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ORIGINAL RESEARCH

Efficacy and Safety of a 12-week Treatment with Twice-daily Aclidinium Bromide in COPD Patients (ACCORD COPD I)

Edward M. Kerwin[1], Anthony D. D'Urzo[2], Arthur F. Gelb[3], Hassan Lakkis[4], Esther Garcia Gil[5], and Cynthia F. Caracta[4], on behalf of the ACCORD I study investigators

1 Clinical Research Institute, Medford, OR, USA

2 Department of Family and Community Medicine (DFCM), University of Toronto, Toronto, Ontario, Canada

3 Southern California Clinical Trials, Lakewood, California, USA

4 Forest Research Institute, Inc. Jersey City, NJ, USA

5 Almirall, S.A., Barcelona, Spain

Abstract

Background: **This Phase III study evaluated the efficacy and safety of twice-daily aclidinium 200 µg and 400 µg versus placebo in the treatment of moderate-to-severe COPD.** ***Methods:*** **In this 12-week, double-blind, multicenter trial, patients were randomized (1:1:1) to inhaled twice-daily aclidinium 200 µg, aclidinium 400 µg, or placebo. Primary and secondary endpoints were changes from baseline in trough FEV_1 and peak FEV_1 at Week 12, respectively. Health status (St. George's Respiratory Questionnaire [SGRQ]), COPD symptoms (Transitional Dyspnea Index [TDI], night and early morning symptoms), and safety were also assessed.** ***Results:*** **A total of 561 patients (mean age, 64 ± 9 years) with a mean baseline FEV_1 of 1.36 ± 0.54 L (47.2% of predicted value) were randomized. At Week 12, aclidinium 200 µg and 400 µg showed significant improvements from baseline in mean (95% CI) trough FEV_1 compared with placebo by 86 (45, 127) mL and 124 (83,164) mL, respectively, and in peak FEV_1 by 146 (101, 190) mL and 192 (148, 236) mL, respectively ($p \leq 0.0001$ for all). Both aclidinium doses also provided significant improvements in SGRQ, TDI and almost all COPD symptom scores compared with placebo ($p < 0.05$ for all). Incidences of adverse events (AEs) were similar across treatment groups. The incidence of anticholinergic AEs was low and similar across groups (dry mouth: 0.5%–1.6%; constipation: 0%-1.1%).** ***Conclusions:*** **Treatment of moderate-to-severe COPD patients with twice-daily aclidinium 200 µg and 400 µg was associated with significant improvements in bronchodilation, health status, and COPD symptoms. Both doses were well tolerated and had safety profiles similar to placebo.**

Trial Registration: **This ACCORD I study (AClidinium in Chronic Obstructive Respiratory Disease I) was registered on clinicaltrials.gov (NCT00891462) as "Efficacy and Safety of Aclidinium Bromide for Treatment of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)".**

Keywords: Aclidinium, COPD, lung function

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Correspondence to: Edward M. Kerwin, MD, Clinical Research Institute, 3860 Crater Lake Avenue #B, Medford, OR 97504, phone: (541) 773-7881, fax: (541) 734-3596, email: ekerwin@criresearch.com

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterized by airway obstruction that is not fully reversible (1). COPD is a leading cause of morbidity and mortality with significant contributions to healthcare costs (2–4). Bronchodilators are central to symptomatic COPD management, with long-acting agents such as muscarinic antagonists and β-agonists (LAMAs and LABAs, respectively) considered more effective than short-acting alternatives (1). Global Initiative for

Chronic Obstructive Lung Disease (GOLD) guidelines recommend that effective COPD treatment should be achieved with minimal side effects (1).

Aclidinium bromide is a novel, inhaled LAMA with low systemic activity, developed for maintenance treatment of COPD. It is rapidly hydrolyzed into inactive metabolites (5), resulting in low circulating concentration following inhalation (6, 7) suggesting a reduced potential for systemic side effects.

Although previous Phase III studies with once-daily aclidinium 200 µg demonstrated significant trough FEV_1 improvements in COPD patients (8), these increases were below the suggested minimal clinically important difference (MCID) of 100 mL (9), indicating that a higher total daily dose may be more effective. Safety of a higher total daily dose and more frequent aclidinium dosing regimen is supported by data which demonstrate that single aclidinium doses up to 6000 µg and twice-daily aclidinium up to 800 µg were well tolerated in healthy subjects (7, 10).

In a 2-week crossover study in COPD patients, bronchodilation over a 24-hour period with twice-daily aclidinium 400 µg was comparable to that of once-daily tiotropium, the only LAMA currently available (11). Aclidinium also significantly improved the average bronchodilation at night versus tiotropium, suggesting added benefits during the second half of day (11).

Additionally, a dose-finding aclidinium study demonstrated dose-dependent bronchodilation; twice-daily aclidinium 400 µg provided statistically significant bronchodilation when compared to the lowest aclidinium dose tested (100 µg) (12). Therefore, aclidinium 200 ug and 400 ug doses were considered appropriate to be further assessed in Phase III studies. The objective of this Phase III study was to evaluate the efficacy and safety of 12-week twice-daily aclidinium 200 µg and 400 µg in COPD patients.

Methods

Study design

This randomized, double-blind, placebo-controlled, parallel-group study in moderate-to-severe COPD patients consisted of a 2-week run-in, a 12-week treatment period, and a 2-week follow-up phone contact/study visit (NCT00891462). Patients were evaluated for eligibility at screening and at baseline before being randomized (1:1:1) to twice-daily aclidinium 200 µg, aclidinium 400 µg, or placebo. Patients were instructed to administer study treatments at the same time in the morning (between 8:00 and 10:00 AM) and in the evening (between 8:00 and 10:00 PM) via a multiple-dose dry powder inhaler (Genuair®)*. Efficacy and safety of the patients were evaluated during study visits at Week 1, 4, 8 and 12. This study was conducted according to ICH/GCP guidelines and the Declaration of Helsinki in centers in United States and Canada and approved by the Western Institutional Review Board and Biomedical Research Alliance of New York. All patients gave written informed consent before any study procedure.

Study population

Male and female patients ≥40 years of age who were current or former cigarette smokers with a smoking history ≥10 pack-years and diagnosed with moderate-to-severe COPD (postbronchodilator FEV_1/FVC <70% and FEV_1 ≥30% but <80% of predicted) (1) were eligible for study participation. Exclusion criteria included other significant respiratory conditions (including asthma), respiratory infection or COPD exacerbation ≤6 weeks prescreening (≤3 months if it resulted in hospitalization), clinically significant cardiovascular conditions including myocardial infarction during the previous 6 months, unstable arrhythmia, Bazett-corrected QTc >470 msec, and medical conditions wherein anticholinergic drugs are contraindicated.

Permitted concomitant medications included albuterol (rescue medication), inhaled corticosteroids (ICS), systemic corticosteroids equivalent to ≤10 mg/day of prednisone or 20 mg every other day, and theophylline if treatment was stable for ≥4 weeks prior to screening. Inhaled anticholinergics and LABAs were prohibited during the study. Rescue medication was discontinued ≥6 hours before each study visit, while theophylline and ICS were discontinued the morning before each study visit.

Assessments

Standardized spirometry (13) was performed predose (-1 hour and at -10 minutes) at each visit and at 0.5, 1, 2, and 3 hours following the morning dose at each visit after randomization. St. George's Respiratory Questionnaire (SGRQ) and Baseline Dyspnea Index (BDI)/Transition Dypsnea Index (TDI) were completed at baseline and at every month.

COPD symptoms (early morning and at night) and rescue medication use were assessed using a Nighttime Symptoms Questionnaire; sleep quality was assessed using a non-disease-specific Daily Sleep Diary (14). These questionnaires developed by the sponsor were self-administered by the patient each morning using an electronic diary (eDiary), beginning at screening through Week 12 of treatment. The COPD nighttime symptoms questionnaire, designed with a ≤24-hour recall period, assessed the frequency of COPD symptoms during the previous night, the severity and impact of nighttime symptoms (on activity and on sleep) and of early morning symptoms, sputum production, and rescue medication use.

The Sleep Diary questionnaire (14) assessed the time the patient first went to sleep the previous night, the frequency of waking up and having difficulty falling back to sleep, the total number of hours slept, the overall sleep quality the previous night, how rested the patient felt that morning, and how the patient's sleep the prior night compared to their normal sleep.

COPD exacerbations (an increase in COPD symptoms ≥2 consecutive days resulting in medical intervention) were evaluated at each visit and categorized as mild (increased use of rescue medication), moderate (treatment with antibiotics and/or systemic corticosteroids), or severe (hospitalization). Safety was assessed using adverse events (AEs), laboratory tests, vital signs, and ECGs.

Endpoints

The primary efficacy endpoint was change from baseline to Week 12 in morning predose (trough) FEV_1, the average of 2 predose FEV_1 values. The secondary efficacy endpoint was change from baseline to Week 12 in peak FEV_1, the highest value observed within 3 hours postmorning dose. Additional pulmonary function endpoints included changes from baseline on Day 1 (peak FEV_1 only), Weeks 1, 4, and 8 (trough and peak FEV_1) and Week 12 ($AUC_{0\text{-}3/3h}$ FEV_1, trough, peak, and $AUC_{0\text{-}3/3h}$ FVC, and trough IC).

Additional efficacy endpoints were changes from baseline at Weeks 4, 8 and 12 in SGRQ and TDI (including percentage of subjects with a clinically meaningful improvement [decrease of ≥4 points for SGRQ (15) or increase of ≥1 unit for TDI (16)]), changes from baseline at Week 12 in COPD Nighttime Symptoms Questionnaire and Daily Sleep Diary scores, rescue medication use over 12 weeks, and COPD exacerbation rate.

Statistical analysis

Demographic, baseline, and safety data were summarized by treatment group for the safety population, defined as subjects who took ≥1 dose of study treatment.

All efficacy analyses were based on the intent-to-treat (ITT) population, defined as subjects in the safety population who had baseline and at least 1 postbaseline FEV_1 assessment. Efficacy outcomes were analyzed using ANCOVA with treatment group and gender as factors and baseline value and age as covariates. Results are presented as estimated adjusted treatment effects (least square means [LSM] and LSM differences) with 95% confidence intervals (CIs) and two-sided p-values. Missing values were imputed using the last-observation-carried-forward approach. Assuming a 240 mL standard deviation, 165 patients per treatment arm would give >90% statistical power to detect a 100-mL treatment difference in trough FEV_1, adjusting for multiple comparisons.

The percentage of patients who achieved clinically meaningful improvements from baseline in SGRQ total score (≥4 points) or TDI focal score (≥1 unit) was analyzed using a logistic regression model with treatment group, sex, age, and baseline value as explanatory variables. Statistical significance was based on the Wald test. The effect of aclidinium treatment compared with placebo was estimated by odds ratio and its 95% CI.

Mean (SD) values for the daily COPD symptoms and sleep scores were calculated using weekly averages from the sum of daily averages starting from the week prior to randomization (baseline) until Week 12. Overall daily rescue medication use was calculated using the total number of puffs of rescue medication used divided by the number of nonmissing days during the period from first dose of study drug to last available rescue medication use recorded in the eDiary. COPD symptoms, sleep, and rescue medication use were analyzed using an ANCOVA model with treatment group as a factor and the baseline value as covariate. The number of COPD exacerbations per patient/year was analyzed using Poisson regression with overdispersion for rates and with treatment, sex, and baseline COPD severity as factors and age as covariate.

Results

Patient demographics and baseline characteristics

Of the 561 randomized subjects, 467 completed the study (Figure 1). Although the percentage of patients who discontinued due to consent withdrawal and AEs was generally similar across treatment groups, there was a dose-related trend toward fewer discontinuations due to COPD exacerbation or lack of efficacy with aclidinium versus placebo. Demographic and baseline characteristics were similar across treatment groups (Table 1). Patients had a mean (SD) age of 64 (9) years and a baseline FEV_1 of 1.36 (0.54) L (47.2 [14.1] % of predicted value). A majority of the patients in all treatment groups used COPD medications before screening and these medications were taken by similar proportions of patients in each group (Table 1).

Pulmonary function

After 12 weeks of treatment, twice-daily aclidinium 200 μg and 400 μg significantly improved the change from baseline in trough FEV_1 over placebo by 86 mL and 124 mL, respectively ($p < 0.0001$; Figure 2A). Additionally, aclidinium 200 μg and 400 μg significantly improved the change from baseline in peak FEV_1 over placebo by 146 mL and 192 mL, respectively ($p < 0.0001$; Figure 2B).

Changes from baseline in trough and peak FEV_1 were significantly higher with aclidinium than placebo at all study visits ($p < 0.0001$ for all). Maximum bronchodilation provided by aclidinium was reached on the first timepoint assessed (first day for peak FEV_1 and first week for trough FEV_1) and maintained throughout the 12-week study period (Figure 2). At 30 minutes after treatment administration on Day 1, the first postdose FEV_1 time point assessed in the study, significant improvements in the change from baseline in FEV_1 were already observed with aclidinium 200 μg and 400 μg over placebo (89 mL and 125 mL, respectively, $p < 0.0001$ for both).

Similar results were observed for $AUC_{0\text{-}3/3h}$ FEV_1, with mean improvements over placebo at Week 12 of 144 mL and 192 mL for aclidinium 200 μg and 400 μg, respectively ($p < 0.0001$ for both). Both aclidinium doses also showed significant improvements in FVC (trough,

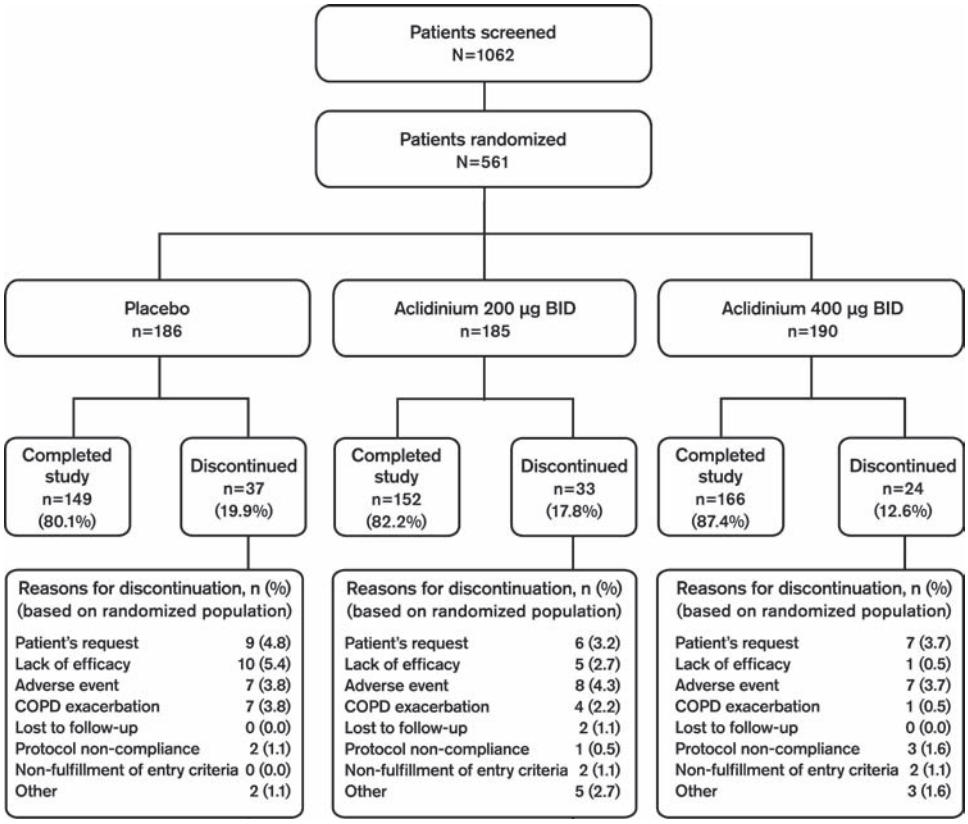


Figure 1. Study flow chart.

peak, and $AUC_{0\text{-}3/3h}$) and trough IC compared with placebo (Table 2).

Aclidinium 400 µg provided greater placebo-adjusted improvements in bronchodilation than aclidinium 200 µg throughout the study, with statistically significant differences in peak FEV_1 at Day 1 and Week 12, in favor of the higher dose (p=0.004 and 0.041, respectively).

Clinical outcomes

Significant improvements in SGRQ total scores were observed at all study visits with aclidinium (Figure 3A). The largest improvement was at Week 4, with differences over placebo of –3.2 and –3.6 for aclidinium 200 µg and 400 µg, respectively ($p < 0.001$ for both). At study end, improvements in SGRQ total score over placebo were –2.7 (aclidinium 200 µg, p = 0.013) and –2.5 (aclidinium 400 µg, p = 0.019). At all timepoints, a higher percentage of patients in each aclidinium group (ranging from 41% [Week 4, 400 µg] to 49% [Week 12, 200 µg]) achieved a clinically meaningful improvement in SGRQ total score (≥4-point decrease from baseline) (15) compared with placebo (ranging from 27% to 36%; $p < 0.05$ for all versus placebo based on odds ratios, except at Week 12 for the aclidinium 400 µg group, p = 0.139; Figure 4A).

Similarly, both aclidinium doses significantly improved TDI focal scores compared with placebo at each study visit ($p < 0.05$ for all except at Week 8 for aclidinium 200 µg, p = 0.060; Figure 3B), with maximum differences from placebo for aclidinium 200 ug and 400 µg observed at Week 4 (1.4) and Week 12 (1.0), respectively ($p < 0.005$ for both). Aclidinium 200 µg resulted in a 0.9 difference in TDI focal score from placebo at Week 12 (p = 0.005). A higher percentage of patients in each aclidinium group (ranging from 48% [Week 12, 400 µg] to 55% [Week 4, 200 µg]) achieved a clinically meaningful improvement in TDI (≥1 unit) (16) compared with placebo (ranging from 31% to 34%) at all timepoints ($p < 0.05$ for all versus placebo based on odds ratios, Figure 4B).

Nighttime Symptoms, Sleep, and Rescue Medication Use

Compared with placebo at Week 12, both aclidinium doses significantly reduced frequency of nighttime symptoms (breathlessness, cough, sputum production, and wheezing), severity and impact of breathlessness and cough on nighttime activity, severity and impact of breathlessness on early morning activity, and 24-hour sputum production ($p < 0.05$ for all versus placebo; Table 3). Sputum produced during sleeping hours at Week 12 was not significantly reduced with aclidinium compared with placebo. Almost all nighttime symptom improvements at Week 12 with aclidinium 400 µg were numerically higher than those with aclidinium 200 µg (Table 3).

Generally, sleep diary results were not significantly different between treatment groups; however, a significant difference in the frequency of nighttime awakenings

Table 1. Demographic data and baseline characteristics (safety population)

Characteristic	Placebo (n=186)	Aclidinium 200 µg (n=184)	Aclidinium 400 µg (n=190)	Total (N=560)
Age, mean (SD), years	65.1 (9.2)	63.1 (9.5)	64.9 (9.5)	64.3 (9.4)
Male, n (%)	96 (51.6)	101 (54.9)	100 (52.6)	297 (53.0)
Caucasian, n (%)	175 (94.1)	169 (91.8)	181 (95.3)	525 (93.8)
BMI, mean (SD), kg/m^2	27.5 (5.2)	27.3 (5.1)	27.6 (5.0)	27.5 (5.1)
Current smoker, n (%)	87 (46.8)	84 (45.7)	80 (42.1)	251 (44.8)
Smoking history, mean (SD), pack-years	52.7 (28.1)	53.0 (23.3)	57.2 (28.5)	54.3 (26.8)
Baseline FEV_1, mean (SD), L	1.38 (0.57)	1.36 (0.56)	1.33 (0.49)	1.36 (0.54)
Baseline FEV_1, mean (SD), % of predicted value	48.1 (14.5)	46.3 (14.9)	47.0 (12.8)	47.2 (14.1)
Postbronchodilator FEV_1, mean (SD), % of predicted value	54.6 (13.5)	52.8 (13.7)	54.1 (12.9)	53.8 (13.4)
Postbronchodilator FEV_1/FVC ratio, mean (SD), %	52.7 (10.5)	50.9 (10.6)	51.5 (10.2)	51.7 (10.5)
Bronchodilator reversibility,[a] mean (SD), %	17.1 (15.5)	16.7 (15.5)	15.5 (12.0)	16.5 (14.4)
SGRQ[b] total score, mean (SD)	45.1 (16.3)	45.9 (17.2)	48.3 (17.8)	46.5 (17.1)
BDI[c] focal score, mean (SD)	6.5 (2.2)	6.4 (2.1)	6.2 (2.1)	6.4 (2.1)
COPD medications used before screening, n (%)				
SABA[d]	114 (61.3)	118 (64.1)	127 (66.8)	359 (64.1)
LABA[e] + ICS[f]	64 (34.4)	73 (39.7)	73 (38.4)	210 (37.5)
LAMA[g]	56 (30.1)	60 (32.6)	53 (27.9)	169 (30.2)
ICS	19 (10.2)	12 (6.5)	16 (8.4)	47 (8.4)
Oxygen	12 (6.5)	10 (5.4)	11 (5.8)	33 (5.9)
SAMA[h]	5 (2.7)	7 (3.8)	16 (8.4)	28 (5.0)
LABA	12 (6.5)	9 (4.9)	6 (3.2)	27 (4.8)
Xanthines	2 (1.1)	1 (0.5)	5 (2.6)	8 (1.4)
SABA + SAMA	0	0	2 (1.1)	2 (0.4)

[a]Bronchodilator reversibility was computed as the change in FEV_1 10–15 minutes postsalbutamol 400 µg compared with the presalbutamol value; [b]SGRQ, St. George's Respiratory Questionnaire; [c]BDI, baseline dyspnea index; [d]SABA, short-acting $\beta_2$agonist; [e]LABA, long-acting $\beta_2$agonist; [f]ICS, inhaled corticosteroid; [g]LAMA, long-acting muscarinic antagonist; [h]SAMA, short-acting muscarinic antagonist.

was observed with aclidinium 400 µg versus placebo at Week 12 ($p < 0.05$).

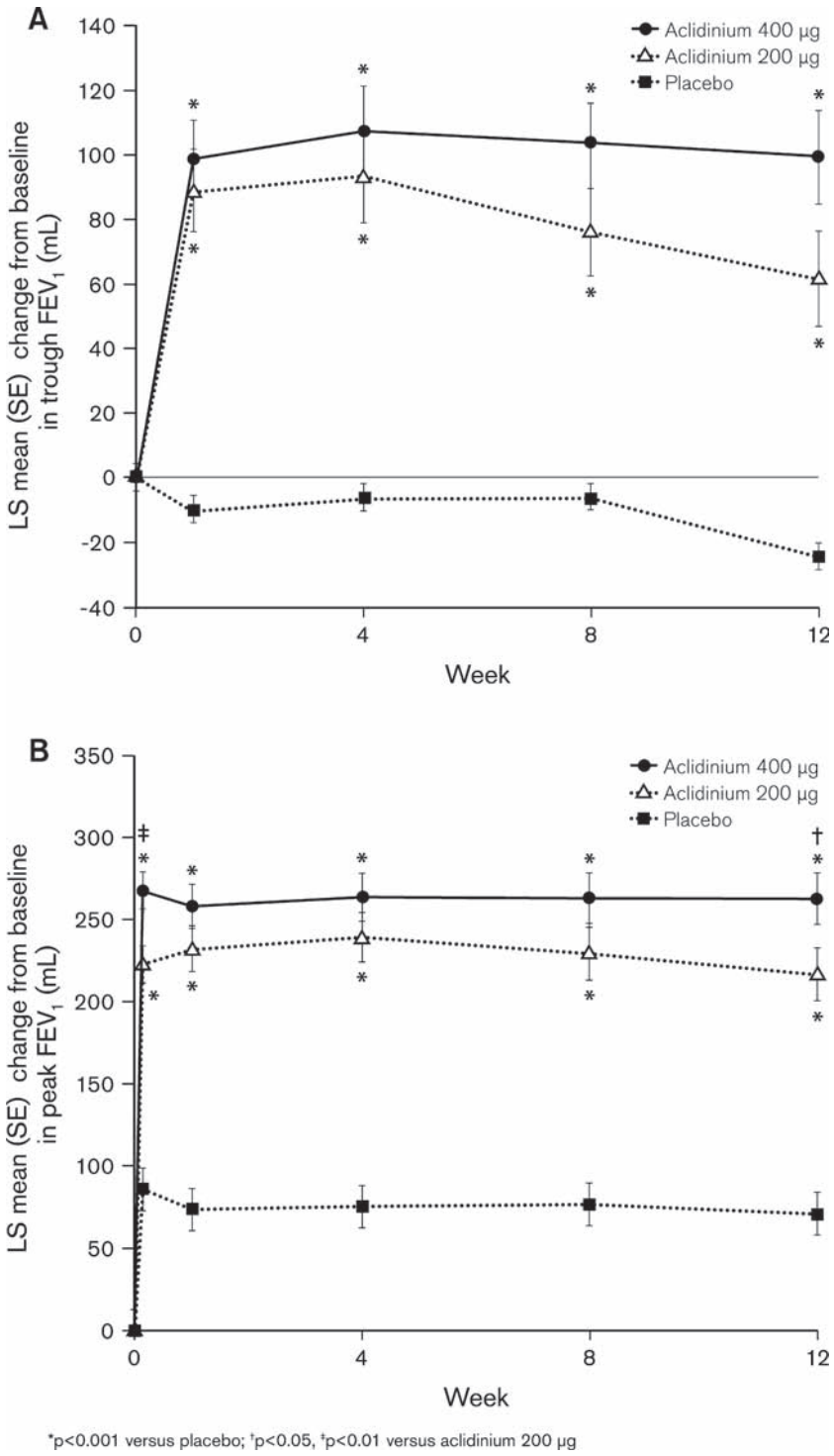
Aclidinium 200 µg and 400 µg significantly reduced total daily rescue medication use from placebo over the 12-week period by 0.7 puffs/day ($p = 0.001$) and 0.9 puffs/day ($p < 0.0001$), respectively.

COPD exacerbations

A trend towards a reduction in the rate of moderate-to-severe COPD exacerbations per patient/year were observed with aclidinium 200 µg and 400 µg (i.e., 33% and 34%, respectively, compared with placebo), although these changes were not significant ($p = 0.103$ and $p = 0.091$, respectively). Rates of exacerbation of any severity per patient/year were low (i.e., 0.79, 0.55, and 0.41 for placebo, aclidinium 200 µg, and 400 µg, respectively), with a significant reduction with aclidinium 400 µg versus placebo (rate ratio = 0.52, $p = 0.009$).

Safety

Twice-daily aclidinium 200 µg and 400 µg were well tolerated; most AEs were mild to moderate in severity. A numerically smaller percentage of patients treated with aclidinium 400 µg (44.7%) reported a treatment-emergent



*p<0.001 versus placebo; †p<0.05, ‡p<0.01 versus aclidinium 200 µg

Figure 2. Mean (SE) change from baseline in (A) trough FEV_1 and (B) peak FEV_1 at Day 1 (peak only) and at Weeks 1, 4, 8 and 12.

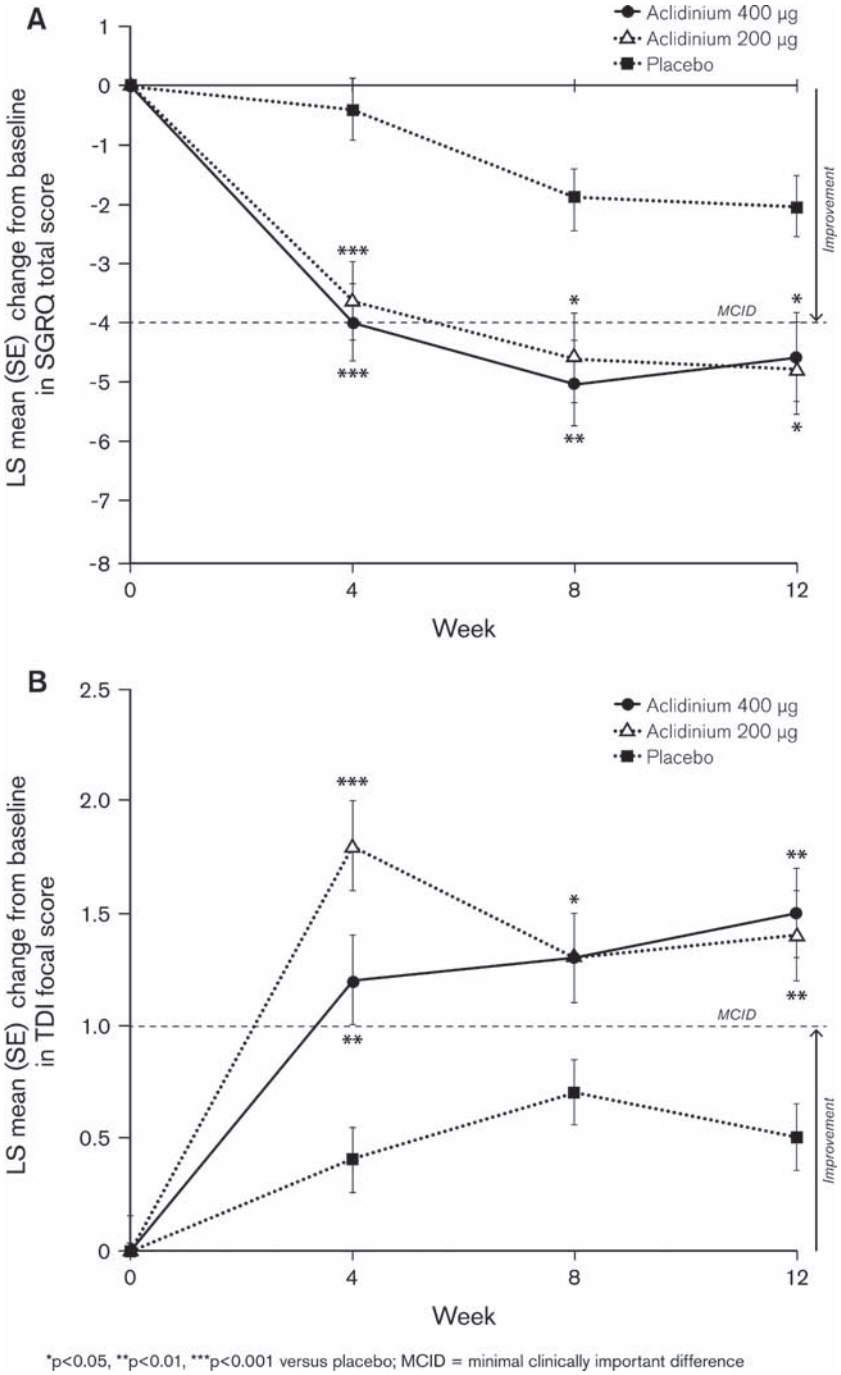
AE (TEAE) versus aclidinium 200 µg (50.5%) or placebo (52.2%). COPD exacerbation was the only AE reported by >5% of patients in all groups, with a lower incidence with aclidinium 400 ug versus aclidinium 200 µg and placebo (Table 4). Incidences of anticholinergic-related AEs (dry mouth, constipation) and cardiac AEs were low and similar across treatment groups (<2% for any event in any group).

The percentage of subjects experiencing a serious AE (SAE) was low and similar among the treatment groups (2.2% placebo, 4.3% aclidinium 200 µg, and 3.2% aclidinium 400 µg). The most frequently reported SAE was COPD exacerbation (n = 1 each for placebo and aclidinium 200 µg, n = 3 for aclidinium 400 µg). One subject in the aclidinium 400 µg group died due to metastatic lung cancer 23 days after first drug intake; this was not

Table 2. Mean (SE) change from baseline in pulmonary function parameters (FVC and IC) after 12 weeks of treatment (ITT population)

Parameter	Change from baseline, L (mean [SE])			Treatment differences, L (mean [95% CI])	
	Placebo (n=185)	Aclidinium 200 µg BID (n=184)	Aclidinium 400 µg BID (n=190)	Aclidinium 200 µg BID - placebo	Aclidinium 400 µg BID – placebo
Trough FVC	–0.003 (0.023)	0.162 (0.023)*	0.217 (0.022)*	0.165 (0.102, 0.228)*	0.219 (0.157, 0.282)*
Peak FVC	0.194 (0.026)	0.456 (0.026)*	0.472 (0.026)*	0.262 (0.190, 0.335)*	0.279 (0.207, 0.351)*
$AUC_{0\text{-}3/3h}$ FVC	0.064 (0.025)	0.312 (0.025)*	0.359 (0.025)*	0.249 (0.179, 0.318)*	0.295 (0.226, 0.363)*
Trough IC	–0.071 (0.022)	0.048 (0.023)**	0.067 (0.022)*	0.119 (0.056, 0.181)**	0.138 (0.076, 0.199)*

*p < 0.0001, **p < 0.001 vs placebo.



*p<0.05, **p<0.01, ***p<0.001 versus placebo; MCID = minimal clinically important difference

Figure 3. Mean (SE) change from baseline in A) SGRQ total score and B) TDI focal score at Weeks 4, 8, and 12.

Table 3. Mean (SD) change from baseline in daily average of COPD nighttime and early morning symptom scores at Week 12 (ITT population)

Parameter	Placebo (n=185)	Aclidinium 200 µg (n=184)	Aclidinium 400 µg (n=190)
Frequency of nighttime symptoms[a]			
Breathlessness	–0.13 (0.92)	–0.44 (1.03)**	–0.44 (1.12)**
Cough	0.10 (1.36)	–0.35 (1.24)***	–0.36 (1.29)***
Sputum production	0.05 (0.98)	–0.18 (1.09)*	–0.37 (0.92)***
Wheezing	–0.00 (1.15)	–0.44 (1.20)**	–0.53 (1.27)***
Severity and impact of nighttime symptoms on activity[b]			
Breathlessness (during previous 12 hours)	–0.19 (0.70)	–0.41 (0.78)**	–0.44 (0.86)***
Cough (during sleep at night)	–0.10 (0.78)	–0.28 (0.84)*	–0.24 (0.76)*
Severity and impact of nighttime symptoms on sleep[c]			
Breathing symptoms	–0.06 (0.59)	–0.17 (0.60)	–0.24 (0.57)**
Severity and impact of early morning symptoms			
Severity of breathlessness in first hour after waking up[b]	–0.09 (0.61)	–0.31 (0.77)**	–0.32 (0.79)***
Impact of breathlessness on morning activities[d]	–0.03 (0.56)	–0.22 (0.69)**	–0.28 (0.76)***
Sputum production[e]			
Nighttime production	–0.12 (0.52)	–0.17 (0.68)	–0.24 (0.62)
24-hour production	0.04 (0.61)	-0.10 (0.68)*	–0.14 (0.67)**

*p<0.05, ** p<0.01, *** p<0.001 versus placebo.

[a]Frequency was calculated as the daily average over a 1-week period and scored from 0 (never) to 4 (≥7 times); [b]Daily average rating of severity and impact was scored from 0 (none) to 4 (severe symptoms that interfered with normal activities); [c]Daily average rating of symptoms affecting sleep was scored from 0 (none) to 4 (symptoms were so severe that I could not sleep at all); [d]Daily average rating of restriction of usual activities was scored from 0 (none) to 4 (severe symptoms that interfered greatly with morning activities); [e]Amount was calculated as the daily average over a 1-week period and scored from 0 (none) to 3 (>1 tablespoon).

considered related to study treatment. No clinically significant differences in clinical laboratory values, vital signs, or ECG parameters were observed.

Discussion

In this study, twice-daily aclidinium 200 µg and 400 µg resulted in significant bronchodilation compared with placebo in moderate-to-severe COPD patients, as assessed by morning predose (trough) FEV_1 and peak FEV_1 after 12 weeks of treatment. These improvements were evident by the first day of treatment (for peak FEV_1) and maintained throughout the 12-week study period.

Although an MCID in FEV_1 has not yet been clearly defined, the improvement over placebo in trough FEV_1 with aclidinium 400 µg in this study (124 mL at Week 12) is within the suggested MCID of 100–140 mL (9, 17), similar to what was previously reported in an earlier Phase II study with twice-daily aclidinium (11). The improvements in trough FEV_1 with aclidinium reported here are comparable to those observed in tiotropium registration studies (120–150 mL) (18–20).

The comparable improvements in peak FEV_1 observed at Day 1 and Week 12 with aclidinium 400 µg twice daily in this study suggest that aclidinium reaches its maximum effect with the first dose. As delayed onset of effect is considered a potential barrier to adherence to prescribed therapies in COPD patients (21), the rapid onset of action seen with aclidinium treatment may positively affect patient compliance.

The numerically greatest number of patient discontinuations was found in the placebo group while the least number of discontinuations was observed in the aclidinium 400 µg group, similar to the pattern of differential withdrawal frequently observed in COPD trials (18, 19, 22, 23). In particular, the aclidinium 400 µg group had the numerically least number of patient discontinuations due to COPD exacerbation or lack of efficacy, suggesting that the higher aclidinium dose

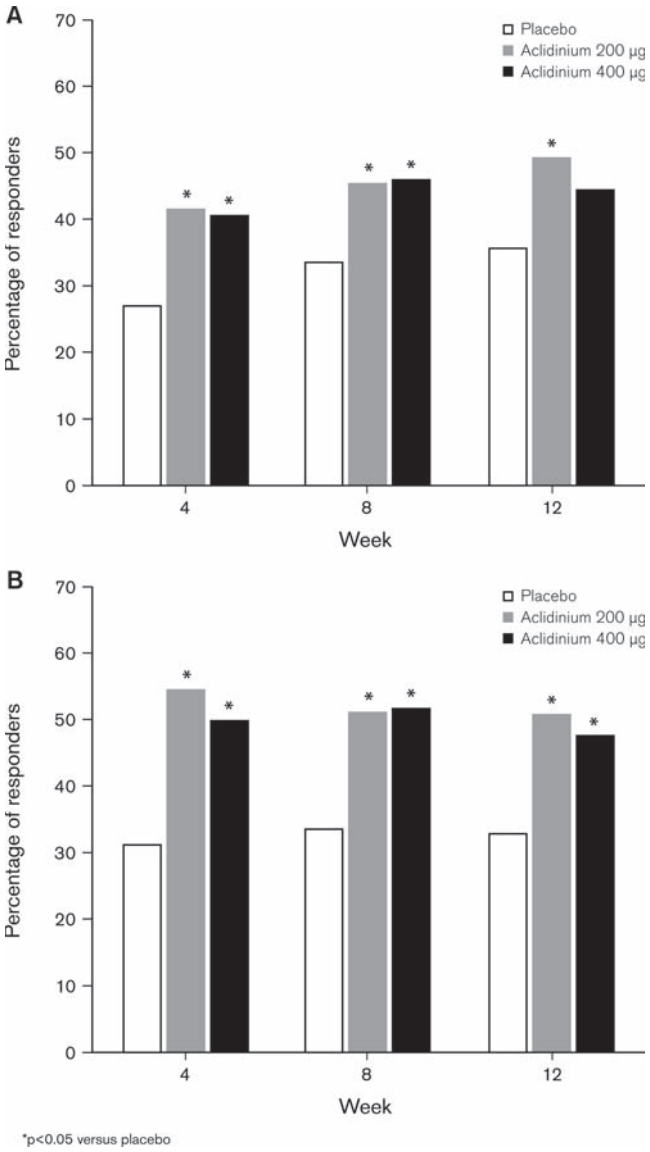


Figure 4. Percentage of patients who achieved a clinically meaningful difference in (A) SGRQ total score (≥4 units) and (B) TDI focal score at Weeks 4, 8 and 12.

provides greater efficacy in COPD patients compared with the lower dose.

The GOLD guidelines emphasize that treatment of stable COPD should include managing symptoms and improving health status (1). In this study, both aclidinium doses significantly improved dyspnea, with a clinically meaningful improvement in TDI focal score (≥1 unit) (16) at Week 12 with aclidinium 400 µg. Although significant improvements from baseline in SGRQ were observed with aclidinium over placebo throughout the study, the MCID (≥4 units) (15) was not met, most probably due to the short study duration. These results suggest that aclidinium may improve health status and that a longer treatment period (i.e., 6 months) may be needed to better evaluate such changes. A similar phenomenon has been observed in recent studies wherein the magnitude of improvement in SGRQ total scores with tiotropium versus placebo increased with longer study duration (24, 25).

Nighttime COPD symptom incidence has not been extensively studied but it has been reported that 89% of COPD patients experience ≥1 nighttime symptom (26) and that COPD symptoms are at their worst at night or early morning (27, 28). These could result in nocturnal awakenings and difficulties with morning activities, negatively impacting patient quality of life. Thus, it is essential to evaluate the effect of COPD treatment on these parameters. Since no validated instrument currently exists to assess COPD nighttime symptoms and their influence on morning activities, a questionnaire was developed for this study to evaluate these aspects. Similar to the reduction in nighttime symptoms observed in a 2-week study with twice-daily aclidinium 400 µg (11), twice-daily aclidinium 200 µg and 400 µg reduced the

Table 4. Most frequently reported (≥2% of subjects in any group) adverse events by treatment group (n [%]; safety population; N=560)

Preferred term	Placebo (n = 186)	Aclidinium 200 µg (n = 184)	Aclidinium 400 µg (n = 190)
COPD exacerbation	23 (12.4)	17 (9.2)	14 (7.4)
Dyspnea	6 (3.2)	4 (2.2)	5 (2.6)
Arthralgia	1 (0.5)	4 (2.2)	5 (2.6)
Cough	5 (2.7)	4 (2.2)	4 (2.1)
Diarrhea	3 (1.6)	3 (1.6)	4 (2.1)
Oropharyngeal pain	3 (1.6)	2 (1.1)	4 (2.1)
Fatigue	4 (2.2)	0 (0)	4 (2.1)
Headache	4 (2.2)	6 (3.3)	3 (1.6)
Nasopharyngitis	2 (1.1)	6 (3.3)	3 (1.6)
Insomnia	6 (3.2)	3 (1.6)	3 (1.6)
Urinary tract infection	4 (2.2)	2 (1.1)	3 (1.6)
Back pain	1 (0.5)	5 (2.7)	3 (1.6)
Upper respiratory tract infection	7 (3.8)	2 (1.1)	2 (1.1)
Nausea	4 (2.2)	2 (1.1)	2 (1.1)
Dizziness	1 (0.5)	4 (2.2)	2 (1.1)
Bronchitis	4 (2.2)	2 (1.1)	0 (0)

frequency, severity, and impact of nighttime symptoms compared with placebo in COPD patients after 12 weeks of treatment.

The amount of sputum produced during sleeping hours at Week 12 was the only symptom parameter that did not show a significant reduction with aclidinium treatment compared with placebo at study end; however, this may have been due to a reduction in sputum production in the placebo group at this time point. Results from this study suggest that the evening dose of aclidinium provides sustained bronchodilation and improvement of nighttime and early morning symptoms, although no direct correlation was investigated between these parameters. Other twice-daily COPD medications have been reported to improve nighttime awakenings (29–32), morning activity (33), and daytime symptoms (34).

However, the study reported here provides a more detailed investigation and is the first to evaluate the effect of treatment on particular COPD symptoms (ie, breathlessness, cough, sputum production) and their severity and impact specifically at night and at early morning. The positive impact of twice-daily aclidinium on COPD nighttime and early morning symptoms will need to be confirmed in future studies.

Although a trend towards a reduction in moderate-to-severe exacerbation rates with aclidinium was observed in this study, this trial was not designed to assess exacerbation frequency. Studies with an enriched population for patients at risk for COPD exacerbations, longer treatment duration, and adequate power to determine between-group differences are necessary to establish the treatment benefit of aclidinium on COPD exacerbations.

In this 12-week study, both aclidinium doses had safety profiles similar to placebo. Incidences of anticholinergic and cardiac AEs with aclidinium were low and also similar to placebo. This is most likely due to the low and transient systemic exposure of aclidinium, a result of its rapid hydrolysis in plasma (5-7). Studies with a longer treatment duration would enable a more comprehensive evaluation of the safety profile of aclidinium.

Conclusions

Overall, twice-daily aclidinium 200 µg and 400 µg significantly improved lung function, health status, and reduced COPD symptoms, with aclidinium 400 µg providing numerically greater benefits than aclidinium 200 µg throughout the study. Both doses were well tolerated and had similar safety profiles. Twice-daily aclidinium may thus be an effective new treatment option for COPD patients.

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Declaration of Interest

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