PASS Study Report	
Active substance	Aclidinium bromide
Product reference	D6560R00004
Version number	*1.0*
Date	*06 June 2019*

Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Congestive Heart Failure

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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:

[redacted]

Principal Investigator, Cristina Rebordosa, MD, PhD

16 JUNE 2019
Date

PASS INFORMATION

Title	Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Congestive Heart Failure
Version identifier of the final study report	1.0
Date of last version of the final study report	06 June 2019
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 **congestive heart failure**; acute myocardial infarction, including community coronary heart disease death; stroke; 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 **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. • To evaluate the effect of duration of each of the study medications on the risk of each individual endpoint. 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. This report addresses the **congestive heart failure** component of the PASS programme among users of aclidinium (monotherapy or concomitant with formoterol not in fixed-dose combination). This report also includes results of the descriptive analyses of the incidence rates of acute myocardial infarction (AMI) and stroke and recalculation of the sample size for these study endpoints, per the PASS protocol milestones.
Country(-ies) of study	United Kingdom: the Clinical Practice Research Datalink (CPRD)
Author	Cristina Rebordosa, MD, PhD, RTI Health Solutions [redacted] MD, MPH, RTI Health Solutions

APPROVAL PAGE: RTI HEALTH SOLUTIONS

Project Title: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Congestive Heart Failure

Authors:	Cristina Rebordosa, MD, PhD, and [redacted] MD, MPH, FISPE
Report version:	1.0
Date:	06 June 2019

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

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16 JUNE 2019
Date

APPROVAL PAGE: ASTRAZENECA—CLINICAL LEAD

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Project Title: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Congestive Heart Failure

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1 ABSTRACT

Title: Aclidinium Bromide Post-Authorisation Safety Study to Evaluate the Risk of Cardiovascular Endpoints: Congestive Heart Failure

Version: 1.0, 06 June 2019

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

Keywords: aclidinium bromide; LAMA; chronic obstructive pulmonary disease; congestive heart failure; 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 have been planned to evaluate potential cardiovascular safety concerns identified in the aclidinium risk management plan, to address cardiovascular concerns associated with LAMA use. The first substudy did not observe an increased risk of all-cause mortality associated with the use of aclidinium. The second of these substudies focuses on the risk of congestive heart failure. This report also includes the descriptive analysis of incidence rates of AMI and stroke in order to evaluate future substudies and address the need to recalculate the study size for those endpoints.

Research question and objectives: (1) To compare the risk of congestive heart failure, defined as first ever hospitalisation for heart failure among patients without prior hospitalisation for heart failure (primary endpoint), in patients with COPD initiating treatment with aclidinium bromide and other selected COPD medications with the risk in patients with COPD initiating treatment with long-acting beta2-agonists (LABA). An additional analysis was added to evaluate the risk of first hospitalisation for heart failure during the study period among patients with or without prior hospitalisation for heart failure (secondary endpoint). (2) To compare the risk of congestive heart failure between use of aclidinium and use of each of the selected COPD medications. (3) To evaluate the effect of duration of use.

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

Setting: The General Practitioner Online Database (GOLD) of the Clinical Practice Research Datalink (CPRD) in the United Kingdom, from September 2012 through June 2017. For a subset of practices where linkage was available, the study also included information from the Office for National Statistics (ONS) and the Hospital Episode Statistics database (HES).

Subjects and study size, including dropouts: A total of 6,896 new users of aclidinium were identified; 5,696 met eligibility criteria (82.6%); 1,200 of those (21.1%) had exclusion criteria; 4,493 (65.2%) were included in the analysis of the secondary endpoint; an additional 143 of those had a prior hospitalisation for heart failure (3.2%). After all of these exclusions, 4,350 (63.1%) were included in the assessment of the primary endpoint for aclidinium.

Variables and data sources: Exposure to the study medications was ascertained through prescription information recorded in the CPRD. Hospitalisations for heart failure were identified through primary and secondary discharge diagnoses in HES for linked practices and through primary care codes for heart failure associated with hospitalisation codes in the CPRD GOLD for unlinked practices. All events were validated through questionnaires sent to the general practitioners and through review of the recorded clinical information. The main risk factors evaluated included age, sex, smoking, COPD severity, comorbidity, comedications, and utilisation of health care resources. Crude incidence rates for hospitalisation for heart failure 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 4,350 new users of aclidinium, 23,405 new users of tiotropium, 6,977 new users of other LAMA, 3,132 new users of LAMA/LABA, 26,093 new users of LABA/ICS, and 5,678 new users of LABA without prior history of hospitalisation for heart failure. Depending on the study medication, the number of new users was between 3.2% and 5.3% higher for the evaluation of the secondary endpoint, i.e., including patients with or without prior history of hospitalisation for heart failure. The distributions of age, sex, race, current smoking, body mass index (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 (35.4%) and users of other LAMA (30.9%) than in users of other medications.

Out of 2,283 first ever hospitalisations for heart failure identified within study period, 656 (55.8%) could be validated, and of those, 434 (66.2%) were confirmed. Positive predictive values (PPVs) differed between cases identified through hospital primary discharge diagnosis (PPV = 95.1%), secondary discharge diagnosis (PPV = 48.0%), or through a primary care code for heart failure (Read code) plus a record for hospitalisation in the CPRD GOLD primary care database (PPV = 82.8%). The main analysis and most of the analyses included all cases identified through HES primary discharge diagnosis or through the CPRD GOLD plus only confirmed cases that were identified through HES secondary discharge diagnosis.

Crude incidence rates per 1,000 person-years of first ever hospitalisation for heart failure, during current use, were 9.5 for aclidinium, 7.9 for other LAMA, 8.3 for LAMA/LABA, 6.9 for LABA,

7.6 for tiotropium, and 7.3 for LABA/ICS. The adjusted IRR for first ever hospitalisation for heart failure was 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 first ever hospitalisation for heart failure 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)
LABA	30	4,339	6.91 (4.66-9.87)	1.0 (REF)	1.0 (REF)
Aclidinium	36	3,783	9.52 (6.66-13.17)	1.38 (0.85-2.23)	0.90 (0.53-1.53)
Tiotropium	186	24,490	7.59 (6.54-8.77)	1.10 (0.75-1.62)	1.02 (0.69-1.51)
Other LAMA	40	5,036	7.94 (5.67-10.82)	1.15 (0.72-1.84)	0.86 (0.50-1.47)
LAMA/LABA	13	1,571	8.27 (4.41-14.15)	1.20 (0.62-2.29)	1.09 (0.41-2.92)
LABA/ICS	213	29,036	7.34 (6.38-8.39)	1.06 (0.72-1.55)	1.01 (0.69, 1.48)

CI = confidence interval; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LAMA = long-acting anticholinergic; 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] All the models were adjusted by age, sex, COPD severity, prior outpatient diagnosis of congestive heart failure, diuretic use, ICS use, asthma, and calendar year at start date, unless one of these variables was used for stratification.

Adjusted IRRs 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, except for LAMA/LABA, where the IRRs were higher for current single use. The adjusted IRR was 0.60 (95% confidence interval [CI], 0.25-1.45) for current single use of aclidinium and 0.75 (95% CI, 0.38-1.48) for current multiple use of aclidinium. Results from the analysis including those with a first hospitalisation for heart failure during the study period (secondary endpoint) did not differ from the results among patients without prior hospitalisation for heart failure.

When compared with aclidinium, there was no increased risk of first ever hospitalisation for heart failure comparing current use of each study medication. Adjusted IRRs versus current use of aclidinium were 0.93 (95% CI, 0.64-1.35) for tiotropium, 0.84 (95% CI, 0.53-1.35) for other LAMA, 0.73 (95% CI, 0.34-1.56) for LAMA/LABA, 0.89 (95% CI, 0.62-1.28) for LABA/ICS, and 1.11 (95% CI, 0.65-1.90) for LABA.

No increased risk of first ever hospitalisation for heart failure 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.

The study results were consistent across subgroup analyses. In general, IRRs were similar across subgroups with some variations. No association with first ever hospitalisation for heart failure was observed between use of any study medication compared with LABA for any of the subgroups. For some subgroups, precision of effect estimates was low.

The results were also consistent across sensitivity analysis using an alternative definition of duration of exposure, analyses restricted to patients with linkage to HES and ONS, analyses restricted to confirmed cases only, and analysis using propensity score stratification.

Incidence rates (per 1,000 person-years) of AMI ranged from 10.21 for aclidinium to 5.60 for LABA. Incidence rates (per 1,000 person-years) of stroke ranged from 6.05 for LABA/ICS to 3.54 for LABA.

Discussion:

Overall, results from this study indicate that the use of aclidinium, tiotropium, other LAMA, LAMA/LABA, or LABA/ICS is not associated with an increased risk of congestive heart failure compared with the use of LABA.

The incidence rates of AMI and stroke were lower than those obtained from the literature in the original protocol. Based on study size recalculation, it is estimated that by the start of data collection for the AMI and stroke substudy (first semester 2020), there will be enough aclidinium users to discard an IRR with the upper limit of the 95% CI below 1.5 for AMI and below 2 for stroke.

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

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