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Aclidinium Bromide Drug Utilisation Post-Authorisation Safety Study

Common Protocol, Version 1.1

14 April 2014

Prepared for

Esther Garcia Gil

Head of Late Stage Development Respiratory
Almirall, S.A.
Ctra. Laureà Miró, 408-410
Sant Feliu de Llobregat, 08980
Barcelona, Spain
Telephone: +34.93.291.7519
E-mail: esther.garciagil@almirall.com

Prepared by

Cristina Varas-Lorenzo, MD, PhD
Jordi Castellsague, MD, MPH
Susana Perez-Gutthann, MD, PhD, FRCP, FISPE

RTI Health Solutions
Barcelona, Spain, and Research Triangle Park, NC
E-mail: cvaras@rti.org

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Authors	Cristina Varas-Lorenzo, MD, PhD; Jordi Castellsague, MD, MPH; Susana Perez-Gutthann, MD, PhD (RTI Health Solutions)
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The following people have reviewed the protocol and give their approval:

RTI Health Solutions

Cristina Varas-Lorenzo, MD, PhD Director, Epidemiology	*Signature*	*Date*
Susana Perez-Gutthann MD, PhD Vice-President, Global Head Epidemiology	*Signature*	*Date*

Almirall, S.A.

Esther Garcia Gil, MD Head of Late Stage Development Respiratory Global Clinical Development	*Signature*	*Date*
Gemma Jiménez, EU QPPV Corporate Drug Safety	*Signature*	*Date*

Database Investigators

	Signature	*Date*
	Signature	*Date*
	Signature	*Date*

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ABBREVIATIONS

AIDS	acquired immune deficiency syndrome
AMI	acute myocardial infarction
ATC	Anatomical Therapeutic Chemical (classification)
BMI	body mass index
CAT	CAT= COPD assessment test
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Database (UK)
DDD	defined daily dose
DUS	drug utilisation study
EBM	Einheitlicher Bewertungsmaßstab codes (Germany)
EMA	European Medicines Agency
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	general practitioner
GPP	Good Pharmacoepidemiology Practices
GPRD	General Practice Research Database (UK)
HES	Hospital Episode Statistics (UK)
HIV	human immunodeficiency virus
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICD-10-CM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification
ICD-10-GM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, German Modification
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ID	identification number
ISPE	International Society for Pharmacoepidemiology
LA	long-acting
LABA	long-acting beta-agonist
OPED	Odense University Pharmacoepidemiology Database
PASS	post-authorisation safety study
PPV	positive predictive value
PSUR	Periodic Safety Update Report
RMP	risk management plan
RTI-HS	RTI Health Solutions
SA	short-acting
SES	socioeconomic status
SHI	statutory health insurance agency (Germany)

STROBE	Strengthening the Reporting of Observational Studies in Epidemiology (checklist)
UK	United Kingdom
WHO	World Health Organization

1 TITLE

Aclidinium Bromide Drug Utilisation Post-Authorisation Safety Study: Common Protocol, Version 1.1

2 MARKETING AUTHORISATION HOLDER

Almirall, S.A.

3 RESPONSIBLE PARTIES

RTI Health Solutions—Barcelona Trav. Gracia 56, Atico 1 08006 Barcelona, Spain
Cristina Varas-Lorenzo, MD, PhD; Director, Epidemiology
Jordi Castellsague, MD, MPH; Director, Epidemiology
Susana Perez-Gutthann MD, PhD, FRCP, FISPE*;* Vice-President, Global Head Epidemiology

Almirall, S.A. Ctra. Laureà Miró, 408-410 Sant Feliu de Llobregat, 08980 Barcelona, Spain
Esther Garcia Gil, MD; Head of Late Stage Development Respiratory
Gemma Jiménez, EU QPPV, Head of Corporate Drug Safety

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

4 ABSTRACT

Title

Aclidinium Bromide Drug Utilisation Post-Authorisation Safety Study: Common Protocol, Version 1.1, 14 April 2014

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

Rationale and Background

Aclidinium bromide (Eklira/Bretaris Genuair) is a new, long-acting and potent antagonist of lung M3 receptors indicated as maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

A pharmacovigilance plan, including a post-authorisation safety study (PASS), for Eklira/Bretaris Genuair will be implemented as part of the marketing authorisation in Europe. The first step in the European PASS is to cover aspects related to drug utilisation, off-label use, and identification of patient groups with missing information in the risk management plan (RMP).

A multicountry database drug utilisation study (DUS) in a cohort of new users of aclidinium bromide and new users of other inhaled medications frequently used by patients with COPD will be implemented.

Research Question and Objectives

The objectives of this DUS are as follows:

- To describe the characteristics and patterns of use of new users of aclidinium bromide and new users of other selected COPD treatments.
- To evaluate the potential off-label use of aclidinium bromide
- To describe users of aclidinium bromide in subgroups of patients for whom there is missing information in the RMP
- To establish a core cohort of new users of aclidinium bromide for the future evaluation of safety concerns described in the RMP

Study Design

Non-interventional, multicountry European cohort study of new users of aclidinium bromide and new users of tiotropium, glycopyrronium bromide, fixed-dose combinations of long-acting beta-agonists with inhaled corticosteroids (LABA+ICS), and LABA.

New users of the study medications will be characterised (1) at the index date according to prior clinical information and prior and concurrent use of medications and (2) during

the year following the index date to assess patterns of use of aclidinium bromide including duration, dose, switching, and concomitant use of other medications.

Population

New users of aclidinium bromide, tiotropium, LABA+ICS, and LABA will be identified in selected European databases. Patients will be required to have at least 1 year of enrolment in the database and to have not been prescribed aclidinium bromide or a study medication of interest during the 6 months before the date of the first prescription for each study medication.

Health Databases

This study will be conducted using information collected in automated health care databases. Based on the latest available launch sequence and the projected number of patients to be treated by country, the primary potential databases are the Clinical Practice Research Datalink (CPRD)—formerly the General Practice Research Database (GPRD)—in the United Kingdom, the German Pharmacoepidemiological Research Database (GePaRD) at the Leibniz Institute for Prevention Research and Epidemiology (BIPS GmbH) in Germany (approvals pending), and the national health databases in Denmark. The DUS will be implemented in these three databases if possible. However, actual capture of the use of aclidinium bromide can be monitored in other available databases in Spain and Italy to finally select the three best candidates based on the number of users.

Variables

Comorbidities of interest will be assessed by outpatient visits, hospitalisations, and procedures, as available in each database.

Baseline Characteristics, Comorbidities, and Comedications

The following characteristics will be ascertained for the year before the index date of each study medication:

- Demographics: age and sex
- Lifestyle (smoking, body mass index) and socioeconomic status (SES) indicators
- Diagnosis of COPD including emphysema or chronic bronchitis
- Indicators of COPD severity, including recent exacerbations
- History of cardiovascular diseases and baseline cardiovascular risk profile, including diabetes, recent acute myocardial infarction (AMI), unstable angina, arrhythmias, or heart failure
- Renal impairment
- Hepatic impairment

- Benign prostatic hyperplasia, bladder neck obstruction, urinary retention
- Narrow-angle glaucoma
- Overall comorbidity index
- Use of respiratory medications
- Comedications
- Pregnancy

Identification of Potential Off-Label Use

Off-label use will be evaluated by treatment indications, based on available diagnostic information or by the presence of an aclidinium bromide prescription with a diagnosis of asthma with or without any records (drugs or diagnoses) suggesting a COPD diagnosis. The proportion of patients with codes for both COPD and asthma will be evaluated.

The potential frequency of use in the pediatric population or during pregnancy will be evaluated.

Exposures

The exposures of interest are aclidinium bromide, tiotropium, glycopyrronium bromide, LABA+ICS, and LABA. LABA+ICS includes formoterol plus budesonide and salmeterol plus fluticasone propionate. LABA includes formoterol, salmeterol, and indacaterol. Any LABA+ICS combinations that may become available during the study period will be included if users are captured in the databases.

Patterns of use of each study medication will be ascertained among patients diagnosed with COPD by the total number of prescriptions, prescription rates, duration of use, switching patterns, and concomitant use of other medications.

Duration of use will be estimated through the number of consecutive prescriptions with a maximum interval of 60 days between them.

Data Sources

Study variables including endpoints, exposures, and covariates will be ascertained in the database(s) selected for this study according to the definitions and procedures provided in the corresponding section on variables.

Study Size

All available new users of aclidinium bromide at study initiation in each database will be included. The estimated study target for the DUS is between 1,500 and 2,000 new users of aclidinium bromide and a random sample of 2,000 new users of each of the comparators—tiotropium, LABA+ICS, and LABA—in each country-specific database.

A study size between 1,500 and 2,000 new users of aclidinium bromide per database offers an acceptable level of precision in the different scenarios when estimating the percentage of off-label use or use by different subgroups with missing information in the RMP.

Data Analysis

The analysis will be implemented in two phases:

Phase 1. Baseline analysis:

- Age and sex distribution of users
- Proportion of patients with the above listed characteristics, comorbidities, and comedications for up to 1 year before the index date.
- Proportion and description of patients with off-label use.

Phase 2. Follow-up analysis:

- Assessment of relevant comorbidities, pregnancies, and treatment patterns (duration, dose, and switching patterns) during 1 year after the index date.

Milestones

In 2012 Eklira/Bretaris Genuair was launched in Denmark, Germany, and the United Kingdom. The launch in Spain occurred in January 2013. Monitoring of the number of users of aclidinium bromide in each database started in December 2013, and data collection is expected to start in 2015. In each study database, phase 1 analyses will be conducted when the number of users of aclidinium bromide reaches the target range, and phase 2 analyses are anticipated to occur 1 year after the phase 1 analyses. Study progress reports will be submitted at 6-month intervals, with the Periodic Safety Update Reports. A final report of study results is anticipated 6 months following the phase 2 analyses.

5 AMENDMENTS AND UPDATES

Number	Date	Section of Study Protocol	Amendment or update	Reason
1	10 Mar 2014	Abstract, 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
1	10 Mar 2014	Milestones	Timelines have been adjusted	Number of aclidinium users in the CPRD is lower than expected.

6 MILESTONES AND TIMELINE

Milestone	Date
Launch[a] of aclidinium in the United Kingdom	October 2012
Launch[a] of aclidinium in Germany	October 2012
Launch of aclidinium in Denmark	September 2012
Launch of aclidinium in Spain[a]	January 2013
Common protocol v1.0, 23 January 2013 endorsed by EMA	30 April 2013
EU PAS registration	Planned 2Q 2014
Start monitoring number of users	December 2013
Start of data collection[b]	Expected in 2015
End of data collection for phase 1[c]; phase 1 analysis	Expected in 2015; Time period will be adjusted based on the use in the target countries and final confirmation of databases
End of data collection for phase 2[c]; Phase 2 analysis	1 year after the phase 1 analysis
Study progress report(s)	6-month intervals, with PSURs
Interim report(s) of study results, if applicable	NA
Final report of study results	6 months following after phase 2 analysis start.

[a] Aclidinium reimbursement is available in the United Kingdom, Germany, Denmark, and Spain.

[b] The date from which data extraction starts.

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

EMA = European Medicines Agency.

Note: Contracts with some research organizations 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

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality worldwide (Mannino and Buist, 2007). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defined COPD as "*a preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients*." (GOLD, 2011). The updated GOLD report provided the foundation for a global strategy for the diagnosis, management, and prevention of COPD. Different pharmacologic approaches are recommended to reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. GOLD identified four categories—determined by the patient's lung function as measured by spirometry, presence of symptoms, and number of exacerbations per year—to guide the initial pharmacological management of COPD, including the use of long-acting inhaled anticholinergics.

In July 2012, Eklira/Bretaris Genuair (aclidinium bromide 322 µg twice daily) was approved in the European Union (EU) for maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD (European Medicines Agency [EMA], 2012a). The Food and Drug Administration (FDA) in the United States (US) also approved aclidinium bromide for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema (National Health Service, 2012).

The active substance, aclidinium bromide (Anatomical Therapeutic Chemical [ATC] category R03BB, anticholinergics), is a kinetically selective, long-acting, and potent muscarinic receptor antagonist whose relevant pharmacological effect is on lung M3 receptors, antagonising the bronchoconstrictive response of acetylcholine, leading to smooth muscle relaxation.

A pharmacovigilance plan, including a post-authorisation safety study (PASS), for Eklira/Bretaris Genuair will be implemented as part of the marketing authorisation in Europe. The first step in the European PASS is to cover aspects related to drug utilisation, off-label use, and identification of patient groups with missing information in the risk management plan (RMP), version 2.3, May 2012 (see the specific objectives listed on the next page in Section 8). To investigate these aspects, we propose to conduct a multicountry database drug utilisation study (DUS) in a cohort of new users of aclidinium bromide and new users of other inhaled medications frequently used by patients with COPD. The study will be conducted using information from automated health databases that record clinical information on an ongoing basis. This common protocol is based on the study protocol summary included in Annex 5 of the risk management programme for aclidinium bromide in Europe.

The patients included in this DUS will also become the core of a larger patient cohort in which many of the safety concerns outlined in the RMP can be evaluated in a later stage.

8 RESEARCH QUESTION AND OBJECTIVES

Epidemiological studies on the use of drugs are essential to evaluate the intended and adverse effects of prescription medications as they are used in clinical practice across populations under different health care systems. Drug use studies allow for characterisation of users of the medication in terms of age and sex, treatment indication, use of concurrent medications, prior morbidity, and other characteristics including those subgroups for which there is missing information in the RMP. The description of users of aclidinium bromide according to their clinical indication for use will allow for the evaluation of potential off-label use.

The main objectives of the DUS for aclidinium bromide are as follows:

- To describe the characteristics of new users of aclidinium bromide and of other selected COPD treatments, including agents in the same class, regarding age, sex, history of chronic disease including cardiovascular diseases, COPD severity, and prior use of COPD medications and other medications
- To describe the patterns of use of aclidinium bromide and other selected COPD treatments, among new users, regarding duration of treatment, dose, switching patterns, and use of concomitant medications
- To evaluate the potential off-label use of aclidinium bromide in adults and children
- To identify and describe users of aclidinium bromide in patient subgroups for which there is missing information in the RMP
- To establish the core of a cohort of new users of aclidinium bromide for the future evaluation of safety concerns described in the RMP

After launch, the number of users of aclidinium bromide will be monitored until the target number of new users required for analysis is reached in targeted population-based databases (see Section 9.4).

The following specific evaluations will meet the main objectives and enable the EMA reviewers' requests to be addressed:

Describe new users of aclidinium bromide and other COPD regimens—including tiotropium, glycopyrronium bromide, the inhaled long-acting beta-agonists (LABA) formoterol, salmeterol, and indacaterol; the fixed-dose combinations of LABA (formoterol or salmeterol) with inhaled corticosteroids (ICS) currently available plus any LABA+ICS combinations that may become available during the study period if users are captured in

the databases—at the first prescription (index date) according to medical history during the year before the index date.

- Characterise new users according to the following characteristics, as available:
  - Age and sex distribution
  - Smoking history or status
  - Diagnosis of COPD including emphysema or chronic bronchitis
  - Indicators of COPD severity
  - History of cardiovascular diseases and baseline cardiovascular risk profile, including diabetes
  - Overall comorbidity index
  - Use of respiratory medications
- Characterise potential off-label use in adults and the paediatric population
  - The frequency of users of aclidinium bromide who have an asthma diagnosis concomitantly with COPD or in the absence of other drugs or diagnoses suggestive of COPD
  - The frequency of pregnancies during use of medication
  - The frequency of use and indication in the paediatric population and comorbidity profile in paediatric patients.
- Obtain baseline frequency of the following groups of patients, to the extent that information is available, for whom the RMP lists important information as missing:
  - Patients with recent acute myocardial infarction (AMI), unstable angina, unstable arrhythmias, or heart failure
  - Patients with renal or hepatic impairment
  - Patients with benign prostatic hyperplasia, bladder neck obstruction, urinary retention, or narrow-angle glaucoma
  - Patients who have experienced a recent exacerbation
- Describe the patterns of use of new users of aclidinium bromide and other selected COPD medications regarding duration of use, dose, switching patterns, and concomitant use of other medications.

9 RESEARCH METHODS

Observational research methodology will be applied to accomplish the objectives listed above.

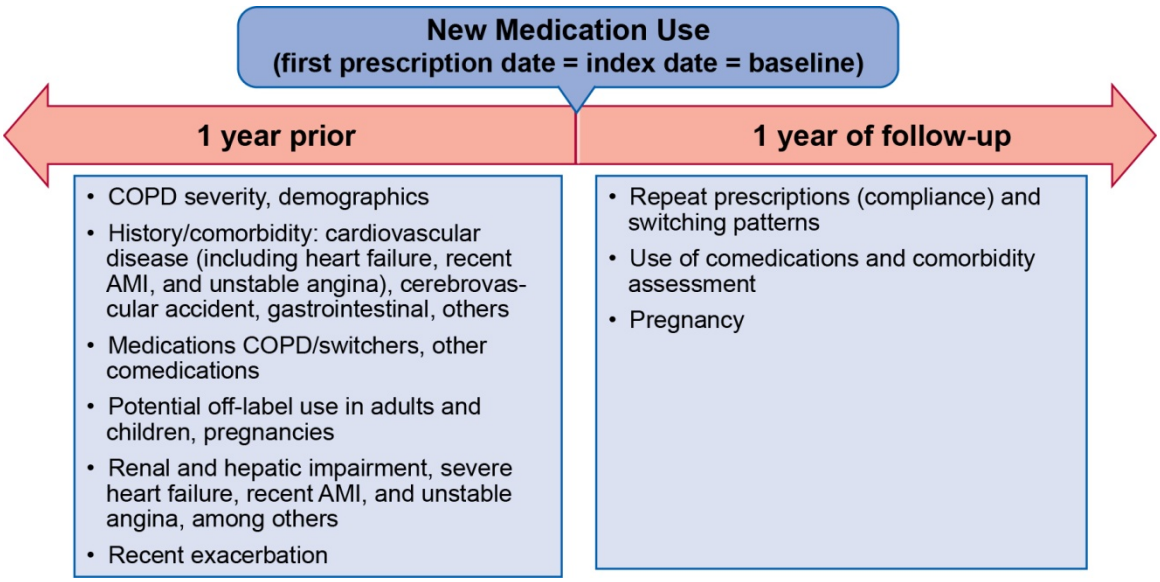
9.1 Study Design

This common protocol is for a descriptive, non-interventional, multicountry European cohort study of new users of aclidinium bromide and new users of other selected treatments for COPD including tiotropium, glycopyrronium bromide, inhaled long-acting beta-agonists (LABAs), and fixed-dose combinations of LABA+ICS (formoterol plus budesonide, salmeterol plus fluticasone propionate, and any combinations that may become available during the study period) (see Section 9.3.8).

A ***new user*** will be defined as a patient who receives a first prescription for aclidinium bromide or one of the other listed COPD drugs of interest during the study period and has no previous prescription for that specific drug in the 6 months before that first prescription. The date of the first prescription for a given medication during the study period will define the index date for that individual new user.

New users of aclidinium bromide or of the other selected COPD medications will be characterised (1) at the index date according to prior clinical information and prior and concurrent use of medications and (2) during the year following the index date to assess patterns of use of aclidinium bromide including duration, dose, switching, and concomitant use of other medications (Figure 1).

Figure 1. Study Overview



Note: The same approach will be used for the aclidinium bromide user group and for the comparator groups.

9.1.1 Follow-up

To evaluate the patterns of use of the medications of interest, each member of the study cohorts will be followed from the first date the patient is prescribed aclidinium bromide or another selected COPD medication to the earliest of the following dates:

(1) 1 year from index date, or

(2) Death, or

(3) Disenrolment from the database.

9.1.2 Study Period

The ***study period*** will encompass the time period from the launch of aclidinium bromide in each country until the target number of new users is reached in each selected country-specific database and these new users complete the 1-year follow-up period. The country-specific studies may start on different dates and may have study periods of different durations.

9.2 Setting

9.2.1 Study Cohorts

New users of aclidinium bromide, tiotropium, glycopyrronium bromide, LABA (formoterol, salmeterol, or indacaterol), and LABA+ICS (formoterol plus budesonide, salmeterol plus fluticasone propionate, and any combinations that may become available during the study period) will be identified and included in the specific exposure cohort of interest.

9.2.1.1 Inclusion Criteria

Patients in the study will be required to meet the following criteria, as ascertained from each of the automated databases:

- To have at least 1 year of enrolment in the database.
- To have not been prescribed aclidinium bromide during the 6 months before the date of first prescription of aclidinium bromide.

The same inclusion criteria will be applied for each of the comparator drugs.

9.2.1.2 Exclusion Criteria

No age restrictions or exclusion criteria will be applied. This will allow for the characterisation of all users of aclidinium bromide and comparator drugs irrespective of the indication for which these medications are used. Identification of potential off-label

use of aclidinium bromide in the paediatric and adult populations is one of the specific objectives of this DUS.

9.2.2 Index Prescription

The first captured prescription for aclidinium bromide in the study period for each new user in the source population will be the *index prescription*. Aclidinium bromide is assigned an ATC code R03BB05 classified under the inhalant anticholinergic category (ATC R03BB). The ATC codes for the other available long-acting inhaled anticholinergics (tiotropium) and for the other study exposures of interest are included in Table 1.

Table 1. Inhaled Long-Acting Anticholinergic and Selective Beta$_2$-Adrenoreceptor Agonists Drugs Used for COPD

ATC Code	Category Description	Defined Daily Dose[a] Units (Administration Route)
R03	**Drugs for obstructive airway diseases**	
R03B	**Other drugs for obstructive airway diseases, inhalants**	
R03BB	Anticholinergics	
R03BB04	Tiotropium bromide (long-acting)	18 mcg (aerosol) 5 mcg (solution)
R03BB05	Aclidinium bromide	NA [b]
R03BB06	Glycopyrronium bromide	NA [b]
R03A	**Adrenergics, inhalants**	
R03AC	Selective beta$_2$-adrenoreceptor agonists	
R03AC12	Salmeterol (long-acting)	0.1 mg (aerosol powder)
R03AC13	Formoterol (long-acting)	24 mcg (aerosol powder)
R03AC18	Indacaterol	0.15 mg (inhaled powder)
R03AK	Adrenergics and other drugs for obstructive airway diseases	
R03AK06	Salmeterol and other drugs for obstructive airway diseases	
R03AK07	Formoterol and other drugs for obstructive airway diseases	

ATC = Anatomical Therapeutic Chemical (classification system); NA = not yet available in the online ATC/DDD index

[a] The defined daily dose is the assumed average maintenance dose per day for a drug used for its main indication in adults.

[b] Calculated DDD: For aclidinium bromide = 750 mcg (inhaled powder); For glycopyrronium bromide = 55 mcg, inhaled powder

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

9.2.3 Health 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 latest available launch sequence and projected estimated number of patients to be treated by country, the number of new users is planned to be monitored in the United Kingdom (UK), Germany, and Denmark, the first countries where aclidinium bromide is already available. For the initial monitoring, the Clinical Practice Research Datalink (CPRD)—formerly the General Practice Research Database (GPRD)—in the UK, the German Pharmacoepidemiological Research Database (GePaRD) at the Leibniz Institute for Prevention Research and Epidemiology (BIPS GmbH) in Germany (approvals pending), and the national health databases in Denmark are proposed as primary potential population data sources. The plan is to conduct the DUS in three populations that will be selected finally based on data availability. Table 2 on page 22 provides a summarised overview of the main features of these three initially proposed databases, including population coverage and data availability.

Based on the sales forecast provided by Almirall, S.A., (Almirall) and population coverage, the number of users of aclidinium bromide in each database has been estimated; the schedule will be updated as new information becomes available. Other potential candidate databases, such as the Italian Regional Databases in Friuli Venezia Giulia and the Information System for the Advancement of Research in Primary Care (SIDIAP) database in Catalonia in Spain can be explored during the monitoring phase to offer alternatives if the expected number of new users of aclidinium bromide is not reached in the planned countries during a reasonable time frame. At this time, no contacts have yet been established to explore interest in this study and availability of the database custodians to participate in this study.

9.2.3.1 CPRD, United Kingdom

The CPRD (http://www.cprd.com/) contains diagnostic and prescribing information recorded by general practitioners (GPs) as part of their routine clinical practice in the UK. The database covers approximately 5 million of the UK population (the population coverage and linkage are expected to increase in the next years). Patients registered 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 GPRD 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 GPRD and Hospital Episode Statistics (HES) data enables access to hospital discharge diagnosis and procedural coding. The validity of the GPRD as a reliable data source for drug safety studies in numerous therapeutic areas is well established (Jick et al., 1991; Jick et al., 2003).

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 (Soriano et al., 2005). 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 (Soriano et al., 2001).

Estimated Use of Aclidinium Bromide

Based on forecasts provided by Almirall, between 2013 and 2014, this database is expected to capture an estimated 1,500 to more than 3,000 users of aclidinium bromide.

9.2.3.2 National Databases, Denmark

The Danish health care system provides universal coverage to all Danish residents (5.5 million inhabitants). Health care coverage includes visits to general practitioners and specialists, hospital admissions, and outpatient visits. The costs of medicines are partially covered by the Danish health system. The centralised Civil Registration System in Denmark allows for personal identification of each person in the entire Danish population and for the possibility of linkage to all Danish registries containing civil registration numbers such as the Danish National Registry of Patients, Danish National Prescription Database, Prescription Databases of the Central Denmark Region, and the Danish Registry of Causes of Death. Data collected in these registries are available for research purposes. The process requires collaboration with a local university or investigator affiliated with a research institute to access the data and ethics committee notification or approval to handle data (Danish Data Protection Agency, 2011; Danish National Board of Health, 2011). ICD-10-CM codes are used for disease diagnoses.

Denmark's primary health care sector, which includes general practitioners, specialists, and dentists, generates about 96% of the prescription sales, most of which are reimbursable and are dispensed by community pharmacies. Each dispensing record

contains information on the patient, drug, and prescriber. Dispensing records retain the patient's universal personal identifier, allowing for individual-level linkage to all Danish registries and medical databases.

Denmark has two regional prescription databases established for research purposes: the Odense University Pharmacoepidemiology Database (OPED) covers a stable population of about 470,000 residents in the county of Funen, and the Aarhus University Prescription Database collects data on reimbursed medications dispensed at all community pharmacies of the North Denmark Region and the Central Denmark Region, covering a combined population of 1.8 million inhabitants. These regional databases, which include detailed clinical information but collect data only on reimbursed drugs, are easily accessible for data linkage.

Studies have been performed in patients with COPD using databases in Denmark, including safety evaluations of the use of tiotropium (for example, de Luise et al., 2007).

Estimated Use of Aclidinium Bromide

Based on forecasts provided by Almirall, between 2013 and 2014, the national database is expected to capture an estimated 5,900 to more than 12,300 users of aclidinium bromide.

9.2.3.3 GePaRD, Germany

The GePaRD is a population-based database obtained from statutory health insurance agencies (SHIs) in Germany (Pigeot and Ahrens, 2008). Files of SHIs are linked with drug dispensing data from a pharmacies' electronic data processing centre on an individual basis using the unique subject identification number (ID) at a trusted third-party centre. The database covers approximately 14 million SHI members and provides data on hospital diagnoses, ambulatory care diagnoses and procedures, and ambulatory prescriptions including date of prescription and date of pharmacy dispensing from all SHI members who have been enrolled in one of the SHIs. Membership is fairly stable over time.

The German modification of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10-GM) is used for coding diagnoses, and OPS (Operationen und Prozedurenschlüssel) codes are used for surgical and diagnostic procedures. Types of treatments and diagnostic procedures with exact date are registered according to EBM (Einheitlicher Bewertungsmaßstab) codes, developed for payment of physicians for the outpatient treatment of German SHI patients.

Estimated Use of Aclidinium Bromide

Based on forecasts provided by Almirall, between 2013 and 2014, this database is expected to capture an estimated 9,400 to more than 30,500 users of aclidinium bromide.

Table 2. 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 Pharmaco-epidemiological 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, 4 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%
Potential aclidinium bromide country-users in 2013-2014[b]	19,000 to 41,000	5,900 to 12,000	55,000 to 178,000
Estimated number of users captured in the prescription databases			
2013	1,500	5,900	9,400
2014	3,300	12,300	30,500
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 SIHs
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

Description	United Kingdom, CPRD (N = 62,435.709)[a]	Danish Patient and Prescription National Databases (N = 5,552,037)[a]	German Pharmaco-epidemiological Research Database (N = 81,751,602)[a]
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
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 procedures 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)	1.5-1.8 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 SHI 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.

[b] Estimates based on anticipated sales data from Almirall S.A.

9.3 Variables

9.3.1 Demographic Variables

Age and sex will be included in the set of variables for description of the population. Age is an important risk factor for COPD and also an important determinant of prognosis. Lung function starts to decline in the third and fourth decade. Age will be calculated at the index date from the date of birth. Also, some analysis will be stratified by age groups (≥ 65 to 74 years; ≥ 75 to 84 years, and ≥ 85 years).

Race and ethnicity, although of interest, might not be included because electronic health databases do not have this information available due to data privacy rules.

9.3.2 Lifestyle and Socioeconomic Variables

Exposure to tobacco smoke is the most important cause of COPD. However, information on smoking and other lifestyle factors is not available in most health care databases unless they are based on medical records. Primary care databases like the Clinical Practice Research Database (CPRD)—formerly the General Practice Research Database (GPRD), in the United Kingdom (UK)—usually records this type of information. The CPRD will be a good candidate database to obtain information on current and past smoking as recorded by the general practitioner.

Codes suggesting alcohol abuse/dependence and obesity can also be included. However, information for these variables will be incomplete in most databases. In the CPRD, general practitioners (GPs) systematically record their patients' body mass index (BMI) and patient's reported daily quantity of alcohol consumption, 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 metres (kg/m^2). The following World Health Organization (WHO) categories will be used to classify BMI: 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) (WHO, 2012).

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 (CPRD, 2012). Information on the participating practices where patients are enrolled will be also included.

9.3.3 Treatment Indication and Identification of Off-Label Use

Aclidinium bromide is indicated for the maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Indication for treatment with aclidinium bromide will be assessed according to the data provided by each database. The diagnosis associated with a new course of treatment is, in general, recorded in primary care databases like the CPRD, but not in a systematic way. Other databases (such as the GePaRD in Germany) might not have a similar associated diagnosis, but searches on the diagnoses surrounding the initial prescription will be implemented to identify proxies for the indication that triggered the introduction of new medications.

9.3.3.1 Manual Patient Profile Review

In a primary care database (i.e., CPRD), we propose to assess the treatment indication of the first aclidinium bromide prescription in a random sample of users through the manual review of computerised patient profiles created from the database. The patient profile is a de-identified chronological list of medical events and drug prescriptions based on the computerised database information, including free-text information if available. Review of these profiles by clinicians will provide insight into medical events leading up to the prescription of a new course of medication. This information will also be used to validate the computer algorithms created to identify proxies for clinical indications. The approximate target number will include between 5% and 10% of the new users of aclidinium bromide identified in each database. From the initial estimated study size requirements, we expect to review a sample of 100-200 patient profiles per database.

9.3.4 Identification of Patients With COPD

The subpopulation of 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. The three initial databases proposed for the implementation of this DUS use the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) dictionary for hospitalisation diagnoses (in the UK, ICD-10 codes are used for the HES database, which can be linked to information from general practices and other links available at the CPRD); therefore, we provide the preliminary lists of diagnosis codes under this coding system. If the CPRD is used, ICD-10 codes will be mapped to Read codes through diagnosis descriptions used by the GPs in the clinical practices.

Table 3 provides a list of ICD-10 codes for to identify patients with COPD and other respiratory diseases using either primary or secondary hospital discharge codes. The proportion of patients with these diagnosis codes will be assessed at baseline (at index date) and during a 1-year follow-up (1 year after the index date).

Table 3. Diagnoses to Identify Users of Aclidinium Bromide, by Indication

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

9.3.4.1 COPD Diagnosis Validity

The validity of diagnostic codes to identify patients with COPD has been studied. The positive predictive value (PPV) of compatible clinical diagnostic Read codes for COPD recorded by general practitioners in the CPRD-registered general practices has been reported to be about 70% (Soriano et al., 2001). Cooke et al. (2011) used multiple diagnostic codes in combination with pharmacy data to improve the ability to accurately identify patients with COPD. The overall PPV of acute COPD discharge diagnoses in the Danish National Patient Registry is high, 92% (95% confidence interval [CI], 91%-93%) (Thomsen et al., 2011). In addition, among patients coded with pneumonia or respiratory failure but not COPD, 19% (95% CI, 17%-21%) had COPD, corresponding to a negative predictive value for COPD of 81% (95% CI, 79%-83%).

9.3.4.2 COPD Severity and Exacerbations

The degree of COPD severity is an important prognostic factor for morbidity and mortality. Several studies in patients with COPD have included measures of COPD severity and some also evaluated the validity of methods used to determine severity (Curkendall et al., 2006; Eisner et al., 2005; Ogale et al., 2010; Soriano et al., 2001; Verhamme et al., 2012). For example, the algorithm used by Verhamme and colleagues (2012) assessed baseline severity of COPD by the frequency of use of COPD medications, frequency and duration of use of systemic steroids as a marker of COPD exacerbations, use of oxygen therapy, and prior number of hospitalisations for COPD, as available in each database.

In the CPRD, evaluation of health care resource utilisation including hospitalisations, general practice visits, referrals, and emergency department admissions might require the manual review of computerised medical profiles from a sample of patients. Terms such “acute,” “attack,” or “exacerbation” included in the description of the Read code can also be used to identify COPD exacerbations. Addition of oral steroids or short-term antibiotics (less than 4 weeks duration) to the patient’s study medication has been used by others to assess exacerbations (Griffin et al., 2008).

Among patients diagnosed with COPD, severity will be classified at the index date according to baseline data available in each database. Severity of COPD will be assessed with an adaptation of the algorithm validated by Verhamme and colleagues (2012), for which the severity level was confirmed in 82% of the patients with COPD with spirometry information. The adapted version of the validated algorithm for the planned study is displayed in Table 4.

Table 4. 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 drug 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

In addition, new users of the medications of interest will be described according to other factors that have been reported as determinants of COPD severity (Curkendall et al., 2006):

- Any nebulizer dispensed in the previous 6 months
- Previous COPD hospitalisation in the previous 1 year
- Acute COPD exacerbation defined by antibiotic use in the presence of a respiratory diagnosis in the previous 6 months
- Pneumonia diagnosis in the previous 1 year
- Emphysema diagnosis during the patient’s available history

9.3.5 Identification of Potential Off-Label Use

Off-label use will be evaluated by treatment indications, if available, or by the presence of an aclidinium bromide prescription with a diagnosis of asthma with or without any records (drugs or diagnoses) suggesting a COPD diagnosis. The proportion of patients with codes for both COPD and asthma will be evaluated.

The ICD-10 codes that will be used to identify patients with asthma are J45-J46. The validity of the asthma diagnosis has been reported in several populations. For example, the PPV of the diagnosis of asthma in the Danish national registry of patients, which uses ICD-10 codes, was reported to be 65% (95% CI, 62%-68%), using hospitalisations, outpatient clinic contacts, and emergency department visits (Jensen et al., 2010). However, in this study, asthma diagnoses recorded in the military draft board (conscription records) were used as the gold standard, meaning that the validation study was performed only in men. In this type of records, the diagnosis of asthma might be underrecorded if another condition is already present as the primary reason for military exemption, and mild cases of asthma or incipient episodes might also be underreported. The result of this study contrasts with those from another Danish study conducted in children aged 6 to 14 years using actual medical records as the gold standard, which reported a sensitivity of 90%, specificity of 99%, and PPV of 85% (Moth et al., 2007).

Pregnancies during use of medication will be identified at baseline and during follow-up. ICD-10 codes are O00-O99 for pregnancy and Z30-Z39 for health care encounters related to reproduction; however, other algorithms will be developed to identify pregnancies based on available data in each of the databases.

Potential off-label use in the paediatric population will be assessed through the age distribution of the study cohorts. The present European paediatric regulatory age is defined as the part of the population from birth to 18 years of age. Therefore, we will consider off-label paediatric use to be aclidinium bromide users aged 18 years or younger.

In addition, in the CPRD, samples of electronic patient profiles (i.e., electronic chronological information recorded in the database including free-text annotations) could be manually reviewed among those patients without a clear treatment indication based on computerized code identification.

9.3.6 Comorbidities of Interest Including Those With Missing Information in the RMP

Comorbidities of interest will be assessed separately at baseline (at the index date) and after 1 year of follow-up (1 year after the index date) by outpatient visits, hospitalisations, and procedures, as available. Definitions will be based on codes for diagnoses, procedures, and treatments recorded in each database. The main

comorbidities planned for evaluation are displayed with the relevant ICD-10 codes in Table 5. This list will be complemented with a list of procedural codes, including codes relevant to identification of comorbidities of interest. For the identification of some specific subgroups (e.g., pregnancy, heart failure), algorithms based on diagnostic markers or proxies will be developed according to available information. As an example, in some databases, heart failure can be identified through hospitalisations for this condition and by the use of certain medications recommended to be added to the treatment as heart failure develops and progresses (e.g., diuretics and digitalis, inotropic support).

The degree of completeness of identifying these specific subgroups of patients will differ by the type of data source.

Table 5. Comorbidities—Including Those Listed in the Risk Management Plan as Having Missing Information

ICD-10 Code Description	ICD-10 Code
Diseases	
Malignant neoplasms	C00-C75
Lung cancer	C34
Diabetes	E10-E14
Obesity	E66
Glaucoma	H40-H42
Primary angle-closure glaucoma	H40.2
Glaucoma secondary to drugs	H40.6
Hypertension	I10-I15
Ischaemic heart disease	I20-I25
Acute myocardial infarction	I21
Subsequent myocardial infarction	I22
Complications of myocardial infarction	I23
Old myocardial infarction	I25.2
Angina	I20
Heart conduction disorders	I44-I45
Arrhythmias	I47-I49
Heart failure	I50
Cerebrovascular diseases	I60-I69
Pneumonia	J10.0, J11.0, J12-J18
Renal failure	N17-N19
Prostatic hyperplasia	N40
Bladder neck obstruction	N32.0
Urinary tract infection, site not specified	N39.0
Liver disorders	K70-K77
Pulmonary embolism	I26.0-I26.9

ICD-10 Code Description	ICD-10 Code
Osteoporosis	M80- M81
Depressive disorders	F32-F33
Procedures	
Cardiac pacemaker	Z95.0
Aortocoronary bypass graft	Z95.1
Heart valve replacement	Z95.2-Z95.4
Coronary angioplasty	Z95.5
Cardiac and vascular implant and graft, other or unspecified	Z95.8, Z95.9

Source: Word Health Organization. International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Version 2010. Available at: http://apps.who.int/classifications/icd10/. Accessed 23 December 2012.

9.3.7 Overall Comorbidity Index

The Charlson Comorbidity Index will be used to summarise the overall comorbidity for each patient based on the available data. It is a weighted index of 19 comorbid diseases that takes into account both the number and severity of the conditions (Charlson et al., 1987). Its validity has been studied extensively in different patient populations and research settings. This comorbidity index is a significant predictor of health outcomes and of health services utilisation in populations with low and high prevalence of comorbid diseases.

Table 6 displays the diagnostic categories and components of the index. Diagnostic categories and descriptions of the Charlson comorbidity index components can be mapped to ICD-10 codes. An adapted and validated version of this index is also available for Read codes (Khan et al., 2010).

Table 6. The Charlson Comorbidity Index Components and Weights

Diagnostic Category	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	▪ Chronic obstructive pulmonary disease ▪ Pneumoconioses ▪ Chronic respiratory conditions due to fumes and vapors	1

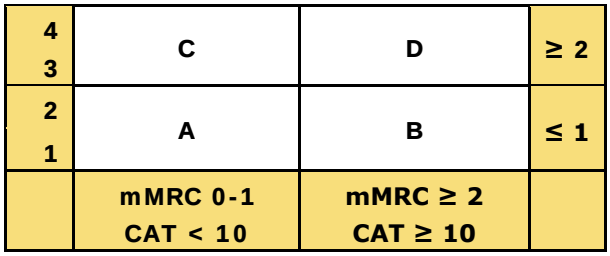
Diagnostic Category	Description	Weight
Connective tissue disease	▪ Systemic lupus erythematous ▪ Systemic sclerosis ▪ Polymyositis ▪ Rheumatoid arthritis ▪ Polymyalgia rheumatica	1
Peptic ulcer disease	▪ Gastric, duodenal, and gastrojejunal ulcers ▪ Chronic forms of peptic ulcer disease	1
Cerebrovascular 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	▪ Malignant neoplasms	2
Leukaemia	▪ Leukaemia	2
Lymphoma	▪ Lymphoma	2
Moderate or severe hepatic disease	▪ Hepatic coma, portal hypertension, other sequelae of chronic liver disease ▪ Oesophageal varices	3
Metastatic solid tumour	▪ Secondary malignant neoplasm of lymph nodes and other organs	6
AIDS	▪ HIV infection with related specified conditions	6

9.3.8 Exposures

The main exposures of interest are aclidinium bromide, tiotropium, glycopyrronium bromide, LABAs, and LABA+ICS. Table 7 summarises guidelines for the initial pharmacologic treatment of COPD according to category of COPD severity summarized in Figure 2 (GOLD, 2011). According to the GOLD guidelines, COPD severity is categorized according to current level of symptoms, severity of spirometric abnormality, and exacerbation history. Short- and long-acting inhaled anticholinergics are considered both

effective and safe for the management of COPD and are recommended by international clinical guidelines. Under these guidelines, aclidinium bromide and the rest of the study medications are recommended for moderate to very severe COPD (categories B, C, and D) (Figure 2 and Table 7).

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



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, 2011.

Table 7. Initial Pharmacologic Management of COPD According to European Clinical Guidelines

COPD Severity Category	First-Choice Medications	Second-Choice Medications
A		
Low risk, fewer symptoms	▪ SA anticholinergics prn OR ▪ SA beta$_2$-agonist prn	▪ LA anticholinergics OR ▪ LA beta$_2$-agonist OR ▪ SA anticholinergics AND SA beta$_2$-agonist
B		
Low risk, more symptoms	▪ LA anticholinergics OR ▪ LA beta$_2$-agonist	▪ LA anticholinergics AND LA beta$_2$-agonist

COPD Severity Category	First-Choice Medications	Second-Choice Medications
C		
High risk, fewer symptoms	▪ Inhaled corticosteroids plus LA beta$_2$-agonist OR ▪ LA anticholinergics	▪ LA anticholinergics AND LA beta$_2$-agonist
D		
High risk, more symptoms	▪ Inhaled corticosteroids plus LA beta$_2$-agonist OR ▪ LA anticholinergics	▪ Inhaled corticosteroids AND LA anticholinergics OR ▪ Inhaled corticosteroids plus LA beta$_2$-agonist AND LA anticholinergics OR ▪ Inhaled corticosteroids plus LA beta$_2$-agonist AND Phosphodiesterase-4 inhibitor OR ▪ LA anticholinergics AND LA beta$_2$-agonist OR ▪ LA anticholinergics AND Phosphodiesterase-4 inhibitor

CAT = COPD assessment test; LA = long-acting; prn = as needed; SA = short-acting.

Note: Within a cell, medications are mentioned in alphabetic order, not necessarily by order of preference. See Annex 1 for ATC codes for medications of interest in this study.

Source: Adapted from GOLD, 2011.

In addition to COPD severity, adherence to current guidelines is influenced by the health status of individual patients, the health care system, and physician preferences (Asche et al., 2012; Franssen et al; 2011). It is expected that use of inhaled long-acting bronchodilators and corticosteroids will differ across country-specific databases. Therefore, evaluation of the patterns of use and adherence to each of the frequently used COPD inhaled medications is of relevance for the safety evaluation of these medications. Persistence with inhaled COPD medications has been reported to be in general low, although some differences were seen between medications (Breekveldt-Postma et al., 2007; Cramer et al., 2007). Persistence with tiotropium has been reported to be about 50% at 6 months and 37% at 1 year; persistence at 1 year was found to be even lower for ipratropium (14%), LABA (13%), and LABA+ICS (17%) (Breekveldt-Postma et al., 2007). In another study, at 1 year, patients taking tiotropium had longer persistence (53%) than patients taking other therapies (7% to 30%), and fewer patients had switched to alternative medications (Cramer et al., 2007).

9.3.8.1 Patterns of Use and Adherence

Patterns of use of aclidinium bromide and of each comparator drug will be ascertained among patients diagnosed with COPD by the total number of prescriptions, prescription rates, duration of use, switching patterns, and concomitant use of other medications.

Duration of use will be estimated through the number of consecutive prescriptions or the days of supply of each prescription, as available in each database. Consecutive prescriptions are defined as those with a maximum gap of 60 days between the date of prescriptions. Treatment persistence with inhaled medications for COPD has been defined as the proportion of patients refilling prescriptions within 60 days from the end of the previous prescription (Cramer et al., 2007). Sensitivity analysis based on 30-day and 60-day gap periods will be performed. For those patients who do not persist within the year of follow-up, the pattern of switching to the other medications of interest will be described.

In pharmacy record databases, refill adherence over 1 year will be assessed. Dispensed refills covering 100% ± 20% of the prescribed treatment time has been defined as satisfactory refill adherence (Krigsman et al., 2007). However, refill adherence based on a 1-year period seems to underestimate undersupply and overestimate oversupply compared with a longer time period.

9.3.8.2 Assessment of Dose

The daily dose for each treatment will be derived from the recorded dose or from the time between consecutive prescriptions and prescribing information (strength, number of units, and number of boxes) according to the available information in each database.

The distribution of the daily prescribed dose at the index date will be described for all new users of aclidinium bromide and by main patient subgroups of interest.

The dose described will be the one associated with the index prescription. The daily dose of medications is recorded in the CPRD (UK) but not in the other initially selected databases.

9.3.8.3 Use of Respiratory Medications

Use of the following respiratory medications (ATC code) will be assessed for the year before and the year after the index date:

- Anticholinergics, short-acting (ipratropium) and long-acting (tiotropium, glycopyrronium bromide) (see Annex 1 for ATC codes)
- Short- and long-acting $beta_2$-agonists (fenoterol or salbutamol; formoterol, salmeterol, or indacaterol) (see Annex 1)
- Combination short-acting $beta_2$-agonist (fenoterol or salbutamol) plus anticholinergic (ipratropium) (see Annex 1)

- Combination long-acting beta$_2$-agonists plus inhaled glucocorticoids (formoterol plus budesonide, salmeterol plus fluticasone propionate, and any other combination may become available during the study period) (see Annex 1)
- Inhaled glucocorticoids (see Annex 1)
- Xanthines (R03DA, R03DB)
- Adrenergics for systemic use (R03C)
- Leukotriene receptor antagonists and other systemic drugs for obstructive airway disease (R03DC, R03DX)
- Mucolytics (R05CB), includes carbocysteine (R05CB03)
- Oral glucocorticoids, short- and long-term (H02AB)
- Phosphodiesterase-4 inhibitors (R03DX07, Roflumilast)
- Oxygen therapy, as available in each database (V03AN01)
- Cromones: cromoglicic acid (R03BC01) and nedocromil (R03BC03)

9.3.8.4 Use of Other Comedications

Use of other medications will be assessed at the index date and for the year following the index date. Relevant medications (ATC code) include the following:

- Antihistamines for systemic use (R06)
- Antitussives (R05, cough and cold preparations)
- Antibiotics (J01, antibacterial for systemic use)
- 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)
- Drugs used in diabetes (A10)
  - Insulins (A10A)
  - Blood glucose–lowering drugs (A10B)
- Other to be specified

9.4 Data Sources

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

9.5 Study Size

The study size will be driven by the uptake of aclidinium bromide in the populations from which the automated databases obtain data. All the new users of aclidinium bromide captured in each database will be included in the study. The estimated study target for the DUS is about 2,000 new users of aclidinium bromide per each country-specific database, and a simple random sample of 2,000 new users of each of the comparators—tiotropium, formoterol, salmeterol, and combinations of formoterol or salmeterol with inhaled corticosteroids.

Based on current sales estimates, Almirall expects that this figure might be reached during or soon after the first year following launch. A study size between 1,500 and 2,000 new users per database offers an acceptable level of precision in the different scenarios when estimating the percentage of off-label use or by different subgroups with missing information (see Table 8).

Table 8. Binomial Confidence Intervals for Different Study Sizes and Possible Percentages of Off-Label Use

Number of Patients	Lower and Upper Bounds of 95% Confidence Intervals for Various Percentages of Potential Off-Label Use									
	1%		2%		5%		7%		10%	
1,000	0.5	1.8	1.2	3.1	3.7	6.5	5.5	8.8	8.2	12.0
1,500	0.6	1.6	1.4	2.8	4.0	6.2	5.8	8.4	8.5	11.6
2,000	0.6	1.5	1.4	2.7	4.1	6.0	5.9	8.2	8.7	11.4
3,000	0.7	1.4	1.5	2.6	4.2	5.8	6.1	8.0	8.9	11.1
4,000	0.7	1.4	1.6	2.5	4.3	5.7	6.2	7.8	9.1	11.0

Note: Calculations were performed using Stata software.

9.5.1 Monitoring of Aclidinium Bromide Users

The number of users of aclidinium bromide in the database will be requested to database custodians periodically after the launch. The timing of the start and periodicity of the monitoring will be determined based on the lag time and update schedule for prescription data in each specific database. The study will be initiated once the predetermined number of users of aclidinium bromide (n = 1,500-2,000) is available.

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 programmes. Each 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 each research centre to restore files in the event of a hardware or software failure.

9.7 Data Analysis

The analysis will be descriptive at baseline and at 1 year after index date. The analysis will be planned in two phases.

Phase 1: Baseline analysis: Assessment of the characteristics of new users of aclidinium bromide and of new users of each comparator. Assessment at baseline will include data up to 1 year before the index date.

- Age and sex distribution
- Proportion of patients with a prior diagnosis of COPD including chronic bronchitis and emphysema, asthma, and overlapping between these diagnoses.
- Proportion of patients according to COPD severity categories
- Proportion of patients with specific diseases prior to the index date: cardiovascular diseases (i.e., "any AMI" and AMI within the last 6 months prior index date, heart failure, unstable angina, cerebrovascular disease, and arrhythmias), diabetes, and renal and hepatic impairment
- Proportion of patients with recent exacerbation (within 6 months prior to index date)
- General comorbidity index
- Proportion of elderly patients with comorbid conditions (age groups: ≥ 65 to 74 years; ≥ 75 to 84 years, and ≥ 85 years)
- Proportion of patients using respiratory medications: other anticholinergics, short- and long-acting beta$_2$-agonists, methylxanthines, combination short-acting beta$_2$-agonists plus anticholinergics, inhaled glucocorticoids, combination long-acting beta$_2$-agonists plus inhaled glucocorticoids, oral glucocorticoids, phosphodiesterase-4 inhibitors, oxygen therapy

- Proportion of off-label use
  - Adults (aged > 18 years) with asthma only
  - Children (aged ≤ 18 years)
  - Pregnant women
- Proportion of patients with symptomatic benign prostatic hyperplasia, bladder neck obstruction, urinary retention, and narrow-angle glaucoma

Phase 2: Follow-up analysis to 1 year after the index date: assessment of relevant comorbidities and treatment patterns will be ascertained in the subgroup of patients with COPD and stratified by age groups of interest.

- Number of users during pregnancy
- Patterns of use of aclidinium bromide and each comparator: duration of use, dose, switching between COPD medications, and comedications
- Adherence evaluation within 1 year: proportion of patients refilling prescriptions within 60 days from the end of the previous prescription. Sensitivity analysis based on 30-day and 60-day gap periods will be performed. Measures of adherence to inhaled therapies might be adapted for each selected database.

Subgroup analyses of patients aged 40 years or older, and also for other age groups (e.g., ≥ 65 to 74 years; ≥ 75 to 84 years, and ≥ 85 years), will be performed.

To describe subgroups, proportions for categorical variables and means and medians for continuous variables (with 95% confidence intervals) will be estimated within each subgroup.

All the results will be presented for each country-specific database. As part of the analysis, tables presenting the results as specified in the protocol will be generated. Shells for the main tables will be included in an annex of the final protocol.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 (e.g., smoking status, BMI), for databases with no information on a variable of interest, we will not include that variable in the analysis. For databases with partial information on a variable (i.e., data on smoking is available for some subjects but missing for others), we will do no imputation of missing data but instead we will describe the frequency of subjects with missing values.

Programming will be conducted using SAS statistical software (SAS Institute, Cary, North Carolina). Stata software (StataCorp LP, College Station, Texas) may be used for some components.

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 to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

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-HS, 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 description of new users of aclidinium bromide and assessment of the extent to which aclidinium bromide is prescribed outside of its authorised indication, COPD. The proportion of off-label use in each study population, including the paediatric population, will be estimated. The 1-year follow-up of new users will allow evaluation of the patterns of use of aclidinium bromide, tiotropium, glycopyrronium bromide, LABA (formoterol and salmeterol), and the fixed-dose combinations of LABA+ICS (formoterol plus budesonide, salmeterol plus fluticasone propionate, and any other combination that may become available during the study period).

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 at least two population-based databases that collect data on a regular basis. Logistic and scientific coordination across the research centres is of critical importance to standardise data extraction and analysis under this common protocol.

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 each country.

- Population 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.
- The lag time for capturing the main exposure of interest, which ranges from a few months to 1 year across proposed databases, needs to be considered when estimating the availability of the number of users needed for the study and the implications on the availability of study results.
- 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. Therefore, it is expected that some prescriptions will be follow-up prescriptions in recent initiators rather than incident prescriptions.
- The quantity and quality of the data available might differ among the different databases. Information relating to clinical indication, lifestyle, SES, or a specific comorbidity might be missing or of insufficient quality in some of the databases.
- The degree of completeness in recording information for some variables, such as indicators of severity COPD, might vary across databases.
- Misclassification of the clinical diagnoses of COPD, asthma, emphysema, and chronic bronchitis is a potential issue for all of these databases. However, studies evaluating data already collected may be the most efficient way to assess potential off-label use.

10 PROTECTION OF HUMAN SUBJECTS AND 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.

The study will be conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) (2007) 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 (ENCePP, 2012). The completed ENCePP Checklist for Study Protocols (ENCePP, 2011) is in Annex 2. The study will be registered in the ENCePP electronic register of post-authorisation studies (EU PAS register) (ENCePP, 2010) as detailed in the module VIII of the EU Guideline on Good Pharmacovigilance Practices (GVP) (EMA, 2012a).

The study is a post-authorisation safety study (PASS) and will comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/EC and its refinement provided in Chapter I.7 Section 1 of Volume 9A of the Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use (European Commission, 2008) and referred to in the ICH harmonised tripartite guideline Pharmacovigilance Planning E2E (ICH, 2004) and with the 2012 Guideline on Good Pharmacovigilance Practices (GVP) module VIII on post-authorisation safety studies (EMA, 2012b). 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. Approval will be obtained from the institutional review board (IRB) at RTI International (of which RTI Health Solutions is a part). A waiver of individual patient informed consent will be requested due to the nature of this study.

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

10.1 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 (ISAC) for database research is required.

10.2 GePaRD, Germany

For the GePaRD, approval is needed from the four 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.

10.3 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 (Danish Data Protection Agency, 2011; Danish National Board of Health, 2011).

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

Based on current guidelines from the International Society for Pharmacoepidemiology (ISPE) (2007, Section VI) and the EMA Guideline on Good Pharmacovigilance Practices (GVP) (EMA, 2012c, Section VI C.1.2.1), 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. Study results will be published following guidelines of the International Committee of Medical Journal Editors (2010), 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 (STROBE, 2007).

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" (ISPE, 2007, Section V). This would include results pertaining to the safety of a marketed medication. According to GVP guidelines on post-authorisation studies, Almirall, S.A., 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. Almirall, S.A., will be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication (EMA, 2012b, Section VIII.B.7).

13 REFERENCES

Asche CV, Leader S, Plauschinat C, Raparla S, Yan M, Ye X, Young D. Adherence to current guidelines for chronic obstructive pulmonary disease (COPD) among patients treated with combination of long-acting bronchodilators or inhaled corticosteroids. Int J Chron Obstruct Pulmon Dis. 2012;7:201-9.

Breekveldt-Postma NS, Koerselman J, Erkens JA, Lammers JW, Herings RM. Enhanced persistence with tiotropium compared with other respiratory drugs in COPD. Respir Med. 2007;101:1398-405.

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987;40:373-83.

Clinical Practice Research Datalink. Access to data: census data. 2012. Available at: http://www.cprd.com/dataAccess/. Accessed 17 July 2012.

Cooke CR, Joo MJ, Anderson SM, Lee TA, Udris EM, Johnson E, Au DH The validity of using ICD-9 codes and pharmacy records to identify patients with chronic obstructive pulmonary disease. BMC Health Serv Res; 2011;11:37.

Cramer JA, Bradley-Kennedy C, Scalera A. Treatment persistence and compliance with medications for chronic obstructive pulmonary disease. Can Respir J. 2007;14:25-9.

Curkendall SM, Lanes S, de Luise C, Stang MR, Jones JK, She D, et al. Chronic obstructive pulmonary disease severity and cardiovascular outcomes. Eur J Epidemiol 2006;21:803-13.

Danish Data Protection Agency. Web site. Apr 14, 2011. Available at: http://www.datatilsynet.dk/english/. Accessed 5 Jul 2011.

Danish National Board of Health. Web site. 2011. Available at: http://www.sst.dk/English.aspx. Accessed 5 Jul 2011.

de Luise C, Lanes SF, Jacobsen J, Pedersen L, Sørensen HT. Cardiovascular and respiratory hospitalizations and mortality among users of tiotropium in Denmark. Eur J Epidemiol 2007;22:267-72.

Eisner MD, Trupin L, Katz PP, Yelin EH, Earnest G, Balmes J, Blanc PD. Development and validation of a survey-based COPD severity score. Chest. 2005;127:1890-7.

European Commission. Volume 9A of the rules governing medicinal products in the European Union: guidelines on pharmacovigilance for medicinal products for human use. Sep 2008. Available at: http://ec.europa.eu/health/documents/eudralex/vol-9/index_en.htm. Accessed 10 May 2012.

European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products. June 22, 2012c. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129135.pdf. Accessed 23 June 2012.

European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies. June 22, 2012b. Available at: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf. Accessed 23 June 2012.

European Medicines Agency. Summary of opinion (initial authorisation): Eklira Genuair (aclidinium bromide). 24 May 2012a. Available at: http://www.ema.europa.eu/ema/index.jsp?curl = pages/medicines/human/medicines/002211/smops/Positive/human_smop_000374.jsp&mid = WC0b01ac058001d127. Accessed 19 July 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCePP checklist for study protocols (revision 1). 19 August 2011. Available at: http://www.encepp.eu/standards_and_guidances/index.html. Accessed 10 May 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). ENCePP study seal. Last updated: 3 February 2012. Available at: http://www.encepp.eu/encepp_studies/index.html. Accessed 28 August 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on methodological standards in pharmacoepidemiology. 11 July 2012. Available at: http://www.encepp.eu/standards_and_guidances/index.html. Accessed 28 August 2012.

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Electronic register of studies. Version 3.0.46. 2010. Available at: http://www.encepp.eu/encepp/studiesDatabase.jsp. Accessed 28 August 2012.

Franssen FM, Spruit MA, Wouters EF. Determinants of polypharmacy and compliance with GOLD guidelines in patients with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2011;6:493-501.

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Revised, 2011. Available at http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011Dec30.pdf. Accessed Jun 10, 2012.

Griffin J, Lee S, Caiado M, Kesten S, Price D. Comparison of tiotropium bromide and combined ipratropium/salbutamol for the treatment of COPD: a UK General Practice Research Database 12-month follow-up study. Prim Care Respir J. 2008;17:104-10.

ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). Pharmacovigilance planning. E2E. 2004. Available at: http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/pharmacovigilance-planning.html. Accessed 10 May 2012.

International Committee of Medical Journal Editors (ICMJE). Uniform requirements for manuscripts submitted to biomedical journals: writing and editing for biomedical publication. Updated April 2010. Available at: http://www.icmje.org/urm_main.html. Accessed 10 May 2012.

International Society for Pharmacoepidemiology (ISPE). Guidelines for good pharmacoepidemiology practices (GPP). Revision 2. April 2007. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm. Accessed 10 May 2012.

Italian Medicines Agency [Agenzia Italiana del Farmaco]. Registry of observational studies [Registro Studi Osservazionali]. Available at: http://osservazionali.agenziafarmaco.it/. Accessed 15 May 2012.

Jensen AØ, Nielsen GL, Ehrenstein V. Validity of asthma diagnoses in the Danish National Registry of Patients, including an assessment of impact of misclassification on risk estimates in an actual dataset. Clin Epidemiol. 2010;2:67-72.

Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. BMJ 1991;302:766-8.

Jick SS, Kaye JA, Vasilakis-Scaramozza C, García Rodríguez LA, Ruigómez A, Meier CR, Schlienger RG, Black C, Jick H. Validity of the general practice research database. Pharmacotherapy. 2003;23:686-9.

Khan ND, Perera R, Harper S, Rose PW. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases BMC Family Practice 2010, 11:1http://www.biomedcentral.com/1471-2296/11/1

Krigsman K, Nilsson JL, Ring L. Refill adherence for patients with asthma and COPD: comparison of a pharmacy record database with manually collected repeat prescriptions. Pharmacoepidemiol Drug Saf. 2007;16:441-8.

Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007;370:765-73.

Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet. 2001;357:1191-4.

Moth G, Vedsted P, Schiøtz PO. National registry diagnoses agree with medical records on hospitalized asthmatic children. Acta Paediatr. 2007;96:1470-3.

National Health Service. UK Medicines Information. New drugs online: aclidinium bromide. 2012. Available at: http://www.ukmi.nhs.uk/applications/ndo/record_view_open.asp?newDrugID=4515. Accessed 28 August 2012.

Ogale SS, Lee TA, Au DH, Boudreau DM, Sullivan SD. Cardiovascular events associated with ipratropium bromide in COPD. Chest 2010;137:13-9.

Pigeot I, Ahrens W. Establishment of a pharmacoepidemiological database in Germany: methodological potential, scientific value and practical limitations. Pharmacoepidemiol Drug Saf. 2008;17:215-23.

Soriano JB, Maier WC, Visick G, Pride NB. Validation of general practitioner-diagnosed COPD in the UK General Practice Research Database. Eur J Epidemiol. 2001;17:1075-80.

Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest 2005;128:2099-107

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement. STROBE checklist. 2007. Available at: http://www.strobe-statement.org/index.php?id = available-checklists. Accessed 15 May 2012.

Thomsen RW, Lange P, Hellquist B, Frausing E, Bartels PD, Krog BR, Hansen AM, Buck D, Bunk AE. Validity and underrecording of diagnosis of COPD in the Danish National Patient Registry. Respir Med. 2011;105:1063-8.

Verhamme KM, Afonso AS, van Noord C, Haag MD, Koudstaal PJ, Brusselle GG, et al. Tiotropium Handihaler and the risk of cardio- or cerebrovascular events and mortality in patients with COPD. Pulm Pharmacol Ther. 2012;25:19-26.

World Health Organization. BMI classification. Updated 18 July 2012. Available at: http://apps.who.int/bmi/index.jsp?introPage = intro_3.html. Accessed 18 July 2012.

Annex 1.
ATC Codes: Respiratory Medications and Other Medications of Interest

Table 1-1. Inhaled Selective Beta$_2$-Adrenoreceptor Agonists and Anticholinergics Used for COPD

ATC Code	Name	DDD Units (Administration Route)
R03	**Drugs for obstructive airway diseases**	
R03A	**Adrenergics, inhalants**	
R03AC	*Selective beta$_2$-adrenoreceptor agonists*	
R03AC02	Salbutamol *(short acting)*	▪ 0.8 mg (aerosol, powder) ▪ 0.10 mg (solution)
R03AC03	Terbutaline	▪ 2 mg (aerosol, powder) ▪ 20 mg (solution)
R03AC04	Fenoterol *(short acting)*	▪ 0.6 mg (aerosol, powder) ▪ 4 mg (solution)
R03AC05	Rimiterol	▪ 1.6 mg (aerosol)
R03AC06	Hexoprenaline	▪ 1.5 mg (aerosol)
R03AC07	Isoetarine	
R03AC08	Pirbuterol	▪ 1.2 mg (aerosol)
R03AC09	Tretoquinol	
R03AC010	Carbuterol	
R03AC011	Tulobuterol	▪ 1.6 mg (aerosol)
R03AC012	Salmeterol *(long acting)*	▪ 0.1 mg (aerosol, powder)
R03AC013	Formoterol *(long acting)*	▪ 24 mcg (aerosol, powder)
R03AC014	Clenbuterol	
R03AC015	Reproterol	
R03AC016	Procaterol	▪ 60 mcg (aerosol)
R03AC017	Bitolterol	
R03AC018	Indacaterol	▪ 0.15 mg (powder)
R03AK	*Adrenergic and another drugs for obstructive airway disease*	
R03AK01	Epinephrine and other drugs for obstructive airway diseases	
R03AK02	Isoprenaline and other drugs for obstructive airway diseases	
R03AK03	Fenoterol and other drugs for obstructive airway diseases	
R03AK04	Salbutamol and other drugs for obstructive airway diseases	
R03AK05	Reproterol and other drugs for obstructive airway diseases	
R03AK06	Salmeterol and other drugs for obstructive airway diseases	
R03AK07	Formoterol and other drugs for obstructive airway diseases	

ATC Code	Name	DDD Units (Administration Route)
R03B	**Other drugs for obstructive airway diseases, inhalants**	
R03BB	*Anticholinergics*	
R03BB01	Ipratropium bromide *(short acting)*	▪ 0.12 mg (aerosol, powder) ▪ 0.3 mg (solution)
R03BB02	Oxitropium bromide *(short acting)*	▪ 0.6 mg (aerosol) ▪ 4 mg (solution)
R03BB04	Tiotropium bromide *(long acting)*	▪ 18 mcg (aerosol) ▪ 5 mcg (solution)
R03BB05	Aclidinium bromide	▪ NA
R03BB06	Glycopyrronium bromide	▪ NA

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.

Note: calculated DDD for aclidinium bromide = 750 mcg, inhaled powder; for glycopirrolate bromide=55 mcg, inhaled powder

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

Table 1-2. Inhaled Glucocorticoids Used for COPD

ATC Code	Name	DDD Units (Administration Route)
R03B	**Other drugs for obstructive airway disease, inhalant**	
R03BA	*Glucocorticoids*	
R03BA01	Beclometasone	▪ 0.8 mg (aerosol, powder) ▪ 1.5 mg (solution)
R03BA02	Budesonide	▪ 0.8 mg (aerosol, powder) ▪ 1.5 mg (solution)
R03BA03	Flunisolide	▪ 1 mg (aerosol)
R03BA04	Betamethasone	▪ NA
R03BA05	Fluticasone	▪ 0.6 mg (aerosol, powder) ▪ 1.5 mg (solution)
R03BA06	Triamcinolone	▪ NA
R03BA08	Mometasone	▪ 0.4 mg (powder)
R03BA06	Ciclesonide	▪ 0.16 mg (aerosol)

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

Source: WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2012. Updated 19 December 2011. Available at: http://www.whocc.no/atc_ddd_index/. Accessed 21 July 2012.

Annex 2.
ENCePP Checklist for Study Protocols

London, 25 July 2011
Doc.Ref. EMEA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 1)

Adopted by the ENCePP Steering Group on 19/08/2011

The purpose of the Checklist developed by ENCePP is to stimulate consideration of important epidemiological principles when designing a pharmacoepidemiological or pharmacovigilance study and writing a study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. ENCePP welcomes innovative designs and new methods of research. 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 of the questions 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.

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the formulation of the research question clearly explain:				
1.1.1 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)	x			13-14
1.1.2 The objectives of the study?	x			14-15
1.2 Does the formulation of the research question specify:				

Section 1: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
1.2.1 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	x			14-16
1.2.2 Which formal hypothesis(-es) is (are) to be tested?			x	
1.2.3 if applicable, that there is no *a priori* hypothesis?			x	

Comments:

Drug utilization study without specified hypothesis

Section 2: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Is the source population described?	x			19-23
2.2 Is the planned study population defined in terms of:				
2.2.1 Study time period?	x			17
2.2.2 Age and sex?	x			17
2.2.3 Country of origin?	x			19-23
2.2.4 Disease/indication?	x			19-23
2.2.5 Co-morbidity?	x			19-23
2.2.6 Seasonality?			x	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	x			17-18

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?			x	NA: DUS
3.2 Is the study design described? (e.g., cohort, case-control, randomised controlled trial, new or alternative design)	x			16
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)			x	

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.4 Is sample size considered?	x			36
3.5 Is statistical power calculated?	x			36*

Comments:

The DUS is a descriptive study; *binomial 95% CI.

Section 4: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
4.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	x			19-23
4.1.2 Endpoints? (e.g., clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc)			x	
4.1.3 Covariates?	x			19-23
4.2 Does the protocol describe the information available from the data source(s) on:				
4.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	x			19-23
4.2.2 Endpoints? (e.g., date of occurrence, multiple event, severity measures related to event)			x	
4.2.3 Covariates? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	x			18-23
4.3 Is the coding system described for:				
4.3.1 Diseases? (e.g., International Classification of Diseases (ICD)-10)	x			19-23
4.3.2 Endpoints? (e.g., Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)			x	
4.3.3 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	x			19-23
4.4 Is the linkage method between data sources described? (e.g., based on a unique identifier or other)	x			19-23

Comments:

Summary table with description of data sources is on pages 22-23.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g., operational details for defining and categorising exposure)	x			31-33
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)	x			31-33
5.3 Is exposure classified according to time windows? (e.g., current user, former user, non-use)	x			31-33
5.4 Is exposure classified based on biological mechanism of action?			x	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?			x	31-34*

Comments:

* Evaluation of patterns of use includes dose and duration

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?			x	
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)			x	

Comments:

DUS. The validity of COPD diagnosis and severity are described on pages 27.

Section 7: Biases and Effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address:				
7.1.1 Selection biases?			x	
7.1.2 Information biases? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)			x	
7.2 Does the protocol address known confounders? (e.g., collection of data on known confounders, methods of controlling for known confounders)			x	
7.3 Does the protocol address known effect modifiers? (e.g., collection of data on known effect modifiers, anticipated direction of effect)			x	
7.4 Does the protocol address other limitations?	x			39-40

Comments:

Descriptive study to be implemented using information collected in electronic health databases

Section 8: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the plan include measurement of absolute effects?	☐	☐	x	
8.2 Is the choice of statistical techniques described?	☐	☐	x	
8.3 Are descriptive analyses included?	x	☐	☐	37-38
8.4 Are stratified analyses included?	x	☐	☐	37-38
8.5 Does the plan describe the methods for identifying: 8.5.1 Confounders?	☐	☐	x	
8.5.2 Effect modifiers?	☐	☐	x	
8.6 Does the plan describe how the analysis will address: 8.6.1 Confounding?	☐	☐	x	
8.6.2 Effect modification?	☐	☐	x	

Comments:

Drug utilization study with descriptive analysis

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	x	☐	☐	39
9.2 Are methods of quality assurance described?	x	☐	☐	39
9.3 Does the protocol describe quality issues related to the data source(s)?	x	☐	☐	39-40
9.4 Does the protocol discuss study feasibility? (e.g., sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	x	☐	☐	19-23
9.5 Does the protocol specify timelines for 9.5.1 Study start?	x	☐	☐	12
9.5.2 Study progress? (e.g., end of data collection, other milestones)	x	☐	☐	12
9.5.3 Study completion?	x	☐	☐	12
9.5.4 Reporting? (i.e., interim reports, final study report)	x	☐	☐	12
9.6 Does the protocol include a section to document future amendments and deviations?	x	☐	☐	12

Section 9: Quality assurance, feasibility and reporting	**Yes**	**No**	**N/A**	**Page Number(s)**
9.7 Are communication methods to disseminate results described?	x			42
9.8 Is there a system in place for independent review of study results?		x		

Comments:

Timelines are dependent on real use of the drug and lag time in each database to capture use

Section 10: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	x			40-41
10.2 Has any outcome of an ethical review procedure been addressed?			x	
10.3 Have data protection requirements been described?	x			40-41

Comments:

Name of the coordinating study entity[1]:__RTI-Health Solutions_____

Name of (primary) lead investigator[2]: __Cristina Varas-Lorenzo_____

Date: 14/April/2014

Signature: _____

[1] A legal person, institution or organisation which takes responsibility for the design and/or the management of a study. The (primary) lead investigator is the person authorised to represent the coordinating study entity.

[2] A person with the scientific background and experience required for the conduct of a particular pharmacoepidemiological or pharmacovigilance study. The lead investigator is responsible for the conduct of a study at a study site. If a study is conducted at several study sites by a team of investigators, the (primary) lead investigator is the investigator who has overall responsibility for the study across all sites.