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REVIEW

Aclidinium Bromide Twice Daily for the Treatment of Chronic Obstructive Pulmonary Disease: A Review

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ABSTRACT

The inhaled, long-acting muscarinic antagonist, aclidinium bromide, was indicated in July 2012 in Europe and the USA for the maintenance of bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD) in adults. Although initially investigated as a once-daily agent, a lower than expected improvement in trough forced expiratory volume over 1 s prompted re-evaluation as a twice-daily (b.i.d.) regimen. The dose approved for use in Europe, 400 µg b.i.d., achieved statistically significant improvements in lung function, reductions in breathlessness, and improved health-related quality of life (HRQoL) for up to 24 weeks of treatment in the pivotal phase 3 trials (AClidinium in Chronic Obstructive Respiratory Disease I [ACCORD COPD I] [12 weeks] and Aclidinium To Treat Airway obstruction In COPD patieNts [ATTAIN] [24 weeks]). These improvements were sustained during maintenance therapy of up to 52 weeks. Pooled data from the ATTAIN and ACCORD studies (both included a placebo arm) showed that exacerbation frequency was significantly reduced, although neither study was prospectively designed to evaluate this endpoint. Pharmacological and preclinical studies demonstrated the low systemic bioavailability of aclidinium and the low propensity to induce cardiac arrhythmias. The good tolerability of aclidinium was confirmed in the phase 3 program up to 52 weeks of treatment. The adverse event (AE) profile of the approved dose, 400 µg b.i.d., was similar to that of placebo, with a low incidence of anticholinergic and cardiac AEs. Aclidinium is delivered via the Genuair® multidose dry powder inhaler (Almirall Sofotec GmBH, Bad Homburg, Germany). The device is simple to use with multiple feedback mechanisms ensuring consistent dose delivery. In summary, aclidinium 400 µg b.i.d. is effective for the treatment of patients with COPD, offering

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improvements in lung function, breathlessness, and HRQoL, with a good safety profile and a low incidence of anticholinergic and cardiac AEs.

Keywords: ACCORD COPD I; Aclidinium bromide; Anticholinergic; ATTAIN; Cardiology; Chronic obstructive pulmonary disease; Exacerbations; Multidose dry powder inhaler

INTRODUCTION

Aclidinium bromide, a novel, long-acting, inhaled muscarinic antagonist, has been developed for the treatment of chronic obstructive pulmonary disease (COPD) [1, 2]. COPD is characterized by persistent airflow limitation that is not fully reversible and is usually progressive. It is associated with considerable and chronic morbidity, and is currently the fourth leading cause of death worldwide [3].

The goals of treatment for patients with COPD are relief of symptoms, a reduction in the frequency and severity of acute COPD exacerbations, and improved health status and exercise tolerance [3]. Inhaled bronchodilator therapy is the mainstay of treatment and several drug classes are currently approved for use in this setting, including the anticholinergics, beta$_2$ agonists, theophyllines, and combinations thereof. Anticholinergic therapy is recommended as a first choice, either alone in patients with significant symptoms and less frequent exacerbations, or possibly in combination with an inhaled corticosteroid for those with more severe disease (significant symptoms and more frequent exacerbations) [3].

In July 2012, aclidinium 400 μg twice daily (b.i.d.; corresponding to 322 μg delivered dose) was approved for use in the European Union (EU), some non-EU member countries (Iceland and Norway), and the USA for maintenance bronchodilator treatment to relieve symptoms in adults with COPD [4, 5]. This agent was originally evaluated for once-daily (q.d.) dosing. However, clinical studies showed that the trough forced expiratory volume over 1 s (FEV_1) for this regimen did not achieve the level of bronchodilation anticipated from preclinical studies [6]. Consequently, a further clinical trial program was initiated to evaluate b.i.d. dosing, and it was this program that resulted in approval in Europe and the USA.

This paper will provide an overview of the pharmacology, preclinical and clinical profile of aclidinium, and will discuss the role of this new long-acting inhaled muscarinic antagonist, delivered by a novel, breath-actuated, multidose dry powder inhaler (Genuair®; Almirall Sofotec GmBH, Bad Homburg, Germany), in the treatment of COPD.

PRECLINICAL PROFILE

Aclidinium is a quaternary ammonium derivative of a (3R)-quinuclidinol ester (Fig. 1) [2]. 3R-quinuclidinol esters are established as potent muscarinic antagonists and quaternization of this structure minimizes absorption across membranes, a desirable feature for a compound in which a low oral bioavailability is required in order to minimize systemic exposure.

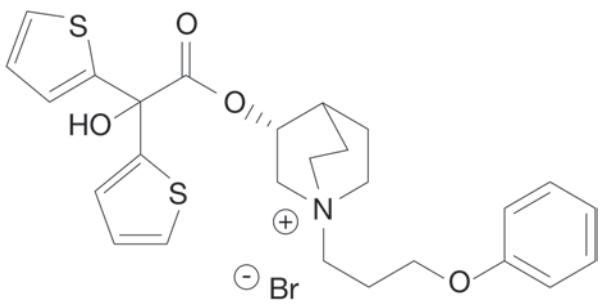

Fig. 1 Chemical structure of aclidinium

METHODS

Studies were identified by searching PubMed with the terms "aclidinium" and "Genuair." Reports detailing the results of preclinical and clinical studies were considered relevant for the purposes of the current review. Recent review papers were also identified and the reference listings searched to identify further studies. Congress databases (European Respiratory Society, American Thoracic Society, British Thoracic Society; 2010–2012) were searched using the same search terms to identify reports of as yet unpublished studies.

Pharmacology and Mode of Action

Receptor Binding Profile

Preclinical studies have shown that aclidinium exhibits potent and selective antagonism of human muscarinic receptors with a long residence time at M_3 receptors, and a shorter residence time at M_2 receptors (Table 1 [1, 2]). Table 1 illustrates the pharmacology of aclidinium compared to the short-acting antimuscarinic ipratropium and the long-acting agent tiotropium. Aclidinium demonstrated considerably longer residence time at the M_3 receptor compared with ipratropium in vitro and faster onset with comparable duration of action compared with tiotropium in vivo [1]. The M_3 receptors, expressed on bronchial smooth muscle, are primarily responsible for bronchial and tracheal smooth muscle contraction [7]. M_2 receptors promote bronchodilation through their action at parasympathetic nerve endings at the neuromuscular junction, but they are also responsible for cardiac side effects such as tachycardia. Consequently, the desirable M_3 receptor antagonism of aclidinium persists for considerably longer than the unwanted M_2 receptor blockade [1, 2].

Preclinical Activity and Safety

In isolated guinea-pig trachea, aclidinium demonstrated potent inhibition of carbachol-induced contraction comparable to that observed for other anticholinergic agents, including tiotropium and ipratropium [1].

Table 1 Pharmacology of aclidinium and other inhaled anticholinergic agents [1]

Activity	Aclidinium	Tiotropium	Ipratropium
In vitro studies			
Binding affinity[a]			
M_1	0.10 ± 0.00	0.13 ± 0.00	1.31 ± 0.15
M_2	0.14 ± 0.04	0.13 ± 0.04	1.12 ± 0.13
M_3	0.14 ± 0.02	0.19 ± 0.04	1.24 ± 0.08
M_4	0.21 ± 0.04	0.30 ± 0.09	1.92 ± 0.18
M_5	0.16 ± 0.01	0.18 ± 0.06	3.22 ± 0.15
Receptor residence time, h			
M_2	4.69	15.11	0.08
M_3	29.24	62.19	0.47
In vivo studies			
Onset of effect, h	0.5	1.3	0.5
Duration of effect, h	29	64	8

[a] Mean ± standard error

These studies demonstrated a more rapid onset of effect and comparable duration of action to that seen with tiotropium, and a significantly longer duration of action compared with ipratropium [1]. In an in vivo guinea-pig model, nebulized aclidinium displayed a rapid onset of inhibition of acetylcholine-induced bronchoconstriction and a long duration of effect [1]. The preclinical cardiac safety of aclidinium, either alone or in combination with formoterol, has recently been reported [8]. Each agent was administered intravenously to dogs with subsequent electrocardiographic monitoring for up to 25 h post-dose. Following formoterol administration, cardiac arrhythmias (ventricular tachycardia and premature ventricular complexes) were noted up to 24 h after dosing with formoterol but not with aclidinium. Cardiac arrhythmias were also noted after coadministration of these agents, but at the same rate as with formoterol alone.

Metabolism

The metabolism of aclidinium has been well characterized. Inhaled aclidinium is poorly absorbed into plasma resulting in limited systemic exposure. The portion of the inhaled dose that is absorbed into plasma is rapidly hydrolyzed by butyrylcholinesterase with an estimated half-life of around 2 min, resulting in a low and only transient systemic exposure to active drug following inhalation [2, 9, 10]. The results of these studies suggest a low propensity for aclidinium to be associated with clinically relevant drug–drug interactions. The main metabolites have no significant affinity for any of the muscarinic receptors [11].

Pharmacokinetics

The pharmacokinetic (PK) profile of aclidinium in humans has also been comprehensively evaluated. In 2011, Lasseter and co-workers reported the results of a 7-day, single-blind study in healthy volunteers (n = 30) of doses up to 800 µg b.i.d. [12]. Steady state was achieved within 2 days for all aclidinium doses tested (200, 400, and 800 µg b.i.d.) and exposure increased in a less than dose-proportional manner between the 400 and 800 µg doses. Studies have also shown that very little active drug is excreted in the urine, and renal impairment does not appear to increase systemic exposure [13]. In a cohort of 24 adults with renal function ranging from normal to severe insufficiency (<30 mL/min), Schmid et al. found that the plasma PK profile of aclidinium did not alter significantly with increasing renal impairment [13]. De la Motte and co-workers [14] evaluated the impact of age on the PK of aclidinium, studying young (40–59 years; n = 12) and elderly (≥70 years; n = 12) patients with COPD. Patients were treated with 200 and 400 µg doses under single and repeated q.d. dosing schedules. The results of the study showed that the PK profile of aclidinium was similar in both age groups, indicating that no dose adjustment is required when treating elderly patients with COPD.

CLINICAL STUDY PROGRAM

Clinical Efficacy in Patients with COPD

Defining the q.d. Dose

A phase 2b dose-finding study was conducted in 79 patients with moderate-to-severe COPD to establish the most appropriate regimen for phase 3 evaluation [15]. Patients received aclidinium 100, 200, or 400 µg b.i.d., formoterol 12 µg, or placebo for 7 days and the change in FEV_1 was measured and used to calculate the FEV_1 normalized area under the curve over the first 12 h following dosing ($AUC_{0\text{-}12h}$). Aclidinium significantly improved the FEV_1 $AUC_{0\text{-}12h}$

compared with placebo after 7 days of treatment ($P < 0.0001$) in a dose-dependent manner. Based on the results of this study, the 200 and 400 μg b.i.d. doses were selected for further clinical evaluation [15].

Improvements in Lung Function

In a phase 2a, 15-day crossover trial, patients with COPD ($n = 30$) received aclidinium 400 μg b.i.d., tiotropium 18 μg q.d., or placebo [16]. Significantly greater improvements in lung function (FEV_1 $AUC_{0\text{-}24h}$) were observed for aclidinium compared with placebo ($P < 0.0001$), which were comparable with those recorded for tiotropium. COPD symptoms also improved significantly with aclidinium compared with placebo ($P < 0.05$), but not with tiotropium.

Three phase 3 studies have been conducted for aclidinium in COPD; AClidinium in Chronic Obstructive Respiratory Disease I (ACCORD COPD I) [17], Aclidinium To Treat Airway obstruction In COPD patieNts (ATTAIN) [18] (Fig. 2), and ACCORD COPD II [19]. In the ACCORD COPD II study, analysis of the baseline

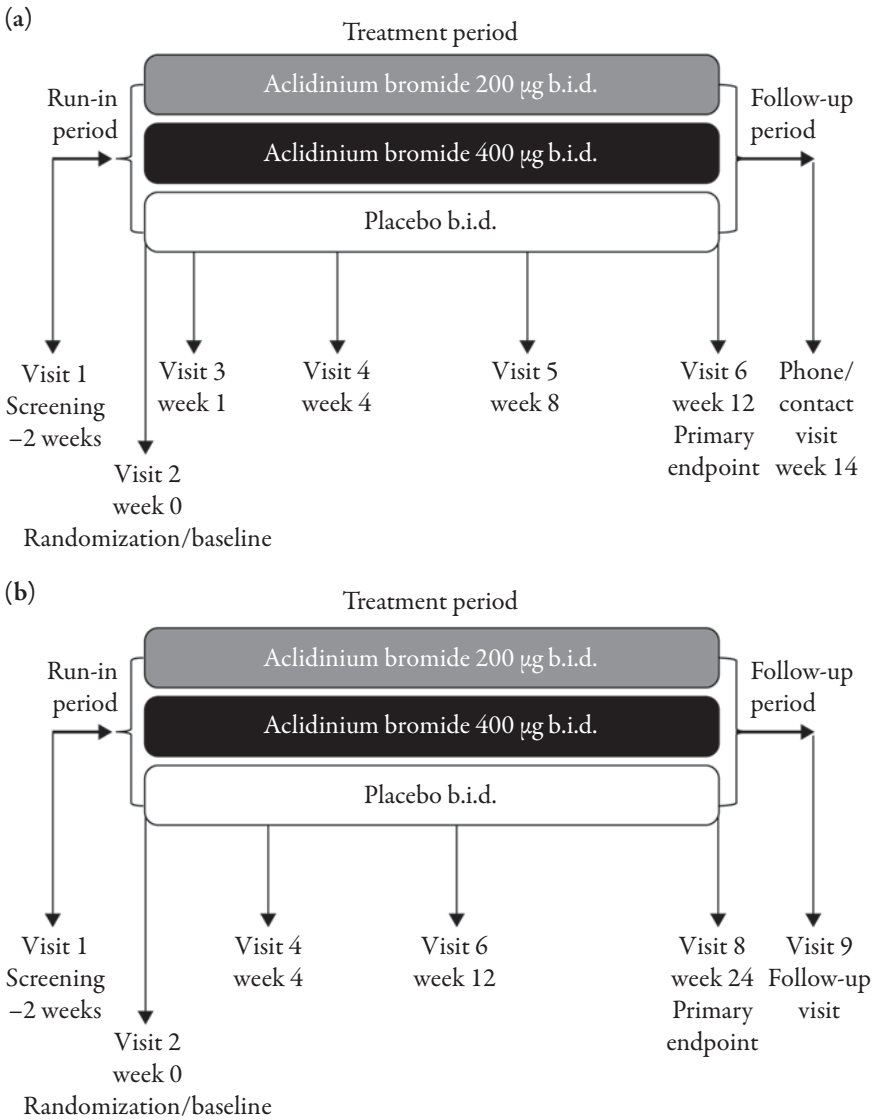

Fig. 2 Study designs for the two pivotal twice-daily phase 3 studies, (**a**) ACCORD COPD I [17] and (**b**) ATTAIN [18]. *b.i.d.* twice daily

characteristics of the populations randomized to each treatment arm (aclidinium 200 and 400 μg, and placebo) revealed statistically significant imbalances in terms of baseline FEV_1 and COPD severity ($P \leq 0.0009$). This has made interpretation of the results of this study challenging, so the study is regarded as supportive rather than pivotal.

The ACCORD COPD I study was a 12-week, placebo-controlled trial of aclidinium b.i.d. (200 and 400 μg doses) in 561 patients with moderate-to-severe COPD (Table 2 [6, 17, 18, 19–21]). In this study, the primary endpoint was trough FEV_1 (the morning pre-dose measurement). It showed that patients treated with aclidinium 200 or 400 μg b.i.d. achieved significant improvements from baseline in both mean trough FEV_1 (86 mL and 124 mL vs. placebo, respectively; $P \leq 0.0001$) and peak FEV_1 (146 mL and 192 mL vs. placebo, respectively; $P \leq 0.0001$) after 12 weeks. The peak FEV_1 achieved with aclidinium was significantly greater than for placebo from the first dose onwards ($P < 0.0001$).

The 24-week ATTAIN study also recruited patients with moderate-to-severe, stable COPD (Table 2 [18]). At week 24, the improvements in trough FEV_1 (the primary endpoint) were 99 ± 22 mL and 128 ± 22 mL for the 200 and 400 μg doses, respectively ($P < 0.0001$). With both aclidinium doses, these improvements were significantly greater than placebo from week 1 onwards. Improvements in peak FEV_1 at week 24 (185 and 209 mL, respectively) were greater with aclidinium versus placebo ($P < 0.0001$) from the first dose, a benefit that was noted to the end of the study.

Pooled data analyses from the ACCORD COPD I and ATTAIN studies provide further confirmation that patients with moderate-to-severe COPD treated with aclidinium 200 or 400 μg b.i.d. achieve clinically significant improvements in lung function [22]. Trough and peak FEV_1 were significantly greater for both aclidinium doses versus placebo from week 1 (day 1 for peak FEV_1) through to week 12 ($P < 0.0001$; [22]). The improvement in trough FEV_1 achieved with aclidinium 400 μg b.i.d. (112 mL at week 12) was above the level usually judged to be clinically meaningful (>100 mL) and greater than that achieved for the 200 μg b.i.d. dose ($P < 0.05$).

The ACCORD COPD II study was also a 12-week, placebo-controlled trial of aclidinium b.i.d. (200 and 400 μg doses) [19]. A total of 541 patients with moderate-to-severe COPD took part (Table 2). Patients treated with aclidinium 200 or 400 μg b.i.d. achieved statistically significant improvements from baseline in mean trough FEV_1 compared with placebo of 51 mL ($P < 0.01$) and 72 mL ($P < 0.05$), respectively. As noted above, the smaller apparent effect size observed in the ACCORD COPD II compared with ACCORD COPD I and ATTAIN is likely due to imbalances at baseline in the characteristics of the patients randomized to each study arm in the ACCORD COPD II study that were not seen in either of the other studies. These included a greater proportion of patients, 55%, with Stage III (severe) COPD in the aclidinium 400 μg b.i.d. arm compared with the aclidinium 200 μg b.i.d. (47%) or placebo (37%) arms.

Two additional studies support the long-term maintenance of improvements in lung function with aclidinium. In a 52-week study (LAS-MD-35) in a very similar population of patients to those recruited to ACCORD COPD I and ATTAIN, patients were randomized to one of the two aclidinium doses [20]. For both doses, improvements in FEV_1 from baseline were sustained to week 52 (Table 1). Trough and peak FEV_1 values were both numerically higher for the 400 μg dose compared with the 200 μg dose. An extension phase of the ACCORD COPD I study allowed patients to

Table 2 Overview of the phase 3 and long-term trials of aclidinium in COPD *(continued on next page)*

Study acronym and reference	Study treatments	*N*	Duration (weeks)	Key efficacy outcomes
Twice-daily dosing studies				
ACCORD COPD I [17]	Aclidinium 200 μg b.i.d. Aclidinium 400 μg b.i.d. Placebo	185 190 186	12	Trough FEV_1 change from baseline vs. placebo • 200 μg: 86 mL (95% CI 45–127; $P \leq 0.0001$) • 400 μg: 124 mL (95% CI 83–164; $P \leq 0.0001$) Peak FEV_1 change from baseline vs. placebo • 200 μg: 146 mL (95% CI 101–190; $P \leq 0.0001$) • 400 μg: 192 mL (95% CI 148–236; $P \leq 0.0001$)
ATTAIN [18]	Aclidinium 200 μg b.i.d. Aclidinium 400 μg b.i.d. Placebo	277 269 272	24	Trough FEV_1 change from baseline vs. placebo • 200 μg: 99 mL ($P < 0.0001$) • 400 μg: 128 mL ($P < 0.0001$) Peak FEV_1 change from baseline vs. placebo • 200 μg: 185 mL ($P < 0.0001$) • 400 μg: 209 mL ($P < 0.0001$)
ACCORD COPD II [19]	Aclidinium 200 μg b.i.d. Aclidinium 400 μg b.i.d. Placebo	182 177 182	12	Trough FEV_1 change from baseline vs. placebo • 200 μg: 51 mL ($P < 0.01$) • 400 μg: 72 mL ($P < 0.05$) Peak FEV_1 change from baseline vs. placebo • 200 μg: 115 mL ($P < 0.0001$) • 400 μg: 125 mL ($P < 0.0001$)
ACCORD COPD I extension [21]	Aclidinium 200 μg b.i.d. Aclidinium 400 μg b.i.d. *(Patients previously receiving placebo were re-randomized to one of the two aclidinium doses)*	291	52	Improvements in peak and trough FEV_1 achieved during the lead-in phase were maintained to the end of the extension phase (week 64)

Table 2 continued

Study acronym and reference	Study treatments	*N*	Duration (weeks)	Key efficacy outcomes
Twice-daily dosing studies (continued)				
LAS-MD-35 [20]	Aclidinium 200 μg b.i.d. Aclidinium 400 μg b.i.d.	312 293	52	Trough FEV_1 change from baseline at week 52 (maximal values during the study) • 200 μg: 34 mL (62 mL) • 400 μg: 72 mL (101 mL) Peak FEV_1 change from baseline at week 52 (maximal values during the study) • 200 μg: 185 mL (226 mL) • 400 μg: 214 mL (235 mL)
Once-daily dosing studies				
ACCLAIM COPD I [6]	Aclidinium 200 μg q.d. Placebo	627 216	52	**Week 12:** Trough FEV_1 change from baseline vs. placebo: 61 mL ($P < 0.001$) **Week 28:** Trough FEV_1 change from baseline vs. placebo: 67 mL ($P < 0.001$) More patients achieved a clinically meaningful improvement in SGRQ (≥4 points) at week 52 (48.1% vs. 39.5%; $P = 0.025$)
ACCLAIM COPD II [6]	Aclidinium 200 μg q.d. Placebo	600 204	52	**Week 12:** Trough FEV_1 change from baseline vs. placebo: 63 mL ($P < 0.001$) **Week 28:** Trough FEV_1 change from baseline vs. placebo: 69 mL ($P < 0.001$) Time to first moderate-severe COPD exacerbation significantly delayed vs. placebo (HR 0.7; 95% CI 0.55-0.92; $P = 0.01$)

b.i.d. twice daily, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *FEV_1* forced expiratory volume over 1 s, *HR* hazard ratio, *q.d.* once daily, *SGRQ* St George's Respiratory Questionnaire

continue aclidinium b.i.d. for up to 52 weeks; placebo patients were re-randomized to one of the aclidinium doses [21]. Improvements from baseline in FEV_1 with both aclidinium doses were sustained to week 52.

Most recently, data have been reported from a 6-week trial comparing aclidinium 400 µg b.i.d. with placebo and tiotropium 18 µg q.d. in 414 patients with stable, moderate-to-severe COPD [23]. Aclidinium was associated with clinically meaningful improvements in lung function compared with placebo (normalized FEV_1 $AUC_{0\text{-}24h}$ change from baseline vs. placebo 150 mL; $P < 0.0001$). By contrast, the benefit for tiotropium versus placebo was 140 mL ($P < 0.0001$). The larger effect of aclidinium in this study was due mainly to better bronchodilation during the second half of the day (the *P*-value for FEV_1 $AUC_{12\text{-}24h}$ was 0.0018 for aclidinium vs. tiotropium) [19].

Improvements in Health Status and COPD Symptoms

In ACCORD COPD I [17], patients treated with aclidinium experienced significant improvements in COPD symptom scores and dyspnea score measured with the Transition Dyspnea Index (TDI) versus placebo ($P < 0.05$) and significant improvements in health status (as measured by the St George's Respiratory Questionnaire [SGRQ]; $P < 0.05$). Night-time COPD symptoms, including breathlessness, cough, sputum production, and wheeziness, were all significantly reduced among patients treated with aclidinium compared with those who received placebo, as was the severity of breathlessness in the morning and the impact of breathlessness on early morning activities ($P < 0.05$ for aclidinium vs. placebo for all measures). Similarly, in ATTAIN, patients treated with aclidinium experienced clinically significant improvements in dyspnea (mean difference in TDI focal score at week 24 vs. placebo was 0.6 and 1.0 unit for the 200 and 400 µg doses, respectively; $P < 0.001$) [18, 24]. The difference in the mean change from baseline in the SGRQ total score was –3.6 and –4.3 units for the 200 and 400 µg doses, respectively, compared with placebo ($P < 0.0001$) [18]. Thus, the improvement for the aclidinium 400 µg b.i.d. dose exceeded the minimum clinically important difference (MCID) of at least 1.0 point on the TDI and of 4.0 points on the SGRQ [25, 26].

In the ATTAIN study, the EXAcerbations of Chronic Pulmonary Disease Tool - Respiratory Systems (EXACT-RS) daily diary was used as an exploratory outcome measure. This showed that both doses of aclidinium improved the total score and the component scores (breathlessness, chest symptoms, and cough and sputum) significantly more than placebo ($P < 0.05$ to $P < 0.001$), and in each case the higher dose produced a numerically greater symptomatic improvement than the lower dose [27].

In the 52-week studies, LAS-MD-35 and the ACCORD COPD I extension, patients treated with either dose achieved a clinically significant improvement from baseline in health status [20, 21]. In the LAS-MD-35 study, the reduction in the SGRQ total scores from baseline to week 52 was 5.3 and 5.2 units for the 200 and 400 µg doses, respectively, both exceeding the MCID of 4.0 points [20]. A similar pattern was observed in the ACCORD COPD I extension study, with improvements from baseline in SGRQ score in the range of 4.9–7.9 points [20].

Exacerbations

A pooled analysis of data from ACCORD COPD I [17] and ATTAIN [28] has been conducted [29]. Two methods were used to capture COPD exacerbations. The first was healthcare resource utilization (HCRU) in which

an exacerbation was defined as an increase in symptoms on ≥2 consecutive days requiring a change in treatment. The second was the EXACT [30] by which an exacerbation is defined as a persistent increase in the EXACT total score of ≥9 points for ≥3 days or ≥12 points for ≥2 days. Regardless of the method of assessment, the rate of any exacerbation was significantly lower among patients treated with aclidinium b.i.d. than among those treated with placebo. Using HCRU criteria for moderate and severe exacerbations (i.e., those requiring treatment with antibiotics ± systemic corticosteroids ± hospitalization), the reduction in the annualized exacerbation rate with aclidinium 200 μg was 33.0% and 25.8% in the ACCORD I COPD and ATTAIN studies, respectively [29]. For the aclidinium 400 μg dose, the reduction in the rate of moderate or severe exacerbations was 33.7% and 27.7% in the two studies, respectively [30]. Pooled data from the two studies showed a significant reduction in the rate of moderate-to-severe exacerbations for the aclidinium 400 μg dose compared with placebo (0.31 vs. 0.44; rate ratio 0.71; $P = 0.01$) [29].

Exercise Endurance

In 2011, Maltais and co-workers reported the results of a study among 181 adult patients with moderate-to-severe COPD designed to examine the impact of aclidinium on exercise endurance [31]. Patients were randomized to aclidinium 200 μg q.d. or placebo for 6 weeks. Patients treated with aclidinium experienced significantly improved exercise endurance compared with placebo on day 1 (benefit in endurance time vs. placebo of 143 s; $P = 0.0002$). This benefit was sustained at both weeks 3 (benefit of 126 s; $P = 0.0007$) and 6 (benefit of 116 s; $P = 0.0042$). Airflow obstruction (trough FEV_1) was also improved with aclidinium compared with placebo ($P < 0.05$ at both weeks 3 and 6), as was lung hyperinflation as measured by improvements in inspiratory capacity (IC) and the IC/total lung capacity ratio ($P < 0.05$ for all comparisons [31]). Evaluation of the impact of the licensed dosing regimen on exercise endurance is ongoing, with results expected in 2013 (ClinicalTrials.gov #NCT01471171). However, the encouraging data from the once-daily regimen suggest that aclidinium q.d. should also improve exercise endurance in patients with COPD.

Safety and Tolerability

Studies in healthy subjects have demonstrated the low systemic bioavailability and favorable safety profile of aclidinium at single doses up to 6,000 μg and multiple doses up to 800 μg b.i.d. for 7 days [32–35]. The cardiovascular safety of aclidinium at doses up to 800 μg has been examined in healthy individuals; no safety concerns were raised and no effect on QT interval was observed [12].

These early indicators of safety and tolerability have translated into a good tolerability profile for aclidinium b.i.d. in the pivotal phase 3 studies ACCORD COPD I [17] and ATTAIN [18]. In the 12-week ACCORD COPD I study, the overall incidence of adverse events (AEs) was comparable between both aclidinium doses and placebo. COPD exacerbation was the only AE reported in >5% of patients in any of the three treatment groups and was reported at a lower rate in the aclidinium groups (200 μg, 9.2% of patients; 400 μg, 7.4% of patients) compared with placebo (12.4%). Anticholinergic and cardiac AEs occurred infrequently, in <2% of patients in any treatment group. Similarly, good tolerability and safety were observed in the 24-week ATTAIN study, with a low rate of anticholinergic and cardiac AEs with aclidinium, similar to that observed for placebo [18].

The extension phase of the phase 3 ACCORD COPD I study has confirmed the good safety and tolerability profile of aclidinium among patients with COPD for up to 52 weeks [21]. Aclidinium was associated with low rates of anticholinergic-related AEs similar to that reported in the placebo arm [20]. The most commonly reported AEs across all treatment groups were COPD exacerbation, headache, nasopharyngitis, diarrhea, and cough. The overall rate of adverse cardiovascular events was 11.7% in the 200 μg arm and 6.6% for those treated with aclidinium 400 μg [21]. The 52-week LAS-MD-35 study reported by Gelb and co-workers [36] provided further support for the long-term safety of aclidinium 200 and 400 μg b.i.d. In that study, the most commonly reported AEs were COPD exacerbations, nasopharyngitis, cough, sinusitis, and headache (Table 3) [6, 17, 18, 20, 21]. Again, anticholinergic AEs were uncommon, occurring in <3% of patients in either treatment group. Finally, cardiovascular events occurred in 7.7% of patients in the 200 μg group and 4.1% of the 400 μg group, although the incidence of individual cardiac AEs was low (<2% in either treatment group).

DRUG DELIVERY: THE GENUAIR INHALER

Aclidinium is a dry powder formulation delivered via a novel, breath-actuated, multidose dry powder inhaler, the Genuair inhaler [37, 38]. The device is simple to use and provides multiple feedback messages to ensure consistent dose delivery [37]. These include a control window that changes from red to green to indicate to the patient that the device is ready to use and an audible click once the dose has been delivered successfully. A dose indicator tracks the number of remaining doses and a red line appears when the patient is close to the last dose. In addition, a lock-out mechanism prevents use of the device once the last dose has been delivered. Data suggest that the critical error rate (those which reduce or prevent appropriate drug delivery to the lungs) for this device is low compared with other inhalers for the delivery of inhaled medications for COPD [39–41].

DISCUSSION

Aclidinium 400 μg b.i.d. is effective for the treatment of patients with COPD. It offers significant, clinically relevant, and sustained improvements in lung function as well as improved COPD symptoms, at night and in the morning, and reduced breathlessness, all leading to improvements in health-related quality of life (HRQoL). The b.i.d. regimen has also demonstrated a good safety and tolerability profile, with an AE profile similar to that of placebo and low rates of anticholinergic and cardiac AEs. Early indications from a 6-week study suggest that aclidinium b.i.d. may offer a benefit over tiotropium q.d. due to the sustained bronchodilation during the second half of the 24-h period.

For the future, long-term studies will be required to evaluate the potential benefit of aclidinium with regard to the rate of COPD-related hospitalizations, mortality and long-term decline in lung function.

CONCLUSION

In Europe, aclidinium is indicated as maintenance bronchodilator to relieve symptoms in adults with COPD. The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) 2011 strategy document suggests that a long-acting beta$_2$ agonist or long-acting muscarinic antagonist could be used as first-choice therapy for patients with symptomatic COPD.

Table 3 Overview of the adverse event profile of aclidinium in the phase 3 and long-term trials of aclidinium in COPD

Study acronym and treatments	Total AEs (% patients)	Individual cardiac AEs (% patients)	Most common AEs (>10% patients in any group)
Twice-daily dosing studies			
ACCORD COPD I [17]			
Aclidinium 200 μg b.i.d.	50.5	<2% for any group	**Aclidinium 200 μg:** No event >10% (COPD exacerbation, 9.2%)
Aclidinium 400 μg b.i.d.	44.7		**Aclidinium 400 μg:** No event >10% (COPD exacerbation 7.4%)
Placebo	52.2		**Placebo:** COPD exacerbation (12.4%)
ATTAIN [18]			
Aclidinium 200 μg b.i.d.	54.5	<1% for any group	**Aclidinium 200 μg:** COPD exacerbation (15.9%), headache (10.8%), nasopharyngitis (11.6%)
Aclidinium 400 μg b.i.d.	53.2		**Aclidinium 400 μg:** COPD exacerbation (14.1%), headache (12.3%), nasopharyngitis (11.2%)
Placebo	57.1		**Placebo:** COPD exacerbation (20.5%), headache (8.1%), nasopharyngitis (8.4%)
ACCORD COPD I extension [21]			
Aclidinium 200 μg b.i.d.	77.4	<5% for any group	**Aclidinium 200 μg:** COPD exacerbation (25.5%)
Aclidinium 400 μg b.i.d.	73.7		**Aclidinium 400 μg:** COPD exacerbation (21.7%)
LAS-MD-35 [20]			
Aclidinium 200 μg b.i.d.	88.7	<5% for any group	**Aclidinium 200 μg:** COPD exacerbation (19.3%)
Aclidinium 400 μg b.i.d.	86.9		**Aclidinium 400 μg:** COPD exacerbation (19.9%)
Once-daily dosing studies			
ACCLAIM COPD I [6]			
Aclidinium 200 μg q.d.	56.6	8.6	**Aclidinium 200 μg:** Nasopharyngitis (16.3%); headache (11.3%)
Placebo	59.3	13.0	**Placebo:** Nasopharyngitis (14.4%); headache (12.5%)
ACCLAIM COPD II [6]			
Aclidinium 200 μg q.d.	79.8	12.5	**Aclidinium 200 μg:** Nasopharyngitis (12.7%); headache (14.2%); upper respiratory tract infection (10.8%)
Placebo	75.5	14.2	**Placebo:** Nasopharyngitis (11.3%); headache (12.7%)

AE adverse event, *b.i.d.* twice daily, *COPD* chronic obstructive pulmonary disease, *q.d.* once daily

Aclidinium 400 µg b.i.d. delivered by the Genuair inhaler clearly has properties that merit its prescription as first-choice therapy in such patients.

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