**PASS Study Report**

Active substance Aclidinium bromide

Product reference D6560R00004

Version number *1.0*

Date *10 November 2017*

# Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: All-Cause Mortality

**Marketing Authorisation Holder(s)**

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|---|---|
| **Marketing authorisation holder(s)** | AstraZeneca AB<br>SE-151 85 Södertälje<br>Sweden |
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**Approved by:**

Principal Investigator Date

## PASS INFORMATION

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|---|---|
| **Title** | Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: All-Cause Mortality |
| **Version identifier of the final study report** | 1.0 |
| **Date of last version of the final study report** | 10 November 2017 |
| **EU PAS register number** | ENCEPP/SDPP/13616; 23 May 2014 |
| **Active substance** | Aclidinium bromide (ATC code: R03BB05)<br>Aclidinium bromide/formoterol fumarate dihydrate (ATC code: R03AL05) |
| **Medicinal product** | Eklira® Genuair®/Bretaris® Genuair®<br>Duaklir® Genuair®/Brimica® Genuair® |
| **Product reference** | Eklira® Genuair®: H0002211<br>Bretaris® Genuair®: H0002706<br>Duaklir® Genuair®: H0003745<br>Brimica® Genuair®: H0003969 |
| **Procedure number** | Eklira® Genuair®: EMEA/H/C/002211<br>Bretaris® Genuair®: EMEA/H/C/002706<br>Duaklir® Genuair®: EMEA/H/C/003745<br>Brimica® Genuair®: EMEA/H/C/003969 |
| **Marketing authorisation holder(s)** | AstraZeneca AB<br>SE-151 85 Södertälje<br>Sweden |
| **Joint PASS** | No |
| **Research question and objectives** | The overall objective of this PASS is to evaluate the potential cardiovascular safety concerns and all-cause mortality described in the risk management plan for aclidinium bromide, through sequential, nested case-control studies for each endpoint of interest. Specific objectives are as follows: |

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| | To compare the risk of congestive heart failure; acute myocardial infarction (AMI), including community coronary heart disease death; stroke; and **all-cause mortality** in patients with COPD initiating treatment with aclidinium bromide (monotherapy; concomitant with formoterol not in fixed-dose combination; and fixed-dose combination with formoterol, when available) and other inhaled COPD medications with the risk in patients with COPD initiating treatment with LABAs.<br><br>To compare the risk of congestive heart failure, acute myocardial infarction, stroke, and **all-cause mortality** in patients with COPD initiating treatment with aclidinium bromide (monotherapy; concomitant with formoterol not in fixed-dose combination; and fixed-dose combination with formoterol, when available) with the risk in patients with COPD initiating other inhaled treatments for COPD.<br><br>To evaluate the effect of duration of each of the study medications on the risk of each individual endpoint.<br><br>When the fixed-dose combination of aclidinium/formoterol becomes available, new users will be included in the cohort for evaluation. A new additional endpoint of cardiac arrhythmias will be evaluated for this cohort.<br><br>This report addresses the **all-cause mortality** component of the PASS programme. |
| **Country(-ies) of study** | United Kingdom: the Clinical Practice Research Datalink (CPRD) |
| **Author** | [redacted], MD, MPH; Cristina Rebordosa, MD, PhD |

## APPROVAL PAGE: RTI HEALTH SOLUTIONS

Project Title: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: All-Cause Mortality

| | |
|---|---|
| Authors: | [redacted], MD, MPH; Cristina Rebordosa, MD, PhD |
| Report version: | 1.0 |
| Date: | 10 November 2017 |

The following people have reviewed the report and give their approval:

| | |
|---|---|
| Susana Perez-Gutthann, MD, MPH, PhD, FISPE, FRCP<br>Vice President and Global Head of Epidemiology<br>RTI Health Solutions | Date |

## APPROVAL PAGE: ASTRAZENECA—CLINICAL LEAD

Project Title: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: All-Cause Mortality

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|---|---|
| Authors: | [redacted], MD, MPH; Cristina Rebordosa, MD, PhD |
| Report version: | 1.0 |
| Date: | 10 November 2017 |

The following people have reviewed the report and give their approval:

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|---|---|
| [redacted], MD<br>Head of Tezepelumab and Duaklir, Global Medical Affairs | Date |

## APPROVAL PAGE: ASTRAZENECA—QPPV

Project Title: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: All-Cause Mortality

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|---|---|
| Authors: | [redacted], MD, MPH; Cristina Rebordosa, MD, PhD |
| Report version: | 1.0 |
| Date: | 10 Novermber 2017 |

The following people have reviewed the report and give their approval:

| | |
|---|---|
| [redacted]<br>AstraZeneca Deputy EU QPPV<br>as delegated by [redacted],<br>AstraZeneca EU QPPV | Date |

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# 1. ABSTRACT

**Title**: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: All-Cause Mortality

Version: 1.0, 10 November 2017

Authors: [redacted], MD, MPH; Cristina Rebordosa, MD, PhD

**Keywords**: Aclidinium bromide; LAMA; chronic obstructive pulmonary disease; mortality; database study

**Rationale and background:** Aclidinium bromide is an inhaled long-acting anticholinergic (LAMA) approved in Europe in 2012 as maintenance bronchodilator treatment to relieve symptoms in adults with chronic obstructive pulmonary disease (COPD). A series of studies has been planned to evaluate potential cardiovascular safety concerns identified in the aclidinium risk management plan. The first of these studies is on the risk of all-cause mortality.

**Research question and objectives:** To compare the risk of all-cause mortality in patients with COPD initiating treatment with aclidinium and other selected COPD medications with the risk in patients initiating treatment with long-acting beta-agonists (LABA). To compare the risk of all-cause mortality between aclidinium and each of the selected COPD medications. To evaluate the effect of duration of use.

**Study design**: Non-interventional database cohort and nested case-control study of patients with COPD aged 40 years or older starting (new users) treatment with aclidinium, tiotropium, other LAMA (glycopyrronium and umeclidinium), LABA/inhaled corticosteroids (LABA/ICS), or LABA. Each case (death) was matched to four controls on year of birth, sex, and year of cohort entry.

**Setting:** The Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK), from September 2012 through March 2017.

**Subjects and study size, including dropouts:** A total of 6,544 new users of aclidinium were identified; 5,426 met eligibility criteria (82.9%); 1,871 (34.5%) had exclusion criteria; and 3,555 (54.3%) were included in the study.

**Variables and data sources:** Exposure to the study medications was ascertained through prescription information recorded in the CPRD. Deaths were identified in the Hospital Episode Statistics (HES) and the Office for National Statistics (ONS) for linked practices and in the CPRD for unlinked practices. Deaths with inconsistent information on death or date of death between data sources were validated through review of the recorded clinical information. Main risk factors evaluated included smoking, COPD severity, comorbidity, comedications, and utilisation of health care resources. Crude and age- and sex-standardised mortality rates were estimated for current use of each study medication. In the nested case-control study, crude and adjusted relative risks (RRs) for mortality were estimated for current, recent, and past use of each

study medication versus current use of LABA. Relative risks were also estimated for current single use, current multiple use, and duration of current use of the study medications. Several subgroup and sensitivity analyses were conducted.

**Results**: The study included 3,555 new users of aclidinium, 19,413 new users of tiotropium, 5,308 new users of other LAMA, 21,718 new users of LABA/ICS, and 4,797 new users of LABA. Out of 3,822 deaths identified, 3,819 (99.9%) were confirmed. Age- and sex-standardised mortality rates per 1,000 person-years of current use were 32.91 deaths for aclidinium, 37.97 for other LAMA, 38.12 for LABA, 43.76 for tiotropium, and 47.14 for LABA/ICS. A total of 3,808 confirmed deaths (99.7%) were matched to 15,207 controls. The risk of mortality was lower for current use of aclidinium and other LAMA than for current use of LABA (Abstract Table 1). No association was found for current use of tiotropium or LABA/ICS versus current use of LABA.

**Abstract Table 1. Risk of mortality associated with current use of the study medications versus current use of LABA**

| Current Use | Cases (%) (N=3,808) | Controls (%) (N=15,207) | Crude Relative Risk of Mortality (95% CI) | Adjusted Relative Risk of Mortality (95% CI) |
|---|---|---|---|---|
| LABA | 190 (5.0) | 924 (6.1) | Ref | Ref |
| Aclidinium | 103 (2.7) | 565 (3.7) | 0.89 (0.68-1.15) | 0.54 (0.40-0.72) |
| LABA | 104 (2.7) | 599 (3.9) | Ref | Ref |
| Tiotropium | 1, 350 (35.5) | 5, 437 (35.8) | 1.44 (1.16-1.78) | 0.96 (0.76-1.21) |
| LABA | 177 (4.6) | 917 (6.0) | Ref | Ref |
| Other LAMA | 147 (3.9) | 693 (4.6) | 1.11 (0.87-1.41) | 0.76 (0.58-0.99) |
| LABA | 164 (4.3) | 854 (5.6) | Ref | Ref |
| LABA/ICS | 1, 850 (48.4) | 7, 315 (48.1) | 1.31 (1.10-1.56) | 1.08 (0.90-1.31) |

CI = confidence interval; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LAMA = long-acting anticholinergic.

Note: The number of cases and controls for current use of LABA (reference category) differed across the study medications. Current users of both LABA and the specific study medication of interest were excluded from each corresponding analysis.

Relative risks for current single use of each study medication were similar to those observed for current use that included single and multiple use of the study medications. The RR for current single use of aclidinium was 0.38 (95% CI, 0.20-0.72). Switching of COPD medications, except aclidinium, was associated with a higher risk of mortality. Among current single users, RRs comparing recent switching of each study medication to the use of LABA without switching were 1.84 (95% CI, 0.89-3.81) for LABA, 0.30 (95% CI, 0.07-1.36) for aclidinium, 1.50 (95% CI, 1.05-2.13) for tiotropium, 1.54 (95% CI, 0.68-3.50) for other LAMA, and 1.59 (95% CI, 1.14-2.21) for LABA/ICS.

Except for aclidinium, multiple use of the study medications was also associated with an increased risk of mortality, although RRs were lower than those for switching. The RR for multiple use of aclidinium was 1.02 (95% CI, 0.71-1.48).

The risk of mortality comparing current use of each study medication versus current use of aclidinium was higher for all the study medications except other LAMA. Relative risks versus current use of aclidinium were 1.50 (95% CI, 1.18-1.91) for tiotropium, 0.79 (95% CI, 0.36-1.73) for other LAMA, 2.41 (95% CI, 1.35-4.28) for LABA/ICS, and 1.55 (95% CI, 1.17-2.05) for LABA.

The risk of mortality was higher at the start of treatment with LABA than at the start of treatment with the rest of COPD medications or with longer treatment. Relative risks for short duration of use (< 30 days) ranged from 0.23 (95% CI, 0.06-0.84) for aclidinium to 0.81 (95% CI, 0.50-1.32) for LABA/ICS. Relative risks for long duration of use (≥ 30 days) ranged from 0.38 (95% CI, 0.17-0.84) for aclidinium to 1.16 (95% CI, 0.73-1.85) for LABA/ICS. Relative risk for long versus short duration of LABA use was 0.79 (95% CI, 0.46-1.37).

Results for current use of the study medications were similar in the analysis stratified by categories of COPD severity, measures of airflow limitation, age, and history of asthma. Among patients with a history of cardiovascular disease, the risk of mortality was lower in users of each study medication than in users of LABA, although precision was low. The study results were consistent across sensitivity analyses for alternative definitions of duration of exposure and COPD severity and in analyses restricted to new users or to patients with linkage to HES and ONS.

**Discussion**:

This is the first observational study on all-cause mortality in users of aclidinium and new LAMA medications. A few studies raised concerns about the cardiovascular safety of tiotropium; however, results of this study are consistent with those reported in phase 3 clinical trials for aclidinium and tiotropium and most observational studies of tiotropium, which did not find an increased risk of mortality. The effect estimate for aclidinium showing reduced risk of mortality was driven by the current single use category (patients not using other COPD study medications), and precision was very low due to the low number of exposed cases (n = 13). Selective prescribing of LABA to more fragile patients could contribute to the lower risk of mortality observed in users of aclidinium. There was no difference in mortality among aclidinium users in the multiple use category (those patients using other COPD study medications in addition to aclidinium), which comprised approximately 70% of the aclidinium study cohort. The highest risk of mortality in patients switching or concurrently treated with multiple COPD medications could be compatible with residual confounding from the inability to adequately control for worsening of COPD symptoms or exacerbations leading to death. A causal effect, with combinations of these medications increasing the risk of conditions such as tachyarrhythmia, cannot be ruled out. Misclassification of exposure derived from uncertainty regarding the actual duration of use of the study medications or the lack of recorded information on the first prescription of new medications issued by specialists probably had little impact on

the study results, as shown in the sensitivity analyses with alternative definitions of exposure. Outcome misclassification is unlikely as deaths were identified mainly in HES and ONS, and deaths with inconsistent information were validated through a review of the recorded clinical information. One of the strengths of the study is that we adjusted effect estimates by COPD severity according to the GOLD 2016 classification, which uses data on symptoms, exacerbations, hospitalisations, and airflow limitation. In addition, results from analyses stratified by COPD severity and airflow limitation and from sensitivity analyses measuring COPD severity before the index date instead of before the start date were consistent with the overall results. Misclassification of COPD and asthma, and potential increased risk of mortality in patients with both conditions, did not affect the study results, as indicated in the stratified analysis by history of asthma.

Overall, results from this study indicate that the use of aclidinium, tiotropium, other LAMA, or LABA/ICS is not associated with an increased risk of all-cause mortality as compared to the use of LABAs. Results from the aclidinium cardiovascular PASS programme on heart failure, stroke, acute myocardial infarction, and arrhythmias will provide more information on the cardiovascular safety of aclidinium and other COPD medications.

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# 2. LIST OF ABBREVIATIONS

| Abbreviation or special term | Explanation |
|---|---|
| / | in the form “medication 1/medication 2,” indicates a fixed-dose combination |
| + | in the form “medication 1+medication 2,” indicates concurrent therapy not in a fixed-dose combination |
| AMI | acute myocardial infarction |
| ATC | Anatomical Therapeutic Chemical (classification) |
| BMI | body mass index |
| CAT | COPD assessment test |