

# Acridinium 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

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### Study ID

42316

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### DARWIN EU® study

No

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### Study countries

 United Kingdom

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### Study description

Acclidinium 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 acclidinium 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 acclidinium 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 acclidinium 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 acclidinium and formoterol and other fixed-dose combination COPD medications with new users of LABA,
  - 2) New users of fixed-dose combination of acclidinium 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.

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## **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](mailto:crebordosa@rti.org)

**Study contact**

[crebordosa@rti.org](mailto: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

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**Study start date**

Planned: 31/10/2016

Actual: 27/01/2017

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**Data analysis start date**

Planned: 31/10/2017

Actual: 16/10/2017

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**Date of interim report, if expected**

Planned: 28/06/2019

Actual: 06/06/2019

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**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)

## Regulatory

### **Was the study required by a regulatory body?**

Yes

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### **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

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##### **Study type:**

Non-interventional study

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##### **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 acclidinium 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

### **Medicinal product name**

BRETARIS

[BRETARIS GENUAIR](#)

BRIMICA

[BRIMICA GENUAIR](#)

DUAKLIR

[DUAKLIR GENUAIR](#)

EKLIRA

[EKLIRA GENUAIR](#)

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

ACLIDINIUM BROMIDE

FORMOTEROL FUMARATE DIHYDRATE

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### **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

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## **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)
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### **Estimated number of subjects**

105000

## Study design details

### **Outcomes**

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

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### **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 acclidinium and of each study medication with current use of LABAs

--Current single use of acclidinium and of each study medication with current single use of LABAs

--Current single use of acclidinium 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)

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### 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 acclidinium bromide and o...](#)

[Use of acclidinium 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...](#)

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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

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### **Data source(s), other**

Hospital Episode Statistics inpatient data, Office of National Statistics data

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### **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

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**Check completeness**

Unknown

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**Check stability**

Unknown

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**Check logical consistency**

Unknown

## Data characterisation

**Data characterisation conducted**

No