PASS Study Report	
Active substance	Aclidinium bromide
Product reference	D6560R00004
Version number	1.0
Date	01 June 2021

Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Acute Myocardial Infarction and Stroke

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Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	AstraZeneca AB SE-151 85 Södertälje Sweden
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Approved by:

Principal Investigator, Cristina Rebordosa, MD, PhD — Date

PASS INFORMATION

Title	Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Acute Myocardial Infarction and Stroke
Version identifier of the final study report	1.0
Date of last version of the final study report	01 June 2021
EU PAS register number	ENCEPP/SDPP/13616; 23 May 2014
Active substance	Aclidinium bromide (ATC code: R03BB05) Aclidinium 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 post-authorisation safety study (PASS) is to evaluate the potential cardiovascular safety concerns and all-cause mortality described in the risk management plan for aclidinium bromide through sequential, cohort substudies for each endpoint of interest. Specific objectives are as follows: • To compare the risk of **acute myocardial infarction**, including community coronary heart disease death; **stroke**, including community cerebrovascular disease death; composite endpoint of major adverse cardiac events; congestive heart failure; and all-cause mortality in patients with chronic obstructive pulmonary disease (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 long-acting beta2-agonists (LABAs). • To compare the risk of **acute myocardial infarction, stroke**, composite endpoint of major adverse cardiac events, congestive heart failure, 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. • To evaluate the effect of duration of each of the study medications on the risk of each individual endpoint. This report addresses the **acute myocardial infarction, stroke, and composite of major adverse cardiac events** components of the PASS programme among users of aclidinium bromide (monotherapy or concomitant use with formoterol not in fixed-dose combination) and among users of aclidinium/formoterol. New users of the fixed-dose combination of aclidinium/formoterol are also included as a separate cohort for evaluation. A new additional endpoint of cardiac arrhythmias will be evaluated for this cohort.

	This report also includes the following information: • Results of the descriptive analyses of the incidence rates for cardiac arrhythmias and recalculation of the sample size for this study endpoint, per the PASS protocol milestones. • Results of the descriptive analyses of the incidence rates for congestive heart failure and all-cause mortality among users of aclidinium/formoterol and an evaluation of potential differences with the incidence rates among users of aclidinium bromide.
Country(-ies) of study	United Kingdom: the Clinical Practice Research Datalink (CPRD)
Author	Cristina Rebordosa, MD, PhD, RTI Health Solutions [redacted] MD, MPH, FISPE, RTI Health Solutions

APPROVAL PAGE: RTI HEALTH SOLUTIONS

Project Title: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Acute Myocardial Infarction and Stroke

Authors:	Cristina Rebordosa, MD, PhD, and [redacted] MD, MPH, FISPE
Report version:	1.0
Date:	01 June 2021

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

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APPROVAL PAGE: ASTRAZENECA—CLINICAL LEAD

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Report version:	1.0
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1 ABSTRACT

Title: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Acute Myocardial Infarction and Stroke

Version: 1.0, 01 June 2021

Authors: Cristina Rebordosa, MD, PhD, and [redacted], MD, MPH, FISPE

Keywords: aclidinium bromide; LAMA; chronic obstructive pulmonary disease; myocardial infarction; stroke; 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 substudies were planned to evaluate potential cardiovascular safety concerns identified in the aclidinium risk management plan, to address cardiovascular concerns associated with LAMA use. The first and second substudies did not observe an increased risk of all-cause mortality or congestive heart failure associated with the use of aclidinium. Results of the third and fourth substudies, which focused on the risk of acute myocardial infarction (AMI) and stroke, are presented in the current report. This report also includes (1) the descriptive analysis of incidence rates for cardiac arrhythmias (to be evaluated in a future substudy) and recalculation of the study size for this endpoint, and (2) the descriptive analysis of incidence rates for all-cause mortality and congestive heart failure in order to evaluate if there are differences between the incidence rates for these endpoints in aclidinium users and aclidinium/formoterol users.

Research question and objectives: (1) To compare the risk of AMI and stroke in patients with COPD initiating treatment with aclidinium and other selected COPD medications with the risk in patients with COPD initiating treatment with long-acting beta2-agonists (LABAs). (2) To compare the risk of AMI and stroke between use of aclidinium and use of each of the selected COPD medications. (3) To evaluate the effect of duration of use. (4) To estimate the incidence rates for all-cause mortality and first-ever hospitalisation for heart failure among new users of aclidinium/formoterol in a fixed-dose combination and compare them with the incidence rates among new users of aclidinium bromide in the current study.

Study design: Non-interventional database cohort study of patients with COPD aged 40 years or older starting (new users) treatment with aclidinium, aclidinium/formoterol, tiotropium, other LAMA (glycopyrronium or umeclidinium), LAMA/LABA, LABA/inhaled corticosteroids (LABA/ICS), or LABA.

Setting: The primary care Aurum database of the Clinical Practice Research Datalink (CPRD) in the United Kingdom, from September 2012 through June 2019. The study included all practices where linkage was available to obtain information on date and cause of death from the Office for National Statistics (ONS) and information on hospitalisations from the Hospital Episode Statistics (HES) database.

Subjects and study size, including dropouts: A total of 18,112 new users of aclidinium were identified; 15,221 met eligibility criteria (84.0%) and 11,121 (61.4%) were included in the assessment of AMI and stroke endpoints for aclidinium. Similarly, a total of 7,621 new users of aclidinium/formoterol were identified; 6,701 met eligibility criteria (87.9%) and 4,804(63.0%) were included in the assessment of AMI and stroke endpoints for aclidinium.

Variables and data sources: Exposure to the study medications was ascertained through prescription information recorded in the CPRD. The endpoint AMI was defined as hospitalisation for AMI, either non-fatal or fatal, plus out-of-hospital ("community") coronary heart disease (CHD) deaths. Stroke was defined as acute stroke, either fatal (i.e., in-hospital deaths) or non-fatal, and included hospital admission and emergency department visit or referral to a specialist (neurologist) plus community cerebrovascular disease (CeVD) deaths. The composite endpoint of major adverse cardiac events (MACE) included the first occurrence of either AMI, stroke, community CHD death, or CeVD death. The main risk factors evaluated included age, sex, smoking, body mass index (BMI), COPD severity, comorbidity, comedications, and utilisation of health care resources. Crude incidence rates for hospitalisation for AMI and stroke were estimated for current use of each study medication. Crude and adjusted incidence rate ratios (IRRs) were estimated for current, recent, and past use of each study medication versus current use of LABA. Risks were also estimated for current single use and current multiple use and by duration of current use of the study medications. Several subgroup and sensitivity analyses were conducted.

Results: The study included 11,121 new users of aclidinium, 4,804 new users of aclidinium/formoterol, 56,198 new users of tiotropium, 23,856 new users of other LAMA, 17,450 new users of LAMA/LABA, 70,289 new users of LABA/ICS, and 13,716 new users of LABA. The distributions of age, sex, race, current smoking, BMI, alcohol abuse, and deprivation index were similar across the study medications. Severity category "D" (the most severe category) was more frequent in users of aclidinium (33.4%) and users of other LAMA (29.5%) than in users of LAMA/LABA (25.9%), tiotropium (24.7%), LABA/ICS (22.9%), and LABA (17.9%).

Crude incidence rates per 1,000 person-years for AMI, during current use, ranged from 8.7 for aclidinium/formoterol to 12.4 for LAMA/LABA. The crude incidence rates for stroke, during current use, ranged from 4.8 among users of aclidinium/formoterol to 7.2 among users of LAMA/LABA. Crude incidence rates per 1,000 person-years for MACE, during current use,

ranged from 13.5 for aclidinium/formoterol to 19.3 for LAMA/LABA. The adjusted IRRs for AMI, stroke, and MACE were around 1 for all study drugs when compared with current use of LABA (Abstract Table 1); therefore, no substantial differences were seen between medication groups.

Abstract Table 1. Risk of AMI and stroke associated with current use of the study medications versus current use of LABA

Current use	Number of events	Person-years	Crude incidence rate per 1,000 PY (95% CI)	Crude incidence rate ratio (95% CI)	Adjusted[a] incidence rate ratio (95% CI)
AMI					
LABA	144	13,681	10.53 (8.88-12.39)	1.0 (REF)	1.0 (REF)
Aclidinium	143	13,902	10.29 (8.67-12.12)	0.98 (0.78-1.23)	1.00 (0.76-1.31)
Aclidinium/formoterol	34	3,929	8.65 (5.99-12.09)	0.82 (0.57-1.19)	0.95 (0.60-1.52)
Tiotropium	967	85,368	11.33 (10.62-12.06)	1.08 (0.90-1.28)	1.06 (0.88-1.26)
Other LAMA	318	26,808	11.86 (10.59-13.24)	1.13 (0.93-1.37)	1.03 (0.81-1.29)
LAMA/LABA	187	15,027	12.44 (10.72-14.36)	1.18 (0.95-1.47)	1.23 (0.91-1.67)
LABA/ICS	1,292	118,145	10.94 (10.35-11.55)	1.04 (0.87-1.23)	1.03 (0.86-1.22)
Stroke					
LABA	93	13,682	6.80 (5.49-8.33)	1.0 (REF)	1.0 (REF)
Aclidinium	83	13,902	5.97 (4.76-7.40)	0.88 (0.65-1.18)	0.86 (0.62-1.18)
Aclidinium/formoterol	19	3,937	4.83 (2.91-7.54)	0.71 (0.43-1.16)	0.64 (0.39-1.06)
Tiotropium	587	85,463	6.87 (6.32-7.45)	1.01 (0.81-1.26)	1.02 (0.81-1.27)
Other LAMA	171	26,793	6.38 (5.46-7.41)	0.94 (0.73-1.21)	0.89 (0.69-1.17)
LAMA/LABA	108	15,023	7.19 (5.90-8.68)	1.06 (0.80-1.40)	0.95 (0.71-1.26)
LABA/ICS	801	118,280	6.77 (6.31-7.26)	1.00 (0.80-1.23)	1.02 (0.82-1.26)
MACE					
LABA	234	13,583	17.23 (15.09-19.58)	1.0 (REF)	1.0 (REF)
Aclidinium	221	13,810	16.00 (13.96-18.26)	0.93 (0.77-1.12)	0.93 (0.75-1.16)
Aclidinium/formoterol	53	3,913	13.54 (10.15-17.72)	0.79 (0.58-1.06)	0.94 (0.64-1.37)
Tiotropium	1,523	84,706	17.98 (17.09-18.91)	1.04 (0.91-1.20)	1.04 (0.90-1.20)
Other LAMA	484	26,628	18.18 (16.59-19.87)	1.06 (0.90-1.23)	1.03 (0.86-1.24)
LAMA/LABA	289	14,948	19.33 (17.17-21.70)	1.12 (0.94-1.33)	1.24 (0.97-1.59)
LABA/ICS	2,055	117,149	17.54 (16.79-18.32)	1.02 (0.89-1.17)	1.02 (0.89-1.17)

AMI = acute myocardial infarction; CHD = coronary heart disease; CI = confidence interval; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LAMA = long-acting anticholinergic; MACE = major adverse cardiovascular event; PY = person-years; REF = reference category.

Note: The number of events and person-years 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.

[a] For AMI, the models were adjusted by age; sex; COPD severity; calendar period; smoking; history of CHD; asthma; heart failure; number of prescriptions for respiratory medications in the 12 months prior to the start date; and use of LABA /ICS, LAMA/LABA, ICS, mucolytics, lipid-lowering drugs, beta-blockers, and vaccines in the 12 months prior to the start date. For stroke, the models were adjusted by age; sex; COPD severity; history of cerebrovascular disease; arrhythmias; asthma; heart failure; number of prescriptions for respiratory medications in the 12 months prior to the start date; and use of LABA, mucolytics, and oral glucocorticoids in the 12 months prior to the start date. For MACE, the models were adjusted by age; sex; COPD severity; calendar period; smoking; history of CHD; cerebrovascular disease; arrhythmias; heart failure; asthma; number of prescriptions for respiratory medications in the 12 months prior to the start date; and prior use of LABA, LABA/ICS, LAMA/LABA, ICS, mucolytics, oral glucocorticoids, beta-blockers, lipid-lowering drugs, and vaccines in the 12 months prior to the start date.

Comparing each study medication to LABA, adjusted IRRs for AMI and MACE for recent and past use and the adjusted IRRs for stroke for past use were similar to those observed for current use. The adjusted IRRs for stroke for recent use were generally higher than those observed for current use for all study medications groups compared with LABA. Compared with recent use of LABA, the adjusted IRR for stroke was 1.79 (95% confidence interval [CI], 1.06-3.00) for recent use of aclidinium bromide and 1.18 (95% CI, 0.50-2.74) for recent use of aclidinium/formoterol.

Comparing each study medication to LABA, adjusted IRRs for AMI, stroke, and MACE for current single and current multiple use of each study medication were similar to those observed for current use that included single and multiple use of the study medications. For aclidinium bromide, the adjusted IRR for AMI was 1.06 (95% CI, 0.72-1.54) for current single use and 1.13 (95% CI, 0.73-1.73) for current multiple use. For aclidinium/formoterol, the adjusted IRR for AMI was 1.03 (95% CI, 0.60-1.77) for current single use and 0.20 (95% CI, 0.03-1.54) for current multiple use. For aclidinium, the adjusted IRR for stroke was 0.78 (95% CI, 0.49-1.24) for current single use and 0.82 (95% CI, 0.52-1.29) for current multiple use. For aclidinium/formoterol, the adjusted IRR for stroke was 0.51 (95% CI, 0.28-0.94) for current single use and 1.04 (95% CI, 0.40-2.72) for current multiple use. For aclidinium bromide, the adjusted IRR for MACE was 0.94 (95% CI, 0.70-1.27) for current single use and 0.99 (95% CI, 0.70-1.38) for current multiple use. For aclidinium/formoterol, the adjusted IRR for MACE was 0.84 (95% CI, 0.54-1.31) for current single use and 0.63 (95% CI, 0.25-1.54) for current multiple use.

When compared with aclidinium bromide, there was no meaningful increased risk of AMI, stroke, or MACE for current use of each study medication. When compared with aclidinium/formoterol, an increased risk of AMI, stroke, and MACE was observed for current use of each study medication. The adjusted IRRs ranged from 1.05 (95% CI, 0.65-1.68) for AMI

to 1.56 (95% CI, 0.95-2.59) for stroke, both for current use of LABA compared with current use of aclidinium/formoterol.

No meaningful increased risk of AMI, stroke, or MACE was observed for short or long duration of current use of any of the study medications compared with current short or long use of LABA, respectively, except for long duration of use of LAMA/LABA versus long duration of use of LABA, which showed an adjusted IRR for AMI of 1.68 (95% CI, 1.10-2.55) and an adjusted IRR for MACE of 1.68 (95% CI, 1.20-2.36).

The study results were consistent across subgroup analyses. In general, IRRs were similar across subgroups, with some variations. No meaningful increased risk with AMI, stroke, or MACE was observed between use of any study medication compared with LABA for any of the subgroups. For some subgroups, precision of effect estimates (IRRs) was low. The results were also consistent across sensitivity analysis using an alternative definition of duration of exposure, an alternative definition of stroke, and analyses using propensity score stratification.

Crude incidence rates for all-cause mortality and for hospitalisation for heart failure were estimated using the updated data. The crude incidence rate per 1,000 person-years for all-cause mortality was 16.4 among users of aclidinium/formoterol and 21.7 among users of aclidinium, and the 95% CIs of these incidence rates overlapped. Use of aclidinium/formoterol was not associated with a meaningful decreased risk of all-cause mortality (adjusted IRR, 0.79; 95% CI, 0.60-1.04) or a meaningful increased risk for hospitalisation for heart failure (adjusted IRR, 1.17; 95% CI, 0.88-1.54) compared with users of aclidinium.

Discussion: Overall, results from this study indicate that the current use of aclidinium, aclidinium/formoterol, tiotropium, other LAMA, LAMA/LABA, or LABA/ICS is not associated with a meaningful increased risk of AMI, stroke, or MACE compared with the use of LABA. The differences in the risks observed in some of the analyses for specific medications, and in the analyses stratified by subgroups of patients, may be explained by random variability from the low number of events and unmeasured confounding.

Results from the current substudy indicate that the risk of all-cause mortality and first-ever hospitalisation for heart failure among users of aclidinium/formoterol is similar to the risk among users of aclidinium, where no increased risk was observed when compared with users of LABA. Therefore, there is no need at this time to update analyses for these endpoints.

Results from the next substudy in the aclidinium cardiovascular post-authorisation safety study (PASS) programme on arrhythmias will provide more information on the cardiovascular safety of aclidinium and other COPD medications.