Boehringer Ingelheim

Protocol for observational studies based on existing data

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BI Investigational Product(s):	Olodaterol
Title:	Cohort study of cardiovascular events in patients with chronic obstructive pulmonary disease initiating olodaterol or other long-acting beta2-agonists
Protocol version identifier:	3.0
Date of last version of protocol:	14 Oct 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):	
Joint PASS:	No
Date:	28 October 2016

Additional Information

Research question and objectives:	• Examine the risk of selected cardiac arrhythmias in patients with chronic obstructive pulmonary disease (COPD) exposed to olodaterol compared with the risk in patients exposed to other long-acting beta2-agonists (LABAs) • Examine the risk of acute myocardial infarction (AMI) and other serious ischaemic heart disease events, including unstable angina, in patients with COPD exposed to olodaterol compared with the risk in patients exposed to other LABAs • Secondarily, examine the mortality risk in patients with COPD exposed to olodaterol compared with the risk in patients initiating other LABAs
Country(-ies) of study:	Denmark
Author:	
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 CONTENT

2. LIST OF ABBREVIATIONS

AMI	Acute Myocardial Infarction
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
CAT	COPD Assessment Test
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CPRD	Clinical Practice Research Datalink
DAMD	Danish General Practice Database
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-9	International Classification of Diseases, 9th Revision
ICPC	International Classification of Primary Care
ICS	Inhaled Glucocorticosteroid
IRD	Incidence Rate Difference
IRR	Incidence Rate Ratio
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
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 and with the study sponsor on protocol development.

formerly of , currently retired

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Striverdi, Respimat			
Name of active ingredient: Olodaterol			
Protocol date: 13 Feb 2014	**Study number:** 1222.54	**Version/Revision:** 3.0	**Version/Revision date:** 28 October 2016
Title of study:	Cohort study of cardiovascular events in patients with chronic obstructive pulmonary disease initiating olodaterol or other long-acting beta2-agonists		
Rationale and background:	Inhaled long-acting beta2-agonist (LABA) drugs are used in chronic obstructive pulmonary disease (COPD) to relieve bronchial constriction and associated symptoms. At present, formoterol, salmeterol, and indacaterol are the three major LABAs approved for COPD treatment. The clinical long-term safety experience of the LABA olodaterol is based on four phase 3 randomised, placebo-controlled, parallel-group studies, two of which included formoterol as an active comparator in addition to placebo. No imbalances were detected in this study pool with regard to any cardiovascular effect during the 48-week study period. Nevertheless, cardiac arrhythmia and myocardial ischaemia are acknowledged class effects of LABAs and have been included as potential risks in the risk management plan for olodaterol. Within the Decentralised Procedure for Striverdi Respimat, the health authorities of the European Union/European Economic Area Member States requested that a post-authorisation safety study (PASS) to gather additional data on safety in long-term use of olodaterol be included in the risk management plan framework. The results of this study will provide insight into the absolute and relative frequency of cardiac arrhythmias and myocardial ischaemia events of interest in comparison to alternative LABA therapies for COPD.		

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Research question and objectives:	Primary objectives: • Examine the risk of selected cardiac arrhythmias in patients with chronic obstructive pulmonary disease (COPD) exposed to olodaterol compared with the risk in patients exposed to other long-acting beta2-agonists (LABAs) • Examine the risk of acute myocardial infarction (AMI) and other serious ischaemic heart disease events, including unstable angina, in patients with COPD exposed to olodaterol compared with the risk in patients exposed to other LABAs Secondary objective: • Examine the risk of overall mortality in patients with COPD exposed to olodaterol compared with the risk in patients exposed to other LABAs		
Study design:	This will be an observational cohort study of patients diagnosed with COPD aged 40 years or older and initiating olodaterol or an alternative LABA indicated for use in COPD.		
Population:	The study population will consist of patients with COPD (disease cohort) aged 40 years or older in Denmark, a country where olodaterol, either alone or in a fixed combination with tiotropium, is available and where a large proportion of the population is included in health care databases used for pharmacoepidemiologic research. Patients will be new users of olodaterol or any other LABA, with no dispensing of any LABA in the 6 months before the first prescription of olodaterol or LABA during the study period (index date) and at least 1 year of enrolment in the electronic database.		

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Name of active ingredient: Olodaterol			
Protocol date: 13 Feb 2014	**Study number:** 1222.54	**Version/Revision:** 3.0	**Version/Revision date:** 28 October 2016
Variables:	Primary outcomes in new users • Incidence of atrial fibrillation or flutter during new use • Incidence of hospitalisation for ventricular tachycardia, including ventricular fibrillation/flutter and cardiac arrest • Incidence of supraventricular tachycardia (other than atrial fibrillation/flutter) • Incidence of hospitalisation for acute myocardial infarction • Incidence of hospitalisation for serious acute coronary heart disease, including unstable angina Exposures of interest are (1) new use of olodaterol and (2) new use of any other LABA. Covariables of interest are severity of COPD and a history of any the following conditions prior to the index date: comorbidities such as cardiovascular disease, hypertension, diabetes, hyperlipidemia, high body mass index, smoking, chronic kidney disease, liver disease, osteoporosis, pneumonia, and cancer.		
Data sources:	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 Denmark.		
Study size:	To achieve an 80% probability of detecting a true risk ratio of 2.5 (3.0 for ventricular tachycardia), assuming a minimum ratio of 4:1 unexposed (any other LABA) to exposed (olodaterol) subjects, a two-sided alpha level of 0.05, and a range of expected incidence rates of each study endpoint, the minimum number of olodaterol-exposed person-years ranges from 100 person-years for all-cause mortality to 8,380 person-years for ventricular tachycardia.		

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Data analysis:	The incidence rate ratio (IRR) and incidence rate difference (IRD) for each event of interest in the olodaterol-exposed group relative to that in the comparator group will be derived. The effects of demographics and specified baseline characteristics will be assessed, and adjusted IRR will be calculated by adjusting for each covariate one at a time. A fitted propensity score model will be used to estimate a propensity score for each patient, and the IRRs for each event of interest will be stratified by propensity score deciles. For each endpoint, IRR and IRD will be stratified by propensity score deciles, and the overall adjusted IRR and IRD and associated 95% confidence intervals will be derived by weighting each stratum by the prevalence among the olodaterol cohort.		
Milestones:			

5. AMENDMENTS AND UPDATES

Version 3.0 includes clarifications to the milestone table, available databases within Denmark, and clarification that another country may be added in the future.

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1		6	Update of milestones	Delay in finalisation of protocol to respond to regulatory authority review
2		9.3.3 9.7.1.1 9.7.1.3	Clarification of handling of missing data	Response to regulatory review
3		9.5	Clarification of expected study statistical precision for outcome effect measures	Response to regulatory review
4		9.5 9.10	Specification that data from Sweden will be added in the event that the exposed cohort in Denmark is too small	Response to regulatory review
5		9.1, 9.3, 9.11, and across the protocol	Clarified study medications	Clarified that olodaterol includes olodaterol monotherapy and fixed-dose combinations
6		3	Updated list	Previous lead author has retired; added investigator from Denmark
7		6	Updated milestones	Clarified start and end of data collection, as applied to the analysis of secondary databases, and timing for progress reports
8		9.1	Clarified study period	To differentiate from study milestones, clarified study period and look-back period

9		9.3.3	Updated COPD severity definition	To better align with COPD guidelines
10		9.4.1	Deleted Danish General Practice Database (DAMD) as a data source	No longer available for research
11		9.5	Removed the naming of Sweden and replaced with “other country”; added update on the number of users in Denmark	Uptake in Sweden is lower than expected; a specific other country will be identified if needed Provided number of users of olodaterol (olodaterol was not available in Denmark at the time of the previous protocol)
12		9.7.1	Clarified that two propensity score models, one for each “type of COPD treatment initiated” (with or without LAMA) will be performed or an interaction term will be included	To take into account differences between patients initiating LABA alone versus those initiating LABA/LAMA
13				

6. MILESTONES

7. RATIONALE AND BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a serious chronic disease that affects millions of people worldwide. [P13-02399] [P12-14293] 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, and in 2004, the European region had approximately 11.3 million patients with prevalent, symptomatic COPD. [R09-2531] The prevalence of COPD increases with increasing age. In a meta-analysis of 67 publications, the pooled prevalence among people aged younger than 40 years (n = 9 studies) was approximately 3.1 per 100; pooled prevalence among people aged 65 years or older (n=11 studies) was 14.2 per 100.[R06-4117] The health, societal, 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 older populations in many countries. [P13-02399]

The major types of comorbidities in patients with COPD are cardiovascular disease, osteoporosis, anxiety and depression, lung cancer, serious infections, metabolic syndrome, and diabetes. [P13-02399] The incidence of cardiovascular outcomes in patients with COPD is about two times greater than in individuals without COPD. [R09-0579] [R07-2623]

Inhaled long-acting beta2-agonist (LABA) drugs are used in COPD to relieve bronchial constriction and associated symptoms. At present, formoterol, salmeterol, and indacaterol are the three major LABAs approved for COPD treatment.

The clinical long-term safety experience of the LABA olodaterol is based on four phase 3 randomised, placebo-controlled, parallel-group studies, two of which included formoterol as an active comparator in addition to placebo. No imbalances were detected in this study pool with regard to any cardiovascular effect during the 48-week study period. Nevertheless, cardiac arrhythmia and myocardial ischaemia are acknowledged class effects of LABAs [P12-09395] [P12-09396] and have been included as potential risks in the risk management plan for olodaterol.

Within the Decentralised Procedure for Striverdi Respimat, the health authorities of the European Union/European Economic Area Member States requested that a post-authorisation safety study (PASS) to gather additional data on safety in long-term use of olodaterol be included in the risk management plan framework. The results of this study will provide insight into the absolute and relative frequency of cardiac arrhythmias and myocardial ischaemia events of interest in comparison to alternative LABA therapies for COPD. The country of implementation of this study is Denmark.

8. RESEARCH QUESTION AND OBJECTIVES

This study aims to quantify the frequency of selected adverse cardiovascular conditions among users of olodaterol compared with users of other LABAs. Study objectives are as follows:

Primary objective:

- Examine the risk of selected cardiac arrhythmias in patients with COPD newly exposed to olodaterol compared with the risk in patients newly exposed to any other LABA
- Examine the risk of acute myocardial infarction (AMI) and other serious acute ischaemic heart disease events, including unstable angina, in patients with COPD newly exposed to olodaterol compared with the risk in patients newly exposed to any other LABA

Secondary objective:

- Examine the risk of overall mortality in patients with COPD newly exposed to olodaterol compared with the risk in patients newly exposed to any other LABA

9. RESEARCH METHODS

9.1 STUDY DESIGN

This will be an observational cohort study of patients diagnosed with COPD aged 40 years or older and initiating olodaterol either alone or in free- or fixed-dose combination with a LAMA or an alternative LABA alone or in a free- or fixed-dose combination with a LAMA indicated for use in COPD. The study period will start at the time of olodaterol launch in Denmark (March 2014) and will end in Q1 2019 (i.e., the last date with data available for the data cut for the final report in Q1 2020), due to a 1-year time lag in the availability of data in the data source.

The study will be conducted using existing population-based health care databases in Denmark. A cohort study will be conducted so that the incidence of each of the events of interest among olodaterol initiators can be estimated. The age is limited to individuals aged 40 years and older to maximise the likelihood that all subjects in each exposure group are receiving LABA for treatment of COPD. [R06-4117] Any olodaterol initiator with a COPD diagnosis at any time after 1994 and the first prescription of olodaterol or indacaterol will be included. Similarly, individuals in the comparator cohort must have a record of a COPD diagnosis. If the sizes of each exposure cohort permits, stratification on presence or absence of a diagnosis of asthma will be implemented. To establish that members of each exposure cohort are new users, each study subject must have at least 12 months of enrolment in the database prior to the index date.

It is not atypical for new users of a new medication, before starting the medication, to be at higher risk of the events of interest than individuals with the same disease and taking medications traditionally available. To address this issue, the study requires that all olodaterol users and users of the comparator LABAs have no previous use of any LABA in the 6 months preceding study medication initiation. The protocol synopsis specified a definition of no recent other LABA use measured during the12 months before new use of a study LABA. However, to maximise study size, the definition of no recent other LABA use now requires absence of other study LABA use during the 6 months before the index date. Also, 6 months is sufficient time that no adverse impact from earlier LABA use will remain.

In addition, this study will control for severity of COPD and presence of other cardiovascular disease risk factors, as much as such factors can be ascertained from the entire available medical history in the data source since converting to ICD-10 in 1994 (see Section 9.3.3, Covariates). Propensity scores will be developed, and propensity score categories (deciles if study size allows) will be used for stratification of incidence rate ratios and incidence rate differences and derivation of the overall adjusted incidence rate ratio and adjusted incidence rate difference (see Section 9.7).

9.2 SETTING

The database selection criteria were the following:

- There is published research experience on the use of the data to study drug safety questions and on the validity of the outcomes identified via hospital discharge codes
- The database contains the earliest and largest available number of olodaterol initiators at the time of study implementation
- The database must permit identification of the following information:
- Dates and discharge diagnoses for hospitalisations for arrhythmias and ischaemic cardiac events
- Severity of COPD defined by patterns of use of LABA, antibiotic use for respiratory infection, oxygen therapy, nebuliser therapy, hospitalisation for COPD, diagnosis of pneumonia, use of systemic corticosteroids, and diagnosis of emphysema, information that is frequently recorded in prescription and hospital records
- The database must have a reliable recording of outpatient dispensings or prescriptions
- The database must have completed data collection for at least 12 months before the index prescription

The national health registers of Denmark, covering 100% of the population in Denmark, are expected to yield the largest study size. Key data features of this database are summarised in Table 1. A detailed description of the study database is provided in Section 9.4.

Table 1 Selected characteristics of the study data source

Type of Data	**National Registers, Denmark**
Hospital inpatient discharge diagnoses	Yes
Hospital inpatient procedures	Yes
Hospital/clinic outpatient diagnoses	Yes
General practitioner diagnoses	No
Pharmacy-dispensed medications	Yes
Prescribed medications	No

New users will be characterised by past medical history and use of medications (Table 2). Diagnoses are coded using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10). Procedures are coded using ICD-10 codes. The Anatomical Therapeutic Chemical (ATC) classification is used to code dispensed medications.

Table 2 Types of diagnoses, procedures, and medication codes in the National Registers of Denmark

Type of Code	Coding System Used
Diagnoses	ICD-10 (since 1994)
Procedures	NCSP, version 1.16:2012
Medications	ATC

ATC = Anatomical Therapeutic Chemical; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*; NCSP = *Nordic Medico-Statistical Committee Classification of Surgical Procedures*.

9.3 VARIABLES

9.3.1 Exposures

Olodaterol became available in Denmark in March 2014, and olodaterol/tiotropium became available in July 2015. Members of each exposure cohort will be identified from available outpatient pharmacy dispensing files.

9.3.1.1 Definition of new use

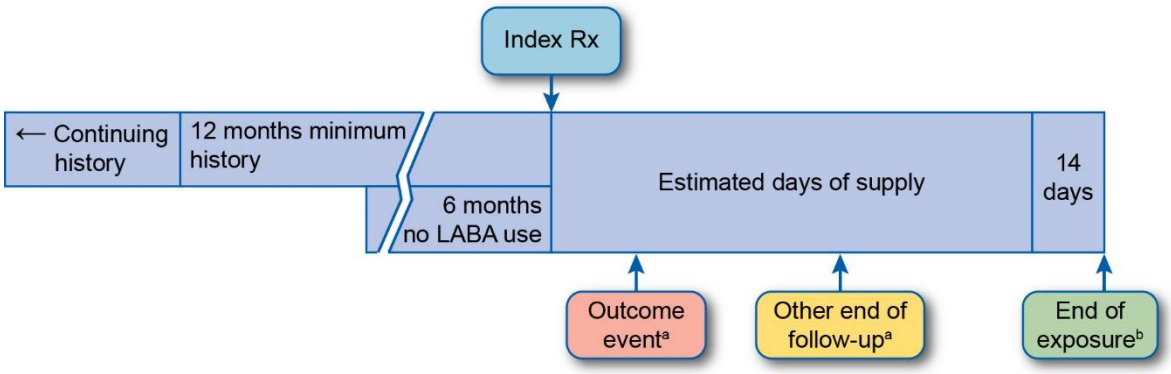
A new user will be defined as a patient with a diagnosis of COPD who receives a first dispensing for a study LABA during the study period and no prescriptions for any LABA in the 6 months prior to the first dispensing for LABA during the study period. The LABA initiated at cohort entry will be referred to as the index LABA. To meet the objectives, the study will assess the incidence ratio for each endpoint of interest among new users of olodaterol compared with the incidence among new users of the alternative LABAs combined as a comparator group.

Potential confounding by use of concomitant dispensing of inhaled steroids or other respiratory medications (listed in Annex 4) will be addressed in the analysis.

9.3.1.2 Follow-up

Patients will be followed from the first dispensing for the index LABA after the patient has fulfilled all other eligibility criteria (Figure 1). Follow-up will continue until the earliest of the following possible termination dates:

- Disenrolment from the database
- 14 days after estimated discontinuation of the last dispensing for the index LABA (e.g., after switching or stopping index LABA use)
- Addition of a second LABA
- Death
- End of study period, the date of the latest available data from the data source



LABA = long-acting beta2-agonist; Rx = prescription.

a. Outcome event or other end-of-follow-up criteria: disenrolment from the database, addition of a second LABA, death, or end of study period (date of the latest available data from the data source).

b. End of exposure is 14 days after estimated discontinuation of the last dispensing for the index LABA. Duration of exposure will depend on the number of days supplied.

Figure 1 Diagram of study follow-up

9.3.1.2.1 Exposure definition

Exposure data will be assessed from recorded dispensings for each of the study LABAs.

Exposure will be classified by the subjects' index LABA, which could be in a free- or fixed-dose combination with a LAMA, at the time of their first prescription for that LABA (e.g., new user of olodaterol). For each person, duration of exposure to olodaterol or comparator LABA will be defined as starting on the dispensing date and ending 14 days after the end of days' supply or defined daily doses recorded on each prescription. Additional days are added to the duration of the dispensing to estimate actual use that may not adhere to recommendations and to capture events in individuals who switch because of early symptoms of the outcome of interest. Definitions may be slightly modified if otherwise indicated in the data.

Total patient-years of time at risk from current use of each medication of interest will be calculated as the sum of days supplied plus 14 days for consecutive prescriptions. Only the first episode of consecutive use will be considered. Calculations of consecutive use will allow for a maximum gap of 14 days between the estimated end of use of one prescription and the dispensing date of the following prescription. Overlapping time at risk from consecutive prescriptions of the study medications will be concatenated, with the overlapping time counted only once. For individuals switching at the end of study LABA use, there will be no adjustment for the newly started LABA. Switching at the end of study exposure will be characterised in the descriptive analysis.

Sensitivity analyses will explore the impact of using 30-day and 60-day extensions of the time windows for duration of exposed follow-up (instead of 14 days). Provided there is sufficient sample size, two additional sensitivity analyses will explore subgroup analyses of different regimens: (1) study LABAs initiated as monotherapy and (2) LABAs initiated in free- or fixed-dose combinations with LAMAs.

To capture other exposures during the 14-day extension, medical and recent prescription history at the time of event for each type of outcome will be described.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

Cardiac arrhythmias and myocardial ischaemia have been identified in the Olodaterol Risk Management Plan as potential risks of olodaterol use.

The primary outcomes are as follows:

- Incidence of atrial fibrillation or flutter during new use
- Incidence of hospitalisation for ventricular tachycardia, including ventricular fibrillation/flutter and cardiac arrest during new use
- Incidence of supraventricular tachycardia (other than atrial fibrillation/flutter) during new use
- Incidence of hospitalisation for acute myocardial infarction during new use
- Incidence of hospitalisation for serious acute coronary heart disease, including unstable angina, during new use

Incidence rate ratio and incidence rate difference for each of the five listed outcome categories among new users of olodaterol (either in free- or fixed-dose combination with tiotropium or other LAMAs) will be assessed relative to the incidence among new users of other LABAs (either in free- or fixed-dose combination with tiotropium or other LAMAs). Non-serious events, such as angina, electrocardiographic signs of ischaemia without immediate clinical consequence, or non-serious arrhythmia, may frequently not receive medical attention and are not always detectable in the database. Such events have not been validated and therefore will not be assessed.

9.3.2.1.1 Case ascertainment

Potential cases of the outcomes listed above will be ascertained during the follow-up period for each study subject by using validated diagnostic code algorithms to identify the outcomes in the automated data. Linkage to hospital discharge diagnoses listed in national hospital files to identify relevant hospitalisations for arrhythmias and also to outpatient hospital diagnoses will be conducted as appropriate and available. (See Annex 5 for relevant ICD-10 codes.)

Studies validating cardiovascular outcomes have been published for Denmark. Using data from one region of Denmark, the PPV of atrial fibrillation or flutter among users of non-steroidal anti-inflammatory drugs was 90%.[P11-08175] Studies have reported the validity of myocardial infarction in the Danish National Patient Registry. For acute myocardial infarction, the PPV was 82% to 94%. [R14-0355] R14-0358]

Validated in other population-based data sources in other countries, algorithms to identify AMI including out-of-hospital coronary heart disease deaths can be used according to the availability of data. [P09-14662] [P04-09631] [R11-4316] [P10-05107] [P09-14650] The

PPV for AMI diagnosis was reported to be about 93% (95% confidence interval [CI], 90%-96%) in a United Kingdom database of GP records. [R11-2266] In addition, other published algorithms used in other databases for atrial fibrillation, [R10-0756] [R13-1398] ventricular arrhythmia, [R13-1391] and serious coronary heart disease including revascularisation procedures and unstable angina [P10-05107] [R13-1397] may be useful.

9.3.2.1.2 Review of automated longitudinal health profiles

Where feasible, a random sample of up to 100 patient profiles (the chronological electronic listings of the diagnoses, procedures, and medications [but no free text]) will be reviewed by a clinician blinded to the exposures of interest. This is an important step to assure that coding algorithms identify individuals who have disease natural history consistent with the events of interest.

9.3.2.2 Secondary outcomes

Cardiac arrhythmia and myocardial ischaemia, in severe conditions, can contribute to mortality in a vulnerable COPD population. Therefore, the secondary outcome of interest for this study is mortality from all causes.

In Denmark, the fact and date of death are obtained for research studies through linkage to the national death files. The Danish Civil Registration System includes the fact and date of death, but not the cause of death. [R16-2604] The Danish Registry of Causes of Death includes all records of deaths in Denmark since 1943. The record lists the name, personal identification (the unique CPR number assigned to all Danish citizens and other residents of Denmark since 1968), and information from the death certificate, including birthplace, date, and place of death and classification of the underlying and contributory causes of death.

9.3.3 Covariates

All covariables will be ascertained on or before the index date. The look-back observation period to define covariables of interest will be specified for each variable in the statistical analysis plan, e.g., ever before for most comorbidities. In general, in database analyses, the absence of information such as an outpatient diagnosis is classified as the absence of the condition. All subjects without a dispensing for a medication will be considered unexposed, and all subjects without a diagnosis will be considered as not having the condition. Age on the index date and patient sex are readily available. Information on lifestyle factors can be obtained only from the general practitioner outpatient database, which is no longer available.

9.3.3.1 Medical characteristics at baseline

9.3.3.1.1 Severity of COPD

Guidelines of the Global Initiative for Obstructive Lung Disease (GOLD) recommend evaluating the severity of COPD and its impact on the health of patients by the combination of the (1) current level of symptoms, (2) severity of the spirometric abnormality, and (3) risk of exacerbations. [P13-02399] The presence of comorbidities also influences the severity of COPD, which is a predictor of morbidity and mortality. According to these parameters, severity of COPD is classified into four severity groups as illustrated in Figure 2.

Risk GOLD classification of airflow limitation			**Risk** Exacerbation history
4 **3**	**C**	**D**	**≥ 2 without hospitalisation or > 1 hospitalisation**
2 **1**	**A**	**B**	**≤ 1 without hospitalisation 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 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 partially recorded in automated health databases. These 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. [P07-09136] [R13-1392] [P09-04948] [R08-1492] [P11-13226]

A summary of the evaluation of severity of COPD in health database studies is presented in Annex Table 3:1. In a study conducted in the General Practice Research Database (GPRD) (forerunner to the current Clinical Practice Research Datalink [CPRD]) in 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 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 to results from spirometry. In a study conducted in the Saskatchewan Health databases in Canada, determinants of COPD severity were the presence of emphysema, use of nebuliser therapy, use of oxygen therapy, use of inhaled and/or systemic glucocorticosteroids, intensity of bronchodilator use, pneumonia, and prior COPD exacerbation. [P07-09136] These factors were associated with increased cardiovascular morbidity and mortality.

9.3.3.1.2 Definition of COPD Severity

Severity of COPD will be evaluated among new users of olodaterol and other LABAs 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] and taking into account the updated GOLD recommendations [P16-00121] (see Table 3).

Table 3 Definition criteria of COPD severity

Severity of COPD	**Definition**
Mild	Fewer than two dispensings of the same COPD drug class with a maximum interval of 6 months in the 12 months before the index date
Moderate	Regular treatment defined as having at least two 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 12 months 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 12 months 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. [P11-13226]; Soriano et al. [R08-1492]; Curkendall et al.; [P07-09136] and GOLD, 2016 [P16-00121].

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

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

Indicators of severity presented in Table 3 will be mutually exclusive, and patients that fulfil criteria for more than one category will be classified as being in the most severe category. The operational definition of severity is as follows:

- Same class of "COPD drugs": the following drug classes will be considered (see): Annex 4
  - Bronchodilators: inhaled short-acting muscarinic antagonists (SAMAs), inhaled long-acting muscarinic antagonists (LAMAs), inhaled short-acting beta2-agonists (SABAs), inhaled long-acting beta2-agonists (LABAs), and fixed combinations of SABA and SAMA
  - Inhaled glucocorticosteroids (ICS): ICS alone, fixed combinations of SABA and ICS, fixed combinations of LABA and ICS
  - Systemic (oral) glucocorticosteroids
  - Systemic beta2-agonists

  - Xanthines
  - Roflumilast
- Hospitalisation for COPD
  - Primary or secondary hospital discharge diagnosis for COPD
  - ICD-10 codes J40-J44
- Recorded diagnosis of pneumonia
  - Primary or secondary hospital discharge diagnosis or outpatient hospital clinic diagnosis for pneumonia
  - ICD-10 codes J09-J18
- Second course of antibiotics for respiratory tract infection
  - A single course of antibiotic treatment involving multiple dispensings is defined as that involving consecutive dispensings of antibiotics with fewer 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 single course of systemic corticosteroids involving multiple dispensings is defined as that involving consecutive dispensings with fewer 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
- Two diagnoses of COPD exacerbation without hospitalisation
- Outpatient hospital clinic diagnosis of COPD exacerbation
- ICD-10 codes: J44.1
- Oxygen therapy. ATC code: V03AN01; NCSP code: BGXA5
- Nebuliser therapy. To be identified in each database using national drug codes or NCSP code: BGXA10
- Emphysema
  - Primary or secondary hospital inpatient discharge diagnosis or outpatient hospital clinic diagnosis of emphysema at any time before the index date
  - ICD-10 code: J43
- Other characteristics include the following:
  - Asthma (from outpatient hospital clinic and inpatient diagnoses)
  - History of COPD, chronic bronchitis, or emphysema (from outpatient hospital clinic and inpatient diagnoses)

9.3.3.2 Other Characteristics

The following indicators of general comorbidity and cardiovascular disease or risk factors for cardiovascular disease at any time in the past or on the day of cohort entry will be utilised.

- Comorbidities will be ascertained from hospital discharge diagnoses, when available (see Annex 5 for codes). Outpatient dispensings may also be used to identify relevant treatments for conditions of interest, as follows:
  - Coronary heart disease, including myocardial infarction, angina, and revascularisation procedures
  - Atrial fibrillation, other supraventricular arrhythmias, and ventricular arrhythmias
  - Heart failure
  - Stroke and transient ischaemic attack
  - Hypertension
  - Diabetes
  - Hyper- or dyslipidaemia
  - Chronic kidney disease
  - Liver disease
  - Osteoporosis
- Pneumonia (see Section 9.3.3.1.2 for codes)
  - Cancer diagnosis
- History of medications dispensed in the 12 months before or on the index date will be identified from the pharmacy dispensing history (see Annex 5 for codes):
  - Cardiovascular drugs: antihypertensives, antiarrhythmics, nitrates, other
  - Lipid-lowering medications
  - Blood glucose–lowering medications
  - Anticoagulants and antiplatelet agents
  - Antibiotics
  - Antineoplastic agents

9.4 DATA SOURCE

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 Denmark. New users will be characterised in terms of past medical history and use of medications. An overview of the information on diagnoses and procedures is shown in Table 4, Section 9.4.2.

9.4.1 Denmark

The Danish health care system provides universal coverage to all Danish residents (5.6 million inhabitants). Health care coverage includes visits to general practitioners (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 (all registries contain civil registration numbers), such as the Danish National Registry of Patients, 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 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]

9.4.2 Planned data source summary

Table 4 shows the characteristics of the planned data source in Denmark where olodaterol use may be sufficient to address the study questions.

Table 4 Overview of planned data source, contingent upon approval

Data Element	**National Registers, Denmark**
Database type	National health record and prescription databases linked through the unique civil personal registration number
Database population	Denmark
Country population[1]	5,602,628
Approximate proportion of the country's population covered by the database	100%
Representativeness of patients and practices	Complete, given that the total country population is included
Linkage	Unique patient-specific identifiers
Data on medications	Pharmacy-dispensed prescriptions
Dose	Formulation strength
Duration	Based on prescriptions
Drug dictionary codes/ therapeutic classification	ATC

Table 4 (cont'd) Overview of planned data source, contingent upon approval

Data Element	**National Registers, Denmark**
Number of indacaterol prescriptions2 (approximate)	47,400 (years 2010-2011)
Clinical indication	Not recorded per se but may be surmised based on proxies (i.e., prescribed medication, hospital discharge diagnosis, and outpatient diagnosis history)
Outpatient diagnosis	From hospital outpatient specialty clinics
Hospital diagnosis	Yes, ICD-10
Procedure codes	Yes, NCSP version 1.16:2012
Pulmonary function testing	From hospital clinics and also from primary care when recorded
Information on death	Fact and date in the Civil Registration System, and underlying cause of death available in National Death Register
Access to medical records	No
Lifestyle risk factors	No, only some if recorded among inpatients (body mass index, and alcohol only from diagnosis codes, smoking not available, and socioeconomic status proxies not available)
Data availability	Since 1994
Updates	Annual
Approximate time lag	1 year
Data transfer	Not permitted; requires collaboration with Danish investigator[3]
Approval process	Danish Data Protection Agency approval required

ATC = Anatomical Therapeutic Chemical; ICD-10 = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision; Nordic Medico-Statistical Committee Classification of Surgical Procedures.*

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

2 Indacaterol was selected as an example of a LABA indicated only for COPD.

3 Collaboration of local investigator has not been obtained and is contingent upon staffing availability.

9.5 STUDY SIZE

Table 5 shows for the situation where the IRR for the events of interest for olodaterol use compared with other LABAs is 1 and the number of person-years of olodaterol use necessary to obtain a probability of 0.80 that the upper bound of the 95% confidence interval of the IRR is below 1.5, 2.0, 2.5, and 3.0. If all olodaterol initiators in the Denmark data source are eligible for the study, the study size could be sufficient by calendar year 2019 or 2020 to

demonstrate an IRR less than 3.0 for AMI and atrial fibrillation and less than 1.5 for all-cause mortality if the true IRR for olodaterol compared with other LABAs is 1.0. As three or more other LABAs are already available in these countries, a relatively low use of olodaterol is expected. As per Section 9.1, the study is proposed for a 5-year duration. For each study outcome, the IRR will be calculated if the number of exposed person-years is sufficient for the upper bound of the 95% confidence interval around the IRR to be approximately 2.5; for ventricular tachycardia, including ventricular fibrillation/flutter and cardiac arrest, the IRR will be calculated if the number of exposed person-years is sufficient for the upper bound of the 95% confidence interval is approximately 3.If the number of olodaterol users in Denmark is insufficient to meet these statistical goals, another country (e.g., Netherlands) will be added as an additional study population, and combined estimates will be generated, if appropriate. If total olodaterol use is lower than expected or analyses from Denmark and the other country cannot be pooled, analyses will be restricted to descriptive analyses only.

Table 5 Number of exposed person-years necessary to have a probability of 0.80 that the upper bound of the 95% confidence interval of the IRR is below the specified value, assuming IRR in the population is 1.0

Safety endpoint	Rate per 1,000 person-years in unexposed persons with COPD	Upper bound of 95% CI of IRR for olodaterol versus comparator			
		1.5	2	2.5	3
AMI	6.3[1]	9,890	3,390	1,940	1,350
	9.5[2]	6,230	2,130	1,220	850
Atrial fibrillation	5.9[2]	10,060	3,450	1,970	1,370
	2.5[3]	23,820	8,150	4,670	3,250
Ventricular tachy-cardia, ventricular fibrillation, or cardiac arrest	0.97[2]	61,470	21,040	12,040	8,380
Other arrhythmias	2.96[2,4]	20,110	6,880	3,940	2,740
All-cause mortality	106.58[5]	510	180	100	70

AMI = acute myocardial infarction; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CPRD = Clinical Practice Research Datalink; IRR = incidence rate ratio; LABA = long-acting beta2-agonist.

Note: Calculations are for a 1:4 olodaterol:comparator person-year ratio and population incidence rate ratio = 1.0. This table was prepared with the use of Episheet—spreadsheets for the analysis of epidemiologic data. [R13-1396]

1 García-Rodríguez et al. [R12-3322]; CPRD, United Kingdom; new diagnosis of an outcome during the study period in general practitioner medical records and hospital summaries.

2 Sidney et al. [R07-2623]; Kaiser Permanente, United States; primary hospital discharge diagnoses.

3 Ruigómez et al. [R10-0421]; CPRD, chronic atrial fibrillation in COPD, aged 40-89 years; estimated by multiplying incidence in the general population (1.7 per 1,000 person-years) by the relative risk of atrial fibrillation associated with chronic respiratory disease (1.5).

4 Other arrhythmias included paroxysmal supraventricular arrhythmias, cardiac dysrhythmias, and premature beats.

5 Curkendall et al. [R09-0579]; Saskatchewan Health, Canada; incidence of primary hospital discharge diagnoses or underlying cause of death.

Data from 2014 became available during the second quarter of 2015. Based on feasibility data for Denmark, there were over 600 unique users of olodaterol in 2014. Actual counts of patients using olodaterol in 2015 are not yet available, but will be monitored and reported in the study progress reports. In addition, the entire pool of patients with COPD in Denmark can be approximated. During a recent 4-year period (2005-2008), 38,527 individuals in Denmark received hospital care (outpatient or inpatient) for COPD for the first time, or approximately 9,630 per year. [R12-3324]

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

The research institution conducting analysis of data from the data source has been reviewed and qualified by the Office of Quality Assurance. The research team will follow its own established procedures. All summary tables of results, and no individual patient identifiers, will be provided to , who will develop the report. 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. Imputation methods may be used to estimate key missing values such as dosage of exposure of interest, smoking status, or body mass index.

For requests to access to data for audit purposes, only aggregated data from the research centre will be available. 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 the 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 the database research centre. The research team will follow its established data management procedures for handling patient-specific data. A data management plan specific to the contracted research centre will be included in the statistical analysis plan, a separate document not yet developed.

9.7 DATA ANALYSIS

9.7.1 Main analysis

Descriptive analyses by exposure category, overall and stratified by pre-defined strata, will be provided. Categorical variables will be summarised with counts and percentages. Continuous variables will be summarised with univariate statistics (e.g., mean, standard deviation, 95% confidence intervals).

9.7.1.1 Description of cohort characteristics

All covariables will be ascertained on or before the index date. Age on the index date and patient sex are readily available. When presenting results stratified on a single variable, subjects missing the variable will be reported as a separate category.

- Reasons for exclusion among all identified olodaterol initiators and among the “other LABA” initiators will be summarised.

- Demographic and medical characteristics (e.g., medical history) at the index date will be summarised by cohort and stratified also by COPD severity, stratified by history of outcome of interest.
- Prior medications dispensed before the index date and concomitant medications dispensed on index date will be summarised by cohort.

9.7.1.2 Characteristics of follow-up

To assess the potential for differential loss-to-follow-up, the distribution of patient-specific person-time at risk will be visually evaluated and compared by exposure group. Reasons for terminating follow-up, e.g. occurrence of event of interest, end of exposure, death, or end of study period, will also be described.

9.7.1.3 Safety endpoints

Incidence rates for each event of interest will be calculated for each cohort as follows:

> Incidence rate (IR_E) = (total number of patients in the olodaterol cohort experiencing an event of interest for the first time during the given time period) / (total time at risk from current use of olodaterol during the given period)
>
> Incidence rate (IR_C) = (total number of patients in the comparator cohort experiencing an event of interest for the first time during the given time period) / (total time at risk from current use of comparator LABAs during the given period)

The incidence rate ratio (IRR) for each event of interest in the olodaterol-exposed group relative to that in the comparator group will be derived as follows:

> Incidence rate ratio = IRE/ IRC, where IRE represents the incidence rate from the olodaterol cohort and IRC represents the incidence rate from the matched comparator cohort.

The IRRs will be calculated and 95% confidence intervals will be derived. Incidence differences and their 95% confidence intervals will also be derived.

The effects of demographics and selected baseline characteristics will be assessed. Adjusted IRR will be calculated by adjusting for each covariate one at a time. The following factors will be considered as potential confounders:

- Age at the index date
- Sex
- Calendar year of the index date
- Use of specific comedications (e.g., ICS, LAMA) at or before the index date
- History of cardiovascular events of interest (number of strata to be evaluated may be constrained by number of events) at or before the index date
- Baseline severity of COPD, measured within 12 months before the index date

- Diagnosis code for COPD only versus diagnosis codes for both COPD and asthma
- Individual cardiovascular risk factors listed in Section 9.3.3.2, such as hypertension, diabetes, hyperlipidaemia.

Additional strata may be defined as needed.

The IRR will be calculated by stratifying on and adjusting for each potential confounder one at a time. A change of less than 10% in the adjusted IRR compared with the crude IRR will serve as an indicator that confounding for that variable is of negligible importance in the data. Variables associated with a change in the IRR greater than 10% will be included in the propensity score model.

A fitted propensity score model will be used to estimate a propensity score for each patient. If enough patients are exposed among (1) initiators of olodaterol or other LABA alone and (2) initiators of olodaterol or LABA in combination with a LAMA (in free- or fixed-dose combination) (≥ 1,000), two propensity score models will be fitted, one for each group. If the numbers are not adequate, then a variable indicating presence or absence of background LAMA, together with its interaction terms with clinically relevant covariables, will be included in one propensity score model as an adjustment variable. [R16-4007, P12-08895] The IRRs for each event of interest will be stratified by propensity score deciles. Adjusted IRRs will be calculated across propensity score deciles, overall and by background treatment, with or without LAMA subgroups. [R10-1239] The propensity scores will be generated using the factors shown to be associated with confounding in the data. For modelling (i.e., when computing exposure propensity scores), variables with a significant amount of missing data (e.g., > 10%) may be imputed.

The distributions of propensity scores in olodaterol and in comparator patients will be examined. Patients with extreme or non-overlapping propensity scores (i.e., ranges in the upper or lower tails of the propensity score distribution within which only patients taking olodaterol or patients taking comparator LABAs fall) will be excluded. This allows for the removal of patients for whom there are no comparable patients in the other cohort.

Person-time and endpoint counts for each cohort will be stratified into deciles of propensity scores defined by the distribution of propensity scores for the olodaterol cohort. To check that the covariables are balanced within each propensity score decile, the distribution of each variable within each propensity score decile will be compared visually between the cohorts to evaluate whether there are clinically relevant differences.

For each endpoint, IRR and incidence rate difference (IRD) will be stratified by propensity score deciles, and the overall adjusted IRR and IRD and associated 95% CIs will be derived by weighting each stratum by the prevalence among the olodaterol cohort.

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 by the RTI International institutional review board, of which is a research unit. Such audits at will be conducted by the Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures. The database research centres will follow its own quality and audit trail procedures. The quality and audit trails may be different from that of the coordinating centre.

Data management and analysis will be conducted in at each participating research centre. Standard operating procedures specific to each research centre 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.

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 of the following known limitations of such data sources:

- The length of medical history in some databases will be limited, and earlier medical events or drug exposures may be unknown. This may especially be true for data sources that have become available for research in the recent past.
- The study's ability to enrol large enough numbers of patients using LABAs and to follow them for an adequate number of person-years will depend on uptake of

olodaterol in each country and on health insurance reimbursement decisions for this medication.

- For severity of COPD, ideally FEV_1 (forced expiratory volume in 1 second) would be used to classify all individuals by application of standard criteria; however, it is anticipated that most databases will not capture this information. Other variables, such as information on hospitalisations for COPD or use of oxygen, may be available.
- The candidate data sources planned for this study reliably contain information on outpatient dispensings, but actual exposure may be misclassified for individuals who do not use their medication as prescribed.
- When outpatient diagnoses are absent, such comorbidities may also be assessed with medication use. Using this approach may result in underestimation if patients are untreated or overestimation if the indicator medication is used for multiple indications.
- Internal and external validity of some cardiovascular endpoints might be of concern. For arrhythmias, using hospitalisation discharge codes will underestimate the occurrence of these events because only the more severe arrhythmias will be captured. Although events diagnosed at hospital outpatient clinics will be included for these endpoints, a proportion of events diagnosed in the primary care sector will be missed if these data are not available to be used. Given that out-of-hospital events are not included, 20% to 30% of AMI outcomes may be missed. This could result in biased IRR estimates if olodaterol were to change the severity of such outcomes.

9.10 OTHER ASPECTS

9.10.1 Study size limitations

The ability to accrue a sufficient study size for patients treated with newly approved olodaterol depends upon the accrual rate of new use of olodaterol in Denmark. In the 2018 progress report analysis (second progress report), the uptake and rate of increase of olodaterol use, including free- and fixed-dose combination with a LAMA, will be evaluated. In the event that uptake is slower than anticipated, another country, such as the Netherlands, will be added as an additional study population, and a meta-analysis will be conducted in the final analysis if appropriate. If total use is lower than expected or analyses from Denmark and from the other country cannot be pooled, analyses will be restricted to descriptive analyses only.

9.10.2 Study standards

The study will be conducted in accordance with the International Society for Pharmacoepidemiology [R11-4318] *Guidelines for Good Pharmacoepidemiology Practices (GPP)* 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* [R13-5419] will be completed, and the study will be registered in the EU PAS register, [R14-0354] as well as in ClinicalTrials.gov.

The study is a PASS and will comply with the definition of the non-interventional (observational) study provided in the 2012 European Medicines Agency (EMA) *Guideline on Good Pharmacovigilance Practice (GVP): Module VIII – Post-Authorisation Safety Studies*. [R16-4611] The study will comply with the nature of non-interventional (observational) studies referred to in the ICH (International Conference on Harmonisation) harmonised tripartite guideline *Pharmacovigilance Planning E2E*. [R11-2259]

9.10.3 Bias and confounding

The most likely source of bias is confounding by indication, e.g., severity of COPD. Because olodaterol will be new to the market, it is likely that early in its availability, olodaterol will be prescribed to individuals who have tried other treatments for COPD. This study design attempts to remove such confounding by limiting the study to individuals who are not switching to a study treatment (olodaterol vs. other LABA) but are naïve to the class, according to the available pharmacy dispensing history. However, this approach may not fully address the channelling bias, will reduce the study size, and will require a longer period of time to accrue initiators of olodaterol naïve to LABA use.

To address the issue of confounding by indication and by other factors in the non-interventional setting, stratification of incidence rate ratios by propensity score (representing the tendency to receive olodaterol) and subsequent derivation of the overall adjusted incidence rate ratio will be implemented, provided that the market uptake of olodaterol in Denmark is large enough to meet the required study size. The ability to control for such differences is dependent upon having data on the key factors that differentiate users of the study medications from each other.

9.11 SUBJECTS

The study population will consist of patients with COPD (disease cohort) aged 40 years or older in a country where olodaterol is available and where a large proportion of the population is included in health care databases for pharmacoepidemiologic research. The study will be conducted by using the national population-based registers in Denmark.

Study subjects will be identified as individuals with an outpatient dispensing for olodaterol, or an alternative LABA, in free- or fixed-dose combination with another LAMA, during the study period and no recent LABA use in the last 6 months. The study period will start at the time that olodaterol is available in Denmark, and the study period will end at the latest date of available research data in the data source. All available patient-specific data covering time before study cohort entry (minimally, outpatient dispensings, and hospital diagnoses) will be used for identification of patient characteristics at the time of cohort entry, i.e., the study index date.

9.11.1 Identification of COPD

Patients diagnosed with COPD will be identified by compatible outpatient and inpatient diagnostic codes for COPD (i.e., ICD-10 codes for COPD, chronic bronchitis, and emphysema). Hospital discharge diagnoses of COPD have been shown to have a positive predictive value (PPV) of 92%.[R14-0359]

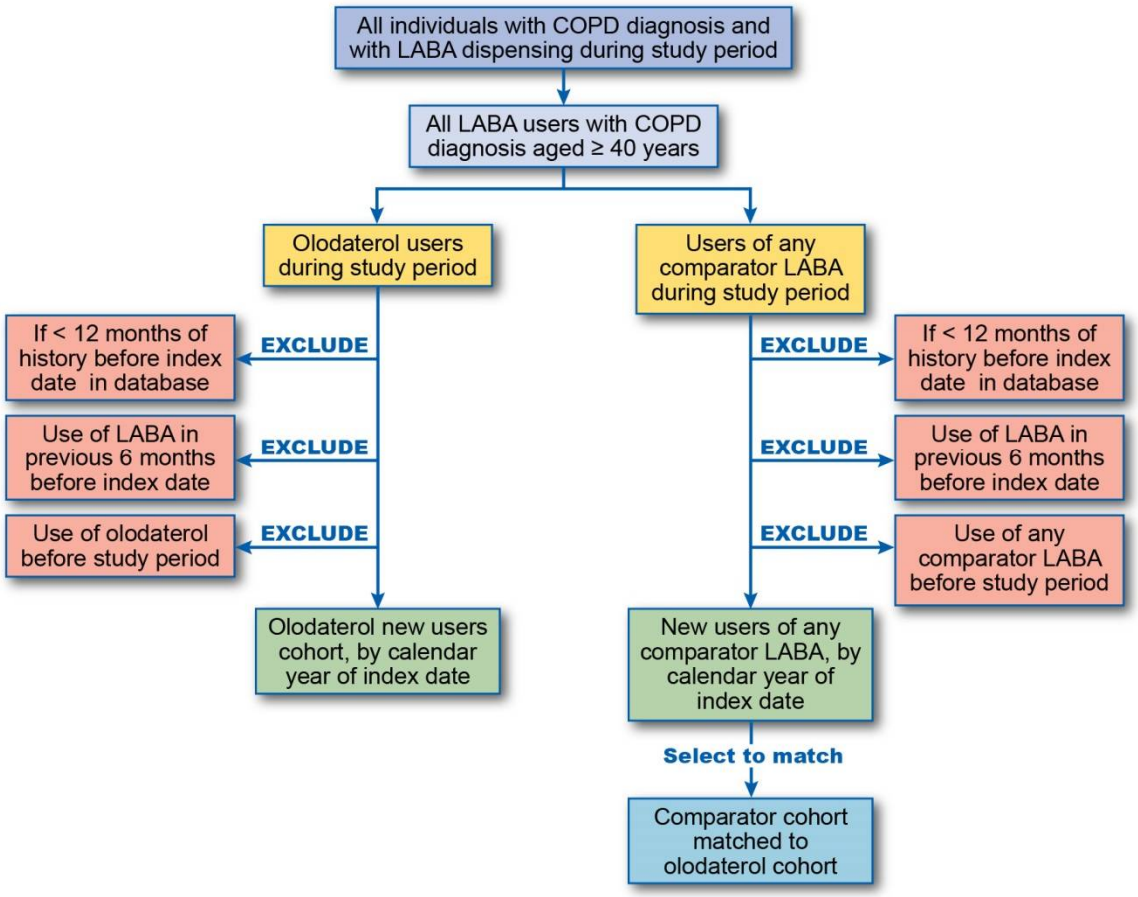
9.11.2 Study cohorts

Two exposure cohorts of patients with diagnosed COPD will be identified and followed via available medical histories in the data source (Figure 3):

- The cohort of new users of olodaterol, i.e., anyone with a dispensing for olodaterol (including either in free- or fixed-dose combination with a LAMA).
- The comparator cohort of new users of indacaterol, salmeterol, or formoterol (including either in free- or fixed-dose combinations with a LAMA).

Individuals selected for the comparator cohort will be frequency-matched to the cohort of olodaterol initiators by 5-year age category, sex, and calendar year of first dispensing of study LABA. The number of comparator patients selected will be from 1 to 5 times the number of olodaterol patients. The date of the first dispensing of study LABA is defined as the index date. Patients with COPD switching LABA at the study index date, indicated by use of another LABA within the previous 6 months, will not be included in either study cohort. The rationale for this exclusion is to maximise similarity of COPD disease between the two exposure cohorts and to remove potential lingering effects of a recently used other LABA. If the drug utilisation study demonstrates that this approach would exclude 25% or more initiators of olodaterol from the study, an alternative approach to balancing exposure groups may be developed and applied; if used, the alternative approach will be described in the report. Use of oral beta2-agonists will not be included as study medications of interest.

Individuals will be randomly selected for the comparator cohort from each stratum of qualifying individuals in the same 5-year age category, sex, and calendar year of index dispensing as an olodaterol initiator.



LABA = long-acting beta2-agonist.
The comparator LABAs are indacaterol, salmeterol, and formoterol in single-agent formulations.

Figure 3 Selection of study cohorts

9.11.3 Inclusion criteria

Patients in both exposure cohorts will be required to meet the following criteria:

- Have been diagnosed with COPD
- Be aged 40 years or older (to minimise the likelihood of including individuals who have asthma only)
- Be a new user of olodaterol or a new user of indacaterol, salmeterol, or formoterol (*not* in fixed-dose combination with an inhaled corticosteroid) and have no dispensing of any LABA in the 6 months before the index date
- Have at least 1 year of enrolment in the electronic database before their first LABA dispensing (defined as the index LABA)
- Have data on sex (i.e., sex must be known)

10. PROTECTION OF HUMAN SUBJECTS

Institutional review board approval and/or any other required reviews of the study protocol by specific committees will be obtained in accord with applicable national and local regulations.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Based on current guidelines from the International Society for Pharmacoepidemiology [R11-4318] and the EMA *Guideline on Good Pharmacovigilance Practices (GVP)*, [R13-1970] non-interventional studies such as the one described in this protocol conducted using or 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, study status, and report(s) will be included in regulatory communications in line with the risk management plan, Periodic 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., International Society for Pharmacoepidemiology) will be considered.

When reporting results of this study, the appropriate STROBE (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

None

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

European Network of Centres for
Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 section number 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). 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:
Cohort study of cardiovascular events in patients with chronic obstructive pulmonary disease initiating olodaterol or other long-acting beta2-agonists

Study reference number:
BI Study Number: 1222.54

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
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)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8

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

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.1
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.1, 9.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	9.1, 9.7

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.4, 9.11
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.1, 9.11
	4.2.2 Age and sex?	☒	☐	☐	9.11
	4.2.3 Country of origin?	☒	☐	☐	9.4, 9.11
	4.2.4 Disease/indication?	☒	☐	☐	9.11
	4.2.5 Duration of follow-up?	☒	☐	☐	9.3.1.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.11

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.2
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3.2

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.10.3
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☐	9.10.3
7.2 Does the protocol address:	☐	☐	☐	9.10.3

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.10.3
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.10.3
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☐	9.10.3

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.2.1, 9.10.3

Comments:

Sensitivity analyses will exclude individuals with history of the outcomes.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 Does the protocol describe the information available from the data source(s) on:				9.4
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3 Is a coding system described for:				9.4
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
Activities (MedDRA))				
9.3.3 Covariates?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7.1
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.3 Are stratified analyses included?	☒	☐	☐	9.7.1
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.1
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.1
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

This is a protocol that will be implemented by a research institution that is qualified and has available staffing at the time of study initiation, i.e. after EMA review, olodaterol is launched. At that time the specifics of data management, quality control, and data security can be specified. To date no advisory board is planned.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.10.3
12.1.2 Information bias?	☒	☐	☐	9.10.3
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.10.3
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.10.1

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.10.2, 10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____

Date: 28/October/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, [P07-09136] Eisner, [R13-1392] and Soriano [R08-1492]	At initial COPD symptoms	At least two 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 the following data: • 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 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 (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 [R08-1492]			
Severity based on only drug data	At first diagnosis of COPD	At least two 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 (CPRD).

ANNEX 4. ATC CODES FOR SELECTED RESPIRATORY MEDICATIONS

Annex Table 4:1 Inhaled selective beta2-adrenoreceptor agonists, anticholinergics, and glucocorticosteroids

ATC Code	**Name**	Defined Daily Dose Units (Administration Route)
Inhaled short-acting beta2-agonists		
R03AC02	Salbutamol	0.8 mg (aerosol, powder) 0.10 mg (solution)
R03AC03	Terbutaline	2 mg (aerosol, powder) 20 mg (solution)
R03AC04	Fenoterol	0.6 mg (aerosol, powder) 4 mg (solution)
R03AC05	Rimiterol	1.6 mg (aerosol)
R03AC06	Hexoprenaline	1.5 mg (aerosol)
R03AC07	Isoetarine	NA
R03AC08	Pirbuterol	1.2 mg (aerosol)
R03AC09	Tretoquinol	NA
R03AC10	Carbuterol	NA
R03AC11	Tulobuterol	1.6 mg (aerosol)
R03AC14	Clenbuterol	NA
R03AC15	Reproterol	NA
R03AC16	Procaterol	60 mcg (aerosol)
R03AC17	Bitolterol	NA
Inhaled long-acting beta2-agonists		
R03AC12	Salmeterol	0.1 mg (aerosol, powder)
R03AC13	Formoterol	24 mcg (aerosol, powder)
R03AC18	Indacaterol	0.15 mg (inhal. powder)
R03AC19	Olodaterol	5mcg (inhal. solution)
Inhaled short-acting muscarinic antagonists		
R03BB01	Ipratropium bromide	0.12 mg (aerosol, powder) 0.3 mg (solution)
R03BB02	Oxitropium bromide	0.6 mg (aerosol) 4 mg (solution)

Annex Table 4:1 (cont'd) Inhaled selective beta2-adrenoreceptor agonists, anticholinergics, and glucocorticosteroids

ATC Code	Name	Defined Daily Dose Units (Administration Route)
Inhaled long-acting muscarinic antagonists		
R03BB04	Tiotropium bromide	18 mcg (aerosol) 5 mcg (solution)
R03BB05	Aclidinium bromide	0.644 mg
R03BB06	Glycopyrronium bromide	44 mcg
R03BB07	Umeclidinium bromide	55 mcg (inhal. powder)
R03BB54	Tiotropium bromide, combinations	
Inhaled glucocorticosteroids		
R03BA01	Beclometasone	0.8 mg (aerosol, powder) 1.5 mg (solution)
R03BA02	Budesonide	0.8 mg (aerosol, powder) 1.5 mg (solution)
R03BA03	Flunisolide	1 mg (aerosol)
R03BA04	Betamethasone	NA
R03BA05	Fluticasone	0.6 mg (aerosol, powder) 1.5 mg (solution)
R03BA06	Triamcinolone	NA
R03BA07	Mometasone	0.4 mg (powder)
R03BA08	Ciclesonide	0.16 mg (aerosol)
R03BA09	Fluticasone furoate	NA

ATC = Anatomical Therapeutic Chemical; NA = not yet available in the online ATC/DDD Index.

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.

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ANNEX 5. CODES FOR COMORBIDITIES AND OTHER MEDICATIONS

Annex Table 5:1 Comorbidity

Disease Description	**ICD-10 Code**
Cardiovascular diseases	**I00-I99**
Ischaemic heart disease	I20-I25 or coronary reperfusion surgery and procedures
Angina pectoris	I20
Acute myocardial infarction	I21
Other acute or subacute ischaemic heart disease	I22-I24
Chronic ischaemic heart disease	I25
Coronary reperfusion surgery and procedures	List of codes to be developed according to each database dictionary
Arrhythmias	I47-I49
Paroxysmal tachycardia	I47
Ventricular tachycardia	I47.0, I47.2
Supraventricular tachycardia and unspecified	I47.1, I47.9
Atrial fibrillation and flutter	I48
Other cardiac arrhythmias	I49
Ventricular fibrillation and flutter	I49.0
Other cardiac arrhythmias	I49.1-I49.9
Conduction disorders	I44-I45
Cardiac arrest	I46
Heart failure	I50
Cerebrovascular disease	I60-I69, G45
Cerebral haemorrhage (subarachnoid, intracerebral, other non-traumatic)	I60-I62
Cerebral infarction and stroke	I63, I64, G46.5
Transient ischaemic attack	G45
Other cerebrovascular disease and sequelae of cerebrovascular disease	I65-I69
Hypertension and hypertensive heart disease	I10-I15

Annex Table 5: 1 (cont'd) Comorbidity

Disease Description	**ICD-10 Code**
Diseases of arteries, arterioles, and capillaries	I70-I79 and peripheral arterial revascularisation procedures
Peripheral arterial revascularisation procedures	List of codes to be developed according to each database dictionary
Other form of heart diseases	I00-I09, I30-I43, I80-I99
Hyperlipidaemia	**E78**
Diabetes mellitus	**E10-E14**
Renal disease	**N00-N39**
Chronic kidney disease	N18
Other renal disorders	N00-N17, N19, N25-N39
Anaemias	**D50-D64**
Nutritional anaemias	D50-D53
Iron deficiency anaemias	D50
Other anaemias	D55-D64
Peptic ulcer disease	**K25-K28**
Liver disease	**K70-K77**
Osteoporosis	**M80-M82**
Rheumatoid arthritis and other inflammatory arthropathies	**M05-M14**
Systemic connective tissue diseases	**M30-M36**
Malignancy	**C00-C97**
Depressive disorders	**F32-F33**
Pregnancy (at the index date)	**O00-O48**

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

Annex Table 5:2 Anatomical Therapeutic Chemical codes for comedications

Medication Description	**ATC Code**
Respiratory medications	
Inhaled short-acting muscarinic antagonists (SAMAs)	See Annex Table 4:1 for ATC codes
Inhaled long-acting muscarinic antagonists (LAMAs)	See Annex Table 4:1 for ATC codes
Inhaled short-acting beta2-agonists (SABAs)	See Annex Table 4:1 for ATC codes
Inhaled long-acting beta2-agonists (LABAs)	See Annex Table 4:1 for ATC codes
Inhaled glucocorticosteroids (ICS)	See Annex Table 4:1 for ATC codes
Fixed combinations of SABA and SAMA	ATC codes not available[1]
Fixed combinations of SABA and ICS	ATC codes not available[1]
Fixed combinations of LABA and ICS	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
Oxygen therapy	V03AN01 or NCSP code: BGXA05
Nebuliser therapy	NCSP code: BGXA10
Cardiovascular medications	All codes listed below in section Cardiovascular medications
Cardiac glycosides and antiarrhythmics, Class I and III	C01A, C01B
Vasodilators used in cardiac diseases	C01D
Cardiac stimulants and other cardiac preparations	C01E, C01C
Diuretics	C03
Peripheral vasodilators	C04
Vasoprotectives	C05
Beta blocking agents	C07
Calcium channel blockers	C08
Antihypertensives	C02

Annex Table 5:2 (cont'd) Anatomical Therapeutic Chemical codes for comedications

Medication Description	**ATC Code**
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 combinations with acetylsalicylic acid	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**
Anti-inflammatory and antirheumatic products, non-steroids (non-steroidal anti-inflammatory drugs)	M01A
Acetylsalicylic acid (other analgesics and antipyretics)	N02BA
Other antirheumatic agents: Anti-inflammatory/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, progestogens and estrogens in combination	G03C, G03D, G03F
Drugs used in nicotine dependence	N07BA

ATC = Anatomical Therapeutic Chemical.

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

ANNEX 6. DATA SOURCE DESCRIPTIONS FROM FEASIBILITY REPORT, 1 NOVEMBER 2013

NATIONAL REGISTRY OF PATIENTS, DENMARK

Database Characteristics

The Danish health care system provides universal coverage to all Danish residents (5.5 million inhabitants). Health care coverage includes visits to general practitioners (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 (individual hospitalised or attending outpatient hospital clinics), Danish National Prescription Database (for outpatient prescriptions), 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. [R13-5415]

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 standardised to the Danish population was estimated at 9%, using a sample of 299,000 residents of two counties. [R12-3265] In general, ICD (*International Classification of Diseases*) 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 was 92%. [R14-0359]

The conduct of research with the Danish National Registry of Patients requires collaboration with a local Danish university or investigator affiliated with a research institute to access the data and ethics committee notification or approval to handle data.

Selected Published Research on Cardiovascular Outcomes

P11-08175 Schmidt M, Christiansen CF, Mehnert F, Rothman KJ, Sørensen HT. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study. BMJ. 2011 Jul 4;343:d3450.

P13-04200 Larsen TB, Rasmussen LH, Skjøth F, Due KM, Callréus T, Rosenzweig M, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. J Am Coll Cardiol. 2013 Jun 4;61(22):2264-73.

P14-01137 Coloma PM, Valkhoff VE, Mazzaglia G, Nielsson MS, Pedersen L, Molokhia M, et al. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. BMJ Open. 2013 Jun 20;3(6).

R14-0355 Joensen AM, Jensen MK, Overvad K, Dethlefsen C, Schmidt E, Rasmussen L, et al. Predictive values of acute coronary syndrome discharge diagnoses differed in the Danish National Patient Registry. J Clin Epidemiol. 2009 Feb;62(2):188-94.

R14-0358 Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. J Clin Epidemiol. 2003 Feb;56(2):124-30.

R14-0393 Kristensen SL, Ahlehoff O, Lindhardsen J, Erichsen R, Jensen GV, Torp-Pedersen C, et al. Disease activity in inflammatory bowel disease is associated with increased risk of myocardial infarction, stroke and cardiovascular death--a Danish nationwide cohort study. PLoS One. 2013;8(2):e56944.

R14-0394 Høgh A, Lindholt JS, Nielsen H, Jensen LP, Johnsen SP. Beta-blocker use and clinical outcomes after primary vascular surgery: a nationwide propensity score-matched study Eur J Vasc Endovasc Surg. 2013 Jul;46(1):93-102.

R14-0427 Krarup LH, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. Neuroepidemiology. 2007;28(3):150-4.

Strengths and Limitations

- The Danish national personal identification number allows linkages of several different registries, including a cause-of-death registry. Therefore, sudden cardiac death occurring in the community can be identified.
- Linkage to hospital diagnoses will result in reliable ascertainment of hospitalised acute myocardial infarction (AMI) events. Use of both hospital discharge diagnoses and hospital outpatient diagnoses can provide a reliable but incomplete ascertainment of potential arrhythmia events.
- The prescription registry covers dispensings of reimbursed prescriptions.
- There is an extensive track record of research in general epidemiology and pharmacoepidemiology, including indications and endpoints relevant to this PASS.
- Overall, uptake of new medications in Nordic countries tends to be slow.