EFFICACY AND SAFETY OF TWICE-DAILY ACLIDINIUM BROMIDE IN COPD PATIENTS: THE ATTAIN STUDY

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**ABSTRACT:** The efficacy and safety of two doses of aclidinium bromide were evaluated in patients with moderate to severe COPD.

In this 24-week, double-blind trial, patients were randomised to twice-daily aclidinium (200 µg or 400 µg) or placebo. The primary efficacy endpoint was change in trough forced expiratory volume in 1 second (FEV₁) at Week 24. Other endpoints included peak FEV₁, health status (St George’s Respiratory Questionnaire; SGRQ) and dyspnoea (Transitional Dyspnoea Index; TDI).

Overall, 828 patients were randomised. At Week 24, significant improvements from baseline were observed with aclidinium 200 µg and 400 µg versus placebo for trough FEV₁ (99 and 128 mL; both p<0.0001) and peak FEV₁ (185 and 209 mL; both p<0.0001). Peak FEV₁ improvements on Day 1 were comparable with Week 24. Aclidinium 200 µg and 400 µg produced significant improvements over placebo in baseline-adjusted mean SGRQ total score (-3.8 and -4.6 units; p<0.001 and <0.0001) and TDI focal score (0.6 and 1.0 units; p<0.05 and <0.001) at Week 24. With both aclidinium doses, the incidence of anticholinergic adverse events was low and similar to placebo.

Twice-daily aclidinium significantly improved bronchodilation, health status and dyspnoea, and was well tolerated in patients with COPD.

**KEYWORDS:** Anticholinergic, bronchodilation, dyspnoea, exacerbations, health status, long-acting muscarinic antagonist
INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an increasing public health problem that imposes a considerable burden in terms of morbidity, mortality and healthcare costs worldwide [1]. Although not curable, COPD is treatable, with bronchodilator therapy being central to the symptomatic management of the disease [2, 3].

Aclidinium bromide, a novel, inhaled long-acting muscarinic antagonist compound with low systemic activity, has been developed for the treatment of COPD. Initially, aclidinium was investigated as a once-daily drug. In Phase III studies, once-daily aclidinium 200 µg significantly improved trough forced expiratory volume in 1 second (FEV₁) in patients with COPD versus placebo [4], but this improvement was below the suggested minimum clinically important difference (MCID) of 100-140 mL [5, 6]. Therefore, additional clinical studies were conducted to investigate twice-daily (BID) aclidinium. A 2-week, crossover study showed that aclidinium 400 µg BID provided 24-hour bronchodilation that was statistically and clinically significant compared with placebo [7]. Subsequently, a 12-week, Phase III study (ACCORD COPD I) with aclidinium 200 µg and 400 µg BID reported significant improvements over placebo in bronchodilation, health status and COPD symptoms [8].

This paper presents results from a Phase III study of longer duration (ATTAIN), which assessed the efficacy and safety of aclidinium 200 µg and 400 µg BID versus placebo over 24 weeks in patients with moderate to severe COPD.
METHODS

**Study subjects**

Male and female patients aged ≥40 years were included if they were current or former cigarette smokers with a smoking history of ≥10 pack-years and had a diagnosis of COPD according to Global Initiative for Chronic Obstructive Lung Disease criteria [2] (post-bronchodilator FEV₁/forced vital capacity (FVC) ratio of <70% and FEV₁ <80% of the predicted value). Patients had to demonstrate good technique during lung function assessments according to American Thoracic Society/European Respiratory Society criteria [9].

Key exclusion criteria were: history or current diagnosis of asthma; respiratory tract infection or COPD exacerbation within 6 weeks (3 months if hospitalisation was required) before screening or during the run-in period; clinically relevant respiratory conditions other than COPD; unstable cardiac conditions including myocardial infarction within the previous 6 months; contraindications to the use of anticholinergic drugs.

Inhaled salbutamol was permitted as needed, but was discontinued 6 hours before and during study visits. The following concomitant medications were allowed if their administration had been stable for ≥4 weeks before screening: inhaled corticosteroids or oral sustained-release theophyllines; systemic corticosteroids at doses equivalent to 10 mg/day of prednisone or 20 mg every other day; oxygen therapy (<15 hours/day).

This study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation/Good Clinical Practice Guidelines and local regulations. The protocol was approved by an independent ethics committee at
each centre before study initiation. All patients gave written informed consent. The study was registered with ClinicalTrials.gov with identifier NCT01001494.

**Study design**

This was a double-blind, randomised, placebo-controlled, parallel-group Phase III study conducted in nine European countries and South Africa. Following screening and a 2-week run-in period to assess disease stability, patients were randomised (1:1:1) to receive aclidinium 200 µg, aclidinium 400 µg or placebo BID for 24 weeks. All study treatments were administered via a multiple-dose dry powder inhaler (Genuair®)*.

A sample size of 244 patients per treatment arm was estimated to provide at least 90% power to detect a difference of 90 mL in trough FEV$_1$ between the aclidinium arms and placebo at Week 24 with a two-sided 5% level of significance, assuming a standard deviation of 240 mL and adjusting for multiple treatment comparisons. The sample size provided sufficient power to detect treatment differences in the secondary endpoints.

**Measurements**

Standardised [9] spirometric measurements (FEV$_1$, FVC and inspiratory capacity [IC]) were conducted before the morning dose on Day 1 (baseline) and during visits at Weeks 1, 4, 8, 12, 18 and 24. Additionally, FEV$_1$ and FVC measurements were obtained at 0.5, 1, 2 and 3 hours post-dose and IC measurements at 3 hours post-dose on Day 1 and Weeks 1, 4, 12 and 24. IC was measured using an inspiratory manoeuvre to total lung capacity from stable tidal breathing [9]. All study centres had identical spirometry equipment, a detailed study manual and training. Spirometry data
were electronically transmitted to a data-management centre for quality review and only technically adequate measurements were accepted.

Health status was evaluated pre-dose at baseline and Weeks 4, 12 and 24 using the St George’s Respiratory Questionnaire (SGRQ). Dyspnoea was assessed at baseline using the Baseline Dyspnoea Index (BDI) and changes were measured using the Transitional Dyspnoea Index (TDI) at Weeks 4, 12 and 24. The BDI and TDI were administered by an independent reviewer before study procedures.

Patients recorded COPD symptoms and relief medication use daily in an electronic diary; concomitant medications were recorded by the patient in a paper diary. At each visit, COPD exacerbations were identified by the investigator by reviewing records of COPD symptoms, use of daily relief medication and concomitant medications. COPD exacerbations were defined as an increase in COPD symptoms over at least two consecutive days, resulting in the increased use of short-acting bronchodilators and/or inhaled corticosteroids (mild exacerbation), treatment with antibiotics and/or systemic corticosteroids (moderate exacerbation), or hospitalisation (severe exacerbation).

Safety was assessed by adverse-event (AE) monitoring, clinical laboratory data, blood pressure and 12-lead electrocardiograms.

**Statistical analysis**

The primary efficacy endpoint was the change from baseline in morning pre-dose (trough) FEV$_1$ at Week 24. Secondary endpoints were the change from baseline in peak FEV$_1$ (highest FEV$_1$ value observed within 3 hours after morning dosing) at Week 24 and the percentages of patients achieving clinically significant improvements in SGRQ total score and TDI focal score at Week 24. For US
regulatory requirements, trough and peak FEV₁ values at Week 12 were also assessed as primary and secondary endpoints, respectively.

Efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all patients who took ≥1 dose of study medication and had a baseline and ≥1 post-baseline FEV₁ assessment. Missing data were imputed using last observation carried forward (LOCF). For spirometry data, linear interpolation and time-matched LOCF were applied. Changes from baseline in lung function parameters and SGRQ and TDI scores were evaluated using analysis of covariance (ANCOVA), with treatment group and sex as factors and age and baseline value as covariates. The percentages of patients with clinically significant improvements in SGRQ (decrease of ≥4 units [10]) and TDI (increase of ≥1 unit [11]) scores were analysed using logistic regression with treatment group, sex, age and baseline value as covariates. Use of relief medication was analysed using normal scores ANCOVA, with treatment group and sex as factors and age and corresponding normal score baseline as covariates. An annualised rate of COPD exacerbations was calculated using Poisson regression with correction for over-dispersion with treatment group, sex and baseline COPD severity as factors and age as a covariate. Logistic regression, including treatment group and baseline COPD severity as covariates, was used to analyse the percentage of patients with ≥1 COPD exacerbation. Safety outcomes were analysed descriptively for the safety population, defined as patients who received ≥1 dose of study medication.
RESULTS

Patient characteristics

Of the 828 randomised patients, 819 patients were included in the ITT and safety populations. Figure 1 shows patient disposition. Baseline demographics and disease status were similar across treatment groups (Table 1).

Efficacy

Lung function

At Week 24, aclidinium 200 µg and 400 µg produced significant improvements from baseline in mean±standard error (SE) trough FEV\textsubscript{1} compared with placebo (by 99±22 mL and 128±22 mL, respectively; p<0.0001 for both; Figure 2). For both aclidinium doses, the improvement in trough FEV\textsubscript{1} was statistically superior to placebo at all measured timepoints from Week 1 to Week 24, ranging from 77 mL (Week 12) to 105 mL (Week 18) for aclidinium 200 µg and from 105 mL (Week 12) to 140 mL (Week 18) for aclidinium 400 µg (Figure 2; Table 2).

Mean±SE peak FEV\textsubscript{1} significantly improved from baseline with aclidinium 200 µg and 400 µg versus placebo at Week 24 (by 185±23 mL and 209±24 mL, respectively; p<0.0001 for both; Figure 3). At Week 12, the corresponding improvements were 182±21 mL and 191±21 mL, respectively (p<0.0001 for both). The improvement in peak FEV\textsubscript{1} provided by both aclidinium doses was statistically superior to placebo at all timepoints from Day 1 to Week 24 (Figure 3; Table 2). Following the first dose of aclidinium, the increase in peak FEV\textsubscript{1} over placebo on Day 1 (187 mL, 400 µg) was comparable to that seen at study end (209 mL, 400 µg). The mean post-dose time to
peak FEV$_1$ was <2 h for aclidinium 200 µg and 400 µg at all timepoints except for Day 1 (127 and 126 minutes, respectively).

Both aclidinium doses resulted in significant improvements over placebo in FVC and IC values throughout the study (Table 2). Numerically greater improvements in trough FVC and trough IC were observed with the 400 µg versus 200 µg dose at all timepoints; these improvements were statistically significant (p<0.05) at Weeks 1, 8, 12 and 18 for trough FVC and at Weeks 1, 12 and 18 for trough IC. Aclidinium 400 µg also produced numerically greater improvements versus aclidinium 200 µg in peak FVC at all timepoints except Week 12; these improvements were statistically significant (p<0.05) at Weeks 1 and 24.

**Health status**

Significantly greater improvements from baseline in mean SGRQ total score were observed with both aclidinium doses versus placebo at all timepoints, except Week 4 with aclidinium 200 µg (Figure 4). By Week 24, the improvement over placebo in baseline-adjusted mean±SE SGRQ total score was -3.8±1.1 units for aclidinium 200 µg (p<0.001) and -4.6±1.1 units for aclidinium 400 µg (p<0.0001). More patients had a clinically significant improvement in SGRQ total score (≥4 units) at Week 24 with aclidinium 200 µg and 400 µg compared with placebo (56.0% and 57.3% versus 41.0%; odds ratio 1.83 and 1.87; p<0.001 for both).

**Dyspnoea and relief medication use**

Both aclidinium doses provided significantly greater improvements from baseline in TDI focal score compared with placebo at all timepoints, except Week 12 for aclidinium 200 µg (Figure 5). The improvement over placebo in baseline-adjusted mean±SE TDI focal score at Week 24 was 0.6±0.3 units for aclidinium 200 µg
(p<0.05) and 1.0±0.3 unit for aclidinium 400 µg (p<0.001). More patients treated with aclidinium 200 µg and 400 µg had a clinically significant improvement in TDI focal score (≥1 unit) at Week 24 compared with placebo (53.3% and 56.9% versus 45.5%; odds ratio 1.47 and 1.68; p<0.05 and <0.01, respectively).

Over 24 weeks, the mean total daily use of relief medication was significantly reduced from baseline with aclidinium 200 µg (by 0.61 puffs/day; p=0.0002) and aclidinium 400 µg (by 0.95 puffs/day; p<0.0001) compared with placebo. The percentage of days without the need for relief medication over 24 weeks was significantly increased over placebo by 11% for both doses of aclidinium (p<0.001 for both).

**COPD exacerbations**

The rate of exacerbations of any severity was lower with aclidinium 200 µg and 400 µg versus placebo (0.43 and 0.40 versus 0.60 per patient per year, respectively). Compared with placebo, the rate ratio with aclidinium 200 µg was 0.72 (95% confidence interval [CI] 0.52-0.99; p<0.05) and 0.67 (95% CI 0.48-0.94; p<0.05) with aclidinium 400 µg. The frequency of moderate or severe exacerbations was also lower for aclidinium 200 µg and 400 µg versus placebo (0.35 and 0.34 versus 0.47 per patient per year, respectively), but the rate ratios did not reach statistical significance (0.74 [95% CI 0.53-1.04] and 0.72 [95% CI 0.51-1.02]; p=0.08 and p=0.06, respectively).

**Safety**

The percentage of patients with at least one treatment-emergent AE was similar for placebo, aclidinium 200 µg and aclidinium 400 µg (57.1%, 54.5% and 53.5%, respectively). Table 3 shows AEs reported by ≥2% of patients in any treatment group.
Potential anticholinergic AEs occurred with an incidence of <1% in any treatment group and were reported at a similar or lower incidence in the aclidinium 200 µg and 400 µg groups compared with placebo, except for urinary tract infection (0.7%, 2.2% and 0.7%, respectively). The percentage of patients reporting dry mouth was low and similar in each group (placebo: 0.4%; aclidinium 200 µg: 0.7%; aclidinium 400 µg: 0.4%).

The percentage of patients experiencing a serious AE (SAE) was similar across the three groups (placebo: 5.5%; aclidinium 200 µg: 4.3%; aclidinium 400 µg: 5.6%). The most common SAE by preferred term was COPD exacerbation, which was reported by 3.7%, 1.4% and 0.7% of patients in the placebo, aclidinium 200 µg and aclidinium 400 µg groups, respectively. Other preferred terms were reported as SAEs by no more than one patient in any treatment group. No SAEs were considered by the local investigator to be related to study medication. Three patients died during the study; one each in the placebo (road traffic accident), aclidinium 200 µg (myocardial infarction) and aclidinium 400 µg (acute cardiac failure) groups. None of the deaths were thought to be related to treatment.

No clinically relevant changes from baseline in laboratory parameters or blood pressure were observed in any group. The mean changes from baseline in 12-lead electrocardiogram parameters were generally small, with no apparent treatment- or dose-related trend: two patients (placebo: n=1; aclidinium 200 µg: n=1) had a QT interval corrected for heart rate using the Fridericia formula (QTcF) of >500 ms, and five patients (placebo: n=2; aclidinium 200 µg: n=3) had a change in QTcF of >60 ms.
DISCUSSION

This study showed that, in patients with moderate to severe COPD, aclidinium 200 µg or 400 µg BID significantly improved lung function assessments over 24 weeks compared with placebo. The improvement in trough FEV₁ with aclidinium 400 µg was 128 mL at Week 24. Improvements in trough FEV₁ with aclidinium 400 µg ranged from 105 (Week 12) to 140 mL (Week 18) throughout the study, which is consistently within the proposed MCID of 100-140 mL [6, 12]. However, the improvement in trough FEV₁ with aclidinium 200 µg was lower, ranging from 77 mL (Week 12) to 105 mL (Week 18). Aclidinium 400 µg also showed numerically greater improvements over the 200 µg dose for FVC, IC and peak FEV₁ values. This is one of the first bronchodilator trials to report IC. For both aclidinium doses, the improvement in peak FEV₁ on Day 1 was comparable with Week 24.

Improving health status and relieving symptoms are important goals in the management of stable COPD [2]. As the relationship between these outcomes and changes in FEV₁ is poor, it is important to measure directly the effect of treatment on health status and symptoms [12]. At 24 weeks, the mean improvement with aclidinium 400 µg versus placebo exceeded the MCID for SGRQ total score and equalled the MCID for TDI focal score. Such large improvements in SGRQ score are reported relatively rarely in clinical trials. With both aclidinium doses, approximately 15% more patients had an improvement that exceeded the SGRQ MCID compared with placebo. For the TDI score, 8% and 11% more patients exceeded the MCID with aclidinium 200 µg and 400 µg, respectively, compared with placebo. These improvements are likely to translate into a noticeable benefit for patients and clinicians in routine clinical practice.
In the placebo arm, FEV₁ response declined during the study, whereas SGRQ total score and TDI focal score improved. A similar lack of concordance between FEV₁ and SGRQ has been observed in numerous other bronchodilator studies [13].

This study was not powered for exacerbations and the population was not enriched by recruiting patients with a history of frequent exacerbations, as reflected by the modest exacerbation rate in the placebo group. Despite the low rate of exacerbations, both aclidinium doses significantly reduced the rate of exacerbations of any severity compared with placebo. However, these results need to be confirmed in adequately powered trials. There was a similar trend in reduced rates for moderate or severe exacerbations in a second, similar, Phase III study [8].

Aclidinium 200 µg and 400 µg BID for 24 weeks was well tolerated, with no differences between the safety profiles of the two doses. The incidence of anticholinergic AEs in both aclidinium groups was low and similar to placebo. Moreover, no serious anticholinergic AEs occurred in any of the study arms. The low incidence of anticholinergic AEs reported with aclidinium is consistent with earlier studies, which showed that aclidinium is rapidly hydrolysed in human plasma into inactive metabolites [14, 15].

Overall, both aclidinium BID doses significantly improved bronchodilation, health status, COPD symptoms and exacerbations (any severity). The study was not powered to detect statistically significant differences between doses. However, the 400 µg dose consistently demonstrated numerically greater efficacy compared with the 200 µg dose and produced clinically significant improvements in lung function, health status and symptoms that were not observed with the lower dose. The range of improvement in trough FEV₁ observed with aclidinium 400 µg over the study period (105-140 mL) was comparable with results from 6- to 12-month studies of tiotropium, in which
improvements ranged from 120 to 150 mL [16–19]. This is consistent with observations from an earlier Phase II study, in which aclidinium 400 µg BID produced 24-hour bronchodilation that was similar to tiotropium 18 µg once-daily [7]. The improvement in trough FEV₁ with aclidinium 400 µg in the present study was also similar to that observed with the same dose in a previous 12-week, Phase III study (124 mL at study end) [8]. The 12-week study showed clinically significant improvements in dyspnoea with aclidinium 400 µg; the improvements in health status were statistically but not clinically significant, which may be because the study duration was not long enough for clinical significance to be reached. As both aclidinium doses had a similar safety profile, the risk-benefit profile appears to support aclidinium 400 µg as the appropriate dose for treatment.

In conclusion, given the sustained bronchodilatory effect and low rate of anticholinergic effects, aclidinium BID may be an effective new LAMA treatment option for patients with stable moderate or severe COPD, with the risk-benefit profile favouring the 400 µg dose.

Acknowledgements

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References


# Table 1. Baseline demographics and disease status

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<thead>
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<th></th>
<th>Placebo (n=273)</th>
<th>Acldinium 200 µg BID (n=277)</th>
<th>Acldinium 400 µg BID (n=269)</th>
<th>Total (n=819)</th>
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<td>of puffs)</td>
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<td>(%)</td>
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<td>Aclidinium 400 µg BID (n=269)</td>
<td>Total (n=819)</td>
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<td>Others**</td>
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<td>35.4</td>
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Data are presented as mean (SD) unless otherwise stated.

*As classified by the Global Initiative for Chronic Obstructive Lung Disease.

**Systemic corticosteroids, influenza vaccine, oxygen, leukotrienes, or SABA + ICS.

BDI, Baseline Dyspnoea Index; BID, twice daily; COPD, chronic obstructive pulmonary disease;
FEV₁, forced expiratory volume in 1 s; SD, standard deviation; SGRQ, St George’s Respiratory Questionnaire; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting β₂-agonist; SAMA, short-acting muscarinic antagonist.
Table 2. Baseline-adjusted mean differences between aclidinium and placebo in lung function parameters at all timepoints over 24 weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Aclidinium 200 µg BID</th>
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<tr>
<td>Trough FEV₁, mL</td>
<td>77-105†</td>
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<tr>
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<tr>
<td>Trough FVC, mL</td>
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<td>184-224‡</td>
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<tr>
<td>Peak FVC, mL</td>
<td>242-276‡</td>
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<td>Trough IC, mL</td>
<td>57-70*</td>
<td>109-133‡</td>
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*\(p<0.05; \)†\(p\leq0.0002; \)‡\(p\leq0.0001; \)§\(p<0.0001\)

Data are reported as the minimum and maximum values over the treatment period; the indicated p-values apply over the entire range.

BID, twice daily; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity
Table 3. Adverse events reported by ≥2% of patients in any treatment group (safety population)

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>No. of patients (%)</th>
<th>Placebo (n=273)</th>
<th>Aclidinium 200 µg BID (n=277)</th>
<th>Aclidinium 400 µg BID (n=269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD exacerbations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>22</td>
<td>(8.1)</td>
<td>30</td>
<td>(10.8)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>23</td>
<td>(8.4)</td>
<td>32</td>
<td>(11.6)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>7</td>
<td>(2.6)</td>
<td>4</td>
<td>(1.4)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>3</td>
<td>(1.1)</td>
<td>5</td>
<td>(1.8)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6</td>
<td>(2.2)</td>
<td>1</td>
<td>(0.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>(3.3)</td>
<td>5</td>
<td>(1.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>5</td>
<td>(1.8)</td>
<td>7</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Toothache</td>
<td>1</td>
<td>(0.4)</td>
<td>3</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>10</td>
<td>(3.7)</td>
<td>12</td>
<td>(4.3)</td>
</tr>
<tr>
<td>Influenza</td>
<td>6</td>
<td>(2.2)</td>
<td>3</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6</td>
<td>(2.2)</td>
<td>5</td>
<td>(1.8)</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>2</td>
<td>(0.7)</td>
<td>6</td>
<td>(2.2)</td>
</tr>
</tbody>
</table>
infection

| Dyspepsia | 6 (2.2) | 5 (1.8) | 1 (0.4) |

BID, twice daily; COPD, chronic obstructive pulmonary disease.
**Figure legends**

**Figure 1.** Patient disposition.

![Figure 1](image)

*Note: nine patients from one centre were counted as randomised only due to missing baseline data; therefore, the numbers of patients who completed or discontinued treatment do not add up to the total number randomised

**Figure 2.** Change from baseline in trough FEV₁ over 24 weeks.
Data reported as least squares mean (standard error).
*p<0.0001 for both treatments vs placebo.
There were no statistically significant differences between the two aclidinium arms.
BID, twice daily; FEV₁, forced expiratory volume in 1 second.

**Figure 2.** Trough FEV₁ response (mL).

**Figure 3.** Change from baseline in peak FEV₁ over 24 weeks.
**Figure 4.** Change from baseline in SGRQ total score over 24 weeks.

*Figure 4*

![Graph showing change from baseline in SGRQ total score over 24 weeks.]

*Placebo BID, Acldinium 200 μg BID, Acldinium 400 μg BID*

*Treatment week*

*Change from baseline in SGRQ total score*

*p<0.01; **p<0.001 vs placebo*

*Data reported as least squares mean (standard error)*

*BID, twice daily; SGRQ, St George’s Respiratory Questionnaire*

*Values on or below the dotted line represent clinically significant improvement*

**Figure 5.** Change from baseline in TDI focal score over 24 weeks.
Figure 5

Change from baseline in TDI focal score

Data reported as least squares mean (standard error)

*p<0.05; **p<0.01, ***p<0.001 vs placebo

BID, twice daily; TDI, Transitional Dyspnoea Index

Values on or above the dotted line represent clinically significant improvement

Data: Placebo BID
Aclidinium 200 µg BID
Aclidinium 400 µg BID

0.6 unit
1.0 unit
0 4 8 12 16 20 24
0 0.5 1.0 1.5 2.0 2.5
Change from baseline in TDI focal score
Treatment week