

ORIGINAL ARTICLE

Efficacy and safety of aclidinium bromide in patients with COPD: A phase 3 randomized clinical trial in a Korean population

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ABSTRACT

Background and objective: Aclidinium bromide ('aclidinium') is a novel, inhaled long-acting muscarinic antagonist. Therapeutic effects of aclidinium on chronic obstructive pulmonary disease (COPD) have been demonstrated in Caucasian populations in several clinical trials. This was a randomized, double-blind, multi-centre phase-3 clinical trial to evaluate the efficacy and safety of aclidinium in a Korean population.

Methods: A total of 263 Korean patients with moderate-to-severe COPD were randomized to receive aclidinium (400 µg, bd) (Genuai) or placebo via a dry-powder inhaler. The primary end point was change in trough forced expiratory volume in one second (FEV₁) at 12 weeks. Other lung function measurements, COPD exacerbation, health status (St George's Respiratory Questionnaire (SGRQ), dyspnoea (Transition Dyspnea Index (TDI) and safety were assessed throughout the study period.

Results: A significant improvement in trough FEV₁ from baseline was shown with aclidinium compared with the placebo (0.126 L, $P < 0.0001$). Significant improvements were also demonstrated in peak FEV₁ (0.190 L, $P < 0.0001$), SGRQ and TDI. Furthermore,

SUMMARY AT A GLANCE

This study demonstrated a favourable safety and efficacy profile of aclidinium bromide in Korean COPD patients that was similar to what was observed in Caucasian populations, suggesting no clinically significant ethnic difference.

aclidinium significantly reduced the prevalence of exacerbations (aclidinium, 5.4%; placebo, 15.6%, $P < 0.05$), and the duration of exacerbations was shorter compared with placebo (rate ratio: 0.27; $P < 0.05$). Aclidinium (400 µg) was well tolerated and the prevalence of adverse events was comparable with the placebo.

Conclusions: Inhaled aclidinium (400 µg) was shown to be safe and efficacious in Korean patients with moderate-to-severe COPD.

Clinical trial registration: NCT01636401 at Clinicaltrials.gov

Key words: aclidinium bromide, cholinergic antagonist, chronic obstructive pulmonary disease, safety, treatment outcome.

Abbreviations: ACCORD I and II trials, aclidinium to treat airway obstruction in COPD patients; AE, adverse events; ATTAIN, aclidinium in chronic obstructive respiratory disease I and II trials; BDI, Baseline Dyspnea Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; HR-QoL, health-related quality of life; IC, inspiratory capacity; ITT, intention-to-treat; M2/3 receptors, muscarinic receptor M2/M3; LOCF, last-observation-carried-forward; LSM, least square mean; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD), one of the primary causes of morbidity and mortality throughout the world, is growing in prevalence.¹ COPD is considered a treatable disease but is often under-diagnosed or undertreated.² The pathogenic features of COPD are characterized by the activation of the parasympathetic nervous system (the dominant pathway of bronchoconstriction and cholinergic tone), which primarily involves the reversibility of airway obstruction.³ Several inhaled muscarinic antagonists (e.g. ipratropium bromide, oxitropium bromide, tiotropium bromide) block muscarinic receptors and have demonstrated benefits in COPD patients, and so have become the mainstay of treatment.⁴

Aclidinium bromide (hereafter termed 'aclidinium') is a new type of inhaled long-acting muscarinic antagonist (LAMA), which demonstrates a long residence time at muscarinic receptor M3 (M3 receptors) and a shorter one at muscarinic receptor M2 (M2 receptors).⁵ Two phase-2 clinical studies have advocated the therapeutic use of aclidinium, which was initially suggested by preclinical studies^{6,7} and confirmed further by three pivotal phase-3 clinical trials, which demonstrated benefits on the overall lung function of COPD patients and health status with a tolerability profile compared with placebo.^{8–10} Aclidinium (400 µg) is approved in Europe and in the United States. Considering the fact that confirmatory phase-3 clinical studies were conducted mainly in Caucasian populations, the present study was designed to investigate the therapeutic benefit of aclidinium (400 µg, bd) in Korean patients with moderate-to-severe COPD.

METHODS

Study design

This was a phase-3, multi-centre (20 institutions in South Korea), randomized, double-blind, 12-week treatment, placebo-controlled study to investigate the safety and efficacy of aclidinium compared with a placebo in patients with moderate-to-severe COPD. This study comprised screening, a 2-week run-in period followed by a 12-week treatment period and a follow-up phone contact.

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was approved by the review board at each center.

Written informed consent was obtained from eligible patients who agreed to participate in this trial. This trial was registered in ClinicalTrials.gov (NCT01636401).

Patient population

Eligible subjects: (i) male or female patients aged ≥ 40 years; (ii) had a smoking history of ≥ 10 pack-years; and (iii) had been diagnosed with stable moderate-to-severe COPD according to guidelines set by the Global Initiative for Obstructive Lung Disease (GOLD).¹¹

The principal exclusion criteria were (i) COPD exacerbation requiring hospitalization in advance, within 3 months of screening; (ii) any respiratory tract infection or COPD exacerbation ≤ 6 weeks before screening; (iii) other clinically significant respiratory conditions; (iv) clinically significant cardiovascular conditions, including myocardial infarction within 6 months or newly diagnosed arrhythmia within 3 months before screening; and (v) history of hypersensitivity reactions or contraindications to inhaled anticholinergic agents.

Randomization

Eligible patients were allocated randomly to aclidinium (400 µg) or a placebo (Almirall SA, Barcelona, Spain) in a 1:1 ratio using an interactive Internet response system stratified by COPD severity at the baseline visit (visit 2). Devices containing aclidinium or the placebo had the same external appearance to ensure the double-blind nature of the trial. The randomization code was prepared by an independent contract research organization and remained blinded until study completion, unless otherwise predefined in the protocol.

Intervention

Patients received inhaled aclidinium (400 µg) or placebo twice daily for 12 weeks depending on the allocated treatment group. Use of salbutamol as rescue medication was allowed for acute relief of symptoms, with a 6-h washout period before each study visit. Theophylline, inhaled corticosteroids and oral/parenteral corticosteroids at ≤ 10 mg daily of prednisone or its corticosteroid equivalent were permitted if the treatment regimen was stable for ≥ 4 weeks before screening. Other inhaled anticholinergics and long-acting β_2 agonists were prohibited during the study.

Outcome assessments

The primary efficacy end point was a change from baseline in morning pre-dose (trough) forced expiratory volume in 1 s (FEV₁) at week 12. The secondary efficacy end point was peak FEV₁ (the highest FEV₁ value observed in the 3 h after morning dosing at 12 weeks). Additional spirometry end points included changes from baseline in trough FEV₁ (at weeks 1, 4 and 8) and in trough forced vital capacity (FVC) and inspiratory capacity (IC) (at weeks 1, 4, 8 and 12). Changes from the baseline, in the area under the curve from 0 h to 3 h, normalized over 3 h (AUC_{0–3 h}), for FEV₁ and FVC were also assessed at weeks 4 and 12.

Other efficacy variables were: St George's Respiratory Questionnaire (SGRQ) for assessment of health status; the Baseline Dyspnea Index (BDI) and the Transition Dyspnea Index (TDI) for dyspnoea evaluation; and COPD exacerbation. Changes in SGRQ (total score, three-dimension scores (symptom, activity and impact)) and TDI (focal score, three-dimension scores (functional impairment, magnitude of task and magnitude of effort)) and the

percentage of patients achieving clinically significant improvements in the SGRQ total score (defined as a decrease of ≥ 4 units) and TDI focal score (defined as an increase of ≥ 1 unit) at weeks 4, 8 and 12 were analysed.

COPD exacerbations were defined as an increase in COPD symptoms during ≥ 2 consecutive days and categorized by severity as 'mild' (self-management by patients at home by increasing rescue medication and/or inhaled corticosteroid), 'moderate' (treatment with antibiotics and/or systemic corticosteroids) and 'severe' (necessitating hospitalization).

Safety variables were adverse events (AE), results of clinical laboratory tests, vital signs, physical examinations and electrocardiograms.

Statistical analysis

A target population of 270 patients was estimated to provide $\geq 90\%$ power to detect a difference of 100 mL in trough FEV₁ between acclidinium and placebo at week 12 with a two-sided 5% level of significance assuming a standard deviation of 226 mL and taking into account a dropout rate of 20%.

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 who had a baseline and at least one post-baseline FEV₁ assessment. Safety results were summarized descriptively based on the study population comprised of all randomized patients who took ≥ 1 dose of study medication. Missing data were imputed by the last-observation-carried-forward (LOCF) approach. For spirometry data, linear interpolation and time-matched LOCF were applied. Primary outcome variables, changes from baseline in lung function parameters, SGRQ score and TDI score were

analysed using an analysis of covariance model with treatment group, gender and baseline COPD severity as factors, and corresponding baseline values and age as covariates. A logistic regression model was used to analyse the percentage of patients achieving clinically meaningful improvements from baseline in SGRQ total score or TDI focal score, and the number of patients with at least one COPD exacerbation. Time-to-first exacerbation was compared through a Cox proportional hazards model. A Poisson regression model was used to analyse the number of exacerbations per patient-year and number of exacerbation days per patient-year.

RESULTS

Patient demographics and baseline characteristics

A total of 339 patients were screened, and 263 were randomized between August 2012 and February 2013 (Fig. 1). Among these, 240 patients (91.3%) completed the study, and completion rates were similar across groups (placebo, 91.5%; acclidinium, 91.0%). A total of 262 patients who received more than one dose of study treatment were included in the study population. Of these patients, 257 patients were ITT population for efficacy analyses. Baseline demographics were shown to be similar between the groups (Table 1).

Lung function

Changes from baseline in trough FEV₁ at week 12 were greater for acclidinium versus placebo, with least square mean (LSM) treatment differences of 0.126 L

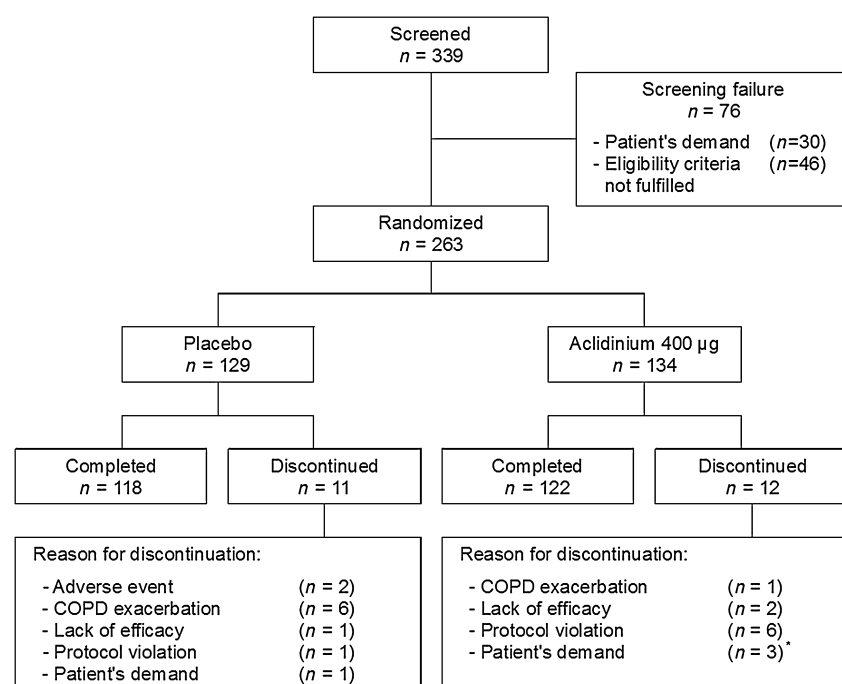


Figure 1 Flowchart of participants in the study following CONSORT diagram. *One patient withdrew the informed consent on the day of randomization without taking any study drug. COPD, chronic obstructive pulmonary disease.

Table 1 Baseline characteristics and demographics

Variable (Unit)	Placebo (<i>n</i> = 129)	Aclidinium 400 µg (<i>n</i> = 133)
Age, mean (SD), years	68.1 (7.5)	68.0 (7.1)
≥40–<60, <i>n</i> (%)	15 (11.6)	19 (14.3)
≥60–<70, <i>n</i> (%)	58 (45.0)	54 (40.6)
≥70, <i>n</i> (%)	56 (43.4)	60 (45.1)
Gender, Male, <i>n</i> (%)	129 (100.0)	128 (96.2)
Body mass index, Mean (SD), kg/m ²	23.1 (3.1)	23.2 (3.3)
Smoking consumption, Mean (SD), pack-years	42.5 (18.3)	39.4 (17.3)
COPD severity, <i>n</i> (%)		
Stage II (Moderate)	73 (56.6)	78 (56.6)
Stage III (Severe)	56 (43.4)	55 (41.4)
Pre-bronchodilator FEV ₁		
Mean (SD), L	1.393 (0.440)	1.408 (0.458)
Mean (SD), % of predicted	46.3 (12.5)	47.0 (12.2)
Post-bronchodilator FEV ₁		
Mean (SD), L	1.586 (0.428)	1.576 (0.464)
Mean (SD), % of predicted	52.8 (11.5)	52.7 (12.0)
SGRQ total score, Mean (SD)	33.1 (17.3)	34.2 (18.1)
BDI focal score, Mean (SD)	7.9 (2.0)	7.9 (1.9)

BDI, baseline dyspnea index; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

Table 2 Change from baseline in morning pre-dose (trough) FEV₁ (L) and other spirometry parameters at week 12 (ITT population)

Variable	Change from baseline (LSM (SE))		Treatment difference (LSM (95% CI))	<i>P</i> -value
	Placebo (<i>n</i> = 128)	Aclidinium 400 µg (<i>n</i> = 129)		
Trough FEV ₁	−0.068 (0.040)	0.057 (0.038)	0.126 (0.086, 0.165)	<0.0001
Peak FEV ₁	0.005 (0.043)	0.195 (0.040)	0.190 (0.148, 0.232)	<0.0001
AUC _{0–3} FEV ₁	0.097 (0.047)	0.311 (0.043)	0.214 (0.168, 0.259)	<0.0001
Trough FVC	−0.142 (0.075)	0.022 (0.070)	0.164 (0.092, 0.237)	<0.0001
Trough IC	−0.116 (0.063)	−0.0064 (0.058)	0.110 (0.048, 0.172)	0.0005

**P* < 0.0001. CI, confidence interval; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; IC, inspiratory capacity; ITT, intention to treat; LSM, least mean square; SE, standard error.

(95% CI: 0.086–0.165) over placebo (*P* < 0.0001) (Table 2). At all study visits, greater changes from baseline in trough FEV₁ in the acclidinium group were also observed over placebo (all visits, *P* < 0.0001) (Fig. 2). Aclidinium showed significant improvement in the change from baseline in peak FEV₁, with LSM treatment differences of 0.190 L (95% CI: 0.148–0.232) over placebo (*P* < 0.0001). Statistically meaningful improvements in normalized AUC_{0–3} FEV₁ were also observed at week 4 and week 12 compared with placebo with LSM treatment differences of 0.194 L and 0.214 L, respectively (*P* < 0.0001). The acclidinium group consistently provided greater improvements in all lung function outcomes versus placebo (Table 2).

Health status and other clinical outcomes

At all study visits, SGRQ total scores improved significantly from baseline with acclidinium. Changes from baseline in SGRQ at weeks 4, 8 and 12 with LSM treat-

ment differences were −3.9, −3.2 and −3.3 (all, *P* < 0.05), respectively (Fig. 3). Aclidinium-treated patients showed significant improvements over placebo in symptom and impact scores at all study visits (LSM treatment differences: symptom scores −4.0, −5.0 and −6.2; impact scores −4.6, −3.6 and −3.7) (all, *P* < 0.05). A trend to improvements in activity scores was observed in the acclidinium-treated group, but the differences were not statistically significant (LSM treatment difference: −2.4, −1.2 and −0.7 at weeks 4, 8, and 12) (all, *P* > 0.05). The percentage of patients who achieved the minimal clinically important difference in SGRQ total scores (i.e. ≥4-unit reduction) at the end of the study was significantly higher in the acclidinium group (53.5%) than placebo (37.0%) (*P* = 0.0162).

Aclidinium-treated patients showed significantly greater improvements over placebo in TDI scores from baseline at all study visits, with LSM treatment differences over placebo of 0.8, 0.8, and 0.7 at weeks 4,

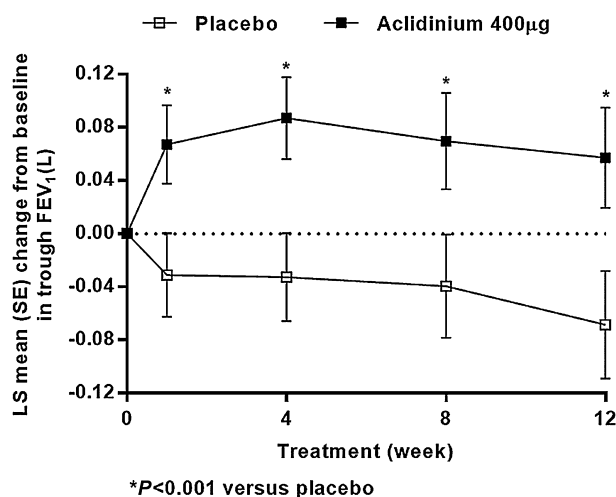


Figure 2 Least square mean change from baseline in morning pre-dose (trough) FEV₁ over 12 weeks. Data are presented as LSM ± SE. LSM, least square mean; SE, standard error.

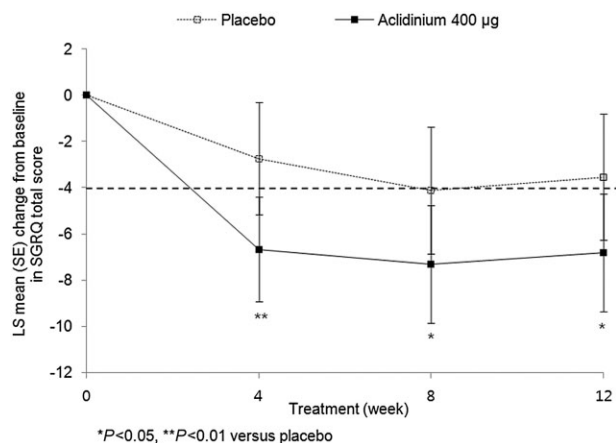


Figure 3 Least square mean change from baseline in SGQR total score over 12 weeks. Data are presented as LSM ± SE. Dash line represents clinically significant improvement. LSM, least square mean; SE, standard error; SGQR, St George's Respiratory Questionnaire.

8 and 12, respectively (all, $P < 0.05$) (Fig. 4). Significant improvements over placebo in functional impairment and magnitude of task were observed at all study visits (LSM treatment differences: functional impairment 0.3, 0.4, and 0.2; magnitude of task 0.3, 0.2, and 0.2) (all, $P < 0.05$). Improvements over placebo in magnitude of effort were observed at all study visits, and these differences were significant at week 4 and week 12 (all, $P < 0.05$).

At week 12, a higher proportion of patients who achieved the ≥ 1 -unit clinical improvement in TDI total scores were observed in the acclidinium group (47.7%) versus placebo (32.8%) ($P < 0.05$).

Significantly lower percentages of patients who experienced COPD exacerbations were observed with acclidinium (5.4%) compared with placebo (15.6%) ($P = 0.0105$). The proportion of patients who experi-

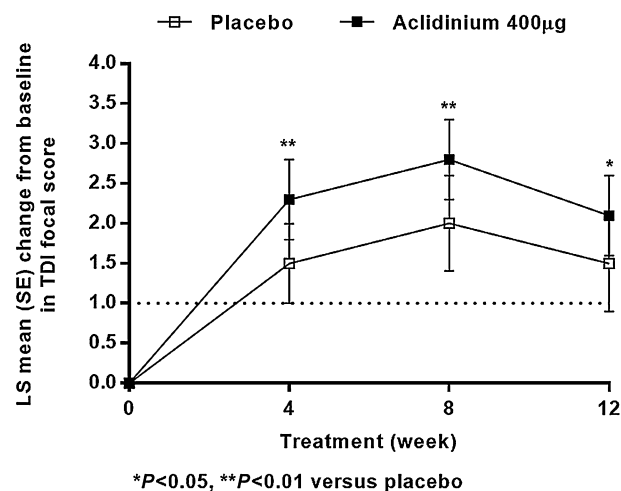


Figure 4 Least square mean change from baseline in TDI focal score over 12 weeks. Data are presented as LSM ± SE. Dash line represents clinically significant improvement. LSM, least square mean; SE, standard error; TDI, Transition Dyspnea Index.

enced moderate or severe exacerbations was lower in the acclidinium group than placebo (4.7% and 13.3%, respectively) (Table 3). In addition, the time-to-first moderate or severe COPD exacerbation was significantly delayed by acclidinium (hazard ratio, 0.3; 95% CI = 0.1–0.9; $P = 0.0229$). The number of COPD exacerbations per patient-year in the acclidinium group was significantly lower than in the placebo group (rate ratio: 0.30; $P = 0.0056$), and the duration of COPD exacerbation days per patient-year was shorter than in the placebo group (rate ratio: 0.27; $P < 0.0001$).

Safety

The overall prevalence of AE was similar in the acclidinium (39.1%) and placebo groups (50.4%). Placebo and acclidinium were well tolerated in general, with most AE being mild to moderate in severity. COPD exacerbation was the most common AE in all treatment groups (placebo, 15.5%; acclidinium, 6.8%). AE observed in $\geq 2\%$ of subjects in both groups were analysed and are presented in Table 4. One acclidinium-treated patient showed T-wave abnormalities which were reported as an adverse event, although not considered to be related to the study drug. The prevalence of AE related to the study drug was comparable across treatment groups (placebo, 2.3%; acclidinium, 3.8%). Anticholinergic AE such as thirst, dry mouth and dysuria were reported in the acclidinium group with a prevalence of only 1.5% and were not reported in the placebo group.

The prevalence of SAE was similar across treatment groups (placebo, 3.9%; acclidinium, 2.3%). The most common SAE in the placebo group were COPD exacerbation (three patients) followed by benign prostatic hyperplasia, gastric cancer and coronary artery disease ($n = 1$ for each SAE). In the acclidinium group, three patients experienced SAE (COPD exacerbation, fibular fracture and pyloric stenosis). None of the SAE

Table 3 Number (%) of patients with at least one COPD exacerbation during the study (ITT population)

Type of exacerbation, <i>n</i> (%)	Placebo (<i>n</i> = 128)	Aclidinium 400 µg (<i>n</i> = 129)	<i>P</i> -value [†]
Any exacerbation	20 (15.6)	7 (5.4)	0.0105
Number of patients by severity			
Mild	5 (3.9)	1 (0.8)	
Moderate	16 (12.5)	6 (4.7)	
Severe	1 (0.8)	0	

[†]*P*-value is obtained from logistic regression model for the number of patients with at least one COPD exacerbation with treatment group and baseline COPD severity as explanatory variables. COPD, chronic obstructive pulmonary disease; ITT, intention to treat.

Table 4 Number (%) of patients having at least 2% of adverse events

Preferred term	Placebo (<i>n</i> = 129)			Aclidinium 400 µg (<i>n</i> = 133)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Patients with at least one AE	32 (24.8)	31 (24.0)	2 (1.6)	32 (24.1)	19 (14.3)	1 (0.8)
COPD exacerbation	3 (2.3)	16 (12.4)	1 (0.8)	1 (0.8)	8 (6.0)	0
Upper respiratory tract infection	7 (5.4)	3 (2.3)	0	4 (3.0)	3 (2.3)	0
Cough	9 (7.0)	1 (0.8)	0	5 (3.8)	1 (0.8)	0
Nasopharyngitis	7 (5.4)	0	0	5 (3.8)	0	0
Productive cough	5 (3.9)	1 (0.8)	0	2 (1.5)	0	0
Sputum increased	3 (2.3)	0	0	3 (2.3)	0	0
Pharyngitis	1 (0.8)	2 (1.6)	0	0	2 (1.5)	0
Bronchitis	0	3 (2.3)	0	1 (0.8)	0	0
Headache	0	1 (0.8)	0	3 (2.3)	0	0
Joint sprain	0	0	0	3 (2.3)	0	0

Patients are counted only once within each preferred term. AE, adverse event; COPD, chronic obstructive pulmonary disease.

was regarded to be treatment related, and all of these SAE (excluding gastric cancer and coronary artery disease) were reversed without sequelae.

DISCUSSION

Long-acting bronchodilators are the first-line treatment for COPD,¹¹ with tiotropium bromide being the most commonly prescribed long-acting anticholinergic drug.^{12,13}

We evaluated the safety and efficacy of aclidinium, a novel inhaled LAMA, in moderate-to-severe COPD, and showed that aclidinium (400 µg) taken twice daily was effective and well tolerated in a Korean study population.

Improvements in trough FEV₁ and peak FEV₁ from baseline were significantly greater in the aclidinium group compared with placebo, with treatment differences of 0.126 L and 0.190 L, respectively. The magnitude of improvements was comparable with the aclidinium in chronic obstructive respiratory disease (ACCORD) I and aclidinium to treat airway obstruction in COPD patients (ATTAIN) trials, but larger than in the ACCORD II trial. This difference is presumably due to the randomization imbalance observed in the ACCORD II study, in which a higher percentage of patients with severe COPD were allocated to the 400-µg group.^{8–10}

In addition to improvements in lung function, aclidinium showed significant improvements in dyspnoea. Breathlessness is considered as the most debilitating symptom for patients with COPD.¹⁴ In the present study, breathlessness, as measured by TDI, was improved from baseline by aclidinium (400 µg) compared with placebo. At week 12, significantly higher percentages of patients who achieved the ≥1-unit clinical improvement in TDI scores were observed for aclidinium versus placebo (47.7% vs 32.8%), similar to the results reported in ACCORD I, ACCORD II and ATTAIN.^{8–10}

An improvement from baseline in health-related quality of life (HR-QoL) was noted in this study. SGRQ was applied to assess HR-QoL, and the percentage of patients who achieved a ≥4-unit decrease from baseline in SGRQ total scores was significantly higher in the aclidinium group than the placebo group (53.5% vs 37.0%). These findings are similar to those in the ACCORD I and ATTAIN studies but in contrast to results reported in ACCORD II.^{8–10} This difference is probably due to the unexpected increase in the SGRQ of the placebo in ACCORD II.⁹ In addition, significant reduction in acute exacerbations was observed with aclidinium versus placebo (rate ratio = 0.30, *P* = 0.0056), and it was in accordance with the data from previous pooled analysis based on Phase III studies in Caucasian population (rate ratio = 0.79, *P* < 0.05).¹⁵

Acclidinium was well tolerated in general, with most AE being mild to moderate in severity. The percentage of AE was comparable between groups (acclidinium 39.1% vs placebo 50.4%). The prevalence of anticholinergic AE was very low (<2%). These favourable safety and tolerability features of acclidinium may be due to rapid plasma hydrolysis of the drug, which contribute to a transient and low systemic exposure.^{5,16–18}

This is the first study to evaluate the safety and efficacy of acclidinium in Korean patients with COPD. The updated Declaration of Helsinki clearly indicates that a new drug should be compared with pre-existing treatments. Hence, it would be much better if this study included a tiotropium arm in addition to acclidinium and placebo. Unlike previous trials with acclidinium, the patients enrolled in this trial were predominantly male, which can be attributed to the relatively low prevalence of female patients with COPD in Asia, and this gender imbalance in this COPD trial is common in Asian studies.¹⁹ The results of the present study must be interpreted with caution if extrapolating the results to female patients because of gender imbalance. However, no clinically significant difference in efficacy and safety of the acclidinium were noted between male and female in previous trial with acclidinium, and some authors consider this gender imbalance to have subtle (if any) impacts on study outcomes, based on clinical experience with similarly acting drugs.

In conclusion, we demonstrated that twice-daily administration of acclidinium provided effective bronchodilation, significant improvements in dyspnoea and HR-QoL with a favourable tolerability and safety profile in a Korean population. These data are comparable with the results from Caucasian populations. This study has shown that twice-daily acclidinium bromide (400 µg) has therapeutic benefit for Korean patients with moderate-to-severe COPD.

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