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Aclidinium bromide improves exercise endurance and lung hyperinflation in patients with moderate to severe COPD

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KEYWORDS
Aclidinium;
Chronic obstructive pulmonary disease;
Exercise endurance;
Lung hyperinflation

Summary
Background: Static and dynamic lung hyperinflation are associated with exercise impairment and poor outcomes in COPD patients. Aclidinium bromide is a novel, long-acting inhaled muscarinic antagonist currently in development for COPD treatment.
Methods: Patients with moderate to severe COPD ($N = 181$) were randomized to once-daily aclidinium 200 μg or placebo for 6 weeks. Constant work rate cycling exercises at 75% of peak work rate were performed at baseline, Day 1, Week 3, and Week 6. The primary efficacy measure was change in exercise endurance time (ET) from baseline to Week 6. Secondary outcomes included changes in trough forced expiratory volume in 1 s (FEV_1), inspiratory capacity (IC), IC/total lung capacity (TLC), and functional residual capacity (FRC) from baseline to Day 1, Week 3, and Week 6. Borg dyspnea scores during exercise, locus of symptom limitation, and safety measures were assessed.
Results: Aclidinium significantly improved ET on Day 1 ($P = 0.0002$), and improvements were sustained through Week 3 ($P = 0.0007$) and Week 6 ($P = 0.0042$) vs placebo. Compared with placebo, aclidinium improved trough FEV_1, IC, and IC/TLC at Weeks 3 and 6 ($P < 0.05$ for all). Exertional dyspnea scores at isotime were reduced on Day 1, Week 3, and Week 6 for aclidinium vs placebo ($P < 0.05$). Furthermore, the likelihood of stopping exercise due to breathing

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discomfort was lower in the aclidinium group at study end ($P = 0.0208$) compared with placebo. No differences in safety outcomes were reported between treatments.
Conclusions: Aclidinium significantly increased exercise tolerance, improved airflow obstruction and lung hyperinflation, and was safe and well tolerated.
Registration of Trial: This trial was registered with ClinicalTrials.gov (NCT00500318) under the name "A Study of Exercise Endurance and Lung Hyperinflation in Patients with Moderate to Severe COPD".

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality worldwide.[1–4] It is a preventable and treatable disease associated with progressive decreases in forced expiratory volume in 1 s (FEV_1) accompanied by lung hyperinflation and exertional dyspnea.[5]

Reduced expiratory airflow is the hallmark of COPD. Together with decreased lung elastic recoil, this leads to lung hyperinflation that is worsened by exacerbations and the progression of COPD.[6,7] Static hyperinflation is associated with increased mortality[8] while exercise-induced or dynamic hyperinflation significantly limits exercise capacity and is associated with breathlessness[9–11] and reduced ability to complete daily living activities.[6,12,13]

Improvements in exercise endurance, lung mechanics and alleviation of dyspnea are important therapeutic goals in COPD.[3] Short-acting[14] and long-acting bronchodilators[15,16] have been shown to improve lung function, minimize dynamic hyperinflation and correspondingly increase exercise endurance time (ET).[9,15] Tiotropium bromide is currently the only available long-acting anticholinergic for COPD.[17,18] As patient responses may vary, additional treatment options are warranted.

Aclidinium bromide is a novel, inhaled, long-acting muscarinic antagonist currently in Phase III development for COPD. Sustained 24-h bronchodilation and favorable tolerability have been demonstrated with aclidinium in COPD patients.[19,20] Aclidinium is rapidly hydrolyzed to two major inactive metabolites,[21–23] and its low circulating concentration following inhalation suggests a reduced potential for systemic side effects. We hypothesized that aclidinium would improve airflow limitation and decrease lung hyperinflation, thereby increasing exercise tolerance in COPD patients. The purpose of this study was to examine the effect of once-daily aclidinium 200 μg on exercise endurance and lung hyperinflation during cycle ergometry, and assess its safety and tolerability in moderate to severe COPD patients.

Methods

Study design

This 6-week, Phase III, randomized, double-blind, placebo-controlled study was conducted in 52 centers (42 US, 10 Canada) according to ICH Good Clinical Practice guidelines and the Declaration of Helsinki and approved by local ethics committees. Following a 2-week run-in, patients were randomized (1:1) to aclidinium 200 μg or placebo once-daily, administered via inhalation through a novel, multidose dry powder inhaler (Genuair®),[f] for 6 weeks. Pulmonary function tests and cycle ergometry performed at study visits (screening, run-in, randomization, Weeks 3 and 6) evaluated bronchodilation and exercise response. Patients gave written informed consent prior to any study procedure.

Study subjects

Participants included males and females ≥40 years, current and ex-smokers with a smoking history ≥10 pack-years, clinical diagnosis of moderate to severe stable COPD (post-bronchodilator FEV_1/forced vital capacity [FVC] < 70% and $FEV_1 \geq$ 30% and <80% predicted), functional residual capacity (FRC) ≥ 120% predicted at screening, and baseline dyspnea index (BDI) focal score ≤7. Subjects were excluded if previously hospitalized for an acute COPD exacerbation ≤3 months pre-screening, or had a respiratory tract infection or COPD exacerbation 6 weeks pre-screening. Patients with a history of asthma, allergic rhinitis or atopy; contraindications to clinical exercise testing according to the American Thoracic Society (2003); cycled ≥20 min during constant work-rate exercise tests during run-in; or participated in current or previous COPD rehabilitation programs ≤6 weeks pre-randomization were also excluded. Levalbuterol (US) or salbutamol (Canada) was allowed as needed, ≥6 h before each visit. Inhaled, oral or parenteral corticosteroids at doses ≤10 mg/day or 20 mg every other day were allowed if use was stable ≥4 weeks before screening. No other COPD medications were allowed throughout the trial. Oxygen therapy was allowed as needed ≤15 h/day but not within 2 h of study visits.

Assessments

Spirometry (FEV_1, FVC, inspiratory capacity [IC], and vital capacity [VC]) and body plethysmography (FRC, total lung capacity [TLC] and residual volume [RV]) were performed pre-dose (trough) and 2 h post-administration of study medication during study visits. Breathlessness at rest was measured at baseline by the Baseline Dyspnea Index (BDI), and at Weeks 3 and 6 by the transitional dypsnea index (TDI).[24] Symptom-limited cycle ergometry during screening determined peak work rate (W_{max}), the highest work rate maintained for 30 s. After 3 min of unloaded pedaling, the work rate was increased in a stepwise manner in

[f] GENUAIR® is a registered trademark of Almirall, S.A.

increments of 10 watts/min, starting at 10 W, until tolerance limit. Constant work rate cycle ergometry at 75% W_{max} was performed 2 times during run-in to familiarize subjects with study procedures, and at 3 h post-administration of the study medication at randomization and Weeks 3 and 6. After 1 min of unloaded pedaling, the work rate was increased to 75% W_{max} and subjects were encouraged to cycle to the point of symptom limitation. ET was defined as time from increase in work rate to 75% W_{max} to point of symptom limitation. Subjects rated intensity of dyspnea and leg discomfort using the modified Borg scale, and the locus of symptom limitation (dyspnea, leg fatigue, or their combination) was evaluated. Ventilatory responses to exercise and dynamic hyperinflation were evaluated at rest, isotime (defined for each subject as the minimum ET among the constant work rate tests at 75% W_{max} at each study visit), and end of exercise using a commercially available exercise circuit system, in addition to blood pressure and electrocardiograms (ECGs). Baseline values were obtained during the second constant work rate cycle ergometry performed during run-in.

Endpoints

The primary efficacy endpoint was change in ET from baseline to Week 6. Secondary efficacy endpoints included changes in ET from baseline to Day 1 (randomization) and Week 3, and changes in trough FEV_1, IC, FRC, IC/TLC from baseline to Day 1, Week 3 and Week 6. Additional efficacy endpoints were assessed throughout the study, including changes from baseline in exercise measures of IC and breathing pattern, dyspnea and leg discomfort.

Safety and tolerability were assessed by monitoring adverse events (AEs), exacerbations, vital signs, physical examinations, laboratory tests (hematology, chemistry, urinalysis), and ECGs.

Statistical analysis

Analyses of efficacy endpoints were performed on the intent-to-treat (ITT) population, defined as patients in the safety population with a baseline value and $\geq$1 post-baseline assessment of ET. Efficacy endpoints were analyzed using analysis of covariance (ANCOVA), with treatment and center as factors, and baseline values as covariate. Treatment effects are presented as least-square (LS) means and standard errors (SE), adjusted for center and baseline. Analyses of safety outcomes were performed on the safety population, which consisted of patients who received $\geq$1 dose of study drug. A total sample size of 266 patients was planned to provide at least 80% power to detect a statistically significant difference of 100 s between aclidinium and placebo in the primary endpoint, assuming a 0.05 two-sided Type I error and a common SD of 290 s.

Results

Patient demographics and baseline characteristics

A total of 587 moderate-to-severe COPD patients were screened and 181 patients were randomized to aclidinium ($n = 86$) or placebo ($n = 95$; Fig. 1). Most of the screening failures were due to patient's personal request (46/406) or non-fulfillment of inclusion or exclusion criteria (309/406), of which the most frequent were FRC not $\geq$120% ($n = 115$) and post-bronchodilator FEV_1 not $\geq$30% and <80% of predicted ($n = 47$; Fig. 1). Baseline demographic characteristics were similar across groups (Table 1). A total of 159 patients completed the study. More patients with placebo discontinued the study vs aclidinium (17.9% vs 5.8%, respectively). The most common reason for discontinuation was AEs ($n = 8$ and $n = 3$ for placebo and aclidinium, respectively). The safety population comprised all 181 randomized patients. One patient randomized to placebo did not have baseline and post-baseline ET, and was not included in the ITT population.

Exercise endurance

The adjusted mean (SE) change in ET from baseline to Week 6 was significantly greater for aclidinium than placebo (129 [31] s vs 13 [31] s, respectively), with a difference between treatment groups of 116 (40) s ($P = 0.0042$; Fig. 2). This effect was observed across time with adjusted mean treatment differences (SE) in ET between aclidinium and placebo on Day 1 and Week 3 equal to 143 (37) s and 126 (36) s, respectively ($P = 0.0001$ for both).

Resting lung function, hyperinflation and dyspnea

Aclidinium increased adjusted mean trough FEV_1 from baseline to Weeks 3 and 6, while slight decreases were observed with placebo (Fig. 3). These changes from baseline were significantly higher for aclidinium over placebo at Weeks 3 and 6 ($P < 0.0001$ for both). Treatment differences in changes from baseline in trough IC were significantly in favor of aclidinium at Week 3 ($P < 0.01$) and Week 6 ($P < 0.05$; Fig. 3). Significant treatment differences in favor of aclidinium were similarly observed for IC/TLC ($P < 0.01$ and $P < 0.05$ for Weeks 3 and 6, respectively). The adjusted mean trough FRC decreased from baseline at Weeks 3 and 6 with both treatments, with no significant difference between groups (Fig. 3). Improvements in resting lung function parameters at 2 h after administration of study medication were significantly greater with aclidinium vs placebo throughout the study (Fig. 3). Significant improvements in dyspnea were observed with aclidinium vs placebo at Weeks 3 and 6, with improvements in adjusted mean TDI scores of 1.19 ($P = 0.005$) and 1.71 ($P = 0.0004$) units, respectively.

Operating lung volumes and ventilatory responses to exercise

Adjusted mean changes from baseline in IC at rest, isotime and peak were numerically higher for aclidinium than placebo on Week 6, with significant treatment differences in favor of aclidinium at Day 1 and Week 3 ($P < 0.05$ for all; Table 2). Aclidinium significantly increased inspiratory reserve volume (IRV) from baseline at rest, isotime and peak vs placebo on Day 1 ($P < 0.01$ for all). Improvements in IRV were also observed with aclidinium at Weeks 3 and 6, but these were generally not statistically significant vs placebo. Aclidinium was also associated with a significant increase from baseline in V_T at both isotime and peak vs

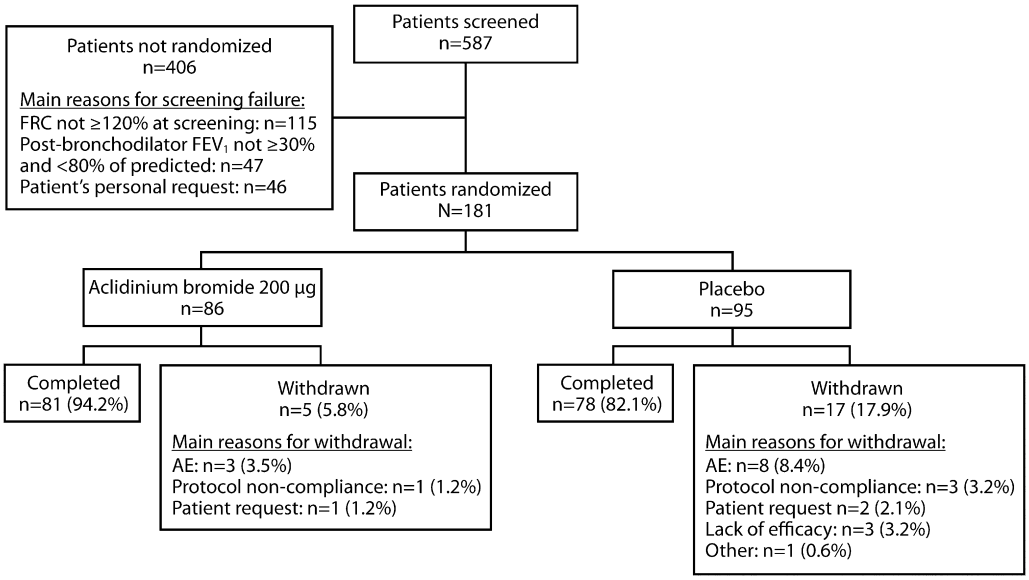

Figure 1 Study flow chart.

placebo at all visits. On other outcomes (RR, V'_E), there was a general trend towards improvement with aclidinium, although differences did not reach statistical significance at most time points.

Exertional dypsnea and leg discomfort

Aclidinium significantly improved exertional dypsnea at iso-time, with a decrease over placebo >1 Borg unit on Day 1 and

Table 1 Baseline demographics and clinical characteristics at screening (safety population).[a]

Variables	Aclidinium 200 µg (n = 86)	Placebo (n = 95)
Age, years	64.0 (9.5)	65.6 (7.8)
Male, *n* (%)	52 (60.5)	53 (55.8)
Caucasian, *n* (%)	83 (96.5)	92 (96.8)
BMI, kg/m^2	26.2 (4.6)	26.6 (4.7)
Current smoker, *n* (%)	38 (44.2)	31 (32.6)
Smoking history, pack-years	56.5 (25.0)	54.4 (21.1)
Pulmonary function (spirometry and body plethysmography)		
Pre-bronchodilator FEV_1, L	1.18 (0.44)	1.29 (0.43)
Post-bronchodilator FEV_1, L	1.43 (0.50)	1.48 (0.48)
Post-bronchodilator FEV_1, % predicted	49.0 (10.6)	52.3 (13.5)
Post-bronchodilator FVC, L	3.28 (1.03)	3.14 (0.85)
Post-bronchodilator FEV_1/FVC ratio, %	44.7 (9.8)	47.4 (9.9)
FRC, L	5.12 (1.23)	4.85 (1.24)
FRC, % predicted	158.6 (29.6)	151.9 (32.5)
TLC, L	6.85 (1.56)	6.68 (1.47)
IC,[b] L	1.96 (0.67)	1.97 (0.54)
RV, L	4.27 (1.25)	4.10 (1.27)
Peak values during incremental exercise		
W_{max}, Watts	65 (25)	66 (24)
RR, breaths/min	32.5 (6.6)	33.5 (8.5)
V'_{O2}, L/min	1.20 (0.88)	1.10 (0.37)
V'_{CO2}, L/min	1.22 (0.84)	1.21 (0.98)
V'_E, L/min	40.2 (13.1)	39.7 (12.8)
V_T, L	1.32 (0.52)	1.28 (0.46)

BMI, body-mass index, FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; FRC, functional residual capacity; TLC, total lung capacity; IC, inspiratory capacity; RV, residual volume; W_{max}, peak work rate; RR, respiratory rate; V'_{O2}, oxygen consumption; V'_{CO2}, carbon dioxide output; V'_E, minute ventilation; V_T, tidal volume.

[a] Data are in adjusted mean (SD), unless otherwise indicated.

[b] Measured during the run-in period (Day −10).

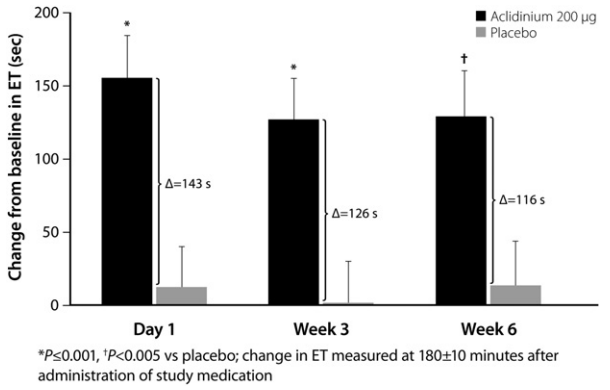

Figure 2 Adjusted mean (SE) change from baseline in endurance time (ET) throughout the study.

Week 3 ($P < 0.0001$ for both), and −0.70 Borg unit at Week 6 ($P < 0.05$; Table 2). Improvement in ET correlated with the reduction in Borg dypsnea scores at isotime ($r = -0.342$, $P = 0.0022$) and an increased IC at isotime ($r = 0.218$, $P = 0.06$) following aclidinium treatment. Leg discomfort was diminished at isotime at Day 1 ($P < 0.01$) and Week 3 ($P < 0.05$), and at peak at Week 6 ($P < 0.05$; Table 2). The probability of stopping exercise because of breathing discomfort was significantly lower with aclidinium vs placebo at Week 6 (odds ratio = 0.45, $P = 0.02$).

Safety

Aclidinium 200 µg was well tolerated, with a safety profile similar to placebo after 6 weeks of treatment. Treatment-emergent AEs (TEAEs) were reported in 57.0% and 46.3% of aclidinium- and placebo-treated patients, respectively. TEAEs reported by >3.0% of patients in either treatment group are shown in Table 3. The majority of TEAEs were mild or moderate in both groups. The only report of dry mouth was in the placebo group ($n = 1$). Five patients experienced serious adverse events (SAEs); none were fatal or deemed to be study drug-related. SAEs were reported by 2/86 (2.3%) patients in the aclidinium group compared with 3/95 (3.2%) placebo-treated patients. No cardiac or cerebrovascular AEs were reported. Laboratory tests, vital signs and ECG findings were similar between treatment groups.

Discussion

This study demonstrates that treatment of moderate-to-severe COPD patients with aclidinium bromide 200 µg once-daily for 6 weeks improved exercise ET and reduced lung hyperinflation and dyspnea. Improving exercise tolerance and alleviating lung hyperinflation and dyspnea are important goals in the therapeutic management of COPD and can help improve quality of life.[9,15] Although the current proposal for what is the minimum clinically important

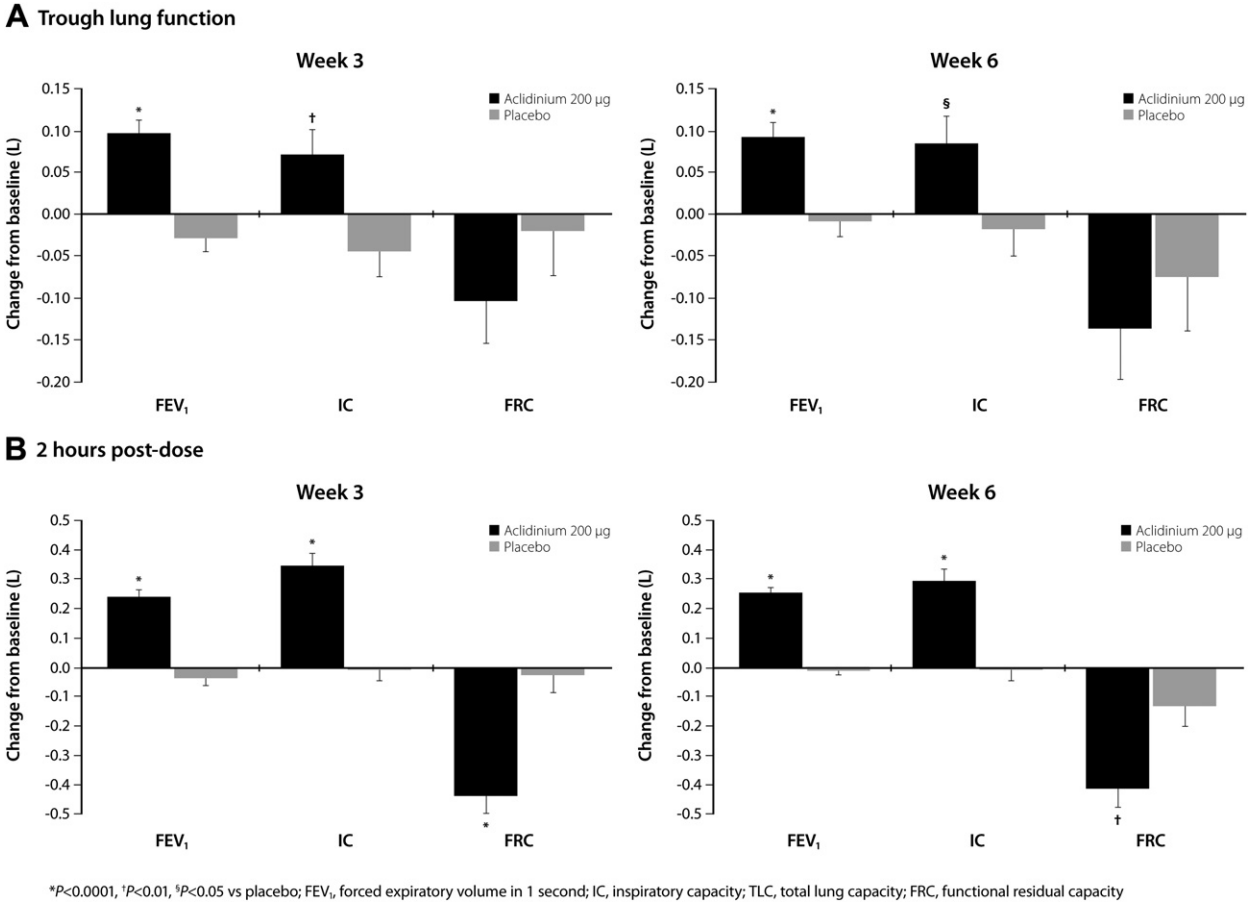

Figure 3 Mean (SE) change from baseline in resting lung flow rates and volumes at trough (A) and 2 h post-dose (B) at Weeks 3 and 6 (left and right panels, respectively).

Table 2 LS mean (95% confidence interval) treatment differences (aclidinium − placebo) in change from baseline[a] in exercise measures throughout the study (ITT population).[a]

	Day 1	Week 3	Week 6
IC, L			
Rest	0.272 (0.162, 0.383)[b]	0.227 (0.114, 0.340)[b]	0.037 (−0.103, 0.177)
Isotime	0.242 (0.136, 0.349)[b]	0.167 (0.056, 0.279)[c]	0.0427 (−0.092, 0.177)
Peak	0.259 (0.156, 0.362)[b]	0.110 (0.002, 0.217)[d]	0.015 (−0.115, 0.145)
IRV, L			
Rest	0.241 (0.105, 0.377)[b]	0.232 (0.105, 0.359)[b]	0.124 (−0.030. 0.278)
Isotime	0.147 (0.038, 0.257)[c]	0.018 (−0.087, 0.123)	−0.053 (−0.180, 0.074)
Peak	0.162 (0.057, 0.266)[c]	−0.018 (−0.120, 0.085)	−0.064 (−0.188, 0.059)
V_T, L			
Rest	0.052 (−0.053, 0.157)	−0.016 (−0.089, 0.056)	−0.077 (−0.147, −0.008)[d]
Isotime	0.143 (0.091, 0.195)[b]	0.126 (0.078, 0.174)[b]	0.111 (0.056, 0.167)[b]
Peak	0.124 (0.074, 0.173)[b]	0.106 (0.053, 0.159)[b]	0.098 (0.042, 0.154)[b]
V'_E, L/min			
Rest	1.454 (0.159, 2.750)[d]	0.106 (−0.986, 1.198)	1.518 (−1.135, 4.172)
Isotime	0.692 (−0.717, 2.101)	1.098 (−0.797, 2.992)	1.019 (−0.601, 2.639)
Peak	1.158 (−0.507, 2.823)	−7.171 (−23.771, 9.428)	1.888 (0.100, 3.676)[d]
RR, breaths/min			
Rest	0.364 (−0.969, 1.697)	0.734 (−0.563, 2.031)	0.918 (−0.262, 2.097)
Isotime	−2.602 (−3.898, −1.307)[b]	−1.235 (−2.648, 0.177)	−0.989 (−2.333, 0.355)
Peak	−0.840 (−2.104, 0.425)	0.181 (−1.358, 1.721)	−0.291 (−1.723, 1.141)
Dyspnea, Borg			
Rest	−0.149 (−0.365, 0.068)	−0.124 (−0.359, 0.111)	0.014 (−0.166, 0.194)
Isotime	−1.142 (−1.688, −0.596)[b]	−1.197 (−1.730, −0.664)[b]	−0.704 (−1.258, −0.151)[d]
Peak	−0.159 (−0.651, 0.332)	−0.655 (−1.228, −0.082)[d]	−0.034 (−0.564, 0.497)
Leg discomfort, Borg			
Rest	−0.146 (−0.425, 0.133)	−0.084 (−0.337, 0.169)	0.050 (−0.138, 0.239)
Isotime	−0.853 (−1.374, −0.333)[c]	−0.603 (−1.12, −0.090)[d]	−0.466 (−1.042, 0.111)
Peak	0.214 (−0.331, 0.760)	0.392 (−0.225, 1.009)	0.636 (0.122, 1.151)[d]

ITT, intent-to-treat population; IC, inspiratory capacity; IRV, inspiratory residual volume; V_T, tidal volume; V'_E, minute ventilation; RR, respiratory rate.

[a] Day −10 data were used for baseline values if Day −5 data were not available.

[b] $P < 0.001$ vs placebo.

[c] $P < 0.01$ vs placebo.

[d] $P < 0.05$ vs placebo.

difference (MCID) for the constant work rate cycle exercise test should not be viewed as definitive, the improvement in ET throughout 6 weeks of aclidinium treatment (116–143 s) reported here is above the suggested value of 105 s.[25] A change of 100–200 s in ET has also been associated with clinically significant improvements in health status.[26]

The treatment effect in ET after 6 weeks of aclidinium treatment is comparable to that observed in two 6-week

Table 3 Adverse events reported by >3% of subjects in either treatment group.

Adverse event	Aclidinium 200 μg (n = 86) n (%)	Placebo (n = 95) n (%)
Headache	5 (5.8)	7 (7.4)
COPD exacerbation	2 (2.3)	7 (7.4)
Cough	5 (5.8)	3 (3.2)
Upper respiratory tract infection	5 (5.8)	2 (2.1)
Nasopharyngitis	4 (4.7)	2 (2.1)
Back pain	3 (3.5)	3 (3.2)
Urinary tract infection	2 (2.3)	4 (4.2)
Pharyngolaryngeal pain	3 (3.5)	1 (1.1)
Dyspepsia	3 (3.5)	1 (1.1)
Dyspnea	1 (1.2)	3 (3.2)
Sinus congestion	0	4 (4.2)

studies with tiotropium (100—105 s, when the median increase in ET is used in one of the studies[16] due to outliers with ET>3000 s)[15,16] and an 8-week study with salmeterol/fluticasone (132 s).[27] However, the increase in ET with tiotropium was observed over time, with the maximal effect at the end of the study. In contrast, the maximal effect on ET in the current aclidinium study was observed after the first day of treatment. A slight decrease in effect was observed between Day 1 and Week 3, but overall, the improvement in ET with aclidinium was maintained throughout the 6-week study.

A clinically significant improvement vs placebo in trough FEV_1 (101 mL) was observed after 6 weeks with aclidinium, which is greater than that observed in earlier aclidinium Phase III studies (60—70 mL).[19,20] This may have been due to differences between study populations since inclusion criteria in the current study had additional requirements regarding lung hyperinflation and the minimum baseline dyspnea level. Statistically significant and clinically relevant improvements in various lung function parameters observed on Day 1 until Week 6 indicate that aclidinium efficacy occurred on the first day of administration and was sustained until the end of the study.

Dynamic hyperinflation is a critical factor in the worsening of exertional dyspnea and reduced exercise capacity in COPD.[10] Aclidinium significantly improved IC measured at isotime (>200 mL) at Day 1 and Week 3, suggesting a beneficial effect on dynamic hyperinflation. It is unclear why changes in dynamic hyperinflation were no longer statistically significant at Week 6, since the beneficial effects of the medication on resting lung function and breathing pattern during exercise were maintained through Week 6. However, technical issues should not be ruled out, as repeated measurements of IC may be challenging to perform consistently in a large multicenter trial. Resting lung hyperinflation is associated with higher mortality[8] and reduced exercise capacity.[28] In this study, aclidinium improved resting lung hyperinflation, demonstrated by the significant improvements in trough IC and trough IC/TLC and a positive trend for FRC at study end. The magnitude of improvements in resting IC reported here is similar to those reported for aclidinium Phase III studies[19,20] and a 6-week tiotropium study.[15]

Aclidinium provided clinically relevant reductions in dyspnea[29] at the end of the study, demonstrated by significant improvements in functional dyspnea (difference in TDI focal scores of 1.71 units over placebo) and exercise-related dyspnea (−0.7 Borg units at isotime over placebo).

The tolerability and favorable safety profile of aclidinium was supported by the low incidence of anticholinergic AEs in this study such as dry mouth, and similar rates of TEAEs and SAEs between groups. There was also no evidence for increased cardiovascular TEAEs. This may be due to rapid plasma hydrolysis of aclidinium and its low systemic bioavailability demonstrated in earlier studies.[21—23]

One potential limitation of this trial is that we could not reach the target sample size. Although it was initially planned to enroll 266 patients, the study was stopped early due to difficulty recruiting patients. However, the final observed difference in ET of 116 s was larger than the target difference of 100 s, clearly confirming that the study was positive. In addition, although the relatively short treatment time prevented observations of effect duration, there was little change between Weeks 3 and 6 of this study.

Overall, aclidinium bromide 200 μg once-daily significantly improved exercise tolerance and dyspnea both at rest and during exercise, and was safe and well tolerated. The maximum treatment effect was seen after only one dose, and the statistically significant effect was maintained for 6 weeks. Aclidinium also provided clinically significant bronchodilation and reduced lung hyperinflation and therefore may be a valuable new option for the treatment of COPD.

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Conflict of interest

This work was funded by Forest Laboratories, Inc. and Almirall, SA. The authors alone had full control over the content and submission of the manuscript. François Maltais received fees for speaking at conferences sponsored by Boehringer Ingelheim, Pfizer and GlaxoSmithKline and served on an advisory board for GlaxoSmithKline and Boehringer Ingelheim. He also received research grants for participating in multicenter trials sponsored by GlaxoSmithKline, Boehringer Ingelheim, ALTANA Pharma, Merck, AstraZeneca, Nycomed and Novartis and received unrestricted research grants from Boehringer Ingelheim and GlaxoSmithKline. He holds a CIHR/GSK research chair on COPD at Université Laval. Bartolome Celli has served on advisory boards for Boehringer Ingelheim, AstraZeneca, Almirall, SA, and GlaxoSmithKline and has received speaking fees from Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline and Almirall, SA. Richard Casaburi has served as an advisory board member for Forest Laboratories, Inc. Janos Porszasz declares that no conflict of interest exists. Diana Jarreta and Beatriz Seoane are employees of Almirall, SA. Cynthia Caracta is an employee of Forest Research Institute.

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