



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)

Marketing authorisation holder(s)	AstraZeneca AB SE-151 85 Södertälje Sweden
MAH contact person	<div>██████████</div> Regulatory Affairs Director e-mail: <div>██</div>

<<TRADEMARK™>> is a trademark of the AstraZeneca group of companies.

This document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Approved by:

Principal Investigator

Date

PASS INFORMATION

Title	Acridinium 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	Acridinium bromide (ATC code: R03BB05) Acridinium bromide/formoterol fumarate dihydrate (ATC code: R03AL05)
Medicinal product	Eklira® Genuair®/Bretaris® Genuair® Duaklir® Genuair®/Brimica® Genuair®
Product reference	Eklira® Genuair®: H0002211 Bretaris® Genuair®: H0002706 Duaklir® Genuair®: H0003745 Brimica® Genuair®: H0003969
Procedure number	Eklira® Genuair®: EMEA/H/C/002211 Bretaris® Genuair®: EMEA/H/C/002706 Duaklir® Genuair®: EMEA/H/C/003745 Brimica® Genuair®: EMEA/H/C/003969
Marketing authorisation holder(s)	AstraZeneca AB SE-151 85 Södertälje 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 acridinium bromide, through sequential, nested case-control studies for each endpoint of interest. Specific objectives are as follows:

PASS Study Report

Active substance Acclidinium bromide

Product reference D6560R00004

Version number 1.0

Date 10 November 2017

	<p>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 acclidinium 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.</p> <p>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; 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.</p> <p>To evaluate the effect of duration of each of the study medications on the risk of each individual endpoint.</p> <p>When the fixed-dose combination of acclidinium/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.</p> <p>This report addresses the all-cause mortality component of the PASS programme.</p>
Country(-ies) of study	United Kingdom: the Clinical Practice Research Datalink (CPRD)
Author	██████████, 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
Vice President and Global Head of Epidemiology
RTI Health Solutions

Date

APPROVAL PAGE: ASTRAZENECA—CLINICAL LEAD

Project Title: Acridinium 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:

[REDACTED], MD
Head of Tezepelumab and Duaklir, Global Medical
Affairs

Date

APPROVAL PAGE: ASTRAZENECA—QPPV

Project Title: Acridinium 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:

[REDACTED]
AstraZeneca Deputy EU QPPV
as delegated by [REDACTED],
AstraZeneca EU QPPV

Date

TABLE OF CONTENTS	PAGE
TITLE PAGE	1
PASS INFORMATION	2
TABLE OF CONTENTS.....	7
1. ABSTRACT	11
2. LIST OF ABBREVIATIONS	14
3. INVESTIGATORS	16
4. OTHER RESPONSIBLE PARTIES	17
5. MILESTONES	17
6. RATIONALE AND BACKGROUND	18
7. RESEARCH QUESTION AND OBJECTIVES.....	19
8. AMENDMENTS AND UPDATES	20
9. RESEARCH METHODS.....	20
9.1 Study design	20
9.2 Setting.....	20
9.3 Subjects	21
9.3.1 Cohort eligibility	21
9.3.2 Selection of cases and controls.....	22
9.4 Variables.....	22
9.4.1 Exposures	22
9.4.2 Study endpoint: all-cause mortality.....	24
9.4.3 Confounding factors.....	24
9.5 Data sources and measurement	27
9.6 Bias	28
9.7 Study size	28
9.8 Data transformation.....	29
9.9 Statistical methods.....	29
9.9.1 Main summary measures.....	29
9.9.2 Main statistical methods.....	29
9.9.3 Missing values.....	32
9.10 Quality control.....	34
10. RESULTS.....	34

10.1	Participants	35
10.2	Descriptive data	37
10.2.1	Baseline characteristics by study cohort	37
10.3	Outcome data.....	47
10.3.1	Identification and validation of deaths	47
10.3.2	Distribution of cases and controls by risk factors	48
10.4	Main results	52
10.4.1	Cohort analysis: crude and adjusted mortality rates.....	52
10.4.2	Nested case-control study.....	53
10.5	Other analyses	67
10.5.1	Analysis restricted to new users at the index date.....	67
10.5.2	Analysis assuming no stockpiling	67
10.6	Adverse events/adverse reactions.....	68
11.	DISCUSSION	68
11.1	Key results.....	68
11.2	Limitations.....	68
11.3	Interpretation	71
12.	GENERALISABILITY	72
13.	OTHER INFORMATION.....	72
14.	CONCLUSION	72
15.	REFERENCES.....	73
16.	APPENDICES.....	77

LIST OF APPENDICES

Annex 1.	List of stand-alone documents	77
----------	-------------------------------------	----

LIST OF TABLES

Abstract Table 1.	Risk of mortality associated with current use of the study medications versus current use of LABA	12
Table 1.	Classification of COPD severity using the GOLD 2016 definition.....	27
Table 2.	Approximate number of patients with COPD Exposed to aclidinium bromide for 1 year to have a 0.80 probability of detecting a relative risk of 1.5, 2, 2.5, and 3	29
Table 3.	Cohort attrition for new users of aclidinium bromide and other study medications	36
Table 4.	Number of new users of specific medications and study cohort	37
Table 5.	Distribution of demographic and lifestyle habits at the start date by study cohort.....	38
Table 6.	Distribution of the components of the GOLD 2016 severity classification at the start date by study cohort	40
Table 7.	Medical history at any time before the start date by study cohort.....	41
Table 8.	Prior use of respiratory medications before ^a the start date by study cohort	44
Table 9.	Use of other medications before ^a the start date by study cohort.....	45
Table 10.	Distribution of health care resource utilisation before ^a the start date by study cohort.....	46
Table 11.	Identification and validation of deaths.....	47
Table 12.	Distribution of cases and controls by risk factors and relative risk (95% CI) in univariate analysis.....	48
Table 13.	Crude and age- and sex-standardised mortality rates during current use of the study medications by study cohort	53
Table 14.	Analysis for current, recent, and past use of the study medications	54
Table 15.	Adjusted relative risk of mortality for current single use and current multiple use of the study medications.....	56
Table 16.	Analysis restricted to patients with linkage to Hospital Episode Statistics and Office for National Statistics Data.....	63
Table 17.	Sensitivity analysis for the adjustment for COPD severity	65
Table 18.	Sensitivity analysis for duration of days of supply and exposure time stockpiling.....	66
Table 19.	Sensitivity analysis for new users at the index date.....	67

LIST OF FIGURES

Figure 1.	Distribution of COPD severity by study cohort.....	39
Figure 2.	Distribution of the Charlson Comorbidity Index score at the start date by study cohort.....	42
Figure 3.	Prior use of study medications by study cohort.....	43
Figure 4.	Adjusted relative risk of mortality for current, recent, and past use of the study medications.....	55
Figure 5.	Adjusted relative risk of mortality for current single and current multiple use.....	57
Figure 6.	Adjusted relative risk of mortality by duration of current single use	58
Figure 7.	Adjusted relative risk of mortality versus current use of aclidinium.....	58
Figure 8.	Adjusted relative risk of mortality for current use of the study medications by COPD severity	60
Figure 9.	Adjusted relative risk of mortality for current use by age group.....	61
Figure 10.	Adjusted relative risk of mortality for current use by history of asthma	62
Figure 11.	Adjusted relative risk of mortality for current use by history of cardiovascular disease.....	63

1. ABSTRACT

Title: Acclidinium 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: Acclidinium bromide; LAMA; chronic obstructive pulmonary disease; mortality; database study

Rationale and background: Acclidinium 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 acclidinium 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 acclidinium 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 acclidinium 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 acclidinium, 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 acclidinium 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 acclidinium, 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 acclidinium was 1.02 (95% CI, 0.71-1.48).

The risk of mortality comparing current use of each study medication versus current use of acclidinium was higher for all the study medications except other LAMA. Relative risks versus current use of acclidinium 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 acclidinium to 0.81 (95% CI, 0.50-1.32) for LABA/ICS. Relative risks for long duration of use (\geq 30 days) ranged from 0.38 (95% CI, 0.17-0.84) for acclidinium 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 acclidinium 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 acclidinium and tiotropium and most observational studies of tiotropium, which did not find an increased risk of mortality. The effect estimate for acclidinium 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 acclidinium. There was no difference in mortality among acclidinium users in the multiple use category (those patients using other COPD study medications in addition to acclidinium), which comprised approximately 70% of the acclidinium 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.

Marketing Authorisation Holder(s)

AstraZeneca AB
SE-151 85 Södertälje
Sweden

Name and affiliation of principal investigator

[REDACTED], MPH; Senior Director, Epidemiology
RTI Health Solutions—Barcelona
Av. Diagonal 605 9-1
08028 Barcelona, Spain

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