PASS Information

Title	Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Common Study Protocol
Protocol version identifier	Version 2.2 (02 June 2015)
Date of last version of protocol	29 July 2014, version 2.1 (Version 2.0, 14 April 2014; Version 1.1, 19 April 2013)
EU PAS register number	Study will be registered prior to start of data collection.
Active substance	Aclidinium bromide (ATC code: R03BB05) Aclidinium bromide/formoterol fumarate dihydrate (ATC code: R03AL05)
Medicinal product	Eklira® Genuair®/Bretaris® Genuair® Duaklir® Genuair®/Brimica® Genuair®
Product reference	Eklira® Genuair®: H0002211 Bretaris® Genuair®: H0002641 Duaklir® Genuair®: H0003745 Brimica® Genuair®: H0003896
Procedure number	Eklira® Genuair®: EMEA/H/C/002211 Bretaris® Genuair®: EMEA/H/C/002641 Duaklir® Genuair®: EMEA/H/C/003745 Brimica® Genuair®: EMEA/H/C/003896
Marketing authorisation holder(s)	AstraZeneca AB
Joint PASS	No
Research question and objectives	The overall objective of this PASS is to evaluate the potential cardiovascular safety concerns and all-cause mortality described in the risk management plan for aclidinium bromide, through sequential, nested case-control studies for each endpoint of interest. Specific objectives are as follows: ▪ To compare the risk of congestive heart failure (CHF); acute myocardial infarction (AMI), including community coronary heart disease (CHD) death; stroke; and all-cause mortality in patients with COPD initiating treatment with aclidinium bromide (monotherapy; concomitant with formoterol not in fixed-dose combination; and fixed-dose combination with formoterol, when available) and other inhaled COPD medications with the risk in patients with COPD initiating treatment with LABAs. ▪ To compare the risk of congestive heart failure, acute myocardial infarction, stroke, and all-cause mortality in patients with COPD initiating treatment with aclidinium bromide (monotherapy; concomitant with formoterol not in fixed-dose combination; and fixed-dose combination with formoterol, when available) with the risk in patients with COPD initiating other inhaled treatments for COPD. ▪ To evaluate the effect of dose and duration of each of the study medications on the risk of each individual endpoint. When the fixed-dose combination of aclidinium/formoterol becomes available, new users will be included in the cohort for evaluation. A

	new additional endpoint of cardiac arrhythmias is planned to be evaluated for this cohort.
Country(-ies) of study	United Kingdom; other country(ies) to be determined
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Approval Page—RTI Health Solutions

Project Title: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints, Common Study Protocol, Version 2.2

Protocol ID Number: M/34273/44

Authors	Cristina Varas-Lorenzo, MD, PhD; Jordi Castellsague, MD, MPH; Susana Perez-Gutthann, MD, PhD (RTI Health Solutions)
Version Date:	02 Jun 2015

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19 NOV 2015

Cristina Varas-Lorenzo, MD, PhD
Director, Epidemiology

Date

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19 NOV 2015

Susana Perez-Gutthann MD, PhD
Vice-President, Global Head Epidemiology

Date

Note: Additional research teams may participate based on the actual use of aclidinium in countries with databases.

Approval Page—AstraZeneca AB

Project Title: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints, Common Study Protocol, Version 2.2

Protocol ID Number: M/34273/44

Authors	Cristina Varas-Lorenzo, MD, PhD; Jordi Castellsague, MD, MPH; Susana Perez-Gutthann, MD, PhD (RTI Health Solutions)
Version Date:	02 Jun 2015

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3/ Dec/ 2015

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3 DEC, 2015

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Date

The protocol Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Common Study Protocol, Version 2.1, was approved as part of the granted marketing authorization of fixed-dose combination Duaklir Genuair as a new medicinal product for human use by the European Medicines Agency in November 2014. The current amendment, Version 2.2, clarifies AstraZeneca as the new MAH.

1 Table of Contents

List of Tables

List of Figures

2 List of Abbreviations

/	as in medication 1/medication 2, indicates a fixed-dose combination
+	as in medication 1+medication 2, indicates concomitant use, not in a fixed-dose combination
ACEI	angiotensin-converting-enzyme inhibitor
AMI	acute myocardial infarction
ARB	angiotensin II receptor blockers
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CABG	coronary artery bypass graft
CAT	COPD Assessment Test
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CT	computed tomography
CVD	cerebrovascular disease
DDD	defined daily dose
DUS	drug utilisation study
ECG	electrocardiogram
EMA	European Medicines Agency
GOLD	Global Initiative for Obstructive Lung disease
GP	general practitioner
GPRD	General Practice Research Database
HES	Hospital Episode Statistics
HIV	human immunodeficiency virus
HR	hazard ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPCI	Integrated Primary Care Information
IRB	institutional review board
ISAC	Independent Scientific Advisory Committee
ISPE	International Society for Pharmacoepidemiology
LA	long-acting
LABA	inhaled long-acting beta$_2$-agonist
LAMA	long-acting anticholinergic; also long-acting muscarinic antagonist
MHRA	Medicines and Healthcare Products Regulatory Agency
NMR	nuclear magnetic resonance (image)
ONS	Office for National Statistics

PASS	post-authorisation safety study
PPV	positive predictive value
PSUR	Periodic Safety Update Report
QRISK	tool that estimates the risk of a person developing cardiovascular disease risk over the next 10 years
RMP	risk management plan
SA	short-acting
SES	socioeconomic status
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SVA	serious ventricular arrhythmias
THIN	The Health Improvement Network
UK	United Kingdom
US	United States
WHO	World Health Organization

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Note: Additional research teams may participate based on the actual use of aclidinium in countries with databases.

4 Abstract

Title

Aclidinium Bromide Post-Authorisation Safety Cohort Study to Evaluate the Risk of Cardiovascular Endpoints: Study Protocol, Version 2.2, 02 Jun 2015

Cristina Varas-Lorenzo, MD, PhD; RTI Health Solutions; Barcelona, Spain

Rationale and Background

Aclidinium bromide is a new, long-acting and potent antagonist of lung M3 receptors, antagonising the bronchoconstrictive response of acetylcholine and leading to smooth muscle relaxation. The proposed indication for aclidinium bromide is maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

This common study protocol describes the study design and methods to conduct a post-authorisation safety study (PASS) to assess the potential cardiovascular safety concerns identified in the European risk management plan (RMP) for aclidinium bromide, further extended to include the fixed-dose combination of aclidinium bromide/formoterol fumarate.

A cohort of new users of aclidinium bromide and new users of other inhaled medications frequently used by patients with COPD will be ascertained. In addition, new users of the fixed-dose combination of aclidinium bromide/formoterol fumarate dihydrate (hereafter

aclidinium/formoterol) will be included in the cohort after this product is launched on the market.

Research Question and Objectives

The objective of this PASS is to evaluate the potential cardiovascular safety concerns and all-cause mortality described in the risk management plan for aclidinium bromide, through sequential, nested case-control studies for each endpoint of interest.

Specific aims are as follows:

- To compare the risk of congestive heart failure (CHF); acute myocardial infarction (AMI), including community coronary heart disease (CHD) death; stroke; and all-cause mortality in patients with COPD initiating treatment with aclidinium bromide (monotherapy; concomitant with formoterol not in fixed-dose combination; and aclidinium/formoterol, when available) and other COPD medications with the risk in patients with COPD initiating treatment with LABAs.
- To compare the risk of congestive heart failure, acute myocardial infarction, stroke, and all-cause mortality in patients with COPD initiating treatment with aclidinium bromide (monotherapy; concomitant with formoterol not in fixed-dose combination; and aclidinium/formoterol, when available) with the risk in patients with COPD initiating other treatments for COPD.
- To evaluate the effect of dose and duration of each of the study medications on the risk of each individual endpoint.

When aclidinium/formoterol becomes available, new users will be included in the cohort for evaluation. A new additional endpoint of cardiac arrhythmias is planned to be evaluated for this cohort. Aclidinium/formoterol and other fixed-dose combination COPD treatments will be compared with each other and with LABAs.

Study Design

This is a population-based cohort of patients with diagnosed COPD initiating treatment with aclidinium bromide (monotherapy; concomitant with formoterol not in fixed-dose combination; and aclidinium/formoterol, when available) and other inhaled COPD treatments that will be identified from the selected data source. Four, sequential nested case-control studies will be conducted to compare the risk of each study endpoint (1) in new users of aclidinium bromide and of each of the other groups of COPD medications with the risk in users of LABAs and (2) between new users of aclidinium bromide and new users of each of the other groups of study medications.

An additional case-control study will evaluate the risk of cardiac arrhythmias in new users of aclidinium/formoterol when users of this combination product become available.

Population

The study will be conducted in patients aged 40 years or older diagnosed with COPD initiating treatment with aclidinium bromide or other inhaled COPD treatments. Patients must have at least 1 year of enrolment in the electronic database and to have not been prescribed the study medication of interest during the 6-months before the date of the first prescription for that specific study medication. Patients with life-threatening non-cardiovascular comorbidity (e.g., malignancy, HIV infection, other) will be excluded.

Databases

The plan is to conduct the study in a single population-based automated health database. Prior to this cardiovascular PASS, a DUS in two waves (DUS1 and DUS2) will be conducted in three different populations. Based on projected sales forecasts, the DUS could be implemented in the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK), the German Pharmacoepidemiological Research Database (GePaRD), and the national health databases of Denmark. The preferred population to implement the cardiovascular PASS is the CPRD in the UK.

Variables

Study Endpoints

The study endpoints are (1) mortality from all causes; (2) first-ever hospitalisation for heart failure; (3) hospitalisation for acute myocardial infarction (AMI), either non-fatal or fatal, including community (out-of-hospital) CHD deaths (hereafter, "AMI"); and (4) acute stroke, either non-fatal or fatal, including community (out-of-hospital) cerebrovascular disease (CVD) deaths (hereafter, "stroke"). If the direction and magnitude of the risk is similar across the individual components, a composite endpoint including acute myocardial infarction, stroke, and out-of-hospital CHD or cerebrovascular deaths will be evaluated. An additional endpoint of cardiac arrhythmias will be evaluated in the cohort of new users of aclidinium/formoterol.

Potential cases will be identified by general practitioner diagnosis, hospital discharge codes, and mortality data from national statistics. Validation of potential cases identified will be conducted by review of the computerised information for all cases and by requesting clinical information from general practitioners (GPs) for a sample of cases of study endpoints with a low positive predictive value from prior studies (e.g., heart failure). The index date for each study endpoint is defined as the date of hospitalisation for each endpoint.

Exposure Assessment

Exposure to each study medication will be classified according to the days' supply of the last prescription before the index date. Exposure will be classified as (1) current use, when the days' supply of the most recent prescription overlapped or ended within 7 days before the index date; recent use, when the days' supply of the most recent prescription ended during the 60 days before the current use period; and past use, when the days' supply of the most recent prescription ended before the recent use period. Daily dose of each study medication will be ascertained for the last prescription before the index date. Duration of current use of each medication of interest will be calculated as the time covered by consecutive prescriptions, allowing for a maximum gap in treatment (e.g., 60 days) between the estimated end of use of one prescription and the dispensing date of the following prescription.

Confounding and Risk Factors

The main potential confounding and risk factors are (1) demographic variables—age and sex; (2) lifestyle and socioeconomic variables—cigarette smoking, alcohol abuse/dependency, body mass index, socioeconomic status (Townsend Index of Multiple Deprivation in the United Kingdom [UK]); (3) utilisation of health services in the year

before the date of cohort entry—hospitalisations, GP visits, referrals to specialists, number of prescriptions received; (4) severity of COPD at the date of cohort entry; (5) history of cardiovascular disease and risk factors at any time before the date of cohort entry; and (6) concurrent use of respiratory and other medications at the index date.

Data Sources

Study variables including endpoints, exposures, and covariates will be ascertained in the final selected study database (i.e., the CPRD) according to the definitions and procedures provided in the section on variables.

Study Size

Sample size calculations have been performed to achieve a probability of 0.80 of detecting true risk ratios ranging from 1.5 to 3, assuming a ratio of unexposed (LABA) to exposed subjects of 4:1, a two-sided alpha level of 0.05, and a range of expected incidence rates of each study endpoint. Under these assumptions, the number of patients with COPD exposed to aclidinium bromide needed to detect a minimum risk ratio of 1.5 is 1,000 users of for all-cause mortality; between 3,200 and 5,600 for heart failure; between 8,400 and 15,400 for AMI; and 11,600 for stroke. Finally, with similar assumptions, the number of patients with COPD exposed to aclidinium/formoterol needed to detect a minimum risk ratio of 2 for cardiac arrhythmias would be between 3,000 and 12,000.

Data Analysis

Cohort Analysis

- Characterise the study cohort according to confounding and risk factors at the date of cohort entry.
- Estimate crude and age-and sex-standardised incidence rates and 95% confidence intervals (CIs) of each study endpoint in current users of each study medication.

Nested Case-Control Analysis

- Describe the distribution of cases and controls according to confounding and risk factors at the index date.
- Conduct conditional multiple logistic regression to estimate crude and adjusted risk ratios (RRs) and 95% CIs for each study endpoint except cardiac arrhythmias, comparing each exposure category (e.g., current use, recent use, past use) (1) between new users of aclidinium bromide (monotherapy, concomitant with formoterol but not in a fixed-dose product, and aclidinium/formoterol), tiotropium, other long-acting anticholinergic (LAMA) (i.e., glycopyrronium bromide, umeclidinium), LABA/inhaled corticosteroid, LABA/LAMA, and new users of LABAs (reference category) and (2) between new users of aclidinium bromide and new users of each of the other study medication groups.
- Conduct conditional multiple logistic regression to estimate crude and adjusted RRs and 95% CIs for arrhythmias, comparing each exposure category (e.g., current use, recent use, past use) (1) between new users of aclidinium/ formoterol, new users of other fixed-dose combination COPD treatments, and new

users of LABAs (reference category) and (2) between new users of aclidinium/formoterol and new users of each of the other fixed-dose combination of COPD treatment groups.

- Conduct stratified analysis to evaluate the risk in subgroups of patients with relevant characteristics (e.g., severity of COPD, prior history of cardiovascular disease).

Milestones

In 2012, Eklira/Bretaris Genuair was launched in the United Kingdom (UK). Monitoring of the number of users of aclidinium bromide in each database started in December 2013, and data collection for DUS1 is expected to start in 2015.

Launch of aclidinium/formoterol is expected to occur in the UK in January 2015. Monitoring of the number of users of the combination product in each database and data collection is expected to start in 2016.

For each study endpoint, data collection will start when the target number of new users of aclidinium described in the Study Size section is reached. Based on sales forecasts and preliminary user data in the CPRD, the expected dates for the first reports for aclidinium monotherapy are as follows: mortality study, first semester 2017; interim descriptive analysis on stroke and AMI and heart failure study, first semester 2018; stroke study, first semester 2019; and AMI study, first semester 2020.

Study progress reports will be submitted at 6-month intervals, with the Periodic Safety Update Reports.

5 Amendments and Updates

Version Number	Date	Section of Study Protocol	Amendment or Update	Reason
2.2	02 Jun 2015	Across protocol	Updates to reflect MAH transfer from Almirall to AstraZeneca for Eklira®, Bretaris®, and Duaklir® Genuair®	MAH transfer from Almirall to AstraZeneca
2.1	29 July 2014	Analysis, effect of dose	Included the description of the daily prescribed dose at the index date of users of concomitant aclidinium and formoterol, stratified by the dose of formoterol	Proposed by PRAC
2.0	14 April 2014	Abstract, Research Question and Objectives, Study Design, Setting	Definition of new user period has been reduced from 1 year to 6 months.	To allow capture of a larger number of new users
2.0	14 April 2014	Milestones	Timelines have been adjusted	Number of aclidinium users in the CPRD was lower than expected
2.0	14 April 2014	Throughout protocol	Add/update design features, variables, analysis, and report to evaluate aclidinium also in a fixed-dose combination with formoterol; incorporated an additional second incidence analysis of the endpoints of interest and a case-control analysis to evaluate the risk of cardiac arrhythmias, focused on the evaluation of aclidinium/formoterol Format according to EMA template	To integrate the cardiovascular safety evaluation of aclidinium/formoterol
2.0	14 April 2014	Variables/ Exposure	Pharmacologic treatment for COPD	Guideline update

6 Milestones and Timeline

Milestone	Actual or Anticipated Date[a]
Launch of aclidinium bromide in the United Kingdom (UK)	October 2012
Common protocol, version 1.1, 19 April 2013 (monotherapy) endorsed by EMA	July 11, 2013 (actual) by EMA
Start to monitor number of users in the UK	December 2013
EU PAS registration	Prior to start of data collection
Start of data collection in the UK (monotherapy)[b]	
Drug utilisation study baseline	Second semester 2015
All-cause mortality study	Second semester 2016
Heart failure study	First semester 2017
Stroke and AMI incidence rate descriptive analysis	First semester 2017
Stroke study	First semester 2018
AMI study	First semester 2019
End of data collection[c]	2-3 months following start of data collection
Study progress report	6-month intervals, with PSURs
Final report of study results (monotherapy)	▪ First semester 2016: DUS baseline ▪ First semester 2017 DUS follow-up ▪ First semester 2017: Mortality study ▪ First semester 2018: Interim descriptive analysis on stroke and AMI ▪ First semester 2018: Heart failure study[d] ▪ First semester 2019: Stroke study ▪ First semester 2020: AMI study
Launch of aclidinium/formoterol (UK)	Expected January 2015

AMI = acute myocardial infarction; CPRD = Clinical Practice Research Datalink; EMA = European Medicines Agency; PSURs = Periodic Safety Update Reports; UK = United Kingdom.

[a] All data-driven timelines are based on Almirall sales forecast figures and may change based on actual uptake of the medication.

[b] The date from which data extraction starts.

[c] The date from which the analytical dataset is completely available.

[d] Requires partial source record validation.

Note: Contracts between the sponsor and research organization(s) and approvals by data protection/data custodian/ethics/scientific review bodies are pending. Timelines may be impacted by duration of contract reviews, approvals of mentioned bodies, and availability of data and staff at research institutions once contracts and approvals are finalized.

7 Rationale and Background

Awareness of the burden of chronic obstructive pulmonary disease (COPD) has been raised worldwide. The World Health Organization[1] estimated that the European region had approximately 11.3 million patients with prevalent, symptomatic COPD. Worldwide, the estimated number of patients with COPD is 63.6 million. The overall pooled estimated prevalence of COPD from 37 studies was 9.8% (95% confidence interval [CI], 8.0%-12.1%) in men and 5.6% (95% CI, 4.4%-7.0%) in women.[2] Prevalence of COPD increases with increasing age, ranging from 3.1 per 100 people aged less than 40 years to 14.2 for those aged 65 years or older.[2] Cigarette smoking is the strongest (most commonly established) risk factor for COPD.

The major types of comorbid disease in patients with COPD are cardiovascular disease, osteoporosis, anxiety and depression, lung cancer, infections, metabolic syndrome, and diabetes.[3] The incidence of cardiovascular conditions in patients with COPD is about two times greater than that in individuals without COPD.[4,5]

Short- and long-acting inhaled anticholinergics (LAMAs) are considered both effective and safe for the management of COPD and are recommended treatment by international clinical guidelines.[6] Available short-acting inhaled anticholinergics are ipratropium bromide and oxitropium bromide. Tiotropium, glycopyrronium bromide and umeclidinium are the currently available long-acting inhaled anticholinergics.

A few studies have raised concerns about the cardiovascular safety of tiotropium and ipratropium bromide. However, the available information comparing the risk of cardiovascular events during the use of these agents in patients with COPD is difficult to evaluate. Clinical trials were not designed prospectively to evaluate the risk of cardiovascular outcomes and therefore were limited by potential misclassification of events and lack of adequate power to detect potential differences among treatments. The additional data provided by the 4-year Understanding the Potential Long-Term Impact of Tiotropium (UPLIFT) trial in patients with COPD randomised to tiotropium or placebo confirmed the lack of association between tiotropium and increased risk of either serious cardiovascular events (risk ratio [RR], 0.82; 95% CI, 0.72-0.94)[7] or serious cardiac events (RR, 0.83; 95% CI, 0.73-0.94).[8] Published population-based studies have reported inconsistent results, depending on the study design, endpoint evaluated, and reference group used.[9-14] In a study conducted using data from the Integrated Primary Care Information (IPCI) in the Netherlands, the adjusted RR of a composite cardiovascular endpoint (fatal and non-fatal stroke, myocardial infarction, heart failure, and arrhythmias) for tiotropium compared with current long-acting beta-agonists (LABAs) in patients with COPD was 0.89 (95% CI, 0.55-1.44).[14] In a cohort study of United States (US) veterans newly diagnosed with COPD, the adjusted hazard ratio [HR] of the composite endpoint (acute coronary syndrome, heart failure, and cardiac dysrhythmia) was 1.29 (95% CI, 1.21-1.38) for any use of anticholinergic drugs in the past year versus non-use of such drugs.[13] The use of composite endpoints, with different components in each of the two observational studies, limits further interpretation of the discrepancies noted between these studies.

A cardiovascular safety evaluation was performed in a cohort of patients registered in the United Kingdom (UK) general practices contributing to The Health Improvement

Network (THIN) database.[11] New users of tiotropium (n = 4,767) and LABAs (n = 6,073) were included in the cohort if patients were aged at least 40 years and did not have a diagnosis of asthma as their only respiratory illness. An increased risk of stroke (HR, 1.49; 95% CI, 0.91-2.45), angina (HR, 1.38; 95% CI, 0.88-2.16), and acute myocardial infarction (HR, 1.26; 95% CI, 0.72-2.21) was observed in new users of tiotropium compared with new users of LABAs. However, tiotropium was associated with a lower rate of total mortality and asthma exacerbations as recorded by the GP.

Aclidinium bromide is a new, kinetically selective, long-acting and potent muscarinic receptor antagonist whose relevant pharmacological effect is on lung M3 receptors, antagonising the bronchoconstrictive response of acetylcholine and leading to smooth muscle relaxation. The approved indication for aclidinium bromide is maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Cardiovascular safety and all-cause mortality are described as potential risks in the aclidinium risk management plan (RMP), version 2.3, dated 24 May 2012.

A post-authorisation safety study (PASS) will be conducted to assess the potential cardiovascular safety concerns described in the European risk management plan (RMP) for aclidinium bromide. Initially in the overall programme, a drug utilisation study (DUS) will cover aspects related to drug utilisation, off-label use, and identification of patient groups with missing information in the RMP—separate protocol.[15] As more patients increase the size of the cohort, we will evaluate whether the use of aclidinium bromide is associated with increased risk of all-cause mortality and cardiovascular events such as congestive heart failure (CHF); acute myocardial infarction, including out-of-hospital coronary heart disease (CHD) death ("AMI"); and stroke. The protocol for the Aclidinium Bromide Post-Authorisation Safety Cohort Study to Evaluate the Risk of Cardiovascular Endpoints: Study Protocol, Version 1.1, 19 April 2013, targeted the monotherapy compound was adopted by the European Medicines Agency in July 11, 2013.

In October 2013, Almirall submitted the EU RMP for the fixed-dose combination of aclidinium bromide/formoterol fumarate 400/12 µg (Duaklir®) delivered via the Genuair® inhaler (hereafter, aclidinium/formoterol). The proposed indication for this dual therapy is maintenance bronchodilator treatment for the relief of symptoms in adult patients with COPD. The safety concerns included in this RMP are the safety concerns identified in the RMP for aclidinium monotherapy. An additional potential cardiac risk is presented for aclidinium/formoterol due to the potential for β2-adrenergic drugs to produce cardiac arrhythmias. Therefore, Almirall proposed, as additional pharmacovigilance activities, to extend the current aclidinium PASS programme (DUS and safety endpoint study) to include aclidinium/formoterol. This extension will include characterisation of patients using aclidinium/formoterol in a second drug utilisation study (DUS 2), described in a separate protocol,[16] and evaluation of overall mortality and cardiovascular safety endpoints, including the additional endpoint of cardiac arrhythmia.

The study protocols developed for aclidinium monotherapy were amended to integrate the evaluation of new users of aclidinium/formoterol in the PASS programme. The design of the integrated aclidinium monotherapy and aclidinium/formoterol PASS studies will take into account the time difference in the availability of aclidinium as monotherapy (already launched in Europe) and the launch sequence and projected use by country for aclidinium/formoterol.

In the rest of the protocol, reference to aclidinium bromide includes aclidinium bromide as monotherapy, used either alone or concomitantly with other respiratory medications (including formoterol not in fixed-dose combination), but also to aclidinium/formoterol.

On 30 July 2014, Almirall entered an agreement with AstraZeneca to transfer the rights of Almirall's respiratory franchise, which includes aclidinium bromide. The transaction was completed on 01 November 2014. On 05 March 2015, the European Commission adopted the decision on the MAH transfer to AstraZeneca for Eklira®, Bretaris®, and Duaklir® Genuair®.

8 Research Question and Objectives

The objective of this study is to evaluate the cardiovascular safety and all-cause mortality of aclidinium bromide and other bronchodilators used in patients with COPD. Specific aims of the research are as follows:

- To compare the risk of congestive heart failure, acute myocardial infarction, stroke, and all-cause mortality in patients with COPD initiating treatment with aclidinium bromide (monotherapy; concomitant with formoterol not in fixed-dose combination; and aclidinium/formoterol, when available) and other COPD medications with the risk in patients with COPD initiating treatment with LABAs (formoterol, salmeterol, or indacaterol).
- To compare the risk of congestive heart failure, acute myocardial infarction, stroke, and all-cause mortality in patients with COPD initiating treatment with aclidinium bromide (monotherapy; concomitant with formoterol not in fixed-dose combination; and aclidinium/formoterol, when available) with the risk in patients initiating treatment with other COPD medications.
- To evaluate the effect of dose and duration of each of the study medications on the risk of each individual endpoint.
- To compare (1) the risk of cardiac arrhythmias in patients with COPD initiating treatment with aclidinium/formoterol and the risk in patients with COPD initiating treatment with other fixed-dose combination COPD treatments with the risk in users of LABA and (2) the risk of cardiac arrhythmias between users of aclidinium/formoterol and users of each of the other fixed-dose combination COPD treatments.

9 Research Methods

Observational (non-interventional) research methodology will be applied to accomplish the specific objectives listed above.

Automated health databases are commonly used for population-based studies designed to assess the use and effects of medications as used in clinical practice. They are a reliable source of information to estimate the risk of adverse effects associated with the use of medications. Information is collected prospectively and may include diagnoses made by general practitioners (GP), hospital discharge diagnoses, and details of prescriptions issued by the GP or dispensed in the pharmacy. The information recorded in databases provides a cost- and time-efficient opportunity to evaluate safety concerns

of new medications soon after their authorisation. Automated health databases have been used routinely and shown to be appropriate to evaluate cardiovascular safety endpoints and all-cause mortality in the general population and in patients with COPD. Many postmarketing safety assessment programmes, including regulatory drug safety studies for tiotropium and other respiratory medications have been conducted in health databases.

9.1 Study Design

A population-based cohort of patients with diagnosed COPD initiating treatment with aclidinium bromide (monotherapy; concomitant with formoterol not in fixed-dose combination; and aclidinium/formoterol, when available) or another COPD treatment will be identified from the selected data source.

The study is a *new-users design*, which allows characterisation of patients before the start of the exposure of interest and prevents bias caused by the inability to control for risk factors that may be modified by the exposure.[17] The new-user design also prevents the potential for survival bias due to underascertainment of events occurring at the beginning of treatment.

Following the initial cohort of new users identified for the DUS, a sequential research programme will be implemented as time progresses after launch of aclidinium bromide and more users are available. Sequential case-control analyses nested in a country-specific dynamic cohort will be performed to evaluate the association of the study exposures with each of the endpoints of interest. Potential databases initially selected for conducting the DUS are the Clinical Practice Research Datalink (CPRD) in the UK, the German Pharmacoepidemiological Research Database (GePaRD), and the national health databases of Denmark. Other European databases might be considered if the number of users is low in one or more of the initially planned databases. Large population US health care databases, i.e., commercial health insurers and/or Medicare, are a second option to expand the study population. However, the plan is that this CV PASS study will be conducted in only one database, and the CPRD is the initial candidate database.

For study size considerations (Section 9.5), the triggers for the different parts of this research programme are as follows:

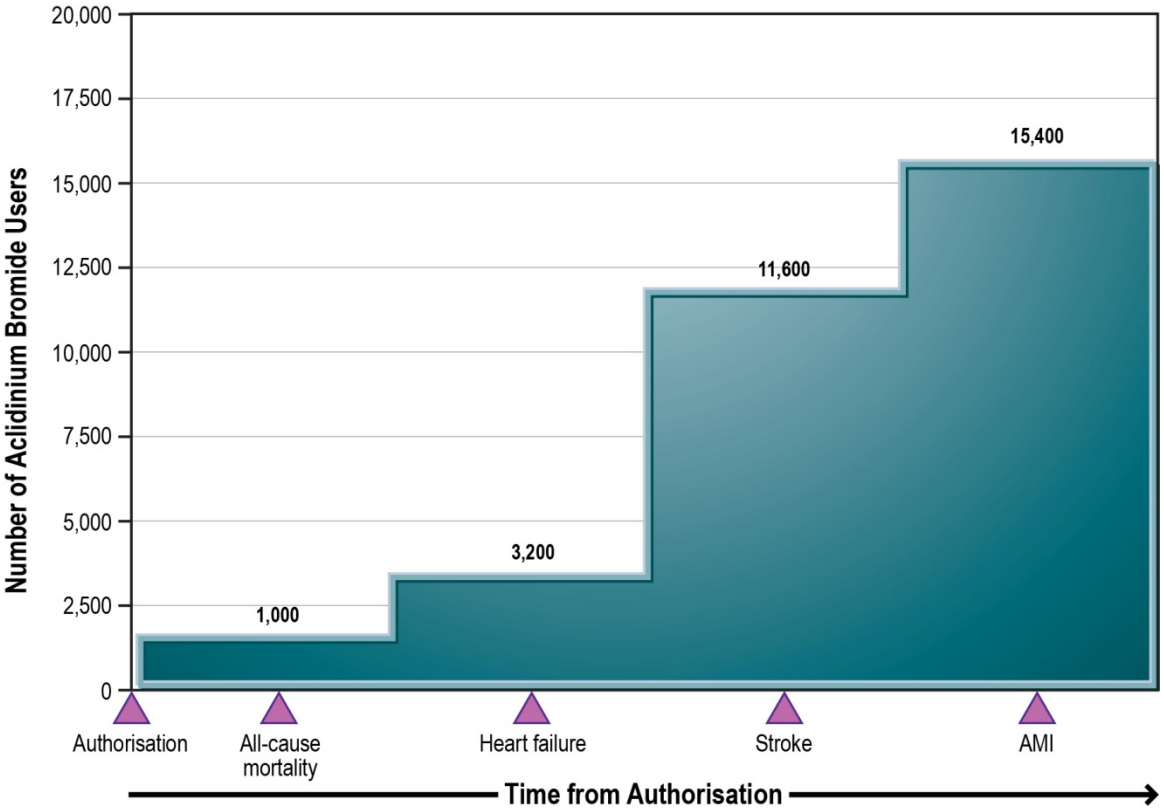
- After the first launch of aclidinium bromide in Europe, periodic monitoring of the number of users will be conducted in the three previously mentioned databases and in other populations covered by automated health care databases (e.g., Italy, Sweden), according to the launch sequence and projected use by country.
- When the number of users of aclidinium bromide (all users, all ages) reaches approximately 1,500 to 2,000 in each of the three finally selected databases, the first DUS (DUS1) will be initiated in the CPRD, GePaRD, and the Danish health databases.[15] Evaluation of the assumptions related to prescriptions and duration of use patterns will be conducted based on the results of the DUS and prior to the implementation of the cardiovascular safety study. A second DUS (DUS2) will be implemented when aclidinium/formoterol becomes available.[16]
- The first nested-case control analysis for the safety study will be performed to evaluate the effect of the study medications on all-cause mortality. This analysis will be performed when approximately 1,000 users of aclidinium bromide with

COPD and aged 40 years or older are available in the selected database (CPRD) and have contributed at least 1 year of follow-up.

- The second case-control study will be performed to estimate the risk of CHF, which is the most common cardiovascular endpoint. The study will be conducted when the number of users of aclidinium bromide with COPD and aged 40 years or older with at least 1 year of follow-up reaches approximately 3,200 in the selected database (CPRD). While conducting this nested case-control analysis, an additional interim descriptive analysis of the frequency of the other cardiovascular endpoints of interest (AMI and stroke) will be performed. Based on these results, study size will be recalculated if necessary.
- The third case-control study will evaluate the risk of stroke, and the fourth will evaluate the risk of AMI; these studies will be conducted after the number of users of aclidinium bromide with COPD and aged 40 years or older with at least 1 year of follow-up reaches approximately 11,600 to 15,400 in the selected database (CPRD). Around this time, it is expected that the database will capture users of aclidinium/formoterol; therefore, a second interim descriptive analysis of the frequency of heart failure and overall mortality will be performed. Based on these results, a potential update of the nested-case control analyses for these endpoints will be proposed in case the incidence rates vary.
- An additional case-control study will evaluate the risk of cardiac arrhythmias in users of aclidinium/formoterol or aclidinium concomitant with formoterol but not in a fixed-dose product. This case-control study will be implemented after DUS2 and the number of total users of aclidinium bromide with formoterol (aclidinium/formoterol or concomitant use) with COPD and aged 40 years or older with at least 1 year of follow-up reaches approximately 10,000 in the selected database (CPRD).

Figure 1 presents the sequence of these studies and the approximate number of new users of aclidinium bromide triggering each of the case-control studies (monotherapy) for a power of 80%. (Please see Section 9.5 for study size calculations).

Figure 1. Sequential Timing of Safety Studies by Approximate COPD Cohort Size (Aclidinium Bromide Monotherapy)



Evaluation of aclidinium/formoterol will be incorporated into the programme. Initially, two waves of the DUS (DUS1 and DUS2) have been proposed in a separate protocol to characterise users of aclidinium monotherapy and users of aclidinium/formoterol and to capture changes in the patterns of use of aclidinium bromide. Because it is expected that users of aclidinium/formoterol will start to be captured in 2017, the first planned case-control studies (mortality, heart failure, and stroke) will include aclidinium monotherapy or aclidinium in combination with formoterol not in fixed-dose combination, but the AMI case-control study will potentially also include users of aclidinium/formoterol.

9.1.1 Definition of New Users

Members of the study cohort will be new users of each of the study medications. A ***new user*** is defined as a patient who receives a first prescription or dispensing for aclidinium bromide or other COPD medication and has no previous prescription for that specific medication in the 6 months before that first prescription. For example, if the first study medication that a patient receives during the study period is tiotropium, that patient will enter the cohort of new users of tiotropium if the patient has not received any prescription for tiotropium in the previous 6 months, within the study period; however, the patient can have received treatment with any of the other study medications (e.g., LABAs). The date of the first prescription for a given medication during the study period will define the entry date for that individual new user. Note that new users of aclidinium/formoterol might have been users of aclidinium monotherapy or formoterol or both.

If sample size is sufficient (see Section 9.5 on study size), a sensitivity analysis will be conducted defining new users as those patients who have not been prescribed any of the study medications in the 6 months prior to the first prescription. Therefore, this analysis will exclude those users who enter the cohort after switching between study medications. The results of the DUS will provide information on the expected number of new users of any of the study medications.

9.1.2 Choice of Comparator Drugs

The GOLD guidelines[6] categorise severity of COPD based on the evaluation of four aspects of the disease separately: current level of symptoms, severity of spirometric abnormality, history of exacerbation, and presence of comorbidities. According to the GOLD guidelines, aclidinium bromide and the rest of the study medications are recommended for moderate to very severe COPD (category B, C, or D) (Figure 2). Aclidinium/formoterol and other LABA/LAMA combinations are alternative choices to initially recommended treatments (Table 1).

Figure 2. Model of Symptoms/Risk of Evaluation for COPD

Risk GOLD classification of airflow limitation				**Risk** Exacerbation history
4 3	**C**	**D**	**≥ 2**	
2 1	**A**	**B**	**≤ 1**	
	mMRC 0-1 CAT < 10	**mMRC ≥ 2 CAT ≥ 10**		

COPD Severity Categories

Severity category	Characteristics	Spirometric classification	Exacerbations per year	mMRC	CAT
A	Low risk, fewer symptoms	GOLD 1-2 (mild-moderate)	≤ 1	0-1	< 10
B	Low risk, more symptoms			≥ 2	≥ 10
C	High risk, fewer symptoms	GOLD 3-4 (severe-very severe	≥ 2	0-1	< 10
D	High risk, more symptoms			≥ 2	≥ 10

CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Obstructive Lung disease; mMRC = Modified British Medical Research Council questionnaire.

Source: Adapted from GOLD, 2014.[6]

Table 1. First-Choice Medications in the Initial Management of COPD According to European Clinical Guidelines

COPD Severity Category (See Figure 2)	First-Choice Medications
A	▪ Short-acting anticholinergic, prn, or ▪ Short-acting beta$_2$-agonist, prn
B	▪ Long-acting anticholinergic, or ▪ Long-acting beta$_2$-agonist
C	▪ Long-acting beta$_2$-agonist/inhaled corticosteroid, or ▪ Long-acting anti-cholinergic
D	▪ Long-acting beta$_2$-agonist/inhaled corticosteroid, or ▪ Long-acting anticholinergic

prn = as needed.

Note: Within a cell, medications are mentioned in alphabetic order, not necessarily by order of preference. See Annex 3 for Anatomical Therapeutic Chemical codes for medications of interest in this study.

Source: Adapted from GOLD, 2014.[6]

The risk of outcome events associated with the use of aclidinium bromide, tiotropium, other LAMAs, (i.e., glycopyrronium bromide, umeclidinium), LABA/inhaled corticosteroid (ICS), and LABA/LAMA will be compared with the risk associated with the use of LABAs. Therefore, each study medication will be compared with a common reference group, users of LABAs. New users of LABAs have been chosen as the reference group because according to COPD treatment guidelines they are recommended for the same initial level of COPD severity (category B) as long-acting anticholinergics. In addition, new users of LABAs have been the most frequently used reference group in published observational studies evaluating the cardiovascular safety of tiotropium.[10,11,14] Therefore, inclusion of new users of LABAs as the reference group will allow evaluation of the results of this study relative to results from some prior studies.

In addition, the risk of the study outcomes associated with aclidinium will be compared with the risk associated with each of the study medications: tiotropium, other LAMAs, LABA/ICS, and LABA/LAMA.

9.1.3 Definition of Index Prescription

The first captured prescription for aclidinium bromide and for each of the other study medications in the study period will be the study entry *index prescription*. Aclidinium bromide has been assigned an Anatomical Therapeutic Chemical (ATC) code of R03BB05, under the inhalant anticholinergic category (ATC R03BB). ATC codes for the other available long-acting inhaled anticholinergics and for the other study exposures of interest are included in Annex Table 3-1.

9.2 Setting

9.2.1 Study Cohort

The study cohort will be composed of patients aged 40 years or older who have previously been diagnosed with COPD and who are new users of aclidinium bromide (monotherapy; concomitant with formoterol not in fixed-dose combination; and aclidinium/formoterol) and new users of other COPD medication groups as follows:

- Tiotropium
- Other long-acting anticholinergic (LAMAs): glycopyrronium bromide, umeclidinium
- LABA: formoterol, salmeterol, indacaterol
- LABA/ICS (LABA in fixed-dose combinations with ICS): formoterol/budesonide, formoterol/beclometasone, formoterol/mometasone, formoterol/fluticasone, salmeterol/fluticasone, and vilanterol/fluticasone.
- LAMA/LABA (approved or under regulatory review or in development): glycopyrrolate/formoterol, glycopyrronium/indacaterol, tiotropium/olodaterol, umeclidinium/vilanterol

Any LAMA, LABA, LABA/ICS, or LAMA/LABA that may become available during the study period and captured in the databases will be incorporated into the above medication groups.

The cohort is restricted to subjects aged 40 years or older because of the low probability that subjects aged less than 40 years will have COPD.

9.2.1.1 Inclusion Criteria

Patients in the study will be required to meet the following criteria:

- Have at least 1 year of enrolment in the electronic database. In the CPRD, only patients with permanent registration status in "up to standard" participant general practices will be included in the cohort.
- Be aged 40 years or older.
- Have a recorded diagnosis of COPD.
- Have not been prescribed a study medication of interest during the 6 months before the date of the first prescription for that specific study medication.

9.2.1.2 Identification of Patients With COPD

Patients diagnosed with COPD will be identified by outpatient visits, hospitalisations, and procedures, as available. Diagnostic codes for COPD, chronic bronchitis, and emphysema, according the disease dictionary system being used in each database, will be used. Because the three initial databases proposed for the implementation of the DUS use the *International Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) for hospitalisation diagnoses, we provide in Table 2 the preliminary lists of ICD-10 diagnosis codes to be used to identify patients with COPD and other respiratory diseases using either primary or secondary hospital discharge codes. If the study is implemented as initially planned in the CPRD, which uses Read codes, ICD-10

codes will be mapped to Read codes through diagnosis descriptions used by the general practitioners (GPs) in the clinical practices. For the clinical practices linkable to the Hospital Episode Statistics (HES) data, the ICD-10 codes will be used to identify hospitalisations associated with COPD.

Table 2. Diagnosis Codes to Identify Patients With COPD

ICD-10 Code Description	ICD-10 Code
Other COPD	J44
Chronic obstructive pulmonary disease with acute lower respiratory infection	J44.0
Chronic obstructive pulmonary disease with acute exacerbation, unspecified	J44.1
Other specified chronic obstructive pulmonary disease	J44.8
Chronic obstructive pulmonary disease, unspecified	J44.9
Chronic bronchitis	J40-J42
Emphysema	J43

Validity of COPD Diagnostic Codes

The use of COPD-related diagnosis to identify patients with COPD in the CPRD has been shown to provide incidence rates of COPD similar to those obtained from morbidity surveys in the UK, whereas rates obtained from COPD diagnosis codes plus the use of a bronchodilator seem to overestimate the incidence of COPD.[18] Rates are even higher when the use of bronchodilator prescriptions alone is used to identify patients with COPD. COPD has been shown to be the indication for inhaled bronchodilators in less than about 2.5% of patients aged younger than 45 years and in 46% of those aged 75-84 years.[18]

The validity of diagnostic codes to identify patients with COPD has been studied. The positive predictive value (PPV) of clinical diagnostic Read codes for COPD recorded by general practitioners in the CPRD-registered general practices has been reported to be about 70%, with a sensitivity of 70.3% and a specificity of 87.7% versus the diagnosis of asthma.[19] These results are comparable to those from other databases with primary care information. In a study conducted in Ontario, the most sensitive definition of COPD was the one including one or more ambulatory claims and/or one or more hospitalisations for COPD, with a sensitivity of 85.0% and a specificity of 78.4%.[20]

For databases that do not have primary care diagnoses, the use of discharge diagnosis codes for hospitalisation for COPD will result in the identification of patients with more severe disease, although the specificity and the PPV are usually high. In the Danish National Patient Registry, the PPV for COPD discharge diagnoses was 92% (95% CI, 91%-93%).[21]

9.2.1.3 Exclusion Criteria

Patients with cancer or other serious, non-cardiovascular, life-threatening conditions or indicators of severe comorbidity will be excluded from the study cohort. These patients are likely to have shorter follow-up than the other patients. Cardiovascular events may be a consequence of these other illnesses (e.g., cardiac arrest in terminal illness) or have a non-atherosclerotic aetiology (cocaine abuse). In addition, information from some special medications used to treat these conditions in the hospital or other special settings might not be completely captured in databases. Therefore, subjects that will be potentially excluded are those with any of the diagnoses or conditions listed in Table 3 recorded in the database at any time before the date of cohort entry.

Table 3. Exclusion Conditions

Medical Condition	Definition	ICD-10 Code
Cancer	Cancer (except non-melanoma skin cancers) or treatment with selected antineoplastic agents	C00-C97 (except C44.9, D48.5, D48.9)
HIV	HIV infection or use of antiretroviral agents for HIV	B20-B24
Respiratory	Respiratory failure, dependence on respirator	J96, Z99.1
Renal	End-stage renal disease and dialysis or procedure code for dialysis	N18.5, Z49.0, Z99.2
Organ transplantation	Transplant of kidney, heart, lung, liver, bone marrow, or pancreas	Z94.0-Z94.4, Z94.9, Z94.9
Drug or alcohol abuse	Alcohol or drug abuse including cocaine abuse or dependence	Z71.5, Z72.1, Z72.2, Z86.4, F10-F19, T40
Coma	Somnolence, stupor, or coma	R40.0-R40.2
Congenital cardiovascular anomalies	Congenital anomalies of heart or great arteries	Q20-Q25

HIV = human immunodeficiency virus.

In addition, specific exclusion criteria might be applied for each outcome in the nested case-control studies. As an example, for the evaluation of incident hospitalisations for heart failure, we will exclude cohort members with one or more hospitalisation with a code of heart failure at baseline.

9.2.1.4 Follow-up

Date of Cohort Entry

For each eligible member of the study cohort, the cohort entry date is the date of the first prescription for one of the study medications. Patients must meet the eligibility criteria at the cohort entry date.

Follow-up

For each study endpoint, members of the study cohort will be followed from the date of cohort entry until the earliest of the following dates:

- Endpoint of interest
- Exclusion criterion met
- Disenrolment from the database
- Death
- End of the study period

9.2.2 Nested Case-Control Studies

Nested case-control studies will examine effects of exposure in various ways and evaluate and control for confounding factors including time-varying confounding. Four case-control studies, one for each endpoint of interest and nested in the cohort of new users of the study medications, will be implemented sequentially as summarised in Section 9.1: first, all-cause mortality; second, heart failure; third, cerebrovascular events; and fourth, AMI. Finally, an additional case-control study will evaluate the risk of cardiac arrhythmias after users of aclidinium/formoterol are captured in the database.

9.2.2.1 Identification of Cases

All cases confirmed through the case ascertainment procedures will be included in the corresponding nested case-control study.

9.2.2.2 Selection of Controls

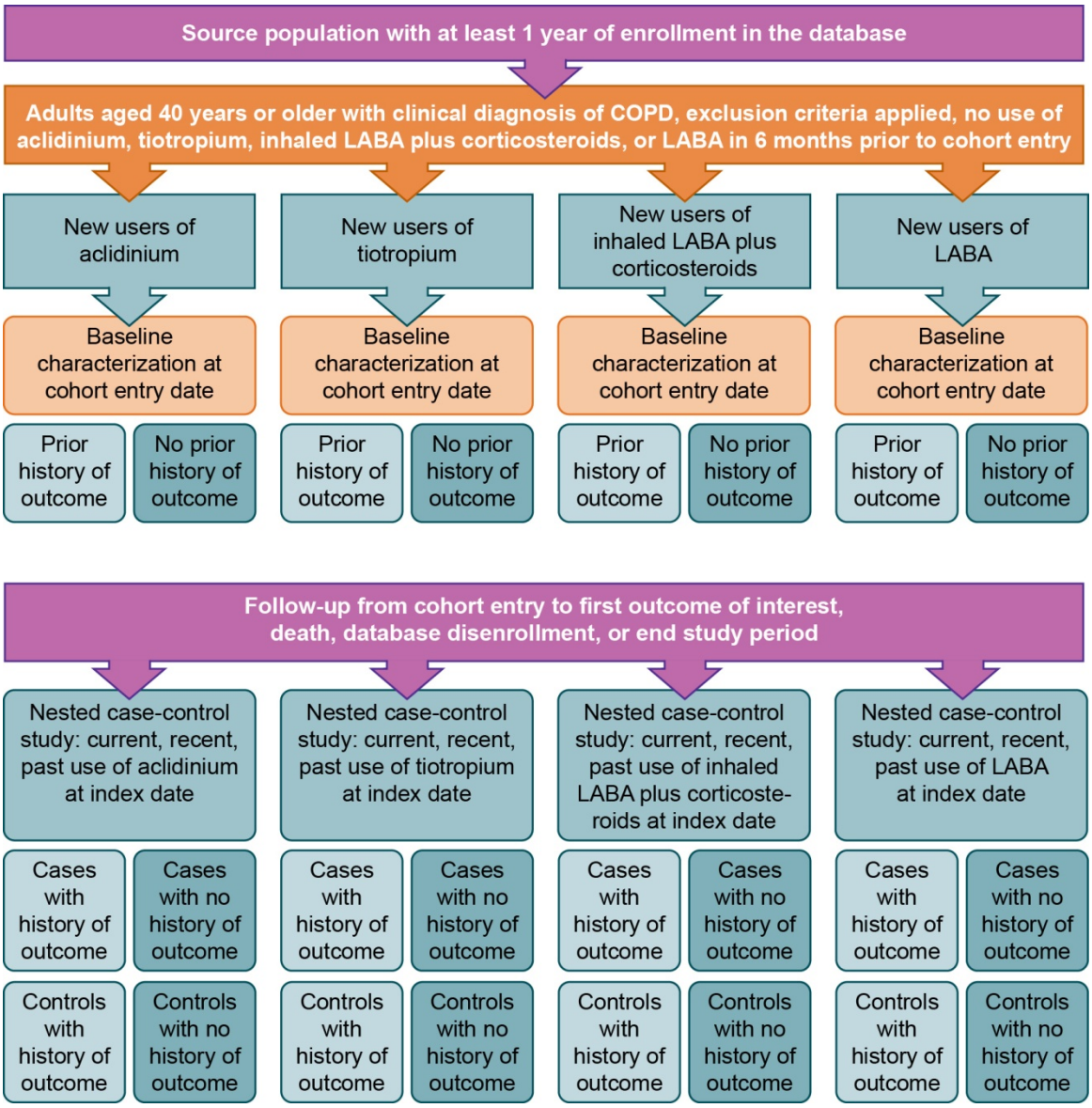
For each case-control study, separate density-based sampling procedures will be used to select 4 controls from the study cohort for each case. In density-based sampling, the probability of each member of the study cohort being selected as a control is proportional to his or her person-time at risk. Density-based sampling in case-control studies provides valid estimates of the incidence rate ratio in the population studied when the sampling is conducted independently of exposure.[22]

9.2.2.3 Definition of Index Date for Cases and Controls

- For cases admitted to the hospital, the index date will be defined as the hospital admission date. For patients not hospitalised, the confirmed date of onset of the acute event or date of diagnosis by the specialist will define the index date. For all-cause mortality including out-of-hospital fatal cases, the index date will be the date of death.
- For controls, the index date will be the index date of the corresponding case. To implement density-based sampling, controls will be randomly selected from the unique set of members of the study cohort who are at risk at the index date of each case (risk set). All selected controls will be eligible to become cases if they experience the endpoint of interest during their eligibility period. Similarly, all selected controls will be eligible to be selected as controls one or more times provided they meet the study eligibility criteria.

An overview of the study design is depicted in Figure 3.

Figure 3. Overview of the Study Design (Monotherapy)



Note: New users of aclidinium will include use as monotherapy; concomitant with formoterol not in fixed-dose combination; and aclidinium/formoterol, when available. New users of other LAMAs (i.e., glycopyrronium bromide, umeclidinium) will be included as an exposure of interest if captured in the database during the study period. New users of any LABA/LAMA and LABA/ICS combinations that become available during the study period, if captured in the database, will be also included.

9.2.3 Health Care Databases

The study will be conducted using information collected in automated health care databases in which information on prescriptions and disease occurrence is recorded on an ongoing basis.

Based on the launch sequence and projected estimated number of patients to be treated by country at the time of aclidinium monotherapy approval, the Clinical Practice

Research Datalink (CPRD)—formerly the General Practice Research Database (GPRD)—in the United Kingdom (UK); the national health databases in Denmark; and the German Pharmacoepidemiological Research Database (GePaRD) at the Leibniz Institute for Prevention Research and Epidemiology (BIPS GmbH) in Germany are proposed as the primary population-based data sources for the DUS. Detailed descriptions of these databases and availability of data can be found in the Annex 4. The estimated number of aclidinium bromide users by year that are expected to be captured in each database at the time of aclidinium monotherapy approval, according to preliminary sales projections for each country, are shown in Table 4. Although fewer users are expected to be captured in the CPRD than in the Danish and German databases, the lag time of data capture is shorter in the CPRD. As of 1Q 2014, the monitoring phase for the DUS1 is beginning, and collaborations are being set up with database custodians in the UK, Denmark, and Germany.

Table 4. Estimated Number of Aclidinium Bromide Users Captured in Each Prescription Database by Year

Year	CPRD, UK	National Health Databases, Denmark	GePaRD, Germany
2013	980	1,000	9,900
2014	2,700	6,000	22,400
2015	4,100	8,000	25,800
2016	5,100	8,000	28,400
2017	5,800	9,000	31,100

CPRD = Clinical Practice Research Datalink; GePaRD = German Pharmacoepidemiological Research Database; UK = United Kingdom.

Note: These estimates are based on sales projections by Almirall, March 2014.

For implementation of the safety endpoint component, only one database will be used. The presence of detailed information on some lifestyle habits, clinical history including chronic conditions, and prescriptions of medications available in electronic medical record, points to the CPRD as one of the best options for the implementation of these safety studies among patients with COPD. A large number of studies in the respiratory indication and a large number of studies with cardiovascular endpoints have been conducted in this population. However, the final database will be selected based on the speed of achieving the number of aclidinium bromide users needed for the study and monitored in the data sources included in the DUS. The number of users in the CPRD will be driven by the uptake of aclidinium bromide in the UK population.

The CPRD in the UK (http://www.cprd.com/home) contains diagnostic and prescribing information recorded by general practitioners (GPs) as part of their routine clinical practice. The database covers approximately 5 million of the UK population, and this number is likely to increase over the years. Patients registered in the CPRD are representative of the whole UK population in terms of age and sex. These data are linkable, at least partially, with other health care data sets (e.g., hospitalisation records, national mortality data) via the patient's National Health Service number, sex, date of birth, and postal code. Updated, valid, linked CPRD data are available through the CPRD exposure Division of the UK Medicines and Health Care Products Regulatory Agency (MHRA).

Detailed information on prescriptions written by GPs, including prescribed dose and duration, is routinely recorded in the database. Read codes are used for diagnoses, and Multilex codes are used for medications. Additional diagnostic and treatment information can be found in free-text fields, letters from specialists and hospitals, and other sources. Identifying patients who have both information from general practices and HES data enables access to hospital discharge diagnosis and procedural coding. The validity of the CPRD as a reliable data source for drug safety studies in numerous therapeutic areas is well established.[23-26]

Studies have been conducted using data from the CPRD to characterise the COPD population and evaluate the safety of medications used for COPD. The demographic and selected clinical characteristics of patients newly diagnosed with COPD were described in a study using information from this population between 1996 and 1999.[27] A total of 2,699 patients with COPD were identified and included in the study. About 55% of patients were aged older than 65 years, and 51% were women. Current smoking was found in about 46% of patients. The patterns of comorbidities were identified in these patients and described in comparison with matched subjects without COPD. Respiratory infections, pneumonia, osteoporosis, myocardial infarction, angina, glaucoma, and fractures were the comorbidities that were more frequent in patients with COPD than in patients without COPD. In addition, the validity of the clinical diagnosis of COPD in practices participating in the CPRD has been reported.[19]

Another study identified a cohort of COPD patients and evaluated the incidence of selected cardiovascular conditions and lung cancer.[28] The risk of cardiac arrhythmias associated with the use of respiratory medications has also been evaluated in the CPRD.[29]

9.3 Variables

9.3.1 Study Endpoints

Individual study endpoints will be the following:

- Mortality from all causes
- First-ever hospitalisation for heart failure
- Hospitalisation for acute myocardial infarction, either non-fatal or fatal, plus community (out-of-hospital) coronary heart disease deaths
- Acute stroke, either non-fatal or fatal, including community (out-of-hospital) cerebrovascular disease deaths
- Finally, a composite endpoint of acute myocardial infarction, stroke, and out-of-hospital CHD or cerebrovascular death will be evaluated if confirmed that the direction and magnitude of the risk is similar across the individual components. The individual endpoints will be evaluated and their compatibility with the hypothesis that all endpoints show the same proportional elevation in risk will be assessed, as measured by a P-value for heterogeneity (chi-square heterogeneity test).

- Incidence of cardiac arrhythmias during the study period:
  - New episode of any type of diagnosed cardiac arrhythmia
  - New episode of atrial fibrillation or flutter (AF), including episodes of paroxysmal (intermittent) atrial fibrillation or a new episode (first ever) of atrial fibrillation in patients without chronic atrial fibrillation or flutter
  - New episodes of serious ventricular arrhythmias (SVA)

To ascertain cardiovascular events, we propose to use standard clinical definitions similar to those that have been used in prior studies, for example, García Rodríguez et al.,[30] Huerta et al.,[31],[32] and Varas-Lorenzo et al.[33]:

- Heart failure is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. It is characterised by specific symptoms (dyspnoea and fatigue) in the medical history and signs (oedema, rales) on the physical examination.
- An AMI is defined by the evidence of myocardial necrosis in a clinical setting consistent with myocardial ischaemia, including ST-elevation myocardial infarction and non–ST-elevation myocardial infarction. Because one-third of the patients suffering an AMI die suddenly before arriving at the hospital, community CHD deaths are also included in the definition of AMI. Community death from CHD will be defined as sudden cardiac death or fatal myocardial infarction deaths in persons outside a hospital setting.
- An acute stroke is defined as the rapid onset of a persistent neurological deficit attributed to an obstruction or rupture of the arterial system supplying the brain. Because some patients having an stroke will die before arriving at a hospital facility, community deaths from cerebrovascular disease will be ascertained.
- Cardiac arrhythmias will be defined as new episodes of any type of cardiac arrhythmia in the study period; in addition, we will define two specific subtypes of cardiac arrhythmias for endpoint ascertainment:
  - Atrial fibrillation is a supraventricular tachyarrhythmia characterised by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. On the electrocardiogram (ECG), AF is characterised by the replacement of consistent P waves with rapid oscillations or fibrillatory waves that vary in amplitude, shape, and timing and are associated with an irregular, frequently rapid ventricular response when atrioventricular (AV) conduction is intact.
  - Serious ventricular arrhythmias are defined as torsade de pointes (TdP), ventricular tachycardia (VT), and ventricular fibrillation/flutter (VF).

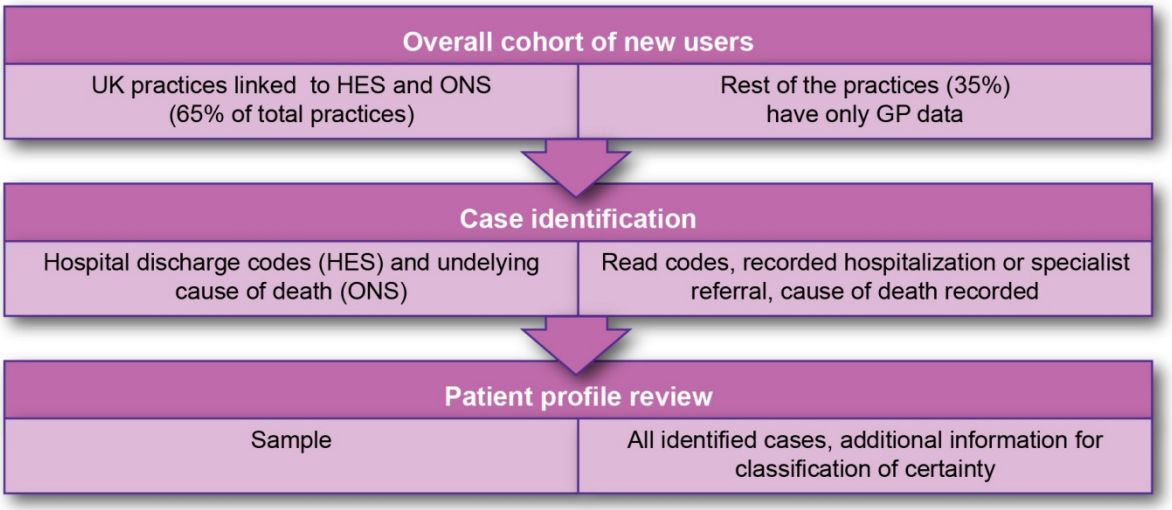
9.3.1.1 Case Ascertainment and Validation

Potential cases can be identified in each database using GP diagnosis and/or hospital discharge diagnosis. Focused on the CPRD, potential cases will be identified by algorithms used in previous studies. Data for about 65% of the UK practices can be linked to the Hospital Episode Statistics (HES) database; potential hospitalisations for patients from these practices will be identified using specific ICD-10 codes. For the rest of the CPRD practices, Read codes, the coding system currently used by GPs in the CPRD, will be mapped to ICD-10 codes. For causes of death, ICD-10 codes will be used

for linkage to the Office for National Statistics (ONS) mortality data (see Figure 4). Data in HES and ONS are updated every 6 months. Therefore, this time should be taken into account for planning the study implementation.

If the German or Danish databases are needed for study implementation, ICD-10 hospital discharge codes will be used to identify potential cases.

Figure 4. Case-Finding Approach Proposed for the CPRD



GP = general practitioner; HES = Hospital Episode Statistics; ONS = Office for National Statistics; UK = United Kingdom.

For cardiac arrhythmias, including atrial fibrillation and SVA, the first occurrence of the event will be determined by both Read codes and hospital discharge codes as available for each patient in the cohort.

9.3.1.2 Ascertainment of Cases of Heart Failure

Records of the first hospitalisation for CHF during the study period will be identified. Patients with a prior record of CHF with hospitalisation will be excluded from the cohort. Although ascertaiment of the complete CHF outcome includes both hospitalisations and outpatient diagnoses, differential clinical diagnoses in patients with COPD might be an issue, especially for outpatient diagnoses. Therefore, we propose to assess the most severe events requiring first-time hospitalisation. These will be patients either diagnosed for the first time with CHF or patients with previous outpatient diagnoses of CHF who progress to a more severe functional class requiring hospitalisation.[31] Prior outpatient diagnoses will be taken into account in the analysis by stratification.

In the study performed by Huerta et al.,[31] 75% of all identified cases were confirmed during the validation process. Because this validation study was not conducted in patients with COPD, we propose a sample validation through surveying GPs for potential cases identified through Read codes.

9.3.1.3 Ascertainment of Cases of AMI

Potential hospitalisations for AMI, either fatal or non-fatal, will be identified using specific ICD-10 and mapped Read codes. Previously validated algorithms to identify AMI (including CHD deaths) will be used.[30,32,33] The PPV of the Read/OXMIS codes for AMI has been reported to be about 93% (95% CI, 90%-96%).[34]

9.3.1.4 Ascertainment of Cases of Stroke

Records of hospitalisation for outpatient diagnoses of either fatal or non-fatal stroke will be identified. In elderly populations, patients suffering small and uncomplicated strokes are not always hospitalised, and these patients, if diagnosed and if possible, should be included in the study to ensure complete case ascertainment of cerebrovascular conditions. In the CPRD, all specific and non-specific Read codes for diagnoses indicating cerebrovascular accidents and specific ICD-10 codes for linkage to the HES will be identified. Hospital admission or referral to a specialist will be required for both ischaemic and haemorrhagic strokes. Prior validated algorithms to identify ischaemic strokes and cerebrovascular events, including deaths, will be used.[32,35-37] For ischaemic stroke, the PPV has been reported to be about 86% (95% CI, 79%-91%) using THIN.[38]

9.3.1.5 Ascertainment of Community Deaths From CHD or CVD

Out-of-hospital deaths from CHD and CVD can be ascertained through diagnoses recorded on autopsy reports and death certificates, as available. The coded diagnosis will be used to determine the cause of death.[30,32,34,39]

In the CPRD, participating GPs are required to record in the database the date and causes of death. Death is well captured in the database, and date of death has been reported to be accurately recorded for most of the recorded deaths.[40] For English participating practices that are linked to the ONS mortality data, cause of death is automatically integrated into the CPRD. It is possible to obtain additional data for those fatal cases with recorded unavailable/unknown cause of death by requesting the death certificate. Prior clinical history will also be useful to categorise these deaths.

CHD deaths will be identified from deaths with the following characteristics:

- Have on the death certificate an underlying cause of death that is compatible with sudden cardiac death or fatal myocardial infarction (Table 5). The specific codes provided in the table are those that have been used in prior studies and validated by Chung et al.[39]
- Have no terminal hospitalisation
- Have a place of death that it is not a hospital institution

A similar approach will be used to identify community cerebrovascular deaths.

Note that if the study is conducted in Germany, the ascertainment of community deaths from CHD or CVD will not be possible due to lack of cause-of-death data.

Table 5. Summary of Information and Codes Used for Case-Finding for Heart Failure, Acute Myocardial Infarction, and Stroke

Congestive Heart Failure	AMI Including Community CHD Deaths	Stroke Including Community CVD Deaths
Hospital primary discharge code (ICD-10 codes)		
▪ I50, Heart failure	▪ I21, Acute myocardial infarction	▪ I60, Subarachnoid haemorrhage ▪ I61, Intracerebral haemorrhage ▪ I63, Cerebral infarction ▪ I64, Stroke, not specified as haemorrhage or infarction
Other information to be used, but not limited to, in those patients without HES linkage		
CHF Read code with hospitalisation AND any of the following:[a] ▪ Digoxin prescription ▪ Diuretic prescription ▪ ACEI/ARB prescription ▪ Carvedilol prescription ▪ Death within 1 month	AMI/chest pain Read code with hospitalisation and any of the following:[a] ▪ Record of ECG or location of infarction ▪ Death within 1 month ▪ CABG or stent ▪ Positive cardiac enzymes recorded ▪ Thrombolytic therapy	Stroke Read code AND hospitalisation or specialist referral and any of the following: ▪ Record of CT, NMR, EEG or location of infarction ▪ Death within 1 month ▪ Stroke-related surgery ▪ Thrombolytic therapy ▪ Evidence of residual damage – Paresis, numbness – Speech, vision, swallowing problems – Rehabilitation or physiotherapy
Underlying cause of death (ONS, ICD-10 codes or mapped Read codes)		
I50, Heart failure	I10, I11.9, I20-I24, I25, I42.8-I42.9, I46, I47.0-I47.2, I49.0, I49.8-I49.9, I51.6, I51.9, I70.9, R96.1, R98 [b]	I60-I69, G45, R96.0, R96.1, R98

ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; CABG = coronary artery bypass graft; CHF = congestive heart failure; CT = computed tomography; ECG = electrocardiogram; EEG = electroencephalogram; HES = Hospital Episode Statistics; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; NMR = nuclear magnetic resonance (image); ONS = Office for National Statistics.

Note: See Annex 3 for a description of codes.

[a] Exact time windows will be determined after patient profiles have been reviewed.

9.3.1.6 Ascertainment of Atrial Fibrillation and Serious Ventricular Arrhythmias

New episodes of cardiac arrhythmias will be identified by algorithms based on broad Read terms and ICD-10 codes and further refined by review of samples of patient profiles. For practices that are not linkable to HES/ONS, ascertainment of specific types of arrhythmias will be through clinical symptoms and diagnoses resulting in referral to a specialist or hospitalisation with objective evidence of AF or VT. For practices linkable to HES, AF and SVA will be ascertained by both diagnoses resulting in referral to a specialist and primary hospital discharge diagnoses (HES) for atrial fibrillation/flutter

(ICD-10:I48) or ventricular tachycardia (ICD-10: I47.0, I47.2) and ventricular fibrillation (ICD-10: I49.0).

For AF, only paroxysmal and first-ever incident cases will be considered. Therefore, chronic cases of AF will be identified and excluded from the case definition.

9.3.1.7 Review of Automated Longitudinal Health Profiles

Patient profiles are chronological listings of the diagnoses, procedures, and medications. A clinician blinded to the exposures of interest will review all the patient profiles of potential study cases identified through only Read codes and a random sample of those identified through the HES linkage and will categorise them according to the prespecified diagnostic criteria. In the CPRD, the review of free-text comments improves validity.[38] For cardiac arrhythmias, samples of patient profiles will be reviewed to refine the identification algorithm based on broad Read and ICD-10 diagnosis codes. For the two specific subtypes of atrial fibrillation and SVA, all the potential identified events will be reviewed.

9.3.2 Exposure Assessment

Exposure to the study medications will be ascertained by the information recorded in each database for prescribed or dispensed medications. Time at risk for the effects of each study medication will be ascertained according to the days' supply of each prescription, defined as the intended duration of use of each prescription in relation with the index date.

Time at risk for each study medication will be classified in the following three mutually exclusive categories:

- Current use: when the days' supply of the most recent prescription overlapped or ended within 7 days before the index date
- Recent use: when the days' supply of the most recent prescription ended during the 60 days before the current use period
- Past use: when the days' supply of the most recent prescription ended before the recent use period.

Sensitivity analyses will be performed using different time windows for the definition of current use (e.g., days' supply ended within 1 day before the index date; days' supply ended within 30 days before the index date). Categories of time at risk and sensitivity analyses will be adjusted based on the patterns of use observed in the DUS.

For each study medication, the main exposure of interest will be current use of that single medication without concurrent or recent use of any of the other study medications. For that purpose, **current use** of each study medication will be classified according to the time at risk of each of the other study medications in the following three mutually exclusive categories:

- Current single use: defined as current use of one single medication group without recent use of a different study medication group. Main exposure category of interest.

- Current use switching: current use of a single medication group with recent use of a different study medication group (e.g., current single use of aclidinium bromide with recent use of LABA/ICS)
- Current multiple use: current use of more than one study medication group with or without switching

An example for the time at risk of aclidinium bromide in relation to any of the rest of the study medication groups is shown in Table 6.

Table 6. Classification of Time at Risk of Current Use of Aclidinium Bromide According to the Use of the Rest of Study Medications

Time at Risk for the Rest of the Study Medications[a]	Classification of Current Use of Aclidinium Bromide
Current use	Current multiple
Recent use	Current switching
Past use or none	Current single

ICS = inhaled corticosteroids; LABA = inhaled long-acting beta-agonist; LAMA = long-acting anticholinergic.

[a] Tiotropium, other LAMAs, LABA/ICS, LABA/LAMA, and LABAs.

9.3.2.1 Ascertainment of Dose and Duration

Daily dose of each study medication will be ascertained for the last prescription before the index date. Daily dose will be derived from the instructions provided by the prescribing physician (e.g., recommended daily dose and/or days' supply). If instructions are not available, daily dose will be estimated from the time between consecutive prescriptions and the recorded prescribing information: strength, number of units, number of boxes, and formulation.

Duration of current use of each medication of interest will be calculated as the total time of continuous use ascertained through consecutive prescriptions. Calculations of consecutive use will allow for a maximum gap in treatment (e.g., 60 days) between the estimated end of use of one prescription and the dispensing date of the following prescription; the length of the gap will be determined by the pattern-of-use evaluation in the DUS.

9.3.3 Risk Factors and Confounding

Confounding factors are those associated with both exposure to the study medications and the endpoint of interest. Potential confounding factors include age, sex, body mass index, socioeconomic status, cardiovascular risk factors such as smoking and hyperlipidaemia, diabetes, severity of COPD, prior cardiovascular disease, other severe chronic disease, and concurrent use of medications. The definition of confounding factors will be based on the diagnosis, procedures, and prescription of medications recorded in each database.

A general description of the main potential confounding factors is provided below. The complete list of these factors is presented in Annex 5 with ICD-10 codes for diagnoses

and ATC codes for medications. ATC codes will be mapped to Multilex codes if the study is conducted in the CPRD.

9.3.3.1 Demographic Variables

Demographic variables will be ascertained at the index date. Age and sex are relevant risk factors for cardiovascular conditions and are associated with the prognosis of COPD. Lung function starts to decline in the third and fourth decade. Race and ethnicity will not be included as most of the electronic health databases, including the CPRD, do not have this information due to data privacy rules.

9.3.3.2 Lifestyle and Socioeconomic Variables

Lifestyle and socioeconomic variables will be ascertained at the index date.

Exposure to tobacco smoke is the most important cause of COPD. However, information on smoking and other lifestyle factors are available only in databases using electronic medical records, as in the CPRD.

Information on alcohol abuse/dependence and obesity is not available or is recorded inconsistently in most databases except in the CPRD, in which the GPs routinely record their patients' body mass index (BMI) and patient's reported daily quantity of alcohol consumed, although the degree of completeness might vary. If using the CPRD, these quantitative variables will be described according to categories. BMI is defined as the weight in kilograms divided by the square of the height in meters (kg/m^2). We will be using those categories available in the database, or the following World Health Organization (WHO) categories can be used to categorise BMI if the continuous variable is available: underweight (BMI < 18.50), normal weight (BMI ranging from 18.50-24.99), and overweight (BMI > 25). The overweight category will be subclassified into preobesity (BMI, 25.00-29.99) and obesity (BMI > 30).[41]

Socioeconomic status (SES) is associated with the risk of COPD. In addition, SES is a determinant of prescribing and utilisation of medical services including primary care. Indicator variables of SES will be used as available in each database. In the CPRD, socioeconomic data on individuals is not available. However, for English practices, measures of deprivation such as Townsend data and the Index of Multiple Deprivation are available through linkages to census data by postal code. The components of this index are based on income, employment, health deprivation and disability, educational skills and training, housing, and geographic access to services in the neighbourhood. Using the distribution of the Townsend multiple deprivation index, characteristics of patients and drug utilisation can be described by subgroups of deprivation (http://www.cprd.com/dataAccess/Default.asp). Information on the participating practices where patients are enrolled will be also included.

9.3.3.3 Utilisation of Health Services

Utilisation of health services will be evaluated for the year before the date of cohort entry. Utilisation will include the number of hospitalisations, GP visits, referrals to specialists, prescriptions received for respiratory medications, and prescriptions received for other types of medications.

9.3.3.4 COPD Severity

Severity of COPD is an important prognostic factor for morbidity and mortality. Several studies in patients with COPD have included and validated measures of COPD severity.[13,14,19,42,43] For example, the algorithm used by Verhamme and colleagues[14] assessed baseline severity of COPD by the frequency of use of COPD medications, frequency and duration of use of systemic corticosteroids as a marker of COPD exacerbations, use of oxygen therapy, and prior number of hospitalisations for COPD. The authors defined four levels of severity, which were confirmed by spirometry in 82% of patients.[14] Use of a nebuliser or a diagnosis of pneumonia, emphysema, or concurrent asthma have also been associated with increased COPD severity.[42] Some authors have measured COPD exacerbations by the use of short-term courses, less than 4 weeks, of antibiotics.[44]

In this study, we will evaluate severity of COPD both at the date of entry in the study cohort and at the index date. We will define severity of COPD according to the algorithm validated by Verhamme and colleagues[14] (Table 7). In addition, we will assess separately the following markers of COPD severity[42]:

- A nebuliser prescribed/dispensed in the prior 6 months
- At least one COPD hospitalisation in the prior year
- At least one acute COPD exacerbation in the prior 6 months, measured as having at least one prescription for an antibiotic concurrent to a respiratory diagnosis
- A diagnosis of pneumonia in the prior year
- A diagnosis of emphysema at any time before the entry date
- A diagnosis of asthma at any time before the entry date

Table 7. Assessment of COPD Severity

Severity of COPD	Definition
Mild	First recorded diagnosis of COPD with up to 2 prescriptions in the last year for a bronchodilator of the same dug class with more than 6 months between them
Moderate	On regular bronchodilator treatment defined as at least 2 prescriptions or refills of the same drug class with a maximum interval of 6 months in the last year
Severe	Occurrence of at least one of the following events in the prior year ▪ Hospitalisation for COPD ▪ Third course of antibiotics for respiratory tract infections ▪ Second course of systemic corticosteroids for the treatment of COPD exacerbation
Very severe	Use of oxygen therapy or scheduled for lung transplant

9.3.3.5 History of Cardiovascular Diseases and Risk Factors

History of cardiovascular diseases and risk factors will be measured at the date of cohort entry. The main cardiovascular diseases will include angina, myocardial infarction, arrhythmias, stroke, transient ischaemic attack, peripheral vascular disease, heart

failure, hypertension, diabetes, renal disease, and hyperlipidaemia. After the database has been selected for the study, we will explore the feasibility of generating a cardiovascular risk profile using the available recorded information or using developed risk scores (e.g., Framingham risk scores, QRISK).

To ascertain an overall index of severe comorbidity, we will adapt the Charlson Comorbidity Index to compute an overall score for chronic disease. The adapted comorbidity index will exclude the components for COPD diagnosis and those corresponding to the exclusion criteria (Table 3).

9.3.3.6 Concurrent Use of Respiratory Medications

Concurrent use of respiratory medications will be evaluated at the index date. Respiratory medications will include those indicated for COPD and asthma.

9.3.3.7 Concurrent Use of Other Medications

Concurrent use of other medications will be evaluated at the index date. Medications will include cardiovascular medications, antihistaminics, antitussives, antibiotics, vaccines, insulins, and oral antidiabetics.

9.4 Data Sources

Study variables including endpoints, exposures, and covariates will be ascertained in the final database selected for this study (the CPRD) according to the definitions and procedures provided in Section 9.3, Variables.

9.5 Study Size

The size of the study to be implemented in the CPRD will be driven by the uptake of aclidinium bromide in the UK population.

We have performed calculations to estimate the approximate number of patients exposed to aclidinium bromide during 1 year that would be required to achieve a 0.80 probability of detecting true RRs (compared with patients treated with LABAs) ranging from 1.5 to 3 for all-cause mortality, heart failure, stroke, and AMI under the following assumptions: (1) a ratio of unexposed to exposed subjects equal to 4:1, (2) significance tested at the two-sided alpha = 0.05 level, and (3) a range of expected incidence rates of the safety events of interest that were taken from published incidence rates in COPD populations (Table 8). We provide estimates first by assuming that each patient contributes a full year of person-time at risk of current use and second by assuming that each patient contributes only 6 months of person-time at risk of current use, which doubles the number of exposed patients and the required sample size.

Under all these assumptions, the number of patients with COPD exposed to aclidinium bromide needed to identify a significant risk ratio if the true risk ratio is equal to or greater than 1.5 are the following (see also Table 8):

- All-cause mortality: 1,000 patients
- Heart failure: 3,200 to 5,600

- AMI: 8,400 to 15,400 patients
- Stroke: 11,600 patients

For cardiac arrhythmias, under the same assumptions, the number of patients with COPD exposed to aclidinium/formoterol needed to identify a significant risk ratio if the true risk ratio is equal to or greater than 2 will be between 3,000 and 12,000 (see also Table 8). It is expected that AF will be among the most frequent incident arrhythmias.

These sample size calculations do not take into account the study exclusion criteria, which can be relevant for all-cause mortality. Per the calculations shown in Table 8, the first of a series of case-control studies nested in the safety cohort will be initiated to estimate the risk of all-cause mortality when a total of 1,000 aclidinium bromide users with COPD aged 40 years or older have been identified and followed for 1 year in the selected database. When the number of aclidinium bromide users with COPD aged 40 years or older reaches a total of about 3,200 in the selected database, the second nested case-control study, of the more common cardiovascular endpoint (CHF), will be implemented. Based on the descriptive interim analysis planned when the second nested case-control study is being conducted, if deemed necessary, the study size will be recalculated and the dates for initiation of the subsequent case-control studies in the sequence can be adjusted. The case-control studies for stroke and AMI are expected to be initiated when the number of aclidinium bromide new users with COPD aged 40 years or older and with 1 year of follow-up reaches between 11,600 and 15,400.

Table 8. Approximate Number of Patients With COPD Exposed to Aclidinium Bromide for 1 Year to Have a 0.80 Probability of Detecting Risk Ratios of 1.5, 2, 2.5, and 3

		Risk Ratio to be Detected			
Safety endpoint	**Incidence[a]**	**1.5**	**2**	**2.5**	**3**
All-cause mortality	106.58[a]	400	100	< 100	< 100
Assumed 50% of person-time at risk[e]		800	200	< 200	< 200
Heart failure	17[b]	2,800	800	400	250
	30[c,d]	1,600	450	250	150
Assumed 50% of person-time at risk,[e] range		3,200-5,600	900-1,600	500-800	300-500
AMI	6[d]	7,700	2, 200	1,200	700
	11[c]	4,200	1,200	600	400
Assumed 50% of person-time at risk,[e] range		8,400-15,400	2,400-4,400	1,200-2,400	800-1,400
Stroke	8[f]	5,800	1,700	900	500
Assumed 50% of person-time at risk[e]		11,600	3,400	1,800	1,000
Cardiac arrhythmias	2.2[g]	21,100	6,000	2,900	1,800
	9.1[h]	5,000	1,400	700	425
Assumed 50% of person-time at risk,[e] range		10,000-42,200	2,800-12,000	1,400-5,800	850-3,600

[a] Estimated incidence per 1,000 person-years in patients with COPD.

[b] Verhamme et al.[14]; Integrated Primary Care Information (IPCI) database (The Netherlands).

[c] Curkendall et al.[4]; Saskatchewan Health (Canada); incidence of primary hospital discharge diagnoses or underlying cause of death.

[d] Rodríguez et al.[28]; CPRD (United Kingdom); new diagnosis of an outcome during the study period in GP medical records and hospital summaries.

[e] A published study evaluating tiotropium in the Danish general population reported that patients might contribute only 50% of the person-time at risk within a 1-year period.[9] Counts in this row assume that each patient contributes 6 months at risk in a 1-year period.

[f] Sidney et al.[5]; Kaiser Permanente (United States); primary hospital discharge diagnoses.

[g] Huerta et al.[29]; GPRD (UK), incidence of diagnosis confirmed by specialist. The incidence of AF was 1.4 per 1,000 person-years. Patients with recorded diagnoses of asthma, COPD, or both.

[h] Schneider et al.[45]; GPRD (UK), incidence of recorded diagnosis in COPD patients.

9.6 Data Collection and Management

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality control checks of all programs. Database custodian will maintain any patient-identifying information securely on site according to internal standard operating procedures.

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 (i.e., storage on CD-ROM or DVD), with periodic backup of files to tape. Standard procedures will be in place at the research centre to restore files in the event of a hardware or software failure.

9.7 Data Analysis

A general description of the analyses to be conducted is presented in this section. A more detailed description of the analyses and final shell tables will be provided in the statistical analysis plan.

9.7.1 Cohort Description

Users of each study medication will be characterised at the date of cohort entry according to confounding and risk factors detailed in Section 9.3.3 and Annex 5. The following main variables will be used:

- Demographic: age and sex
- Lifestyle and socioeconomic: smoking, alcohol use, BMI, SES
- Utilisation of health services in the year before the date of cohort entry: number of hospitalisations, GP visits, referrals to specialists, prescriptions received for respiratory medications, and prescriptions received for other types of medications.

- COPD severity
- Medical history at any time before the date of cohort entry: cardiovascular diseases and risk factors and chronic diseases
- Use of respiratory and other medications in the following time periods:
  - The year before the date of cohort entry
  - The 60 days before the date of cohort entry

9.7.2 Cohort Analysis

Person-years and number of cases for each study endpoint will be computed for current use of each study medication. Crude and age- and sex-standardised incidence rates will be estimated for current use of each study medication (Table 9). The Poisson distribution will be used to calculate exact 95% Cis for the incidence rates. Age- and sex-standardised incidence rates will be estimated using the age and sex distribution of person-time in current users of aclidinium bromide.

Table 9. Shell Table for the Estimation of Crude and Age- and Sex-Standardised Incidence Rates and 95% Confidence Intervals for Each Study Endpoint

Current use	Person-years	Number of cases	Crude incidence rate per 1,000 person-years (95% CI)	Age- and sex-standardised incidence rate per 1,000 person-years (95% CI)[a]
LABA	xx	xx	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide	xx	xx	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide + formoterol	Xx	Xx	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide/ formoterol	Xx	Xx	xx (xx, xx)	xx (xx, xx)
Tiotropium	xx	xx	xx (xx, xx)	xx (xx, xx)
Other LAMAs[a]	xx	xx	xx (xx, xx)	xx (xx, xx)
LABA/ICS	xx	xx	xx (xx, xx)	xx (xx, xx)
LABA/LAMA	xx	xx	xx (xx, xx)	xx (xx, xx)

CI = confidence interval; ICS = inhaled corticosteroids; LABA = inhaled long-acting beta-agonists; LAMA = long-acting anticholinergics.

[a] Other LAMAs: glycopyrronium bromide; umeclidinium.

9.7.3 Nested Case-Control Analysis

Sequential case-control analyses will be nested into the cohort to compare (1) the risk of each study endpoint, except cardiac arrhythmias, associated with the use of aclidinium bromide (monotherapy; concomitant with formoterol not in fixed-dose combination; and aclidinium/formoterol, when available), tiotropium, other LAMAs (i.e., glycopyrronium bromide, umeclidinium), LABA/ICS, and LABA/LAMAs compared with the risk in users of

LABAs (reference category) and (2) the risk associated with aclidinium with the risk associated with each group of study medications. The nested case-control approach combines strengths of both the cohort and the case-control designs and is an efficient alternative for analysis of a cohort when time-dependent covariates are included.

An additional nested case-control analysis will estimate the risk for cardiac arrhythmias, comparing each exposure category (e.g., current use, recent use, past use) (1) between users of aclidinium/formoterol and users of other fixed-dose combination COPD treatments with users of LABAs (reference category) and (2) between users of aclidinium bromide/formoterol and users of each of the other fixed-dose combination COPD treatments.

For each study endpoint, the distribution of potential confounding and risk factors (Section 9.3.3 and Annex 5) will be described for cases and controls. Crude and adjusted RRs and 95% CIs will be estimated for each potential confounding and risk factor.

Conditional multiple logistic regression will be used to estimate crude and adjusted relative risks (RRs) and 95% CIs for each study endpoint. Clinically relevant risk factors will be forced in the final regression model (e.g., age, sex, COPD severity, cardiovascular disease). Each of the remaining factors will be included in the regression model if it produces a change of 10% or more in the magnitude of the parameter estimate. Shell tables for the results of these analysis are presented in Table 10 for the overall current, recent, and past use of the study medications, Table 11 for the analysis restricted to current users of the study medications, and Table 12 for the comparison of current single use of aclidinium with current single use of each of the rest of the study medications.

Table 10. Shell Table for the Estimation of Crude and Adjusted Relative Risk (95% CI) for Each Study Endpoint Comparing Current, Recent, and Past Use of Each Study Medication With Current Use of Long-Acting Beta-Agonists

Exposure Category	Number of Cases (%)	Number of Controls (%)	Crude Risk Ratio (95% CI)	Age- and Sex-Adjusted Relative Risk (95% CI)	Adjusted Relative Risk[a] (95% CI)
LABA					
Current use	xx (%)	xx (%)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)
Recent use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Past use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Recent use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Past use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide + formoterol	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Recent use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Past use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium/formoterol	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Recent use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Past use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Tiotropium					
Current use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Recent use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Past use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Other LAMAs[b]					
Current use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Recent use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Past use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
LABA/ICS					
Current use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Recent use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Past use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
LABA/LAMA					
Current use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Recent use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Past use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)

CI = confidence interval; ICS = inhaled corticosteroids; LABA = inhaled long-acting beta$_2$-agonists; LAMA = long-acting anticholinergics.

[a] Adjusted for all confounding factors including age and sex. [b] Glycopyrronium bromide, umeclidinium.

Table 11. Shell Table for the Estimation of Crude and Adjusted Relative Risk Ratios (95% CI) for Each Study Endpoint Among Current User Subgroups of the Study Medications

Exposure Category	Number of Cases (%)	Number of Controls (%)	Crude Risk Ratio (95% CI)	Age- and Sex-Adjusted Relative Risk (95% CI)	Adjusted Relative Risk[a] (95% CI)
LABA					
Current single use	xx (%)	xx (%)	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Aclidinium bromide	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current single use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current switcher	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current multiple	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide + formoterol	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current single use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current switcher	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current multiple	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide/formoterol	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current single use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current switcher	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current multiple	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Tiotropium					
Current single use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current switcher	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current multiple	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Other LAMAs[b]					
Current single use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current switcher	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current multiple	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
LABA/ICS					
Current single use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current switcher	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current multiple	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
LABA/LAMA					
Current single use	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current switcher	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Current multiple	xx (x)	xx (x)	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)

CI = confidence interval; ICS = inhaled corticosteroids; LABA = inhaled long-acting beta-agonists; LAMA = long-acting anticholinergics.

[a] Adjusted for all confounding factors including age and sex.

[b] Glycopyrronium bromide, umeclidinium.

Table 12. Shell Table for the Estimation of Crude and Adjusted Relative Risk (95% CI) for Each Study Endpoint Comparing Current Single Use of Aclidinium Bromide With Current Single Use of Each Study Medication Other Than LABA

Comparison, Current Single Use	Crude Risk Ratio (95% CI)	Age- and Sex-Adjusted Relative Risk (95% CI)	Adjusted Relative Risk[a] (95% CI)
Aclidinium bromide vs. tiotropium	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide vs. glycopyrronium	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide vs. LABA/ICS	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide vs. LABA/LAMA	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide + formoterol vs. tiotropium	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide +formoterol vs. glycopyrronium	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide +formoterol vs. LABA/ICS	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide +formoterol vs. LABA/LAMA	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide/formoterol vs. tiotropium	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide/formoterol vs. glycopyrronium	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide/formoterol vs. LABA/ICS	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)
Aclidinium bromide/formoterol vs. LABA/LAMA	xx (xx, xx)	xx (xx, xx)	xx (xx, xx)

CI = confidence interval; ICS = inhaled corticosteroids; LABA = inhaled long-acting beta-agonists.

[a] Adjusted for all confounding factors including age and sex.

9.7.4 Subgroup Analyses

Several analyses stratified by subgroups of patients with special characteristics are anticipated for the estimation of crude and adjusted RRs (95% CI) for each study endpoint among current users of the study medications. In these subgroups of patients, each of the individual medications of interest—aclidinium bromide, tiotropium, other LAMAs (i.e., glycopyrronium bromide, umeclidinium), LABA/ICS, and LABAs—might be used selectively according to guidelines and competing indications.

The following subgroup analyses are of interest:

- Categories of severity of COPD
- Elderly patients (aged 65 to 74 years; aged 75 years or older) with significant comorbid conditions
- Treatments for comorbidities

- Use of inhaled corticosteroids
- Patients with COPD with and without history of asthma
- Patients with prior history of cardiovascular disease: AMI, CHD, cerebrovascular disease, heart failure
- Patients with a moderate to high cardiovascular risk profile calculated by risk scores or equations developed for cardiovascular risk prediction (e.g., Framingham risk scores, QRISK)
- Patients with other relevant comorbidities (i.e., pulmonary embolism, osteoporosis, or depressive disorders)

9.7.5 Effect of Dose and Duration

The effect of dose and duration of use will be estimated among current single users of each study medication as described in Section 9.3.2.1. For each study medication, dose will be categorised as low-medium or high using as the cut-off value the defined daily dose (DDD) for each formulation (e.g., inhaled powder, inhaled solution). Low-medium dose is defined as a daily dose equal or lower than the DDD. High dose is defined as a daily dose above the DDD. The DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. For each medication, the risk associated with each dose category (low-medium and high) will be compared with the risk associated with the low-medium dose category of each specific comparator (e.g., LABA).

In patients using aclidinium concomitantly with formoterol, the daily prescribed dose at the index date will be stratified by the formoterol dose.

A similar approach will be used to assess the effect of duration of current use. Duration of current use of each medication can be categorised as short or long according to the values of the distribution of duration (e.g., short as equal or lower than the median duration and long as any duration longer than the median duration). We will first examine the distribution of duration and categorise it into tertiles or quartiles for the analyses. Estimation of RR by duration categories of use will allow evaluation of the effect of the study medication according to the time since the initiation of treatment.

9.7.6 Errors, Inconsistent Values, and Missing Data

The frequency distribution of values for all variables to be used in the analyses will be obtained to identify possible errors or inconsistent values. Based on the detected potential errors or inconsistent values, we will explore how best to correct the error, when possible.

Regarding handling of missing values (i.e., smoking status, BMI) in this study, we have initially selected the CPRD in the UK because of the richness of detailed information on lifestyle habits and clinical conditions. However, there will be partially recorded information for some of these variables (i.e., data on smoking is available for some subjects but missing for others). We will use multiple imputation techniques to impute values for subjects with missing values. This will allow inclusion of observations with missing values in any analyses where that variable is essential, such as when the

variable is used as a predictor in the conditional logistic regression. If information is missing on only a small proportion of subjects (e.g., < 5% for all variables) we will not impute missing values but instead will exclude from an analysis subjects who are missing a value for a variable that is essential to that particular analysis.

If a database is ultimately used that does not contain information on a variable of interest (e.g., smoking, BMI), we will not include that variable in the analysis.

9.8 Quality Control

Standard operating procedures at each research centre will be used to guide the conduct of the study. These procedures include internal quality 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.

At RTI-HS, all programming written by one study analyst will be independently reviewed by a different analyst, with oversight by a senior statistician. All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

For RTI Health Solutions, an independent Office of Quality Assurance will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry and data transfer procedures and documentation, and institutional review board documentation. Such audits will be conducted by the Office of Quality Assurance according to established criteria in standard operating procedures and other applicable procedures.

A quality-assurance audit of this study may be conducted.

9.9 Limitations of the Research Methods

The design of this study will allow sequential evaluation of the risk of overall mortality and cardiovascular endpoints in new users of aclidinium bromide diagnosed with COPD. These risks will also be evaluated in new users of tiotropium, fixed-dose combinations of formoterol plus budesonide and salmeterol plus fluticasone propionate, and LABAs. The common reference group will be new users of LABAs.

Bias related to differential reporting of prescriptions or impacts of contacts with patients and health care professionals will be minimised because the study will be conducted using health information recorded in a population-based database that collect data on a regular basis.

The main limitations of this planned research are as follows:

- The timeline and ultimate precision of the results depends on the level of use of aclidinium bromide in the UK. If uptake in this country is less than expected, we propose to implement the study in Denmark. Lag time for capturing information on the main exposure of interest needs to be taken into account.

- Population-based databases record information routinely on full populations; however, the data were not originally intended for research purposes, meaning that some information desired for research may be incomplete.
- Prescriptions issued in the hospital setting will be missed, but this is expected to be minimal for aclidinium bromide. Data on pharmacy-dispensed medications (Denmark, Germany) or medications prescribed by physicians in the primary care setting (CPRD) will be captured. In the CPRD, prescriptions initiated by a specialist (e.g., pneumologist) may not be recorded in the database, but subsequent prescriptions are managed and recorded by the GP.
- Data on dose will be available if using information from medications prescribed by physicians in the primary care setting (CPRD). However, if the study is implemented in Denmark, dose information will need to be estimated from information on pharmacy-dispensed medications.
- Information relating to lifestyle, SES, or some specific comorbidities will be available only in the CPRD. This database has richer, more detailed clinical information as recorded by the GPs than the Danish national health databases.
- The degree of completeness in recording information for some variables, such as indicators of COPD severity, needs to be evaluated in the DUS.
- Misclassification of the clinical diagnoses of COPD, asthma, emphysema, and chronic bronchitis is a potential issue.
- If the study is implemented in Germany, out-of-hospital cardiovascular deaths will not be captured. Access to source medical records for sample validation of endpoints is not possible at this time in Germany and is possible on only a limited basis in Denmark.
- The availability of aclidinium/formoterol will impact the drug prescription patterns during the study period and prescription of new combinations, fixed or not; switching is expected to occur. The use of aclidinium monotherapy may decline after aclidinium/formoterol becomes available. The results of DUS 1 and DUS 2 will assist in evaluating this impact, and the CV PASS programme will be adjusted accordingly.

9.10 Other Aspects

The study will be conducted in accordance with the International Society for Pharmacoepidemiology (ISPE)[46] *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*.[47] The completed ENCePP Checklist for Study Protocols[48] is in Annex 2. The study will be registered in the ENCePP electronic register of post-authorisation studies (EU PAS register)[49] as detailed in the module VIII of the EMA *Guideline on Good Pharmacovigilance Practices (GVP)*.[50]

10 Protection of Human Subjects and Other Good Research Practice

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. In addition, the legal and IRB requirements for accessing and using de-identified, individual, patient–level data in the selected databases will be followed. Approval will be obtained from the institutional review board (IRB) at RTI International (of which RTI Health Solutions is a part).

CPRD, UK

The CPRD has obtained ethical approval from a Multi-centre Research Ethics Committee (MREC) for this type of observational research using CPRD data. However, approval from the MHRA's Independent Scientific Advisory Committee (http://www.gprd.com/ISAC/default.asp) for database research is required for each new study.[51]

GePaRD, Germany

For the GePaRD, approval is needed from the four Statutory Health Insurance (SHI) agencies providing data to the GePaRD. A summary of the protocol, outlining the public health importance of the research question, will be provided to the SHI agencies. After obtaining approval from the SHI agencies, approval of the project has to be obtained from the regulatory authorities responsible for such research in Germany. Approval from an IRB is not required in Germany because this study is based on pseudonymous data.

Denmark

Implementing the study in Denmark requires collaboration with a local university or investigator affiliated with a research institute to access the data and ethics committee notification and/or approval to handle data.[52,53]

10.1 Informed Consent

Not applicable.

10.2 Participant Confidentiality

Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

The study is a post-authorisation safety study (PASS) and will comply with the definition of the non-interventional (observational) study referred to in the ICH harmonised tripartite guideline Pharmacovigilance Planning E2E[54] and with the 2013 *Guideline on Good Pharmacovigilance Practices (GVP)* module VIII on post-authorisation safety studies.[50] This study does not pose any risks for patients. All data collected in the study will be de-identified with no breach of confidentiality with regards to personal identifiers or health information. Each database research partner will apply for an independent ethics committee review and/or other approvals according to local regulations.

10.3 Compensation

As this is a study using de-identified information from health care databases, no compensation will be provided to individuals whose data are used in this study.

11 Management and Reporting of Adverse Events/Adverse Reactions

Based on current guidelines from the International Society for Pharmacoepidemiology (ISPE)[46] and the EMA *Guideline on Good Pharmacovigilance Practices (GVP)*,[55] non-interventional studies such as the one described in this protocol conducted using medical chart reviews or electronic health care records do not require expedited reporting of suspected adverse events/reactions. Based on the data used for this study, no suspected adverse events/reactions are expected.

12 Plans for Disseminating and Communicating Study Results

Regulatory Communication Plan. The study protocol, study status, and report(s) will be included in regulatory communications in line with the risk management plan, Periodic Safety Update Report (PSUR), and other regulatory milestones and requirements.

Publication and Communication Plan. As per module VIII of the 2013 EMA *Guideline on Good Pharmacovigilance Practices (GVP)*,[50] the studies will be included in the EU PAS register.[49] Study results will be published following guidelines of the International Committee of Medical Journal Editors,[56] and communication in appropriate scientific venues, e.g., ISPE, will be considered. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be followed.[57]

In its *Guidelines for Good Pharmacoepidemiology Practices (GPP)*, ISPE contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance."[46] This would include results pertaining to the safety of a marketed medication. According to GVP guidelines on post-authorisation studies, AstraZeneca AB, and the investigator plan to agree upon a publication policy allowing the principal investigator to independently prepare publications based on the study results, irrespective of data ownership. AstraZeneca AB, will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.[50]

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Annex 1.
List of Stand-Alone Documents

None.

Annex 2. ENCePP Checklist for Study Protocols

Doc.Ref. EMEA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2, amended)

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

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

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

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Common Study Protocol

Study reference number:

[The EU PAS registry number will be added after registration]

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	15
1.1.2 End of data collection[2]	☒	☐	☐	15
1.1.3 Study progress report(s)	☒	☐	☐	15
1.1.4 Interim progress report(s)	☐	☐	☒	NA
1.1.5 Registration in the EU PAS register	☒	☐	☐	15
1.1.6 Final report of study results	☒	☐	☐	15

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	16-18
2.1.2 The objectives of the study?	☒	☐	☐	10, 18
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	10, 24-25
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	NA*
2.1.5 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	NA

Comments:

*The underlying "null hypothesis" in this observational comparative study is that there are not effect differences on the risk of each of the outcomes of interest between exposed and unexposed subjects

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, categorised controlled trial, new or alternative design)	☒	☐	☐	10, 18-21
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	11, 30-31
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	42-46

Comments:

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

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

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	11, 28-30
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	28-30
4.2.2 Age and sex?	☒	☐	☐	28-30
4.2.3 Country of origin?	☒	☐	☐	28-30
4.2.4 Disease/indication?	☒	☐	☐	28-30
4.2.5 Co-morbidity?	☒	☐	☐	28-30
4.2.6 Seasonality?	☐	☐	☒	NA
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	24, 26

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorizing exposure)	☒	☐	☐	35
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	35
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	11
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	NA
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	36

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	30-31
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	30

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	36, 74-79
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	35

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	28-30, 71-73
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	28-30, 71-73
8.1.3 Covariates?	☒	☐	☐	28-30, 71-73
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	28-30, 71-73
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	28-30, 71-73
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	28-30, 71-73
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	28-30
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	28-30
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	1, 28-30, 65-70
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	28-30, 30-34, 71-73

Comments:

ATC codes for exposures and comedications are also detailed in Annex 3.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	12, 39-41

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	41
10.2 Is the choice of statistical techniques described?	☒	☐	☐	41
10.3 Are descriptive analyses included?	☒	☐	☐	41
10.4 Are stratified analyses included?	☒	☐	☐	41
10.5 Does the plan describe the methods for adjusting for confounding?	☒	☐	☐	41
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	41

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	47-48
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	48
11.3 Are methods of quality assurance described?	☒	☐	☐	48
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	28-30, 32-33
11.5 Is there a system in place for independent review of study results?	☐	☐	☒	NA*

Comments:

*At this time, no independent advisory body is planned. For data management and quality control at RTI-HS, all programing written by one study analyst will be independently reviewed by a second analyst (see page 47).

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☐	☐	☒	NA
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	NA
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	12, 26-27
12.3 Does the protocol address other limitations?	☒	☐	☐	48-49

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/ Institutional Review Board approval been described?	☒	☐	☐	49-50
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	NA
13.3 Have data protection requirements been described?	☒	☐	☐	50

Comments:

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

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	51
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	51

Comments:

Name of the main author of the protocol: Cristina Varas-Lorenzo, M.D.

Date: 02 Jun 2015

Signature: [redacted]

Annex 3.
Codes for Medications and Diagnoses

Annex Table 3-1. ATC Codes and Defined Daily Doses by Therapeutic Class

Therapeutic Class	Substance Name	ATC Code	DDD		
			Inhaled Aerosol	Inhaled Powder	Inhaled Solution
Short-acting anticholinergics	Ipratropium bromide	R03BB01	0.12 mg	0.12 mg	0.3 mg
	Oxitropium bromide	R03BB02	0.6 mg		4 mg
Long-acting anticholinergics	Tiotropium bromide	R03BB04		18 mcg	5 mcg
	Aclidinium bromide	R03BB05		0.644 mg[a]	
	Glycopyrronium bromide	R03BB06		44 mcg[a]	
Short-acting beta$_2$-agonists	Salbutamol	R03AC02	0.8 mg	0.8 mg	10 mg
	Terbutaline	R03AC03	2 mg	2 mg	20 mg
	Fenoterol	R03AC04	0.6 mg	0.6 mg	4 mg
	Rimiterol	R03AC05	1.6 mg		
	Hexoprenaline	R03AC06	1.5 mg		
	Isoetarine	R03AC07			
	Pirbuterol	R03AC08	1.2 mg		
	Tretoquinol	R03AC09			
	Carbuterol	R03AC10			
	Tulobuterol	R03AC11	1.6 mg		
	Reproterol	R03AC15			
	Procaterol	R03AC16	60 mcg		
	Bitolterol	R03AC17			
Long-acting beta$_2$-agonists	Salmeterol	R03AC12	0.1 mg	0.1 mg	
	Formoterol	R03AC13	24 mcg	24 mcg	
	Clenbuterol	R03AC14			
	Indacaterol	R03AC18		0.15 mg[b]	
	Olodaterol	R03AC19			
Combinations short-acting beta$_2$-agonists and other drugs for obstructive airways disease	Epinephrine and other drugs for obstructive airway diseases	R03AK01			
	Isoprenaline and other drugs for obstructive airway diseases	R03AK02			
	Salbutamol and sodium cromoglicate	R03AK04			
	Reproterol and sodium cromoglicate	R03AK05			

Therapeutic Class	Substance Name	ATC Code	DDD		
			Inhaled Aerosol	Inhaled Powder	Inhaled Solution
Combinations long-acting beta$_2$-agonists and other drugs for obstructive airways disease	Salmeterol and fluticasone	R03AK06			
	Formoterol and budesonide	R03AK07			
	Formoterol and beclometasone	R03AK08			
	Formoterol and mometasone	R03AK09			
	Vilanterol and fluticasone furoate	R03AK10			
	Formoterol and fluticasone	R03AK11			
Inhaled glucocorticoids	Beclometasone	R03BA01	0.8 mg	0.8 mg	1.5 mg
	Budesonide	R03BA02	0.8 mg	0.8 mg	1.5 mg
	Flunisolide	R03BA03	1 mg		
	Betamethasone	R03BA04			
	Fluticasone	R03BA05	0.6 mg	0.6 mg	1.5 mg
	Triamcinolone	R03BA06			
	Mometasone	R03BA08		0.4 mg	
	Ciclesonide	R03BA06	0.16 mg		
Methylxanthines and adrenergics		R03DA, R03DB			
Adrenergics for systemic use		R03C			
Leukotriene receptor antagonists and other systemic drugs		R03DC, R03DX			
Mucolytics		R05CB			
	Carbocisteine	R05CB03			
Systemic glucocorticoids		H02AB			
Phosphodiester-ase-4 inhibitors	Roflumilast	R03DX07			
Cromones	Cromoglicic acid	R03BC01	40 mg	80 mg	80 mg
	Nedocromil	R03BC03	8 mg		
Oxygen	Oxygen	V03AN01			

ATC = Anatomical Therapeutic Chemical; DDD = defined daily dose. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. NA = not yet available in the online ATC/DDD Index.

[a] Note: calculated DDD: aclidinium bromide, 0.644 mg (inhaled powder); glycopyrronium bromide, 44 mcg (inhaled powder).

[b] In Europe, the dose of 300 ug once daily is also approved.

Source: WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2014. Updated 19 December 2013. Available at: http://www.whocc.no/atc_ddd_index/. Accessed 20 January 2014.

Annex Table 3-2. Concurrent Use of Other Medications

Therapeutic Class	ATC code
Antihistamines for systemic use	R06
Antitussives	R05
Antibiotics	J01
Vaccines	J07
Cardiovascular medications	C01-C10
Lipid-lowering drugs	C10
Agents acting on rennin-angiotensin system	C09
Beta-blockers	C07
Calcium channel blockers	C08
Diuretics	C03
Other antihypertensive medications	C02
Antiarrhythmics	C01B
Nitrates	C01DA
Antithrombotic agents	B01A
Drugs used in diabetes	A10
Insulins	A10A
Blood glucose–lowering drugs	A10B
Other to be specified	

Annex Table 3-3. ICD 10 Codes to Identify Underlying Cause of Death for Potential Community Coronary Heart Disease and Cerebrovascular Disease Deaths

Coronary Heart Disease Deaths	Cerebrovascular Disease Deaths
I10, Essential hypertension	I60, Subarachnoid haemorrhage
I11.9, Hypertensive heart disease, w/o heart failure	I61, Intracerebral haemorrhage
I20, Angina pectoris	I62, Other non-traumatic intracranial haemorrhage
I21, Acute MI (AMI)	I63, Cerebral infarction
I22, Subsequent MI	I64, Stroke, not specified as haemorrhage or infarction
I23, Certain current complications of AMI	I65, Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I24, Other acute ischaemic heart disease	I66, Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I25.2, Old MI	I67, Other cerebrovascular diseases
I25, Chronic ischaemic heart disease	I68, Cerebrovascular disorders in diseases classified elsewhere
I42.8-.9, Cardiomyopathy, unspecified	I69, Sequelae of cerebrovascular disease
I46, Cardiac arrest & sudden cardiac death	G45, Transient cerebral ischaemic attacks and related syndromes
I47.0-.2, Ventricular tachycardia	
I49.0, Ventricular fibrillation and flutter	
I49.8.-9, Cardiac arrhythmia, unspecified	
I51.6, Cardiovascular disease, unspecified	
I51.9, Heart disease, unspecified	
I70.9, Generalised and unspecified atherosclerosis	
R96.1, Death < 24 hours after symptoms	R96.1, Death < 24 hours after symptoms
R98, Unattended death	R98, Unattended death

AMI = acute myocardial infarction; ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; MI = myocardial infarction; NOS = not otherwise specified.

Annex 4.
Proposed European Databases

Annex Table 4-1. Main Features of Proposed European Databases

Description	United Kingdom, CPRD (N = 62,435.709)[a]	Danish Patient and Prescription National Databases (N = 5,552,037)[a]	German Pharmacoepidemiological Research Database (N = 81,751,602)[a]
Database type	Primary health care electronic medical record database plus partial linkage to HES and other data	National health record databases capable of linkage with other databases through a unique personal identification number	Claims databases, four Statuary Health Insurance (SHI) plans
Database population	5.1 million	5.6 million	14 million
Proportion of the country's population covered by the database	8%	100%	17%
Representativeness of patients	Representative of sex and age of UK population	Total population covered	Representative of sex and age of German population
Data on medications and type of prescriptions	Prescriptions issued by GPs	Pharmacy-dispensed prescriptions, reimbursed and unreimbursed In regional databases, only reimbursed prescriptions	All dispensed drugs prescribed in ambulatory settings, which are reimbursed by the SHIs
Dose	Prescribed dose	Formulation strength	Formulation strength
Duration	As indicated in the prescription	Based on prescriptions	Based on prescriptions
Drug dictionary codes/ therapeutic classification	Multilex/British National Formulary	ATC	ATC
Clinical indication	Diagnosis associated with new courses of medications, but completeness is variable Computerised free-text information is available for review	Not specifically recorded but based on proxies	Not specifically recorded but based on proxies

Description	United Kingdom, CPRD (N = 62,435.709)[a]	Danish Patient and Prescription National Databases (N = 5,552,037)[a]	German Pharmacoepidemiological Research Database (N = 81,751,602)[a]
Outpatient diagnosis	Yes	Only outpatient hospital diagnosis in the national patient registry In regional databases (Aarhus, OPED), ambulatory care diagnoses available	Yes (diagnoses can be allocated quarterly each year but no exact date is available)
Hospital diagnosis	Recorded by GPs and partial linkage to HES	Yes	Yes
Disease and procedure codes	Read codes ICD-10-CM codes (HES)	ICD-10-CM	ICD-10-GM
Lifestyle risk factors	Yes	Partially, in regional databases	No
Data availability	Since 1987	Since 1994	Since 2004
Approximate time lag (updates per year)	6-12 weeks (3-4 per year)	National data, 1 year Regional data, 1-2 months (1 per year)	1.8 year (1 per year)
Approval process for database research	Independent Scientific Advisory Committee approval of protocol	Data application and ethics committee approval required depending on level of data	Approvals by SHIs and Health Ministry are required

ATC = Anatomical Therapeutic Chemical; CPRD = Clinical Practice Research Datalink; GP = general practitioner; HES = Hospital Episode Statistics (database); ICD-10 = International Statistical Classification of Diseases and Related Health Problems, 10th Revision; ICD-10-GM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification; OPED = Odense University Pharmacoepidemiology Database; SHI = Statuary Health Insurance (Germany); UK = United Kingdom.

[a] Population data from Eurostat. 2011. Available at: http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/database. Accessed 12 July 2012.

Annex 5. Potential Confounding and Risk Factors

Annex Table 5-1. Demographic, Lifestyle, and Use of Health Services

Variable	Variable definition
Age	Years
Sex	Female Male
Calendar year	Year
SES indicator	Townsend categories in linked English practices
Smoking	Never smoker, current smoker, former smoker, unknown
Body mass index (kg/m2)	BMI< 18.50, underweight
	BMI 18.50-24.99, normal weight
	BMI 25.00-29.99, pre-obesity
	BMI > 30
	Unknown
Alcohol consumption (g/L)	Number of g/L
Use of health services in the year before the date of cohort entry	
Number of hospitalisations	Number
Number of GP visits	Number
Number of referrals to specialist	Number
Number of prescriptions received for respiratory medications	Number
Number of prescriptions received for other medications	Number

Annex Table 5-2. Medical History

Variable	ICD-10 Codes
Cardiovascular disease	
Cardiovascular risk category	Algorithm[a]
Angina	I20
Myocardial infarction	I21-I23, I25.2
Other coronary heart disease	I24-I25.0-I25.1, I25.3-I25.9
Valvular heart disease	I05-I08,I34-I39
Atrial fibrillation/flutter	I48
Other arrhythmias	I47, I49
Conduction disorders	I44-I45
Cardiac arrest with resuscitation	I46.0
Stroke	I60-I61, I63-I64, I69.0-I69.3
Transient ischaemic attack (TIA)	I65-I66; G45
Other cerebrovascular disease	I62, I68
Peripheral vascular disease	I70.2,I73.9
Heart failure	I50
Hypertension	I10-I15
Hyperlipidaemia	E78
Other cardiovascular diseases	I00-I02, I09,I30-I33, I40-I43, I51-I52, I95-I99
Other cardiovascular symptoms	R00, R01, R03, R06, R07,R09.8
Diabetes	E10-E14
Chronic renal failure	N18 excluding N18.5, N19
Chronic liver disease	K70.0-K70.3, K70.9, K71.0, K71.2-K71.9, K73, K74, K75, K76.0, K76.1, K76.3-K76.6, K76.8, K76.9
Connective tissue disease	M30-M36
Peptic ulcer disease	K25-K28
Pulmonary embolism	I26.0-I26.9
Osteoporosis	M80- M81
Depressive disorders	F32-F33
Dementia	F00-F03
Summary score of adapted Charlson Comorbidity Index[b]	Annex Table 5-3

Variable	ICD-10 Codes
Respiratory disease	
COPD severity	Classification detailed in Table 7
Nebuliser prescribed/dispensed in the prior 6 months	(Read codes)
COPD hospitalisation in the prior year	J44, J40-J42, J43
Diagnosis of pneumonia in the prior year	J10.0, J11.0, J12-J18
Diagnosis of emphysema at any time before the date of cohort entry	J43
Diagnosis of asthma at any time before the date of cohort entry	J45

[a] The cardiovascular risk profile generated at baseline can be used to stratify all patients by the extent to which their recent cardiovascular profiles are similar across treatment cohorts. The final cardiovascular risk equation to be used will be selected based on the availability of data on each cardiovascular risk factor and the estimated performance on the selected population.

[b] The Charlson Comorbidity Index[58] will be adapted to exclude from the components COPD diagnosis and those diagnoses corresponding to overall exclusion criteria (i.e., malignancies)

Annex Table 5-3. Adaptation of the Charlson Comorbidity Index Components and Weights

Diagnostic Category ***(excluded)***	**Description**	**Weight**
Myocardial infarction	▪ Acute myocardial infarction ▪ Old myocardial infarction	1
Congestive heart failure	▪ Heart failure	1
Peripheral vascular disease	▪ Peripheral vascular disease, including intermittent claudication ▪ Aortic aneurism ▪ Gangrene ▪ Blood vessel replacement of lower limb arteries	1
Chronic pulmonary disease (excluded)	▪ *Chronic obstructive pulmonary disease* ▪ *Pneumoconioses* ▪ *Chronic respiratory conditions due to fumes and vapors*	*1*
Connective tissue disease	▪ Systemic lupus erythematous ▪ Systemic sclerosis ▪ Polymyositis ▪ Rheumatoid arthritis ▪ Polymyalgia rheumatica	1
Peptic ulcer disease	▪ Gastric, duodenal, and gastrojejunal ulcers ▪ Chronic forms of peptic ulcer disease	1
Cerebrovascular disease	▪ Cerebrovascular disease	1
Dementia	▪ Senile and presenile dementias	1
Mild liver disease	▪ Alcoholic cirrhosis ▪ Cirrhosis, without mention of alcohol ▪ Biliary cirrhosis ▪ Chronic hepatitis	1
Diabetes	▪ Diabetes with or without acute metabolic disturbances ▪ Diabetes with peripheral circulatory disorder	1
Diabetes with chronic complications	▪ Diabetes with renal, ophthalmic, or neurological manifestations	2
Hemiplegia, paraplegia	▪ Hemiplegia ▪ Paraplegia	2
Moderate or severe renal disease	▪ Chronic glomerulonephritis ▪ Nephritis and nephropathy ▪ Chronic renal failure ▪ Renal failure, unspecified ▪ Disorders resulting from impaired renal function	2
Malignancies (excluded)	▪ *Malignant neoplasms*	*2*
Leukaemia (excluded)	▪ *Leukaemia*	*2*
Lymphoma (excluded)	▪ *Lymphoma*	*2*

Diagnostic Category *(excluded)*	**Description**	**Weight**
Moderate or severe hepatic disease	▪ Hepatic coma, portal hypertension, other sequelae of chronic liver disease ▪ Oesophageal varices	3
Metastatic solid tumour (excluded)	▪ *Secondary malignant neoplasm of lymph nodes and other organs*	*6*
AIDS (excluded)	▪ *HIV infection with related specified conditions*	*6*