ORIGINAL RESEARCH

Efficacy of Aclidinium Bromide According to Baseline Therapy: Post-Hoc Analysis of ASCENT-COPD Randomized Trial

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ABSTRACT

Introduction: Long-acting muscarinic antagonists (LAMAs), long-acting β_2-agonists (LABAs), inhaled corticosteroids (ICS), and their combinations, are recommended for the treatment of chronic obstructive pulmonary disease (COPD). This study aimed to determine whether the safety and efficacy of aclidinium bromide differs by baseline maintenance LABA and ICS therapies.

Methods: ASCENT-COPD was a phase 4, multicenter, double-blind, randomized, placebo-controlled, parallel-group study of patients with moderate-to-very severe COPD and increased cardiovascular risk. Patients were randomized 1:1 to receive aclidinium 400 µg or placebo twice daily, via a multidose dry-powder inhaler for up to 3 years. Outcomes included time to first major adverse cardiovascular events (MACE), all-cause mortality, change from baseline in trough forced expiratory volume in 1 s (FEV_1), and COPD assessment test (CAT) total score over 3 years, and annual moderate-to-severe COPD exacerbation rate in patients receiving aclidinium or placebo with maintenance LABA monotherapy, ICS monotherapy, LABA + ICS (fixed/free), or no maintenance therapy (neither LABA nor ICS) at baseline.

Results: A total of 3589 patients were included (LABA, *n* = 227; ICS, *n* = 290; LABA + ICS, *n* = 2058; no maintenance, *n* = 1130). Aclidinium did not increase the risk of MACE or all-cause mortality versus placebo, regardless of baseline maintenance treatment. Reductions in moderate-to-severe exacerbation rates were observed with aclidinium versus placebo in all subgroups [LABA 43% (*P* = 0.046); ICS 25% (*P* = 0.202); LABA + ICS 22% (*P* = 0.003); no

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maintenance 18% ($P = 0.130$)]. Aclidinium improved morning trough FEV_1 irrespective of baseline therapy and CAT total scores, except for LABA and ICS subgroups, versus placebo at several time points.

Conclusion: In patients with moderate-to-severe COPD and CV risk factors, the addition of aclidinium to maintenance therapy with LABA or LABA + ICS provided further benefit.

Trial Registration: ClinicalTrials.gov identifier NCT01966107.

Keywords: Aclidinium bromide; Chronic obstructive pulmonary disease; Muscarinic antagonists

Key Summary Points

Why carry out this study?

Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with accelerated loss of lung function, increased risk of major adverse cardiovascular events (MACE), and decreased survival

This post-hoc analysis of ASCENT-COPD evaluated whether aclidinium provided an added benefit in reducing the risk of moderate-to-severe exacerbation in patients with moderate-to-very severe COPD and elevated risk of cardiovascular (CV) events who were already taking other maintenance therapies at baseline. We also wanted to know whether aclidinium was associated with differential risk of MACE or all-cause mortality in patients who were already taking other maintenance therapies at baseline

What was learned from the study?

Aclidinium is effective in reducing rates of moderate-to-severe exacerbation in patients with stable, moderate-to-severe COPD, and CV risk factors, regardless of baseline maintenance therapy

Aclidinium did not increase the risk of MACE or all-cause mortality versus placebo, regardless of baseline maintenance therapy

There is benefit in adding aclidinium to commonly prescribed maintenance therapies for patients with moderate-to-severe COPD

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a leading global cause of morbidity and mortality [1–3]. COPD is independently associated with cardiovascular (CV) diseases, such as ischemic heart disease and heart failure, which contribute significantly to all-cause mortality [4, 5]. Exacerbations of COPD are significant events that are associated with increased disease progression, including decreased lung function [6, 7], increased risk of major adverse cardiovascular events (MACE) [8–11], and increased mortality [12–14].

Long-acting muscarinic antagonists (LAMAs), long-acting β_2-agonists (LABAs), and combinations of the two are recommended for the maintenance treatment of stable COPD [1]. Both LAMAs and LABAs improve lung function and dyspnea; however, evidence suggests that LAMAs have a greater impact on exacerbations [15–18]. The addition of inhaled corticosteroids (ICS) to LABA/LAMA combinations may be considered for the treatment of patients with persistent symptoms and recurrent exacerbations [1].

Two recent post-hoc studies (WISDOM and IMPACT) have demonstrated that clinical efficacy and safety outcomes vary in COPD subgroups, based on their baseline maintenance treatment [19, 20]. In both studies, patients with COPD and a history of exacerbations receiving triple therapy at baseline had an increased risk of moderate-to-severe exacerbations versus the overall population or patients receiving dual therapy at baseline or LAMA monotherapy. This would perhaps be expected given that triple therapy is currently recommended for those with severe disease [1]. In the

WISDOM study, withdrawal of ICS did not increase exacerbation risk versus the overall population [20]. In addition, in the IMPACT study, patients receiving triple therapy at baseline, that was maintained throughout the study, had a reduced risk of death versus patients who stepped down to LABA/ICS or LAMA/LABA [19]. Since the reduction versus LAMA/LABA did not achieve significance, this suggests that LAMA may contribute to the survival observed with triple therapy.

There has been some uncertainty regarding the CV safety of LAMAs in patients with COPD [21–25]. However, a recent multicenter, double-blind, randomized, placebo-controlled, parallel-group phase 4 study (ASCENT-COPD [NCT01966107]) [26] demonstrated that the LAMA aclidinium bromide was noninferior to placebo for the risk of MACE over 3 years, and reduced the rate of moderate-to-severe COPD exacerbations over 1 year in patients with moderate-to-very severe COPD and at high risk of CV events [27].

Here, we report the results of a post-hoc analysis of the ASCENT-COPD study, evaluating whether aclidinium has an added benefit to patients who were already on other baseline maintenance therapies (ICS alone or in combination with LABA) without an increased safety risk, specifically in terms of the risk of moderate-to-severe exacerbation, MACE, and all-cause mortality.

METHODS

Study Design

The methodology and patient population of ASCENT-COPD has been reported in detail previously [26, 27]. In brief, ASCENT-COPD was a phase 4, multicenter, double-blind, randomized, placebo-controlled, parallel-group study conducted at 522 sites in the USA and Canada [27]. The study comprised a 2-week washout period followed by a double-blind treatment phase, in which patients were randomized 1:1 to receive aclidinium 400 μg or placebo twice daily administered via a multidose dry-powder inhaler (Genuair/Pressair; AstraZeneca) for up to 3 years. The event-driven study was to end when ≥ 122 patients experienced an adjudicated major adverse CV event.

Protocol and informed consent procedures for the study were approved by the Institutional Review Board at each study site. All patients provided written informed consent and the study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The ASCENT-COPD study was initially funded by Forest Laboratories and later funded by AstraZeneca and Circassia. AstraZeneca was involved in data collection and interpretation, along with the development and review of this manuscript; however, the decision to submit the manuscript for publication was made by the authors.

Study Population

Patient eligibility has been described previously [26]. In brief, eligible patients were ≥ 40 years of age with stable, moderate-to-very severe COPD (forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] < 70% and FEV_1 < 80% predicted) and had a smoking history of ≥ 10 pack-years. In addition, patients were required to have ≥ 1 of the following CV risk factors: cerebrovascular disease (e.g., stroke or transient ischemic attack and/or carotid stenosis); coronary artery disease (e.g., angioplasty/stent/bypass, angina, and/or myocardial infarction); peripheral vascular disease; or a history of claudication. Alternatively, patients were required to have ≥ 2 atherothrombotic risk factors, which are detailed in the supplement. Initially, eligible patients had ≥ 1 COPD exacerbation in the year prior to screening; however, this requirement was removed after approximately half of the patients were enrolled to increase accrual and to allow for a broader patient population. At that time, the upper limit of post-bronchodilator FEV_1 was also increased from 70 to 80% predicted [27].

Patients were excluded if they were receiving triple therapy (ICS/LABA/LAMA) at screening, had a respiratory infection or COPD exacerbation ≤ 4 weeks prior to screening, had unstable or life-threatening COPD or CV disease, had a comorbid lung disease other than COPD, had

Table 1 Patient demographics and baseline characteristics (full analysis set)

Characteristics	Overall population		LABA monotherapy		ICS monotherapy		LABA + ICS[a]		No maintenance	
	Aclidinium (n = 1791)	Placebo (n = 1798)	Aclidinium (n = 104)	Placebo (n = 123)	Aclidinium (n = 143)	Placebo (n = 147)	Aclidinium (n = 1023)	Placebo (n = 1035)	Aclidinium (n = 574)	Placebo (n = 556)
Age, years, mean (SD)	67.1 (8.5)	67.2 (8.3)	68.5 (8.1)	68.5 (8.6)	67.7 (8.4)	67.3 (8.6)	67.4 (8.5)	67.3 (8.2)	66.4 (8.5)	66.7 (8.3)
Male, %	59.1	58.2	66.4	55.3	64.3	52.4	58.1	57.6	59.8	60.4
White, %	89.5	91.8	90.4	95.1	87.4	89.1	89.8	91.3	89.0	92.6
BMI, kg/m^2, mean (SD)	29.7 (6.8)	29.5 (6.9)	29.7 (5.9)	29.1 (7.0)	29.7 (6.2)	29.5 (7.3)	29.7 (7.0)	29.6 (7.1)	29.8 (6.6)	29.1 (6.5)
Obese (≥ 30 kg/m^2), %	43.1	41.1	46.2	40.7	44.1	40.8	42.9	41.1	43.0	41.7
Current smoker, %	43.8	43.3	31.7	30.9	39.2	38.1	41.5	40.0	50.2	51.8
Total CAT score, mean (SD)	20.7 (7.3)	20.7 (7.2)	19.0 (7.8)	19.8 (7.5)	20.1 (7.7)	19.9 (7.5)	20.8 (7.2)	21.0 (7.1)	20.7 (7.1)	20.4 (7.3)
Post-BD FEV$_1$% predicted, mean (SD)	47.7 (14.9)	47.8 (15.2)	43.5 (15.3)	47.5 (15.8)	45.3 (14.3)	47.7 (15.2)	47.1 (15.1)	46.2 (15.1)	49.4 (14.4)	50.8 (14.7)
COPD severity, %										
Moderate	44.4	44.9	36.5	43.9	37.1	45.6	42.7	39.8	49.7	54.0
Severe	41.4	39.7	47.1	39.0	49.7	40.1	41.5	42.4	39.0	35.1
Very severe	12.3	13.6	15.4	16.3	11.9	14.3	13.8	16	9.4	8.6
Exacerbations in previous year, %	59.6	60.5	57.7	62.6	62.9	61.2	60.1	61.6	58.2	57.7
≥ 2 prior exacerbations, %	15.8	15.5	13.5	17.1	18.9	18.4	17.0	16.8	12.9	12.4

Table 1 continued

Characteristics	Overall population		LABA monotherapy		ICS monotherapy		LABA + ICS[a]		No maintenance	
	Aclidinium (n = 1791)	Placebo (n = 1798)	Aclidinium (n = 104)	Placebo (n = 123)	Aclidinium (n = 143)	Placebo (n = 147)	Aclidinium (n = 1023)	Placebo (n = 1035)	Aclidinium (n = 574)	Placebo (n = 556)
Exacerbation rate in previous year, mean (SD)	0.8 (0.9)	0.8 (1.0)	0.9 (1.1)	0.9 (0.9)	0.9 (1.0)	0.9 (1.0)	0.8 (1.0)	0.9 (1.0)	0.8 (0.9)	0.8 (1.0)

BD bronchodilator, *BMI* body mass index, *CAT* COPD assessment test, *ICS* inhaled corticosteroid, *LABA* long-acting β$_2$-agonist, *n* number of patients in each group; *SD* standard deviation

[a] Fixed and free combinations. Fixed combinations were defined as > 1 drug in a single device; free combinations used multiple individual devices

Baseline users include patients who took treatment within 15 days prior to the administration of the first dose study treatment, regardless of continuation. Of note, monotherapy subgroups were defined as those not taking fixed combination; therefore, they were not exclusive from other subgroups. Of the 517 patients receiving LABA or ICS monotherapy, 116 were taking a free combination of LABA and ICS

a planned lung transplant or a lung volume reduction surgery, or had malignancy requiring intervention ≤ 5 years prior to screening [26].

Concomitant use of other COPD medications was permitted (including a LABA with or without an ICS), except for anticholinergics and chronic treatment with regularly scheduled short-acting β$_2$-agonists, such as albuterol or salbutamol. Episodic use of sponsor-provided albuterol/salbutamol was permitted, except for within 6 h prior to any visit. Oral or parenteral corticosteroids were permitted, provided the patient was stable for ≥ 2 weeks before screening; however, they may have been initiated, or the dose may have changed during the study, only at the discretion of the investigator [26].

Outcomes

This study performed two subgroup analyses: a post-hoc analysis on baseline maintenance therapy use and a pre-specified analysis based on concomitant maintenance therapy use. Baseline users were defined as patients who took treatment within 15 days prior to the administration of the first dose of study treatment (Fig. S1), regardless of continuation. Of note, monotherapy subgroups were defined as those not taking a fixed combination, but may have been taking free combination; therefore, they were not excluded from other subgroups. The post-hoc analysis assessed time to first MACE, all-cause mortality risk and COPD mortality risk over 3 years, annual moderate-to-severe COPD exacerbation rate, annual severe COPD exacerbation rate, change from baseline in morning pre-dose trough FEV$_1$, and COPD assessment test (CAT) total score over 3 years, in patients receiving aclidinium or placebo with maintenance LABA monotherapy (alone or in free combination with ICS), ICS monotherapy (alone or in free combination with LABA), LABA with ICS (LABA + ICS, fixed and free combinations), and no maintenance therapy (neither LABA nor ICS) at baseline. Concomitant users include patients who initiated treatment prior to randomization and continued beyond the first dose of study treatment (Fig. S1). The pre-specified subgroup analysis assessed the annual

moderate-to-severe exacerbation rate, a primary outcome, change from baseline in trough FEV_1, and CAT total score over 3 years in patients receiving aclidinium versus placebo and concomitant treatment with LABA with or without ICS ($\pm$ ICS, fixed and free combinations) and LABA + ICS (fixed and free combinations). Exacerbations were defined as increased COPD symptoms lasting ≥ 2 days that required treatment with antibiotics and/or systemic corticosteroids, or led to hospitalization or death [27].

Statistical Analyses

The full analysis set included all patients randomized to treatment who received ≥ 1 dose of the study treatment [26]. Time to first MACE, all-cause mortality, and COPD mortality were analyzed using Cox proportional hazard models with randomized treatment group (aclidinium/placebo), baseline CV risk group (≥ 2 CV risk factors or ≥ 1 non-fatal stroke or non-fatal myocardial infarction), smoking status, and baseline treatment (LABA monotherapy/ICS monotherapy/LABA + ICS/ no maintenance therapy) as factors, and the interaction between baseline treatment and randomized treatment group for time to first MACE. The rate of moderate-to-severe COPD exacerbations and severe exacerbations was analyzed using a negative binomial regression model with treatment group, baseline ICS use, baseline COPD severity, history of ≥ 1 exacerbation in the past year, and smoking status as factors. Changes from baseline in trough FEV_1 and CAT total scores were analyzed using a mixed model for repeated measures (MMRM) with corresponding baseline values as covariates, plus pre- and post-bronchodilator (albuterol/salbutamol) FEV_1 at screening visit as a covariate for trough FEV_1, and treatment group, smoking status, baseline ICS use, visit, and treatment-group-by-visit interaction as fixed effect factors for both.

The subgroups included in this study were analyzed separately in some end points. Testing was performed at the 0.05 significance level for all end points [26]; however, P values were not corrected for multiplicity, and therefore only nominal statistical significance could be inferred if $P < 0.05$.

RESULTS

Baseline Demographics and Characteristics

Of 3589 patients included in the full analysis set (aclidinium, $n = 1791$; placebo, $n = 1798$), 227 (6.3%) received LABA monotherapy, 290 (8.1%) received ICS monotherapy, 2058 (57.3%) received LABA + ICS, and 1130 (31.5%) received no maintenance therapy (neither LABA nor ICS) at baseline (Fig. S2a). Of note, of the 517 patients receiving LABA or ICS monotherapy, 116 were taking a free combination of LABA and ICS. A higher percentage of patients receiving no maintenance therapy at baseline were smokers (51.0%) and had moderate COPD (51.8%) versus other treatment subgroups (smoking: LABA monotherapy 31.3%; ICS monotherapy 38.6%; LABA + ICS 40.8%; moderate COPD: LABA monotherapy 40.5%; ICS monotherapy 41.4%; LABA + ICS 41.3%). In addition, the percentage of patients experiencing ≥ 2 exacerbations in the previous year was higher in those using ICS monotherapy (18.6%) versus other treatment subgroups (LABA monotherapy 15.4%; LABA + ICS 16.9%; no maintenance therapy 12.7%). Of note, 2243 (62.5%) and 2016 (56.2%) patients received concomitant treatment (treatment initiated prior to randomization and continued beyond the first dose of study treatment; Fig. S2b) with LABA ($\pm$ ICS) and LABA + ICS, respectively. Patient demographics and baseline characteristics were similar between patients receiving aclidinium and placebo (Table 1).
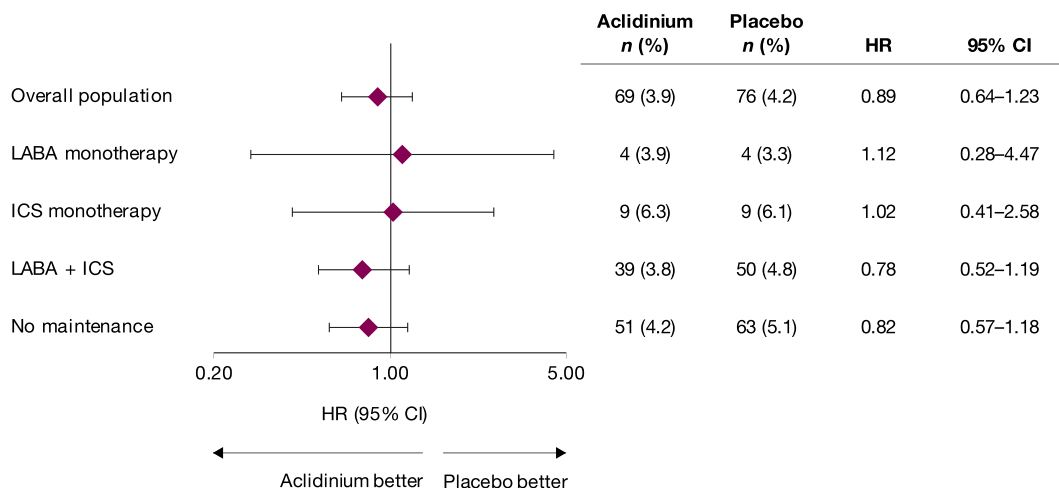
Safety

Aclidinium did not increase the risk of MACE or all-cause mortality compared with placebo, regardless of maintenance treatment at baseline (Figs. 1 and 2). Of note, only a small number of events were observed for patients receiving LABA monotherapy and ICS monotherapy at

(a)

(b)

		Aclidinium n (%)	Placebo n (%)	HR	95% CI
Overall population		69 (3.9)	76 (4.2)	0.89	0.64–1.23
LABA monotherapy		4 (3.9)	4 (3.3)	1.12	0.28–4.47
ICS monotherapy		9 (6.3)	9 (6.1)	1.02	0.41–2.58
LABA + ICS		39 (3.8)	50 (4.8)	0.78	0.52–1.19
No maintenance		51 (4.2)	63 (5.1)	0.82	0.57–1.18
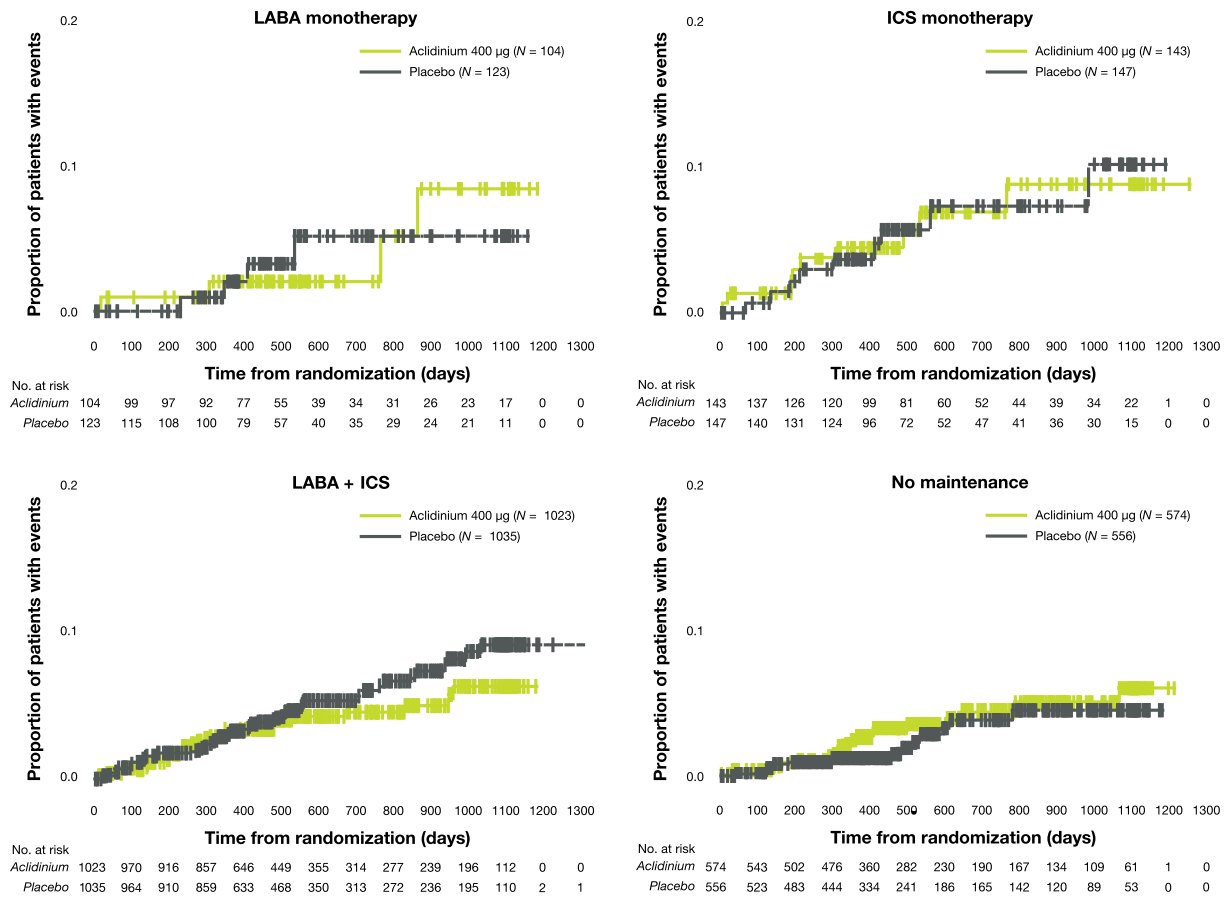
◄ **Fig. 1 a** Time to first adjudicated MACE and **b** the risk of MACE on study, by patient baseline treatment subgroup. *CI* confidence interval, *CV* cardiovascular, *HR* hazard ratio, *ICS* inhaled corticosteroid, *LABA* long-acting β₂-agonist, *n* number of patients in the analysis, *N* number of patients in the treatment group. Data derived using the Cox proportional hazard regression model with treatment group, baseline CV risk, smoking status, and baseline treatment use as factors, and the interaction between baseline treatment use and treatment group. Baseline users include patients who took treatment within 15 days prior to the administration of the first dose study treatment, regardless of continuation

baseline, likely due to the low numbers in these subgroups. The percentage of deaths was numerically higher for patients receiving ICS monotherapy at baseline for aclidinium versus placebo (9.8% versus 5.4%, respectively); however, differences were not statistically significant. In addition, there was no increase in the risk of COPD mortality across baseline treatments for aclidinium versus placebo, although event numbers were low [LABA monotherapy: HR 1.2; 95% CI 0.08, 19.21 (aclidinium, $n = 1$; placebo, $n = 1$); ICS monotherapy: HR data not calculable (aclidinium, $n = 3$; placebo, $n = 0$); LABA + ICS: HR 0.81; 95% CI 0.37, 1.78 (aclidinium, $n = 11$; placebo, $n = 14$); no maintenance: HR 0.61; 95% CI 0.10, 3.68 (aclidinium, $n = 2$; placebo, $n = 3$)].

Efficacy

Reductions in the rate of moderate-to-severe COPD exacerbations during the first year were observed with the addition of aclidinium versus placebo in all treatment subgroups. The magnitude of reduction due to aclidinium treatment was similar to that observed in the overall population (22%) for patients receiving ICS monotherapy, LABA + ICS, and no maintenance therapy at baseline (25%, 22%, and 18%, respectively; Fig. 3) and greater than the overall population for patients receiving LABA monotherapy at baseline (43%). The reductions in moderate-to-severe COPD exacerbation rate with additional aclidinium versus placebo were

significant for patients receiving LABA monotherapy and LABA + ICS at baseline ($P = 0.046$ and $P = 0.003$, respectively) and were numerically lower, but not nominally significant, for patients receiving ICS monotherapy and no maintenance therapy at baseline. Of note, although the mean moderate-to-severe exacerbation event rates in the aclidinium treatment arm were similar for all baseline treatment subgroups (ranging from 0.43 to 0.49), the mean moderate-to-severe exacerbation event rate for patients receiving placebo was lower for those not receiving maintenance therapy (0.53) versus other treatment subgroups (ranging from 0.60 to 0.77). Rates of severe COPD exacerbations demonstrated a similar pattern of reductions across baseline maintenance treatment groups for aclidinium versus placebo as those seen with moderate-to-severe COPD exacerbations; however, due to a low number of events, only patients receiving LABA + ICS at baseline had a nominally significant reduction in rates (31%; $P = 0.048$).

In addition, for patients who took concomitant LABA with or without ICS (± ICS) and LABA + ICS during the first year of treatment, those additionally treated with aclidinium had a 23% reduction in the annual rate of moderate-to-severe COPD exacerbations versus placebo [rate ratio (RR), 0.77 [95% confidence interval (95% CI) 0.66–0.89] and RR, 0.77 (95% CI 0.60–0.90), respectively; $P < 0.001$; Fig. S3].

Aclidinium provided improvements from baseline in trough FEV₁ versus placebo at most time points, with nominally significant improvements over the whole first year for all subgroups except those receiving LABA and ICS monotherapy at baseline (Fig. 4). In general, the addition of aclidinium to LABA monotherapy provided a lower treatment effect on trough FEV₁ versus other baseline treatment subgroups; however, this subgroup had the lowest number of patients and wide CI values. For the other treatment subgroups, improvements were generally comparable with those observed in the overall population. In addition, for patients who received concomitant LABA (± ICS) and LABA + ICS over the entire study period, adding aclidinium improved lung function versus placebo over the first year (both $P < 0.001$;

(a)

(b)

		Aclidinium n (%)	Placebo n (%)	HR	95% CI
Overall population		116 (6.5)	118 (6.6)	0.99	0.76–1.28
LABA monotherapy		8 (7.7)	9 (7.3)	1.02	0.39–2.64
ICS monotherapy		14 (9.8)	8 (5.4)	1.76	0.74–4.21
LABA + ICS		73 (7.1)	69 (6.7)	1.09	0.79–1.52
No maintenance		27 (4.7)	34 (6.1)	0.76	0.46–1.25
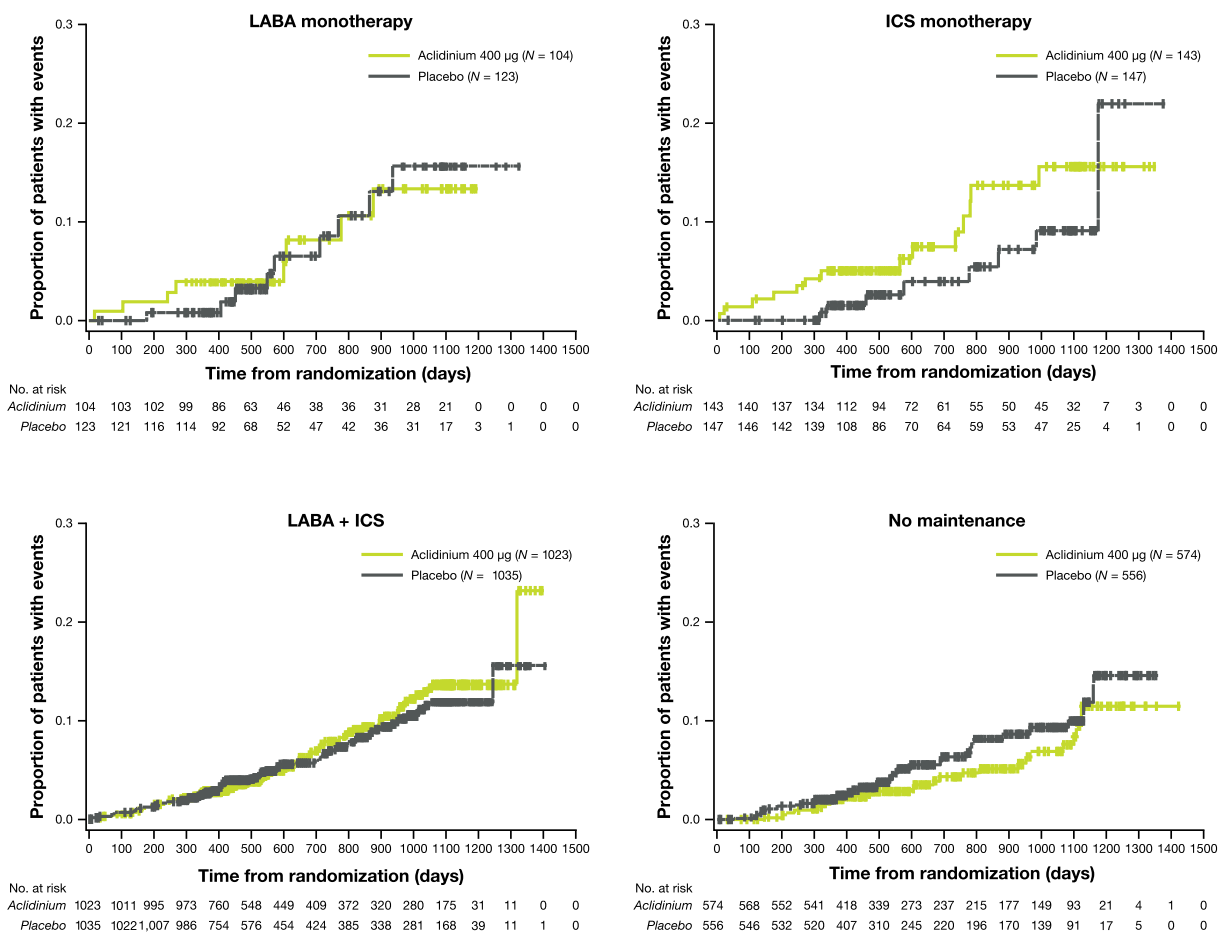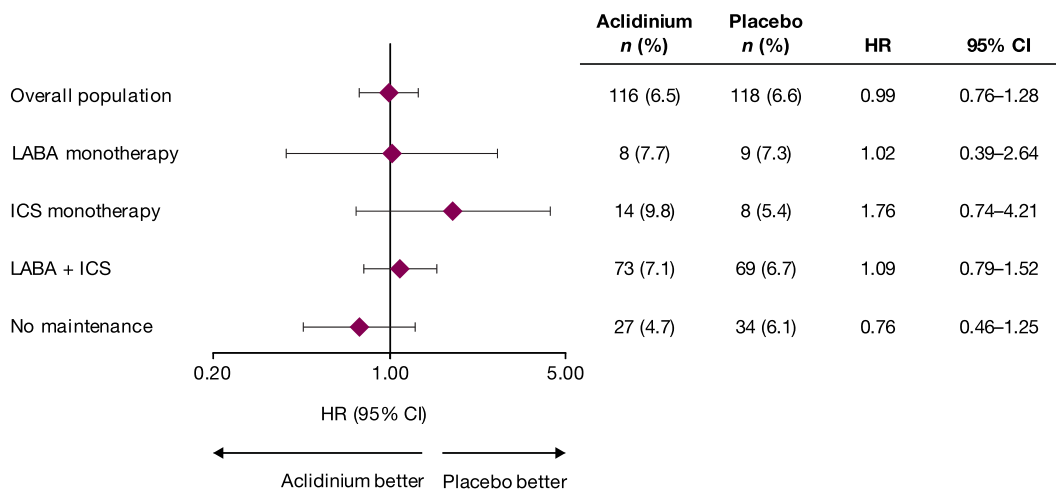
◀ **Fig. 2** **a** Time to death and **b** risk of all-cause mortality on study, by patient baseline treatment subgroup. *CI* confidence interval, *CV* cardiovascular, *HR* hazard ratio, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *n* number of patients in the analysis, *N* number of patients in the treatment group. Data derived using the Cox proportional hazard regression model with treatment group, baseline CV risk, smoking status, and baseline treatment use as factors. Baseline users include patients who took treatment within 15 days prior to the administration of the first dose study treatment, regardless of continuation

Fig. S4). The treatment effect of aclidinium was sustained beyond 1 year in some subgroups; however, patient numbers were small so results should be interpreted with caution.

While improvements were not nominally significant, numerical improvements from baseline in CAT total score were observed at most time points with aclidinium versus placebo, except where patients were receiving maintenance LABA or ICS monotherapy at baseline (Fig. 5); however, results for the LABA and ICS monotherapy subgroups, and all subgroup results observed beyond the first year,

should be interpreted with caution due to small patient numbers. Numerical improvements were also observed with aclidinium versus placebo in the overall population, up to week 130. Similarly, in patients who received concomitant LABA (± ICS) and LABA + ICS over the entire study period, adding aclidinium numerically improved CAT total score versus placebo at all but one time point (Fig. S5).

DISCUSSION

Further to the results of the primary analysis of the ASCENT-COPD study, in which aclidinium treatment was not associated with an increased risk of MACE versus placebo [27], this post-hoc analysis did not find an increased risk of MACE or all-cause mortality with aclidinium versus placebo, regardless of the maintenance baseline therapy. A small numerical increase in all-cause mortality was observed with aclidinium versus placebo for patients receiving ICS monotherapy at baseline; however, this increase in mortality was not evident in the larger subgroup of patients receiving maintenance ICS/LABA at baseline [28]. Of note, ICS monotherapy is not

	Aclidinium			Placebo					
	Events	PY	Event rate	Events	PY	Event rate	RR	95% CI	P value
Overall population	644	1412.20	0.44	792	1363.40	0.57	0.78	0.68–0.89	< 0.001
LABA monotherapy	42	87.2	0.44	68	93.3	0.77	0.57	0.33–0.99	0.046
ICS monotherapy	51	113.6	0.49	69	116.8	0.66	0.75	0.48–1.17	0.202
LABA + ICS	394	803.9	0.47	488	776.6	0.60	0.78	0.66–0.92	0.003
No maintenance	179	450.9	0.43	202	424.0	0.53	0.82	0.63–1.06	0.130

RR (95% CI)

Aclidinium better ← → Placebo better

Fig. 3 Moderate-to-severe COPD exacerbations during the first year, by patient baseline treatment subgroup (on-treatment). *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *PY* patient-years, *RR* rate ratio. Data derived using the negative binomial regression model with treatment group, baseline ICS use, baseline COPD severity, history of ≥ 1 exacerbation in the past

year, and smoking status as factors, and the log of the exposure time adjusted for the time patients experience exacerbations as an offset variable. Baseline users include patients who took treatment within 15 days prior to the administration of the first dose study treatment, regardless of continuation
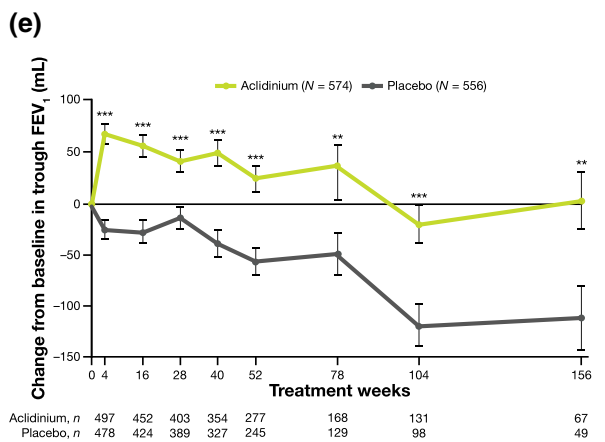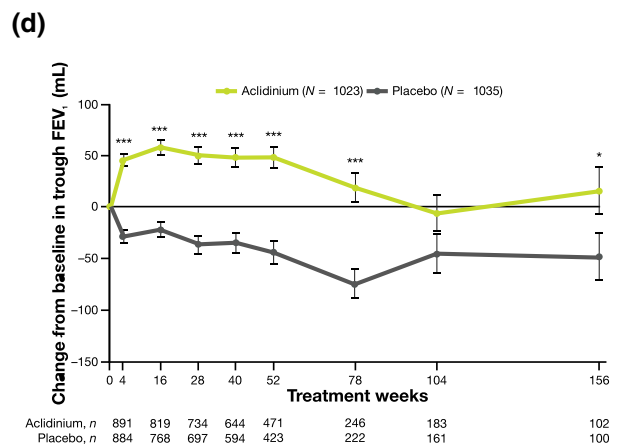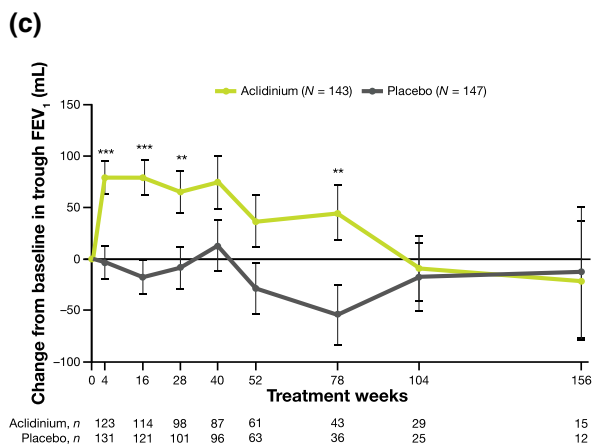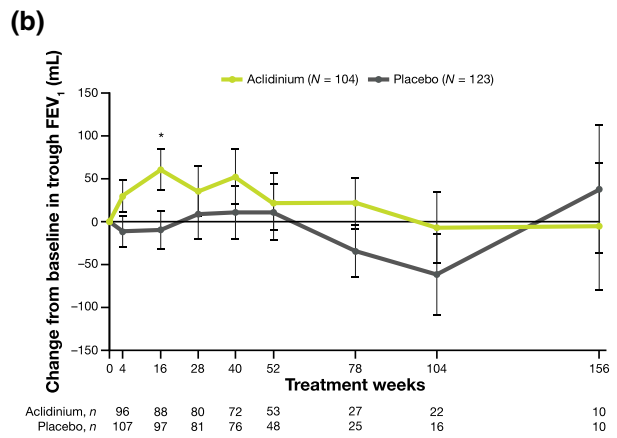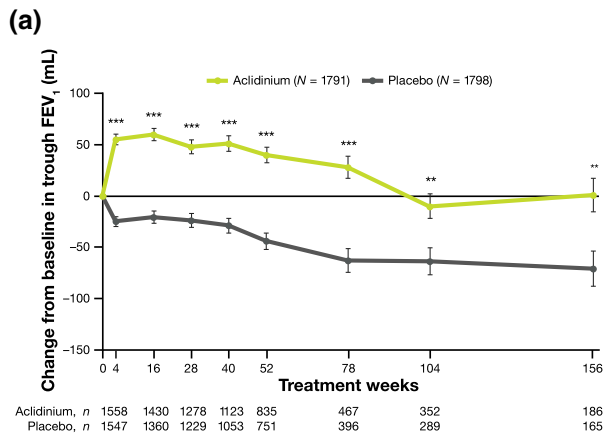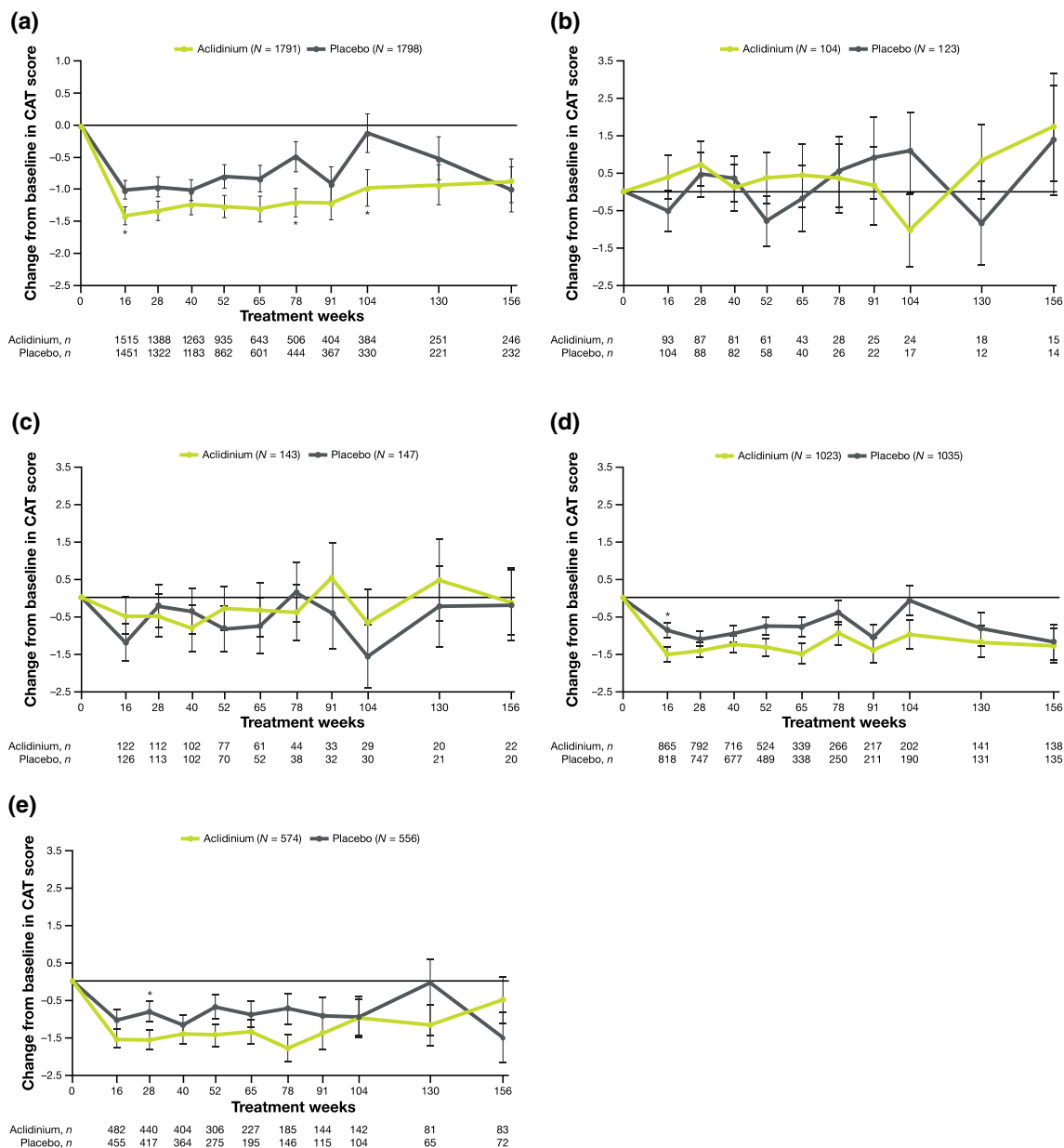
◀ **Fig. 4** Change from baseline in trough FEV_1 over 156 weeks in **a** overall population, **b** patients receiving LABA monotherapy at baseline, **c** patients receiving ICS monotherapy at baseline, **d** patients receiving LABA + ICS at baseline, and **e** patients not receiving maintenance therapy at baseline. FEV_1 forced expiratory volume in 1 s, ICS inhaled corticosteroid, LABA long-acting β₂-agonist, MMRM mixed model for repeated measures, n number of patients in the analysis, N number of patients in the treatment group. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ for aclidinium versus placebo. Data are least squares means ± standard error. The analysis was based on an MMRM for change from baseline in trough FEV_1 with pre- and post-bronchodilator (albuterol/salbutamol) FEV_1 at screening visit and baseline FEV_1 as covariates, and treatment group, smoking status, baseline ICS use, visit, and treatment-group-by-visit interaction as fixed effect factors. Visit is fitted as a categorical variable, and the variance–covariance matrix is assumed to be unstructured. Week 156 includes assessments from patients who completed 3 years treatment or who were on-treatment when the study was stopped. Baseline users include patients who took treatment within 15 days prior to the administration of the first dose study treatment, regardless of continuation

recommended for COPD maintenance therapy [1]. Furthermore, only a small number of deaths were observed for patients receiving ICS monotherapy, LABA monotherapy, or no maintenance therapy at baseline and, therefore, these results should be interpreted with caution. Similarly, there was no increase in COPD mortality for patients receiving aclidinium versus placebo across treatment subgroups.

Aclidinium provided nominally significant reductions in the rate of moderate-to-severe exacerbations versus placebo over the first year for patients receiving LABA monotherapy or LABA + ICS at baseline. Numerical improvements in exacerbation rates were also observed for patients using ICS monotherapy or no maintenance therapy at baseline, which likely did not achieve significance because of the small number of patients in the ICS monotherapy subgroup, given the significant improvement observed in the LABA + ICS subgroup, and a comparatively low exacerbation rate in the placebo arm of the no maintenance therapy subgroup. Across treatment subgroups,

only patients receiving baseline treatment with LABA + ICS demonstrated improvements in rates of severe exacerbations for patients receiving aclidinium versus placebo.

Improved lung function versus placebo was also observed throughout the first year for patients receiving ICS monotherapy, LABA + ICS, or no maintenance therapy at baseline; however, aclidinium appeared to provide minimal additional benefit to patients receiving LABA monotherapy at baseline versus other treatment subgroups. Of note, these results should be interpreted with caution since patient numbers in the monotherapy subgroups, and other treatments beyond the first year, were too small to draw meaningful conclusions. In addition, numerical improvements from baseline in patient-reported health-related quality of life (HRQoL) were observed following further treatment with aclidinium versus placebo for patients receiving LABA + ICS or no maintenance therapy at baseline. No improvement was observed following the addition of aclidinium to LABA and ICS monotherapy subgroups; however, as discussed, these subgroups had small patient numbers and showed high variability.

Similar results were observed for all outcomes measured in patients who were taking concomitant LABA (± ICS) and LABA + ICS throughout the study period, with the addition of aclidinium to maintenance treatment resulting in improvements in exacerbation rate, lung function, and HRQoL, versus placebo, providing further evidence that aclidinium provided additional benefit to background LABA therapy.

These results were comparable with a recent subgroup analysis of the FUFIL study, in which LAMA/LABA/ICS improved trough FEV_1 and St George's Respiratory Questionnaire total scores versus LABA/ICS, regardless of the medication received at screening, including LABA alone, LAMA + LABA, and LAMA + LABA + ICS [29]. In addition, significant reductions in annual exacerbation rates were observed for LAMA/LABA/ICS versus LABA/ICS in patients receiving prior LABA + ICS [29]. Similar results were also observed in a systematic review showing that, when compared with LABA alone, combination

Fig. 5 Change from baseline in CAT total score over 156 weeks in **a** overall population, **b** patients receiving LABA monotherapy at baseline, **c** patients receiving ICS monotherapy at baseline, **d** patients receiving LABA + ICS at baseline, and **e** patients not receiving maintenance therapy at baseline. *CAT* COPD assessment test, *ICS* inhaled corticosteroid, *LABA* long-acting β₂-agonist, *MMRM* mixed model for repeated measures, *n* number of patients in analysis, *N* number of patients in the treatment group. *$P < 0.05$ for aclidinium versus placebo. Data are least squares means ± standard error. The analysis was based on an MMRM for change from baseline in CAT score with baseline CAT total score as a covariate, and treatment group, smoking status, baseline ICS use, visit, and treatment-group-by-visit interaction as fixed effect factors. Visit is fitted as a categorical variable, and the variance–covariance matrix is assumed to be unstructured. Week 156 includes assessments from patients who completed 3 years treatment or who were on-treatment when the study was stopped. Baseline users include patients who took treatment within 15 days prior to the administration of the first dose study treatment, regardless of continuation

therapy with aclidinium and LABA significantly reduced exacerbations requiring steroids or antibiotics, and may have improved quality of life (minimal clinically important difference not achieved for either group) with no difference in all-cause mortality [30]. These results support those of the exploratory analysis reported here, that in patients with stable, moderate-to-severe COPD and CV risk factors, adding aclidinium to maintenance therapy with LABA + ICS, and potentially LABA, was beneficial.

Limitations of the current study included the small patient numbers discussed above. Similar to other investigations, we found no evidence of synergy between LABA and LAMA bronchodilators in any of the outcome measures recorded [31]. We cannot rule out a synergistic effect occurring in a subset of patients based on pharmacogenetic differences [32].

CONCLUSION

In conclusion, this study demonstrated that aclidinium is effective in patients with stable, moderate-to-severe COPD and CV risk factors, regardless of baseline maintenance therapy with LABA monotherapy, ICS monotherapy, LABA + ICS, or no maintenance therapy, and that there is further benefit to adding aclidinium to maintenance therapy with LABA or LABA + ICS, which are commonly prescribed, in this patient population.

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