Boehringer Ingelheim

Protocol for observational studies based on existing data

Document Number:	c02329987-02
BI Study Number:	1222.53
BI Investigational Product(s):	Olodaterol
Title:	Drug Utilisation Study for Olodaterol
Protocol version identifier:	Version 2.0
Date of last version of protocol:	13 Feb 2014
PASS:	Yes
EU PASS register number:	Study not registered
Active substance:	Olodaterol
Medicinal product:	Striverdi, Respimat
Product reference:	BI 1744
Procedure number:	Not applicable
Marketing authorisation holder(s):	Boehringer Ingelheim GmbH
Joint PASS:	No
Date:	14 Oct 2014

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 Sweden
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Marketing authorisation holder(s):	
MAH contact person:	
EU-QPPV:	
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically

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
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
SABA	Short-Acting Beta2-Agonist
SAMA	Short-Acting Muscarinic Antagonist
SD	Standard Deviation
WHO	World Health Organization

3. RESPONSIBLE PARTIES

The following individual is the author of this protocol:

The following individuals have collaborated with the author on protocol development.

, RTI Health Solutions
RTI Health Solutions

The following institutions will implement the study:

PHARMO Institute, the Netherlands
Denmark – To be determined
Karolinska Institutet, Sweden

Note: Investigators at these institutions will be named after they have reviewed the protocol and agreed to participate.

4. ABSTRACT

Name of company: Boehringer Ingelheim GmbH			
Name of finished medicinal product: Striverdi, Respimat			
Name of active ingredient: Olodaterol			
Protocol date: 13 Feb 2014	**Study number:** 1222.53	**Version/Revision:** 2.0	**Version/Revision date:** 14 Oct 2014
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 Sweden.		

Population:	The source population is all subjects enrolled in the selected study databases at the date olodaterol and indacaterol are 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 National Registers in Sweden A description of each database is provided in Section 9.4; further details from the feasibility report are provided in ANNEX 5. The study will be conducted by using data on drug prescriptions and disease occurrence routinely collected on an ongoing basis for large population-based automated health care databases in the Netherlands, Denmark, and Sweden.
Study size:	Actual counts of numbers of patients using olodaterol in European countries are not yet available since it is not yet marketed in Europe.
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 (contingent on approval, reimbursement, and uptake of olodaterol): • Denmark: Q1 2015 • The Netherlands: Q4 2015 • Sweden: Q4 2015 End of data collection: Q1 2018 Interim reports of study results: Q3 2017 Final report of study results: 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 finalization 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

6. MILESTONES

Milestone	**Planned Date** [1]
Start of data collection (expected availability of data on earliest exposure group entry)2:	Denmark: Q1 2015 The Netherlands: Q4 2015 Sweden: Q4 2015
End of data collection (latest possible exposure group entry):	Denmark: Q1 2018 The Netherlands: Q1 2018 Sweden: Q1 2018
Study progress report(s):	TBD
Interim report(s) of cumulative study results:	Q3 2017
Registration in the EU PAS register:	After regulatory endorsement of the protocol
Final report of study results from all databases:	Q3 2018

TBD = to be determined. Contact with database custodians is pending.

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

2 Considering launch dates and approximately 1-year lag time in database. Launch dates are March 2014 in Denmark, February 2014 in the Netherlands, and August 2014 in Sweden.

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 three major LABAs in COPD, formoterol, salmeterol, and indacaterol, is maintenance or long-term use. Formoterol and salmeterol are also approved for use in asthma; for this condition, simultaneous use with corticosteroids is strongly recommended. 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 Sweden. 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 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 Sweden. The study period will be 3 consecutive years, with annual cross-sectional descriptions of new users of olodaterol and indacaterol. Evaluation of off-label use and characterisation of new users will be conducted at the **index date**, defined as the date an eligible patient receives the first dispensing of olodaterol or indacaterol.

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 National Registers in Sweden. 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, 9.4.2 and 9.4.3.

Table 1 Selected characteristics of the study databases

Type of Data	PHARMO, the Netherlands	National Registers, Denmark	National Registers, Sweden
Hospital inpatient discharge diagnoses	Yes	Yes	Yes
Hospital inpatient procedures	Yes	Yes	Yes
Hospital/clinics outpatient diagnoses	No	Yes	Yes
General practitioner diagnoses	Yes, in data subset PHARMO-GP[1]	Yes, for selected general practices in the Danish General Practice Database[2]	Yes, for general practices from the counties of Stockholm and Göteborg[3]
Pharmacy-dispensed medications	Yes	Yes	Yes
Prescribed medications	Yes in data subset PHARMO-GP[1]	Yes[2]	Yes[3]

GP = General Practitioner.

1 PHARMO-GP includes approximately 440,000 subjects.

2 The Danish General Practice Database includes approximately 1 million subjects.

3 Population from the counties of Stockholm and Göteborg is about 25% of the total Swedish population

In each country, new users of olodaterol and indacaterol will be identified in the prescription databases, which record information on the medications dispensed in the pharmacies (Figure 1). New users will be characterised in terms of past medical history and use of medications. Past medical history will be evaluated by linkage via unique patient-specific identifiers using the hospitalisation databases, which provide information on hospital and outpatient discharge diagnoses and procedures. Use of medications will be evaluated using the prescription databases. Off-label prescribing will be evaluated for those new users for whom general practitioner diagnoses are available because information from general practitioners is considered the most appropriate for evaluating the indication and potential off-label use of medications.

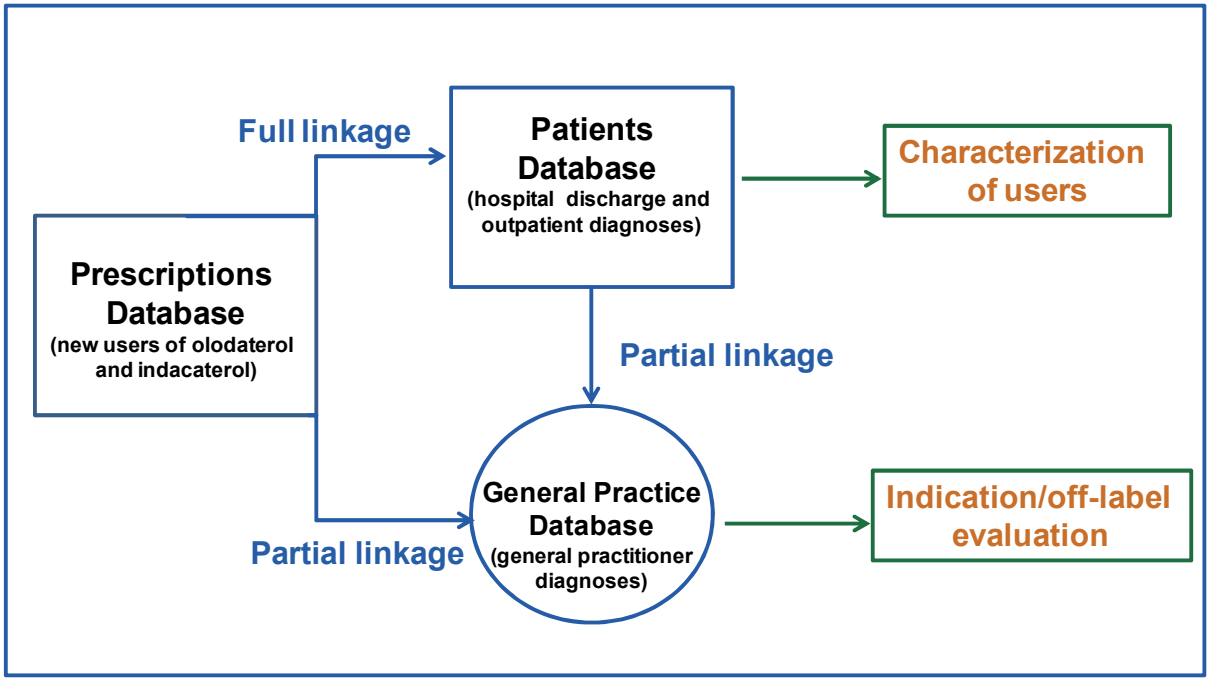


Figure 1 Overall study design

The coding of diagnoses and procedures varies across databases (Table 2). In PHARMO, diagnoses are coded using the *International Classification of Diseases, 9th Revision* (ICD-9); whereas in Denmark and Sweden, diagnoses are coded using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10). In PHARMO, procedures are coded using ICD-9 codes; in Denmark, using ICD-10 codes; and in Sweden, using the 2012 Nordic Medico-Statistical Committee's Classification of Surgical Procedures, version 1.16.[R14-0443] The Anatomical Therapeutic Chemical (ATC) classification is used in all three databases to code dispensed medications.

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

Type of Code	PHARMO, The Netherlands	National Registers, Denmark	National Registers, Sweden
Diagnoses	Hospital: ICD-9 Primary health care: ICPC[1]	ICD-10 Primary health care: ICPC[1]	ICD-10
Procedures	ICD-9	ICD-10	NCSP 1.16, 2012
Medications	ATC	ATC	ATC

ATC = Anatomical Therapeutic Chemical; GP = General Practitioner; ICD-9 = *International Classification of Diseases, 9th Revision*; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICPC = International Classification of Primary Care; NCSP = *Nordic Medico-Statistical Committee's Classification of Surgical Procedures.*

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 olodaterol and indacaterol are available in each database's country.

9.2.2 Study period

The start of the study period is at the index date, defined as the dates of the first recorded dispensings of olodaterol and indacaterol in each database. New users of olodaterol and indacaterol will be identified in each of 3 consecutive years, with annual cross-sectional evaluations of off-label use and of characteristics of users.

9.2.3 Study groups

Study groups are those subjects from the source population who (1) receive a first dispensing for single-agent formulations of olodaterol or indacaterol 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 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).

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 dispensing for LABAs 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.

9.2.3.1 Inclusion criteria

To be included in a study group, patients must have at least 12 consecutive months of enrolment in the database before the index date. This will allow evaluation of the medical history and prior use of medications of included patients.

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 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 are not recorded in the study databases; therefore, the indication of treatment and potential off-label use of olodaterol and indacaterol will be inferred from the diagnoses codes recorded before the index date or at the index date and complemented by the clinical review of the computerised information. The indication and potential off-label use will be evaluated in the subset of new users whose information is linked to the general practice (primary care) registers that include diagnoses recorded by general practitioners. Information from general practitioners is considered the most appropriate for assessing the indication and potential off-label use of medications. Primary care data are available in the following study databases:

- PHARMO-GP covering about 440,000 population
- Danish General Practice Database covering about 1 million population
- Swedish General Practice Database in the counties of Stockholm and Göteborg

Potential off-label use will be evaluated separately by the following age groups:

- 0 to 17 years
- 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 any patient with a diagnosis of COPD, chronic bronchitis, or emphysema recorded in the database at any time before the index date or at 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 general practice diagnoses and hospital outpatient and inpatient discharge diagnoses. No validation data are available for COPD diagnoses recorded in PHARMO. In general, in Denmark and Sweden, 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) was 92%. [R14-0359] In Sweden, a COPD validation study showed that the COPD diagnosis (ICD-9: 491-492, 496; ICD-10: J41-J44) recorded in the National Inpatient Registry was considered as proven in 21.7% of cases, probable in 35.5%, possible in 34.0%, uncertain in 2.1%, and unlikely in 7.0%. [R14-0456] The proportion of patients with asthma misclassified as having COPD was 2.1%, and the overall degree of misclassification was less than 10%. The registry was considered of acceptable validity for epidemiological research of COPD.

The ICD-10 and ICD-9 codes to identify the diagnosis of COPD are detailed in Table 3. Diagnosis codes include COPD, chronic bronchitis, and emphysema.

Table 3 ICD-10 and ICD-9 diagnoses and codes to identify patients with COPD

ICD-10 Code Description	ICD-10 Code	ICD-9 Code
Chronic bronchitis	J41-J42	491
Emphysema	J43	492
Other COPD	J44	496
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-9 = *International Classification of Diseases, 9th Revision*; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.

9.3.2.2 Off-label prescribing

Patients without a recorded diagnosis of COPD at any time before 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. 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.

Few studies have examined the validity of ICD codes for identifying patients with asthma. In a validation study conducted in Sweden, the PPV for the diagnosis of asthma (ICD-10 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 code 493 and information from the medical chart was 81.6%.[R14-0351]

The ICD-10 and ICD-9 codes to identify patients with asthma are detailed in Table 4.

Table 4 ICD-10 and ICD-9 diagnoses and codes to identify patients with asthma

ICD-10 Code Description	ICD-10 Code	ICD-9 Code
Asthma	J45	493
Predominantly allergic asthma	J45.0	493.0[1]
Non-allergic asthma	J45.1	493.1[1]
Mixed asthma	J45.8	—
Asthma, unspecified	J45.9	493.9[1]
Chronic obstructive asthma	—	493.2[1]
Other forms of asthma	—	493.8
Status asthmaticus	J46	

ICD-9 = *International Classification of Diseases, 9th Revision*; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*.

[1] The following fifth-digit subclassification is for use with category 493.0-493.2, 493.9: 0, unspecified; 1, with status asthmaticus; 2, with (acute) exacerbation

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 the first exposure to the respective drug. Patient profiles are chronological listings of the codes that represent clinical events recorded in the study databases for individual patients. These listings include general practitioner diagnoses, outpatient and hospital discharge diagnoses and procedures; and dispensings of medications. The clinical review of patient profiles will provide the most accurate information for evaluation of the indication and potential off-label use of olodaterol and indacaterol. This information will be useful for developing clinical algorithms that can be applied to the evaluation of all new users of olodaterol and indacaterol whose information is linked to general practitioner diagnoses.

The random sampling of patient profiles for review will be stratified by age (0-17 years, 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, 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 5).

Table 5 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.

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 8 on page 30 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 ICD-9 codes for diagnoses and procedures and ATC codes for medications.

9.3.3.1 Demographics and lifestyle habits at the index date

- 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 6).

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 6 Respiratory comorbidity and allergies

Disease Description	**ICD-10**	**ICD-9**
COPD	J41-J44	491, 492, 496
Chronic bronchitis	J41-J42	491
Emphysema	J43	492
Other COPD	J44	496
Asthma	J45, J46	493
Pneumonia	J09-J18	480-486
Allergic rhinitis	J30	477

COPD = Chronic Obstructive Pulmonary Disease; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*. ICD-9 = *International Classification of Diseases, 9th Revision*.

9.3.3.3 Severity of COPD

The guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 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. [P13-02399] 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**	
2 1	**A**	**B**	**≤ 1**	
	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	0-1	< 10
B	Low risk, more symptoms			≥ 2	≥ 10
C	High risk, fewer symptoms	GOLD 3-4 (severe-very severe	≥ 2	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, 2013. [P13-02399]

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 Current Practice Research Database) 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] 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. Severity of COPD will be evaluated at the index date by a modified version of the algorithm developed by Verhamme and colleagues [P11-13226] (see Table 7).

Table 7 Definition criteria of COPD severity

Severity of COPD	**Definition**
Mild	Less than 2 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 2 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] • Third course of antibiotics for respiratory tract infections[2] • Second course of systemic corticosteroids for the treatment of COPD exacerbation[2]
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]; and Curkendall et al., 2006. [P07-09136]

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]

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

The 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):
  - Inhaled short-acting muscarinic antagonists (SAMAs)
  - Inhaled long-acting muscarinic antagonists (LAMAs)

  - Inhaled short-acting beta2-agonists (SABAs)
  - Inhaled LABAs
  - Inhaled glucocorticosteroids (ICSs)
  - Fixed combinations of SABAs and SAMAs
  - Fixed combinations of SABAs and ICSs
  - Fixed combinations of LABAs and ICSs
  - Systemic glucocorticosteroids
  - Systemic beta2-agonists
  - Xanthines
  - Roflumilast
- Hospitalisation for COPD
  - Primary or secondary hospital discharge diagnosis for COPD
  - ICD-10 codes: J40-J44; ICD-9 codes: 491, 492, 496
- Recorded diagnosis of pneumonia
  - Primary or secondary hospital discharge diagnosis for pneumonia
  - ICD-10 codes J09-J18; ICD-9 codes: 480-486
- Third course of antibiotics for respiratory tract infections
  - A course with antibiotic is defined as that involving consecutive dispensings of antibiotics with less than 7 days between the end of days of supply of one dispensing and the date of the next 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 dispensings with less than 7 days between the end of days of supply of one dispensing and the date of the next dispensing.
  - ATC codes for systemic glucocorticosteroids: H02AB
- Oxygen therapy, ATC code: V03AN01
- Nebuliser therapy (to be identified in each database using national drug codes)
- Primary or secondary hospital outpatient or inpatient discharge diagnosis of emphysema at any time before the index date
  - ICD-10 code: J43; ICD-9 code: 492

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 ICD-9 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 medications 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**.

- Total number of dispensing; all medications included in Annex Table 4:2
- Total number of dispensings for respiratory medications; all medications included in the section of 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 J40-J44; ICD-9 codes: 491, 492, 496
- Total number of hospitalisations for asthma; number hospitalisations with a primary discharge code for asthma; ICD-10 codes J45, J46; ICD-9 code: 493

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

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

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
- National Registers in Sweden

A description of each database is provided in the following sections; further details are provided from the feasibility report, dated 1 November 2013, and in ANNEX 5. The study will be conducted by using data on drug dispensings and disease occurrence routinely collected on an ongoing basis for large population-based automated health care databases in the Netherlands, Denmark, and Sweden (see Table 1 and Table 2 for characteristics of these databases). New users will be characterised in terms of past medical history and use of medications. Off-label prescribing will be evaluated for those new users for whom general practitioner diagnoses are available. An overview of the information on diagnoses and procedures by data source is shown in the table below (Table 8).

9.4.1 PHARMO Database Network

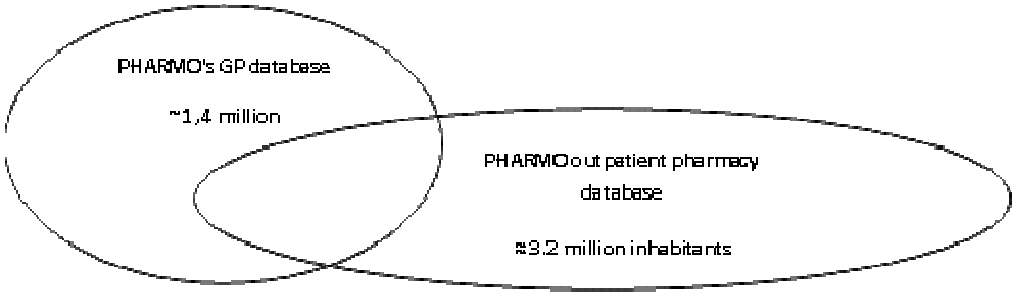
9.4.1.1 Database characteristics

The PHARMO Database Network consists of multiple databases containing data files on approximately 3.2 million community-dwelling inhabitants in geographically defined areas covering approximately 20% of the Netherlands. Data sources include information from general practitioners (GPs), community pharmacies, hospitals, and laboratory sources.

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 dispensing (outpatient pharmacy) database covering 3.2 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 (100% overlap between outpatient

and hospitalisation database). Approximately 440,000 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 1.4 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 (440,000) 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 (5.5 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 containing civil registration numbers, such as the Danish National Registry of Patients, Danish National Prescription Database, the Prescription Databases of the Central Denmark Region, and the Danish Registry of Causes of Death. Data collected in these registries are available for research purposes. The availability of the Danish General Practice Database (DAMD) is a recent development in the group of Danish databases used for research. It provides information from selected general practices nationwide, with the purposes of promoting and improving the quality of care in general practice and providing data for research concerning general practice. [R13-5415] The DAMD currently covers about 1 million population.

For 1980-2008, The National Registry of Patients 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 Sweden

Since 1987, Sweden has mandated collection of hospital care data nationally; same-day surgery and psychiatric care have since been added to the database. [R14-0444] The hospital data are held in the Swedish National Patient Register (NPR) (sometimes called the Hospital Discharge Register), along with a Cause of Death Register. The Swedish NPR comprises all admissions to hospital care and hospital outpatient diagnoses. Primary and several secondary

diagnoses are recorded. With the national personal identification number, patients can be tracked over time and from one hospital to another. As of 2004, few admissions were missing a personal identification number; for example, for stroke, 0.5% of hospitalisations lacked an identification number in a study of two counties. For acute hospital care, more than 99% of the hospital stays had at least a primary diagnosis recorded. [R14-0356] A validation review of the NPR by the National Board of Health and Welfare showed that 85% to 95% of all diagnoses are valid. [R14-0357]

Primary care data in Sweden may be available for the counties of Stockholm and Göteborg through the County Council health registers. The population of these two counties covers approximately 25% of the total Swedish population.

Ascertained from the Obstructive Lung Disease in Northern Sweden study, the prevalence of patients with diagnosed COPD in a subset of the study cohort and aged 46 years or older was 14.3%, when evaluated by GOLD criteria, and 8.1% when evaluated by British Thoracic Society criteria. [R13-1576] From the National Oxygen Register, the estimated number of patients with severe COPD was 8,712. [R14-0353]

9.4.4 Summary of study databases

Table 8 shows and compares the characteristics of the study databases.

Table 8 Overview of the study databases

Data Element	PHARMO (Netherlands)	National Registers, Denmark	National Registers, Sweden
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	National health record databases capable of linkage through the unique civil personal registration number
Database population	3.2 million	Denmark	Sweden
Country population[1]	16,779,575	5,602,628	9,555,893
Approximate proportion of the country's population covered by the database	20%	100%	100%

Table 8 (con't) Overview of the study databases

Data Element	**PHARMO (Netherlands)**	**National Registers, Denmark**	**National Registers, Sweden**
Representative-ness of patients and practices	Known to be representative [P93-73309] [P14-01899]	Complete, given that the total country population is included	Complete, given that the total country population is included
Data on medications	Dispensings from community pharmacies and prescriptions from GP database	Pharmacy-dispensed prescriptions	All pharmacy-dispensed prescriptions
Dose	Yes	Formulation strength	Formulation strength
Duration	Yes	Based on prescriptions	Based on dispensed prescriptions
Drug dictionary codes/therapeutic classification	ATC	ATC	ATC
Indacaterol	4,000	47,400 (2010-2011)	6,361 (2010-2011)
Number of users of indacaterol	1,200	6,093 (2010-2011)	110 (2010) 2,565 (2011)
Clinical indication	For approximately 440,000 PHARMO subjects (included in outpatient database), via linkage to GP files and proximity of clinical diagnoses; for all subjects in GP database	Not recorded but may be surmised based on GP diagnoses for GP-linked practices and proxies (i.e., prescribed medication and hospital discharge diagnosis history) for not-linked practices	Not recorded but may be surmised based on GP diagnoses for GP-linked practices and proxies (i.e., prescribed medication and hospital discharge diagnosis history) for not-linked practices
Prescriber characteristics	GP vs. specialist	GP vs. specialist	Profession Level of education Speciality

Table 8 (con't) Overview of the study databases

Data Element	PHARMO (Netherlands)	National Registers, Denmark	National Registers, Sweden
Outpatient diagnosis	For all PHARMO subjects (included in outpatient databases): main diagnoses in ICD-9-CM 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 outpatient diagnoses General practitioner diagnoses for about 1 million population recorded via ICPC coding	Hospital diagnoses. General practitioner diagnoses for the counties for Stockholm and Göteborg recorded via ICPC coding
Hospital diagnosis	Main hospital diagnostic/surgical procedures	Yes	Yes
Procedure codes	Available for approximately 1 million of pharmacy file patients; GP laboratory tests for all patients in GP database	Yes, ICD-10	Yes, NCSP version 1.16:2012
Pulmonary function testing	With difficulty	From hospital clinics and also from primary care when recorded	From hospital clinics and also from primary care when recorded
Information on death	Fact and date of death, Mortality Register	Fact, date, and underlying cause of death available in National Death Register	Fact, date, and underlying cause of death available in National Death Register
Access to medical records	Variable	No	No

Table 8 (con't) Overview of the study databases

Data Element	PHARMO (Netherlands)	National Registers, Denmark	National Registers, Sweden
Lifestyle risk factors (smoking status, BMI, alcohol intake)	Yes, if recorded by GPs	Yes, if recorded by GPs	Yes, if recorded by GPs
Data availability	Annual	Since 1994	Since 2005
Updates	Pharmacy data: 2 months All other data: annual; available following Q3-Q4	Annual	Annual
Approximate time lag	No	1 year	2012 data will be available in 3Q-4Q 2013
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 and ethics committee approval required	Data application and ethics committee approval required

ATC = Anatomical Therapeutic Chemical; BMI = Body Mass Index; GP = General Practitioner; ICD-9-CM = *International Classification of Diseases, 9th Revision, Clinical Modification*; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICD-10-CM = *International Classification of Diseases, 10th Revision, Clinical Modification;* ICPC = International Classification of Primary Care; NCSP = *Nordic Medico-Statistical Committee's Classification of Surgical Procedures*.

1 Eurostat. 2013. Available at: website: epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&init=1&language=en&pcode=tps00001&plugin=1. Accessed January 28, 2014.

9.5 STUDY SIZE

Actual counts of numbers of patients using olodaterol in European countries are not yet available. Table 9 shows the confidence intervals around estimated prevalence of comorbidity and comedications under various exposure group size scenarios.

Table 9 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]

A small number of users of olodaterol in each database during the first years (2014-2016) after launch may result in imprecise prevalence estimates for conditions with a prevalence of 10% and below, especially when stratified analyses are conducted.

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 license 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. Analyses will be conducted annually for three consecutive years. Each year will include all patients starting treatment with olodaterol or indacaterol in that specific year. 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).

9.7.1 Main analysis

9.7.2 Indication and potential off-label prescribing

Number and proportion of new users for each indication (COPD only, COPD and asthma, asthma only, and no COPD or asthma) associated with the initiation of treatment.

This analysis will be conducted using data linked to diagnoses recorded by general practitioners (primary care information):

- PHARMO-GP, covering about 440,000 population
- Danish General Practice Database, covering about 1 million population
- Swedish General Practice Database for the counties of Stockholm and Göteborg

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 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

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 5 that was recorded at any time before the index date.

Severity of COPD: 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 Table 8 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 dispensings: 0, 1 to 4, 5 to 9, 10 or more
- Total number of dispensings for respiratory medications (Annex Table 4:2): 0, 1 to 4, 5 to 9, 10 or more
- Total number of dispensings for systemic glucocorticosteroids: 0, 1 to 4, 5 to 9, 10 or more
- Total number of 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 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.
- For Denmark and Sweden, this study will be conducted by researchers affiliated with institutions that have access to the national registers. Thus, the conduct of the study in these countries will depend on the scientific and regulatory interest of these researchers, as well as on their availability during the study period.
- 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, and because use of hospital discharge diagnoses does not ascertain patients diagnosed with COPD who are not hospitalised, off-label use will be assessed in the subset of new users linked to the general practice (primary care) registers. In the three countries primary care data are only available for a subset of the population.

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

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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 PAS registration 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
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)	☒	☐	☐	15
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

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?	☒	☐	☐	28
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 dataset or, in the case of secondary use of data, the date from which data extraction starts.
2 Date from which the analytical dataset is completely available.

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

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 DUS is limited to characterizing 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?	☒	☐	☐	20
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	19-22

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 is 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.)	☒	☐	☐	19
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	20
8.1.3 Covariates?	☒	☐	☐	23
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	19
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	20
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	23
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	21-22
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	21-22
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	31
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	29

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	35

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?	☒	☐	☐	36
10.3 Are descriptive analyses included?	☒	☐	☐	36
10.4 Are stratified analyses included?	☒	☐	☐	36
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?	☒	☐	☐	35
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☒	☐	38
11.3 Are methods of quality assurance described?	☒	☐	☐	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,	☒	☐	☐	37-38

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
validation sub-study, use of validation and external data, analytical methods)				
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	37-38
12.3 Does the protocol address other limitations?	☒	☐	☐	37-38

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?	☒	☐	☐	40
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☐	☒	☐	35

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?	☒	☐	☐	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)?	☒	☐	☐	41
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	41

Comments:

Name of the main author of the protocol: _____ _____

Date: 30 September 2014

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

Annex Table 3:1 (con't) 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	ICD-9 Code
Cardiovascular diseases	**I00-I99**	**390-459**
Ischaemic heart disease	I20-I25 or coronary reperfusion surgery and procedures	410-414 or coronary reperfusion surgery and procedures
Angina pectoris	I20	413, 411.1
Acute myocardial infarction	I21	410
Other acute or subacute ischaemic heart disease	I22-I24	411.0, 411.8
Chronic ischaemic heart disease	I25	412, 414
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	427.0-427.4, 427.6-427.9
Paroxysmal tachycardia	I47	427.0-427.2
Ventricular tachycardia	I47.0, I47.2	427.1
Supraventricular tachycardia and unspecified	I47.1, I47.9	427.0, 427.2
Atrial fibrillation and flutter	I48	427.3
Other cardiac arrhythmias	I49	427.4, 427.6, 427.8, 427.9
Ventricular fibrillation and flutter	I49.0	427.4
Other cardiac arrhythmias	I49.1-I49.9	427.6, 427.8, 427.9
Conduction disorders	I44-I45	426
Cardiac arrest	I46	427.5
Heart failure	I50	428
Cerebrovascular disease	I60-I69, G45	430-438
Cerebral haemorrhage (subarachnoid, intracerebral, other non-traumatic)	I60-I62	430-432

Annex Table 4:1 (con't) Other comorbidity

Disease Description	**ICD-10 Code**	**ICD-9 Code**
Cardiovascular diseases	**I00-I99**	**390-459**
Cerebral infarction and stroke	I63, I64, G46.5	433.1, 434.1, 436
Transient ischaemic attack	G45	435
Other cerebrovascular disease and sequelae of cerebrovascular disease	I65-I69	433.0, 434.0, 437, 438
Hypertension and hypertensive heart disease	I10-I15	401-405
Diseases of arteries, arterioles, and capillaries	I70-I79, and peripheral arterial revascularisation procedures	440-449 and peripheral arterial revascularisation procedures
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	390-398, 420-425, 429, 440-459
Hyperlipidaemia	**E78**	**272**
Diabetes mellitus	**E10-E14**	**250**
Renal disease	**N00-N39**	**580-599**
Chronic kidney disease	N18	585
Other renal disorders	N00-N17, N19, N25-N39	
Anaemias	**D50-D64**	**280-285**
Nutritional anaemias	D50-D53	280-281
Iron deficiency anaemias	D50	280
Other anaemias	D55-D64	282-285
Peptic ulcer disease	**K25-K28**	**531-534**
Liver disease	**K70-K77**	**570-573**
Osteoporosis	**M80-M82**	**733.0**
Rheumatoid arthritis and other inflammatory arthropathies	**M05-M14**	**712-714, 716, 696.0**
Systemic connective tissue diseases	**M30-M36**	**710**
Malignancy	**C00-C97**	**140-209**
Depressive disorders	**F32-F33**	**311,**
Pregnancy (at the index date)	**O00-O48**	**630-649**

ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; ICD-9 = *International Classification of Diseases, 9th Revision.*

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
Inhaled glucocorticosteroid	
Beclometasone	R03BA01
Budesonide	R03BA02

Annex Table 4:2 (con't) Anatomical Therapeutic Chemical codes for comedications

Medication Description	**ATC Code**
Respiratory medications	
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
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

Annex Table 4:2 (con't) Anatomical Therapeutic Chemical codes for comedications

Medication Description	**ATC Code**
Cardiovascular medications	**All codes listed below in section Cardiovascular medications**
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
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**

Annex Table 4:2 (con't) Anatomical Therapeutic Chemical codes for comedications

Medication Description	**ATC Code**
Immunosuppressants	**L04**
Antivirals for systemic use	**J05**
Hormone-replacement therapy: Estrogens, progestogensprogestogens, 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.

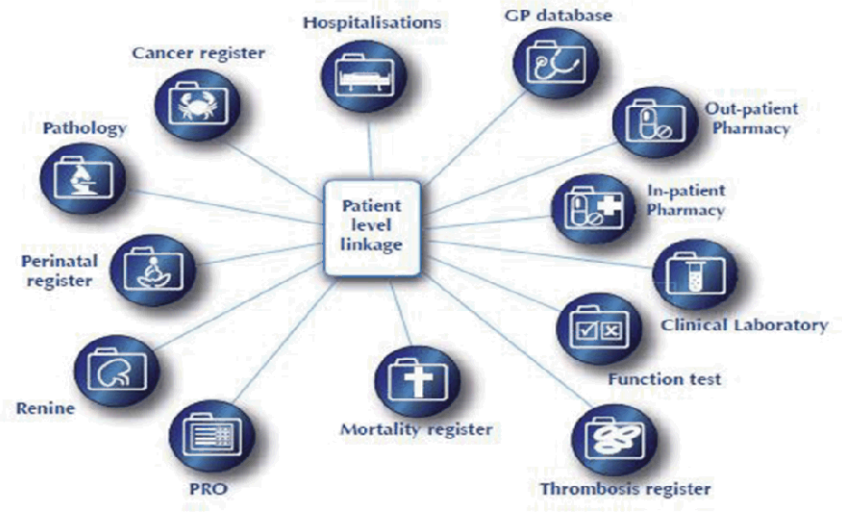
ANNEX 5. DETAILS ON EACH DATABASE FROM THE FEASIBILITY REPORT (1 NOVEMBER 2013)

PHARMO, THE NETHERLANDS

Database Characteristics

Database Description

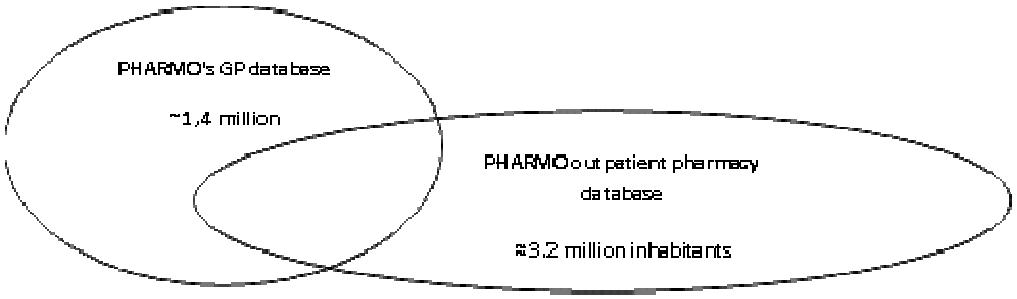
The PHARMO Database Network consists of multiple databases containing data files on approximately 3.2 million community-dwelling inhabitants in geographically defined areas covering approximately 20% of the Netherlands. Annex Figure 5:1 shows the databases included in the PHARMO Database Network. Data sources include information from GPs, community pharmacies, hospitals, and laboratory sources.



GP = General Practitioner; PRO = Patient-Reported Outcome.

Annex Figure 5:1 Data sources within the PHARMO Database Network

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 patients are in more than one database, they can be linked to construct the medical history as shown in Annex Figure 5:2 Thus, high-quality research has been conducted with ascertainment of patient demographics, drug dispensings, hospital morbidity, clinical laboratory results, and date of death.



GP = general practitioner.

Annex Figure 5:2 Schematic overview of overlap example among databases included in the PHARMO Database Network