Supplementary Online Content

Wise RA, Chapman KR, Scirica BM, et al. Effect of aclidinium bromide on major cardiovascular events and exacerbations in high-risk patients with chronic obstructive pulmonary disease: the ASCENT-COPD randomized clinical trial [published May 7, 2019]. *JAMA*. doi:10.1001/jama.2019.4973

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Imputation of Missing Data

Primary Safety Analysis: Time to First Major Adverse Cardiovascular Event (On-study)

To assess possible effects of premature censoring, a sensitivity analysis (on-study analysis) was done as follows: for patients in the aclidinium group, events were added for patients with the shortest censoring times first and were assumed to occur at the time of censoring. Events were added until the null hypothesis of inferiority could not be rejected, and conservatively assuming no further events accumulated in the placebo group. It was found that 22 events needed to be added in patients who were prematurely censored in the aclidinium group, in order for the null hypothesis of inferiority to no longer be rejected (hazard ratio 1.31; 95% confidence interval [CI] 0.94 to 1.82).

Primary Efficacy Analysis: Rate of Moderate/severe Chronic Obstructive Pulmonary Disease Exacerbations, During the First Year of Treatment

To assess the robustness to variations of the data assumptions underlying the primary analysis on the primary efficacy endpoint, jump to reference (J2R), copy reference (CR) and tipping point analyses were conducted.[1] The sensitivity analysis using the J2R approach showed an annual rate of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations during the first year of treatment of 0.46 in the aclidinium group versus 0.56 in the placebo group (rate ratio [RR] 0.83; 95% CI: 0.73 to 0.94; *P* = .004). The sensitivity analysis using the CR approach showed an annual rate of moderate or severe COPD exacerbations during the first year of treatment of 0.43 in the aclidinium group versus 0.52 in the placebo group (RR 0.82; 95% CI: 0.73 to 0.94; *P* = .003). The sensitivity analysis using the tipping point approach was conducted by imputing missing counts of moderate or severe COPD exacerbations for a patient according to the mean of the treatment group the patient was randomized to, multiplied by a factor delta. This analysis showed that, when fixing the delta in the placebo group to 1 and applying a penalized delta of 1.55 in the aclidinium group, the *P*-value for the rate ratio between aclidinium and placebo tipped over 0.05 (95% CI: 0.77 to 1.00). These analyses supported the conclusion of the primary efficacy analysis.

eTable 1. Major Protocol Amendments and Other Significant Changes to Study Conduct

	Key details of amendment	Reason for amendment
Amendments made after the start of subject recruitment		
Protocol amendment 2 (Sep 15, 2015)	Modification of text to state that AEs and SAEs were recorded until 15 days after last treatment dose and SAEs were collected until the last visit/end of study for patients who discontinued prematurely from treatment	To account for the short half-life of aclidinium, the duration for collecting AEs after the last dose of treatment was reduced from 30 days to 15 days
	Replacing value of post-bronchodilator FEV_1 <70% predicted with <80%	To allow the assessment of the CV safety risk in a broader segment of the aclidinium patient population more representative of the target patient population of aclidinium indication
	Addition of requirement of evidence of renal dysfunction (eGFR <60 mL/min) and microalbuminuria (eGFR was based on modification of diet in renal disease equation; microalbuminuria defined as ≥30–300 µg/mg creatinine on a spot urine or ≥30 mg creatinine on a 24-hour urine test)	To specify an additional group of patients with increased CV risk. Evidence of renal dysfunction and microalbuminuria is an additional atherothrombotic risk factor that could increase the risk of MACE events in the patient population
	Removal of inclusion criterion that stipulates patient has to have ≥1 documented moderate or severe COPD exacerbation within 1 year prior to screening	To broaden the severity of the patients with COPD included in the study and to have a study population more representative of the target patient population. This criterion was added in protocol amendment 1 and removed as per protocol amendment 2 as it was negatively affecting recruitment

Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; FEV_1, forced expiratory volume in 1 second; MACE, major adverse cardiovascular event; SAE, serious adverse event.

eTable 2. Major Changes to Planned Analyses

	Key details of change	Reason for change
Changes made before unblinding of study data		
Protocol amendment 2 (Sep 15, 2015)	Addition of history of ≥1 COPD exacerbation in the past year as covariate to the analysis model of the primary efficacy endpoint and the CAT endpoint	To account for the change in the inclusion criterion and potential enrollment of subjects with no prior history of exacerbation, the covariate history of ≥1 exacerbation in the past year is added to the model
	Modification of text concerning the primary safety analysis. The time to the first MACE event was analyzed "on-study", defined as all events that occurred while the patients were in the study period, irrespective of treatment exposure. An on-treatment analysis was also conducted and included two ascertainment windows, on-treatment and on-treatment +15 days	The choice of on-study and on-treatment analyses (applying different censoring scheme) was made consistent with other studies assessing all-cause mortality
	Modification of text concerning the power calculation for primary efficacy endpoint analysis. The sample size of 4000 patients after 1 year of treatment had ~89% (instead of ~96%) power to detect a reduction in the rate of moderate or severe COPD exacerbations per patient per year during the first year of treatment of 14% (instead of 20%) (rate ratio of 0.86 [instead of 0.80] in aclidinium bromide relative to placebo) at 0.05 (instead of 0.00125) alpha level. The 89% power was calculated assuming a discontinuation rate of 30% during the first year, a placebo rate of 0.81 exacerbation per patient per year (reduced from 1 to 0.8 as not all patients will have a history of exacerbation prior to randomization), and an over-dispersion factor of 0.67	Updates reflect the change in the inclusion criteria and the change in the alpha level (0.00125 to 0.05, 2-tailed), and clarify how the power and sample size were calculated
Statistical analysis plan amendment 2 (7 Jun, 2017)	For the analysis of the primary efficacy endpoint (rate of moderate or severe COPD exacerbations per patient per year during the first year of treatment), on-study analysis was added as secondary analysis	The FDA recommended an on-study analysis targeting the *de facto* estimate and including all observed data regardless of adherence
	Addition of jump-to-reference approach as sensitivity analysis	In the jump-to-reference approach, dropouts on test treatment are assumed to have been on test treatment rather than the reference prior to dropout. In the FDA's opinion, this may be more reasonable than the copy reference approach, given that the copy reference approach may carry forward a treatment effect (ie, if a patient had a decreased rate while on treatment)

Abbreviations: CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FDA, Food and Drug Administration; MACE, major adverse cardiovascular event.

eTable 3. Chronic Pulmonary Disease-Related Prior Medications That Were Stopped Prior to Randomization and Concomitant Medications (Full Analysis Set)

	Prior medication stopped before randomization, n (%)		Concomitant medication[a], n (%)	
Medication	**Aclidinium (N = 1791)**	**Placebo (N = 1798)**	**Aclidinium (N = 1791)**	**Placebo (N = 1798)**
Any, n (%)	1289 (72.0)	1338 (74.4)	1527 (85.3)	1540 (85.7)
SABA[b]	1064 (59.4)	1110 (61.7)	927 (51.8)	938 (52.2)
LABA + ICS (fixed combination)	39 (2.2)	41 (2.3)	1002 (56.0)	1007 (56.0)
LAMA	288 (16.1)	329 (18.3)	3 (0.2)	2 (0.1)
Leukotriene inhibitor	4 (0.2)	4 (0.2)	151 (8.4)	128 (7.1)
SABA + SAMA	136 (7.6)	128 (7.1)	8 (0.5)	8 (0.4)
Oxygen	1 (0.1)	2 (0.1)	123 (6.9)	124 (6.9)
SAMA	80 (4.5)	82 (4.6)	9 (0.5)	7 (0.4)
Systemic corticosteroids	17 (1.0)	18 (1.0)	54 (3.0)	63 (3.5)
ICS	7 (0.4)	7 (0.4)	88 (4.9)	85 (4.7)
LABA + LAMA + ICS (free combination)	8 (0.5)	9 (0.5)	1 (0.1)	2 (0.1)
LABA + ICS free	0	1 (0.1)	54 (3.0)	64 (3.6)
LAMA + ICS free	11 (0.6)	8 (0.4)	0	1 (0.1)
LABA + LAMA (fixed combination)	30 (1.7)	29 (1.6)	0	1 (0.1)
Xanthines	1 (0.1)	1 (0.1)	28 (1.6)	29 (1.6)
LABA + LAMA (free combination)	8 (0.5)	5 (0.3)	0	0
LABA	3 (0.2)	0	50 (2.8)	57 (3.2)
PDE4 inhibitor	2 (0.1)	1 (0.1)	17 (1.0)	23 (1.3)
Vaccines	2 (0.1)	10 (0.6)	3 (0.2)	0
Cromones	0	0	1 (0.1)	1 (0.1)
LABA + ICS fixed and LABA + LAMA fixed, separately	0	1 (0.1)	0	1 (0.1)
Monoclonal antibody	0	0	1 (0.1)	0

Treatments were not mutually exclusive. Fixed combinations were defined as >1 drug in a single device; free combinations used multiple individual devices. Patients included in fixed or free combinations did not appear in the monotherapy categories. Upon discontinuation of a component of a free combination, each discontinued component was recorded individually and the patient continued on the remaining treatment(s).

[a]Includes treatments that were taken before randomization and continued beyond the first dose of treatment.

[b]Patients were required to switch from their previous SABA rescue medication to the SABA provided by the sponsor. This may have led to a discrepancy in the patients reported to have stopped SABA treatment prior to randomization. In addition, some sites considered SABA to be part of the study treatment and therefore may not have accurately recorded its use as being concomitant.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; PDE4, phosphodiesterase 4; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist.

eTable 4. Cardiovascular Risk Factors by Treatment Group

	Aclidinium (N = 1791)	Placebo (N = 1798)	Total (N = 3589)
≥1 prior cardiovascular event, n (%)	840 (46.9)	872 (48.5)	1712 (47.7)
Cerebrovascular or coronary artery disease, n (%)	741 (41.4)	763 (42.4)	1504 (41.9)
Cerebrovascular disease[a], n (%)	226 (12.6)	246 (13.7)	472 (13.2)
Coronary artery disease[b], n (%)	626 (35.0)	645 (35.9)	1271 (35.4)
Peripheral vascular disease or claudication, n (%)	249 (13.9)	243 (13.5)	492 (13.7)
≥2 atherothrombotic risk factors[c], n (%)	1722 (96.2)	1719 (95.6)	3441 (95.9)
Atherothrombotic risk factors[c] only, n (%)	942 (52.6)	923 (51.3)	1865 (52.0)
Atherothrombotic risk factors[c] + prior event, n (%)	780 (43.6)	796 (44.3)	1576 (43.9)
Atherothrombotic risk factors			
Male ≥65 years or female ≥70 years, n (%)	994 (55.5)	989 (55.0)	1983 (55.3)
Diabetes, n (%)	542 (30.3)	533 (29.6)	1075 (30.0)
Dyslipidemia, n (%)	1354 (75.6)	1386 (77.1)	2740 (76.3)
Hypertension, n (%)	1495 (83.5)	1511 (84.0)	3006 (83.8)
Waist circumference in males ≥40 inches or in females ≥38 inches, n (%)	1177 (65.7)	1134 (63.1)	2311 (64.4)
Evidence of renal dysfunction[d], n (%)	39 (2.2)	43 (2.4)	82 (2.3)

[a]Stroke or transient ischemic attack, carotid stenosis.
[b]Angina, myocardial infarction, angioplasty/stent/bypass.
[c]Patients who had ≥2 of the 6 atherothrombotic risk factors.
[d]Estimated glomerular filtration rate <60 mL/min and microalbuminuria (defined as ≥30–300 μg/mg creatinine on a spot urine test or ≥30 mg creatinine on a 24-hour urine test).

eTable 5. Major Adverse Cardiovascular Events and Other Serious Cardiovascular Events of Interest (On-Study)

	Aclidinium n (%)	Placebo n (%)	HR	1-sided 97.5% CI
MACE and other serious CV events of interest	168 (9.4)	160 (8.9)	1.03	0 to 1.28

Other serious CV events included events from cardiac tachyarrhythmias (narrow and broad SMQ) plus PTs tachycardia, heart rate increase, and palpitation; cardiac failure (narrow SMQ); bradycardia (narrow SMQ) and PTs sinus arrest and sinus bradycardia; conduction defects (narrow SMQ); conditions associated with central nervous system hemorrhages and cerebrovascular accidents (SMQ); and selected PTs included in the other ischemic heart disease (SMQ). Estimate of the HR and its 95% CI for comparing aclidinium 400 µg with placebo were derived using the Cox proportional hazard model with treatment group, baseline CV severity, and smoking status as factors. A HR <1 represents a favorable outcome for aclidinium. On-study analysis includes the events collected during the treatment period and during the follow-up period.

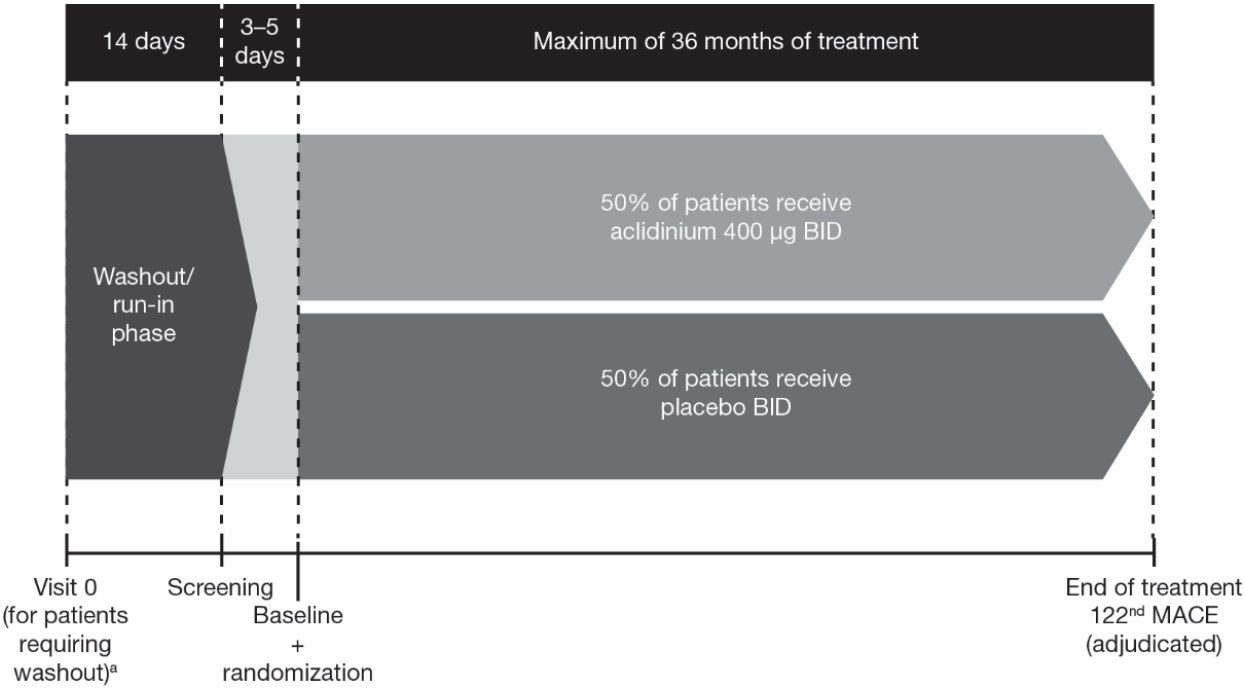
Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; PT, preferred term; SMQ, Standardized Medical Dictionary for Regulatory Activities Query.

eTable 6. Treatment-Emergent Adverse Events (Full Analysis Set)

Event	Aclidinium (N = 1791)	Placebo (N = 1798)
Any treatment-emergent AE, n (%)	1187 (66.3)	1133 (63.0)
Any treatment-emergent SAE, n (%)	409 (22.8)	356 (19.8)
Any treatment-emergent AE leading to discontinuation, n (%)	149 (8.3)	152 (8.5)
AEs occurring in ≥5% of patients in any treatment group, n (%)		
Pneumonia	109 (6.1)	105 (5.8)
Urinary tract infection	93 (5.2)	89 (5.0)
Upper respiratory tract infection	86 (4.8)	101 (5.6)
SAEs occurring in ≥1% of patients in any treatment group, n (%)		
Pneumonia	66 (3.7)	58 (3.2)
Atrial fibrillation	24 (1.3)	17 (1.0)
Cardiac failure congestive	21 (1.2)	18 (1.0)
Coronary artery disease	21 (1.2)	8 (0.4)

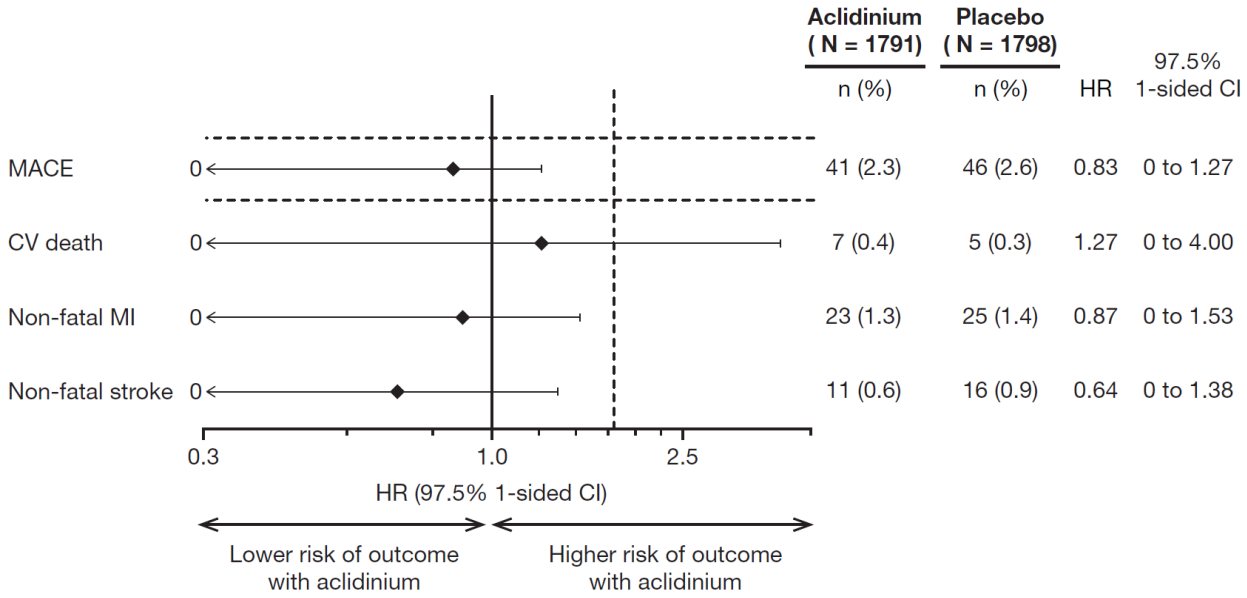
Includes AEs with an onset date on or after the date of first dose up to and including 15 days following the date of the last dose of treatment.
Abbreviations: AE, adverse event; SAE, serious adverse event.

eFigure 1. Study Design[2]



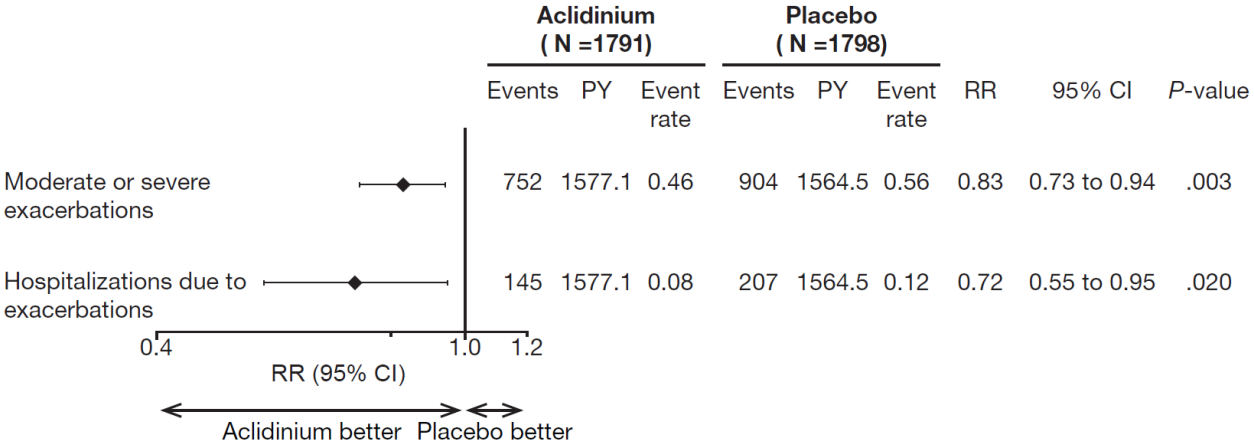
[a]Patients requiring LAMA washout were switched to an alternative therapy (eg, LABA with or without ICS).
Abbreviations: BID, twice daily; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MACE, major adverse cardiovascular event.
Reprinted with permission from *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation* (Wise RA, Chapman KR, Scirica BM, et al). Long-term evaluation of the effects of aclidinium bromide on major adverse cardiovascular events and COPD exacerbations in patients with moderate to very severe COPD: Rationale and design of the ascent COPD study. *Chronic Obstr Pulm Dis.* 2018;5(1):5-15. doi: http://doi.org/10.15326/jcopdf.5.1.2017.0149)

eFigure 2. Risk of Major Adverse Cardiovascular Events With Aclidinium Versus Placebo (On-Treatment)



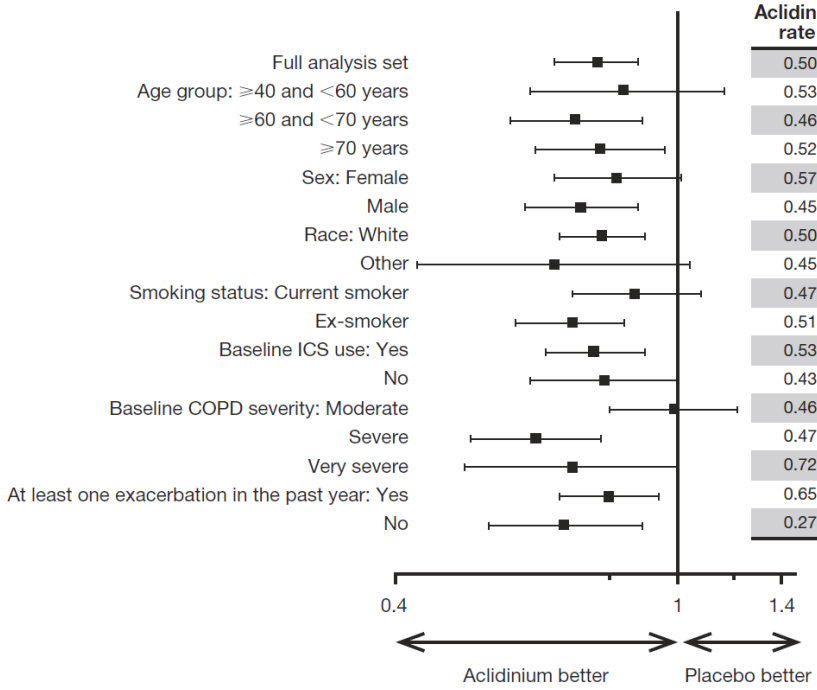
Estimate of HR and 1-sided 97.5% CI were derived using the Cox proportional hazard model with treatment group, baseline CV severity, and smoking status as factors. HR >1.0 indicates higher risk of MACE with aclidinium. HR <1.0 indicates lower risk of MACE with aclidinium. The dashed vertical line indicates the non-inferiority margin, 1.8.
Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction.

eFigure 3. Chronic Obstructive Pulmonary Disease Moderate/Severe Exacerbations and Hospitalizations Due to Exacerbations During the First Year of Treatment (On-Study)



Negative binomial analysis.
Abbreviations: CI, confidence interval; PY, patient-years; RR, rate ratio.

eFigure 4. Moderate/Severe Chronic Obstructive Pulmonary Disease Exacerbations During the First Year by Patient Subgroup (On-Treatment)

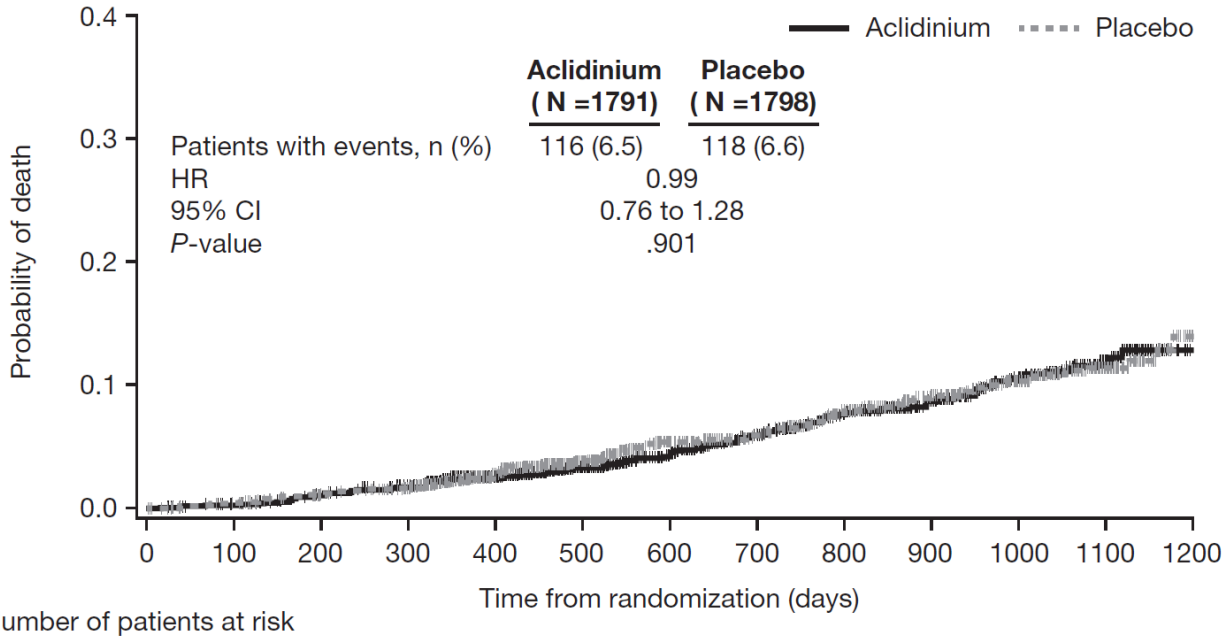


	Aclidinium rate	Placebo rate	RR	95% CI	Interaction *P*-value
Full analysis set	0.50	0.64	0.77	0.67 to 0.88	
Age group: ⩾40 and <60 years	0.53	0.63	0.84	0.62 to 1.16	.696
⩾60 and <70 years	0.46	0.63	0.72	0.58 to 0.89	
⩾70 years	0.52	0.67	0.78	0.63 to 0.96	
Sex: Female	0.57	0.70	0.82	0.67 to 1.01	.425
Male	0.45	0.61	0.73	0.61 to 0.88	
Race: White	0.50	0.64	0.78	0.68 to 0.90	.507
Other	0.45	0.68	0.67	0.43 to 1.04	
Smoking status: Current smoker	0.47	0.54	0.87	0.71 to 1.08	.129
Ex-smoker	0.51	0.72	0.71	0.59 to 0.84	
Baseline ICS use: Yes	0.53	0.70	0.76	0.65 to 0.90	.811
No	0.43	0.54	0.79	0.62 to 1.00	
Baseline COPD severity: Moderate	0.46	0.46	0.99	0.80 to 1.21	.011
Severe	0.47	0.75	0.63	0.51 to 0.78	
Very severe	0.72	1.02	0.71	0.50 to 1.00	
At least one exacerbation in the past year: Yes	0.65	0.82	0.80	0.68 to 0.94	.340
No	0.27	0.38	0.69	0.54 to 0.89	

The estimate of the rates, RR, and 95% CI were based on negative binomial regression. Baseline ICS use included ICS/LABA use. Baseline COPD severity was defined as follows: moderate, 50% ≤FEV_1 <80% predicted; severe, 30% ≤FEV_1 <50% predicted; very severe, FEV_1 <30% predicted.[3]

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; RR, rate ratio.

eFigure 5. All-Cause Mortality (Full Analysis Set)

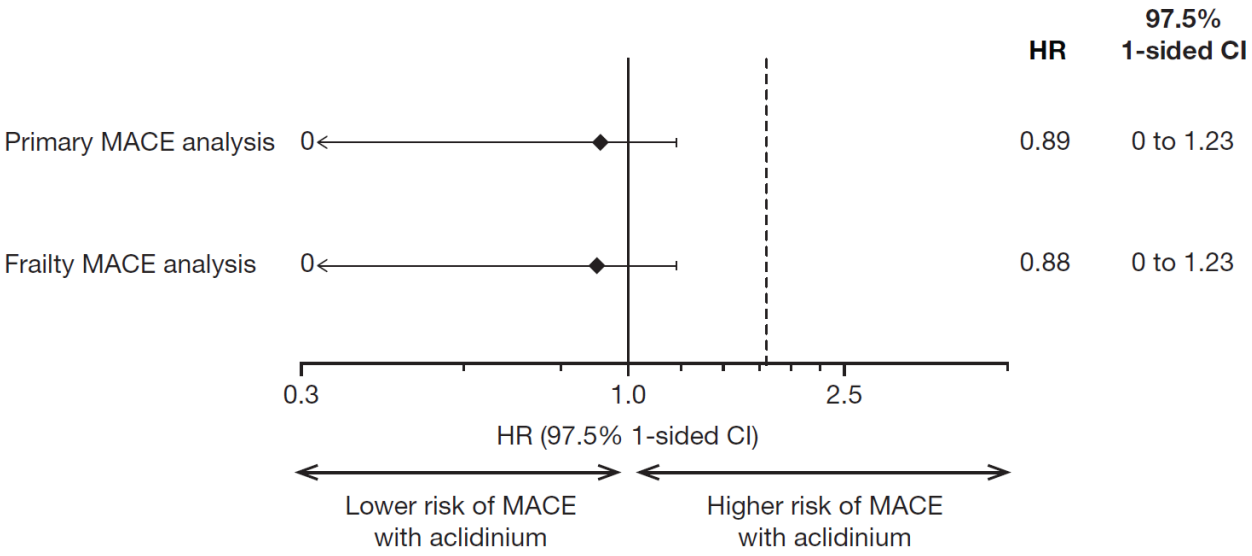


Number of patients at risk

Aclidinium	1791	1770	1735	1698	1333	1007	815	727	662	563	489	310	59
Placebo	1798	1773	1738	1701	1314	1001	791	729	657	575	479	292	62

Table includes 17 patients who prematurely discontinued from the study but were subsequently confirmed to be alive prior to database lock.
Censored observations; Cox regression analysis.
Abbreviations: CI, confidence interval; HR, hazard ratio.

eFigure 6. Frailty Analysis of Risk of Major Adverse Cardiovascular Events (On-Study)



Estimate of HR and 1-sided 97.5% CI were derived using the Cox proportional hazard model with treatment group, baseline CV severity, and smoking status as factors and site as a frailty term with a log-normal distribution. HR >1.0 indicates higher risk of MACE with aclidinium. HR <1.0 indicates lower risk of MACE with aclidinium. The dashed vertical line indicates the non-inferiority margin, 1.8.
Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event.

eReferences

1. Keene ON, Roger JH, Hartley BF, Kenward MG. Missing data sensitivity analysis for recurrent event data using controlled imputation. *Pharm Stat.* 2014;13(4):258-264.

2. Wise RA, Chapman KR, Scirica BM, et al. Long-term evaluation of the effects of aclidinium bromide on major adverse cardiovascular events and COPD exacerbations in patients with moderate to very severe COPD: rationale and design of the ASCENT COPD study. *Chronic Obstr Pulm Dis.* 2018;5(1):5-15.

3. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2019. Available from: https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf. Accessed February 7, 2019.