An assessment of the functional profile of aclidinium bromide in human bronchi and left atria

Javier Milara,[1] Elena Gabarda,[2] Amadeu Gavaldà,[3] Montserrat Miralpeix,[3] Jorge Beleta,[3] Esteban Morcillo,[2] Julio Cortijo[4]

[1]CIBERES, Health Institute Carlos III, Valencia, Spain; [2]Department of Pharmacology, Faculty of Medicine, University of Valencia, Spain; [3]Almirall, R&D Centre, Barcelona, Spain; [4]Research Unit, University General Hospital Consortium, Valencia, Spain

Introduction

- Anticholinergic treatments for chronic obstructive pulmonary disease (COPD) act by inhibiting pulmonary M_3 receptors, which are responsible for mediating bronchoconstriction and mucus hypersecretion.[1] Activity at other muscarinic receptors outside of the respiratory tract confers a potential for unwanted side effects; for example, tachycardia induced by inhibition of cardiac M_2 receptors.[2]
- Currently available muscarinic antagonists used in the treatment of COPD, the long-acting tiotropium and the short-acting ipratropium, are associated with systemic anticholinergic side effects including tachycardia.[3,4]
- Aclidinium bromide is a novel, second-generation, low systemic activity, inhaled long-acting muscarinic antagonist compound, currently under review by the EMA and FDA for the maintenance treatment of COPD.
- *In vitro* studies using guinea pig trachea and left atria have shown that, compared with tiotropium, aclidinium has a similar potency and duration of action at M_3 receptors, but a lower potency and a shorter duration of action at M_2 receptors.[5]
- The aim of this study was to investigate the *in vitro* effects of aclidinium at M_3 and M_2 receptors in human bronchial and left-atrial tissue, respectively. Tiotropium and ipratropium were used as comparators.

Methods

Assessment of M_3-mediated smooth muscle relaxant effects in isolated human bronchi

Preparation of human bronchial strips

- Macroscopically tumour-free bronchial tissue was harvested from patients undergoing surgery for lung carcinoma and used immediately. The protocol was approved by the local ethics committee.
- Bronchial strips, free from parenchyma, were mounted in a superfusion chamber containing oxygenated Krebs solution at 37°C. Spontaneous tone, induced by endogenous leukotrienes and histamine, was inhibited by zileuton (10 µM) and fexofenadine (10 µM), respectively.
- Each bronchial strip was connected to a force transducer and isometric changes were recorded using standard software. An initial load of 2 g was used to obtain a stable resting tone prior to the initiation of electrical stimulation.
- Contractile responses were induced by electrical stimulation, delivered by bipolar electrodes in 10-second bursts of square-wave pulses (8 Hz, 40–50 V and 0.5 ms duration) every 120 seconds using a Grass stimulator. Responses to electrical stimulation were allowed to stabilise prior to antagonist testing.

Assessment of potency

- Increasing concentrations of aclidinium, tiotropium or ipratropium (0.3 nM–10 nM) were cumulatively added to the superfusion chamber and an IC_{50} for inhibition of tone was calculated.
- Antagonist potency was determined as -log IC_{50} (pIC_{50}) values.

Assessment of onset and offset

- Aclidinium, tiotropium or ipratropium (10 nM) was added to inhibit approximately 75% of baseline contraction. After 30 minutes, the tissue was washed free of antagonist and recovery of tone was recorded for 14–15 hours.
- Onset of action ($t_{½}$) was defined as the time taken from antagonist addition to achieve 50% inhibition of tone.
- Offset of action ($t_{½}$) was defined as the time taken from antagonist washout to achieve 50% recovery of tone.
- Differences between onset and offset values were determined by analysis of variance.

Assessment of duration of action at M_2 receptors in isolated human atria

Preparation of human atrial strips

- Left-atria tissue was harvested from patients undergoing surgery for cardiac bypass and used immediately. The protocol was approved by the local ethics committee.
- Atrial strips were mounted in a superfusion chamber containing oxygenated Krebs solution at 37°C.
- The strips were connected to a force transducer and isometric changes were recorded using standard software. An initial load of 2 g was used to obtain a stable resting tone prior to the initiation of electrical stimulation.
- Atrial contraction was induced by electrical stimulation, delivered by bipolar electrodes at 1 Hz, 5 ms duration and 2–5 V (20% higher than the threshold for contraction) using a Grass stimulator. Responses to electrical stimulation were allowed to stabilise prior to antagonist testing.

Estimation of offset

- The stimulated atrial strips were pre-treated with carbachol (10 µM) to inhibit electrically induced contractions via the M_2 receptor.
- Aclidinium, tiotropium or ipratropium were added to the carbachol-treated atria at a concentration that inhibited approximately 70% of the maximum carbachol-induced relaxation (70, 50 and 80 nM, respectively).
- After 20–30 minutes, preparations were washed three times to remove free antagonist and the atrial strips were re-treated with carbachol (10 µM) for 240 minutes.
- The time to achieve 50% recovery of the maximum carbachol-induced relaxation ($t_{½}$; offset) was calculated using one-phase (aclidinium and tiotropium) or two-phase (ipratropium) exponential decay.

Data analysis

- Statistically significant differences between onset and offset values were determined by parametric analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test.

Results

M_3-mediated smooth muscle relaxant effects in isolated human bronchi

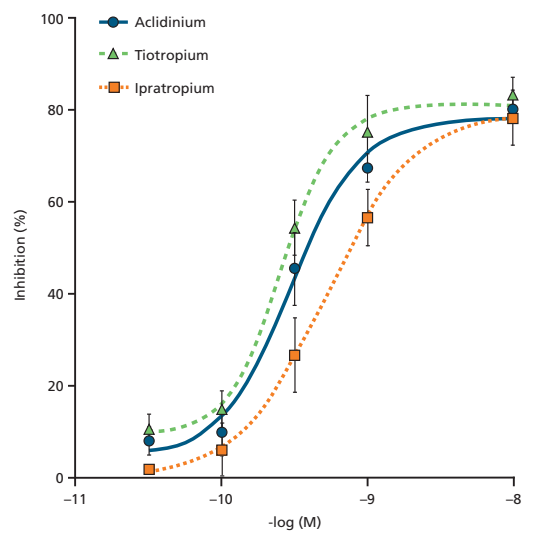
- Aclidinium, tiotropium and ipratropium inhibited electrically stimulated contraction with similar potency (Table 1; Figure 1).

Table 1. Potency of antagonists as inhibitors of the contractile response induced by electrical stimulation of human bronchial strips

	pIC_{50}
Aclidinium	9.5 ± 0.1
Tiotropium	9.6 ± 0.1
Ipratropium	9.3 ± 0.0

Data reported as mean ± standard error for 3–5 experiments using 3 patient samples

Figure 1. Concentration response curves for aclidinium, tiotropium and ipratropium in electrically stimulated human bronchial strips



Data reported as mean ± standard error for 3–5 experiments using 3 patient samples

- The onset of action of aclidinium was similar to that of ipratropium and significantly faster than tiotropium ($p<0.05$; Table 2).

Table 2. Onset and offset of aclidinium, ipratropium and tiotropium against the contraction induced by electrical stimulation of human bronchial strips

	n/p	Maximal inhibition of contraction (%)	Onset time ($t_{½}$; min)	Offset time ($t_{½}$; min)
Aclidinium (10 nM)	8/6	74.9 ± 3.3	4.4 ± 0.7#	334 ± 49*
Tiotropium (10 nM)	5/4	76.6 ± 3.9	7.4 ± 1.3*	NR (⩾10 h)
Ipratropium (10 nM)	5/3	71.1 ± 3.6	3.3 ± 0.6	76 ± 9

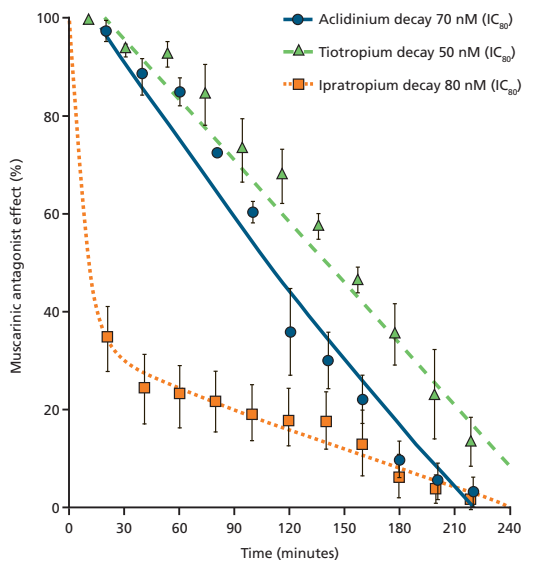
*$p<0.05$ vs ipratropium; #$p<0.05$ vs tiotropium
Data reported as mean ± standard error
n, number of individual bronchial strips; NR, no recovery of tension observed after 10 h;
p, number of patients

- The offset time for aclidinium was significantly longer than that of ipratropium ($p<0.05$). Tiotropium recovery was sustained with no recovery of tone after washout within the duration of the study (Table 2).

Duration of action at M_2 receptors in isolated human atria

- Aclidinium inhibition of the M_2-mediated bradycardiac effect of carbachol had a longer offset time than ipratropium and a shorter offset time than tiotropium (Table 3; Figure 2)

Figure 2. Duration of action (offset) for aclidinium, tiotropium and ipratropium at M_2 receptors in electrically stimulated human left-atrial strips treated with carbachol



Data reported as mean ± standard error for 3 experiments using different patient samples

Table 3. Duration of action (offset) for aclidinium, tiotropium and ipratropium at M_2 receptors in electrically stimulated human left-atrial strips treated with carbachol

	n/p	Inhibition of maximum carbachol-induced relaxation (%)	Offset time ($t_{½}$; min)
Aclidinium	3/3	68.4 ± 5.6	110.2 ± 5.2*,#
Tiotropium	3/3	72.1 ± 2.3	159.3 ± 10.5*
Ipratropium	3/3	69.8 ± 1.5	16.6 ± 0.3

*$p<0.01$ vs ipratropium; #$p<0.01$ vs tiotropium
Data reported as mean ± standard error
n, number of individual bronchial strips; p, number of patients

Conclusions

- **Aclidinium and tiotropium have similar potency at M_3 receptors in isolated human bronchi. Aclidinium has a faster onset of action than tiotropium. Both aclidinium and tiotropium show a long-lasting pharmacological effect in this model.**
- **Aclidinium has a shorter duration of action than tiotropium at M_2 receptors in isolated human atria. These data are consistent with previous observations in guinea pig models[5] and suggest that aclidinium may have lower potential for cardiovascular side effects.**

References

1. Barnes PJ. Muscarinic receptor subtypes in airways. Life Sci 1993; 52: 521-527.
2. Eglen RM. Muscarinic receptor subtype pharmacology and physiology. Prog Med Chem 2005; 43: 105-136.
3. Barr RG, Bourbeau J, Camargo CA, et al. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis. Thorax 2006; 61: 854-862.
4. Kesten S, Jara M, Wentworth C, et al. Pooled clinical trial analysis of tiotropium safety. Chest 2006; 130: 1695-1703.
5. Gavaldà A, Calama E, Gomez-Angelats M, et al. In vitro functional profile of aclidinium bromide in isolated guinea pig trachea and left atria. Am J Respir Crit Care Med 2009; 179: A4555 (abstract).

Acknowledgements

This study was supported by Almirall S.A., Barcelona, Spain.

Poster presented at the European Respiratory Society Annual Congress, Amsterdam, The Netherlands, 24-28 September 2011

Effects of aclidinium bromide on airway remodelling in guinea pigs chronically exposed to cigarette smoke

David Domínguez-Fandos,[1] Raquel Puig-Pey,[1] Elisabet Ferrer,[1] Cristina Carreño,[2] Mònica Aparici,[2] Jorge Beleta,[2] Neus Prats,[2] Montserrat Miralpeix,[2] Amadeu Gavaldà,[2] Víctor I Peinado,[1,3] Joan Albert Barberà[1,3]

[1]Department of Pulmonary Medicine, Hospital Clínic-IDIBAPS, Barcelona, Spain; [2]Almirall, R&D Centre, Barcelona, Spain; [3]CIBER de Enfermedades Respiratorias, Barcelona, Spain

Introduction

- Airway remodelling, triggered by the inhalation of cigarette smoke (CS) and other noxious substances, is a significant contributor to the development of airflow obstruction in chronic obstructive pulmonary disease (COPD).
- Aclidinium bromide is a novel, second-generation, low systemic activity, inhaled long-acting muscarinic antagonist compound, currently under review by the EMA and FDA for COPD treatment.

Objective

- To investigate the effect of aclidinium on airway remodelling in guinea pigs chronically exposed to CS for 6 months.

Methods

Animal groups

- Male Hartley guinea pigs (n=46, ~415 g) were housed under a 12-h light/dark cycle and randomised to 6 groups:
  - Vehicle sham: treated with vehicle and exposed to room air (n=8)
  - Vehicle CS: treated with vehicle and exposed to CS (n=10)
  - Ac10 sham: treated with aclidinium 10 µg/mL and exposed to room air (n=7)
  - Ac10 CS: treated with aclidinium 10 µg/mL and exposed to CS (n=6)
  - Ac30 sham: treated with aclidinium 30 µg/mL and exposed to room air (n=7)
  - Ac30 CS: treated with aclidinium 30 µg/mL and exposed to CS (n=8).

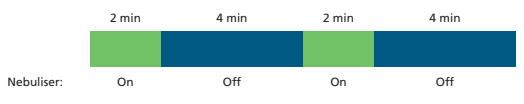
Cigarette smoke exposure

- Guinea pigs were exposed to the smoke of 6 non-filtered research cigarettes (3R4F Kentucky University) using a nose-only system for 5 days/week for 24 weeks.
- Control animals were sham-exposed to room air for 24 weeks.

Aclidinium administration

- Guinea pigs were nebulised with vehicle (water) or aclidinium in a gas mixture containing 5% CO_2, 21% O_2 and 74% N_2 (ultrasonic Devilbiss Ultraneb 3000 nebuliser, flow of 3 L/min), 1 hour prior to CS exposure (Figure 1).

Figure 1. Nebulisation protocol



Morphological studies

- Lungs were removed and the lobes inflated and fixed in formalin 4%.

Airway remodelling

- Total wall thickness, and thickness of adventitia, muscularis and mucosal layers, were measured in sections by planimetry.
- Sections were immunostained with a primary monoclonal mouse anti-human smooth muscle actin (SMA).
- The median of internal luminal perimeter was used to stratify airways into large (above the median) or small (below the median), and to normalise assessments.

Inflammatory cells

- The number of neutrophils, eosinophils and macrophages was counted in alveolar septa and airway adventitia in sections stained with hematoxylin-eosin (H&E), Congo red and PAS, respectively.

Emphysema and goblet cell metaplasia

- The presence of emphysema was evaluated in sections stained with H&E by measuring the mean linear intercept of alveolar septa.
- Secretory cells in the airway epithelium were counted in sections stained with alcian blue.

Results

Airway remodelling

- CS exposure caused enlargement of airway wall layers, particularly in smaller airways (Table 1; Figure 2).
- Thickening of the muscularis in small airways was significantly prevented in animals chronically exposed to CS and treated with aclidinium (Figure 3). The amount of SMA (α-actin) in the small airways was also significantly prevented with both doses of aclidinium tested (10 µg/mL and 30 µg/mL) (Table 1).
- Thickening of adventitial and mucosal layers was not significantly prevented with aclidinium (Table 1).

Inflammatory cells

- Guinea pigs exposed to CS showed infiltration of inflammatory cells in alveolar septa and airways (data not shown). The amount of infiltration was unaffected by aclidinium treatment (Figure 4).

Emphysema and goblet cell metaplasia

- Emphysematous lesions in parenchyma and goblet cell metaplasia in airways of guinea pigs exposed to CS were not reduced with aclidinium administration (Figure 5; Table 2).

Table 1. Effects of aclidinium on airway remodelling in guinea pigs exposed to CS

	Airway size (ILP)	Vehicle		Ac10 µg/mL		Ac30 µg/mL	
		Sham (n=8)	CS (n=10)	Sham (n=7)	CS (n=6)	Sham (n=7)	CS (n=8)
Total wall thickness (µm)	Large	66 ± 8	108 ± 9*	73 ± 5	99 ± 8*	79 ± 5	106 ± 6*
	Small	57 ± 9	120 ± 52*	68 ± 15	81 ± 17	66 ± 9	95 ± 24*
Mucosal thickness (µm)	Large	27 ± 2	53 ± 6*	33 ± 3	50 ± 4*	31 ± 2	45 ± 3*
	Small	29 ± 5	59 ± 38*	34 ± 5	41 ± 8	33 ± 4	46 ± 10*
Muscularis thickness (µm)	Large	21 ± 2	32 ± 5	23 ± 2	26 ± 3	27 ± 2	31 ± 2
	Small	16 ± 3	32 ± 9*	19 ± 7	18 ± 4#	20 ± 3	21 ± 5#
α-actin+thickness (µm)	Large	19 ± 8	28 ± 14	22 ± 6	24 ± 6	26 ± 7	31 ± 7
	Small	14 ± 4	28 ± 8*	17 ± 7	16 ± 4#	19 ± 3	21 ± 5#
Adventitial thickness (µm)	Large	17 ± 4	23 ± 3	16 ± 3	24 ± 4	21 ± 3	29 ± 4
	Small	12 ± 5	30 ± 17*	15 ± 7	22 ± 6	15 ± 5	29 ± 15*

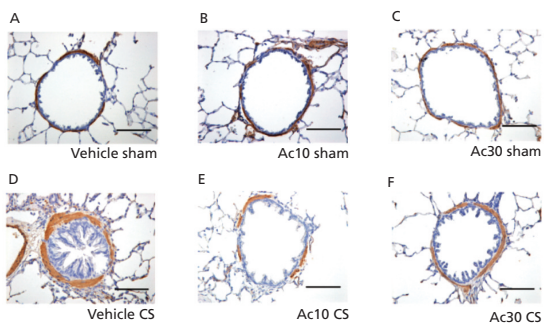
Data reported as mean ± standard deviation; *p<0.05 compared with sham-exposed under the same treatment; #p<0.05 compared with vehicle+CS-exposed
Results are stratified into large (>median) and small (<median) airways
CS, cigarette smoke; ILP, internal luminal perimeter

Table 2. Goblet cell metaplasia and emphysema

	Airway size (ILP)	Vehicle		Ac10 µg/mL		Ac30 µg/mL	
		Sham (n=8)	CS (n=10)	Sham (n=7)	CS (n=6)	Sham (n=7)	CS (n=8)
Goblet cells (cells/mm)	Large	3.2 ± 4.1	22.8 ± 14.6*	6.2 ± 8.4	17.9 ± 11.4	9.2 ± 10.3	15.9 ± 10.6
	Small	0.2 ± 0.5	6.0 ± 5.5*	1.0 ± 1.9	7.0 ± 6.1*	0.1 ± 0.2	9.9 ± 8.9*
Emphysema (µm)		34.2 ± 2.3	48.5 ± 9.1*	36.8 ± 3.4	41.8 ± 3.9*	38.3 ± 8.0	43.3 ± 5.4

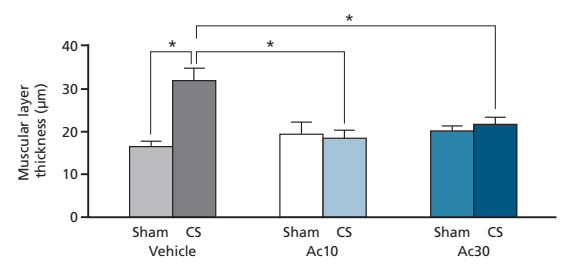
Data reported as mean ± standard error; *p<0.05 compared with sham-exposed under the same treatment
Results are stratified into large (>median) and small (<median) airways
CS, cigarette smoke; ILP, internal luminal perimeter

Figure 2. Airway remodelling



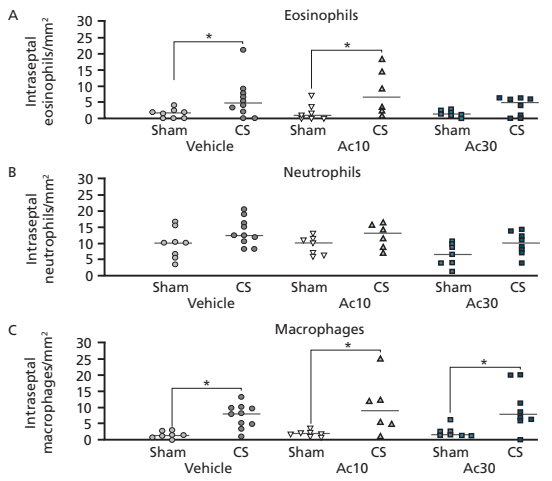
Immunohistochemistry for α-actin. Scale bar, 100 µm. CS, cigarette smoke

Figure 3. Effects of aclidinium on muscular thickness in small airways



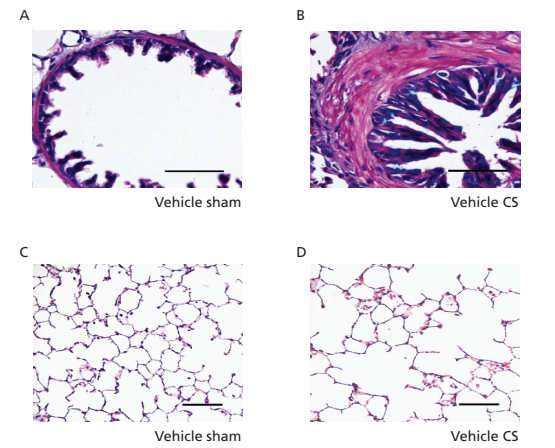
Data reported as mean ± standard error; n=6–10
*p<0.02
CS, cigarette smoke

Figure 4. Inflammatory cell counts in alveolar septa



Horizontal bar shows median values
*p<0.05
CS, cigarette smoke

Figure 5. Goblet cell metaplasia and emphysema. Alcian blue staining (A, B) and hematoxylin-eosin (C, D)



Scale bar, 50 µm
CS, cigarette smoke

Conclusions

- Guinea pigs exposed to CS for 6 months showed:
  - Thickening of the airway wall
  - Infiltration of inflammatory cells (for example, eosinophils, neutrophils and macrophages) in the airways and alveolar septa
  - Goblet cell metaplasia and emphysema.
- Aclidinium 10 µg/mL and 30 µg/mL significantly reduced the increase in muscular thickness of small airways induced by CS exposure.
- This chronic model of COPD suggests that aclidinium is efficacious in preventing smooth muscle remodelling in small airways.

Acknowledgements

This study was supported by Almirall S.A., Barcelona, Spain, and Consorcios Estratégicos Nacionales en Investigación Técnica (CENIT), Spain.

Poster presented at the European Respiratory Society Annual Congress, Amsterdam, The Netherlands, 24-28 September 2011

Effects of aclidinium bromide on respiratory function in guinea pigs chronically exposed to cigarette smoke

Elisabet Ferrer,[1] David Domínguez-Fandos,[1] Raquel Puig-Pey,[1] Cristina Carreño,[2] Mònica Aparici,[2] Jorge Beleta,[2] Neus Prats,[2] Amadeu Gavaldà,[2] Montserrat Miralpeix,[2] Víctor I Peinado,[1,3] Joan Albert Barberà[1,3]

[1]Department of Pulmonary Medicine, Hospital Clínic-IDIBAPS, Barcelona, Spain; [2]Almirall, R&D Centre, Barcelona, Spain; [3]CIBER de Enfermedades Respiratorias, Barcelona, Spain

Introduction

- Inhalation of cigarette smoke (CS) is a major cause of chronic obstructive pulmonary disease (COPD), a condition characterised by airflow obstruction and symptoms of chronic cough, sputum production, dyspnoea, wheezing and fatigue.
- Aclidinium bromide is a novel, second-generation, low systemic activity, inhaled long-acting muscarinic antagonist compound, currently under review by the EMA and FDA for the treatment of COPD.

Objective

- To evaluate the effects of aclidinium on respiratory function and signs of bronchial irritation in guinea pigs chronically exposed to CS for 6 months.

Methods

Animal groups

- Male Hartley guinea pigs (n=46, ~415 g) were housed under a 12-h light/dark cycle and randomised to 6 groups:
  - Vehicle sham: treated with vehicle and exposed to room air (n=8)
  - Vehicle CS: treated with vehicle and exposed to CS (n=10)
  - Ac10 sham: treated with aclidinium 10 µg/mL and exposed to room air (n=7)
  - Ac10 CS: treated with aclidinium 10 µg/mL and exposed to CS (n=6)
  - Ac30 sham: treated with aclidinium 30 µg/mL and exposed to room air (n=7)
  - Ac30 CS: treated with aclidinium 30 µg/mL and exposed to CS (n=8).

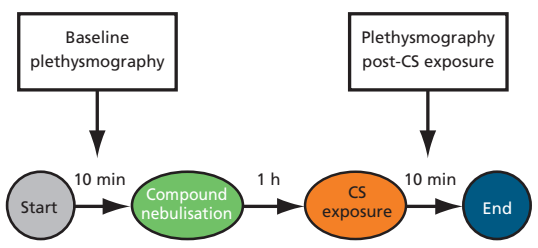
Cigarette smoke exposure

- Guinea pigs were exposed to the smoke of 6 non-filtered research cigarettes (3R4F Kentucky University) using a nose-only system for 5 days/week for 24 weeks.
- Control animals were sham-exposed to room air for 24 weeks.

Aclidinium administration

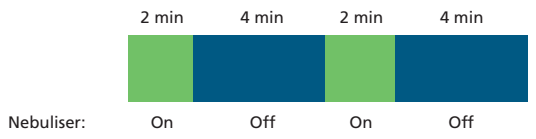
- Guinea pigs were nebulised with vehicle (water) or aclidinium in a gas mixture containing 5% CO_2, 21% O_2 and 74% N_2 (ultrasonic Devilbiss Ultraneb 3000 nebuliser, flow of 3 L/min), 1 hour prior to CS exposure (Figures 1 and 2).

Figure 1. Experimental protocol diagram



CS, cigarette smoke

Figure 2. Nebulisation protocol



Plethysmography and respiratory signs

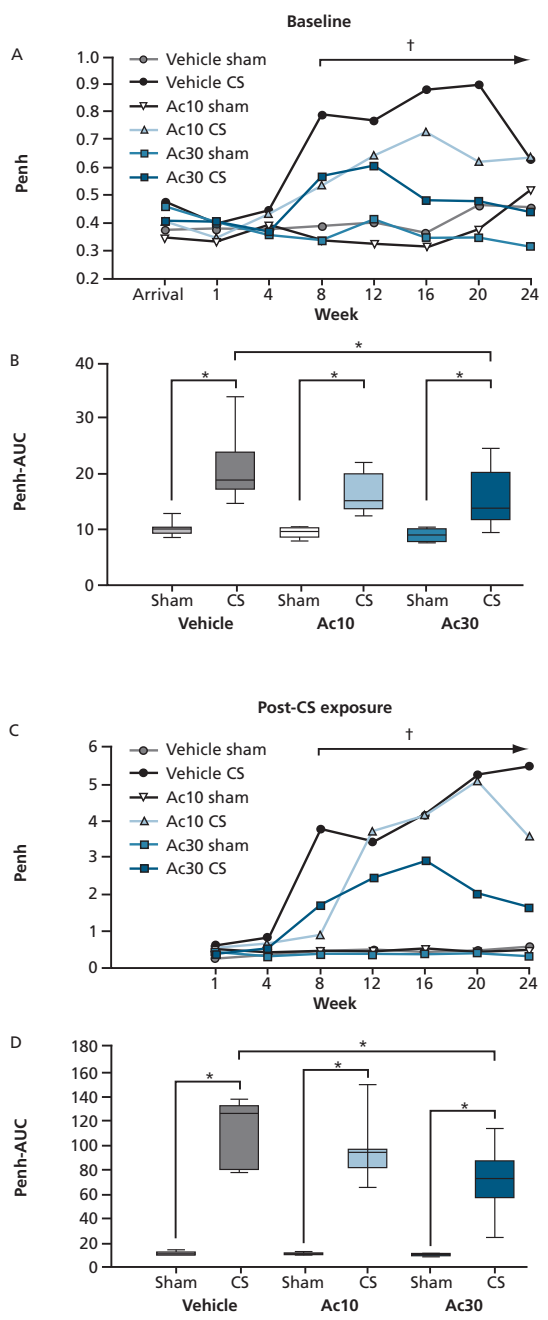
- Pulmonary function was evaluated weekly using an unrestrained plethysmography system (Buxco).
- Plethysmography was performed before (baseline) and 10 minutes post-CS exposure (Figure 1).
- Breathing frequency, tidal volume and enhanced pause (Penh) were recorded for 3 minutes. Penh was used as an indicator parameter of airflow limitation.
- Episodes of cough that occurred during the first minute post-CS exposure were counted each week from Week 9 to Week 24.
- Episodes of bronchoconstriction during CS exposure were counted during the whole study period.

Results

Respiratory function

- CS increased Penh, pre- and post-CS exposure (Figure 3).
- Aclidinium 30 µg/mL significantly reduced Penh pre- and post-CS exposure (Figure 3B and 3D) compared with CS.
- No changes in breathing frequency or tidal volume were observed between the vehicle and treatment groups, post-CS exposure (Table 1).

Figure 3. Penh evolution during the 24 weeks: (A) baseline, (C) post-CS exposure; and box plot of area under curve (AUC): (B) baseline, (D) post-CS exposure

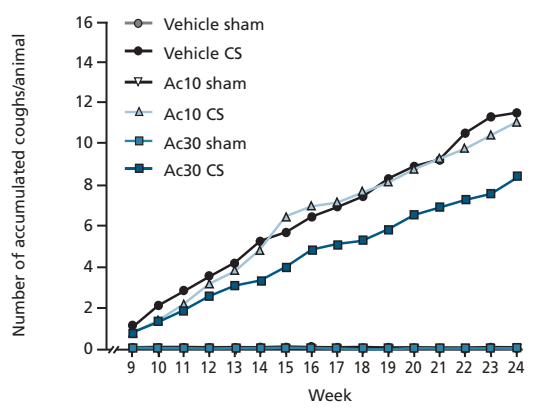


†p<0.05 CS effect, two-way ANOVA; *p<0.05 CS, Mann-Whitney
CS, cigarette smoke; Penh, enhanced pause

Respiratory signs: episodes of cough and bronchoconstriction

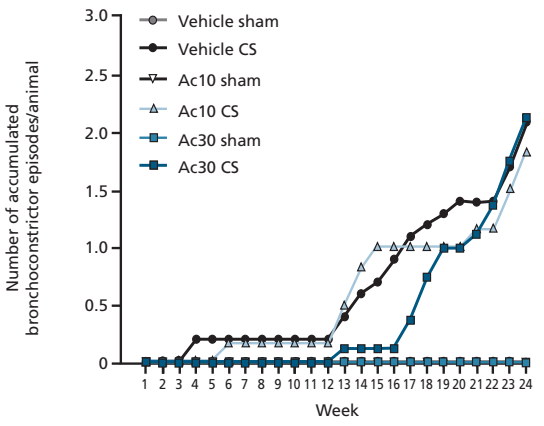
- Animals exposed to CS had more frequent episodes of cough and bronchoconstriction compared with non-CS-exposed animals.
- Aclidinium 30 µg/mL showed a trend to reduce the occurrence of cough and delay the occurrence of bronchoconstriction episodes (Figures 4 and 5).

Figure 4. Accumulated episodes of cough



CS, cigarette smoke

Figure 5. Accumulated episodes of bronchoconstriction



CS, cigarette smoke

Conclusions

- **Aclidinium 30 µg/mL attenuated airflow limitation in the guinea pigs exposed to CS.**
- **Aclidinium 30 µg/mL tended to reduce the signs of bronchial impairment induced by CS exposure.**

Acknowledgements

This study was supported by Almirall S.A., Barcelona, Spain, and Consorcios Estratégicos Nacionales en Investigación Técnica (CENIT), Spain.

Poster presented at the European Respiratory Society Annual Congress, Amsterdam, The Netherlands, 24-28 September 2011

Table 1. Respiratory profile at baseline and post-CS exposure

		Vehicle		Ac10 µg/mL		Ac30 µg/mL	
		Sham-exposed (n=8)	CS-exposed (n=8)	Sham-exposed (n=7)	CS-exposed (n=6)	Sham-exposed (n=7)	CS-exposed (n=8)
Breath frequency	Baseline	2409 (2219-2951)	2719 (2625-2818)	2280 (2409-2707)	2812 (2666-3006)*	2071 (2014-2105)	2839 (2447-2957)*
	Post-CS	1845 (1749-1896)	2316 (2010-2492)*	1879 (1764-1949)	2494 (2366-2761)*	1808 (1669-1855)	2463 (2053-2804)*
Tidal volume	Baseline	17192 (15591-18862)	17189 (15034-18190)	17424 (15482-18111)	17419 (16029-20638)	14522 (14255-15344)	16797 (15540-18553)*
	Post-CS	12905 (11862-13534)	22749 (20101-27916)*	13261 (13037-13846)	23744 (22031-26398)*	12433 (11834-13157)	22592 (21018-25651)*

Values are median and inter-quartile range; *p<0.05 vs corresponding sham-exposed, Mann-Whitney
CS, cigarette smoke

Effects of aclidinium bromide on cigarette smoke-induced fibroblast activation *in vitro*

Javier Milara,[1] Teresa Peiró,[2] Adela Serrano,[3] Gustavo Juan,[4]
Amadeu Gavaldà,[5] Montserrat Miralpeix,[5] Esteban Morcillo,[3] Julio Cortijo[2]

[1]CIBERES, Health Institute Carlos III, Valencia, Spain; [2]Research Unit, University General Hospital Consortium, Valencia, Spain; [3]Department of Pharmacology, Faculty of Medicine, University of Valencia, Spain; [4]Respiratory Unit, University General Hospital Consortium, Valencia, Spain; [5]Almirall, R&D Centre, Barcelona, Spain

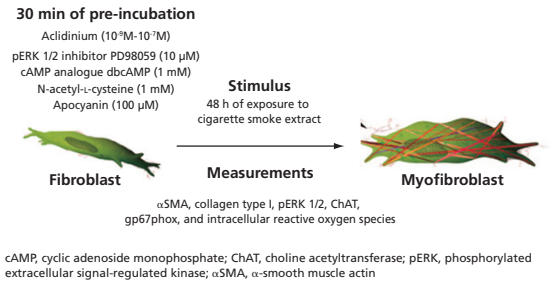
Introduction

- Inhalation of cigarette smoke (CS) is the main risk factor for chronic obstructive pulmonary disease (COPD), and has recently been shown to promote lung fibroblast proliferation and airway remodelling by means of non-cholinergic system activation.[1]
- Activation of lung fibroblasts produces a more contractile, proliferative and secretory myofibroblast phenotype that is characterised by increases in the myofibroblast markers α-smooth muscle (αSMA) and collagen type-I expression.
- Therefore, changes in myofibroblast markers can be used to study fibroblast activation and the process of airway remodelling.
- Aclidinium bromide is a novel, second-generation, low systemic activity, inhaled long-acting muscarinic antagonist compound, currently under review by the EMA and FDA for the treatment of COPD. This study explores the effects of aclidinium on human lung fibroblast activation following CS exposure *in vitro*.

Methods

- αSMA and collagen type-I expression were measured by real-time RT-PCR and Western blot (Figure 1).

Figure 1. Experimental procedures



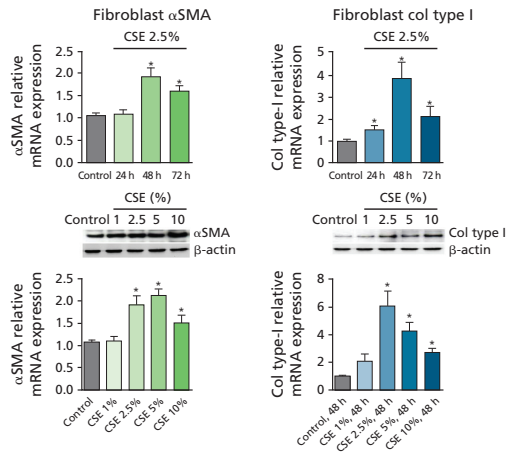
cAMP, cyclic adenoside monophosphate; ChAT, choline acetyltransferase; pERK, phosphorylated extracellular signal-regulated kinase; αSMA, α-smooth muscle actin

- ERK 1/2 phosphorylation was measured by Western blot.
- Intracellular reactive oxygen species (ROS) was measured by DCFDA fluorescence dye.
- Protein expression from the NADPH complex gp67phox and choline acetyltransferase (ChAT) were measured by Western blot.

Results

- Exposure to cigarette smoke extract (CSE) resulted in a concentration- and time-dependent increase in the mRNA and protein levels of αSMA and collagen type I by 2- and 6-fold, respectively, after 48 hours of CSE 2.5% exposure (Figure 2).

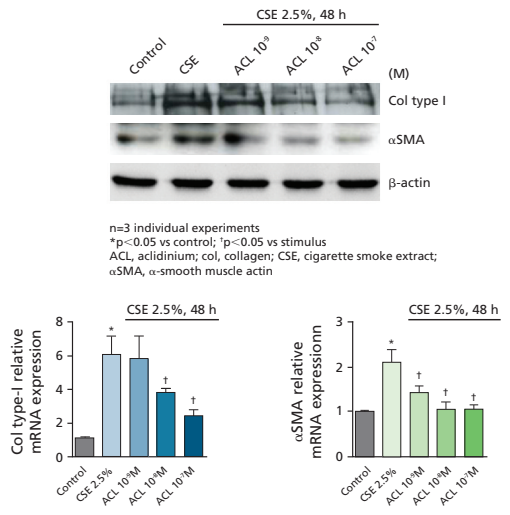
Figure 2. CSE induces αSMA and collagen type-I expression



Data are mean ± standard error of the mean; n=4 individual experiments
*p<0.05 vs control
col, collagen; CSE, cigarette smoke extract; αSMA, α-smooth muscle actin

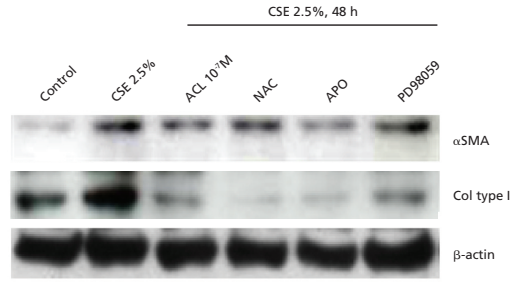
- Aclidinium dose-dependently attenuated the expression of αSMA and collagen type I induced by CSE 2.5%, with complete suppression at 10^{-7}M (Figure 3).
  - N-acetyl-L-cysteine (NAC) and apocyanin (both antioxidants), and PD98059 (inhibitor of pERK1/2), also prevented the expression of αSMA and collagen type I induced by CSE (Figure 4).

Figure 3. Aclidinium reduces CSE-induced αSMA and collagen type-I expression



n=3 individual experiments
*p<0.05 vs control; †p<0.05 vs stimulus
ACL, aclidinium; col, collagen; CSE, cigarette smoke extract; αSMA, α-smooth muscle actin

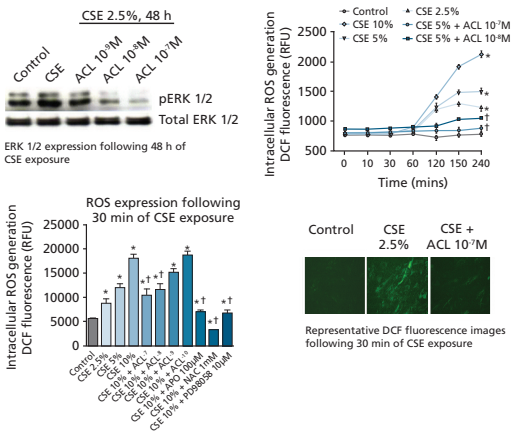
Figure 4. CSE-induced αSMA and collagen type-I expression are prevented by NAC, apocyanin and PD98059



ACL, aclidinium; col, collagen; APO, apocyanin; CSE, cigarette smoke extract; NAC, N-acetyl-L-cysteine; αSMA, α-smooth muscle actin

- Aclidinium attenuates CSE-induced phospho-ERK 1/2 and intracellular ROS (Figure 5):
  - Phospho-ERK 1/2 protein synthesis was increased by CSE 2.5%, which was attenuated by aclidinium in a dose-dependent manner
  - Intracellular ROS was promoted by CSE; highest concentration was reached after 4 hours
  - ROS generated by CSE was attenuated by aclidinium 10^{-7}M to 50% of control, and by PD98059 to 20% of control
  - Both NAC and apocyanin completely suppressed ROS induced by CSE.

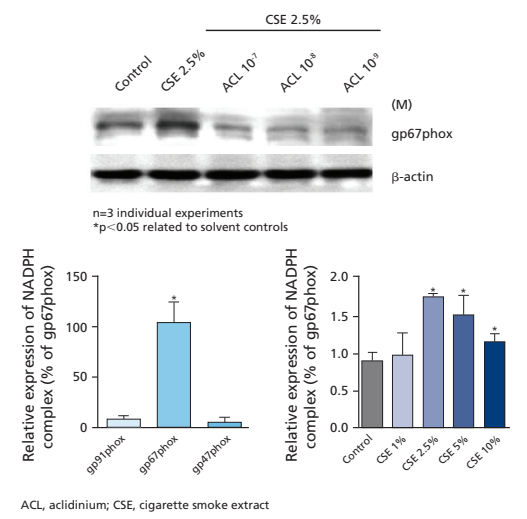
Figure 5. CSE-induced phospho-ERK 1/2 and intracellular ROS are attenuated by aclidinium



*p<0.05 vs control; †p<0.05 vs stimuli
Data are mean ± standard error of the mean
The fluorescence was generated *in vivo* by the change of non-fluorescence DCFDA to fluorescence DCF induced by intracellular ROS
ACL, aclidinium; CSE, cigarette smoke extract; NAC, N-acetyl-L-cysteine; ROS, reactive oxygen species

- CSE increased gp67phox expression by 1.75-fold. This was completely suppressed by aclidinium 10^{-7}M (Figure 6).
- CSE 2.5% induced ChAT upregulation, which suggests an autocrine acetylcholine regulation in response to CSE (Figure 7).

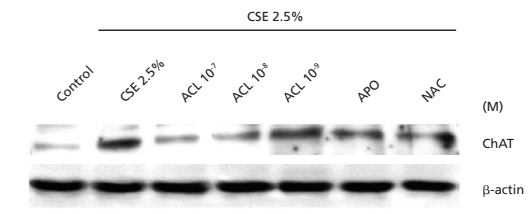
Figure 6. CSE-increased NADPH oxidase expression is suppressed by aclidinium



n=3 individual experiments
*p<0.05 related to solvent controls

ACL, aclidinium; CSE, cigarette smoke extract

Figure 7. CSE-increased ChAT expression is attenuated by aclidinium

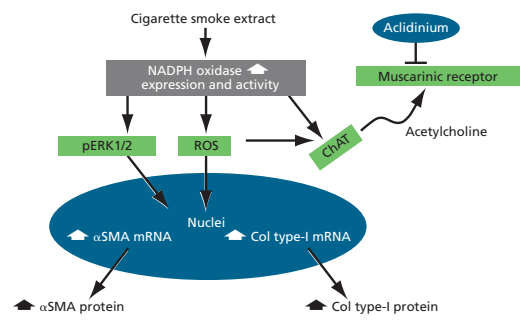


n=3 individual experiments
ACL, aclidinium; APO, apocyanin; CSE, cigarette smoke extract; NAC, N-acetyl-L-cysteine

Conclusions

- **The myofibroblast markers αSMA and collagen type I are increased in human lung fibroblast by CSE.**
- **Aclidinium attenuates the CSE-induced αSMA and collagen type-I protein expression in a dose-dependent manner.**
- **CSE-induced αSMA and collagen type I are mediated by intracellular ROS and ERK 1/2 phosphorylation.**
- **Aclidinium attenuated CSE-induced ROS generation.**
- **CSE increases ChAT expression, which suggests an autocrine acetylcholine regulation in response to CSE.**
- **Aclidinium attenuates CSE-induced lung fibroblast activation *in vitro* (Figure 8) and may have a similar effect in patients with COPD.**

Figure 8. Aclidinium attenuates CSE-induced lung fibroblast activation



ChAT, choline acetyltransferase; col, collagen; pERK, phosphorylated extracellular signal-regulated kinase; ROS, reactive oxygen species; αSMA, α-smooth muscle actin

Reference

1. Profita M, Bonanno A, Siena L, et al. Smoke, choline acetyltransferase, muscarinic receptors, and fibroblast proliferation in chronic obstructive pulmonary disease. J Pharmacol Exp Ther 2009; 329: 753-763.

Acknowledgements

This study was supported by Almirall S.A., Barcelona, Spain.

Poster presented at the European Respiratory Society Annual Congress, Amsterdam, The Netherlands, 24-28 September 2011

Effects of aclidinium bromide on human lung fibroblast activation *in vitro*

Javier Milara,[1] Adela Serrano,[2] Teresa Peiró,[2] Ricardo Guijarro,[3] Amadeu Gavaldà,[4] Montserrat Miralpeix,[4] Esteban Morcillo,[2] Julio Cortijo[5]

[1]CIBERES, Health Institute Carlos III, Valencia, Spain; [2]Department of Pharmacology, Faculty of Medicine, University of Valencia, Spain; [3]Thoracic Surgery Unit, University General Hospital Consortium, Valencia, Spain; [4]Almirall, R&D Centre, Barcelona, Spain; [5]Research Unit, University General Hospital Consortium, Valencia, Spain

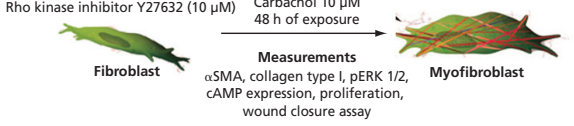
Introduction

- Airway remodelling contributes to the development of chronic obstructive pulmonary disease (COPD) and represents a challenging area of disease management. Lung fibroblast activation is known to be involved in this pathological remodelling process. Upon activation, resident fibroblasts are transformed into a more contractile, proliferative and secretory-active myofibroblast phenotype characterised by increased expression of α-smooth muscle actin (αSMA) and collagen type I.
- Muscarinic stimulation has recently been implicated in airway remodelling. For example:
  - A non-cholinergic system initiates remodelling propagated by structural cells, for example, fibroblasts and bronchial epithelial cells[1]
  - The muscarinic receptor agonist, carbachol, stimulates collagen synthesis and proliferation of lung fibroblasts.
- Aclidinium bromide is a novel, second-generation, low systemic activity, inhaled long-acting muscarinic antagonist compound in Phase III development for the treatment of COPD. This study investigates the effect of aclidinium on human lung fibroblasts, following carbachol exposure *in vitro*.

Methods

- αSMA and collagen type-I expression were assessed by real-time RT-PCR, Western blot and immunofluorescence (Figure 1).

Figure 1. Experimental procedures



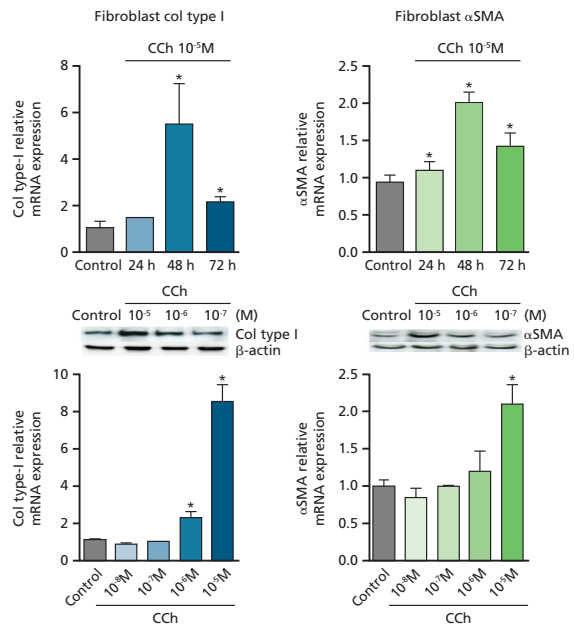
cAMP, cyclic adenoside monophosphate; pERK, phosphorylated extracellular signal-regulated kinase; αSMA, α-smooth muscle actin

- pERK 1/2 phosphorylation and RhoA-GTP activation were assessed by Western blot, and concentration of intracellular cAMP by cAMP Biotrak enzyme immunoassay.
- Fibroblast proliferation was assessed by BrdU kit, and fibroblast migration by wound closure assay.

Results

- Exposure to carbachol resulted in a concentration- and time-dependent increase in the mRNA and protein levels of αSMA and collagen type I by 2- and 8-fold, respectively (Figure 2).

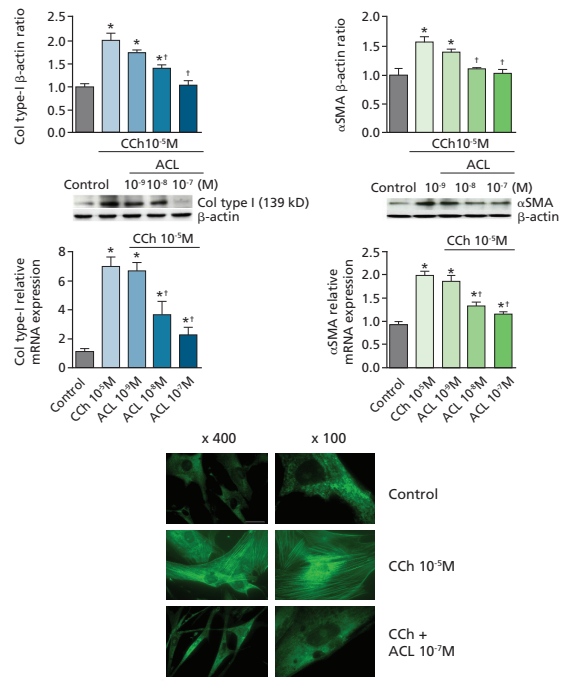
Figure 2. CCh induces αSMA and collagen type-I expression



Data are mean ± standard error of the mean; n=4 individual experiments
*p<0.05 vs control
CCh, carbachol; col, collagen; αSMA, α-smooth muscle actin

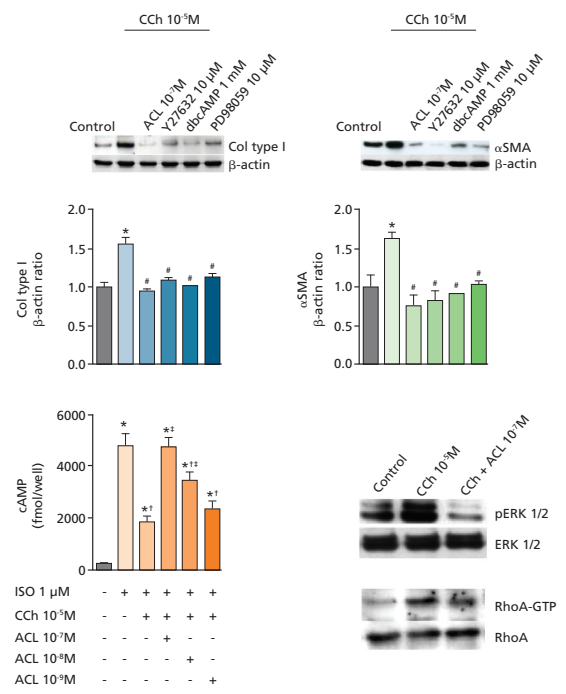
- Aclidinium dose-dependently inhibited the αSMA and collagen type-I expression induced by carbachol, resulting in complete suppression at 10^{-7}M. Furthermore, aclidinium (10^{-7}M) reduced carbachol-induced myofibrillar αSMA formation by 75% (Figure 3).

Figure 3. Aclidinium reduces CCh-induced αSMA and collagen type-I expression



Data are mean ± standard error of the mean; n=3 individual experiments
*p<0.05 vs control; †p<0.05 vs stimulus
Cells were immunostained with monoclonal anti-human αSMA followed by an appropriate secondary-FITC antibody
ACL, aclidinium; CCh, carbachol; col, collagen; αSMA, α-smooth muscle actin

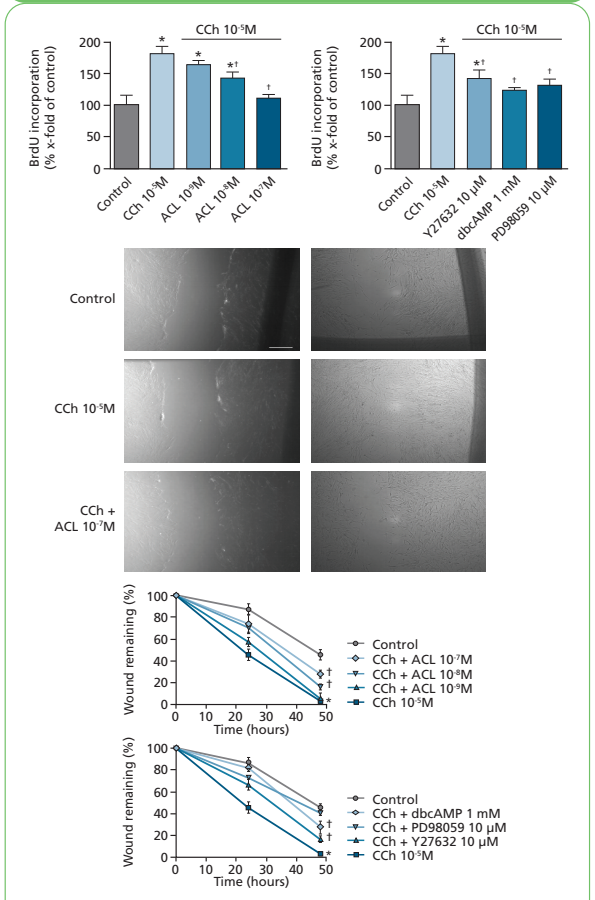
Figure 4. CCh induces αSMA and collagen type I by means of RhoA and ERK1/2 activation and cAMP downregulation



Data are mean ± standard error of the mean; n=3 individual experiments
*p<0.05 vs solvent controls; #p<0.05 vs CCh; †p<0.05 vs isoprenaline (ISO); ‡p<0.05 vs CCh plus ISO
ACL, aclidinium; CCh, carbachol; col, collagen; αSMA, α-smooth muscle actin

- Y27632, PD98059 and dbcAMP also prevented the carbachol-induced expression of αSMA and collagen type I (Figure 4).
- Aclidinium prevented the increase in pERK1/2 and RhoA-GTP following carbachol stimulation.
- Carbachol (10 μM, incubated for 10 min before isoprenaline) effectively prevented the upregulation of cAMP induced by isoprenaline (1 μM) which was completely reversed by aclidinium 10^{-7}M (added 10 min before carbachol).
- Carbachol increased lung fibroblast proliferation by 2-fold which was prevented by aclidinium 10^{-7}M (1.1-fold), Y27632 (1.4-fold), dbcAMP (1.2-fold) and PD98059 (1.3-fold) (Figure 5).

Figure 5. Aclidinium attenuated CCh-induced fibroblast proliferation and migration



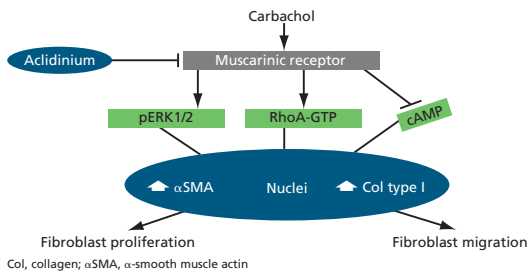
Data are mean ± standard error of the mean; n=3 individual experiments
*p<0.05 vs solvent controls; †p<0.05 vs stimulus
ACL, aclidinium; CCh, carbachol

- Fibroblast wound closure was completed after 48 hours of carbachol treatment.
- Fibroblast treated with aclidinium 10^{-7}M, Y27632, PD98059 or dbcAMP reduced wound closure by 30%, 20%, 28% and 40%, respectively.

Conclusions

- **Carbachol increased the myofibroblast markers, αSMA and collagen type I.**
- **Aclidinium inhibits carbachol-induced αSMA, and collagen type-I protein expression and αSMA microfilaments, in a dose-dependent manner.**
- **Carbachol-induced SMA and collagen type-I expression, fibroblast proliferation and migration are mediated by RhoA-GTP and ERK1/2 activation, and cAMP downregulation.**
- **Aclidinium inhibits carbachol-induced lung fibroblast proliferation and migration (Figure 6).**
- **Aclidinium may alleviate lung fibroblast activation in patients with asthma and COPD.**

Figure 6. Aclidinium attenuates CCh-induced lung fibroblast activation



Col, collagen; αSMA, α-smooth muscle actin

Reference

1. Gosens R, Zaagsma J, Meurs H, et al. Muscarinic receptor signaling in the pathophysiology of asthma and COPD. Respir Res 2006; 7: 73.

Acknowledgements

This study was supported by Almirall S.A., Barcelona, Spain.

Poster based on oral presentation at the European Respiratory Annual Congress, Amsterdam, The Netherlands, 24-28 September 2011

ACCORD COPD I: Twice-daily aclidinium improves quality of life and dyspnoea in COPD patients

Arthur F. Gelb,[1] James F. Donohue,[2] Anthony D'Urzo,[3] Ludmyla Rekeda,[4] Esther Garcia Gil,[5] Jordan Lateiner[4]

[1]Southern California Clinical Trials, Lakewood, USA; [2]University of North Carolina, Chapel Hill, USA; [3]University of Toronto, Toronto, Canada; [4]Forest Research Institute, Jersey City, USA; [5]Almirall R&D Centre, Barcelona, Spain

Introduction

- COPD symptoms often impact patients' ability to function and perform normal daily activities. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, thus, emphasizes that the treatment of patients with stable COPD should include managing symptoms and improving health-related quality of life (HRQoL).[1]
  - The St. George's Respiratory Questionnaire (SGRQ) is a disease-specific, patient-reported instrument that is used to evaluate quality of life and health status in COPD patients.[2] The SGRQ focuses on symptoms (frequency and severity), activities (causing or limited by breathlessness), and impact (social functioning, psychological) of the disease.
  - The Transition Dyspnoea Index (TDI) is an independent clinician-reported instrument that evaluates breathlessness, a key COPD symptom that can have a significant impact on quality of life.
- Aclidinium bromide is a novel, long-acting muscarinic antagonist that is under review by the EMA and FDA for the twice-daily maintenance treatment of moderate-to-severe COPD.
  - Previously reported primary efficacy and safety results from a Phase III study demonstrated that twice-daily treatment with aclidinium 200 µg and 400 µg administered via the Genuair® inhaler provides sustained bronchodilation and a favourable safety profile in patients with moderate-to-severe COPD.[3]
  - Results for the primary efficacy endpoint showed that change from baseline in morning pre-dose (trough) FEV_1 at Week 12 was statistically and clinically significantly greater for both aclidinium 200 µg and 400 µg BID as compared with placebo (86 mL and 124 mL, respectively; p<0.0001 for both).[3]
  - Here we report the effects of aclidinium 200 µg and 400 µg BID on health-related quality of life and dyspnoea in patients with COPD.

Methods

Study design

- This was a 12-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial evaluating the efficacy and safety of aclidinium bromide 200 µg and 400 µg administered twice daily.
- Patients (N=561) were randomised (1:1:1) to aclidinium bromide (200 µg or 400 µg BID) or placebo.
- Quality of life and dyspnoea were evaluated at baseline (randomisation) and every 4 weeks up to Week 12.

Study population

Inclusion criteria

- Male and female patients aged ≥40 years
- Diagnosis of moderate-to-severe stable COPD (forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio <70%; FEV_1 ≥30% and <80% of predicted)
- Current or ex-smokers with a smoking history of ≥10 pack-years

Exclusion criteria

- History or current diagnosis of asthma
- Respiratory infection or COPD exacerbation within 6 weeks (3 months if it resulted in hospitalisation) prior to screening
- Clinically relevant cardiovascular conditions or respiratory conditions (other than COPD) and abnormalities in laboratory values or electrocardiogram (ECG) parameters

Allowed concomitant medications

- Albuterol (USA)/Salbutamol (Canada) as needed
- Inhaled corticosteroids (CS) and oral or parenteral CS at doses equivalent to 10 mg/day or 20 mg every other day (if stable at the equivalent dose for 4 weeks before Visit 1)

Study endpoints

- The change from baseline in SGRQ total score and TDI focal score at Weeks 4, 8, and 12
- The percentage of patients with a clinically meaningful improvement in SGRQ total score (≥4 units decrease) and TDI focal score (≥1 unit increase) at Weeks 4, 8, and 12

Statistical analysis

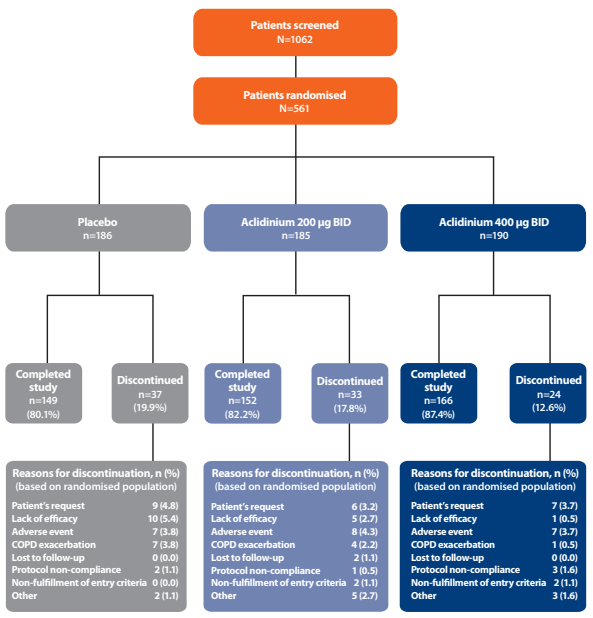
- SGRQ and TDI endpoints were analysed using the ANCOVA model with sex and treatment group as factors and age and baseline SGRQ (total score) or baseline dyspnoea index (BDI; focal score) as covariates.
- A logistic regression model was used to analyse the percentages of patients who achieved an improvement of ≥4 units in SGRQ total score or ≥1 unit in TDI focal score with treatment group, sex, age, and baseline SGRQ total score or BDI as explanatory variables, respectively.
- The intent-to-treat (ITT) population was used for analyses for both SGRQ and TDI.

Results

Baseline demographics

- Of the 561 patients randomised, 467 completed the study (87.4% in the aclidinium 400 µg group, 82.2% in the aclidinium 200 µg group, and 80.1% in the placebo group; Figure 1).

Figure 1. Study flow chart



One patient randomised to aclidinium 200 µg discontinued prior to receiving any study medication and was not included in the safety or ITT populations.

- Baseline demographics were similar across all treatment groups (Table 1).

Table 1. Demographic and baseline characteristics (ITT population)

Characteristic	Placebo (n=185)	Aclidinium 200 µg (n=184)	Aclidinium 400 µg (n=190)	Total (N=559)
Age, mean (SD), years	65.0 (9.2)	63.1 (9.5)	64.9 (9.5)	64.3 (9.4)
Male, n (%)	96 (51.4)	101 (54.9)	100 (52.6)	296 (53.0)
Caucasian, n (%)	174 (94.1)	169 (91.8)	181 (95.3)	524 (93.7)
BMI, mean (SD), kg/m²	27.5 (5.2)	27.3 (5.1)	27.6 (5.0)	27.5 (5.1)
Current smoker, n (%)	87 (47.0)	84 (45.7)	80 (42.1)	251 (44.9)
Smoking history, mean (SD), pack-years	52.9 (28.1)	53.0 (23.3)	57.2 (28.5)	54.4 (26.8)
SGRQ total score, mean (SD)	45.1 (16.3)	45.9 (17.2)	48.3 (17.8)	46.5 (17.1)
BDI focal score, mean (SD)	6.5 (2.2)	6.4 (2.1)	6.2 (2.1)	6.4 (2.1)
Baseline (Visit 2) FEV_1, mean (SD), L	1.38 (0.6)	1.36 (0.6)	1.33 (0.5)	1.36 (0.5)
Post-bronchodilator FEV_1, mean (SD), % of predicted value	54.7 (13.4)	52.8 (13.7)	54.1 (12.9)	53.9 (13.3)
Post-bronchodilator FEV_1/FVC ratio, mean (SD), %	52.8 (10.5)	50.9 (10.6)	51.5 (10.2)	51.8 (10.4)
COPD severity, n (%)				
Stage II (moderate)	111 (60.0)	98 (53.3)	118 (62.1)	327 (58.5)
Stage III (severe)	72 (38.9)	80 (43.5)	68 (35.8)	220 (39.4)
Stage IV (very severe)	1 (0.5)	3 (1.6)	1 (0.5)	5 (0.9)

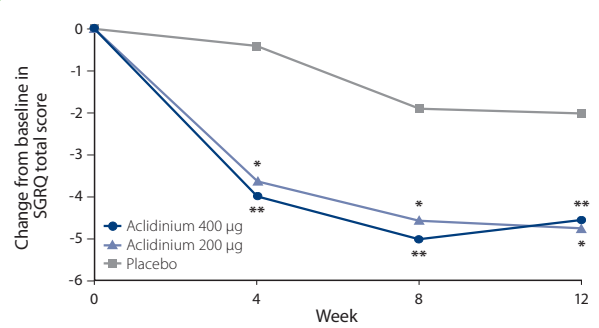
BMI, body mass index

Health-related quality of life

SGRQ total score

- Patients in both the aclidinium 200 µg and 400 µg groups showed a statistically significantly greater improvement in change from baseline SGRQ total score at all time points as compared with placebo (Figure 2).

Figure 2. Change from baseline in SGRQ total score at Weeks 4, 8, and 12



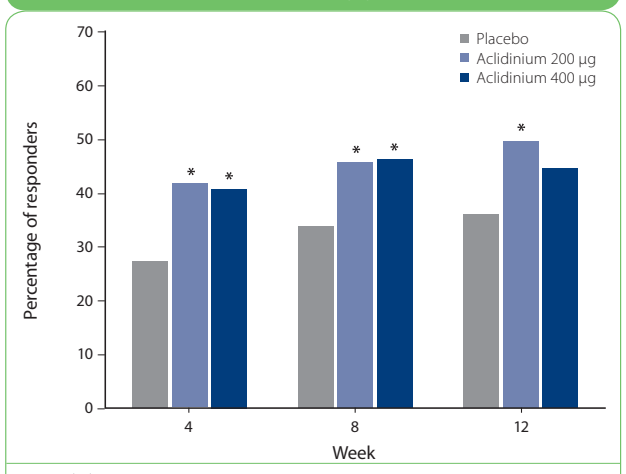
*Aclidinium 200 µg BID vs placebo, p<0.05; **Aclidinium 400 µg BID vs placebo, p<0.05
Minimal clinically important difference is a ≥4-point difference in SGRQ total score.[4]

- At Week 4, the largest improvement in SGRQ total score was observed with an adjusted mean difference vs placebo of -3.2 and -3.6 for aclidinium 200 µg and 400 µg, respectively (p<0.001 for both).
- The adjusted mean differences vs placebo in the change from baseline in SGRQ total score at Week 12 (study end) were -2.7 for aclidinium 200 µg (p=0.013) and -2.5 for aclidinium 400 µg (p=0.019).

Clinically meaningful improvements in quality of life

- A significantly higher percentage of patients in each of the aclidinium treatment groups achieved a clinically meaningful improvement in SGRQ total score (≥4-point decrease from baseline)[4] compared with placebo at all time points (p<0.05 for all based on odds ratios, except at Week 12 for aclidinium 400 µg, p=0.139; Figure 3).

Figure 3. Percentage of patients who achieved a clinically meaningful difference in SGRQ total score at Weeks 4, 8, and 12



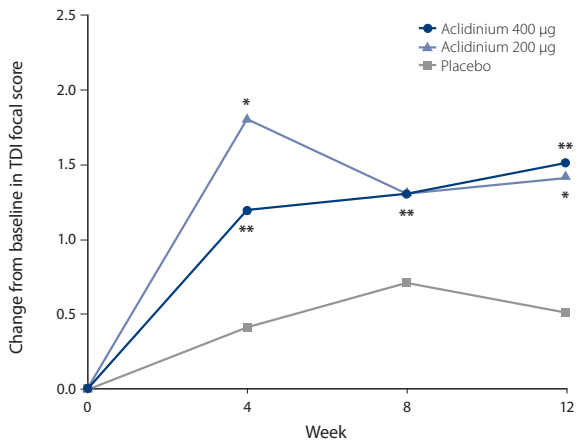
*p<0.05 vs placebo

Dyspnoea

TDI

- Treatment with both aclidinium doses resulted in a statistically significantly greater improvement in breathlessness, as measured by the TDI focal score, vs placebo across all time points (except at Week 8 for aclidinium 200 µg, p=0.060; Figure 4).
- The maximum improvement in TDI focal score was seen at Week 4 for aclidinium 200 µg and at Week 12 for aclidinium 400 µg. The adjusted mean differences vs placebo in TDI focal score were 1.4 and 1.0 for the 200 µg and 400 µg groups, respectively (p<0.005 for both).
- Treatment with aclidinium 200 µg resulted in an adjusted mean difference in TDI focal score vs placebo of 0.9 at Week 12 (p=0.005).
- At Week 12, treatment with aclidinium 400 µg resulted in a clinically meaningful improvement in TDI focal score (≥1-unit increase) as compared with placebo (p<0.05).

Figure 4. Change from baseline in TDI focal score at Weeks 4, 8, and 12

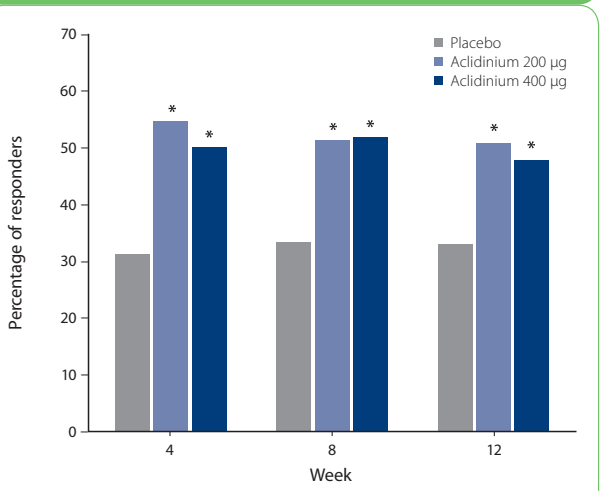


*Aclidinium 200 µg BID vs placebo, p<0.05; **Aclidinium 400 µg BID vs placebo, p<0.05
Minimal clinically important difference is ≥1-point increase in TDI focal score.

Clinically meaningful improvements in dyspnoea

- In each of the aclidinium treatment groups, a significantly higher percentage of patients achieved a clinically meaningful improvement in TDI focal score compared with placebo at all time points (p<0.05 for both, Figure 5).

Figure 5. Percentage of patients who achieved a clinically meaningful difference in TDI focal score at Weeks 4, 8, and 12



*p<0.05 vs placebo

Limitations

- As this study was conducted over a short period of time (12 weeks), long-term studies investigating the effects of aclidinium on COPD symptoms are warranted.
- The study duration was not sufficient to detect differences in improvements in symptoms and quality of life between the 2 aclidinium doses.

Conclusions

- **In this study, treatment with twice-daily aclidinium resulted in improvements in quality of life and dyspnoea in patients with COPD as measured by SGRQ and TDI.**
- **Both doses of aclidinium significantly improved patients' SGRQ total scores and TDI focal scores. Additionally, treatment with aclidinium 400 µg resulted in a clinically meaningful change in TDI focal score at study end.**
- **A significantly greater percentage of patients in the aclidinium groups achieved clinically meaningful differences in both SGRQ total score and TDI focal score as compared to the placebo group during this 12-week study.**

References

1. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007; 176(6): 532-555.
2. Jones PW, Quirk FH, Baveystock CM, et al. A self complete measure for chronic airflow limitation: the St. George's Respiratory Questionnaire. Am Rev Respir Dis 1992; 145(6): 1321-1327.
3. Kerwin E, D'Urzo A, Gelb A, et al. Twice-daily aclidinium bromide in COPD patients: Efficacy and safety results from ACCORD COPD I. Eur Resp J 2010; 36(Suppl 54): 219s.
4. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD 2005; 2(1): 75-79.

Acknowledgements

This study was supported by Forest Laboratories, Inc., New York, USA, and Almirall SA, Barcelona, Spain. Funding for poster development was provided by Forest Laboratories, Inc. to Prescott Medical Communications Group, Chicago, USA.

Poster presented at the European Respiratory Society Annual Congress, Amsterdam, Netherlands, 24-28 September 2011

ACCORD COPD I: Improvements in nighttime symptoms and rescue medication use in COPD with twice-daily aclidinium bromide

Edward Kerwin,[1] Stephen Rennard,[2] Arthur F. Gelb,[3] Ludmyla Rekeda,[4] Esther Garcia Gil,[5] Cynthia Caracta[4]

[1]Clinical Research Institute, Medford, USA; [2]University of Nebraska Medical Center, Omaha, USA; [3]Southern California Clinical Trials, Lakewood, USA; [4]Forest Research Institute, Jersey City, USA; [5]Almirall, R&D Centre, Barcelona, Spain

Introduction

- Chronic obstructive pulmonary disease (COPD) is a treatable airway disease characterised by airway obstruction that is not fully reversible.[1] COPD is projected to be the third leading cause of death worldwide by 2020.[2]
- COPD patients have reported that their symptoms are worse at night and in the early morning[3], which may result in disturbed sleep and limitations on morning activities. Little has been published about the effects of currently available COPD medications on nighttime symptoms and sleep.
- Aclidinium bromide is a novel, potent, long-acting muscarinic antagonist that is under review by the EMA and FDA for the twice-daily maintenance treatment of COPD. Previous clinical studies have reported sustained bronchodilation and a favourable safety and tolerability profile with twice-daily aclidinium.[4,5]
- The primary objectives of this Phase III study were to assess the efficacy and safety of twice-daily aclidinium 200 µg and 400 µg administered via the Genuair® inhaler in moderate-to-severe COPD patients.
  - Results for the primary efficacy endpoint of this study showed that change from baseline in morning pre-dose (trough) FEV_1 at Week 12 was statistically and clinically significantly greater for both aclidinium 200 µg and 400 µg BID as compared with placebo (86 mL and 124 mL, respectively; p<0.0001 for both).[5]
  - Here we report the effect of twice-daily aclidinium bromide 200 µg and 400 µg on nighttime symptoms, sleep, and rescue medication use in patients with moderate-to-severe COPD.

Methods

Study design

- This was a 12-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial evaluating twice-daily aclidinium 200 µg and 400 µg.
- A total of 561 patients were randomised (1:1:1) to aclidinium (200 µg or 400 µg BID) or placebo.

Study population

Inclusion criteria

- Male and female patients aged ≥40 years
- Diagnosis of moderate-to-severe stable COPD (forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio <70%; FEV_1 ≥30% and <80% of predicted)
- Current or ex-smokers with a smoking history of ≥10 pack-years

Exclusion criteria

- History or current diagnosis of asthma
- Respiratory infection or COPD exacerbation within 6 weeks (3 months if it resulted in hospitalisation) prior to screening
- Clinically significant or relevant cardiovascular conditions, laboratory test, electrocardiogram (ECG) parameters, or respiratory conditions (other than COPD)

Allowed concomitant medications

- Albuterol (USA)/Salbutamol (Canada) inhaler as needed
- Inhaled corticosteroids (CS) at any dose and oral or parenteral CS at doses not exceeding 10 mg/day or 20 mg every other day (if stable for 4 weeks before Visit 1)

Health outcome measures

- Each morning the COPD Nighttime Symptoms Questionnaire and Sleep Diary were self-administered using an electronic diary (eDiary), starting at screening (2 weeks before randomisation) through study end (Week 12).
- Additionally, each morning patients recorded the use of rescue medication (number of puffs) over the previous 12 hours and 24 hours in the eDiary, starting at screening through study end.

COPD nighttime symptoms questionnaire

- The questionnaire was designed with a 24-hour recall period.
  - The frequency of the following nighttime symptoms were assessed: breathlessness, cough, sputum production, and wheezing.
  - Additional questionnaire items assessed morning activity restriction due to breathlessness, level of breathlessness in the first hour upon getting up, effect of breathlessness and cough on activities in the previous 12 hours, amount of sputum production during sleeping hours, amount of sputum production in the previous 24 hours, and the effect of COPD symptoms on sleep.

Sleep diary[6]

- This was a 10-item questionnaire that assessed the time that the patient went to sleep for the first time the previous night, how long it took to fall asleep, the frequency of waking up during the night, the frequency of waking up and having difficulty falling back to sleep, the time that the patient woke up that morning, whether the patient woke up at the desired time, the total number of hours slept, the overall sleep quality the previous night, how rested the patient felt that morning, and how the patient's sleep the prior night compared to their normal sleep.

Statistical analysis

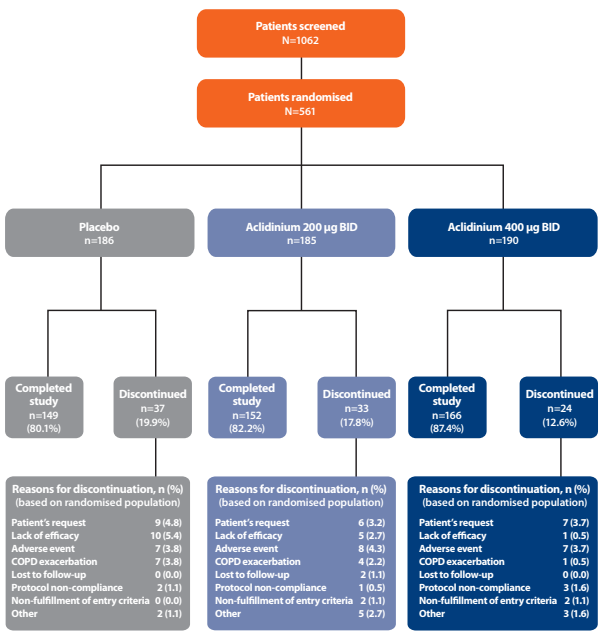
- Weekly averages were calculated using the sum of daily averages for each week from baseline until Week 12.
- Change from baseline to Weeks 1, 4, 8, and 12 in the COPD Nighttime Symptoms Questionnaire and Daily Sleep Diary scores, as well as rescue medication use, were analysed using the intention-to-treat (ITT) population and an ANCOVA model with treatment as factor and the corresponding baseline as covariate.

Results

Baseline demographics

- A total of 561 patients were randomised and 467 patients completed the study (80.1% of the placebo group, 82.2% of aclidinium 200 µg, and 87.4% of aclidinium 400 µg; Figure 1).

Figure 1. Study flow chart



One patient randomised to aclidinium 200 µg discontinued prior to receiving any study medication and was not included in the safety or ITT populations.

- Baseline demographics and clinical characteristics were comparable across all treatment groups.
- Baseline (Visit 2) mean (SD) FEV_1 and percent predicted were 1.36 (0.54) L and 47.2 (14.1) %, respectively.
- The mean (SD) values for all nighttime symptom (Table 1) and sleep diary parameters (Table 2) were similar between all treatment groups at baseline.
- Mean baseline rescue medication use (number of puffs) was comparable among treatment groups: 3.9 for placebo, 3.7 for aclidinium 200 µg, and 4.4 for aclidinium 400 µg.

Table 1. Mean (SD) values of nighttime COPD symptoms at baseline (ITT population)

Characteristic	Placebo (n=185)	Aclidinium 200 µg (n=184)	Aclidinium 400 µg (n=190)
Frequency of occurrence in the previous night			
Breathlessness[a]	1.4 (1.2)	1.5 (1.1)	1.4 (1.3)
Cough[a]	2.1 (1.5)	2.1 (1.6)	1.9 (1.6)
Sputum production[a]	1.3 (1.4)	1.3 (1.5)	1.4 (1.5)
Wheezing[a]	1.3 (1.5)	1.5 (1.5)	1.3 (1.5)
Severity and impact of early morning symptoms			
Usual activities restricted by breathlessness in the morning[b]	1.4 (0.9)	1.4 (0.9)	1.4 (0.9)
Severity of breathlessness for the first hour on getting up in the morning[c]	1.6 (0.9)	1.6 (1.0)	1.5 (0.9)
Severity and impact of nighttime symptoms			
Severity of breathlessness symptoms and impact on activity[d]	1.8 (0.9)	1.8 (0.9)	1.7 (0.9)
Severity of cough and impact on activity[d]	1.5 (0.9)	1.5 (0.9)	1.4 (1.0)
Amount of sputum production			
During sleeping hours[e]	0.7 (0.8)	0.7 (0.8)	0.7 (0.8)
During previous 24 hours across days[e]	1.6 (1.0)	1.5 (1.0)	1.5 (1.1)
Rescue medication			
Total use, puffs	3.9	3.7	4.4
Daytime use, puffs	3.3	3.1	3.6
Nighttime use, puffs	0.6	0.6	0.8
COPD symptoms affecting sleep			
Breathing symptoms affecting sleep at night[f]	0.8 (0.7)	0.9 (0.8)	0.9 (0.8)

[a]0 = never; 1 = 1-2 times; 2 = 3-4 times; 3 = 5-6 times; 4 = 7 or more times
[b]0 = none; 1 = symptoms present, but caused little or no restriction on morning activities; 2 = mild symptoms that were unpleasant, but caused little restriction on morning activities; 3 = moderate symptoms that caused discomfort and moderately restricted morning activities; 4 = severe symptoms that interfered greatly with morning activities
[c]0 = none; 1 = symptoms present, but caused little or no discomfort; 2 = mild symptoms that were unpleasant, but caused little or no discomfort; 3 = moderate symptoms that caused discomfort, but did not affect normal activities; 4 = severe symptoms that interfered with normal activities
[d]0 = none; 1 = symptoms present, but caused little or no discomfort; 2 = mild symptoms that were unpleasant, but caused little or no discomfort; 3 = moderate symptoms that caused discomfort, but did not affect normal daily activities; 4 = severe symptoms that interfered with normal daily activities
[e]Amount of sputum produced was scored from 0 = none; 1 = amount of 1 teaspoon; 2 = amount of 1 tablespoon; 3 = more than 1 tablespoon
[f]Symptoms causing early awakening or awakening during the night: 0 = none; 1 = once during the night; 2 = 2 or more times during the night; 3 = most times during the night; 4 = symptoms which were so severe that I could not sleep at all

Table 2. Baseline sleep diary parameters (ITT population)

Characteristic	Placebo (n=185)	Aclidinium 200 µg (n=184)	Aclidinium 400 µg (n=190)
Time it took to fall asleep, minutes, mean (SD)	21. 8 (11.7)	23.2 (11.8)	21.8 (11.2)
Frequency of waking up during the night, mean (SD)	1.8 (1.0)	1.7 (1.0)	1.7 (1.1)
Frequency of waking up and having difficulty falling back to sleep, mean (SD)	0.7 (0.9)	0.8 (0.8)	0.8 (1.0)
Whether the patient woke up at the desired time,[a,b] n (%)			
Earlier than planned	33 (17.8)	62 (33.7)	52 (27.4)
On time	114 (61.6)	98 (53.3)	95 (50.0)
Later than planned	9 (4.9)	8 (4.3)	13 (6.8)
Earlier than planned/On time	9 (4.9)	6 (3.3)	10 (5.3)
Earlier than planned/Later than planned	1 (0.5)	2 (1.1)	3 (1.6)
On time/Later than planned	3 (1.6)	0 (0.0)	7 (3.7)
Earlier than planned/On time/Later than planned	2 (1.1)	1 (0.5)	0 (0.0)
Total number of hours slept, mean (SD)	7.0 (1.1)	7.0 (1.2)	7.0 (1.2)
Overall sleep quality the previous night,[c] mean (SD)	2.9 (0.7)	2.9 (0.8)	2.9 (0.8)
How rested the patient felt that morning,[d] mean (SD)	2.6 (0.7)	2.5 (0.8)	2.6 (0.8)
How the patient's sleep the prior night compared to their normal sleep,[e] mean (SD)	2.8 (0.6)	2.8 (0.7)	2.8 (0.7)

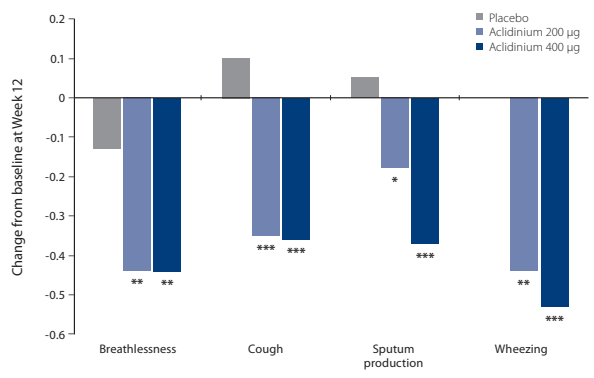
[a]Values from patients who did not have ≥4 entries at baseline were not included; [b]Measured at baseline visit using the average of the values from the previous week; [c]Rated from 0 (extremely poor) to 5 (extremely good); [d]Rated from 0 (well rested) to 5 (not at all rested); [e]Rated from 0 (much worse than normal) to 5 (much better than normal)

Nighttime COPD symptoms

Frequency

- Compared to placebo, treatment with aclidinium 200 µg and 400 µg significantly reduced daily average frequency of nighttime COPD symptoms for nighttime breathlessness, cough, sputum production, and wheezing at Week 12 (p<0.05, 200 µg and p<0.001, 400 µg; Figure 2).

Figure 2. Mean change from baseline in daily average frequency of nighttime symptoms[†] at Week 12 (ITT population)

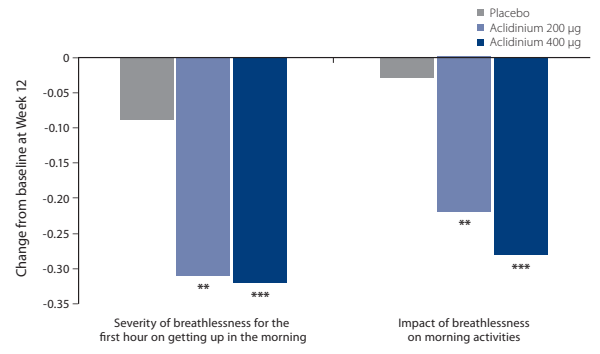


[†]Frequency of each of the variables was scored daily as follows: 0 = Never, 1 = 1-2 times, 2 = 3-4 times, 3 = 5-6 times, 4 = 7 or more times; weekly averages were analysed.
*p<0.05, **p<0.01, ***p<0.001 vs placebo

Severity and impact of early morning breathlessness

- The severity of early morning (first hour) breathlessness and restriction of morning activities due to breathlessness were reduced with aclidinium 200 µg (p<0.01) and 400 µg (p<0.001) vs placebo at Week 12 (Figure 3).

Figure 3. Mean change from baseline in severity[‡] and impact[‡] of early morning breathlessness at Week 12 (ITT population)



[‡]Severity of breathlessness was rated from 0 (none) to 4 (severe symptoms that interfered with normal activities).
[‡]Impact of breathlessness was rated from 0 (none) to 4 (severe symptoms that interfered greatly with morning activities).
**p<0.01, ***p<0.001 vs placebo

- Both aclidinium doses resulted in significant improvements as compared with placebo in the severity of 12-hour nighttime breathlessness and cough and their impact on activity at study endpoint (Week 12; Table 3).

Table 3. Mean (SD) change from baseline in severity and impact of nighttime breathlessness and cough on morning activities[a] at Week 12 (ITT population)

Characteristic	Placebo (n=185)	Aclidinium 200 µg (n=184)	Aclidinium 400 µg (n=190)
Breathlessness (during previous 12 hours)	-0.19 (0.70)	-0.41 (0.78)**	-0.44 (0.86)***
Cough (during previous 12 hours)	-0.10 (0.78)	-0.28 (0.84)*	-0.24 (0.76)*

[a]The amount of sputum produced was scored from 0 (none) to 3 (more than 1 tablespoon).
*p<0.05, **p<0.01, ***p<0.001 vs placebo

Sputum production

- The amount of sputum produced over 24 hours was significantly reduced from baseline with aclidinium 200 µg (p<0.05) and 400 µg (p<0.01) at Week 12 compared with placebo (Table 4).
- At Week 12, sputum production during sleeping hours was not significantly reduced from baseline with aclidinium compared with placebo, possibly due to a reduction in sputum production in the placebo group at this time point (Table 4).

Table 4. Mean (SD) change from baseline in amount of sputum[a] at Week 12 (ITT population)

Characteristic	Placebo (n=185)	Aclidinium 200 µg (n=184)	Aclidinium 400 µg (n=190)
24-hour production	0.04 (0.61)	-0.10 (0.68)*	-0.14 (0.67)**
Production during sleeping hours	-0.12 (0.52)	-0.17 (0.68)	-0.24 (0.62)

[a]The amount of sputum produced was scored from 0 (none) to 3 (more than 1 tablespoon).
*p<0.05, **p<0.01 vs placebo

Rescue medication use

- Compared with placebo, both aclidinium 200 µg and 400 µg significantly reduced total daily rescue medication use over the 12-week treatment period by 0.7 (p=0.0010) and 0.9 (p<0.0001) puffs per day, respectively.
- The adjusted mean difference (95% CI) in change from baseline in total rescue medication use at Week 12 was -0.4 (-1.0, 0.1) and -0.6 (-1.1, -0.1) puffs for aclidinium 200 µg and 400 µg, respectively (p<0.001 vs placebo for both).

Sleep results

- At Week 12, the severity and impact of breathing symptoms on sleep was significantly improved from baseline with aclidinium 400 µg as compared with placebo (-0.24 vs -0.06, respectively, p<0.01).
- Overall, the results on sleep diary parameters were not statistically significantly different between the aclidinium arms and placebo. However, significant differences were observed with aclidinium 400 µg vs placebo in the frequency of nighttime awakenings and ability to fall back asleep at Week 12 (p<0.05).

Conclusions

- Twice-daily aclidinium 200 µg and 400 µg reduced the frequency of nighttime episodes of breathlessness, cough, sputum production, and wheezing compared with placebo.
- Both aclidinium doses significantly reduced the severity and impact of nighttime and early morning symptoms compared with placebo.
- Treatment with aclidinium 200 µg and 400 µg BID significantly reduced rescue medication use over this 12-week study.
- Aclidinium 400 µg significantly improved quality of sleep by reducing nighttime awakenings as well as difficulty in falling back to sleep.
- The relief from nighttime symptoms provided by twice-daily aclidinium may make it a valuable new treatment option for patients with moderate-to-severe COPD.

References:

1. Rabe KF, Hurd S, Anzueto A et al. Global Strategy for the Diagnosis, Management, and Prevention Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2007; 176: 532-555.
2. Murray CJ and Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997; 349(9064): 1498-1504.
3. Partridge MR, Karlsson N, Small IR. Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey. Curr Med Res Opin 2009; 25(8): 2043-2048.
4. Fuhr H, Magnussen H, Panke K, et al. Efficacy and safety of aclidinium bromide 400 µg BID compared with placebo and tiotropium in patients with moderate to severe COPD CHEST 2010; in press.
5. Kerwin E, D'Urzo A, Gelb A, et al. Twice-daily aclidinium bromide in COPD patients: Efficacy and safety results from ACCORD COPD I. Eur Respir J 2010; 36(suppl 54): 219s.
6. Haythornthwaite JA, Hegel MT, Kerns RD. Development of a sleep diary for chronic pain patients. J Pain Symptom Manage 1991; 6(2): 65-72.

Acknowledgements

This study was supported by Forest Laboratories, Inc., New York, USA, and Almirall SA, Barcelona, Spain. Funding for poster development was provided by Forest Laboratories, Inc. to Prescott Medical Communications Group, Chicago, USA.

Poster presented at the European Respiratory Society Annual Congress, Amsterdam, Netherlands, 24-28 September, 2011

ACCORD COPD I: Safety and tolerability of twice-daily aclidinium bromide in COPD patients

Anthony D'Urzo,[1] Barry J. Make,[2] Edward M. Kerwin,[3] Ludmyla Rekeda,[4] Esther Garcia Gil,[5] Cynthia Caracta,[4] Brian Maurer[4]

[1]University of Toronto, Toronto, Canada; [2]National Jewish Health, Denver, USA; [3]Clinical Research Institute, Medford, USA; [4]Forest Research Institute, Jersey City, USA; [5]Almirall, R&D Centre, Barcelona, Spain

Introduction

- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends using long-acting bronchodilators for the management of chronic obstructive pulmonary disease (COPD).[1]
- Aclidinium bromide is a novel, long-acting muscarinic antagonist bronchodilator that is under review by the EMA and FDA for the twice-daily maintenance treatment of COPD.
- Previous clinical studies of aclidinium have shown long-lasting bronchodilation and a favourable safety profile.[2-4] Aclidinium has also been shown to be rapidly hydrolyzed in human plasma, suggesting a low potential for systemic side effects.[5,6]
- The primary objectives of this Phase III study were to assess the efficacy and safety of twice-daily aclidinium 200 µg and 400 µg via the Genuair® inhaler in moderate-to-severe COPD patients.
  - Results for the primary efficacy endpoint of this study showed that change from baseline in morning pre-dose (trough) FEV_1 at Week 12 was statistically and clinically significantly greater for both aclidinium 200 µg and 400 µg BID as compared with placebo (86 mL and 124 mL, respectively; p<0.0001 for both).[7]
  - The safety and tolerability of aclidinium 200 µg and 400 µg BID are presented here.

Methods

Study design

- This was a 12-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial evaluating aclidinium 200 µg and 400 µg BID.
- Patients (N=561) were randomised (1:1:1) to aclidinium bromide (200 µg or 400 µg BID) or placebo.
- Patients were evaluated at screening, at baseline following a 2-week run-in period, at Weeks 1, 4, 8, and 12 during the treatment period, and 2 weeks following treatment end.

Study population

Inclusion criteria

- Male and female patients aged ≥40 years
- Diagnosis of moderate-to-severe stable COPD (forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio <70%; FEV_1 ≥30% and <80% of predicted)
- Current or ex-smokers with a smoking history of ≥10 pack-years

Exclusion criteria

- History or current diagnosis of asthma
- Respiratory infection or COPD exacerbation within 6 weeks (3 months if it resulted in hospitalisation) prior to screening
- Clinically relevant respiratory conditions (other than COPD) and abnormalities in laboratory values or electrocardiograms (ECG)
- Patients with clinically significant cardiovascular conditions, including myocardial infarction during the previous 6 months, newly diagnosed arrhythmia within the previous 3 months, unstable angina, unstable arrhythmia that had required changes in pharmacological therapy or other intervention, and/or hospitalisation within the previous 12 months

Allowed concomitant medications

- Albuterol (USA)/salbutamol (Canada) inhaler as needed
- Inhaled corticosteroids (CS) and oral CS at doses equivalent to 10 mg/day or 20 mg every other day (if stable for 4 weeks before Visit 1)

Study endpoints

- Safety was assessed via adverse events (AEs), clinical laboratory tests, vital signs, ECGs, and (in a subset of patients) Holter monitoring.

Statistical analysis

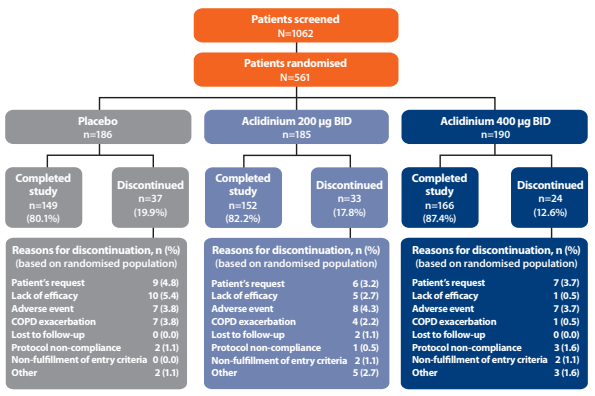
- The safety population (all randomised patients who took at least 1 dose of double-blind study treatment) was used to analyse safety outcomes which were summarised using descriptive statistics.

Results

Baseline demographics

- A total of 561 patients were randomised and 467 patients completed the study (87.4% aclidinium 400 µg, 82.2% aclidinium 200 µg, 80.1% placebo; Figure 1).

Figure 1. Study flow chart



One patient randomised to aclidinium 200 µg discontinued prior to receiving any study medication and was not included in the safety population.

- Baseline demographics were similar across all treatment groups (Table 1).

Table 1. Demographic and baseline characteristics (safety population)

Characteristic	Placebo (n=186)	Aclidinium 200 µg (n=184)	Aclidinium 400 µg (n=190)	Total (N=560)
Age, mean (SD), years	65.1 (9.2)	63.1 (9.5)	64.9 (9.5)	64.3 (9.4)
Male, n (%)	96 (51.6)	101 (54.9)	100 (52.6)	297 (53.0)
Caucasian, n (%)	175 (94.1)	169 (91.8)	181 (95.3)	525 (93.8)
BMI, mean (SD), kg/m²	27.5 (5.2)	27.3 (5.1)	27.6 (5.0)	27.5 (5.1)
Current smoker, n (%)	87 (46.8)	84 (45.7)	80 (42.1)	251 (44.8)
Smoking history, mean (SD), pack-years	52.7 (28.1)	53.0 (23.3)	57.2 (28.5)	54.3 (26.8)
FEV_1, mean (SD), L	1.38 (0.6)	1.36 (0.6)	1.33 (0.5)	1.36 (0.5)
FEV_1, mean (SD), % of predicted value	54.6 (13.5)	52.8 (13.7)	54.1 (12.9)	53.8 (13.4)
Post-bronchodilator FEV_1/FVC ratio, mean (SD), %	52.7 (10.5)	50.9 (10.6)	51.5 (10.2)	51.7 (10.5)

BMI, body-mass index

Treatment-emergent AEs (TEAEs)

- The percentage of patients who reported a TEAE was lower in the aclidinium 400 µg group (44.7%) compared with the aclidinium 200 µg and the placebo groups (50.5% and 52.2%, respectively).
- The only TEAE reported by at least 5% of patients was COPD exacerbation, with an incidence that was lower in the aclidinium groups vs placebo (Table 2). Additionally, the incidence of COPD exacerbations was lower with the higher dose of aclidinium (7.4%) compared with aclidinium 200 µg (9.2%) or placebo (12.4%).
- The TEAEs reported in at least 2% of the patients in any group and that occurred more frequently in any aclidinium group compared with the placebo group were arthralgia, diarrhoea, oropharyngeal pain, headache, nasopharyngitis, back pain, and dizziness.

Table 2. Number (%) of patients with adverse events reported by ≥2% of patients in the aclidinium treatment groups (safety population)

Characteristic	Placebo (n=186)	Aclidinium 200 µg (n=184)	Aclidinium 400 µg (n=190)
COPD exacerbation	23 (12.4)	17 (9.2)	14 (7.4)
Dyspnoea	6 (3.2)	4 (2.2)	5 (2.6)
Arthralgia	1 (0.5)	4 (2.2)	5 (2.6)
Cough	5 (2.7)	4 (2.2)	4 (2.1)
Diarrhoea	3 (1.6)	3 (1.6)	4 (2.1)
Oropharyngeal pain	3 (1.6)	2 (1.1)	4 (2.1)
Fatigue	4 (2.2)	0 (0)	4 (2.1)
Headache	4 (2.2)	6 (3.3)	3 (1.6)
Nasopharyngitis	2 (1.1)	6 (3.3)	3 (1.6)
Back pain	1 (0.5)	5 (2.7)	3 (1.6)
Dizziness	1 (0.5)	4 (2.2)	2 (1.1)

- The incidence of on-therapy serious AEs (SAEs) was low in all groups (2.2% placebo, 4.3% aclidinium 200 µg, 3.2% aclidinium 400 µg).
  - The most frequently reported SAE was exacerbation of COPD: 1 patient in the placebo group, 1 patient in the aclidinium 200 µg group, and 3 patients in the aclidinium 400 µg group. None of the COPD exacerbations resulted in discontinuation from the study.

Anticholinergic AEs

- Typical anticholinergic-related effects such as dry mouth and constipation were low and generally comparable between treatment arms (Table 3).

Table 3. Number (%) of patients with potential anticholinergic AEs by system organ class and preferred term (safety population)

System organ class Preferred term	Placebo (n=186)	Aclidinium 200 µg (n=184)	Aclidinium 400 µg (n=190)
Cardiac disorders			
Sinus tachycardia	0 (0)	0 (0)	1 (0.5)
Supraventricular tachycardia	2 (1.1)	2 (1.1)	2 (1.1)
Ventricular tachycardia	1 (0.5)	0 (0)	2 (1.1)
Heart rate increased	1 (0.5)	0 (0)	0 (0)
Gastrointestinal disorders			
Constipation	1 (0.5)	2 (1.1)	0 (0)
Dry mouth	2 (1.1)	3 (1.6)	1 (0.5)
Infections and infestation disorders			
Urinary tract infection	4 (2.2)	2 (1.1)	3 (1.6)
Cystitis	1 (0.5)	1 (0.5)	0 (0)

Study discontinuations and deaths

- The most frequently reported event resulting in study discontinuation was COPD exacerbation (n=7, placebo; n=4, aclidinium 200 µg; n=1, aclidinium 400 µg) followed by dyspnoea (n=2 each, placebo and 400 µg) and ventricular tachycardia (n=2, 400 µg; n=1, placebo; Table 4). No other TEAEs resulted in study discontinuation of more than one patient.

Table 4. Adverse events leading to study discontinuation in ≥1 patient in any treatment group (safety population), n (%)

System organ class Preferred term	Placebo (n=186)	Aclidinium 200 µg (n=184)	Aclidinium 400 µg (n=190)
COPD exacerbation	7 (3.8)	4 (2.2)	1 (0.5)
Dyspnoea	2 (1.1)	0 (0)	2[a] (1.1)
Ventricular tachycardia	1 (0.5)	0 (0)	2 (1.1)

[a]One AE was considered to be related to study treatment.

- One patient died due to metastatic lung cancer 23 days after first study drug intake (aclidinium 400 µg group); the event was not considered to be related to treatment.

Other safety assessments

- Changes from baseline in clinical laboratory tests and vital signs were small and similar across treatment groups; none were considered to be of clinical relevance.
- None of the patients in the aclidinium groups experienced any potentially clinically significant ECG abnormalities in heart rate or QT interval (Table 5).

Table 5. Number (%) of patients with potentially clinically significant (PCS) 12-lead ECG values (safety population)

Parameter	PCS criteria unit	Placebo (n=186)	Aclidinium 200 µg (n=184)	Aclidinium 400 µg (n=190)
QTcF interval	>500 msec	0 (0)	0 (0)	0 (0)
	Increase ≥60 msec[a]	1 (0.5)	0 (0)	0 (0)
Tachycardia event	≥120 bpm if baseline <120 bpm	0 (0)	0 (0)	0 (0)
Bradycardia event	≤40 bpm if baseline >40 bpm	1 (0.5)	0 (0)	0 (0)

[a]Change from baseline

Conclusions

- **Twice-daily treatment with aclidinium 200 µg and 400 µg was safe and well tolerated in moderate-to-severe COPD patients.**
- **The incidence of anticholinergic-related adverse events was low and similar between all treatment groups in this study.**
- **There were no differences in safety profiles between the 200 µg and 400 µg doses of aclidinium administered twice daily.**

References

1. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD Executive Summary. Am J Respir Crit Care Med 2007; 176: 532-55.
2. Jones PW, Agusti A, Chanez P, et al. A phase III study evaluating aclidinium bromide, a novel long-acting antimuscarinic, in patients with COPD: ACCLAIM/COPD I. Am J Respir Crit Care Med 2009; 179: A6180.
3. Rennard S, Donohue J, Bateman E, et al. Efficacy and safety of the novel, long-acting antimuscarinic, aclidinium bromide, in COPD patients in a phase III study: ACCLAIM/COPD II. Am J Respir Crit Care Med 2009; 179: A6178.
4. Magnussen H, Llovera AR, Kirsten A-M, et al. Efficacy and safety of aclidinium bromide 400 µg BID compared with placebo and tiotropium in patients with moderate to severe COPD. Am J Respir Crit Care Med 2010; 181: A4440.
5. Sentellas S, Ramos I, Albertí J, et al. Aclidinium bromide, a new, long-acting, inhaled muscarinic antagonist: In vitro plasma inactivation and pharmacological activity of its main metabolites. Eur J Pharm Sci 2010; 39(5): 283-290.
6. Jansat JM, Lamarca R, Garcia Gil E, et al. Safety and pharmacokinetics of single doses of aclidinium bromide, a novel long-acting, inhaled antimuscarinic, in healthy subjects. Int J Clin Pharmacol Ther 2009; 47(7): 460-468.
7. Kerwin E, D'Urzo A, Gelb A, et al. Twice-daily aclidinium bromide in COPD patients: Efficacy and safety results from ACCORD COPD I. Eur Resp J 2010; 36(suppl 54): 219s.

Acknowledgements

This study was supported by Forest Laboratories, Inc., New York, USA and Almirall SA, Barcelona, Spain. Funding for poster development was provided by Forest Laboratories, Inc. to Prescott Medical Communications Group, Chicago, USA.

Poster presented at the European Respiratory Society Annual Congress, Amsterdam, Netherlands, 24-28 September 2011

The ATTAIN study: bronchodilatory effect of aclidinium bromide in chronic obstructive pulmonary disease

Dave Singh,[1] Eric D Bateman,[2] Paul W Jones,[3] Alvar Agusti,[4] Rosa Lamarca,[5] Gonzalo de Miquel,[5] Cynthia Caracta,[6] Esther Garcia Gil[5]

[1]Medicines Evaluation Unit Ltd, Manchester, UK; [2]University of Cape Town, Cape Town, South Africa; [3]St George's University of London, London, UK; [4]Thorax Institute, Hospital Clínic, Barcelona, and CIBER Enfermedades Respiratorias and Fundació Caubet-Cimera, Spain; [5]Almirall, R&D Centre, Barcelona, Spain; [6]Forest Research Institute, New Jersey, USA

Introduction

- Aclidinium bromide, a novel, second-generation, low systemic activity, inhaled long-acting muscarinic antagonist compound, is under review by the EMA and FDA for the twice-daily (BID) maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).
- The bronchodilatory effects of aclidinium 200 µg and 400 µg BID have previously been investigated in a 12-week, Phase III study in patients with moderate to severe COPD.[1] At study end, aclidinium 200 µg and 400 µg BID both significantly increased the change from baseline in forced expiratory volume in 1 second (FEV_1) compared with placebo (by 86±21 and 124±21 mL, respectively; $p<0.0001$).
- Here we report lung-function data from the Phase III ATTAIN study, which was conducted to assess the long-term efficacy and safety of aclidinium 200 µg and 400 µg versus placebo in patients with moderate to severe COPD.

Methods

Study design and treatment

- This was a 24-week, double-blind, randomised, placebo-controlled, parallel-group multicentre study.
- Following screening and a 14-day run-in period, patients were randomised (1:1:1 ratio) to receive aclidinium 200 µg, aclidinium 400 µg or placebo BID via the Genuair®* inhaler.

Study population

Inclusion criteria

- Male and female patients aged ⩾40 years with moderate to severe stable COPD.
- Post-bronchodilator FEV_1/forced vital capacity (FVC) ratio <70%.
- Post-bronchodilator FEV_1 ⩾30% and <80% of the predicted value.
- Current or ex-smokers with a smoking history of ⩾10 pack-years.

Exclusion criteria

- History or current diagnosis of asthma.
- Respiratory infection or COPD exacerbation within 6 weeks (3 months if it resulted in hospitalisation) prior to screening.
- Clinically relevant cardiovascular or respiratory conditions.

Allowed concomitant medications

- Salbutamol as needed.
- Inhaled corticosteroids (CS) and oral or parenteral CS at doses equivalent to 10 mg/day or 20 mg/day every other day (if stable for 4 weeks before study entry). Oral sustained-release theophyllines were also permitted.

Lung-function endpoints

- Change from baseline in morning pre-dose (trough) FEV_1 at Week 24 (primary efficacy endpoint) and Weeks 1, 4, 8, 12 and 18.
- Change from baseline in peak FEV_1 at Week 24 (secondary efficacy endpoint) and Day 1 and Weeks 1, 4 and 12.
- Time to peak FEV_1 on Day 1 and Weeks 1, 4, 12 and 24.
- Change from baseline in normalised area under the curve from 0 to 3 hours ($AUC_{0\text{-}3h}$) FEV_1 on Day 1 and Weeks 1, 4, 12 and 24.

Statistical analyses

- All patients who took at least one dose of the study medication and had a baseline and at least one post-baseline FEV_1 assessment were included in the intention-to-treat (ITT) population.
- All efficacy outcomes, except time to peak FEV_1, were analysed using the ANCOVA model, with treatment and sex as factors and baseline and age as covariates. Time to peak FEV_1 was descriptively analysed.

Results

Study population

- A total of 828 patients were randomised into the study, 819 of whom were included in the ITT population.
- Demographic and baseline characteristics were similar across all treatment groups (Table 1).

Table 1. Patient demographics and baseline characteristics (ITT population)

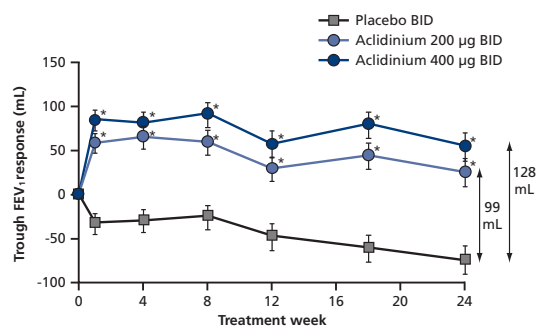
Characteristics	Placebo (n=273)	Aclidinium 200 µg (n=277)	Aclidinium 400 µg (n=269)	Total (n=819)
Age (years) (mean, SD)	62.0 (8.0)	62.3 (7.8)	62.9 (8.4)	62.4 (8.0)
Gender (% male)	69.2	65.3	67.7	67.4
COPD severity (%)				
Moderate COPD*	65.9	69.6	68.7	68.1
Severe COPD*	34.1	30.4	31.3	31.9
Current smoker (%)	52.8	50.5	55.0	52.8
Smoking history (pack-years) (mean, SD)	38.9 (18.3)	40.0 (19.8)	41.7 (21.1)	40.2 (19.8)
Baseline FEV_1 (L) (mean, SD)	1.48 (0.5)	1.49 (0.48)	1.48 (0.49)	1.48 (0.49)
Post-salbutamol FEV_1, (mean, SD) % of predicted value	56.6 (12.8)	57.6 (13.2)	56.2 (12.2)	56.8 (12.8)

*As classified by the Global Initiative for Chronic Obstructive Lung Disease
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ITT, intention-to-treat; SD, standard deviation

Trough FEV_1

- At Week 24, trough FEV_1 was significantly improved from baseline with aclidinium 200 µg and 400 µg compared with placebo (by 99±22 mL and 128±22 mL, respectively; $p<0.0001$ for both; Figure 1).

Figure 1. Change from baseline in trough FEV_1 over time



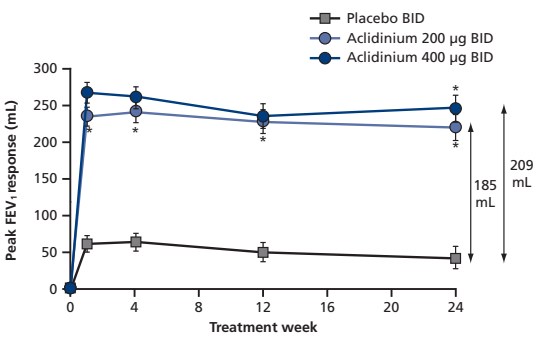
Data reported as least squares mean (standard error)
*p⩽0.0001 for both treatments vs placebo
BID, twice daily; FEV_1, forced expiratory volume in 1 second

- For both aclidinium doses, the improvement in trough FEV_1 was statistically superior to placebo at all time points from Week 1 to Week 24 ($p\leqslant0.0001$ for all; Figure 1).
- The improvement in trough FEV_1 was numerically greater for aclidinium 400 µg versus the 200 µg dose at all time points throughout the study; however, these differences were not statistically significant.

Peak FEV_1

- At Week 24, aclidinium 200 µg and 400 µg significantly improved peak FEV_1 from baseline compared with placebo (by 185±23 mL and 209±24 mL, respectively; $p<0.0001$; Figure 2).
- The improvement in peak FEV_1 provided by both aclidinium doses was statistically superior to placebo at all time points from Day 1 to Week 24 (Figure 2).

Figure 2. Change from baseline in peak FEV_1 over time



Data reported as least squares mean (standard error)
*p<0.0001 for both treatments vs placebo
BID, twice daily; FEV_1, forced expiratory volume in 1 second

- In both aclidinium groups, the improvement in peak FEV_1 achieved on Day 1 was similar to that observed at the end of the study (Week 24).
- The 400 µg dose of aclidinium was associated with a numerically greater improvement in peak FEV_1 compared with the 200 µg dose at all time points over the study period, but this was not statistically significant.

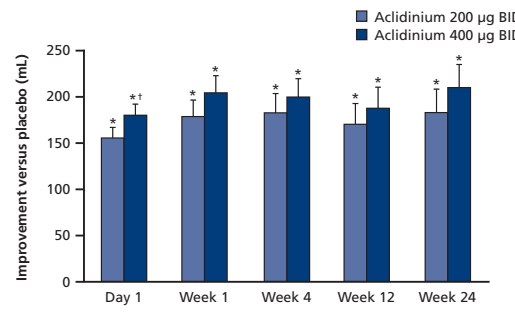
Time to peak FEV_1

- The mean time to peak FEV_1 was <2 h post-dose for aclidinium 200 µg and 400 µg at Weeks 1, 4, 12 and 24, but not on Day 1.
- On Day 1, the mean time to peak FEV_1 for aclidinium 200 µg and 400 µg was 127 min and 126 min, respectively.

$AUC_{0\text{-}3h}$ FEV_1

- Aclidinium 200 µg and 400 µg significantly improved normalised $AUC_{0\text{-}3h}$ FEV_1 compared with placebo at all time points from Day 1 to Week 24 (Figure 3).

Figure 3. Change from baseline in $AUC_{0\text{-}3h}$ FEV_1 over time



Data reported as least squares mean difference (standard error)
*p<0.0001 for both treatments vs placebo
†p=0.0371 for aclidinium 400 µg BID vs aclidinium 200 µg BID

- No statistically significant differences were observed between the two aclidinium doses at Weeks 1, 4, 12 or 24; however, on Day 1, normalised $AUC_{0\text{-}3h}$ FEV_1 was significantly improved with aclidinium 400 µg compared with the 200 µg dose (by 25 mL; p=0.0371).

Summary

- Aclidinium 200 µg and 400 µg significantly improved airflow limitation compared with placebo in patients with moderate to severe COPD.
- The improvements in airflow limitation were observed from the first dose and throughout the 24-week study period.

Conclusion

- **The significant bronchodilatory effect of aclidinium suggests it may offer a valuable new treatment option for patients with moderate to severe COPD.**

Reference

1. Kerwin EM, D'Urzo A, Gelb AF, et al. Twice-daily aclidinium bromide in COPD patients: Efficacy and safety results from ACCORD COPD I. Eur Respir J 2010; 36: 219s (abstract).

Acknowledgements

This study was supported by Almirall S.A., Barcelona, Spain, and Forest Laboratories, Inc., New York, USA.

*Genuair® is a registered trademark of Almirall S.A.

Poster presented at the European Respiratory Society Annual Congress, Amsterdam, The Netherlands, 24-28 September 2011

Improvement in symptoms and rescue medication use with aclidinium bromide in patients with chronic obstructive pulmonary disease: results from ATTAIN

Alvar Agusti,[1] Paul W Jones,[2] Eric D Bateman,[3] Dave Singh,[4] Rosa Lamarca,[5] Gonzalo de Miquel,[5] Cynthia Caracta,[6] Esther Garcia Gil[5]

[1]Thorax Institute, Hospital Clínic, Barcelona, and CIBER Enfermedades Respiratorias and Fundació Caubet-Cimera, Spain; [2]St George's University of London, London, UK; [3]University of Cape Town, Cape Town, South Africa; [4]Medicines Evaluation Unit Ltd, Manchester, UK; [5]Almirall, R&D Centre, Barcelona, Spain; [6]Forest Research Institute, New Jersey, USA

Introduction

- Chronic obstructive pulmonary disease (COPD) is characterised by symptoms of chronic cough, excessive sputum production, wheeze, breathlessness (dyspnoea) on exertion and chest tightness.[1] These symptoms are progressive and become increasingly debilitating as the disease worsens.
- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines include management of stable COPD as one of the major components of disease management.[1] Symptom relief is a major factor in the management of stable COPD.
- Aclidinium bromide is a novel, second-generation, low systemic activity, inhaled long-acting muscarinic antagonist compound, currently under review by the EMA and FDA for the maintenance treatment of COPD.
- Topline results from the Phase III ATTAIN study showed that twice-daily (BID) aclidinium (200 µg or 400 µg) significantly improved airflow limitation, COPD symptoms and health status in COPD patients.[2] Here we report in detail the COPD symptoms data and the use of relief medication over 24 weeks in the ATTAIN study.

Methods

Study design and treatment

- ATTAIN was a 24-week, double-blind, randomised, placebo-controlled, parallel-group, multicentre study.
- Following screening and a 14-day run-in period, patients were randomised (1:1:1) to receive aclidinium 200 µg, aclidinium 400 µg or placebo BID via the Genuair®* inhaler.

Study population

Inclusion criteria

- Male and female patients aged ⩾40 years with moderate to severe stable COPD.
- Post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity <70%.
- Post-bronchodilator FEV_1 ⩾30% and ⩽80% of predicted value.
- Current or ex-smokers with a smoking history of ⩾10 pack-years.

Exclusion criteria

- History or current diagnosis of asthma.
- Respiratory infection or COPD exacerbation within 6 weeks (3 months if it resulted in hospitalisation) prior to screening.
- Clinically relevant cardiovascular conditions or respiratory conditions.

Allowed concomitant medication

- Salbutamol as needed.
- Inhaled corticosteroids (CS) and oral or parenteral CS at doses equivalent to 10 mg/day every other day (if stable for 4 weeks before study entry). Oral sustained-release theophyllines were also permitted.

Efficacy measures (COPD symptoms and relief medication)

- Dyspnoea status at baseline was assessed by means of the Baseline Dyspnoea Index (BDI) and changes were assessed with the Transitional Dyspnoea Index (TDI) at Weeks 4, 12 and 24.
- Total daily COPD symptoms were assessed using the EXAcerbations of Chronic pulmonary disease Tool (EXACT). An EXACT-Respiratory Symptoms (E-RS) algorithm was used to calculate a daily ER-S total score.
- The occurrence of night-time and early-morning COPD symptoms was recorded and scored using an electronic diary.
- Patients recorded the daily number of puffs of salbutamol 100 µg.

COPD symptom variables

- Percentage of patients with a clinically meaningful improvement in TDI focal score (⩾1-unit increase) at Week 24.
- Change from baseline in E-RS total and three domain (breathlessness, chest symptoms, and cough and sputum) scores.
- Change in night-time and early-morning symptoms as a percentage of nights and mornings with symptoms.

Relief medication use variables

- Change from baseline in the daily use of relief medication and the percentage of days without the need for relief medication.

Statistical analysis

- The percentage of patients who achieved a clinically meaningful improvement in TDI focal score was analysed using a logistic regression model, with treatment group, sex, age and BDI as explanatory variables.
- TDI endpoints were analysed using the analysis of covariance (ANCOVA) model, with sex and treatment groups as factors, and age and BDI (focal or dimension score) as covariates.
- Change from baseline in night-time and early-morning symptoms, daily E-RS total score and change in use of relief medication were analysed by means of an ANCOVA model, with sex and treatment groups as factors, and age and baseline as covariates.
- The intention-to-treat (ITT) population was used for the analysis.

Results

Study population

- A total of 828 patients were randomised in the study. Of these, 819 patients were included in the ITT population.
- Demographics and baseline characteristics were similar across treatment groups (Table 1).

Table 1. Patient demographics and baseline characteristics (ITT population)

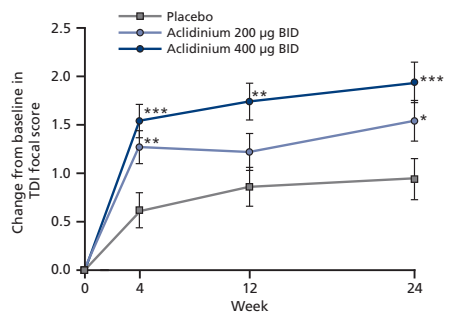
Characteristics	Placebo (n=273)	Aclidinium 200 µg (n=277)	Aclidinium 400 µg (n=269)	Total (n=819)
Age (years) (mean, SD)	62.0 (8.0)	62.3 (7.8)	62.9 (8.4)	62.4 (8.0)
Gender (% male)	69.2	65.3	67.7	67.4
COPD severity (%)				
Moderate COPD*	65.9	69.6	68.7	68.1
Severe COPD*	34.1	30.4	31.3	31.9
Current smoker (%)	52.8	50.5	55.0	52.8
Smoking history (pack-years) (mean, SD)	38.9 (18.3)	40.0 (19.8)	41.7 (21.1)	40.2 (19.8)
Baseline FEV_1 (L) (mean, SD)	1.48 (0.5)	1.49 (0.48)	1.48 (0.49)	1.48 (0.49)
Post-salbutamol FEV_1, (mean, SD) % of predicted value	56.6 (12.8)	57.6 (13.2)	56.2 (12.2)	56.8 (12.8)
BDI focal score, mean (SD)	6.7 (2.0)	7.0 (2.2)	6.7 (2.1)	6.8 (2.1)
Baseline E-RS total score, mean (SD)	13.6 (6.6)	13.2 (6.4)	14.1 (6.4)	–

*As classified by the Global Initiative for Chronic Obstructive Lung Disease
BDI, Baseline Dyspnoea Index; COPD, chronic obstructive pulmonary disease; E-RS, EXACT-Respiratory Symptoms; FEV_1, forced expiratory volume in one second; ITT, intention-to-treat; SD, standard deviation

COPD symptoms

- Both doses of aclidinium resulted in a significantly greater improvement in TDI focal score, compared with placebo, at all time points (except at Week 12 for the aclidinium 200 µg group, p=0.181; Figure 1).
  - At Week 24, the difference in the mean change from baseline in TDI focal score versus placebo was 0.6 units for aclidinium 200 µg (p<0.05) and 1.0 unit for aclidinium 400 µg (p<0.001).

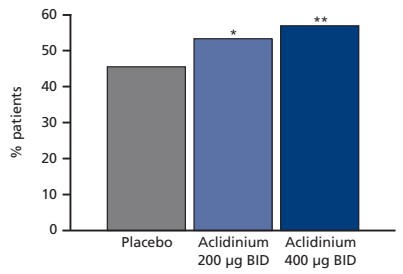
Figure 1. Change from baseline in TDI focal score at Weeks 4, 12 and 24 (ITT population)



Data reported as least squares mean (standard error)
*p<0.05; **p<0.01; ***p<0.001 vs placebo
BID, twice daily; TDI, Transitional Dyspnoea Index

- More patients treated with aclidinium 200 µg and 400 µg had a clinically significant improvement (⩾1-unit increase from baseline) in TDI focal score at Week 24 (53.3% [p<0.05] and 56.9% [p<0.01], respectively, versus placebo, 45.5%; Figure 2).

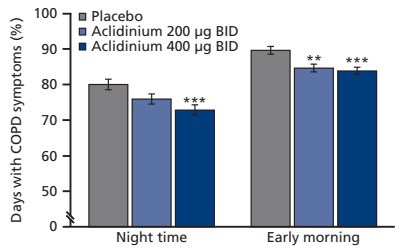
Figure 2. Responders (⩾1-unit improvement) in TDI focal score at Week 24 (ITT population)



*p<0.05; **p<0.01 vs placebo
BID, twice daily; TDI, Transitional Dyspnoea Index

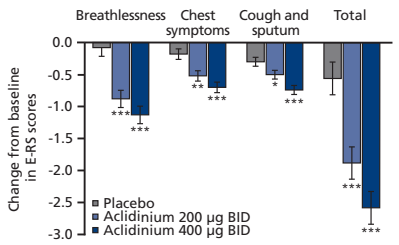
- Over the 24-week study period, aclidinium (both doses) was associated with a lower proportion of days with any night-time or early-morning COPD symptoms (Figure 3).
  - Compared with placebo, the percentage of days with any night-time symptoms was significantly lower with aclidinium 400 µg (p<0.001) and the percentage of days with any early-morning symptoms was significantly lower with aclidinium 200 µg (p<0.01) and 400 µg (p<0.001).
- Aclidinium 200 µg and 400 µg produced a significantly greater improvement in E-RS domain and total scores over the study period compared with placebo (Figure 4).

Figure 3. Percentage of days with night-time and early-morning symptoms over study period (ITT population)



Data reported as least squares mean (standard error)
**p<0.01; ***p<0.001 vs placebo
BID, twice daily; COPD, chronic obstructive pulmonary disease

Figure 4. Change from baseline in daily EXACT (E-RS) scores over study period (ITT population)

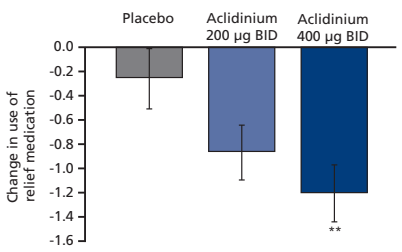


Data reported as least squares mean (standard error)
*p<0.05;**p<0.01;***p<0.001 vs placebo
BID, twice daily; E-RS, EXACT-Respiratory Symptoms

Relief medication use

- Aclidinium provided a dose-dependent reduction in the daily use of relief medication compared with placebo (Figure 5).

Figure 5. Mean change in total daily relief medication over study period (ITT population)



Data reported as least squares mean (standard error)
**p<0.01 vs placebo
BID, twice daily

- Use of aclidinium also increased the percentage of days without the need for relief medication; over the study period, the mean change from baseline in the percentage of days without relief medication was significantly greater with aclidinium 200 µg and 400 µg compared with placebo (11% for both, p<0.001).

Summary

- Treatment with aclidinium improved COPD symptoms as assessed by TDI focal score, E-RS and early-morning symptoms.
  - Aclidinium 400 µg BID provided a clinically significant improvement in TDI focal score and also reduced the percentage of days with night-time symptoms.
- Aclidinium provided a dose-dependent reduction in the use of daily relief medication.

Conclusion

- **Clinically significant improvements in COPD symptoms and a reduced need for relief medication may make aclidinium a valuable new treatment option for patients with moderate to severe COPD.**

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management, and Prevention of COPD. Available at www.goldcopd.com. Last updated 2010. Accessed 29 Jun 2011.
2. Jones PW, Agusti A, Bateman ED, Singh D, Lamarca R, de Miquel G, Caracta C, Garcia Gil E. Aclidinium bromide in patients with chronic obstructive pulmonary disease: efficacy and safety results from ATTAIN. Am J Respir Crit Care Med 2011; 183: A6350.

Acknowledgements

This study was supported by Almirall S.A., Barcelona, Spain, and Forest Laboratories, Inc., New York, USA.

*Genuair® is a registered trademark of Almirall S.A.

Poster presented at the European Respiratory Society Annual Congress, Amsterdam, The Netherlands, September 24-28, 2011

Aclidinium bromide in patients with chronic obstructive pulmonary disease: improvement in health status in ATTAIN

Paul W Jones,[1] Alvar Agusti,[2] Eric D Bateman,[3] Dave Singh,[4] Rosa Lamarca,[5] Gonzalo de Miquel,[5] Cynthia Caracta,[6] Esther Garcia Gil[5]

[1]St George's University of London, London, UK; [2]Thorax Institute, Hospital Clínic, Barcelona, and CIBER Enfermedades Respiratorias and Fundació Caubet-Cimera, Spain; [3]University of Cape Town, Cape Town, South Africa; [4]Medicines Evaluation Unit Ltd, Manchester, UK; [5]Almirall, R&D Centre, Barcelona, Spain; [6]Forest Research Institute, New Jersey, USA

Introduction

- One of the major goals of the management of chronic obstructive pulmonary disease (COPD) is to reduce patients' symptoms and improve their daily activity and health status.[1]
- Aclidinium bromide is a novel, second-generation, low systemic activity, inhaled long-acting muscarinic antagonist compound, currently under review by the EMA and FDA for the maintenance treatment of COPD.
- Preliminary efficacy and safety results from the Phase III ATTAIN study have been reported previously which demonstrate that twice-daily aclidinium, 200 µg and 400 µg administered via the Genuair®* inhaler, significantly improve airflow limitation and are well tolerated compared with placebo.[2] Here we report the effects of twice-daily aclidinium 200 µg and 400 µg on health status, in patients with COPD.

Methods

Study design and treatment

- This was a 24-week, double-blind, Phase III study.
- Patients were randomised (1:1:1) to aclidinium 200 µg, 400 µg or placebo twice daily via the Genuair®* inhaler.
- Patients were evaluated at screening, at baseline following a two-week run-in period, and at Weeks 1, 4, 8, 12, 18 and 24 during the treatment period.

Study population

Inclusion criteria

- Male and female patients aged ⩾40 years with moderate to severe stable COPD.
- Post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity ratio <70%.
- Post-bronchodilator FEV_1 ⩾30% and <80% of the predicted value.
- Current or ex-smokers with a smoking history of ⩾10 pack-years.

Exclusion criteria

- History or current diagnosis of asthma.
- Respiratory infection or COPD exacerbation within 6 weeks (3 months if it resulted in hospitalisation) prior to screening.
- Clinically relevant cardiovascular conditions or respiratory conditions.

Allowed concomitant medications

- Salbutamol as needed.
- Inhaled corticosteroids (CS) and oral or parenteral CS at doses equivalent to 10 mg/day or 20 mg/day every other day (if stable for 4 weeks before study entry). Oral sustained-release theophyllines were also permitted.

Health outcome assessments

- Health status was assessed using:
  - St George's Respiratory Questionnaire (SGRQ), the total score ranges from 0–100;[3] higher scores indicate poorer health and a change of ⩾4 units from baseline is clinically meaningful.
  - EuroQol Questionnaire (EQ-5D), consists of the weighted health status utility index (0=dead; 1=perfect health)[4] and the visual analogue scale (VAS) which is scored from 0 to 100 (0=worst imaginable state; 100=best imaginable health).
- Percentage of patients with a clinically meaningful improvement in health status as measured by a ⩾4-unit decrease from baseline in SGRQ total score at Weeks 4, 12 and 24.
- Change from baseline in SGRQ total and domain scores (Symptoms, Activity, Impacts) at Weeks 4, 12 and 24.
- Change from baseline in the EQ-5D weighted index and VAS at Weeks 4, 12 and 24.

Statistical analyses

- All efficacy variables were analysed using the intention-to-treat (ITT) population.
- Change from baseline in SGRQ (total and domain scores) and EQ-5D (weighted index and VAS) were analysed by means of an analysis of covariance (ANCOVA) model.
- The percentage of patients with a clinically meaningful improvement in SGRQ total score was analysed using a logistic regression model.

Results

Baseline demographics

- A total of 828 patients were randomised to aclidinium 200 µg (n=280), aclidinium 400 µg (n=272) or placebo (n=276). There were 819 patients in the ITT population.
- Baseline demographics were similar across all treatment groups (Table 1).

Health-related quality of life

SGRQ total score

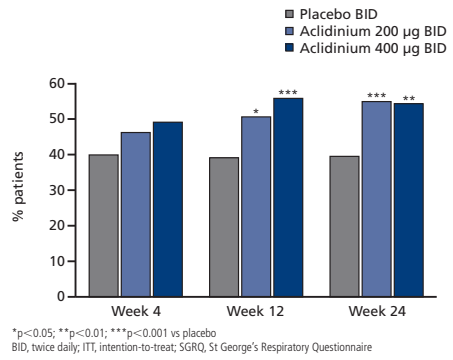
- A greater percentage of patients treated with aclidinium 200 µg and 400 µg had a clinically significant improvement in SGRQ total score at Week 24 (54.9% [p=0.0004] and 54.3% [p=0.0014], respectively), compared with placebo (39.5%) (Figure 1).
- From Week 4, more patients treated with aclidinium 200 µg and 400 µg showed a clinically significant improvement in SGRQ total score compared with placebo; the difference was statistically significant by Week 12 and sustained after 24 weeks of treatment (Figure 1).

Table 1. Patient demographics and baseline characteristics (ITT population)

Characteristic	Placebo (n=273)	Aclidinium 200 µg (n=277)	Aclidinium 400 µg (n=269)	Total (n=819)
Age (years) (mean, SD)	62.0 (8.0)	62.3 (7.8)	62.9 (8.4)	62.4 (8.0)
Gender (% male)	69.2	65.3	67.7	67.4
COPD severity (%)				
Moderate COPD*	65.9	69.6	68.7	68.1
Severe COPD*	34.1	30.4	31.3	31.9
Current smoker (%)	52.8	50.5	55.0	52.8
Smoking history (pack-years) (mean, SD)	38.9 (18.3)	40.0 (19.8)	41.7 (21.1)	40.2 (19.8)
Baseline FEV_1 (L) (mean, SD)	1.48 (0.5)	1.49 (0.48)	1.48 (0.49)	1.48 (0.49)
FEV_1 (% predicted) % (mean, SD)	56.6 (12.8)	57.6 (13.2)	56.2 (12.2)	56.8 (12.8)
Total SGRQ (mean, SD)	45.1 (15.8)	46.3 (16.8)	47.6 (17.7)	46.3 (16.8)

*As classified by the Global Initiative for Chronic Obstructive Lung Disease
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; ITT, intention-to-treat; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire

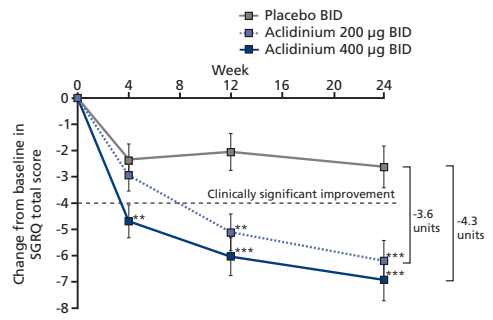
Figure 1. Responders (⩾4-unit improvement) in SGRQ total score at Week 24 (ITT population)



*p<0.05; **p<0.01; ***p<0.001 vs placebo
BID, twice daily; ITT, intention-to-treat; SGRQ, St George's Respiratory Questionnaire

- At Week 24, the difference in mean change from baseline in SGRQ total score versus placebo was -3.6 units for aclidinium 200 µg (p<0.001) and -4.3 units for aclidinium 400 µg (p<0.0001) (Figure 2).

Figure 2. Change from baseline in SGRQ total score at Weeks 4, 12 and 24 (ITT population)



**p<0.01; ***p<0.001 vs placebo
Values are mean ± SE
BID, twice daily; ITT, intention-to-treat; SE, standard error; SGRQ, St George's Respiratory Questionnaire

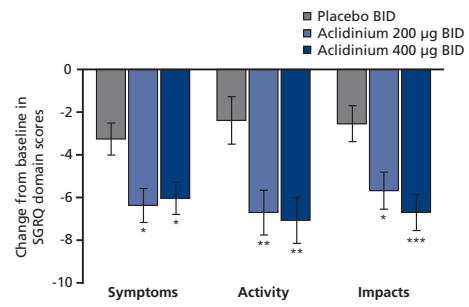
SGRQ domain scores

- The difference in mean change from baseline for the SGRQ domain scores compared with placebo showed increasing improvement over time. This was most notable at Week 24 (Figure 3) when the difference in mean change from baseline in SGRQ domain scores versus placebo was:
  - Symptoms: -3.1 units for aclidinium 200 µg and -2.8 units for aclidinium 400 µg (both p<0.05 vs placebo).
  - Activity: -4.3 units for aclidinium 200 µg and -4.7 units for aclidinium 400 µg (both p<0.01 vs placebo).
  - Impacts: -3.1 units for aclidinium 200 µg and -4.2 units for aclidinium 400 µg (p<0.05 and p<0.001 vs placebo, respectively).

EQ-5D weighted index and VAS

- The mean change from baseline for EQ-5D weighted index and VAS score versus placebo showed increasing improvement over time (Table 2).
- At Week 24, the difference in mean change from baseline in EQ-5D weighted index and VAS for aclidinium 200 µg was 0.03 [p=0.08] and 1.28 [p=0.24], respectively, and for aclidinium 400 µg was 0.03 [p<0.05] and 3.13 [p<0.01], respectively, compared with placebo.

Figure 3. Change from baseline in SGRQ domain scores (Symptoms, Activity, Impacts) at Week 24 (ITT population)



*p<0.05; **p<0.01; ***p<0.001 vs placebo
Values are mean ± SE
BID, twice daily; ITT, intention-to-treat; SE, standard error; SGRQ, St George's Respiratory Questionnaire

Table 2. Mean change from baseline in EQ-5D weighted index and visual analogue scale (VAS) at Weeks 4, 12 and 24 (ITT population)

	Weighted score				VAS			
	Baseline mean (SD)	Week 4	Week 12	Week 24	Baseline mean (SD)	Week 4	Week 12	Week 24
Placebo BID	0.8 (0.2)	0.03	0.02	0.02	62.3 (15.3)	1.93	0.73	1.74
Aclidinium 200 µg BID	0.8 (0.2)	0.03	0.05	0.05	63.5 (15.7)	1.28	2.81*	3.03
Aclidinium 400 µg BID	0.8 (0.2)	0.03	0.04	0.05*	61.6 (15.2)	2.17	4.03**	4.87**

*p<0.05; **p<0.01 vs placebo
Values are reported as least squares mean
BID, twice daily; EQ-5D, EuroQol questionnaire; ITT, intention-to-treat; SD, standard deviation

Summary

- Treatment with twice-daily aclidinium (200 µg, 400 µg) resulted in improvements in markers of patient quality of life as assessed by SGRQ and EQ-5D.
  - A clinically significant improvement in SGRQ total score was seen as early as Week 12 with aclidinium 400 µg BID.
- Both doses of aclidinium significantly improved SGRQ total score. Compared with placebo, a greater percentage of patients achieved a clinically significant improvement in SGRQ total score.
- Aclidinium also statistically significantly improved SGRQ domain scores compared with placebo; with clinically significant improvements in Activity scores (200 µg and 400 µg) at Week 12, and Activity (200 µg and 400 µg) and Impacts scores (400 µg) at Week 24.
- Aclidinium 400 µg significantly improved EQ-5D (weighted index and VAS score) at Week 24, compared with placebo.

Conclusions

- **Both doses of aclidinium produced clinically significant improvements in SGRQ. This is likely to translate into noticeable benefit for patients in routine practice.**
- **Overall, the 400 µg dose twice daily appears to have numerically greater efficacy than 200 µg twice daily.**

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management, and Prevention of COPD. Available at www.goldcopd.com. Last updated 2010. Accessed 29 Jun 2011.
2. Jones P. Aclidinium bromide in patients with chronic obstructive pulmonary disease: Efficacy and safety results from ATTAIN. Am J Resp Crit Care Med 2011; 183: A6350.
3. Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med 1991; 85 Suppl B: 25-31.
4. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001; 33: 337-343.

Acknowledgements

This study was supported by Almirall S.A., Barcelona, Spain, and Forest Laboratories, Inc., New York, USA.
*Genuair® is a registered trademark of Almirall S.A.

Poster presented at the European Respiratory Society Annual Congress, Amsterdam, The Netherlands, 24-28 September 2011

The ATTAIN study: safety and tolerability of aclidinium bromide in chronic obstructive pulmonary disease

Eric D Bateman,[1] Dave Singh,[2] Paul W Jones,[3] Alvar Agusti,[4] Rosa Lamarca,[5] Gonzalo de Miquel,[5] Cynthia Caracta,[6] Esther Garcia Gil[5]

[1]University of Cape Town, Cape Town, South Africa; [2]Medicines Evaluation Unit Ltd, Manchester, UK; [3]St George's University of London, London, UK; [4]Thorax Institute, Hospital Clínic, Barcelona, and CIBER Enfermedades Respiratorias and Fundació Caubet-Cimera, Spain; [5]Almirall, R&D Centre, Barcelona, Spain; [6]Forest Research Institute, New Jersey, USA

Introduction

- Aclidinium bromide, a novel, second-generation, low systemic activity, inhaled long-acting muscarinic antagonist compound, is under review by the EMA and FDA for the maintenance treatment of chronic obstructive pulmonary disease (COPD).
- Previous studies have shown that aclidinium improves lung function and symptomatic endpoints, and has a favourable safety profile in patients with COPD.[1-3] In addition, aclidinium is rapidly hydrolysed in human plasma into inactive metabolites, suggesting a low potential for systemic side effects.[4,5]
- The objectives of the ATTAIN study were to investigate the long-term efficacy and safety of aclidinium 200 µg and 400 µg twice daily (BID) versus placebo in patients with moderate or severe COPD. Here we present the safety and tolerability data from this study.

Methods

Study design and treatment

- This was a 24-week, double-blind, randomised, placebo-controlled, parallel-group, multicentre, Phase III study.
- Patients were randomised (1:1:1 ratio) to receive aclidinium 200 µg, aclidinium 400 µg or placebo BID via the Genuair®* inhaler.
- Assessments were performed at screening, at baseline following a two-week run-in period, at Weeks 1, 4, 8, 12, 18 and 24 during the treatment period, and at two weeks after completion of treatment.

Study population

Inclusion criteria

- Male and female patients aged ⩾40 years with moderate to severe stable COPD.
- Post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity ratio <70%.
- Post-bronchodilator FEV_1 ⩾30% and <80% of the predicted value.
- Current or ex-smokers with a smoking history of ⩾10 pack-years.

Exclusion criteria

- History or current diagnosis of asthma.
- Respiratory infection or COPD exacerbation within 6 weeks (3 months if it resulted in hospitalisation) prior to screening.
- Clinically relevant respiratory conditions including: known active tuberculosis; history of interstitial or pulmonary thromboembolic disease; pulmonary resection or lung volume reduction surgery within 12 months; or history of bronchiectasis secondary to respiratory disease.
- Clinically relevant cardiovascular conditions including: myocardial infarction within 6 months; unstable angina or arrhythmia within 12 months (3 months if newly diagnosed arrhythmia); or hospitalisation within 12 months for heart failure functional classes III and IV (as per the New York Heart Association).

Allowed concomitant medications

- Salbutamol as needed.
- Inhaled corticosteroids (CS) and oral or parenteral CS at doses equivalent to 10 mg/day or 20 mg/day every other day (if stable for 4 weeks before study entry). Oral sustained-release theophyllines were also permitted.

Safety assessments

- Adverse events (AEs), both spontaneously reported by patients in a diary between visits, and elicited by general questioning at each study visit, were recorded. AEs were considered as treatment-emergent if they started or worsened in severity at the time of or following the first administration of study medication and occurred within 15 days after the last treatment administration.
- Safety was also evaluated by clinical laboratory data, blood pressure and 12-lead electrocardiograms (ECGs) performed at baseline, and Weeks 1, 4, 12 and 24.

Statistical analyses

- Safety outcomes were analysed for all randomised patients who received at least one dose of study medication (safety population) and were summarised using descriptive statistics.

Results

Study population

- A total of 828 patients were randomised and 819 patients were included in the safety analyses. Patient disposition in the study is illustrated in Figure 1.
- Demographic and baseline characteristics were similar across all treatment groups (Table 1).

Table 1. Patient demographics and baseline characteristics (safety population)

Characteristic	Placebo (n=273)	Aclidinium 200 µg (n=277)	Aclidinium 400 µg (n=269)	Total (n=819)
Age (years) (mean, SD)	62.0 (8.0)	62.3 (7.8)	62.9 (8.4)	62.4 (8.0)
Gender (% male)	69.2	65.3	67.7	67.4
Moderate COPD* (%)	65.9	69.6	68.7	68.1
Severe COPD* (%)	34.1	30.4	31.3	31.9
Current smoker (%)	52.8	50.5	55.0	52.8
Smoking history (pack-years) (mean, SD)	38.9 (18.3)	40.0 (19.8)	41.7 (21.1)	40.2 (19.8)
Baseline FEV_1 (L) (mean, SD)	1.48 (0.5)	1.49 (0.48)	1.48 (0.49)	1.48 (0.49)
Post-salbutamol FEV_1, (mean, SD) % of predicted value	56.6 (12.8)	57.6 (13.2)	56.2 (12.2)	56.8 (12.8)

*As classified by the Global Initiative for Chronic Obstructive Lung Disease
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; SD, standard deviation

Treatment-emergent AEs

All AEs and serious AEs (SAEs)

- Overall, the percentage of patients with at least one AE was similar for placebo, aclidinium 200 µg and aclidinium 400 µg (57.1%, 54.5% and 53.5%, respectively).
- The most commonly (⩾5% of patients) reported AEs across the three treatment groups were COPD exacerbation, headache and nasopharyngitis; AEs reported by ⩾2% of patients in any treatment group are shown in Table 2.

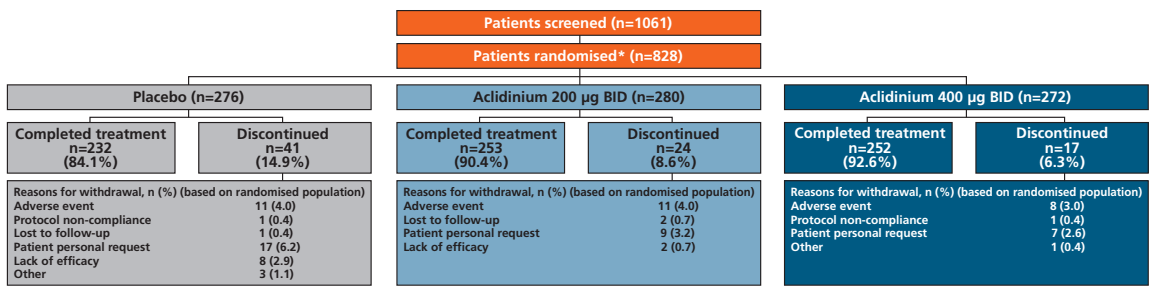
Table 2. Number (%) of patients with adverse events reported by ⩾2% of patients in any treatment group (safety population)

	Placebo (n=273)	Aclidinium 200 µg (n=277)	Aclidinium 400 µg (n=269)
COPD exacerbations	56 (20.5)	44 (15.9)	38 (14.1)
Headache	22 (8.1)	30 (10.8)	33 (12.3)
Nasopharyngitis	23 (8.4)	32 (11.6)	30 (11.2)
Rhinitis	7 (2.6)	4 (1.4)	9 (3.3)
Diarrhoea	3 (1.1)	5 (1.8)	8 (3.0)
Bronchitis	6 (2.2)	1 (0.4)	7 (2.6)
Hypertension	9 (3.3)	5 (1.8)	7 (2.6)
Cough	5 (1.8)	7 (2.5)	7 (2.6)
Toothache	1 (0.4)	3 (1.1)	6 (2.2)
Back pain	10 (3.7)	12 (4.3)	5 (1.9)
Influenza	6 (2.2)	3 (1.1)	5 (1.9)
Arthralgia	6 (2.2)	5 (1.8)	3 (1.1)
Urinary tract infection	2 (0.7)	6 (2.2)	2 (0.7)
Dyspepsia	6 (2.2)	5 (1.8)	1 (0.4)

COPD, chronic obstructive pulmonary disease

- The AEs reported more frequently with either dose of aclidinium compared with placebo and ⩾2% of patients in any treatment group were: headache, nasopharyngitis, diarrhoea, cough and toothache.
- The number of SAEs and percentage of patients with SAEs were similar for placebo (n=18; 5.5%), aclidinium 200 µg (n=19; 4.3%) and aclidinium 400 µg (n=20; 5.6%). The most frequently reported SAE was exacerbation of COPD (n=16; 1.8%) and the incidence was higher in the placebo group than in the aclidinium groups (placebo, 3.7%; aclidinium 200 µg, 1.4%; aclidinium 400 µg, 0.7%). All other SAEs were reported by no more than one patient. No SAEs were considered to be related to study medication.

Figure 1. Study flow chart



*Note: nine patients were counted as randomised only; therefore, the numbers of patients who completed or discontinued treatment do not add up to the total number randomised
BID, twice daily

Anticholinergic AEs

- Potential anticholinergic AEs occurred at a similar low incidence (⩽2.5% of patients) in each treatment group (Table 3). The number of patients reporting dry mouth was low (n=1: placebo; n=2: aclidinium 200 µg; n=1 aclidinium 400 µg).

Table 3. Number (%) of patients with potential anticholinergic events by system organ and preferred term (safety population)

	Placebo (n=273)	Aclidinium 200 µg (n=277)	Aclidinium 400 µg (n=269)
Cardiac disorders			
Sinus tachycardia	1 (0.4)	0 (0)	0 (0)
Palpitations	0 (0)	1 (0.4)	1 (0.4)
Eye disorders			
Vision blurred	0 (0)	1 (0.4)	0 (0)
Gastrointestinal			
Constipation	2 (0.7)	1 (0.4)	0 (0)
Dry mouth	1 (0.4)	2 (0.7)	1 (0.4)
Renal and urinary			
Urinary tract infection	2 (0.7)	6 (2.2)	2 (0.7)
Cystitis	0 (0)	0 (0)	1 (0.4)
Dysuria	0 (0)	0 (0)	1 (0.4)
Respiratory			
Dysphonia	0 (0)	1 (0.4)	1 (0.4)
Oropharyngeal pain	4 (1.5)	3 (1.1)	2 (0.7)
Dry throat	1 (0.4)	0 (0)	0 (0)
Throat irritation	4 (1.5)	0 (0)	1 (0.4)

Study discontinuations and deaths

- The most frequently reported AE leading to study discontinuation was COPD exacerbation (placebo: 5 patients; aclidinium 200 µg: 3 patients; aclidinium 400 µg: 4 patients). No other AEs resulted in the withdrawal of more than one patient in any treatment group.
- Three patients died during the study; one in the placebo group (road traffic accident), one in the aclidinium 200 µg group (myocardial infarction) and one in the aclidinium 400 µg group (acute cardiac failure). None of these deaths were thought to be related to treatment.

Other safety assessments

- The changes from baseline in laboratory tests and blood pressure were small and similar across treatment groups, and were not considered to be clinically relevant.
- The mean changes from baseline in 12-lead ECG parameters were generally small, with no apparent treatment- or dose-related trend; two patients (n=1: placebo; n=1: aclidinium 200 µg) had a QT interval corrected for heart rate using the Fridericia formula (QTcF) of >500 msec, and five patients (n=2: placebo; n=3: aclidinium 200 µg) had a change in QTcF of >60 msec.

Summary

- Treatment with aclidinium 200 µg and 400 µg BID for 24 weeks was safe and well tolerated in this study of patients with moderate to severe COPD.
- No differences in safety and tolerability were observed between the 200 µg and 400 µg doses of aclidinium, and the incidence of anticholinergic AEs was low across all treatment groups.

Conclusions

- **The safety and tolerability profile of aclidinium supports the future use of this treatment in patients with moderate to severe COPD.**
- **The low incidence of anticholinergic AEs observed with aclidinium suggests it may provide a valuable alternative to other anticholinergic medications.**

References

1. Jones PW, Rennard SI, Agusti A, et al. Efficacy and safety of once-daily aclidinium in chronic obstructive pulmonary disease. Respir Res 2011; 12: 1-10.
2. Kerwin EM, D'Urzo A, Gelb AF, et al. Twice-daily aclidinium bromide in COPD patients: Efficacy and safety results from ACCORD COPD I. Eur Respir J 2010; 36: 219s (abstract).
3. Magnussen H, Ribera A, Llovera A, et al. Efficacy and safety of aclidinium bromide 400 µg BID compared with placebo and tiotropium in patients with moderate to severe COPD. Am J Resp Crit Care Med 2010; 181 (abstract).
4. Jansat JM, Lamarca R, Garcia GE, et al. Safety and pharmacokinetics of single doses of aclidinium bromide, a novel long-acting, inhaled antimuscarinic, in healthy subjects. Int J Clin Pharmacol Ther 2009; 47: 460-468.
5. Sentellas S, Ramos I, Alberti J, et al. Aclidinium bromide, a new, long-acting, inhaled muscarinic antagonist: In vitro plasma inactivation and pharmacological activity of its main metabolites. Eur J Pharm Sci 2010; 39: 283-290.

Acknowledgements

This study were supported by Almirall S.A., Barcelona, Spain, and Forest Laboratories, Inc., New York, USA.
*Genuair® is a registered trademark of Almirall S.A.

Poster presented at the European Respiratory Society Annual Congress, Amsterdam, The Netherlands, 24-28 September 2011

Patient assessments of ease of use of Genuair® versus Aerolizer® and HandiHaler®

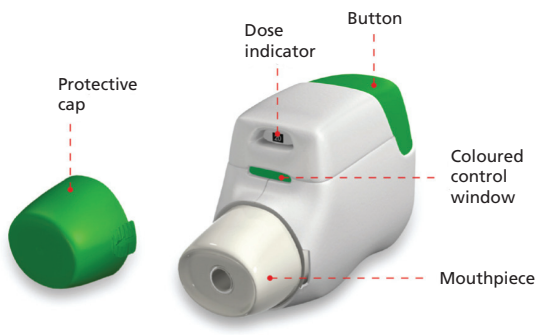
Rainard Fuhr,[1] Helgo Magnussen,[2] Dave Singh,[3] Gonzalo de Miquel,[4] Cynthia Caracta,[5] Esther Garcia Gil[4]

[1]PAREXEL International GmbH, Berlin, Germany; [2]Pulmonary Research Institute, Hospital Grosshansdorf, Grosshansdorf, Germany; [3]Medicines Evaluation Unit Ltd, Manchester, UK; [4]Almirall, R&D Centre, Barcelona, Spain; [5]Forest Research Institute, New Jersey, USA

Introduction

- The airway obstruction associated with chronic obstructive pulmonary disease (COPD) can be partially reversed with inhaled bronchodilation treatment.
- Various types of inhaler are currently available for the administration of COPD medications, and dry powder inhalers (DPIs) are now more commonly used than pressurised metered dose inhalers. For patients to obtain the maximum benefit from their treatment, it is important that inhalers are easy to use, convenient and efficient.
- The Genuair®* inhaler (Figure 1) is a novel, breath-actuated, multidose DPI that has been designed for the effective and reliable delivery of inhaled medications. Genuair® is used for the administration of aclidinium bromide,[1] a novel, second-generation, low systemic activity, inhaled long-acting muscarinic antagonist compound, currently under review by the EMA and FDA for the treatment of patients with COPD.

Figure 1. Design and features of the Genuair® inhaler



- Major features of this inhaler include:
  - multi-sensory feedback to the patient, comprised of a coloured control window that changes from green to red with an audible click on successful actuation of each dose
  - safety mechanism to reduce the potential for accidental double-dosing
  - lock-out mechanism to prevent the use of an empty inhaler.
- Here we report data from two Phase II studies that included patient assessments of the convenience and device preference of Genuair® versus Aerolizer® and HandiHaler®, respectively.

Methods

Study design

- Both studies were randomised, double-blind, double-dummy, cross-over studies in patients with moderate to severe COPD.

Study 1 – Genuair® vs Aerolizer®

- Patients were randomised to seven-day treatments of twice-daily aclidinium 100 µg, 200 µg, 400 µg via Genuair®, formoterol 12 µg via Aerolizer® and placebo.
- The investigator provided appropriate training and written instructions for both Genuair® and Aerolizer® at screening and on Day 1 of each treatment period (prior to dosing) to ensure correct use.

Study 2 – Genuair® vs HandiHaler®

- Patients were randomised to receive 15-day treatments of twice-daily aclidinium 400 µg via Genuair®, once-daily tiotropium 18 µg via HandiHaler® and placebo.
- The investigator provided appropriate training and written instructions for both Genuair® and HandiHaler®. Correct use of the devices was assessed by the investigator at screening and on Day 1 of each treatment period (prior to dosing) to ensure correct use.

Study assessments

- At the end of each of the studies or upon early discontinuation, patients were asked to evaluate their impressions of the inhalers used.
- In both studies, patients were asked about the ease of use of the inhaler, the ease of dose preparation and which device they preferred:
  - How easy was the use of the inhaler? 'Very easy', 'easy', 'normal', 'difficult' or 'very difficult'
  - How easy was the dose preparation of the inhaler? 'Very easy', 'easy', 'normal', 'difficult' or 'very difficult'
  - Which inhaler do you prefer the most? 'Definitely prefer', 'somewhat prefer' or 'no preference'.
- In study 1 only, patients were also asked about correct inhalation:
  - How clearly does Genuair®/Aerolizer® indicate that the dose was correctly inhaled? 'Very easy', 'easy', 'normal', 'difficult' or 'very difficult'.
- In study 2 only, patients were also asked about the features of the device:
  - Is there any particular feature that you liked the most about Genuair®/HandiHaler®? 'Yes' or 'no'
  - Is there any particular feature that you disliked about Genuair®/HandiHaler®? 'Yes' or 'no'.

Statistical analyses

- The results of questionnaires from both studies were analysed using descriptive statistics.

Results

- Patient baseline demographics for studies 1 and 2 are shown in Table 1. Device preference was assessed on the safety populations.

Table 1. Demographics and baseline characteristics for studies 1 and 2 (safety populations)

Characteristic	Study 1 (n=79)	Study 2 (n=30)
Age, mean (SD), years	61.1 (8.5)	58.4 (7.9)
Male, n (%)	59 (74.7)	19 (63.3)
White, n (%)	79 (100.0)	30 (100.0)
Current smoker, n (%)	45 (57.0)	19 (63.3)
Smoking history, mean (SD), pack-years	50.7 (26.8)	41.1 (15.9)
Post-bronchodilator FEV_1, mean (SD), % of predicted	53.7 (11.8)	55.8 (13.7)
Post-bronchodilator FEV_1/FVC ratio, mean (SD), %	45.1 (9.7)	46.2 (10.3)
COPD severity (GOLD stage)		
Stage II (moderate)	46 (59.0)	19 (63.3)
Stage III (severe)	32 (41.0)	10 (33.3)
Stage IV (very severe)	–	1 (3.3)
Missing	1	–

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; SD, standard deviation

- In total, 79 patients assessed the Genuair® inhaler versus Aerolizer® and 30 patients assessed the Genuair® inhaler versus HandiHaler®.

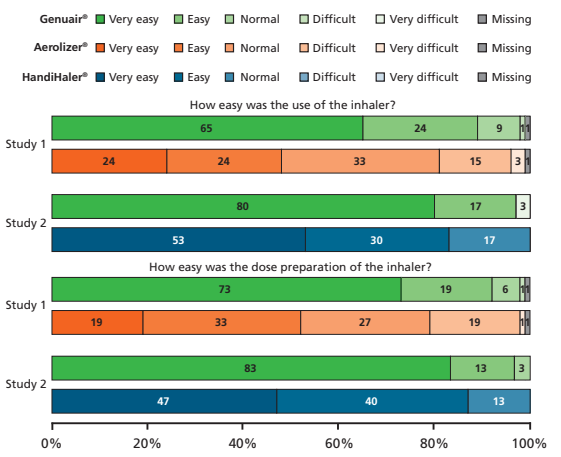
Ease of use

- More patients assessed Genuair® as 'very easy' to use compared with Aerolizer® (65% vs 24%, respectively; Figure 2).
- More patients assessed Genuair® as 'very easy' to use compared with HandiHaler® (80% vs 53%, respectively; Figure 2).

Dose preparation

- More patients indicated that dose preparation was 'very easy' with Genuair® compared with Aerolizer® (73% vs 19%, respectively; Figure 2).
- Dose preparation was also more frequently assessed as 'very easy' with Genuair® compared with HandiHaler® (83% vs 47%, respectively; Figure 2).

Figure 2. Ease of use of device



Correct inhalation

- More patients indicated that it was 'very easy' to see clearly that the dose was correctly inhaled with Genuair® compared with Aerolizer® (37% vs 23%, respectively).

Device features

- Patients indicated no preference for liking or disliking any specific device feature of Genuair® or HandiHaler®.

Device preference

- When asked which device they preferred, more patients 'definitely' (63%) or 'somewhat' (13%) preferred Genuair®, compared with Aerolizer® (6% and 4% of patients, respectively); 14% of patients had no preference for either inhaler (Table 2).
- When patients compared Genuair® and HandiHaler®, more patients 'definitely' (30%) or 'somewhat' (20%) preferred Genuair®, compared with HandiHaler® (7% and 3% of patients, respectively); 40% of patients had no preference for either inhaler (Table 2).

Table 2. Patient inhaler preference

	Study 1		Study 2	
Which device do you prefer the most?	Genuair® n=79	Aerolizer® n=79	Genuair® n=30	HandiHaler® n=30
Definitely prefer	63%	6%	30%	7%
Somewhat prefer	13%	4%	20%	3%
No preference	14%		40%	
Data missing (n)	1% (1)		–	

Conclusions

- **Patients found the Genuair® inhaler easier to use than Aerolizer® or HandiHaler®.**
- **Patients also found it easier to prepare the dose with Genuair® compared with Aerolizer® or HandiHaler®.**
- **Overall, patients' assessments of convenience were higher for Genuair® compared with the other inhalers and more patients preferred Genuair® compared with Aerolizer® and HandiHaler®.**

Reference

1. Jones PW, Rennard SI, Agusti A, et al. Efficacy and safety of once-daily aclidinium in chronic obstructive pulmonary disease. Respir Res 2011; 12: 1-10.

Acknowledgements

These studies were supported by Almirall S.A., Barcelona, Spain, and Forest Laboratories, Inc., New York, USA.

*Genuair® is a registered trademark of Almirall S.A.

Poster presented at the European Respiratory Society Annual Congress, Amsterdam, The Netherlands, 24-28 September 2011