Long-term safety and efficacy of twice-daily aclidinium bromide in patients with COPD

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KEYWORDS
Aclidinium;
Safety;
Bronchodilation;
Health status;
Tolerability;
COPD

Summary

Background: Aclidinium is a novel, long-acting muscarinic antagonist indicated for maintenance treatment of COPD.

Methods: In this 52-week, parallel-group, double-blind study, patients with moderate-to-severe COPD were randomized (1:1) to receive aclidinium twice-daily (BID) 200 µg or 400 µg via a novel, dry powder inhaler (Genuair®/Pressair®) [Registered trademarks of Almirall, SA, Barcelona, Spain for use within the European Union, Iceland, Norway, and Switzerland as Genuair® and within the United States as Pressair®]. Safety, the primary objective, was assessed via adverse events (AEs), clinical laboratory tests, vital signs, and 12-lead electrocardiograms. Efficacy was evaluated using spirometry, SGRQ, and rescue medication use.

Results: A total of 605 patients were randomized in the study. The percentage of patients reporting any treatment-emergent AE (TEAE) was comparable between groups; most TEAEs were mild or moderate. Anticholinergic TEAEs were reported by low percentages of patients in either treatment group (dry mouth: 200 µg, 1.3%; 400 µg, 2.7%; constipation: 200 µg, 2.9%; 400 µg, 1.7%). Cardiac TEAEs were also reported by a low percentage of patients (<2% for any event in any group) and did not appear to be dose dependent. There were no clinically relevant abnormalities in other safety outcomes. Both aclidinium 200 µg and 400 µg resulted in improvements from baseline to Week 52 in FEV1, with numerically greater increases observed with the higher dose. Clinically important improvements in SGRQ scores and a
Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the world [1] and incurs a substantial economic and social burden due to increased healthcare expenditures and lost work productivity [2–4]. Inhaled long-acting bronchodilators are central to the reduction of symptoms and improvement of health status and lung function in patients with COPD. These therapeutic options are therefore recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines for effective disease management [5].

Aclidinium is a novel inhaled long-acting muscarinic antagonist (LAMA) indicated for maintenance treatment of COPD. Due to the heterogeneity of COPD [6] and prevalence of polypharmacy among COPD patients [7,8], the availability of aclidinium as an additional effective therapeutic option with a good safety profile and reduced potential for drug interactions would be valuable for this patient population.

Clinical studies have previously demonstrated that twice-daily (BID) aclidinium 200 μg and 400 μg provided bronchodilation over a 24-h period in patients with COPD, with significantly improved lung function observed as early as the first day of treatment that was sustained until study end [9–12]. Significant reductions in breathlessness and clinically significant improvements in health status have also been reported with aclidinium BID treatment [10,11]. Aclidinium was also shown to be well tolerated in patients with COPD, with safety profiles comparable between doses and similar to that of placebo [9–12]. Furthermore, the rapid plasma hydrolysis of aclidinium into inactive metabolites by butyrylcholinesterase without involvement of cytochrome P450 or serum albumin suggests a reduced potential for systemic side effects and a low likelihood of drug–drug interactions involving aclidinium [13,14]. Various studies have thus demonstrated the efficacy and safety of aclidinium in studies up to 6 months in duration.

As COPD is due to persistent airflow limitation in the lung [15], effective disease management would ideally be achieved with a maintenance therapeutic option that is well tolerated and maintains its efficacy over time. Assessing the effects of long-term treatment with twice-daily aclidinium is therefore essential in comprehensively evaluating its safety and efficacy profile. Here we report the results from a 52-week, randomized, double-blind, multicenter, parallel-group study with twice-daily aclidinium 200 μg and 400 μg in patients with moderate-to-severe COPD. The primary objective of this study was to assess the long-term safety and tolerability of aclidinium treatment. Secondary evaluations included bronchodilator efficacy, health status, and rescue medication use.

Methods

Study design

This was a Phase 3, randomized, double-blind, parallel-group study in patients with moderate-to-severe COPD conducted in 106 centers in the United States and three centers in Canada (NCT01044459). The study consisted of a 2-week run-in period prior to a 52-week double-blind treatment period, with a follow-up telephone call 2 weeks after the last dose of study treatment. Eligible patients were randomized 1:1 to twice-daily aclidinium 200 μg or 400 μg. Both doses were administered via a multidose, dry powder inhaler (Genuair®/Pressair™). The study was conducted according to International Conference on Harmonisation/Good Clinical Practice guidelines and the Declaration of Helsinki; the protocol was approved by the Institutional Review Board at each study center. All patients gave written informed consent before participating in any study procedures.

Patient population

Male and female patients ≥40 years of age were eligible provided that they were current or former smokers with a smoking history of ≥10 pack-years and were diagnosed with stable, moderate-to-severe expiratory airflow obstruction according to GOLD guidelines [16] (postbronchodilator forced expiratory volume in 1 s [FEV1]/forced vital capacity [FVC] <70% and FEV1 ≥30% and <80% predicted). Subjects were excluded if they had a history of hypersensitivity reaction or contraindications to the use of inhaled anticholinergics, experienced a COPD exacerbation requiring hospitalization ≤3 months before screening, any respiratory tract infection or COPD exacerbation ≤6 weeks before screening, any other clinically significant respiratory condition (including asthma), or had clinically significant cardiovascular conditions such as myocardial infarction or newly diagnosed arrhythmia ≤6 months and ≤3 months before screening, respectively, hospitalization within the previous 12 months for heart failure, unstable angina, or unstable arrhythmia that required changes in pharmacological therapy or other invention.

Use of albuterol and salbutamol as rescue medications was permitted. Patients receiving long-acting beta2-agonist (LABA)/inhaled corticosteroid (ICS) maintenance therapy

1 Registered trademarks of Almirall, SA, Barcelona, Spain for use within the European Union, Iceland, Norway, and Switzerland as Genuair® and within the United States as Pressair™.
prior to study entry were withdrawn from the LABA component and maintained on the ICS component. The use of other anticholinergics during the study was not permitted. Other COPD medications, such as theophylline and ICS, oral or parenteral corticosteroids (≤10 mg/day of prednisone or 20 mg every other day) were only allowed if treatment was stable ≥4 weeks prior to screening. Use of rescue medication, theophylline, or ICS was discontinued ≥6 h before a study visit.

Assessments and outcome measures

Safety and efficacy were assessed during study visits at baseline and at Weeks 1, 12, 24, 36, 48, and 52 of the double-blind treatment period. Safety was assessed through reporting of adverse events (AEs), clinical laboratory tests, vital signs, physical examinations, and electrocardiograms (ECGs). An AE was classified as treatment-emergent (TEAE) if it started on or after the date of the first dose of treatment or if it started before the first dose but continued with increasing severity during the study, up to 30 days after the last treatment dose. Standardized spirometric measurements of lung function [17] were conducted at each visit predose (at −45 min and −15 min) and postmorning dose (at 0.5, 1.0, 2.25, and 3.0 h). Health status was assessed at all study visits (except Week 1) using St. George’s Respiratory Questionnaire (SGRQ). Rescue medication use was recorded daily using a paper diary, with baseline use assessed during the 1-week period before treatment initiation.

Key efficacy outcomes included change from baseline to Week 52 in morning predose (trough) FEV₁ (calculated as the average of the two greatest morning predose FEV₁ values) and peak FEV₁ (maximum FEV₁ reading observed ≤3 h postmorning dose). Other outcomes included the change from baseline in SGRQ total and domain scores (symptoms, activity, and impact), the proportion of patients who achieved a clinically important improvement in the SGRQ total score (defined as a decrease of ≥4 points [18]), and rescue medication use during the treatment period.

Statistical analysis

Safety results were summarized descriptively, based on the safety population, which was defined as all randomized patients who took ≥1 dose of study medication. All efficacy analyses were based on the intent-to-treat (ITT) population, which was defined as all randomized patients who took ≥1 dose of study medication and had a baseline and at least one postbaseline FEV₁ assessment; missing data were imputed by the last-observation-carried-forward (LOCF) approach. Bronchodilation and health status outcomes were analyzed using an analysis of covariance (ANCOVA) model with treatment group and sex as factors and corresponding baseline values and age as covariates. Rescue medication outcomes were analyzed similarly, but used only treatment group and baseline value as factor and covariate, respectively. The sample size of at least 600 patients from 1200 patients screened was based on the objective of obtaining long-term safety data; it was not derived through an analysis of statistical power to meet efficacy objectives as these were considered exploratory. As such, no statistical comparisons were made between the treatment groups.

Results

Study population

From the 605 patients with moderate-to-severe COPD who were randomized to twice-daily aclidinium 200 μg or 400 μg in this study, 602 patients received at least 1 dose of study treatment and were included in the safety population. Of these 602 patients, 600 had a baseline and ≥1 postbaseline FEV₁ assessment and were included in the ITT population for efficacy analyses. Baseline demographics were generally similar between the treatment groups (Table 1). A similar percentage of patients in each treatment group completed the 52-week study (200 μg, 57.4%; 400 μg, 55.3%), with withdrawal of consent as the most frequent reason for discontinuation (Fig. 1).

Safety

The percentage of patients reporting any TEAE was similar for aclidinium 200 μg (62.4%) and 400 μg (66.0%); most TEAEs were mild to moderate in severity. COPD exacerbation was the most common TEAE and was reported by comparable proportions of patients between the treatment groups (Table 2). Other commonly reported TEAEs (≥3% in total patient population) included nasopharyngitis, cough, sinusitis, headache, nausea, and upper respiratory infection, none of which appeared to be dose dependent. Diarrhea, dry mouth, back pain, and arthralgia were reported by a greater percentage of patients in the aclidinium 400 μg group compared with the lower dose (>1% vs 200 μg group), all of which were reported by <4% of patients for any event for either dose (Table 2). Diarrhea was considered by investigators to be treatment related in only 1 patient (0.3%) in the 400 μg group. Dry mouth was considered treatment related in all but 1 patient in the 200 μg group. None of the back pain and arthralgia events were considered treatment related for either dose.

Adverse events typically reported with anticholinergic treatment were infrequent and reported by <3% of patients in either treatment group. Of the 14 patients who reported constipation in this study, this AE was considered treatment related in only 1 patient (400 μg), and was considered moderate and led to study discontinuation. Severe constipation was reported in 2 patients in the aclidinium 200 μg group, neither of which resulted in treatment discontinuation. The percentage of patients reporting dry mouth was low (<3% for either treatment group; Table 2), most of which were considered treatment related but none were considered severe. A similarly low percentage of patients reported urinary tract infections (<3%), none of which were considered treatment related. None of the reports of dry mouth or urinary tract infection were considered serious or led to study discontinuation. The overall incidence of tachycardia was low and occurred in 3 patients (1.0%) in the 200 μg group; none were reported in the 400 μg group.
### Table 1  Demographic and baseline characteristics.\(^{a}\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aclidinium 200 µg</th>
<th>Aclidinium 400 µg</th>
<th>Total N = 602</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD), years</strong></td>
<td>63.0 (9.5)</td>
<td>64.2 (9.9)</td>
<td>63.6 (9.7)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>184 (59.2)</td>
<td>167 (57.4)</td>
<td>351 (58.3)</td>
</tr>
<tr>
<td><strong>Caucasian, n (%)</strong></td>
<td>282 (90.7)</td>
<td>272 (93.5)</td>
<td>554 (92.0)</td>
</tr>
<tr>
<td><strong>BMI, mean (SD), kg/m(^2)</strong></td>
<td>27.4 (5.4)</td>
<td>27.5 (5.3)</td>
<td>27.4 (5.4)</td>
</tr>
<tr>
<td><strong>Current smoker, n (%)</strong></td>
<td>164 (52.7)</td>
<td>146 (50.2)</td>
<td>310 (51.5)</td>
</tr>
<tr>
<td><strong>Smoking history, mean (SD), pack-years</strong></td>
<td>53.9 (26.7)</td>
<td>54.7 (31.1)</td>
<td>54.3 (28.9)</td>
</tr>
<tr>
<td><strong>Baseline concomitant ICS use, n (%)</strong></td>
<td>95 (30.5)</td>
<td>105 (36.1)</td>
<td>200 (33.2)</td>
</tr>
<tr>
<td><strong>Postbronchodilator FEV(_1), mean (SD), % of predicted value</strong></td>
<td>53.3 (13.4)</td>
<td>51.2 (12.9)</td>
<td>52.3 (13.2)</td>
</tr>
<tr>
<td><strong>Postbronchodilator FEV(_1)/FVC, mean (SD), %</strong></td>
<td>50.9 (11.0)</td>
<td>49.5 (11.3)</td>
<td>50.3 (11.2)</td>
</tr>
<tr>
<td><strong>Bronchial reversibility,(^{b}) mean (SD), %</strong></td>
<td>14.8 (14.1)</td>
<td>15.3 (15.5)</td>
<td>15.0 (14.8)</td>
</tr>
<tr>
<td><strong>Baseline FEV(_1), mean (SD), L</strong></td>
<td>1.44 (0.57)</td>
<td>1.37 (0.61)</td>
<td>1.41 (0.59)</td>
</tr>
<tr>
<td><strong>SGRQ total score,(^{c}) mean (SD)</strong></td>
<td>48.5 (17.8)</td>
<td>49.8 (18.9)</td>
<td>49.2 (18.4)</td>
</tr>
<tr>
<td><strong>Rescue medication use,(^{c}) mean (SD), puffs/day</strong></td>
<td>2.8 (3.0)</td>
<td>2.9 (3.2)</td>
<td>2.9 (3.1)</td>
</tr>
</tbody>
</table>

BMI, body-mass index; FEV\(_1\), forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; SD, standard deviation; SGRQ, St. George’s Respiratory Questionnaire.

\(^{a}\) Safety population at Visit 1 (enrollment) unless otherwise indicated.

\(^{b}\) Calculated as % change = 100 \times ([postbronchodilator FEV\(_1\)] - [prebronchodilator FEV\(_1\)])/(prebronchodilator FEV\(_1\)).

\(^{c}\) Intent-to-treat population at Visit 2 (randomization).

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**Figure 1**  Study flow chart.
Cardiac TEAEs were reported by a greater percentage of patients in the aclidinium 200 µg group (7.7%) compared with the 400 µg group (4.1%) (Table 3). The most frequent cardiac event was coronary artery disease (0.8%), most of which were mild to moderate in severity. This TEAE was reported by 5 (1.6%) patients in the aclidinium 200 µg group alone, 4 of whom had a history of cardiac disorders prior to study entry. Of the 36 (6.0%) patients in the study who reported a cardiac TEAE, 6 (1.0%) reported cardiac events that were considered treatment related. Two were in the 200 µg group (one patient reported both tachycardia and supraventricular extrasystoles; another patient reported sick sinus syndrome); 4 were in the 400 µg group (n = 1 each for cyanosis, acute myocardial infarction, atrial fibrillation, and ventricular extrasystoles). The atrial fibrillation reported by 1 patient in the 400 µg group was severe and the only treatment-related cardiac AE that led to treatment discontinuation. Medical histories for these patients who reported cardiac TEAEs that were considered treatment related included myocardial infarction, coronary artery disease, atrioventricular block first degree, and hypertension.

Serious AEs (SAEs) were reported by a similar percentage of patients in both treatment groups (200 µg, 9.3%; 400 µg, 10.0%). The most commonly reported SAE was COPD exacerbation (200 µg, 1.6%; 400 µg, 2.1%); all other SAEs were

### Table 3  Treatment-emergent cardiac adverse events reported by ≥2 patients in the total population (safety population).

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Aclidinium 200 µg</th>
<th>Aclidinium 400 µg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 311</td>
<td>n = 291</td>
<td>N = 602</td>
</tr>
<tr>
<td>At least 1 TEAE</td>
<td>24 (7.7)</td>
<td>12 (4.1)</td>
<td>36 (6.0)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5 (1.6)</td>
<td>0 (0)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>2 (0.6)</td>
<td>2 (0.7)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2 (0.6)</td>
<td>2 (0.7)</td>
<td>4 (0.7)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>3 (1.0)</td>
<td>0</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Left/right bundle branch block</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Ventricular extrasystoles</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
<td>3 (0.5)</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>2 (0.6)</td>
<td>0 (0)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2 (0.6)</td>
<td>0 (0)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Extrasystoles</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>2 (0.3)</td>
</tr>
</tbody>
</table>

Data reported as n (%).
reported by less than 1% of patients in either treatment group. One patient in the aclidinium 400 μg group with a history of coronary artery disease, coronary bypass surgery, and hypertension reported a severe, transient ischemic attack that was considered serious but not related to treatment.

COPD exacerbation was the most frequently reported TEAE leading to study discontinuation, which was observed in similar percentages of patients for either dose (Fig. 1). All other AEs resulting in discontinuation were single occurrences in either treatment group. Two patients died during the double-blind treatment period or within 30 days after the last dose of study treatment (1 due to biliary sepsis [200 μg] and 1 due to a subarachnoid hemorrhage [400 μg]). One patient in the aclidinium 200 μg group died more than 30 days after the last aclidinium dose due to malignant lung neoplasm that was diagnosed while the patient was receiving study treatment. None of the deaths were considered by investigators to be related to study treatment. Changes from baseline in clinical laboratory values, vital signs and ECG parameters were similar between treatment groups and not considered to be of clinical concern.

**Lung function**

Mean improvements from baseline in trough FEV₁ were observed during the first assessed time point at Week 1 (200 μg, 64 mL; 400 μg, 91 mL), with maximum improvements of 64 mL (Week 1) and 101 mL (Week 24) for the 200 μg and 400 μg doses, respectively, during the 1-year study (Fig. 2). The improvements in trough FEV₁ observed at the beginning of the study were generally maintained until study end with the aclidinium 400 μg dose, with mean changes from baseline in trough FEV₁ of 72 mL after 52 weeks of treatment. Trough FEV₁ also remained improved from baseline after 1 year of treatment with aclidinium 200 μg, albeit with a numerically lower magnitude (34 mL) compared with the higher dose.

Changes from baseline in peak FEV₁ after the first dose on Day 1 of treatment with aclidinium 200 μg and 400 μg reached 226 mL and 235 mL, respectively (Fig. 3). These improvements were generally maintained until study end (200 μg, 185 mL; 400 μg, 214 mL). Numerically greater improvements were observed with the 400 μg dose compared with the 200 μg dose for all lung function efficacy endpoints throughout the study, demonstrating a dose-dependent effect on bronchodilation throughout 1 year of treatment.

**Health status and rescue medication use**

Clinically important improvements in SGRQ total scores (≥4-point improvement from baseline) were observed at all study visits throughout the 52-week treatment period with aclidinium 200 μg and 400 μg (Fig. 4). The mean improvement from baseline in SGRQ total score was 5.3 units (200 μg) and 5.2 units (400 μg) at study end (Week 52). The improvements from baseline in each of the 3 SGRQ domain scores for the 400 μg dose throughout the study ranged from 5.8–7.6 units for symptoms, 3.8–5.5 units for activity, and 5.5–7.1 units for impact. These were comparable to the improvements observed with the 200 μg dose (6.6–9.1

![Figure 2](image2.png) Mean (SE) change from baseline in trough FEV₁ by study visit.

![Figure 3](image3.png) Mean (SE) change from baseline in peak FEV₁ by study visit.

![Figure 4](image4.png) Mean (SE) change from baseline in SGRQ total score by study visit.
units, 4.3–5.4 units, and 4.9–6.2 units, for each of the domains, respectively).

The percentage of patients who achieved a clinically important improvement in SGRQ total score (ie, ≥4 units) ranged from 41.6% to 46.6% for aclidinium 200 µg and from 45.2% to 49.1% for aclidinium 400 µg at all study visits. The percentage of patients who achieved a clinically important improvement in SGRQ total score was numerically higher in the aclidinium 400 µg group compared with the 200 µg group throughout the study. Rescue medication use during the overall treatment period was 1.5 puffs/day (200 µg) and 1.4 puffs/day (400 µg), which was approximately one-half of the baseline value (Table 1).

Discussion

COPD is a treatable, but only partially reversible, disease warranting continued maintenance treatment for effective management. As patients with COPD tend to be elderly, have various comorbidities, and receive multiple medications, evaluating the long-term safety and tolerability of any new pharmacological treatment is an especially important step in assessing its potential for disease management [7,8]. Furthermore, patients with COPD are often diagnosed with comorbidities such as cardiovascular disease [19–21], making it critical to evaluate cardiac safety of any new potential treatment for this disease.

The current study demonstrates that long-term treatment with twice-daily aclidinium was well tolerated by patients with moderate-to-severe COPD throughout the 52-week treatment period, with similar safety profiles between both doses. Anticholinergic TEAEs such as dry mouth and constipation, which are typically reported with LAMA treatment, were reported by a low percentage of patients treated with aclidinium (<3% for any specific event with either aclidinium dose). Similarly, any specific cardiac TEAE was reported by ≤1% of patients with either aclidinium dose, with a total of 6% of patients in the entire safety population reporting any cardiac event. There was no apparent dose-dependent increase in the percentages of patients reporting any individual anticholinergic or cardiac event, with the exception of dry mouth; none of the dry mouth events were considered severe or serious. The tolerability of aclidinium may be due to its rapid plasma hydrolysis [14,22–24], which suggests that treatment with the drug may lead to fewer systemic side effects. The safety and tolerability observed with long-term aclidinium treatment in this study are consistent with the safety profiles reported in previous Phase 3 studies with twice-daily aclidinium up to 24 weeks [10,11], suggesting that there is no increase in safety concerns with longer aclidinium treatment. In addition, it has been previously reported that a total daily dose of aclidinium 800 µg administered for 3 days in healthy subjects did not show any significant effect on QT interval [25], similar to the lack of clinically relevant changes from baseline in ECG parameters with aclidinium treatment in the current 1-year study. However, given the concern regarding cardiovascular adverse events with muscarinic bronchodilators [26–29] and the prevalence of cardiovascular comorbidities in patients with COPD [30,31], a study is planned to more thoroughly evaluate cardiovascular safety of aclidinium treatment in COPD patients who may be at greater risk for cardiovascular adverse events.

This study also demonstrates that 52-week treatment with twice-daily aclidinium provides improvements in lung function and health status in patients with COPD. Patients treated with aclidinium experienced improvements from baseline in lung function as early as Day 1, the first time point assessed for peak FEV₁ and Week 1, the first time point assessed for trough FEV₁, that were generally maintained until study end. The 400 µg dose consistently provided numerically greater improvements in bronchodilation compared with the lower dose throughout the 52-week treatment period. The lung function results from this long-term study are thus in accordance with previous 12- and 24-week studies that evaluated twice-daily aclidinium 200 µg or 400 µg in patients with COPD; these studies demonstrated significant improvements in bronchodilation on Day 1 which were maintained over the treatment period, with a numerically greater magnitude of improvement observed with the higher dose [10,11]. The maximal bronchodilation observed soon after treatment initiation with aclidinium is consistent with the previously reported achievement of a pharmacokinetic steady state of twice-daily aclidinium doses up to 800 µg by 2 days after dose administration [24], in contrast to the 2–3 weeks reported for tiotropium 18 µg [32,33]. Since delayed onset of action following dosing is associated with poor adherence to treatment regimens [34,35], the rapid onset of improvement seen with aclidinium treatment may improve patient adherence.

The GOLD guidelines emphasize that treatment of stable COPD should include managing symptoms and improving health status in addition to improving lung function [5]. Clinically important improvements in SGRQ total scores were observed with aclidinium treatment throughout this 1-year study. These were similar in magnitude to the changes from baseline in SGRQ total scores with twice-daily aclidinium 200 µg and 400 µg treatment reported in a 6-month study but did not reflect the dose separation observed in that earlier trial [10]. Nevertheless, the current study also showed that long-term treatment with aclidinium was associated with a reduction in rescue medication use, similar to the results of earlier studies of shorter duration [10,11], further supporting the positive effect of aclidinium on health status and symptom management.

One limitation of this study is that a placebo arm was not included; therefore, no adjustments for placebo on outcome measures were possible. Without treatment, an annual decline in trough FEV₁ of 47–79 mL is expected in patients with GOLD stage II or III COPD, according to a recent review of large placebo-controlled COPD studies [36]. As the improvements in trough FEV₁ shown here were changes from baseline values and could not take into account the decline in trough FEV₁ that is typically seen in COPD patients over time, the magnitudes of improvements seen in this study could potentially have been greater if comparisons to a placebo group had been possible. Another limitation is the absence of an active comparator, which prevents a direct comparison of the efficacy of long-term use of aclidinium compared with those of other bronchodilators.

Overall, this study demonstrated that long-term treatment with twice-daily aclidinium was well tolerated, with
no clinically meaningful differences in safety profiles between the two doses and a greater magnitude of improvement in bronchodilation observed with the 400 μg dose compared with the lower dose. Improvements in lung function, observed as early as the first day of aclidinium treatment, were accompanied by improvements in health status and reductions in rescue medication use that were generally maintained throughout the 1-year study. These results thus support the use of twice-daily aclidinium 400 μg as an effective new maintenance treatment option for patients with COPD.

Conflict of interest

This work was funded by Forest Research Institute, Inc. (FRI), a wholly owned subsidiary of Forest Laboratories, Inc., and by Almirall, S.A. Arthur Gelb has served in an advisory position to Forest and received funding for clinical trials sponsored by Forest, Almirall, GSK, Boehringer Ingelheim, Pfizer, and Novartis in the recent past. Donald Tashkin has served as an advisor to and received clinical research funding from Forest, Boehringer Ingelheim, AstraZeneca, Novartis, Merck, Pearl Therapeutics, Mylan, Sunovion and Elevation, served as a consultant to Theravance, received additional research funding from GlaxoSmithKline, and served as a speaker for Forest, Boehringer Ingelheim, Pfizer, AstraZeneca, Novartis and Mylan. Barry Make received payment for service on the advisory boards of Forest Pharmaceuticals, AstraZeneca, Novartis, Merck, Boehringer Ingelheim, Pfizer, Ikaria, and GlaxoSmithKline, consulting fees from Astellas Pharma, and Talecris Biotherapeutics, lecture fees from GlaxoSmithKline, Boehringer Ingelheim, Pfizer, and Forest Pharmaceuticals, payment for video presentation preparation from Boehringer Ingelheim and Pfizer, payment for document reviews from Spiration, and grant support from the National Heart, Lung, and Blood Institute, AstraZeneca, GlaxoSmithKline, Pfizer, Nabi Biopharmaceuticals, Boehringer Ingelheim, Forest, and Sunovion. Esther Garcia Gil is an employee of Almirall, S.A. Xiaoyun Zhong and Cynthia Caracta are employees of FRI. Editorial assistance by Joy Ramos, PhD of Prescott Medical Communications Group, Chicago, IL was funded by FRI. There are no other financial disclosures/conflicts of interest.

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References


