be to estimate (with 95% confidence intervals) the prevalence proportion of off-label use among new users of olodaterol and new users of indacaterol during the study period. This analysis will generate the number and proportion of new users

for each indication associated with the initiation of treatment (COPD only, COPD and asthma, asthma only, and no COPD or asthma). This analysis will be conducted using data linked to diagnoses recorded by general practitioners (primary care information) or inpatient and prescription data in the following databases:

- PHARMO: GP and hospital data
- The Danish National Registries
- IMS RWE LPD in France: GP panel and pulmonologist panel

9.7.3 Number of users and patterns of use

The following analyses will be conducted:

- **Dose at the start date**: Dose at the start date will be the dose prescribed by the physician, when available, or ascertained by the dispensed DDD and the estimation of the daily dose. The estimated daily dose dispensed at the index date will be calculated using the recorded information on strength and quantity dispensed and the days of supply of the first prescription for olodaterol and indacaterol. The mean (SD) number of packages and daily dose will be calculated.
- **Age and sex distribution of users at the index date**: Number and percentage of users of olodaterol and indacaterol at the index date by sex and the following groups of age (in years): 0-17, 18 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79, 80 or older.

9.7.4 Characterisation of new users at the index date

The number and percentage of each variable of interest (as specified in Section 9.3) at the index date will be estimated separately among new users of olodaterol and among new users of indacaterol. All analyses will be stratified by the following variables:

- Age in years, categorised as 0 to 17 years, 18 to 39 years, and 40 years or older
- Sex
- Switchers at the index date (as defined in Section 9.2.3) and treatment-naïve subjects
- Indication
  - COPD only
  - COPD and asthma
  - Asthma only
  - Neither COPD nor asthma
- Calendar year of index date: 2014, 2015, 2016, 2017

The following analyses will be performed:

Time since first recorded diagnosis of COPD: Mean (SD), median, 25th percentile, and 75th percentile.

Lifestyle habits: Distribution of new users by categories of body mass index, smoking status, alcohol consumption, and socioeconomic status at the index date, according to the type of information available in each database.

Respiratory comorbidity and allergies: Number and proportion of new users with at least one diagnosis for each respiratory condition listed in Table 7 that was recorded at any time before the index date.

Severity of COPD (see definitions in Table 8): Number and proportion of new users for each category of severity of COPD: mild, moderate, severe, and very severe.

Other comorbidity: Number and proportion of patients with at least one diagnosis for each of the comorbidity conditions listed in Annex Table 4:1 and recorded at any time before the index date.

Comedications. Number and proportion of patients with at least one dispensing for each of the medications listed in Annex Table 4:2 taking place in the 12 months before the index date.

Health care resources utilisation: Distribution of new users as defined by the following categories of variables evaluated within the 12 months before the index date:

- Total number of prescriptions/dispensings: 0, 1 to 4, 5 to 9, 10 or more
- Total number of prescriptions/dispensings for respiratory medications (Annex Table 4:2): 0, 1 to 4, 5 to 9, 10 or more
- Total number of prescriptions/dispensings for systemic glucocorticosteroids: 0, 1 to 4, 5 to 9, 10 or more
- Total number of prescriptions/dispensings for LABAs: 0, 1 to 4, 5 to 9, 10 or more
- Total number of hospitalisations: 0, 1, 2, 3 to 4, 5 or more
- Total number of hospitalisations for COPD: 0, 1, 2, 3 to 4, 5 or more
- Total number of hospitalisations for asthma: 0, 1, 2, 3 to 4, 5 or more

9.8 QUALITY CONTROL

At the coordinating centre, an independent Office of Quality Assurance performs audits and assessments that involve various aspects of its projects, including but not limited to documentation of education and training, data entry, data transfer, and approval of the institutional review board at RTI International, of which RTI Health Solutions is a research unit. Such audits at RTI Health Solutions will be conducted by the Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures. Each of the database research centres will follow its own quality and audit trail procedures. The quality and audit trails at each centre may be different.

Data management and analysis will be conducted in each database. Standard operating procedures at each database will be used to guide the conduct of the study. These procedures include internal quality audits and the opportunity for external audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control

procedures for programming, standards for writing analysis plans, and requirements for senior scientific review. RTI Health Solutions will follow quality-control procedures for report generation, including senior review by an expert other than the author.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Existing population-based data are very useful for evaluating research questions about real-world clinical practice because of the diversity of patients and medical practices represented therein. However, the results must be interpreted with caution because such data sources are known to misclassify information of interest, in the following ways:

- The length of medical history in some databases will be limited, and earlier medical events or drug exposures may be unknown. Therefore, the prevalence of some conditions may be underestimated.
- Information on prescriber characteristics is likely to be limited in some of the available databases.
- Clinical differential diagnosis between COPD and asthma might be difficult, and it is even more challenging to differentiate these conditions in database studies.
- For severity of COPD, ideally FEV_1 and measures of symptoms (mMRC or CAT scale) would be useful to classify all individuals by application of standard criteria; however, it is anticipated that this information is not recorded systematically in the study databases. Therefore, classification of severity of COPD in database studies uses proxies, such as use of COPD medications and use of health care services.
- Data from the French IMS RWE LPD will be available from the panel of general practitioners and from the panel of pulmonologists. These two panels are not linkable, and some patients may be duplicated. However, data will be described stratified by each type of panel.
- In the French IMS RWE LPD, an associated diagnosis, but not necessarily the clinical indication, is always recorded with an issued prescription; for this reason, prior history of COPD and asthma will also be used to define the indication of use.
- In the French IMS RWE LPD, no hospital data are available, and this will limit the capacity to identify prior hospitalisations for COPD if these are not recorded by the physician.
- Study size depends upon the uptake of olodaterol.

9.10 OTHER ASPECTS

9.10.1 Bias

The use of hospital outpatient and/or inpatient discharge diagnoses can overestimate potential off-label prescribing. For this reason, to maximise the sensitivity and specificity of the algorithms, the algorithms to identify these patients will be adapted to each data source (e.g., using inpatient records only or outpatient and inpatient, ICD-10 or thesaurus coding) and based on available data and prior experience in designing studies evaluating COPD and other diseases. Other respiratory conditions will be characterised in order to identify potential off-

label prescribing, although it is acknowledged that indication will be unknown for a certain portion of patients.

In PHARMO, the indication will be ascertained using hospital data for all patients; in addition, for a subset of patients, primary care data, which will help elucidate the degree of potential underestimation of COPD diagnoses, will be obtained.

10. PROTECTION OF HUMAN SUBJECTS

The study will be conducted in accordance with the International Society for Pharmacoepidemiology's *Guidelines for Good Pharmacoepidemiology Practices* [R11-4318] and in accordance with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology*. [R13-5419] The ENCePP *Checklist for Study Protocols* [R13-1395] is completed (see Annex 2), and the study will be registered in the EU PAS Register. [R14-0354]

The study is a drug utilisation study and will comply with the definition of the non-interventional (observational) study provided in the 2012 *Guideline on Good Pharmacovigilance Practice: Module VIII—Post-Authorisation Safety Studies*. [R13-5420]. The study will comply with the nature of non-interventional (observational) studies referred to in the International Conference on Harmonisation's harmonised tripartite guideline *Pharmacovigilance Planning E2E*. [R11-2259]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Based on current guidelines from the International Society for Pharmacoepidemiology [R11-4318] and the European Medicines Agency (EMA) *Guideline on Good Pharmacovigilance Practices (GVP) Module VI - Management and Reporting of Adverse Reactions to Medicinal Products*, [R13-1970] non-interventional studies such as the one described in this protocol conducted using aggregated patient data from electronic health care records do not require expedited reporting of suspected adverse events/reactions. Based on the data planned for this study, no suspected adverse events/reactions are expected.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol synopsis, study status, and report(s) will be included in regulatory communications in line with the risk management plan, Benefit-Risk Evaluation Report, and other regulatory milestones and requirements.

Study results will be published following the International Committee of Medical Journal Editors recommendations, [R13-5418] and communication in appropriate scientific venues (e.g., the International Society for Pharmacoepidemiology) will be considered.

When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology checklist [R11-4902] will be followed.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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13.2 UNPUBLISHED REFERENCES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

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

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation

safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Drug Utilisation Study for Olodaterol

Study reference number:
1222.53

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]	☒	☐	☐	12
1.1.2 End of data collection[2]	☒	☐	☐	12
1.1.3 Study progress report(s)	☐	☐	☒	12
1.1.4 Interim progress report(s)	☒	☐	☐	12
1.1.5 Registration in the EU PAS Register	☐	☐	☐	12
1.1.6 Final report of study results.	☒	☐	☐	12

Comments:

Timing of registration in the EU PAS Register has not yet been determined.

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)	☒	☐	☐	13

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1.2 The objective(s) of the study?	☒	☐	☐	14
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	19-21
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:

There is no a priori hypothesis, and the objective is to measure the relative frequency of off-label use among olodaterol and comparator.

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)	☒	☐	☐	15
3.2	Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	29
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)	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study data set or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical data set is completely available.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Page Number(s)**
4.1	Is the source population described?	☒	☐	☐	17, 19-20
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	17-18
	4.2.2 Age and sex?	☒	☐	☐	19-20
	4.2.3 Country of origin?	☒	☐	☐	15-18
	4.2.4 Disease/indication?	☒	☐	☐	19-20
	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)	☒	☐	☐	19-21

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)	☒	☐	☐	19
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)	☐	☐	☒	
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
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:

This drug utilisation study is limited to characterising the subjects on and before first use; exposure group of interest consists of all new users

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?	☒	☐	☐	19-22
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)	☒	☐	☐	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)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Confounding and effect modification are not expected to be an issue for this descriptive study.

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.)	☒	☐	☐	30-36

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
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.)	☒	☐	☐	30-36
8.1.3 Covariates?	☒	☐	☐	30-36
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)	☒	☐	☐	30-36
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	30-36
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	30-36
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	30-36
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	30-36
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	30-36
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	30-36

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	37

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	38-40
10.3 Are descriptive analyses included?	☒	☐	☐	38-40
10.4 Are stratified analyses included?	☒	☐	☐	38-40
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

Confounding and effect modification are not relevant to this descriptive study.

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?	☒	☐	☐	37-38
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☒	☐	37-38
11.3 Are methods of quality assurance described?	☒	☐	☐	37-38
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☐	☒	☐	
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

11.1-11.3 This is a core protocol that will be implemented by multiple research institution that are qualified and have available staffing at the time of study initiation, i.e. after EMA review, olodaterol is launched. At that time the specifics of data management for each data source and corresponding research institution, including quality control and data security, can be specified. 11.5 To date no advisory board is planned.

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)	☐ ☒	☐ ☐	☒ ☐	41-42
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	41-42
12.3 Does the protocol address other limitations?	☒	☐	☐	41-42

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?	☒	☐	☐	43
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☐	☒	☐	43

Comments:

For this core protocol, the data protection procedures will be consistent with local procedures and more details will be added into data source-specific study documents

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?	☒	☐	☐	10-11

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)?	☒	☐	☐	45
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	45

Comments:

Name of the main author of the protocol: _____Cristina Rebordosa_____

Date: 11 July 2016

Signature: _____

ANNEX 3. EVALUATION OF COPD SEVERITY IN AUTOMATED HEALTH DATABASES

Annex Table 3:1 Published definitions of COPD severity in studies conducted in automated health databases

Reference, Severity Criteria	COPD Severity		
	Mild	**Moderate**	**Severe**
Integrated Primary Care Information Project, Netherlands [P11-13226]			
With spirometry data, used GOLD criteria [P13-02399] Without spirometry, used methods of Curkendall et al., [R09-0579] Eisner et al., [R13-1392] and Soriano et al. [R08-1492]	At initial COPD symptoms	At least 2 prescriptions of bronchodilators of the same drug class with a maximum interval of 6 months in 1 year	Severe: • Hospitalisation for COPD, or • Third course of antibiotics for respiratory infection in 1 year, or • Second course of systemic corticosteroids for COPD exacerbation in 1 year Very severe: • Oxygen therapy, or • Scheduled for lung transplant
Saskatchewan Health, Canada [R09-0579]			
Case-control study to find severity marker variables, using: • Pre-existing chronic conditions • Recent acute conditions • Recent high use of bronchodilators Specific components of the above are detailed in the article's appendix	Patients ranked into 5 quintiles by likelihood of COPD hospitalisation, from conditional logistic regression model		Factors in previous 180 days associated with severe COPD: • Emphysema • Recent nebuliser use • Home oxygen therapy • Corticosteroid use • Frequent bronchodilator use • Pneumonia • Previous COPD exacerbation

Table Annex 3:1 (cont'd) Published definitions of COPD severity in studies conducted in automated health databases

Reference, Severity criteria	COPD Severity		
	Mild	**Moderate**	**Severe**
General Practice Research Database,[1] United Kingdom Soriano [R08-1492]			
Severity based only on drug data	At first diagnosis of COPD	At least 2 prescriptions of the same COPD drug within 6 months, using data on inhaled or oral bronchodilators, xanthines, cromones, steroids, or combinations	• Oxygen therapy, or • Nebuliser therapy

COPD = Chronic Obstructive Pulmonary Disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease.

1 This database is now known as Clinical Practice Research Datalink.

ANNEX 4. CODES FOR COMORBIDITIES AND OTHER MEDICATIONS

Annex Table 4:1 Other comorbidity

Disease Description	ICD-10 Code	ICPC Code
Cardiovascular diseases	**I00-I99**	**K73-K99**
Ischaemic heart disease	I20-I25 or coronary reperfusion surgery and procedures	
Angina pectoris	I20	K74 Angina pectoris
Acute myocardial infarction	I21	K75 Acute myocardial infarction
Other acute or subacute ischaemic heart disease	I22-I24	K76 Ischaemic heart disease w/o angina
Chronic ischaemic heart disease	I25	No specific code
Coronary reperfusion surgery and procedures	List of codes to be developed according to each database dictionary	List of codes to be developed according to each database dictionary
Arrhythmias	I47-I49	K78-K80
Paroxysmal tachycardia	I47	K79 Paroxysmal tachycardia
Ventricular tachycardia	I47.0, I47.2	No specific code
Supraventricular tachycardia and unspecified	I47.1, I47.9	No specific code
Atrial fibrillation and flutter	I48	K78 Atrial fibrillation/flutter
Other cardiac arrhythmias	I49	K80 Ectopic beats all types
Ventricular fibrillation and flutter	I49.0	No specific code
Other cardiac arrhythmias	I49.1-I49.9	No specific code
Conduction disorders	I44-I45	K84 Heart disease other
Cardiac arrest	I46	No specific code
Heart failure	I50	K77 Heart failure
Cerebrovascular disease	I60-I69, G45	K89-K90
Cerebral haemorrhage (subarachnoid, intracerebral, other non-traumatic)	I60-I62	K89 Transient cerebral ischaemia

Table Annex 4:1 (cont'd) Other comorbidity

Disease Description	**ICD-10 Code**	**ICPC Code**
Cerebral infarction and stroke	I63, I64, G46.5	K90 Stroke/cerebrovascular accident
Transient ischaemic attack	G45	K89 Transient cerebral ischaemia
Other cerebrovascular disease and sequelae of cerebrovascular disease	I65-I69	No specific code
Hypertension and hypertensive heart disease	I10-I15	K85 Elevated blood pressure (excl K86-K87) K86 Hypertension without organ damage K87 Hypertension with organ damage
Diseases of arteries, arterioles, and capillaries	I70-I79, and peripheral arterial revascularisation procedures	K91 Atherosclerosis (excl K76, K90) K92 Atherosclerosis/PVD
Peripheral arterial revascularisation procedures	List of codes to be developed according to each database dictionary	List of codes to be developed according to each database dictionary
Other form of heart diseases	I00-I09, I30-I43, I80-I99	K84.03 Cardiomyopathie K81 Heart/arterial murmur NOS K82 Pulmonary heart disease K83 Heart valve disease NOS K94 Phlebitis/thrombophlebitis K95 Varicose veins of leg K96 Haemorrhoids K99 Cardiovascular disease other
Hyperlipidaemia	**E78**	**T93 Lipid disorder**
Diabetes mellitus	**E10-E14**	**T90 Diabetes mellitus**
Renal disease	**N00-N39**	**U99 Urinary disease, other**
Chronic kidney disease	N18	U99.01 Kidney insufficiency
Other renal disorders	N00-N17, N19, N25-N39	U99 (excl U99.01)

Table Annex 4:1 (cont'd) Other comorbidity

Disease Description	ICD-10 Code	ICPC Code
Anaemias	**D50-D64**	**B78-B82**
Nutritional anaemias	D50-D53	B80
Iron deficiency anaemias	D50	B80 Iron deficiency anaemia
Other anaemias	D55-D64	B78 Hereditary haemolytic anaemia B79 Congen. anom. blood/lymph other B81 Anaemia, Vitamin B12/folate def. B82 Anaemia other/unspecified B83 Purpura/coagulation defect
Peptic ulcer disease	**K25-K28**	**D85 Duodenal ulcer** **D86 Peptic ulcer other**
Liver disease	**K70-K77**	**D97 Liver disease NOS**
Osteoporosis	**M80-M82**	**L95 Osteoporosis**
Rheumatoid arthritis and other inflammatory arthropathies	**M05-M14**	**L88 Rheumatoid/seropositive arthritis**
Systemic connective tissue diseases	**M30-M36**	**No code**
Malignancy	**C00-C97**	**A79 Malignancy NOS** **B72 Hodgkin's disease/lymphoma** **B73 Leukaemia** **B74 Malignant neoplasm blood other** **D74 Malignant neoplasm stomach** **D75 Malignant neoplasm colon/rectum** **D76 Malignant neoplasm pancreas** **D77 Malig. neoplasm digest other/NOS** **F74 Neoplasm of eye/adnexa** **H75 Neoplasm of ear** **K72 Neoplasm cardiovascular**

Table Annex 4:1 (cont'd) Other comorbidity

Malignancy (cont'd)		**N74 Malignant neoplasm nervous system** **R84 Malignant neoplasm bronchus/lung** **R85 Malinant neoplasm respiratory, other** **S77 Malignant neoplasm of skin** **T71 Malignant neoplasm thyroid** **U75 Malignant neoplasm of kidney** **U76 Malignant neoplasm of bladder** **U77 Malignant neoplasm urinary other** **W72 Malignant neoplasm relate to preg.** **X75 Malignant neoplasm cervix** **X76 Malignant neoplasm breast female** **X77 Malignant neoplasm genital other (f)** **Y77 Malignant neoplasm prostate** **Y78 Malign neoplasm male genital other**
Depressive disorders	**F32-F33**	**P76 Depressive disorder**
Pregnancy (at the index date)	**O00-O48**	**W78 Pregnancy** **W79 Unwanted pregnancy**

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*;
ICPC = *International Classification of Primary Care.*

Annex Table 4:2 Anatomical Therapeutic Chemical codes for comedications

Medication Description	**ATC Code**
Respiratory medications	
Inhaled SAMAs	
Ipratropium bromide	R03BB01
Oxitropium bromide	R03BB02
Inhaled LAMAs	
Tiotropium bromide	R03BB04
Aclidinium bromide	R03BB05
Glycopyrronium bromide	R03BB06
Inhaled SABAs	
Salbutamol	R03AC02
Terbutaline	R03AC03
Fenoterol	R03AC04
Rimiterol	R03AC05
Hexoprenaline	R03AC06
Isoetarine	R03AC07
Pirbuterol	R03AC08
Tretoquinol	R03AC09
Carbuterol	R03AC10
Tulobuterol	R03AC11
Clenbuterol	R03AC14
Reproterol	R03AC15
Procaterol	R03AC16
Bitolterol	R03AC17
Indacaterol	R03AC18
Inhaled LABAs	
Salmeterol	R03AC12
Formoterol	R03AC13

Annex Table 4:2 (cont'd) Anatomical Therapeutic Chemical codes for comedications

Medication Description	**ATC Code**
Respiratory medications (cont'd)	
Inhaled LABA/ICS	
Salmeterol and fluticasone	R03AK06
Formoterol and budesonide	R03AK07
Formoterol and beclometasone	R03AK08
Formoterol and mometasone	R03AK09
Vilanterol and fluticasone furoate	R03AK10
Formoterol and fluticasone	R03AK11
Salmeterol and budesonide	R03AK12
Inhaled glucocorticosteroid	
Beclometasone	R03BA01
Budesonide	R03BA02
Flunisolide	R03BA03
Betamethasone	R03BA04
Fluticasone	R03BA05
Triamcinolone	R03BA06
Mometasone	R03BA07
Ciclesonide	R03BA08
Fixed combinations of SABAs and SAMAs	ATC codes not available[1]
Fixed combinations of SABAs and ICSs	ATC codes not available[1]
Fixed combinations of LABAs and ICSs	ATC codes not available[1]
Systemic glucocorticosteroids	H02AB
Systemic beta2-agonists	R03CC
Xanthines and adrenergics	R03DA, R03DB
Roflumilast	R03DX07
Nasal glucocorticosteroids	R01AD
Omalizumab	R03DX05
Leukotriene receptor antagonists	R03DC
Cromoglicic acid	R03BC01
Nedocromil	R03BC03
Methotrexate	L04AX03
Ciclosporin	L04AD01

Annex Table 4:2 (cont'd) Anatomical Therapeutic Chemical codes for comedications

Medication Description	**ATC Code**
Respiratory medications (cont'd)	
Gold preparations	M01CB
Oxygen therapy	V03AN01
Nebuliser therapy	ATC codes not available[1]
Cardiovascular medications	**All codes listed below in section Cardiovascular medications**
Cardiac glycosides and antiarrhythmics, Classes I and III	C01A, C01B
Vasodilators used in cardiac diseases	C01D
Other cardiac preparations	C01B, C01C
Diuretics	C03
Peripheral vasodilators	C04
Beta blocking agents	C07
Calcium channel blockers	C08
Antihypertensives	C02
Agents acting on the renin-angiotensin system	C09
Angiotensin-converting-enzyme inhibitors	C09A, C09B
Angiotensin II receptor antagonists	C09C, C09D
Renin-inhibitors	C09X
Lipid-modifying agents	C10
HMG CoA reductase inhibitors (statins)	C10AA
Other lipid-modifying agents	C10AB, C10AC, C10AD, C10AX
HMG CoA reductase inhibitors (statins), other combination	C10BX
Antithrombotic agents	**B01**
Platelet aggregation inhibitors	B01AC
Systemic antibacterials	**J01**
Iron preparations	**B03A**
Proton pump inhibitors	**A02BC**
Drugs used in diabetes	**A10**
Insulins	A10A
Blood glucose–lowering drugs	A10B, A10X

Annex Table 4:2 (cont'd) Anatomical Therapeutic Chemical codes for comedications

Medication Description	**ATC Code**
Drugs for musculoskeletal system	**M01A, N02BA, M01B, M01C**
Antiinflammatory and antirheumatic products, non-steroids (nonsteroidal anti-inflammatory drugs)	M01A
Acetylsalicylic acid (other analgesics and antipyretics)	N02BA
Other antirheumatic agents: Antiinflammatory/antirheumatic agents in combination, specific antirheumatic agents	M01B-M01C
Antidepressants	**N06A**
Selective serotonin reuptake inhibitors	N06AB
Antineoplastic agents	**L01**
Immunosuppressants	**L04**
Antivirals for systemic use	**J05**
Hormone-replacement therapy: Estrogens, progestogens, and estrogens in combination	**G03C, G03D, G03F**
Drugs used in nicotine dependence	**N07BA**

ATC = Anatomical Therapeutic Chemical; ICS = Inhaled Glucocorticosteroid; LABA = Long-Acting Beta2-Agonist; LAMA = Long-Acting Muscarinic Antagonist; SABA = Short-Acting Beta2-Agonist; SAMA = Short-Acting Muscarinic Antagonist.

1 The national drug code of each database country will be used to identify medications without an individual ATC code.

Source: WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2013. Updated 20 December 2012. Available at: website: whocc.no/atc_ddd_index/. Accessed 21 January 2013.