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

First published: 27/05/2016

Last updated: 02/07/2025

Study Finalised

Administrative details

EU PAS number

EUPAS13616

Study ID

42316

DARWIN EU® study

No

Study countries

☐ United Kingdom

Study description

Aclidinium bromide is a long-acting and potent antagonist of lung M3 receptors indicated as a maintenance bronchodilator treatment to relieve symptoms in adults age 40 or older with chronic obstructive pulmonary disease (COPD).
To evaluate potential cardiovascular safety concerns and all-cause mortality identified in the European risk management plan for aclidinium bromide, a PASS will be conducted through sequential studies for the endpoints of interest.
Specific aims are:
- To compare the risk of congestive heart failure, acute myocardial infarction, stroke, and all-cause mortality in patients with COPD initiating treatment with aclidinium bromide (monotherapy or combination therapy with formoterol (not fixed-dose and fixed-dose) and other COPD medications with the risk in patients with COPD initiating treatment with long-acting beta-agonists (LABAs).
- To compare the risk of the study endpoints of interest in patients with COPD initiating treatment with aclidinium bromide (monotherapy or combination with formoterol, not fixed-dose and fixed-dose) with the risk in patients with COPD initiating treatment with other COPD medications.
- To evaluate the effect of dose and duration of each study medication on the risk of each study outcome.
- To compare the risk of cardiac arrhythmias in patients with COPD between:
1) New users of fixed-dose combination of aclidinium and formoterol and other fixed-dose combination COPD medications with new users of LABA,
2) New users of fixed-dose combination of aclidinium and formoterol with new users of each of the other fixed-dose combination COPD medications.
The first and second nested case-control and cohort studies, initiated in March 2016 and February 2017, evaluate the risk of all-cause mortality and congestive heart failure. Sample size considerations will trigger the start of three additional cohort studies evaluating the risk of acute myocardial infarction, stroke, and cardiac arrhythmias.

Study status

Finalised

Research institutions and networks

Institutions

RTI Health Solutions (RTI-HS)

- [ ] France
- [ ] Spain
- [ ] Sweden
- [ ] United Kingdom
- [ ] United Kingdom (Northern Ireland)
- [ ] United States

First published: 21/04/2010

Last updated: 13/03/2025

Institution | Not-for-profit | ENCePP partner

Contact details

Study institution contact

Cristina Rebordosa crebordosa@rti.org

Study contact

crebordosa@rti.org

Primary lead investigator

Cristina Rebordosa

Primary lead investigator

Study timelines

Date when funding contract was signed
Planned: 29/02/2016

Actual: 10/03/2016

Study start date
Planned: 31/10/2016

Actual: 27/01/2017

Data analysis start date
Planned: 31/10/2017

Actual: 16/10/2017

Date of interim report, if expected
Planned: 28/06/2019

Actual: 06/06/2019

Date of final study report
Planned: 30/12/2023

Actual: 17/12/2023

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

AstraZeneca, Covis Pharma

Study protocol

PASS_PROTOCOL_COMBO_2Jun2015_V 2.2_Redacted2.pdf (1.72 MB)

D6560R00004 PASS protocol v4 signed_redacted.pdf (1.87 MB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

EU RMP category 1 (imposed as condition of marketing authorisation)

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Drug utilisation

Safety study (incl. comparative)

Main study objective:

To compare the risk of all-cause mortality, congestive heart failure, acute myocardial infarction, stroke, and cardiac arrhythmias in patients with COPD initiating treatment with aclidinium bromide with the risk in patients with COPD initiating other treatments for COPD.

Study Design

Non-interventional study design

Case-control

Study drug and medical condition

Name of medicine

BRETARIS

BRETARIS GENUAIR

BRIMICA

BRIMICA GENUAIR

DUAKLIR

DUAKLIR GENUAIR

EKLIRA

EKLIRA GENUAIR

Study drug International non-proprietary name (INN) or common name

ACLIDINIUM BROMIDE

FORMOTEROL FUMARATE DIHYDRATE

Anatomical Therapeutic Chemical (ATC) code

(R03AC12) salmeterol

salmeterol

(R03AC13) formoterol

formoterol

(R03AC18) indacaterol

indacaterol

(R03AC19) olodaterol

olodaterol

(R03AK06) salmeterol and fluticasone

salmeterol and fluticasone

(R03AK07) formoterol and budesonide

formoterol and budesonide

(R03AL03) vilanterol and umeclidinium bromide

vilanterol and umeclidinium bromide

(R03AL04) indacaterol and glycopyrronium bromide

indacaterol and glycopyrronium bromide

(R03AL05) formoterol and aclidinium bromide

formoterol and aclidinium bromide

(R03AL06) olodaterol and tiotropium bromide

olodaterol and tiotropium bromide

(R03AL07) formoterol and glycopyrronium bromide

formoterol and glycopyrronium bromide

(R03BB04) tiotropium bromide

tiotropium bromide

(R03BB05) aclidinium bromide

aclidinium bromide

(R03BB06) glycopyrronium bromide

glycopyrronium bromide

(R03BB07) umeclidinium bromide

umeclidinium bromide

Medical condition to be studied

Chronic obstructive pulmonary disease

Population studied

Age groups

Adults (18 to < 46 years)

Adults (46 to < 65 years)

Adults (65 to < 75 years)

Adults (75 to < 85 years)

Adults (85 years and over)

Estimated number of subjects

105000

Study design details

Outcomes

All-cause mortality, congestive heart failure, acute myocardial infarction, stroke, and cardiac arrhythmias.

Data analysis plan

A descriptive analysis of the study cohorts will be performed. Crude and age and sex- standardized incidence rates will be estimated for each study cohort. A cohort analysis will be performed to estimate crude and adjusted relative risks (RRs) and 95% CIs for each study endpoint using conditional multiple logistic regression to compare:

--Current, recent, and past use of aclidinium and of each study medication with current use of LABAs

--Current single use of aclidinium and of each study medication with current

single use of LABAs
--Current single use of aclidinium with current single use of each study medication. Analyses will also be performed stratified by specific subgroups of patients (e.g. by COPD severity, age groups, or history of cardiovascular disease) among current users of the study medications.
The effect of dose and duration of use will be estimated among current single users of each study medication.

Documents

Study results

4368_Abstract_Final results - Redacted.pdf (346.4 KB)

4669_Abstract_Final results__Redacted.pdf (4.24 MB)

5405_Abstract_Final results__Redacted.pdf (273.71 KB)

6182_Abstract_Final results__Redacted.pdf (179.4 KB)

Study publications

A Cohort Study to Evaluate the Risk of Hospitalisation for Congestive Heart Fai...

Are you really dead? Validation of death and date of death in patients with COP...

Hospitalization for heart failure among patients using aclidinium bromide and o...

Use of aclidinium did not increase the risk of death in a noninterventional coh...

A validation exercise: identifying hospitalizations for heart failure among pat...

Risk Assessment of Acute Myocardial Infarction and Stroke Associated with Long-...

Acute myocardial infarction, stroke, and MACE in COPD patients treated with acl...

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

Clinical Practice Research Datalink

Hospital Episode Statistics

Data source(s), other

Hospital Episode Statistics inpatient data, Office of National Statistics data

Data sources (types)

Administrative healthcare records (e.g., claims)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No