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ORIGINAL RESEARCH

Efficacy and Safety of Aclidinium Bromide Compared with Placebo and Tiotropium in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease: Results from a 6-week, Randomized, Controlled Phase IIIb Study

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Abstract

Background: **This randomized, double-blind, Phase IIIb study evaluated the 24-hour bronchodilatory efficacy of aclidinium bromide versus placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD).** ***Methods:*** **Patients received aclidinium 400 µg twice daily (morning and evening), tiotropium 18 µg once daily (morning), or placebo for 6 weeks. The primary endpoint was change from baseline in forced expiratory volume in 1 second area under the curve for the 24-hour period post-morning dose (FEV_1 $AUC_{0–24}$) at week 6. Secondary and additional endpoints included FEV_1 $AUC_{12–24}$, COPD symptoms (EXAcerbations of chronic pulmonary disease Tool-Respiratory Symptoms [E-RS] total score and additional symptoms questionnaire), and safety.** ***Results:*** **Overall, 414 patients were randomized and treated (FEV_1 1.63 L [55.8% predicted]). Compared with placebo, FEV_1 $AUC_{0–24}$ and FEV_1 $AUC_{12–24}$ were significantly increased from baseline with aclidinium (Δ = 150 mL and 160 mL, respectively; $p < 0.0001$) and tiotropium (Δ = 140 mL and 123 mL, respectively; $p < 0.0001$) at week 6. Significant improvements in E-RS total scores over 6 weeks were numerically greater with aclidinium ($p < 0.0001$) than tiotropium ($p < 0.05$) versus placebo. Only aclidinium significantly reduced the severity of early-morning cough, wheeze, shortness of breath, and phlegm, and of nighttime symptoms versus placebo ($p < 0.05$). Adverse-event (AE) incidence (28%) was similar between treatments. Few anticholinergic AEs (<1.5%) or serious AEs (<3%) occurred in any group.** ***Conclusions:*** **Aclidinium provided significant 24-hour bronchodilation versus placebo from day 1 with comparable efficacy to tiotropium after 6 weeks. Improvements in COPD symptoms were consistently numerically greater with aclidinium versus tiotropium. Aclidinium was generally well tolerated.**

Keywords: 24-hour, bronchodilation, long-acting muscarinic antagonist, nighttime, symptoms

Clinical trial registration: This trial was registered on clinicaltrials.gov (NCT01462929).

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Introduction

Circadian variation in lung function, driven in part by changes in cholinergic tone, has been documented in patients with chronic obstructive pulmonary disease (COPD) (1–3). Variation in COPD daily symptoms has also been reported, with the most severe symptoms generally experienced in the morning followed by during the nighttime (4, 5). Consequently, the importance of identifying and managing early-morning symptoms is generally accepted. However, unlike in asthma where variation in lung function

and symptoms has been better characterized, the clinical relevance of nighttime symptoms can sometimes be underestimated in COPD and a lack of routine assessment means they can be under-reported (6). As symptoms throughout the day impact on patient quality of life (5), maintaining significant bronchodilation and symptom control over 24 hours should be an important goal of therapy.

Inhaled bronchodilatory therapies, including long-acting β_2-agonists and long-acting muscarinic antagonists (LAMAs), are central to COPD management (7); however, until recently, tiotropium bromide was the only available agent in the LAMA class (2, 8). Aclidinium bromide is a LAMA that has recently been approved as a maintenance bronchodilator treatment for patients with COPD (9, 10). In a Phase IIa study, twice-daily (BID) treatment with aclidinium 400 μg was demonstrated to provide significant improvements in 24-hour bronchodilation versus placebo that were generally similar to once-daily (QD) treatment with tiotropium 18 μg after 2 weeks, although significant differences in favor of aclidinium were observed for the nighttime period (11).

The Phase IIIb study reported in this paper was conducted to confirm the 24-hour bronchodilatory efficacy of aclidinium versus placebo and tiotropium over a longer treatment period (6 weeks) and in a larger population. The effects of treatment on COPD symptoms, inhaler preference, and safety were also evaluated in this Phase IIIb study.

Methods

Study design and treatment

This randomized, double-blind, double-dummy, placebo- and active comparator-controlled, multicenter Phase IIIb study was conducted in the Czech Republic, Germany, Hungary, and Poland between October 2011 and March 2012 (clinicaltrials.gov identifier NCT01462929).

Following screening and a 2- to 3-week run-in period, during which disease stability was assessed, patients were randomized (2:2:1) via an interactive voice-response system and computer-generated schedule to receive aclidinium bromide 400 μg (metered dose; equivalent to aclidinium 322 μg delivered dose) BID in the morning and evening via the Genuair®/Pressair™ multidose dry powder inhaler, tiotropium 18 μg QD in the morning via the HandiHaler®, or placebo for 6 weeks.

Two Genuair inhalers (pre-loaded with 1 month's supply [60 doses] of either aclidinium or matched placebo) and one HandiHaler (with 60 capsules of tiotropium or matched placebo) were supplied. To maintain blinding, patients were instructed to use both inhalers each morning (9:00 ± 1 hour) and Genuair only each evening (21:00 ± 1 hour). Patients and study personnel remained blinded to treatment allocation throughout the study. Training on the correct use of the inhalers was provided at screening and before randomization on day 1.

Relief medication (salbutamol pressurized metered-dose inhaler 100 μg/puff) was provided for additional symptom control as needed (except ≤6 hours before each visit). Patients were permitted to continue stable use of oral sustained-release theophylline (use of other methylxanthines was not permitted), inhaled corticosteroids, and oral or parenteral corticosteroids (prednisone ≤10 mg/day or 20 mg/every other day, or equivalent), except ≤6 hours before each visit. Oxygen therapy (except ≤2 hours before each visit) was allowed.

The study was approved by an independent ethics committee at each site and was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization and Good Clinical Practice. Patients provided written informed consent before participating in any study procedures.

Patients

Eligible patients were aged ≥40 years with a clinical diagnosis of stable moderate-to-severe COPD (post-bronchodilator forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] <70%, and FEV_1 ≥30% and <80%) (12) and were either current or former cigarette smokers (smoking history of ≥10 pack-years). Patients with a history or current diagnosis of asthma or other clinically significant respiratory or cardiovascular conditions were excluded, as were those who had experienced any respiratory tract infection or COPD exacerbation ≤6 weeks before screening (≤3 months if exacerbation resulted in hospitalization), or for whom the use of muscarinic antagonists was contraindicated. Additional relevant exclusion criteria included hypersensitivity to inhaled muscarinic antagonists and inability to use the study inhalers properly.

Patients could be discontinued from the study at any time at their own request or in the event of ineligibility, non-compliance, lack of efficacy, loss to follow-up, safety concerns (including moderate or severe COPD exacerbation), or any other reason at the investigator's discretion.

Study Assessments

Lung function

Lung function was assessed over 24 hours following morning treatment on day 1 and at week 6. FEV_1 and FVC were measured using procedures and spirometers that met European Respiratory Society (ERS) and American Thoracic Society (ATS) standards (13). Three manoeuvres were performed at each time point to provide three measurements that met ATS/ERS acceptability and repeatability criteria. Additional measurements could be made (up to a total of eight tests) if the first three were not acceptable.

The primary endpoint was change from baseline in normalized FEV_1 area under the curve over the 24-hour period post-morning dose (AUC_{0-24}) at week 6 (tiotropium administered QD in the morning; aclidinium administered BID in the morning and evening).

Change from baseline in normalized FEV_1 AUC over the nighttime period ($AUC_{12–24}$) at week 6 was the secondary endpoint. Changes from baseline in normalized FEV_1 AUC for the 12-hour period post-morning treatment ($AUC_{0–12}$), morning pre-dose (trough) and peak FEV_1 and FVC were additional endpoints.

COPD daily symptoms and relief medication use

Patients completed the 14-item EXAcerbations of Chronic pulmonary disease Tool (EXACT) each evening before bedtime (recall period of 'today') via electronic diaries. Responses to 11 of 14 EXACT questions that captured changes in specific respiratory symptoms (grouped into breathlessness, cough and sputum, and chest symptom domains) were used to calculate an EXACT-Respiratory Symptoms (E-RS) (14) total score (range 0–40; a higher score indicates more severe symptoms).

An additional COPD symptoms questionnaire (developed by the study sponsor) was completed by patients each morning via electronic diaries to capture the severity of early-morning and nighttime symptoms (5-point scale: 1 = 'did not experience symptoms'; 5 = 'very severe'), and individual morning symptoms of cough, wheeze, shortness of breath, and phlegm (5-point scale: 0 = 'no symptoms'; 4 = 'very severe symptoms'), as well as limitation of morning activities (5-point scale: 1 = 'not at all'; 5 = 'a very good deal') and frequency of nocturnal awakenings as a result of COPD symptoms. Relief medication use was also recorded daily via electronic diaries.

Inhaler preference and willingness to continue

After 6 weeks, overall inhaler preference and preference based on a number of specific inhaler attributes were assessed. Patients were first asked "which inhaler do you prefer?" (Genuair, HandiHaler, or no preference) then, "which device do you prefer in terms of the following attributes: ease of use, convenience, ease of learning to use, ease of holding, ease of operating, ease of preparation of the dose, and feedback to indicate correct inhalation?" Willingness to continue using each inhaler was also rated on a scale from 0 = 'not willing' to 100 = 'definitely willing'.

Safety

Adverse events (AEs) were recorded throughout the study and assessed for severity and relationship to study treatment by the investigator. Other safety assessments included a physical examination and vital signs measurement at screening and week 6.

Statistical Analysis

A target population of approximately 405 patients was planned to provide a sample size of 385 patients, taking into account a 5% dropout rate. This provided >90% power to detect a 130 mL difference between aclidinium and placebo for the primary and secondary endpoints, and >80% power to detect a 70 mL difference between aclidinium and tiotropium for the secondary endpoint, with a two-sided significance level of $p < 0.05$. Assumptions about treatment group differences were made based on observations from the previous Phase IIa study that compared the 24-hour bronchodilatory efficacy of aclidinium with placebo and tiotropium (11).

Efficacy analyses were based on the intent-to-treat population, which included all treated patients (≥1 dose) who had ≥1 baseline and post-baseline FEV_1 value. Endpoints were assessed using an analysis of covariance model with treatment and sex as factors, and age and baseline values as covariates. Between-group least squares mean differences and 95% confidence intervals were calculated for all treatment-group comparisons. The primary and secondary endpoint analyses were conducted in a stepwise manner to control for multiplicity: for FEV_1 $AUC_{0–24}$, the primary comparison was aclidinium versus placebo; for FEV_1 $AUC_{12–24}$, the primary comparison was aclidinium versus placebo, and the secondary comparison was aclidinium versus tiotropium. Other comparisons were considered additional.

Inhaler preference was summarized descriptively and the percentage of patients preferring Genuair was assessed using an exact binomial test. Willingness to continue inhaler use was assessed using an analysis of variance. Safety analyses included all treated patients (safety population) and were descriptive in nature.

Results

Patients

Of 485 patients screened, 414 patients from 41 sites (2.7% from 3 sites in the Czech Republic, 49.5% from 20 sites in Germany, 10.6% from 5 sites in Hungary, and 37.2% from 13 sites in Poland) were randomized, treated, and included in the study analyses, and 400 completed the study (Figure 1). The discontinuation rate was slightly higher in the placebo group (5.9%) compared with the aclidinium (2.9%) or tiotropium (2.5%) groups. In the placebo group, reasons for discontinuation were AEs and lack of efficacy, whereas in the aclidinium and tiotropium groups, reasons for discontinuation were AEs and patient's personal request (Figure 1). No patients were lost to follow-up. Treatment compliance, as assessed by the investigator based on information provided in patients' electronic diaries and the Genuair dose indicator or number of tiotropium pierced capsules, was 94.1%, 98.2%, and 96.8% in the placebo, aclidinium, and tiotropium groups, respectively.

Demographics and baseline characteristics were similar across treatment groups, with the exception of higher proportions of male patients in the aclidinium and tiotropium groups than in the placebo group (Table 1). Mean post-bronchodilator percent predicted FEV_1 at screening (adjusted for gender-related differences) was similar in each treatment group but, reflective of the higher proportion of male patients in the active treatment groups, mean

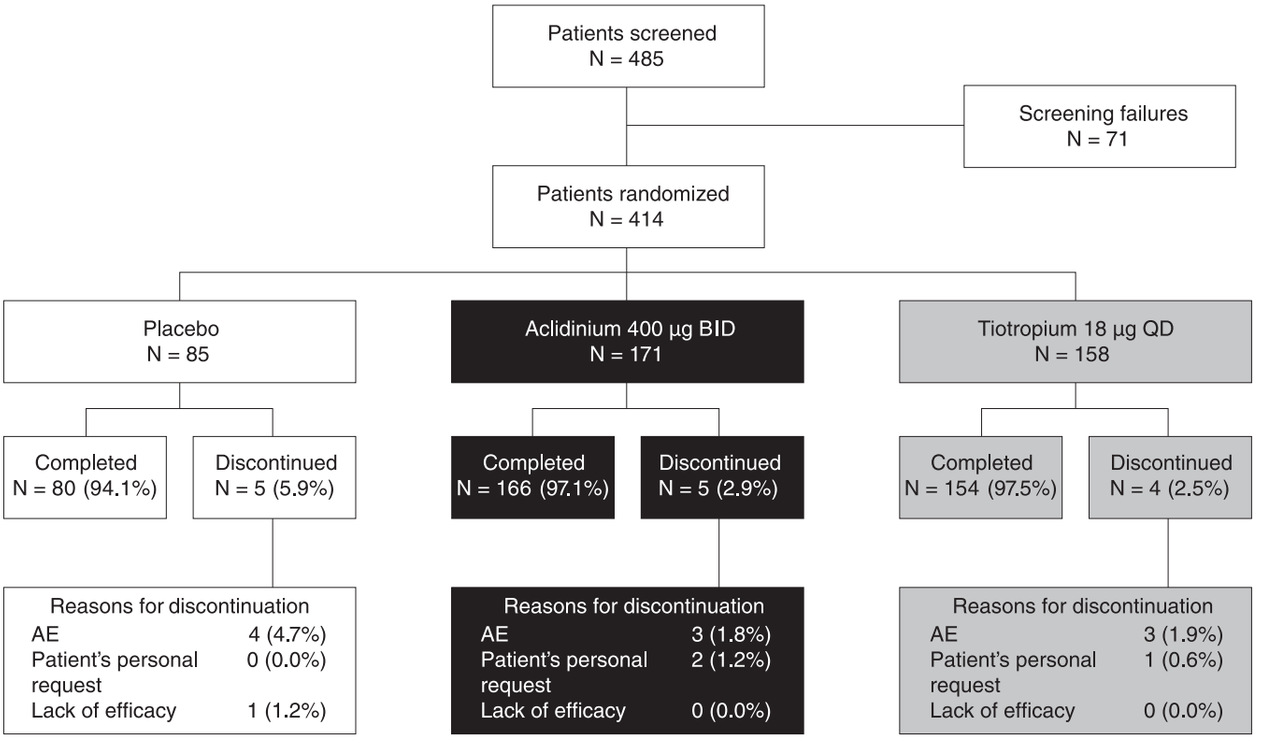

Figure 1. Patient disposition. AE, adverse event; BID, twice daily; QD, once daily.

FEV_1 was slightly higher in these groups versus the placebo group. In total, 86.7% of patients had used COPD medications prior to the start of the study. Anticholinergic therapies (LAMA, short-acting muscarinic antagonist [SAMA], or short-acting β-2 agonist plus SAMA) had been used by 25.6%, 18.8%, and 5.3% of patients, respectively.

Table 1. Demographics and baseline characteristics of the study population (safety population)

	Placebo (N = 85)	Aclidinium 400 µg BID (N = 171)	Tiotropium 18 µg QD (N = 158)
Gender (male), n (%)	48 (56.5)	114 (66.7)	116 (73.4)
Age (years), mean (SD)	62.2 (8.2)	61.8 (8.2)	62.8 (7.9)
Race, n (%)			
White	84 (98.8)	171 (100)	158 (100)
Asian	1 (1.2)	0 (0)	0 (0)
BMI (kg/m^2), mean (SD)	26.7 (4.9)	27.5 (4.9)	27.6 (4.8)
Current smoker, n (%)	47 (53.3)	93 (54.4)	84 (53.2)
Smoking consumption (pack-years), mean (SD)	39.6 (15.4)	41.5 (22.4)	45.0 (21.8)
COPD duration (years), mean (SD)	9.6 (6.7)	8.8 (5.9)	8.2 (6.0)
Post-bronchodilator FEV_1 (L)			
Mean (SD)	1.57 (0.52)	1.61 (0.50)	1.67 (0.54)
% predicted, mean (SD)	55.5 (11.8)	55.8 (13.3)	56.0 (13.2)
COPD severity,[a,b] n (%)			
Moderate	58 (68.2)	108 (63.2)	104 (66.2)
Severe	27 (31.8)	63 (36.8)	53 (33.8)

[a]GOLD Stage II (moderate): $FEV_1/FVC < 0.70$, and post-bronchodilator $FEV_1 \geq 50\%$ and $< 80\%$ predicted; GOLD Stage III (severe): $FEV_1/FVC < 0.70$, and post-bronchodilator $FEV_1 \geq 30\%$ and $< 50\%$ predicted.
[b]COPD severity was missing for one patient in the tiotropium treatment group at screening (pre- and post-salbutamol values determined to be unacceptable following review).
BID, twice daily; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; QD, once daily; SD, standard deviation.

Lung function

On day 1 of treatment, both aclidinium and tiotropium improved 24-hour, nighttime, and day time bronchodilation, as demonstrated by statistically significant increases in FEV_1 $AUC_{0–24}$, FEV_1 $AUC_{12–24}$, and FEV_1 $AUC_{0–12}$ from baseline versus placebo ($p < 0.001$; Figure 2A). Improvements in FEV_1 AUC_{0-24} and FEV_1 $AUC_{12–24}$ were significantly greater with aclidinium versus tiotropium ($p < 0.05$ and $p < 0.01$, respectively) on day 1.

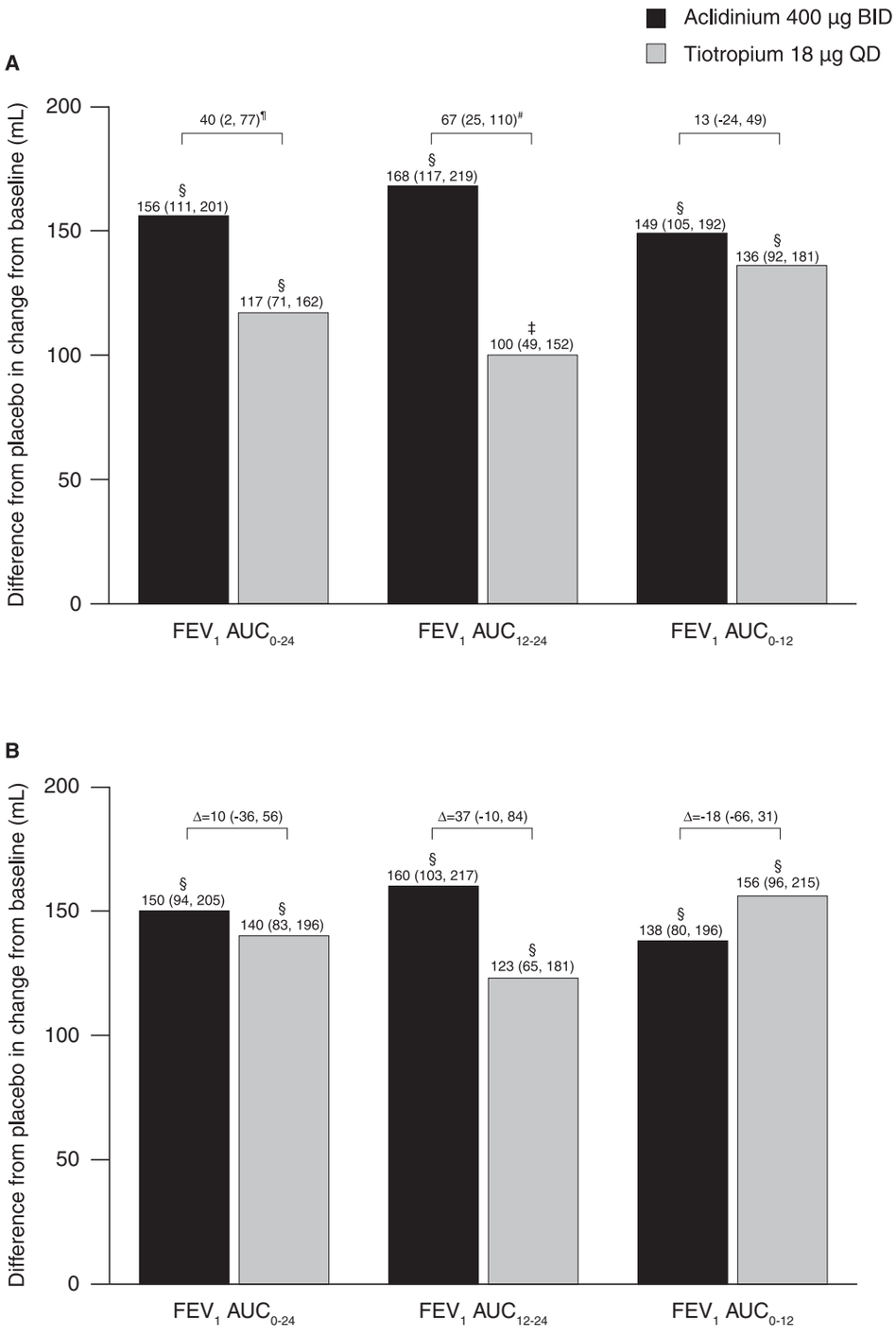

Figure 2. Change from baseline in FEV_1 $AUC_{0–24}$, FEV_1 $AUC_{12–24}$, and FEV_1 $AUC_{0–12}$ compared with placebo (A) on day 1 and (B) at week 6 (ITT population). Data reported as LS mean (95% CI) differences from placebo (ANCOVA). ‡$p < 0.001$; §$p < 0.0001$ for aclidinium or tiotropium versus placebo. ¶$p < 0.05$; #$p < 0.01$ for aclidinium versus tiotropium. ANCOVA, analysis of covariance; AUC, area under the curve; $AUC_{0–24}$, AUC over the 24-hour period post-morning treatment; $AUC_{12–24}$, AUC over the nighttime period; $AUC_{0–12}$, AUC for the 12-hour period post-morning treatment; BID, twice daily; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; ITT, intent-to-treat; LS, least squares; QD, once daily.

In the primary endpoint analysis, FEV_1 $AUC_{0–24}$ was significantly improved with aclidinium compared with placebo at week 6 ($p < 0.0001$; Figure 2B). Compared with placebo, tiotropium also significantly increased FEV_1 $AUC_{0–24}$ from baseline to week 6 ($p < 0.0001$; Figure 2B); the effects of aclidinium and tiotropium over 6 weeks were similar.

Over 6 weeks, FEV_1 $AUC_{12–24}$ and FEV_1 $AUC_{0–12}$ were also significantly increased from baseline with both aclidinium and tiotropium versus placebo ($p < 0.0001$) (Figure 2B). Although the improvement in FEV_1 $AUC_{12–24}$ was numerically greater with aclidinium versus tiotropium, and the improvement in FEV_1 $AUC_{0–12}$ was numerically greater with tiotropium versus aclidinium, there were no significant differences between active treatments ($p = 0.12$ and $p = 0.48$, respectively).

Both aclidinium and tiotropium produced significant increases from baseline in FEV_1 versus placebo at each observation time point from 15 minutes to 24 hours post-dose on day 1 and at week 6 (Figure 3). Both aclidinium and tiotropium also significantly improved morning pre-dose (trough) and peak FEV_1 and FVC compared with placebo on day 1 and at week 6 (Table 2). Improvements were numerically greater with aclidinium versus tiotropium, with significant differences in favor of aclidinium for trough FEV_1 and FVC on day 1.

COPD Symptoms and Relief Medication Use

Over 6 weeks, E-RS total scores were significantly reduced from baseline with both aclidinium ($p < 0.0001$) and tiotropium ($p < 0.05$) versus placebo (Figure 4). Improvements in individual domain scores were numerically greater with aclidinium than tiotropium, and the improvement for cough and sputum was significant versus placebo for aclidinium only ($p < 0.05$). Comparisons of aclidinium versus tiotropium yielded no significant differences.

The severity of early-morning symptoms, overall, was significantly reduced over 6 weeks with aclidinium ($p < 0.001$) and tiotropium ($p < 0.05$) versus placebo (Figure 5A); the difference between active treatments was not statistically significant. Only aclidinium produced significant improvements in individual early-morning symptoms of phlegm, shortness of breath, wheeze, and cough compared with placebo at week 6. Nighttime symptom severity was significantly reduced from baseline over 6 weeks with aclidinium versus placebo but not with tiotropium versus placebo (Figure 5B); the difference between active treatments was not statistically significant. There were no significant changes from baseline in number of nocturnal awakenings in any treatment group. Limitation of activity caused by COPD symptoms was also significantly reduced from baseline over 6 weeks with aclidinium versus placebo but not with tiotropium versus placebo (Figure 5). This improvement in limitation of activity was significantly greater for aclidinium versus tiotropium ($p < 0.05$).

Over 6 weeks, there was a significant increase in relief medication-free days with aclidinium and tiotropium versus placebo (difference of 9.6% and 8.9%, respectively; $p < 0.05$).

Inhaler preference

When asked "which device do you prefer?" at week 6, significantly more patients overall preferred Genuair to HandiHaler (80.1% vs 10.7%; $p < 0.0001$). The option of 'no preference' was chosen by 9.2% of patients. Additionally, >75% of patients preferred Genuair to HandiHaler for each of the individual inhaler attributes assessed (Table 3). Inhaler preference appeared to be independent of whether active medication or placebo was administered via the inhalers: when the aclidinium, tiotropium, and placebo groups were analyzed separately, ≥79% of patients preferred Genuair compared with ≤13% who preferred HandiHaler in each group. Patients were more willing to continue using Genuair than HandiHaler, as indicated by a significant difference in mean ratings at week 6 (88.8 vs 45.4; $p < 0.0001$).

Safety

AE incidence was similar in the placebo (25.9%), aclidinium (27.5%), and tiotropium (29.7%) groups. Nasopharyngitis and headache were most common, each reported by 5.1% of patients overall. Nasopharyngitis occurred more frequently with aclidinium and tiotropium versus placebo (5.8% and 5.7% vs 2.4%, respectively); headache occurred more frequently with aclidinium than with either placebo or tiotropium (7.0% vs 3.5% and 3.8%, respectively). Other common AEs (≥2% of patients overall) were COPD exacerbation (2.4%) and cough (2.2%). The majority of AEs were mild or moderate in intensity. There were few serious AEs (1.7% overall) and no deaths. In total, 8 patients (1.9%) discontinued due to AEs, with COPD exacerbation being the most common cause (n = 2 in each treatment group). No AEs resulting in discontinuation were considered to be treatment-related.

With the exception of dry mouth, which was reported by three patients (0.7%) in total (aclidinium n = 1; tiotropium n = 2), no other treatment-related AEs occurred in >1 patient overall. The incidence of potentially anticholinergic AEs was similarly low across treatment groups (<1.5% in any group). Only dry mouth, pharyngitis (placebo n = 1; aclidinium n = 1; tiotropium n = 2), and constipation (tiotropium n = 2) occurred in >1 patient in any group. No potentially anticholinergic AEs were serious or led to discontinuation. There were no clinically significant physical examination or vital signs findings.

Discussion

This Phase IIIb study was designed to evaluate the 24-hour bronchodilatory efficacy of aclidinium 400 μg BID in patients with moderate-to-severe COPD. Findings from our primary endpoint analysis of change from baseline in FEV_1 $AUC_{0–24}$ after 6 weeks of treatment

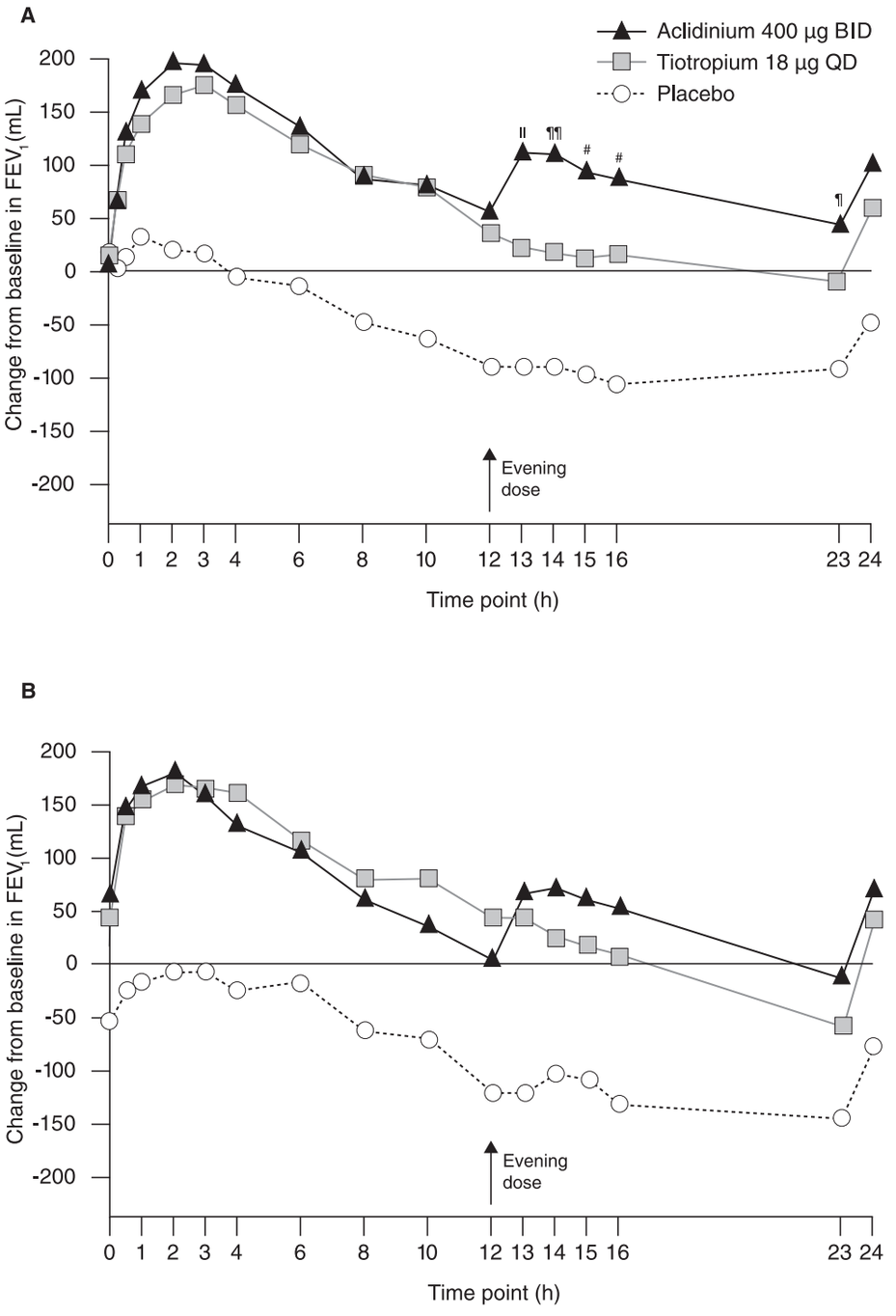

Figure 3. Change from baseline in FEV_1 over 24 hours (A) on day 1 and (B) at week 6. Data reported as LS mean change from baseline (ANCOVA). $p < 0.01$ for aclidinium and tiotropium versus placebo at each time point. ¶$p < 0.05$; #$p < 0.01$; ‖$p < 0.001$; ¶¶$p < 0.0001$ for aclidinium versus tiotropium. ANCOVA, analysis of covariance; BID, twice daily; FEV_1, forced expiratory volume in 1 second; LS, least squares; QD, once daily.

demonstrated a statistically significant improvement with aclidinium versus placebo, and changes from baseline in trough FEV_1 with aclidinium exceeded the proposed minimally important difference for this parameter (100–140 mL) (15, 16). Furthermore, aclidinium significantly improved day time and nighttime bronchodilation over placebo. These findings are consistent with an earlier 15-day Phase IIa cross-over study (n = 30) that also evaluated 24-hour bronchodilation with aclidinium versus placebo and tiotropium, although a larger difference between aclidinium and placebo for the change from baseline in FEV_1 $AUC_{0–24}$ (232 mL) was reported previously, potentially as a result of differences in trial design and duration (11).

Also consistent with previous findings are the numerically greater improvements in nighttime bronchodilation

Table 2. Change from baseline (difference from placebo) in additional lung-function variables (ITT population)

	Aclidinium 400 µg BID (N = 171)	Tiotropium 18 µg QD (N = 158)	Δ (aclidinium vs tiotropium)
Morning pre-dose (trough) FEV_1 (mL)			
Day 1	141[§]	93[‡]	48[¶]
Week 6	141[§]	102[‡]	38
Peak FEV_1 (mL)			
Day 1	154[§]	139[§]	14
Week 6	180[§]	172[§]	8
Morning pre-dose (trough) FVC (mL)			
Day 1	212[§]	127[†]	84[¶]
Week 6	223[§]	144[†]	79
Peak FVC (mL)			
Day 1	201[§]	146[§]	54
Week 6	212[§]	170[†]	42

Data reported as LS mean differences from placebo (ANCOVA).
[†]$p < 0.01$; [‡]$p < 0.001$; [§]$p < 0.0001$ for aclidinium or tiotropium versus placebo.
[¶]$p < 0.05$ for aclidinium versus tiotropium.
ANCOVA, analysis of covariance; BID, twice daily; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ITT, intent-to-treat; LS, least squares; QD, once daily.

Table 3. Patient preference for each inhaler based on specific inhaler attributes at week 6, n (%)

	No. of patients (%)		
Attribute	Genuair	HandiHaler	No preference
Ease of use	357 (86.7)	37 (9.0)	18 (4.4)
Convenience	360 (87.4)	32 (7.8)	20 (4.9)
Ease of learning to use	326 (79.1)	33 (8.0)	53 (12.9)
Ease of holding	329 (79.9)	35 (8.5)	48 (11.7)
Ease of operating	334 (81.1)	38 (9.2)	40 (9.7)
Ease of dose preparation	356 (86.4)	32 (7.8)	24 (5.8)
Feedback to indicate correct inhalation	314 (76.2)	39 (9.5)	59 (14.3)

For all attributes, $p < 0.0001$ for Genuair versus HandiHaler (exact binomial test).

achieved with aclidinium versus tiotropium in this study, with statistically significant improvements favoring aclidinium on day 1 of treatment. These day 1 findings may be explained by differences in the pharmacokinetics of aclidinium and tiotropium, whereby aclidinium reaches steady state more quickly than tiotropium (17, 18). After 6 weeks of treatment, the 24-hour bronchodilatory efficacy of aclidinium and tiotropium was considered to be comparable.

Many patients with COPD experience early-morning or nighttime peaks in symptom severity (5). Although as many as 80%–90% of patients experience nighttime symptoms (19) and sleep disturbance (6), there is a lack of therapeutic options for their management. To date, a small number of studies have evaluated the efficacy of bronchodilatory therapies to improve nighttime lung function and/or sleep quality with mixed findings (2, 20–23). For example, a 6-week study in patients with stable COPD found that evening dosing of tiotropium did not result in improved nighttime bronchodilation compared with morning dosing (2).

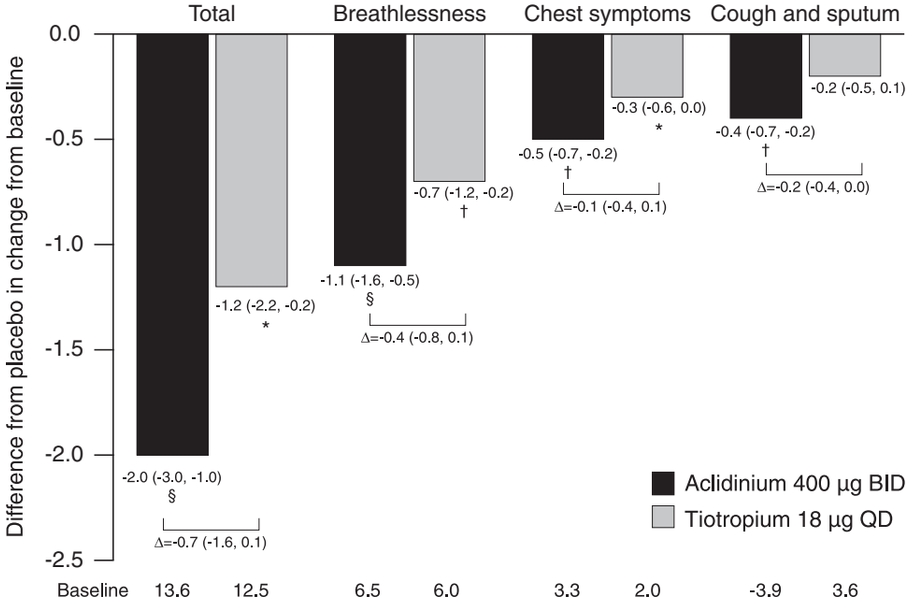

Figure 4. Change from baseline in E-RS total and domain scores over 6 weeks. Data reported as LS mean (95% CI) difference from placebo (ANCOVA). *$p < 0.05$; [†]$p < 0.01$; [§]$p < 0.0001$ for aclidinium or tiotropium versus placebo. ANCOVA, analysis of covariance; BID, twice daily; CI, confidence interval; E-RS, EXAcerbations of Chronic pulmonary disease Tool (EXACT)-Respiratory Symptoms; LS, least squares; QD, once daily.

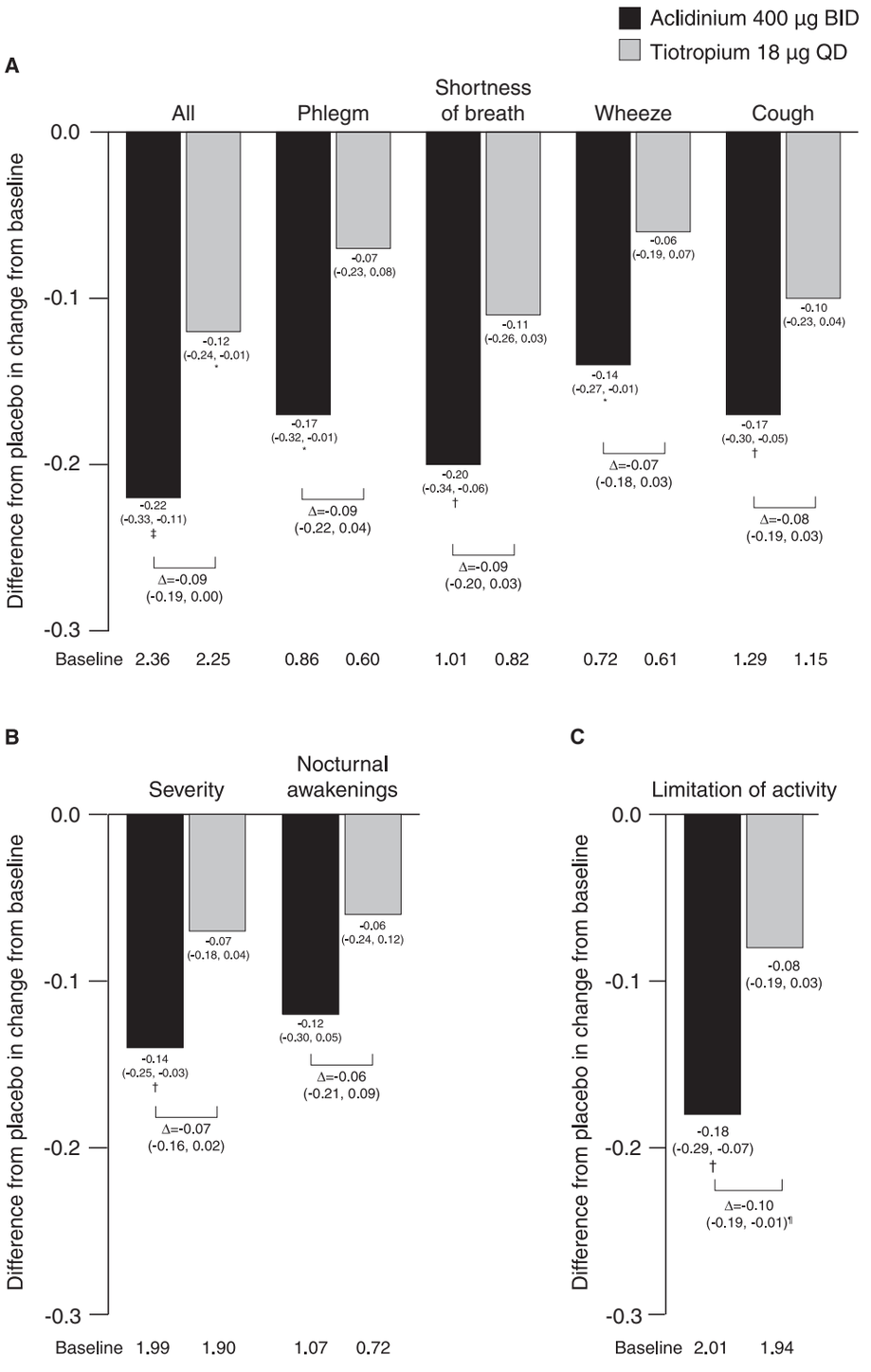

Figure 5. Difference from placebo in change from baseline in (A) severity of early-morning symptoms, (B) severity of nighttime symptoms and number of nocturnal awakenings due to COPD symptoms, and (C) limitation of activity caused by COPD symptoms (COPD additional symptoms questionnaire) over 6 weeks (ITT population). Data reported as LS mean differences from placebo (ANCOVA). *$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ for aclidinium or tiotropium versus placebo. ¶$p < 0.05$ for aclidinium versus tiotropium. Severity of overall early-morning and nighttime symptoms rated on a 5-point scale from 1 = 'did not experience any symptoms' to 5 = 'very severe'; individual morning symptoms rated on a 5-point scale from 0 = 'no symptoms' to 4 = 'very severe'; limitation of activity rated on a 5-point scale from 1 = 'not at all' to 5 = 'a very good deal'. ANCOVA, analysis of covariance; BID, twice daily; COPD, chronic obstructive pulmonary disease; ITT, intent-to-treat; LS, least squares; QD, once daily.

Additionally, reduced daily variation in lung function and improved nighttime oxygen saturation achieved with evening administration of tiotropium in a separate 4-week study in patients with severe COPD did not translate into improved sleep quality (21). Conversely, four-times-daily treatment with ipratropium (a SAMA) has been shown to improve oxygen saturation and sleep quality over 4 weeks in patients with moderate-to-severe COPD (20).

The impact of treatment with aclidinium on sleep quality has not been evaluated in a sleep laboratory setting; however, it has been demonstrated to improve health status and early-morning and nighttime symptoms, and to reduce the frequency of nocturnal awakenings in Phase III studies (ATTAIN and ACCORD COPD I) (24–27). In the present study, changes in COPD daily symptoms following BID dosing of aclidinium and QD dosing of tiotropium compared with placebo were assessed using the E-RS tool (14, 28), and an additional symptoms questionnaire (currently undergoing validation), that was developed by the sponsor in the absence of a validated tool to capture the severity and impact of early-morning and nighttime symptoms.

Our results suggest that aclidinium provides statistically significant improvements in early-morning and nighttime symptoms compared with placebo that were consistently numerically greater than those observed with tiotropium. Improvements in nighttime symptom severity were significantly different versus placebo for aclidinium only, which could suggest that the numerical advantage of aclidinium over tiotropium for greater nighttime bronchodilation may translate into statistically significant changes in patient-reported outcomes. Furthermore, only aclidinium significantly reduced the limitation of activity caused by COPD symptoms compared with placebo. This is the first report of this therapeutic effect with a LAMA but should, along with the other COPD additional symptoms findings, be interpreted with some caution given the generally mild symptoms that patients reported at baseline, the small magnitude of the reductions observed, and the as yet unvalidated state of this tool.

The trend towards greater symptomatic improvement with aclidinium over tiotropium observed in this study may be related to differences in dosing frequency. However, while a second evening dose of aclidinium may be beneficial in terms of improving nighttime and early-morning symptoms under clinical trial conditions, the potential disadvantages of BID versus QD dosing should also be considered. Findings from an observational study have suggested that treatment adherence among patients with COPD declines with increasing dosing frequency (29), but this appears to be a greater concern for three- and four-times-daily regimens, and there is a lack of evidence to support greater adherence to QD versus BID treatment in practice.

Furthermore, poor adherence to prescribed treatment in COPD is multifactorial: it can also be influenced by perceived efficacy of treatment, side effects, number of concomitant medications, patient understanding, inhaler satisfaction or preference, and a number of other issues (30–32). Due to the double-blind, double-dummy design of this study, adherence to tiotropium QD compared with aclidinium BID could not be assessed but may be of interest for future work.

Although not powered for this purpose, patients' preference for Genuair compared with HandiHaler was assessed as an additional endpoint in this study and our findings were consistent with those of a previous study that reported greater preference for, greater satisfaction with, and fewer errors with, Genuair versus HandiHaler after 2 weeks' daily practice with placebo-containing devices (33).

However, in contrast with the previous study, patients inhaled both aclidinium and placebo through Genuair, and both tiotropium and placebo via HandiHaler in the present study. Patients were not asked to consider perceived efficacy when indicating their preferred device and preference for Genuair was maintained regardless of whether it was used to deliver placebo or aclidinium.

Finally, aclidinium was generally well tolerated over 6 weeks in this study, with a similar safety profile to tiotropium. Our findings are consistent with previous Phase III studies in terms of similar incidences of AEs and serious AEs in patients treated with aclidinium or placebo (24, 25). The potential for anticholinergic AEs, such as dry mouth, constipation, urinary retention, and cardiovascular events, is a risk associated with LAMAs.

Aclidinium, however, has been shown to undergo more rapid hydrolysis than tiotropium in human plasma (34, 35) and could, therefore, be considered to have the potential for fewer systemic side effects than tiotropium. Tiotropium has been associated with an increased risk of all-cause and cardiovascular-related mortality when administered via soft mist inhaler (36–38) but not when administered via HandiHaler (39).

In this 6-week study, the incidence of dry mouth, constipation, and other anticholinergic AEs (<1.5% for any event) was somewhat lower than has been observed in a pooled analysis of tiotropium safety data from 26 Phase III and IV studies (39), possibly as a result of the short trial duration and patients' previous exposure to tiotropium. The incidence of anticholinergic AEs was similarly low in the aclidinium treatment group, consistent with findings from other Phase III studies (24, 25).

Conclusions

These findings suggest that in patients with moderate-to-severe COPD, aclidinium 400 μg BID provides significant 24-hour bronchodilation compared with placebo from day 1 and over 6 weeks of treatment. At 6 weeks, the bronchodilatory effects of aclidinium and tiotropium are generally comparable. Aclidinium provides consistently numerically greater improvements in COPD symptoms, including early-morning and

nighttime symptoms, than tiotropium and is well tolerated, with a similar safety profile. Patients in this study preferred Genuair over HandiHaler for the administration of their inhaled medications.

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Declaration of Interest Statement

Jutta Beier has received consulting fees, speaker's fees, and travel expenses from Almirall. Anne-Marie Kirsten has received research grants from Almirall. Rosa Segarra, Ferran Chuecos, and Esther Garcia Gill are employees of Almirall and have stock/stock options in Almirall. Cynthia Caracta is an employee of Forest Research Institute. Robert Mróz declares that he has no conflicts of interest to disclose.

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The authors alone are responsible for the content and [AQ3] writing of the paper.

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