Taylor & Francis
Taylor & Francis Group

Expert Review of Clinical Pharmacology

ISSN: 1751-2433 (Print) 1751-2441 (Online) Journal homepage: http://www.tandfonline.com/loi/ierj20

Aclidinium bromide inhalation powder for the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema

Maria Gabriella Matera, Alessandro Sanduzzi, Roberto Alfano & Mario Cazzola

To cite this article: Maria Gabriella Matera, Alessandro Sanduzzi, Roberto Alfano & Mario Cazzola (2016): Aclidinium bromide inhalation powder for the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema, Expert Review of Clinical Pharmacology, DOI: 10.1586/17512433.2016.1169173

To link to this article: http://dx.doi.org/10.1586/17512433.2016.1169173

Accepted author version posted online: 21 Mar 2016.

Publisher: Taylor & Francis

Journal: *Expert Review of Clinical Pharmacology*

DOI: 10.1586/17512433.2016.1169173

Drug Profile

Aclidinium bromide inhalation powder for the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema

Maria Gabriella Matera[1], Alessandro Sanduzzi[2], Roberto Alfano[3], Mario Cazzola[4]

[1]Department of Experimental Medicine, Second University of Naples, Naples, Italy

[2]Department of Respiratory Diseases, Monaldi Hospital, University Federico II, Naples, Italy

[3]Department of Anaesthesiological, Surgical and Emergency Sciences, Second University of Naples, Naples, Italy

[4]Department of Systems Medicine, University of Rome Tor Vergata, Rome Italy

Correspondence: Prof. Maria Gabriella Matera, mariagabriella.matera@unina2.it

Abstract

Aclidinium is a twice-daily long-acting muscarinic receptor antagonist (LAMA) with an interesting pharmacological profile. Recent evidence indicates that this LAMA, in addition to causing a significant improvement in lung function and other important supportive outcomes, such as health related quality of life, dyspnea and nighttime/early morning symptoms in patients suffering from COPD, is also able to significantly reduce the rate of exacerbations of any severity, is extremely effective in controlling the COPD symptoms, is able to reduce lung hyperinflation, and has an excellent cardiovascular safety profile. Consequently, aclidinium should be considered a first-line approach at least for the symptomatic treatment of COPD although there are still few head-to-head studies comparing this LAMA with other bronchodilators. In any case, aclidinium can be taken into account in the treatment of different COPD phenotypes (emphysema, chronic bronchitis, exacerbators and patients with overlap COPD asthma).

Key words

Aclidinium, COPD, phenotypes.

Introduction

Airway tone is mainly controlled by the vagus nerve [1]. Acetylcholine (ACh), the neurotransmitter of the parasympathetic nervous system, acts via activation of muscarinic receptors [1]. Under "physiological" conditions, the airway smooth muscle contraction induced by ACh is mediated primarily via the M_3 subtype, whereas the M_2 subtype couples to adenyl cyclase via G_i in an inhibitory manner [1].

There is solid documentation that parasympathetic activity is increased in patients with chronic obstructive pulmonary disease (COPD) and appears to be the major reversible component of airway obstruction [1]. This primary reversible component is sensitive to muscarinic receptor antagonists [2]. Therefore, muscarinic receptor antagonists are central to the treatment of COPD [3].

There are currently six licensed muscarinic receptor antagonists for use in the treatment of COPD, the short-acting muscarinic receptor antagonists (SAMAs), ipratropium bromide and oxitropium bromide, and the long-acting muscarinic receptor antagonists (LAMAs), aclidinium bromide, tiotropium bromide, umeclidinium bromide, and glycopyrronium bromide.

In this review we will focus on the development of aclidinium and explain its role in the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease including chronic bronchitis and emphysema.

Preclinical data

Pre-clinical development of aclidinium has allowed investigators to collect important information that helps explain its positioning in the treatment of COPD.

In vitro, aclidinium bromide shows kinetic selectivity for human M_3 receptors over M_2 and rapidly associates at recombinant M_3 receptors (2.6 times faster than tiotropium) [4]. In human bronchial tissue, it has a similar potency at M_3 receptors to that of tiotropium and ipratropium, although its onset of action is significantly faster than tiotropium and its duration of action is significantly longer than ipratropium [5]. Moreover, aclidinium induces a potent concentration-dependent relaxation of human precision-cut lung slices submaximally pre-contracted with acetylcholine and its potency is not significantly different from that of formoterol [6].

In human left atrial tissue, aclidinium has a shorter duration of action at M_2 receptors than tiotropium, but longer than ipratropium [5].

In vitro, aclidinium is rapidly hydrolysed into carboxylic acid and alcohol derivatives in human plasma. In contrast, ≥70% of tiotropium and ipratropium remain unchanged in the plasma after 60 min of incubation [7]. The carboxylic acid and alcohol metabolites have no significant affinity for any of the muscarinic receptors, and show no relevant antibronchoconstrictory activity in vivo.

Clinical development

We have already reviewed the clinical development of aclidinium [8]. The critical analysis of the data available at the time we wrote the review allowed us to conclude that the twice-daily program established aclidinium 400 µg twice-daily (BID) as the lowest effective dose to achieve clinically meaningful improvements in lung function and other important supportive outcomes such as health-related quality of life and dyspnea. We also highlighted that maximum bronchodilation is achieved after the first dose and persists over the time, the effect is similar to that observed with tiotropium and formoterol and the safety database meets regulatory standards and demonstrates aclidinium 400 µg twice-daily is well-tolerated, safe and effective with a positive benefit/risk profile.

Later, other information was delivered to the literature that allows us to better clarify the role of aclidinium in COPD. Table 1 reports the fundamental trials with aclidinium in COPD.

Onset of action

A translational study that has compared, in the same patients and human tissues, the onset of action of aclidinium, glycopyrronium and tiotropium has shown that in isolated airways, glycopyrronium elicited a dose-dependent onset of action that was faster compared to that induced by aclidinium and tiotropium, which halved the contractile tone only at the highest concentration [9]. Nine, eight and twelve out of sixteen COPD patients did not achieve 15% increase of FEV_1 after inhalation of aclidinium 400 µg, glycopyrronium 50 µg and tiotropium 18 µg, respectively. In responders, aclidinium (15.6±7.5 min) and glycopyrronium (17.9±10.4 min) enhanced 15% FEV_1 more rapidly than tiotropium (42.5±19.4 min). These data suggest the importance of the association rate with M_3 receptor in influencing onset of bronchodilation of LAMAs, but due to small

sample sizes of responders in our trial, the true difference in onset of action between aclidinium, glycopyrronium and tiotropium remains unclear.

Recently, Santus et al. [10] demonstrated that both aclidinium and glycopyrronium significantly reduce hyperinflation and dyspnoea in severe and very severe COPD patients. Aclidinium however promoted a faster reduction in residual volume (5 min vs. 60 min) and was the only able to reduce lung ventilation inhomogeneity.

Impact on lung function over time

A 52-week, double-blind, extension study, in which COPD patients previously treated with aclidinium 200 µg or 400 µg BID during a 12-week lead-in study (ACCORD COPD I) continued the same treatment, while patients previously receiving placebo were re-randomized (1:1) to aclidinium 200 µg or 400 µg BID, assessed the long-term efficacy of aclidinium in pulmonary function [11]. Patients who received continuous aclidinium 200 µg or 400 µg demonstrated improvements from baseline in morning predose (trough) FEV_1 throughout the extension studies. Patients who were re-randomized to aclidinium 200 µg or 400 µg from placebo at the end of the 12-week ACCORD COPD I study demonstrated improvements from baseline in trough FEV_1 12 weeks after initiation of treatment with aclidinium 200 µg or 400 µg that were similar to those recorded at the end of 12 weeks of the ACCORD COPD I study in patients treated with aclidinium 200 µg or 400 µg, respectively. However, patients re-randomized from placebo to aclidinium 200 µg showed a fall in trough FEV_1 at the end of 52-week extension, contrary to that observed in other treatment arms and, in particular in those that, already treated with aclidinium 200 µg, continued the same treatment, in which the improvement in trough FEV_1 was maintained.

In another 52-week trial conducted in the U.S. and Canada, which enrolled 605 patients with moderate-to-severe COPD who were randomized to aclidinium 200 µg or 400 µg BID, the improvement in trough FEV_1 observed at the beginning of the study was generally maintained until study end with the aclidinium 400 µg dose, with mean changes from baseline in trough FEV_1 of 72 mL at the end of the study [12]. Numerically greater increases were detected with the 400 µg dose compared with the 200 µg dose for all lung function parameters throughout the study, indicating a dose-dependent effect on bronchodilation throughout 1 year of treatment.

Impact on breathlessness, health status, and COPD symptoms

Significant improvements were seen in breathlessness, health status, and COPD symptoms in the pivotal trials, but there has been a paucity of comparisons of aclidinium vs. other bronchodilators.

Data of 1787 patients with moderate-to-severe COPD from three 6-month, placebo-controlled Phase III trials evaluating aclidinium mono- or combination-therapy showed that aclidinium significantly improved breathlessness assessed using the Transitional Dyspnoea Index (TDI) and the health status assessed using the St George's Respiratory Questionnaire (SGRQ) vs. placebo after a 6-month treatment regardless of GOLD 2013 classification Group [13].

In a pre-specified analysis of pooled data from two 24-week, double-blind, parallel-group, active- and placebo-controlled, multicentre, randomised Phase III studies (ACLIFORM and AUGMENT), overall, 55.7% of patients achieved the minimum clinically important difference in TDI focal score with aclidinium, compared with 57.0% with formoterol and 40.3% with placebo [14].

In the 12-month extension study in the ACCORD COPD I cohort, patients who received continuous treatment with aclidinium 400 µg showed clinically significant improvements from baseline in total SGRQ scores, with an improvement of 7.9 units observed by the end of the study [11]. Also in the U.S. and Canada 52-week trial, aclidinium 400 µg induced clinically meaningful improvements in SGRQ total scores (≥4-point reduction from baseline) at all study visits during the entire treatment period [12]. A numerically higher proportion of patients in the aclidinium 400 µg group achieved the difference of at least 4 units (the threshold of clinical significance) in SGRQ total score *versus* the 200 µg group throughout the study.

Ni et al. [15] performed a Cochrane review from twelve aclidinium clinical studies, the duration of which ranged from four weeks to 52 weeks, in 9,547 COPD patients. Data from 7 trials with 4442 participants documented that aclidinium had been able to improve quality of life by lowering the SGRQ total score with a mean difference of -2.34 when compared to placebo. More patients on aclidinium achieved a clinically meaningful improvement of at least four units decrease in SGRQ total score (OR 1.49; number needed to treat (NNT) = 10) over 12 to 52 weeks than on placebo.

The pooled analysis of two Phase III studies (ATTAIN and AUGMENT) documented that in patients with moderate to severe airflow obstruction, aclidinium 400 µg BID significantly

improved daily respiratory symptoms assessed using the EXAcerbations of Chronic pulmonary disease Tool-Respiratory Symptoms (E-RS) diary, and increased the net response rate compared to placebo, but improvements in E-RS total score ≥2.0 units were seen with aclidinium in patients in GOLD groups B + D (i.e., those with more symptoms) [16].

In a 6-week study of Beier et al. [17] comparing aclidinium 400 µg BID with placebo and tiotropium 18 µg QD in patients with stable, moderate to severe COPD, significant improvements in the E-RS total scores over 6 weeks were numerically greater with aclidinium than tiotropium versus placebo. Both aclidinium and tiotropium significantly improved morning trough FEV_1 and FVC compared with placebo on day 1 and at week 6. Improvements in FEV_1 area under the curve from 0 to 12 h ($AUC_{0–24}$) and FEV_1 area under the curve from 12 to 24 h ($AUC_{12–24}$ were significantly greater with aclidinium versus tiotropium on day 1. Over 6 weeks, FEV_1 $AUC_{0–12}$ and FEV_1 $AUC_{12–24}$ with aclidinium were, respectively, numerically smaller and greater than tiotropium, but differences between the two treatments were not statistically significant. Nevertheless, aclidinium, but not tiotropium, produced significant improvements in individual early morning phlegm, shortness of breath, wheeze, cough and nighttime symptoms compared with placebo at week 6. It is possible to assume that the greater nighttime numerical improvement in lung function induced by aclidinium in the second 12 hours translated into significant changes in patient-reported outcomes. In any case, the limitation of activity caused by COPD symptoms was significantly lower only in patients receiving aclidinium *versus* those receiving placebo.

The pooled analysis of the ATTAIN and AUGMENT studies showed that the percentage of patients achieving a reduction in E-RS total score of ≥2 units was 41.3% with aclidinium, compared with 42.3% with formoterol and 34.4% with placebo [14]. The same pooled analysis documented that improvements in overall night-time symptom severity (aclidinium: –0.16 units; formoterol: −0.19 units) and early-morning symptom severity (aclidinium: −0.14 units; formoterol: −0.17 units) were almost identical [14].

A recent real-life experience with aclidinium showed that after approximately 3 months of treatment, the severity of COPD-related nighttime and early-morning symptoms and the limitation of morning activities were significantly reduced and the health-related quality of life relevantly improved under the conditions of daily clinical practice [18]. Interestingly, beneficial treatment effects were seen in patients with newly diagnosed COPD as well as

in patients with a history of COPD or previously treated with another LAMA, although improvements in the patient-reported outcomes were greater in newly diagnosed patients than in patients with previously known COPD.

Three Phase III studies (ACCORD COPD I [12 weeks], ATTAIN [24 weeks]) and LAS39 [6 weeks]) assessed the effect of aclidinium 400 µg BID on cough and sputum severity in patients with moderate-to-severe COPD (not selected for these symptoms). The retrospective analysis of these trials has documented that E-RS cough/sputum domain scores were lower with aclidinium than placebo [19]. Morning and nighttime cough severity, morning difficulty bringing up phlegm and nighttime sputum production were also reduced with aclidinium.

Rescue medication use

In the 6-week study of Beier et al. [17], the impact of aclidinium and tiotropium has been evaluated also on relief medication use and a significant increase in relief medication-free days with aclidinium and tiotropium versus placebo has been observed. Also in the 12-month extension study in the ACCORD COPD I cohort [11] and in the other 12-month trial [12], a decrease in medication use was recorded. In particular, in the Gelb's trial [12], rescue medication use during the overall treatment period was approximately one-half of the baseline value.

Impact on COPD exacerbations

In a pooled analysis of Phase III trials that included 2521 patients, aclidinium significantly reduced the rate of exacerbations of any severity vs. placebo for all patients [20]. The rate reduction was mainly in symptomatic patients (GOLD groups B + D). Time to first exacerbation (any) was delayed with aclidinium 400 µg vs. placebo in GOLD groups B+D but not GOLD groups A + C.

In their Cochrane review, Ni et al. [15], using data from ten aclidinium clinical studies in 5,624 COPD patients, found that the reduction in moderate exacerbations requiring treatment with systemic steroids and/or antibiotics did not reach significance for aclidinium versus placebo, but aclidinium significantly reduced the frequency of exacerbations requiring hospitalization.

A network meta-analysis of 27 randomized, controlled trials of at least 12 weeks duration, comparing a LAMA with placebo or another LAMA, documented that all LAMAs were able

to reduce the rate of moderate-to-severe exacerbations AECOPD when compared to placebo, but that there were not substantially differences between them [21]. When the analysis was restricted to studies in which the treatment lasted for at least 6 months, aclidinium was associated with the lowest risk for severe exacerbations.

Impact on exercise endurance and lung hyperinflation

A randomized, double-blind Phase IIIb crossover study evaluated the effect of aclidinium 400 µg BID on cycling exercise endurance, exertional dyspnea, and lung hyperinflation in 112 patients with COPD [22]. After 3 weeks, aclidinium significantly increased endurance time, reduced dyspnea intensity at isotime during exercise and improved trough inspiratory capacity vs. placebo. Significant improvements in spirometric, plethysmographic, and some physical activity parameters were also observed with aclidinium versus placebo.

Safety

In the 12-month extension of the ACCORD COPD I study, treatment-emergent adverse events (TEAEs) were mostly mild to moderate in severity and reported by similar percentages of patients across all treatment sequences (200 µg, 77.4%; 400 µg, 73.7%) during extension phase [11]. The manifestation of the classic adverse effects caused by antimuscarinic drugs was very low with both doses, so much that the most classic adverse effect, dry mouth, appeared in only 1 patient with the highest does (400 µg) Also as regards the heart, both doses were safe causing TEAEs in <5% of treated patients with no evidence of a dose-dependent impact

Also in the second 12-month trial [12], which like the other trials of aclidinium excluded patients with a history of clinically significant cardiovascular (CV) disorders, there was no difference in the percentage of TEAEs, which in general were mild or moderate, between the two doses of aclidinium. The percentages of patients with dry mouth (200 µg, 1.3%; 400 µg, 2.7%) and constipation (200 µg, 2.9%; 400 µg, 1.7%), which are the classic TEAEs caused by anticholinergic agents, was low across treatment groups. Only few patients (always <2% for any event in any group) reported CV TEAEs including coronary artery disease (the most frequent cardiac event), which occurred in 1.6% of patients receiving 200 µg aclidinium and none receiving the 400 µg dose and atrial fibrillation that was similarly uncommon in the two treatment groups (0.6 – 0.7%) Apparently, these TEAEs were not dose dependent.

A pooled analysis of six Phase III, placebo-controlled, parallel-group studies (≥1 month to 1 year duration) that included 2781 patients with moderate-to-severe COPD documented the optimum safety of aclidinium 400 µg BID that overall did not differ from that of placebo [23]. In particular, it was possible to document the absolute CV and cerebrovascular safety of aclidinium even in patients with CV risk factors.

Conclusion

Further research on aclidinium 400 µg twice-daily that followed the pivotal clinical trials not only confirmed that this LAMA induces clinically meaningful effects in lung function and other important supportive outcomes, such as health related quality of life, dyspnea and nighttime/early morning symptoms, and is safe, but also showed that aclidinium significantly reduces the rate of exacerbations of any severity, is extremely effective in controlling the COPD symptoms, is able to reduce lung hyperinflation, and has an excellent cardiovascular safety profile.

Expert commentary & five-year view

It is now widely ascertained the choice of a bronchodilator to treat the diagnosed COPD condition depends mainly on individual response, cost, side effects, and availability, and therapy often starts with an empiric choice and recording of clinical response to treatment [24, 25]. This empiric choice is mainly caused by the fact that there are still some crucial questions regarding the use of bronchodilators that require clarification. In particular, we still do not know whether it is better to start with a β_2-agonist or with an anti-muscarinic agent, it is useful to use a bronchodilator with rapid onset of action, and it is preferable to administer a bronchodilator on a once- or twice-daily basis [26].

We believe that the choice of bronchodilator to start treatment with in a patient with COPD mainly depends on the outcome of interest [25, 26]. LAMAs are probably preferable because in the symptomatic patient there is no substantial difference between them and LABAs [27], whereas in frequent exacerbators, they are more effective [28]. Although it is not yet clear if the differences in bronchodilator onset of action (fast-onset action *versus* slow-onset action) have any clinical role in COPD [26], we fully share the view that a bronchodilator with a rapid onset of action could be more effective on morning symptoms

than those with a relatively slow onset of action by providing a rapid relief of symptoms after morning dosing [29].

With regard to the question whether it is preferable to choose once- or twice-daily dosing, a population pharmacodynamic model of the longitudinal FEV_1 response to an inhaled LAMA in COPD patients has suggested that with the same total daily dose of a LAMA, a twice-daily regimen provides higher bronchodilation at trough than a once-daily regimen, the maximum FEV_1 response to once-daily regimen is higher, while the predicted average FEV_1 response is about the same [30]. Consequently, if there is the need for controlling both the nocturnal symptoms and those present on awakening, which epidemiological studies indicate to be the most troublesome for COPD patients [31], the twice-daily dosing of bronchodilators should be considered the most useful approach.

The results of the various studies conducted in recent years already described show that aclidinium is not only a LAMA with an excellent pharmacological profile, but also that it induces a rapid onset of action and is extremely effective in controlling nighttime and early-morning symptoms. This means that aclidinium should be considered a first-line approach, at least for the symptomatic treatment of COPD, although we must admit that there are still few head-to-head studies comparing aclidinium with other bronchodilators. Nonetheless, our opinion is reinforced by the documentation of the absolute cardiovascular safety, something that is very important in view of the frequent occurrence of cardiovascular diseases in patients with COPD [32].

Recognition of the heterogeneity of COPD together with the definition of clinical phenotypes suggests that we might take on a more personalized treatment not only according to the severity of the airflow obstruction, but also conditioned by the clinical phenotype [33]. Different phenotypes characterised by the combination of the classical types of emphysema, chronic bronchitis, exacerbators and patients with overlap COPD asthma have been identified [34]. Chronic bronchitis in patients with COPD is associated with worse respiratory symptoms and a higher risk of exacerbations of COPD [35]. Aclidinium can be considered in the treatment of all these phenotypes. In fact, we have already described the evidence showing that this LAMA lowers the rate of exacerbations of any severity and is able to reduce lung hyperinflation. Aclidinium has not been tested in asthmatic patients, but it is in the same class as tiotropium, which is an effective therapy in asthma [36]. Furthermore, it was found to reduce allergen-induced hyperresponsiveness and eosinophilic airway inflammation in an acute model of asthma [37].

Nevertheless, there is currently a trend to co-administer a LAMA and a LABA in order to optimize bronchodilation [38]. Actually, the combination of aclidinium and formoterol induces moderate to strong synergistic interaction in relaxing human isolated bronchi [6] that has a role also in the clinic setting [39]. However, there is evidence that the regular addition of formoterol to aclidinium improved the SGRQ total score more than formoterol (-6.57 units, and -4.70 units mean changes from baseline at week 24, respectively), but not more than aclidinium (-6.44 units) [40]. This finding makes it possible to question whether we should always use the dual bronchodilation instead of aclidinium monotherapy. Only a large, prospective real life study, in which patients under regular treatment with aclidinium will be enrolled and in one of the two arms formoterol will be added to aclidinium while in the other arm patients continue to take aclidinium alone, will tell us which patients can take a real advantage of the addition of formoterol to aclidinium.

Key issues

- Parasympathetic activity is increased in patients with COPD and appears to be the major reversible component of airway obstruction. This primary reversible component is sensitive to muscarinic receptor antagonists. Therefore, muscarinic receptor antagonists are central to the treatment of COPD.
- Aclidinium is a twice-daily LAMA with an interesting pharmacological profile.
- Pivotal trials have shown that aclidinium induces clinically meaningful effects in lung function and other important supportive outcomes (health related quality of life, dyspnea and nighttime/early morning symptoms) and is a safe bronchodilator.
- Recent evidence indicates aclidinium significantly reduces the rate of exacerbations of any severity, is extremely effective in controlling the COPD symptoms, is able to reduce lung hyperinflation, and has an excellent cardiovascular safety profile.
- Aclidinium should be considered a first-line approach at least for the symptomatic treatment of COPD, but there are still few head-to-head studies comparing this LAMA with other bronchodilators.
- It can be considered in the treatment of different COPD phenotypes (emphysema, chronic bronchitis, exacerbators and patients with overlap COPD asthma).

- Although the addition of formoterol to aclidinium induces a larger bronchodilation than that obtained with aclidinium alone, we still do not know whether we should always use the dual bronchodilation instead of aclidinium monotherapy.

Declaration of Interest:

M Cazzola has received grants and personal fees from Almirall and AstraZeneca. A Sanduzzi has received grants and personal fees from Almirall and AstraZeneca. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

*-Papers of interest

**-Papers of particular interest

1. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. Pharmacol Rev. 2012;64:450-504.
2. Cazzola M, Page C, Matera MG. Long-acting muscarinic receptor antagonists for the treatment of respiratory disease. Pulm Pharmacol Ther. 2013;26:307-17.
3. Matera MG, Rogliani P, Cazzola M. Muscarinic receptor antagonists for the treatment of chronic obstructive pulmonary disease. Expert Opin Pharmacother. 2014;15:961-77.
4. Gavaldà A, Miralpeix M, Ramos I, et al. Characterization of aclidinium bromide, a novel inhaled muscarinic antagonist, with long duration of action and a favorable pharmacological profile. J Pharmacol Exp Ther. 2009;331:740-51.
5. Gavaldà A, Gabarda E, Milara J, et al. Pharmacological assessment of the in vitro functional selectivity of aclidinium bromide at M3 and M2 muscarinic receptors in human tissue. Pulm Ther. 2015;1:103-7.
6. Cazzola M, Calzetta L, Page CP, et al. Pharmacological characterization of the interaction between aclidinium bromide and formoterol fumarate on human isolated bronchi. Eur J Pharmacol. 2014;745:135-43.
7. 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;39:283-90.

8. Cazzola M, Page CP, Matera MG. Aclidinium bromide for the treatment of chronic obstructive pulmonary disease. Expert Opin Pharmacother. 2013;14:1205-14.
9. Rogliani P, Calzetta L, Ora J, et al. Pharmacological assessment of the onset of action of aclidinium and glycopyrronium versus tiotropium in COPD patients and human isolated bronchi. Eur J Pharmacol. 2015;761:383-90.

** A translational study that has compared the onset of action of three LAMAs, aclidinium, glycopyrronium and tiotropium, in the same COPD patients and human tissues.*

10. Santus R, Radovanovic D, Di Marco F, et al. Faster reduction in hyperinflation and improvement in lung ventilation inhomogeneity promoted by aclidinium compared to glycopyrronium in severe stable COPD patients. A randomized crossover study. Pulm Pharmacol Ther. 2015;35:42-9.
11. D'Urzo A, Kerwin E, Rennard S, et al. One-year extension study of ACCORD COPD I: safety and efficacy of two doses of twice-daily aclidinium bromide in patients with COPD. COPD. 2013;10:500-10.

** An important 52-week, double-blind, extension study of 12-week ACCORD COPD I study, the results of which support the use of aclidinium as a long-term maintenance treatment for patients with COPD.*

12. Gelb AF, Tashkin DP, Make BJ, et al. Long-term safety and efficacy of twice-daily aclidinium bromide in patients with COPD. Respir Med. 2013;107:1957-65.

** Another fundamental study showing that long-term treatment with twice-daily aclidinium 200 µg or 400 µg was well tolerated, with no clinically meaningful differences in safety profiles between the two doses and a greater magnitude of improvement in bronchodilation observed with the 400 µg dose compared with the lower dose.*

13. Mróz RM, Ausin MP, Lamarca R, Garcia Gil E. Effect of aclidinium bromide on dyspnoea and health status in patients with stable COPD: Phase III data by GOLD 2013 classification [abstract]. Eur Respir J. 2014;44 Suppl 58:P891.
14. Bateman ED, Chapman KR, Singh D, et al. Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). Respir Res. 2015;16:92.
15. Ni H, Soe Z, Moe S. Aclidinium bromide for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2014;9:CD010509.

**The most comprehensive meta-analysis on aclidinium that has shown that aclidinium is associated with improved quality of life and reduced hospitalisations due to severe exacerbations in patients with moderate to severe stable COPD compared to placebo, but the available data are insufficient and of very low quality in comparisons of the efficacy of aclidinium versus tiotropium.*

16. Jones PW, Leidy NK, Hareendran A, et al. Aclidinium bromide Improves COPD symptoms assessed using the EXAcerbations of Chronic pulmonary disease Tool-Respiratory Symptoms questionnaire: Pooled analysis of two Phase III studies [abstract]. Am J Respir Crit Care Med. 2015;191 (Meeting Abstracts):A3971.
17. Beier J, Kirsten AM, Mróz R, et al. Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled Phase IIIb study. COPD. 2013;10:511-22.
18. Marth K, Schuller E, Pohl W. Improvements in patient-reported outcomes: A prospective, non-interventional study with aclidinium bromide for treatment of COPD. Respir Med. 2015;109:616-24.

A non-interventional study indicated beneficial effects of aclidinium in the treatment of COPD with regard to nighttime and early-morning symptoms, limitation of morning activities, and quality of life under routine conditions.

19. McGarvey L, Morice A, Smith J, et al. The effect of twice-daily aclidinium bromide on cough and sputum in patients with COPD: Results from phase III studies [abstract]. Eur Respir J 2014;44 Suppl 58:P920
20. Wedzicha JA, Donaldson G, Chuecos F, Garcia Gil E. Effect of aclidinium bromide on exacerbations in patients with moderate-to-severe COPD: pooled analysis of phase III studies [abstract]. Eur Respir J. 2014;44 Suppl 58:A1888.
21. Oba Y, Lone NA. Comparative efficacy of long-acting muscarinic antagonists in preventing COPD exacerbations: a network meta-analysis and meta-regression. Ther Adv Respir Dis. 2015;9:3-15.
22. Beeh KM, Watz H, Puente-Maestu L, et al. Aclidinium improves exercise endurance, dyspnea, lung hyperinflation, and physical activity in patients with COPD: a randomized, placebo-controlled, crossover trial. BMC Pulm Med. 2014;14:209.

A study that evaluated the effects of aclidinium on exercise endurance, dyspnea, lung hyperinflation, and physical activity.

23. Chapman KR, Beck E, Alcaide D, Garcia Gil E. Overall and cardiovascular safety of aclidinium bromide in patients with COPD: Results of a pooled analysis [abstract]. Eur Respir J. 2014;44 Suppl 58:P893.
24. Ohar JA, Donohue JF. Mono- and combination therapy of long-acting bronchodilators and inhaled corticosteroids in advanced COPD. Semin Respir Crit Care Med. 2010;31:321-33.
25. Cazzola M, Matera MG. Bronchodilators: current and future. Clin Chest Med. 2014;35:191-201.
26. Cazzola M, Page C. Long-acting bronchodilators in COPD: where are we now and where are we going? Breathe. 2014;10:110-20.
27. Cope S, Donohue JF, Jansen JP, et al. Comparative efficacy of long-acting bronchodilators for COPD – a network meta-analysis. Respir Res. 2013;14:100.
28. Vogelmeier C, Hederer B, Glaab T, et al. Tiotropium *versus* salmeterol for the prevention of exacerbations of COPD. N Engl J Med. 2011;364:1093-103.
29. Roche N, Chavannes NH, Miravitlles M. COPD symptoms in the morning: impact, evaluation and management. Respir Res. 2013;14:11.
30. Wu K, Looby M, Pillai G, et al. Population pharmacodynamic model of the longitudinal FEV1 response to an inhaled long-acting anti-muscarinic in COPD patients. J Pharmacokinet Pharmacodyn. 2011;38:105-19.
31. Kessler R, Partridge MR, Miravitlles M, et al. Symptom variability in patients with severe COPD: a pan-European cross-sectional study. Eur Respir J. 2011;37:264-72.
32. Cazzola M, Calzetta L, Bettoncelli G, et al. Cardiovascular disease in asthma and COPD: a population-based retrospective cross-sectional study. Respir Med. 2012;106:249-56.
33. Segreti A, Stirpe E, Rogliani P, Cazzola M. Defining phenotypes in COPD: an aid to personalized healthcare. Mol Diagn Ther. 2014;18:381-8.
34. Miravitlles M, Soler-Catalunā JJ, Calle M, et al. Spanish guideline for COPD (GesEPOC). Update 2014. Arch Bronconeumol. 2014;50(Suppl 1):1-16.
35. Kim V, Han MK, Vance GB, et al. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. Chest. 2011;140:626-33.
36. McKeage K. Tiotropium Respimat®: A review of its use in asthma poorly controlled with inhaled corticosteroids and long-acting β_2-adrenergic agonists. Drugs. 2015;75:809-16.
37. Damera G, Jiang M, Zhao H, et al. Aclidinium bromide abrogates allergen-induced

hyperresponsiveness and reduces eosinophilia in murine model of airway inflammation. Eur J Pharmacol. 2010;649:349-53.

38. Calzetta L, Matera MG, Cazzola M. Pharmacological interaction between LABAs and LAMAs in the airways: optimizing synergy. Eur J Pharmacol. 2015;761:168-73.
39. Cazzola M, Calzetta L, Ora J, et al. Searching for the synergistic effect between aclidinium and formoterol: From bench to bedside. Respir Med. 2015;109:1305-11.
40. D'Urzo AD, Rennard SI, Kerwin EM, et al. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. Respir Res. 2014;15:123.

Table 1 – Fundamental trials with aclidinium in COPD

Trial	Patients (n.)	Treatments	Duration	Main endpoints
ATTAIN	818	ACLI 200 µg, 400 µg BID vs placebo	24 weeks	Primary endpoint: change from baseline in trough FEV_1 at week 24. Secondary endpoints: change from baseline in peak FEV_1, number of patients achieving an improvement ≥1-unit in TDI focal score, number of patients achieving an improvement ≥4-units in SGRQ total score at week 24.
ACCORD I	561	ACLI 200 µg, 400 µg BID vs placebo	12 weeks	Primary endpoint: change from baseline in trough FEV_1 at week 12. Secondary endpoints: change from baseline in peak FEV_1 at week 12.
ACCORD II	542	ACLI 200 µg, 400 µg BID vs placebo	12 week followed by a 40-week evaluation of the higher dose	Primary endpoints: trough FEV_1 and long-term safety and tolerability of aclidinium treatment.
LAS-MD-35	605	ACLI 200 µg, 400 µg BID	52 weeks	Primary endpoint: change from baseline in morning in trough FEV_1 at Week 52 and long-term safety and tolerability of aclidinium treatment. Secondary endpoints: health status, and rescue medication use.
LAS-MD-36 *(extension ACCORD I)*	291	ACLI 200 µg, 400 µg BID (*patients previously receiving placebo re-randomized to one of the two aclidinium doses*)	52 weeks	Primary endpoint: long-term safety
LAS39	414	ACLI 200 µg, 400 µg BID vs. TIO 18 µg OD or placebo	6 weeks	Primary endpoint: change from baseline in normalized FEV_1 $AUC_{0–24}$ at week 6. Secondary endpoints: change from baseline in normalized FEV_1 $AUC_{12–24}$ and FEV_1 $AUC_{0–12}$ at week 6 and peak FEV_1 and FVC
ACLIFORM-COPD	1,729	ACLI/FORM FDC 400/12 µg or 400/6 µg, ACLI 400 µg, FORM 12 µg or placebo	24 weeks	Coprimary endpoints: change from baseline to week 24 in 1-hour morning postdose FEV_1 and in trough FEV_1. Secondary endpoints: change from baseline in SGRQ total score and improvement in TDI focal score at week 24.
AUGMENT	1,692	ACLI/FORM FDC 400/12 µg or 400/6 µg, ACLI 400 µg, FORM 12 µg or placebo	24 weeks	Coprimary endpoints: change from baseline to week 24 in 1-hour morning postdose FEV_1 and in trough FEV_1. Secondary endpoints: change from baseline in SGRQ total score and improvement in TDI focal score at week 24.

ACLI, aclidinium, FORM, formoterol; TIO, tiotropium; BID, twice-daily; OD, once-daily.