

Protocol for observational studies based on existing data

Document Number:	c02330001-03
BI Study Number:	1222.54
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):	Boehringer Ingelheim International GmbH
Joint PASS:	No
Date:	28 October 2016

Page 1 of 69

Proprietary confidential information

© 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved.

This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission

Additional Information

Research question and objectives:	<ul style="list-style-type: none"> • 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 • Secondly, 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:	Cristina Rebordosa, PhD Senior Research Epidemiologist RTI Health Solutions Trav. Gracia 56, Atico 1 08006 Barcelona, Spain
Marketing authorisation holder(s):	Boehringer Ingelheim International GmbH Binger Str. 173 55216 Ingelheim
MAH contact person:	[REDACTED]
EU-QPPV:	[REDACTED]
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically

1. TABLE OF CONTENT

TITLE PAGE	1
1. TABLE OF CONTENT	3
2. LIST OF ABBREVIATIONS.....	5
3. RESPONSIBLE PARTIES.....	7
4. ABSTRACT.....	8
5. AMENDMENTS AND UPDATES.....	12
6. MILESTONES.....	15
7. RATIONALE AND BACKGROUND.....	16
8. RESEARCH QUESTION AND OBJECTIVES	17
9. RESEARCH METHODS	18
9.1 STUDY DESIGN.....	18
9.2 SETTING.....	18
9.3 VARIABLES	20
9.3.1 Exposures	20
9.3.1.1 Definition of new use.....	20
9.3.1.2 Follow-up.....	20
9.3.1.2.1 Exposure definition.....	21
9.3.2 Outcomes.....	22
9.3.2.1 Primary outcomes	22
9.3.2.1.1 Case ascertainment	22
9.3.2.1.2 Review of automated longitudinal health profiles.....	23
9.3.2.2 Secondary outcomes	23
9.3.2.3 Further outcomes	23
9.3.3 Covariates.....	23
9.3.3.1 Medical characteristics at baseline.....	24
9.3.3.1.1 Severity of COPD	24
9.3.3.1.2 Definition of COPD Severity.....	25
9.3.3.2 Other Characteristics.....	28
9.4 DATA SOURCE.....	28
9.4.1 Denmark.....	29
9.4.2 Planned data source summary	29
9.5 STUDY SIZE	30
9.6 DATA MANAGEMENT.....	32

9.7	DATA ANALYSIS	33
9.7.1	Main analysis.....	33
9.7.1.1	Description of cohort characteristics	33
9.7.1.2	Characteristics of follow-up.....	34
9.7.1.3	Safety endpoints.....	34
9.7.2	Further analysis	36
9.7.2.1	Sensitivity analyses	36
9.8	QUALITY CONTROL	36
9.9	LIMITATIONS OF THE RESEARCH METHODS.....	36
9.10	OTHER ASPECTS	37
9.10.1	Study size limitations	37
9.10.2	Study standards	37
9.10.3	Bias and confounding.....	38
9.11	SUBJECTS.....	38
9.11.1	Identification of COPD	38
9.11.2	Study cohorts.....	39
9.11.3	Inclusion criteria.....	40
10.	PROTECTION OF HUMAN SUBJECTS	41
11.	MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS.....	42
12.	PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS	43
13.	REFERENCES	44
13.1	PUBLISHED REFERENCES.....	44
13.2	UNPUBLISHED REFERENCES.....	49
Annex 1.	List of stand-alone documents	50
Annex 2.	ENCePP checklist for study protocols.....	51
Annex 3.	Evaluation of COPD severity in automated health databases.....	59
Annex 4.	ATC codes for selected respiratory medications	61
Annex 5.	Codes for comorbidities and other medications	63
Annex 6.	Data source descriptions from feasibility report, 1 November 2013.....	67

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

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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:

Cristina Rebordosa, PhD.
Senior Research Epidemiologist
RTI Health Solutions
Barcelona, Spain

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

Patricia Tennis, formerly of RTI Health Solutions, currently retired
Jordi Castellsague, RTI Health Solutions
Alicia Gilsean, RTI Health Solutions
Kristina Laugesen, Aarhus University Hospital
Morten Olsen, Aarhus University Hospital

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:	<p>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.</p> <p>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.</p> <p>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.</p>		

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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
Research question and objectives:	<p>Primary objectives:</p> <ul style="list-style-type: none"> 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 <p>Secondary objective:</p> <ul style="list-style-type: none"> 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.		

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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
Variables:	<p>Primary outcomes in new users</p> <ul style="list-style-type: none"> • 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 <p>Exposures of interest are (1) new use of olodaterol and (2) new use of any other LABA.</p> <p>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.</p>		
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.		

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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
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:	<ul style="list-style-type: none"> ● Start of data collection (i.e., start of data extraction) for final report: Q1 2020 ● End of data collection (i.e., date final analytic data set is available) for final report: Q3 2020 ● Progress report(s): Q3 2017, Q3 2018, and Q3 2019 ● Registration in the EU PAS register: after regulatory endorsement of the protocol ● Final report of study results: Q3 2020 		

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.

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	30 Sep 2014	6	Update of milestones	Delay in finalisation of protocol to respond to regulatory authority review
2	30 Sep 2014	9.3.3 9.7.1.1 9.7.1.3	Clarification of handling of missing data	Response to regulatory review
3	30 Sep 2014	9.5	Clarification of expected study statistical precision for outcome effect measures	Response to regulatory review
4	30 Sep 2014	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	28 Oct 2016	9.1 , 9.3 , 9.11 , and across the protocol	Clarified study medications	Clarified that olodaterol includes olodaterol monotherapy and fixed-dose combinations
6	28 Oct 2016	3	Updated list	Previous lead author has retired; added investigator from Denmark
7	28 Oct 2016	6	Updated milestones	Clarified start and end of data collection, as applied to the analysis of secondary databases, and timing for progress reports
8	28 Oct 2016	9.1	Clarified study period	To differentiate from study milestones, clarified study period and look-back period

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

9	28 Oct 2016	9.3.3	Updated COPD severity definition	To better align with COPD guidelines
10	28 Oct 2016	9.4.1	Deleted Danish General Practice Database (DAMD) as a data source	No longer available for research
11	28 Oct 2016	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	28 Oct 2016	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	28 Oct 2016	9.7.2	Added stratified analysis by “type of COPD treatment initiated” as a potential sensitivity analysis	To provide risk estimates among subgroups of patients initiating LABA or LABA/LAMA

6. MILESTONES

Milestone	Planned Date
Start of data collection (date from which data extraction starts) ¹ :	Q1 2020 ²
End of data collection (date from which analytic set is completely available) ¹ :	Q3 2020
Progress report(s) ¹ :	Q3 2017 Q3 2018 Q3 2019
Registration in the EU PAS Register	After regulatory endorsement of the protocol
Final report of study results:	Q3 2020

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

- Definitions of start and end of data collection and timing of the progress reports are based on definitions in the European Medicines Agency's *Guideline on Good Pharmacovigilance Practices (GVP), Module VIII – Post-authorisation Safety Studies (Rev 2)*. 4 August 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed 03 October 2016.
- Date takes into account launch dates and lag time of approximately 1 year in the data source. Launch was Q1 2014 in Denmark; thus, with a 1-year lag, data for this study will be available from Q1 2014 until approximately Q1 2019.

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 the 12 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:

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

 Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- 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

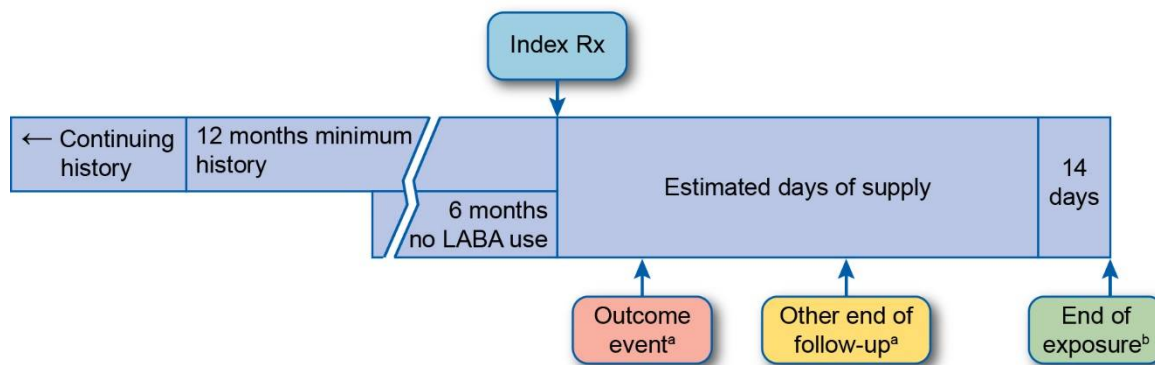
A new user will be defined as a patient with a diagnosis of COPD who receives a first dispensing for a study LABA during the study period and no prescriptions for any LABA in the 6 months prior to the first dispensing for LABA during the study period. The LABA initiated at cohort entry will be referred 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.

9.3.2.3 Further outcomes

None.

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	4 3	C	D	≥ 2 without hospitalisation or > 1 hospitalisation	Risk Exacerbation history
	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: <ul style="list-style-type: none"> • Hospitalisation for COPD² • Recorded diagnosis of pneumonia² • Second course of antibiotics for respiratory tract infections² • Second course of systemic corticosteroids for the treatment of COPD exacerbation² • 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: <ul style="list-style-type: none"> • Dispensed oxygen therapy^{1,2} • Dispensed nebuliser therapy^{1,2} • Diagnosis of emphysema at any time before the index date²

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 prescriptions ² (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 tachycardia, 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 RTI Health Solutions 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 RTI Health Solutions, who will develop the report. RTI Health Solutions will follow quality-control procedures regarding transfer of data.

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

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

The extent of missing data will be evaluated and described. 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 = IR_E / IR_C , where IR_E represents the incidence rate from the olodaterol cohort and IR_C 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) ($\geq 1,000$), 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.

9.7.2 Further analysis

9.7.2.1 Sensitivity analyses

Calculation of exposure time at risk and ascertainment of associated outcomes will be varied by increasing the time after each dispensing to 30 days and 60 days after the expiration of the estimated days supplied.

Assessment of the impact of individuals with history of the outcomes of interest in the two exposure groups will be derived by excluding individuals with history of arrhythmia or AMI.

Depending on the person-years of exposure accrued, calculation of IRRs will also be performed stratifying by type of COPD treatment initiated (i.e., LABA treatment alone or LABA treatment in combination with other LAMA treatment).

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 RTI Health Solutions is a research unit. Such audits at RTI Health Solutions will be conducted by the Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures. 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.

RTI Health Solutions will follow quality-control procedures for report generation, including senior review by an expert other than the author.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Existing population-based data are very useful for evaluating research questions about real-world clinical practice because of the diversity of patients and medical practices represented therein. However, the results must be interpreted with caution because 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 FEV₁ (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]

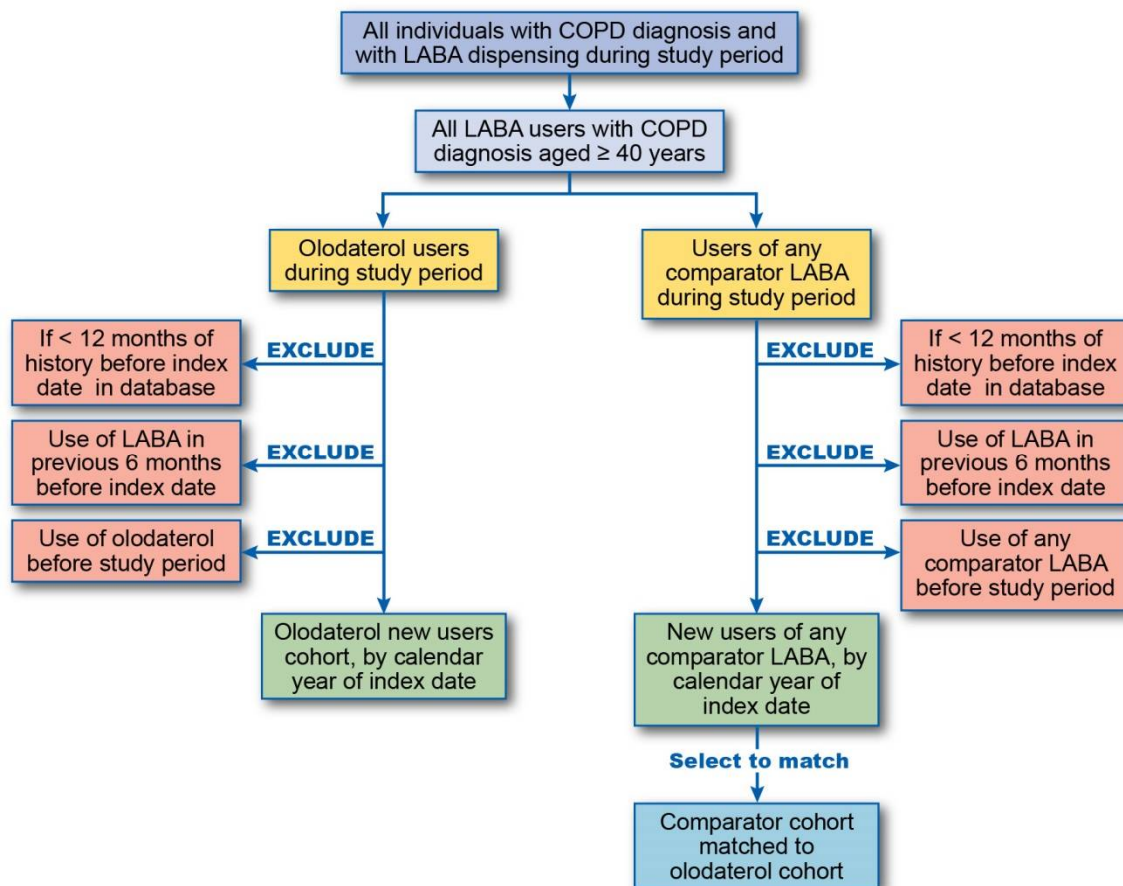
9.11.2 Study cohorts

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

- P04-09631 Garcia-Rodriguez LA, Varas-Lorenzo C, Maguire A, Gonzalez-Perez A. Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. *Circulation*. 2004 Jun 22;109(24):3000-6.
- P07-09136 Curkendall SM, Lanes S, de Luise C, Stang MR, Jones JK, She D, et al. Chronic obstructive pulmonary disease severity and cardiovascular outcomes. *Eur J Epidemiol*. 2006;21(11):803-13.
- P09-04948 Ogale SS, Lee TA, Au DH, Boudreau DM, Sullivan SD. Cardiovascular events associated with ipratropium bromide in COPD. *Chest*. 2010 Jan;137(1):13-9.
- P09-14650 Varas-Lorenzo C, Castellsague J, Stang MR, Perez-Gutthann S, Aguado J, Rodriguez LA. The use of selective cyclooxygenase-2 inhibitors and the risk of acute myocardial infarction in Saskatchewan, Canada. *Pharmacoepidemiol Drug Saf*. 2009 Nov;18(11):1016-25.
- P09-14662 Choma NN, Griffin MR, Huang RL, Mitchel EF, Jr., Kaltenbach LA, Gideon P, et al. An algorithm to identify incident myocardial infarction using Medicaid data. *Pharmacoepidemiol Drug Saf*. 2009 Nov;18(11):1064-71.
- P10-05107 Ray WA, Varas-Lorenzo C, Chung CP, Castellsague J, Murray KT, Stein CM, et al. Cardiovascular risks of nonsteroidal antiinflammatory drugs in patients after hospitalization for serious coronary heart disease. *Circ Cardiovasc Qual Outcomes*. 2009 May;2(3):155-63.
- P11-08175 Schmidt M, Christiansen CF, Mehnert F, Rothman KJ, Sorensen HT. Non-steroidal anti-inflammatory drug use and risk of atrial fibrillation or flutter: population based case-control study. *BMJ*. 2011;343:d3450.
- P11-13226 Verhamme KM, Afonso AS, van Noord C, Haag MD, Koudstaal PJ, Brusselle GG, et al. Tiotropium Handihaler and the risk of cardio- or cerebrovascular events and mortality in patients with COPD. *Pulm Pharmacol Ther*. 2012 Feb;25(1):19-26.
- P12-08895 Rassen JA, Glynn RJ, Rothman KJ, Setoguchi S, Schneeweiss S. Applying propensity scores estimated in a full cohort to adjust for confounding in subgroup analyses. *Pharmacoepidemiol Drug Saf*. 2012 Jul;21(7):697-709.

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- P12-09395 Wilchesky M, Ernst P, Brophy JM, Platt RW, Suissa S. Bronchodilator use and the risk of arrhythmia in COPD: part 1: Saskatchewan cohort study. *Chest*. 2012 Aug;142(2):298-304.
- P12-09396 Wilchesky M, Ernst P, Brophy JM, Platt RW, Suissa S. Bronchodilator use and the risk of arrhythmia in COPD: part 2: reassessment in the larger Quebec cohort. *Chest*. 2012 Aug;142(2):305-11.
- P12-14293 Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax*. 2012 Nov;67(11):957-63.
- P13-02399 GOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2013. Global Initiative for Chronic Obstructive Lung Disease; 2013. Available at: website: goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html. Accessed 17 October 2013.
- P16-00121 GOLD. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2016. Available at: website: <http://goldcopd.org/global-strategy-diagnosis-management-prevention-copd-2016/>. Accessed 10 June 2016.
- R06-4117 Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J*. 2006 Sep;28(3):523-32.
- R07-2623 Sidney S, Sorel M, Quesenberry CP, Jr., DeLuise C, Lanes S, Eisner MD. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest*. 2005 Oct;128(4):2068-75.
- R08-1492 Soriano JB, Maier WC, Visick G, Pride NB. Validation of general practitioner-diagnosed COPD in the UK General Practice Research Database. *Eur J Epidemiol*. 2001;17(12):1075-80.
- R09-0579 Curkendall SM, DeLuise C, Jones JK, Lanes S, Stang MR, Goehring E, Jr., et al. Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. *Ann Epidemiol*. 2006 Jan;16(1):63-70.
- R09-2531 WHO. The global burden of disease: 2004 update. Table 7. Geneva: World Health Organization, Department of Health Statistics and Informatics; 2008. Available at: website: who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. Accessed 14 November 2013.

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- R10-0421 Ruigomez A, Johansson S, Wallander MA, Rodriguez LA. Incidence of chronic atrial fibrillation in general practice and its treatment pattern. *J Clin Epidemiol*. 2002 Apr;55(4):358-63.
- R10-0756 Gage BF, Boechler M, Doggette AL, Fortune G, Flaker GC, Rich MW, et al. Adverse outcomes and predictors of underuse of antithrombotic therapy in medicare beneficiaries with chronic atrial fibrillation. *Stroke*. 2000 Apr;31(4):822-7.
- R10-1239 Greenland S, Rothman KJ. Introduction to stratified analysis. In: Rothman KJ, Greenland S, Lash TL, editors. *Modern epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 258-82.
- R11-2259 ICH. Technical requirements for registration of pharmaceuticals for human use. Pharmacovigilance planning. E2E. International Conference on Harmonisation; November 2004 2004. Available at: website: ich.org/products/guidelines/efficacy/efficacy-single/article/pharmacovigilance-planning.html. Accessed 26 July 2012.
- R11-2266 Hammad TA, McAdams MA, Feight A, Iyasu S, Dal Pan GJ. Determining the predictive value of Read/OXMIS codes to identify incident acute myocardial infarction in the General Practice Research Database. *Pharmacoepidemiol Drug Saf*. 2008 Dec;17(12):1197-201.
- R11-4316 Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *Am Heart J*. 2004 Jul;148(1):99-104.
- R11-4318 ISPE. Guidelines for good pharmacoepidemiology practices (GPP). International Society for Pharmacoepidemiology; April 2007 2007. Available website: pharmacoepi.org/resources/guidelines_08027.cfm. Accessed 01 March 2013.
- R11-4902 STROBE. STROBE checklist. Strengthening the Reporting of Observational Studies in Epidemiology; 2007. Available at: website: strobe-statement.org/index.php?id=available-checklists. Accessed 01 March 2013.
- R12-3265 Hansen JG, Pedersen L, Overvad K, Omland O, Jensen HK, Sorensen HT. The Prevalence of chronic obstructive pulmonary disease among Danes aged 45-84 years: population-based study. *COPD*. 2008 Dec;5(6):347-52.

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- R12-3322 García Rodríguez LA, Wallander MA, Martin-Merino E, Johansson S. Heart failure, myocardial infarction, lung cancer and death in COPD patients: a UK primary care study. *Respir Med.* 2010 Nov;104(11):1691-9.
- R12-3324 Kornum JB, Svaerke C, Thomsen RW, Lange P, Sorensen HT. Chronic obstructive pulmonary disease and cancer risk: a Danish nationwide cohort study. *Respir Med.* 2012 Jun;106(6):845-52.
- R13-1391 de Abajo FJ, Rodriguez LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol.* 1999 Mar;47(3):307-13.
- R13-1392 Eisner MD, Omachi TA, Katz PP, Yelin EH, Iribarren C, Blanc PD. Measurement of COPD severity using a survey-based score: validation in a clinically and physiologically characterized cohort. *Chest.* 2010 Apr;137(4):846-51.
- R13-1396 Rothman KJ. Epishet--spreadsheets for the analysis of epidemiologic data. October 25, 2011, version. 2011. Available at: website: epidemiolog.net/studymat/. Accessed 14 February 2013.
- R13-1397 Shahi CN, Rathore SS, Wang Y, Thakur R, Wu WC, Lewis JM, et al. Quality of care among elderly patients hospitalized with unstable angina. *Am Heart J.* 2001 Aug;142(2):263-70.
- R13-1398 Huerta C, Lanes SF, Garcia Rodriguez LA. Respiratory medications and the risk of cardiac arrhythmias. *Epidemiology.* 2005 May;16(3):360-6.
- R13-1970 EMA. Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. European Medicines Agency; 22 June 2012. Available at: website: emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf. Accessed 8 January 2014.
- R13-5415 Danish Quality Unit of General Practice. Danish General Practice Database (DAMD). 2014. Available at: website: dak.e.dk/flx/english/dak_e_it/danish_general_practice_database_damd/. Accessed 31 January 2014.
- R13-5418 ICMJE. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. International Committee of Medical Journal Editors; August 2013. Available at: website: icmje.org/urm_main.html. Accessed 28 October 2013.

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- R13-5419 ENCePP. Guide on methodological standards in pharmacoepidemiology (revision 2). EMA/95098/2010 Rev.2. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; 18 June 2013. Available at: website: encepp.eu/standards_and_guidances/methodologicalGuide.shtml. Accessed 8 January 2014.
- R13-5420 ENCePP. ENCePP checklist for study protocols (revision 2). European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; 14 January 2013. Available at: website: encepp.eu/standards_and_guidances/checkListProtocols.shtml. Accessed 8 January 2014.
- R14-0354 ENCePP. EU PAS Register. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; 7 January 2014. Available at: website: encepp.eu/encepp_studies/indexRegister.shtml. Accessed 8 January 2014.
- 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.
- R14-0359 Thomsen RW, Lange P, Hellquist B, Frausing E, Bartels PD, Krog BR, et al. Validity and underrecording of diagnosis of COPD in the Danish National Patient Registry. *Respir Med*. 2011 Jul;105(7):1063-8.
- R16-2604 Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014 Aug;29(8):541-9.
- R16-4007 Girman CJ, Gokhale M, Kou TD, Brodovicz KG, Wyss R, Sturmer T. Assessing the impact of propensity score estimation and implementation on covariate balance and confounding control within and across important subgroups in comparative effectiveness research. *Med Care*. 2014 Mar;52(3):280-7.
- R16-4611 EMA. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (Rev 2). European Medicines Agency; 04 August 2016. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed 06 August 2016.

13.2 UNPUBLISHED REFERENCES

None

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.2 End of data collection ²	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.3 Study progress report(s)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.4 Interim progress report(s)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.1.5 Registration in the EU PAS register	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.6 Final report of study results	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	9.1, 9.7

Comments:

--

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4, 9.11
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1, 9.11
4.2.2 Age and sex?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.11
4.2.3 Country of origin?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4, 9.11
4.2.4 Disease/indication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.11
4.2.5 Duration of follow-up?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.11

Comments:

--

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

<u>Section 5: Exposure definition and measurement</u>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.1
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.1

Comments:

--

<u>Section 6: Outcome definition and measurement</u>	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.2

Comments:

--

<u>Section 7: Bias</u>	Yes	No	N/A	Section Number
7.1 Does the protocol describe how confounding will be addressed in the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.10.3
7.1.1. Does the protocol address confounding by indication if applicable?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.10.3
7.2 Does the protocol address:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.10.3

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

<u>Section 7: Bias</u>	Yes	No	N/A	Section Number
7.2.1. Selection biases (e.g. healthy user bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.10.3
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.10.3
7.3 Does the protocol address the validity of the study covariates?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.10.3

Comments:

--

<u>Section 8: Effect modification</u>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.2.1, 9.10.3

Comments:

Sensitivity analyses will exclude individuals with history of the outcomes.

<u>Section 9: Data sources</u>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
9.1.3 Covariates?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

<u>Section 9: Data sources</u>	Yes	No	N/A	Section Number
Activities (MedDRA))				
9.3.3 Covariates?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.4

Comments:

--

<u>Section 10: Analysis plan</u>	Yes	No	N/A	Section Number
10.1 Is the choice of statistical techniques described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.1
10.2 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.1
10.3 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.1
10.4 Does the plan describe methods for adjusting for confounding?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.1
10.5 Does the plan describe methods for handling missing data?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.1
10.6 Is sample size and/or statistical power estimated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5

Comments:

--

<u>Section 11: Data management and quality control</u>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6
11.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.8
11.3 Is there a system in place for independent review of study results?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Comments:

<p>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.</p>

<u>Section 12: Limitations</u>	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.10.3
12.1.2 Information bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	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)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.10.1

Comments:

--

<u>Section 13: Ethical issues</u>	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	10
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.10.2 , 10

Comments:

--

<u>Section 14: Amendments and deviations</u>	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5

Comments:

--

<u>Section 15: Plans for communication of study results</u>	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12

Comments:

Name of the main author of the protocol: Cristina Rebordosa

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]			
<p>With spirometry data, used GOLD criteria [P13-02399]</p> <p>Without spirometry, used methods of Curkendall, [P07-09136] Eisner, [R13-1392] and Soriano [R08-1492]</p>	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	<p>Severe:</p> <ul style="list-style-type: none"> • 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 <p>Very severe:</p> <ul style="list-style-type: none"> • Oxygen therapy, or • Scheduled for lung transplant
Saskatchewan Health, Canada [R09-0579]			
<p>Case-control study to find severity marker variables, using the following data:</p> <ul style="list-style-type: none"> • Pre-existing chronic conditions • Recent acute conditions • Recent high use of bronchodilators <p>Specific components of the above are detailed in the article's appendix</p>	Patients ranked into quintiles by likelihood of COPD hospitalisation, from conditional logistic regression model		<p>Factors in previous 180 days associated with severe COPD:</p> <ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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)

Protocol for observational studies based on existing data

BI Study Number 1222.54

c02330001-03

Proprietary confidential information © 2016 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

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.