

## White Paper

### Long-Acting Muscarinic Agents (LAMAs)

### A New Frontier for COPD and Asthma Treatment



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## 1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health problem with a rising incidence and morbidity representing an important public health challenge that is both preventable and treatable. It has been estimated that in 2030 COPD will be the fourth leading cause of death worldwide resulting in an economic and social burden that is both substantial and increasing.



This increased mortality is mainly driven by the expanding epidemic of smoking, reduced mortality from other common causes of death (e.g. ischemic heart diseases, infectious diseases), and the aging of the world's population. Existing COPD prevalence data show that 9-10% of the adult population aged older than 40 years has been told that they have COPD. COPD has a huge impact on people with the condition; its clinical manifestations such as severity of respiratory symptoms, frequency of exacerbations, severity of spirometric abnormalities and type of co-morbidity cause a gradual decline in functional ability and greater dependence upon health and social care support with both aging and disease progression<sup>1,2,3,4</sup>.

Asthma is the most common respiratory disease in the world and is a significant cause of morbidity worldwide. People of all ages are affected by this chronic airways disorder that, when uncontrolled, can place severe limits on daily life and is sometimes fatal. The prevalence of asthma is increasing in some countries, especially in small children, and is



stable in others. Estimates for mean prevalence vary from 4 to 6% in adults and about 10% in children. The burden of asthma is experienced not only in terms of healthcare costs but also as lost productivity and reduced participation in family life. There is now good evidence that the clinical manifestations of asthma such as day and night respiratory

symptoms, limitation of daily activities, impairment of lung function, use of rescue medication, and asthma exacerbation can be controlled with appropriate treatment. When asthma is under control there should be no more than occasional recurrence of symptoms and severe exacerbations should be rare. In spite of the availability of effective treatments, control of asthma remains suboptimal in many countries<sup>5</sup>.

In the last few years significant pharmacotherapeutic advances have been made in the treatment of these medical conditions particularly focusing on inhaled bronchodilators such as long-acting muscarinic antagonists (LAMAs) and long-acting  $\beta_2$ -agonists (LABAs) with longer duration of action and corticosteroids (ICS) such as fluticasone furoate with more

potent anti-inflammatory activity. When respiratory symptoms are not controlled with monotherapy combination therapy is recommended. A number of companies are therefore developing different strategies to combine different drugs in fixed-dose combination formulations of both novel and established bronchodilators and corticosteroids.

Many factors contribute to the airflow limitation present in chronic lung diseases such as asthma and COPD including hyper-responsiveness to spasmogens and pathological structural changes throughout airways and lungs<sup>6</sup>. A key feature that contributes to the main symptoms and clinical manifestations of asthma and COPD is a dysfunction in autonomic nerve regulation of airways smooth muscle tone<sup>7</sup>. Therefore bronchodilators (long acting muscarinic receptor antagonists or long acting  $\beta$ 2-agonists) are recommended for the regular treatment of stable COPD and at least until now long acting  $\beta$ 2-agonists are the preferred choice associated to anti-inflammatory therapy in the treatment of asthma when the ICS alone is not enough.

Cholinergic parasympathetic nerves contribute to the elevated airways smooth muscle tone in COPD and asthma first releasing specific neuromediators such as acetylcholine (ACh), and this primary component of airway limitation is sensitive to muscarinic receptor antagonists. The effects of ACh are mediated by a family of 5 C-protein coupled receptors (M1-M5), which have distinct anatomical distribution and functions. Only the M1-M3 subtypes are expressed in airways where M3 receptors are those predominantly involved in the contraction of airways smooth muscle cells in response to ACh. M2 receptors are found presynaptically and act as autoreceptors to modulate ACh release. M2 receptors, the predominant muscarinic receptor subtype in the heart, mediate negative chronotropic and inotropic effects and consequently the inhibition of M2 receptors by muscarinic receptor antagonists is responsible for the characteristic tachycardia seen with this class of compound. Therefore the optimal antimuscarinic agent for use in COPD and asthma should have high affinity for M1 and M3 subtype receptors and a relatively low affinity for M2 receptors. As a consequence of the important role of the cholinergic system in the pathophysiology of chronic obstructive disorders, muscarinic receptor antagonists are useful additions to the portfolio of treatments of COPD and asthma<sup>8,9</sup>.

## 2. Tiotropium Bromide

The use of anticholinergic medications is well established as maintenance therapy for COPD. Nowadays there are a few LAMAs available on the market, with tiotropium bromide<sup>10,11</sup> having been launched several years ago. The others are aclidinium bromide and glycopyrronium bromide. All three are approved for treatment of COPD only.

Tiotropium bromide is the first anticholinergic drug with a once-daily (QD) regimen for the long-term, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema, that provides 24-hours bronchodilation effects, improves respiratory symptoms and health-related quality of life. Administered via dry

powder device (HandiHaler®), tiotropium is associated with typical anticholinergic adverse events (AEs) such as dry mouth, which is a consequence of reduced M1/M3 receptor mediated salivary secretion in response to parasympathetic stimulation. When a new formulation of inhaled tiotropium via Respimat® (a propellant-free inhaler that delivers a slow-moving mist of aerosolized solution) was launched onto the market, increasing evidence of cardiovascular AEs has been reported, including an increased risk of mortality.



In order to address this safety issue the Tiotropium Safety and Performance in Respimat® (TIOSPIR) study was performed<sup>12</sup>. It involved 17,135 patients with COPD for a median duration of 835 days, comparing the safety and efficacy of once-daily tiotropium doses of 2.5 µg and 5.0 µg delivered by Respimat® with a once-daily dose of 18 µg of tiotropium delivered by HandiHaler®. Primary end points were the rate of death (noninferiority study for both doses of Respimat® vs. HandiHaler®) and the rate of the first COPD exacerbation (superiority study for Respimat® 5.0 µg vs. HandiHaler®).



Reported results showed no significant difference among the three study groups with respect to death (hazard ratio for Respimat® 5.0 µg vs. Handihaler®, 0.96; 95% CI, 0.84 to 1.09; hazard ratio for Respimat® 2.5 µg vs. Handihaler®, 1.0; 95% CI, 0.87 to 1.14) or the first exacerbation (hazard ratio for Respimat® 5 µg vs. HandiHaler®, 0.98; 95% CI, 0.93 to 1.03). Patients with stable cardiac disease were included in the study, and there was no significant difference in mortality for those with a history of arrhythmia. The incidence of major cardiovascular adverse events was similar in the three study groups.

These results address several previous criticisms leveled against randomized, controlled trials and meta-analyses that did not identify an increased risk of death (or that showed a risk reduction) associated with tiotropium. A major concern was the possibility that the failure to identify a risk of death in some meta-analyses was due to the exclusion of patients with a cardiac history, especially arrhythmia or recent myocardial infarction, or those with other serious coexisting illnesses who might be at risk because of participation in the trial. In the TIOSPIR study, the clinical characteristics, coexisting illnesses, and coprescribed medications of the recruited patients suggest they did represent typical patients with symptomatic COPD, and the rate of follow-up was 99.7%. However, it is important to note that the absence of a placebo group in this study has implications for its interpretation and that it cannot be concluded from these results that tiotropium reduces mortality in patients with COPD.

Current guidelines for treating patients with asthma whose symptoms are not controlled by an intermediate dose of inhaled steroids plus long-acting beta-agonist (LABA) suggests as first option to increase the dose of inhaled steroid to the highest approved dose of ICS in ICS\_LABA combination.

The approach of increasing the dose of ICS to improve asthma control once a patient is already using an ICS+LABA combination was evaluated in the GOAL study. About 60% of the study population got good asthma control using a step up approach of the combination to the highest fluticasone dose i.e. 500 µg twice daily, while some others got good asthma control after adding an oral corticosteroid, whilst others did not achieve control of their asthma at all. This finding is not surprising, since inhaled corticosteroids have a relatively flat dose response curve, meaning that doubling the dose may result in little or no improvement in individual patients. This poses the question of whether other pharmacological options should be considered and there is a growing interest in the use of anticholinergic medications in the treatment of moderate to severe asthma. With this in mind, tiotropium has been evaluated as add on therapy to ICS at different doses of inhaled steroids and in different degrees of asthma severity. Indeed, the possible role of tiotropium in regular treatment of asthma has been recently explored in two trials.

One such study<sup>13</sup> was the Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (TALC) trial, which was performed in patients with mild-to-moderate asthma which was not adequately controlled with a low dose of ICS. It sought to investigate if addition of tiotropium would be superior to doubling the dose of ICS (primary hypothesis) and not inferior to addition of a LABA (secondary hypothesis). The primary outcome was the morning peak expiratory flow (PEF). The trial had a double-blind, 14-week three-way, crossover design, and 210 patients with were randomized. The use of tiotropium resulted in a significantly higher morning PEF than that achieved with doubling the dose of ICS (mean difference = 25.8 L/min,  $p < 0.001$ ) and superiority in most secondary outcomes, including evening PEF, (mean difference = 35.3 L/min,  $p < 0.001$ ); the proportion of asthma control days, (mean difference = 0.079,  $p = 0.01$ ); the forced expiratory volume in 1 second (FEV1) before bronchodilation, (mean difference = 0.10 liters,  $p = 0.004$ ); and daily symptom scores, (mean difference = -0.11 points,  $p < 0.001$ ). The addition of tiotropium was also noninferior to the addition of a LABA (salmeterol) for all assessed outcomes and increased the prebronchodilator FEV1 more than did salmeterol, (mean difference = 0.11 liters,  $p = 0.003$ ).

In the other study, the efficacy and safety of two doses of tiotropium (5 and 10 mg daily) added to the treatment regime of patients with severe uncontrolled asthma whose symptoms were inadequately controlled with at least high-dose ICS plus LABA treatment (GINA step 4-5) was evaluated<sup>14</sup>. The primary end point was peak FEV1 at the end of each 8 week treatment period. In the 100 patients who completed the study, peak FEV1 was



significantly higher than placebo with the addition of both doses of tiotropium (mean increase 139 mL and 170 mL for 5 mg and 10 mg doses respectively, both  $p < .0001$ ). There was no significant difference between the active doses. Trough FEV1 at the end of each dosing interval was significantly higher with tiotropium at both doses (mean increase 86 mL and 113 mL for 5 mg and 10 mg doses respectively, both  $p < .0004$ ). Daily home peak expiratory flow measurements were also higher with both tiotropium doses. There were no significant differences, however, in asthma-related health status or symptoms.

Kerstjen et al (2012)<sup>15</sup> reported results of two replicate, randomized, placebo-controlled trials (PrimoTinA-asthma 1 and PrimoTinA-asthma 2) which studied the efficacy and safety of adding tiotropium delivered by a soft-mist inhaler, as compared with placebo delivered by the same system, to a treatment regimen of glucocorticoids and LABAs. The design of both replicate studies was identical and compared addition of tiotropium (5  $\mu\text{g}/\text{d}$ ) to placebo on lung function and exacerbations over a 48 week study period<sup>15</sup>. A total of 912 symptomatic patients with asthma were studied, with a mean baseline post-bronchodilator FEV1 of 62% of the predicted value and history of at least one severe exacerbation in the previous year. All subjects were receiving inhaled glucocorticoids and LABAs. At week 24 of treatment, the mean change in peak FEV1 from baseline was greater with tiotropium than with placebo (mean difference = 86 mL ( $p = 0.01$ ), in trial 1, and 154 mL ( $p < 0.001$ ) in trial 2. The predose (trough) FEV1 also improved in trials 1 and 2 with tiotropium, as compared with placebo; a difference of 88 mL ( $P = 0.01$ ) and 111 mL ( $P < 0.001$ ), respectively. The addition of tiotropium also increased the time to the first severe exacerbation (282 days vs. 226 days), with an overall reduction of 21% in the risk of a severe exacerbation (hazard ratio, 0.79;  $P = 0.03$ ). No deaths occurred and adverse events were similar in the two groups.

In summary, the addition of tiotropium to ICS as maintenance therapy in asthma seems to be superior than doubling the dose of an inhaled corticosteroid (ICS) in patients who have not achieved control using ICS. It is also superior to placebo when added to a combination therapy with an ICS and a long-acting  $\beta_2$  agonist (LABA) in severe asthma.

### **3. Tiotropium + Olodaterol**

An inhaled combination of tiotropium and the  $\beta_2$ -agonist olodaterol is being developed by Boehringer Ingelheim. At the moment only COPD results presented as a poster at ERS 2010 are available with a fixed dose combination (FDC) of tiotropium bromide (T) and olodaterol (O) administered via Respimat<sup>16</sup>. In a randomized, phase II, double-blind, parallel group, dose finding study, 360 patients with COPD inhaled T+OFDC at different doses of olodaterol or tiotropium once daily for 4wks.

As reported in Table 1, Peak FEV1 response from baseline was significantly increased for all doses of T+OFDC compared with T alone; trough FEV1 response from baseline was

significantly increased for T+O(5/10 µg) FDC compared with T alone. No safety or tolerability concerns were identified in this study.

*Table 1 Effect of Various Fixed Dose Combinations of Tiotropium and Olodaterol on Peak and Trough FEV1 in Subjects with COPD*

		N	Peak FEV1 response (mL)		Trough FEV1 response (mL)	
			Mean (SE)	p-value	Mean (SE)	p-value
T	5µg	90	266 (24)		110 (20)	
T+O FDC	5/2µg	89	353 (24)	0.008	134 (21)	0.38
	5/5µg	93	348 (24)	0.012	143 (20)	0.22
	5/10µg	88	410 (24)	<0.0001	168 (21)	0.034

The authors therefore concluded that T+O FDC (5/10 µg) was more effective than tiotropium 5 µg alone in COPD patients, with superior bronchodilation over 24h following 4 weeks of once daily dosing.

No clinical data are available in asthma.

#### 4. Acridinium Bromide

Acridinium bromide<sup>17,18</sup> delivered by a novel multiple-dose device (Genuair®) is licensed in Europe as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The metered dose of acridinium bromide from the Genuair® inhaler is 400 µg, which corresponds to a delivered dose of 322 µg of acridinium per inhalation which is recommended twice daily with morning and evening administration. Initially this product was studied at once daily regimen but later twice daily posology adopted. Genuair® is a breath-actuated inhaler containing 60 doses, suitable for 1-month supply. The twice daily (b.i.d.) regimen has been reported to be effective in two randomized, double blind, placebo controlled, phase III studies called ACCORD and ATTAIN. In both studies, acridinium provided clinically meaningful improvements in bronchodilation over 24 hours, in health status and dyspnoea in patients with moderate to severe COPD.

The ATTAIN study<sup>19</sup> had a 24-week, double-blind design with 828 subjects randomised to twice-daily acridinium (200 µg or 400 µg) or placebo. The primary efficacy end-point was change in trough FEV1 at week 24. Other end-points included peak FEV1, health status (St George's Respiratory Questionnaire; SGRQ) and dyspnoea (Transitional Dyspnoea Index; TDI). At week 24, significant improvements from baseline were observed with acridinium 200µg and 400µg versus placebo for trough FEV1 (99 and 128 mL; both p<0.0001) and peak FEV1 (185 and 209 mL; both p<0.0001). Peak FEV1 improvements on day 1 were comparable with week 24. Acridinium 200 mg and 400 mg also produced significant improvements over placebo in baseline-adjusted mean SGRQ total score (-3.8 and -4.6 units; p<0.001 and p<0.0001) and TDI focal score (0.6 and 1.0 units; p<0.05 and p<0.001) at week 24. With both acridinium doses the incidence of anticholinergic adverse events was low, and similar to placebo.



The ACCORD study<sup>20</sup> utilised a 12-week, double-blind design in which 561 subjects were randomized (1:1:1) to receive acclidinium 200 µg b.i.d., acclidinium 400 µg b.i.d., or placebo. Primary and secondary endpoints were changes from baseline in trough FEV1 and peak FEV1 at week 12, respectively. Health status (SGRQ), COPD symptoms (TDI, night and early morning symptoms), and safety were also assessed. At week 12, acclidinium 200 µg and 400 µg b.i.d. showed significant improvements from baseline in mean trough FEV1 compared with placebo by 86 mL and 124 mL, respectively, and in peak FEV1 by 146 mL and 192 mL, respectively ( $p \leq 0.0001$  for all). Both acclidinium doses also provided significant improvements in SGRQ, TDI and almost all COPD symptom scores compared with placebo ( $p < 0.05$  for all). Incidences of adverse events were similar across treatment groups. The incidence of anticholinergic adverse events was low and similar across groups (dry mouth: 0.5%–1.6%; constipation: 0%–1.1%). Treatment of moderate-to-severe COPD patients with twice-daily acclidinium 200 µg and 400 µg was associated with significant improvements in bronchodilation, health status, and COPD symptoms. Both doses were well tolerated and had safety profiles similar to placebo.

In conclusion, given the sustained bronchodilatory effect, the improvement in dyspnea and health status and low rate of anticholinergic effects, acclidinium 400 µg dose b.i.d. via Genuair may be an effective new long-acting muscarinic antagonist treatment option for patients with stable moderate or severe COPD, with an acceptable the risk–benefit profile.

No clinical data are available in asthma.

## 5. Acclidinium + Formoterol (ACLIFORM)

A fixed dose combination of acclidinium bromide (LAMA) and formoterol fumarate (LABA), two effective bronchodilators with complementary mechanisms of action delivered by the inhaler Genuair® (Pressair™ in the USA), is being developed by Almirall, S.A. and Forest Laboratories, Inc.

A six month pivotal phase III, randomized, double-blind clinical trial, ACLIFORM/COPD (ACLIdinium/FORMoterol fumarate combination for Investigative use in the treatment of moderate to severe COPD) evaluated 400/6 µg and 400/12 µg fixed dose combinations of acclidinium bromide/formoterol fumarate compared with acclidinium bromide 400µg, formoterol fumarate 12µg and placebo administered BID through the Genuair®/Pressair™ inhalers in 1729 patients with moderate to severe COPD, in 22 countries including Europe, Korea and South Africa<sup>21</sup>.



For the co-primary efficacy endpoint of change from baseline in morning pre-dose trough FEV1 at week 24, acclidinium/formoterol 400/6µg and 400/12 µg demonstrated statistically significant improvements versus formoterol 12µg (53mL and 85mL, respectively) and placebo (111mL and 143mL, respectively). For the second co-primary endpoint of change

from baseline in FEV1 at 1 hour post-dose versus acclidinium 400µg, acclidinium/formoterol 400/6µg and 400/12 µg demonstrated statistically significant improvements versus acclidinium 400µg (69mL and 125mL, respectively) and placebo (244mL and 299mL, respectively).

Both combinations of both fixed-dose combination treatment arms were well tolerated in this study. The most common adverse events (greater than or equal to 3% and reported more frequently with acclidinium/formoterol than placebo) were nasopharyngitis (7.9% for 400/6 µg and 7.8% for 400/12 µg fixed-dose combinations and 7.2% for placebo) and back pain (3.4% for 400/6 µg and 4.7% for 400/12 µg fixed-dose combinations and 4.6% for the placebo group).

Almirall, S.A. recently (4th November 2013) announced that they had filed an MAA for ACLIFORM with the EMA and Forest Laboratories, Inc. also announced (6th April 2013) their intention to file an NDA with the FDA. These submissions are supported by the results of the ACLIFORM COPD study described above and by another virtually identical study performed in the USA, Australia and New Zealand (the AUGMENT/COPD trial).

To date, no clinical data are available in asthma.

## 6. Glycopyrronium Bromide

Glycopyrronium bromide<sup>22</sup> is already available on the European market as Seebri® Breezhaler®, manufactured by Novartis with the indication of maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. Each capsule contains 63 µg of glycopyrronium bromide equivalent to 50 µg of glycopyrronium. Each delivered dose (the dose that leaves the mouthpiece of the inhaler) contains 55 µg of glycopyrronium bromide equivalent to 44 µg of glycopyrronium.



Glycopyrronium bromide has high, non-selective affinity for all five muscarinic receptors subtypes. The dissociation t<sub>1/2</sub> at the M3 receptor is shorter than of acclidinium bromide and glycopyrronium bromide demonstrates kinetic selectivity for M3 over M2, similar to other LAMAs in development. Therefore glycopyrronium bromide provides bronchodilation via M3 blockade long after its less desirable M2 effects (such as an increased heart rate) have subsided.

Two large published clinical trials in patients with stable moderate to severe disease addressed the effect of glycopyrronium bromide on FEV1 in patients with COPD. The GLOW1 (glycopyrronium bromide in COPD airways clinical study1) trial involved a 26 week treatment period, with 822 patients randomized to receive either glycopyrronium bromide 50 µg once daily or placebo in a 2:1 ratio. The primary outcome measure (trough FEV1 at

week 12) was significantly higher in patients receiving glycopyrronium bromide (1.41 L) versus placebo (1.30 L) with a treatment difference of 108 mL ( $p < 0.001$ ). Significant improvements in trough FEV1 were observed at the end of day 1 and sustained through week 26. Notably, FEV1 was significantly improved in the glycopyrronium bromide group versus placebo group throughout a 24-hour period on day 1, at weeks 12 and 26, and at all other scheduled visits and time points.

The GLOW2 study also involved patients with moderate to severe COPD patients, randomizing 802 subjects in equal numbers to receive either glycopyrronium bromide 50  $\mu$ g once daily, open-label tiotropium 18  $\mu$ g once daily or placebo over a 52 week treatment period. The primary outcome measure (trough FEV1 at week 12) was significantly higher in patients receiving glycopyrronium bromide and tiotropium compared with that in patients receiving placebo, with a treatment difference of 97 mL ( $p < 0.001$ ) and 83 mL ( $p < 0.001$ ) respectively. Furthermore, trough FEV1 at week 26 and 52 was significantly higher for patients treated with glycopyrronium bromide group versus placebo and comparable with tiotropium. At these points the treatment difference, compared with placebo, in favor of glycopyrronium bromide, was 134 mL and 108 mL respectively ( $p < 0.001$ ), while the difference in favor of tiotropium was 84 mL and 89 mL, respectively ( $p < 0.001$ ). On day 1, the least squares mean FEV1 treatment difference for glycopyrronium bromide/placebo and tiotropium bromide/placebo was 87 mL and 45 mL at 5 minutes, respectively and 143 mL and 78 mL at 15 minutes, respectively ( $p < 0.001$ ). The latter finding further supports the notion that glycopyrronium bromide has a faster onset of action than other antimuscarinic agents, including tiotropium bromide.

Based on these data, and on the full development clinical program, glycopyrronium bromide has been shown to be an effective, safe and well tolerated long-acting anticholinergic bronchodilator with a fast onset of action. In patients with COPD, glycopyrronium bromide has clinically important effects on FEV1, use of relief medication, daytime dyspnea scores and improved exercise tolerance assessed by inspiratory capacity which translates into a beneficial effect on dynamic hyperinflation, comparable with that of other long acting bronchodilators including tiotropium bromide, indacaterol and aclidinium bromide.

No clinical data are available in asthma at the time of writing.

## **7. Glycopyrronium Bromide + Indacaterol (ULTIBRO<sup>®</sup>)**

Ultibro<sup>®</sup> is a fixed-dose combination of glycopyrronium bromide (50  $\mu$ g; 43  $\mu$ g is the dose that leaves the mouthpiece), a long-acting muscarinic antagonist, and indacaterol (110  $\mu$ g; 85  $\mu$ g is the dose that leaves the mouthpiece), a long-acting beta-2-adrenergic agonist. Recently the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has recommended approval of it as once-daily inhaled bronchodilator for maintenance treatment to relieve symptoms of COPD in adults.



Utlibro<sup>®</sup> is administered by inhalation by Breezhaler<sup>®</sup>, the same device used for Seebri<sup>®</sup> (glycopyrrolate) and Onbrez<sup>®</sup> (indacaterol).

Due to their mechanism of action, indacaterol activating the relaxation of the muscles of the airways, and glycopyrronium blocking the bronchoconstrictor action of acetylcholine on airway smooth muscle cells, they both dilate the airways in different ways. In combination they produce an additional bronchodilation in patients with severe COPD who require intensified therapy to reduce the risk of exacerbations.

Results of large trial, called SPARK, have been recently presented at European Respiratory Society 2013 Annual Congress held in Barcelona. Administered once-daily this fixed-dose combination of 2 bronchodilators improved lung function and reduced exacerbations in patients with severe COPD. The results, showed a 10% overall reduction in exacerbations with the fixed-dose combination, compared with monotherapy<sup>23,24</sup>.

Investigators compared fixed-dose combination of glycopyrronium bromide and indacaterol (QVA149) with two long-acting muscarinic antagonist monotherapies — glycopyrronium and tiotropium. Over the 64-week study period, they assessed rates of COPD exacerbation, lung function, overall health status, and safety in 2224 patients with severe to very severe COPD.

The reduction in mild exacerbations was 15% with the combination, compared with either of the monotherapies (P = .0072). For moderate to severe exacerbations, the reduction was 12%, although it was non-significant (P = .038). Results for FEV1 were significantly better with the combination than with either monotherapy, and were consistent over the study period (P = 0.001). Similarly, scores on the St. George's Respiratory Questionnaire were also significantly better with the combination, the authors stating the difference was approximately 3 units at all time points. Differences of this magnitude are typically noted only when comparing active medications to a placebo arm. In the SPARK study, however, there was no placebo arm due to the severity of disease in the patients included, making a placebo arm unethical.

All treatments had an acceptable safety profile, and there was no meaningful difference between the treatment groups in the incidence of adverse and serious adverse event reporting, the authors reported.

A number of advantages seem to with a fixed combination product. Firstly, the combination of the two drugs provides a greater therapeutic effect than the individual components alone, probably due to an additive effect rather than a synergistic one. Secondly, it seems likely that adherence will be improved if patients feel that symptomatic improvement is better with the combination.

At present, no clinical data are available in asthma.

## 8. Glycopyrronium Bromide + Formoterol

GFF MDI (also called PT003) is a fixed combination of glycopyrrolate (GP) and formoterol (FF) administered twice daily (BID) from an HFA-MDI being developed by Pearl Therapeutics.

Results of pooled analyses of five Phase 2b studies were presented at ERS in Amsterdam in 2011<sup>25</sup>. Patients in the MITT population from five randomized, double-blind, chronic dosing (7-14 days), placebo-controlled, multicenter, crossover studies in patients with COPD were included in pooled analyses of FEV1 AUC0-12 at end of treatment (Day 7 or 14). Doses ranged from 0.6 to 36 µg BID for GP MDI and 1.2/9.6 to 72/9.6 µg BID for GFF MDI. Pooled analyses included 590 patients in the MITT population with FEV1 AUC0-12 end-of-treatment data. For FEV1 AUC0-12, all GFF MDI doses, except 1.2/9.6 µg, were nominally significant ( $p < 0.05$ ) compared to separate components or tiotropium DPI. The greatest benefit was observed with GFF MDI 18/9.6 µg and GFF MDI 72/9.6 µg, providing an advantage over GP MDI 18 µg and FF MDI 9.6 µg approaching or exceeding 100 mL. Peak and trough FEV1 results provided similar findings. The dose responses of GP, FF and GFF MDI have been well characterized. These results showed that glycopyrrolate (GP) 18 µg, formoterol fumarate (FF) 9.6 µg, and GFF 18/9.6 µg are appropriate doses for Phase 3 development.

In COPD, Inspiratory Capacity (IC) is an important marker of exercise impairment. It is inversely correlated to the severity of dyspnea during exercise. GFF MDI has been compared to tiotropium (T) to evaluate the improvement in IC in a chronic dosing in a large Phase IIb study<sup>26</sup>. A randomized, double-blind, customized, unbalanced, incomplete block, crossover study was conducted in patients with moderate to very severe COPD. One objective was to assess changes in IC on Day 7 between two doses of GFF-MDI, (T) and PL. MDIs were administered BID for 1 week; T was administered QD for 1 week. A total of 118 patients were randomized. Results showed that GFF-MDI (72/9.6 and 36/9.6 µg) and T were superior to PL on morning pre-dose trough assessments (255mL, 271mL and 166mL, respectively;  $P \leq 0.0004$  all comparisons) and for peak IC assessments (265mL, 293mL and 170 mL, respectively;  $P \leq 0.0016$  all comparisons). Both GFF-MDI 72/9.6 µg and GFF-MDI 36/9.6 µg were superior to T for pre-dose trough IC (90mL and 105mL, respectively;  $P < 0.05$  both doses) and Peak IC on Day 7 (95mL and 124mL, respectively;  $P < 0.05$  both doses). Both doses of GFF-MDI were superior to PL and T for morning pre-dose and Peak IC assessments. These findings support the further development of GFF-MDI in patients with COPD.

GFF MDI (PT003) is the only LAMA/LABA combination product in late-stage development in an HFA MDI dosage formulation. No clinical data are currently available in asthma.

## 9. Umeclidinium

Umeclidinium (UMEC) is a potent competitive antagonist at recombinant M3 receptors and has a longer duration of action than tiotropium bromide in isolated bronchial strips. Its

inhaled formulation is in development for COPD. In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study involving 206 patients with aged  $\geq 40$  years with moderate to severe COPD, two doses of once daily umeclidinium (UMEC 62.5  $\mu\text{g}$  and, UMEC 125  $\mu\text{g}$ ) showed significantly improved lung function, dyspnea and health status over 12 weeks of treatment, and were well-tolerated<sup>27</sup>.

On Day 85 of treatment, statistically significant improvements in least square (LS) mean change from baseline in trough FEV1 (primary endpoint) were observed for UMEC 62.5  $\mu\text{g}$  (127mL) and 125  $\mu\text{g}$  (152mL) compared with placebo. On Day 84, statistically significant improvements were observed in LS mean change from baseline in 0–6h weighted mean FEV1 for UMEC 62.5 $\mu\text{g}$  (166mL) and 125 $\mu\text{g}$  (191mL) compared with placebo ( $p < 0.001$ ), and in serial FEV1 at all timepoints ( $p \leq 0.003$ ). On Day 84, transitional dyspnoea index focal scores for UMEC 62.5  $\mu\text{g}$  ( $p = 0.050$ ) and 125  $\mu\text{g}$  ( $p < 0.05$ ) were also improved compared with placebo. On average, both UMEC doses had greater decreases in rescue salbuterol use compared with placebo (UMEC 62.5  $\mu\text{g}$ ,  $-0.7$  mean puffs/day; UMEC 125  $\mu\text{g}$ ,  $-0.6$  puffs/day). A greater improvement in LS mean change from baseline in SGRQ total score on Day 84 was observed in UMEC 62.5  $\mu\text{g}$  and 125  $\mu\text{g}$  compared with placebo ( $p < 0.001$ ); placebo on average did not show an improvement. UMEC was rapidly absorbed ( $t_{\text{max}} \sim 5\text{--}15$  min). Accumulation ratios (Day 1 to Day 84) ranged from 1.6–1.8 with overlapping 90% CIs. Adverse events (AEs) were similar for UMEC (39–41%) and placebo (35%). Drug-related AEs included dry throat and dyspnea (UMEC 62.5 $\mu\text{g}$ ), cough (UMEC 125 $\mu\text{g}$ ) and dysphonia (placebo). Four patients reported serious AEs: coronary stenosis and COPD (UMEC 125  $\mu\text{g}$ ), lung neoplasm malignant (UMEC 62.5  $\mu\text{g}$ ) and non-cardiac chest pain (placebo); none were drug-related. No clinically meaningful changes in vital signs, clinical laboratory or 12-lead electrocardiogram assessments were reported.

At present, no clinical data are available in asthma.

## 10. Umeclidinium + Vilanterol

Umeclidinium/vilanterol<sup>28,29</sup> (UMEC/VI) is a new GlaxoSmithKline and Theravance combination inhalation product comprised of a long-acting antimuscarinic agent (LAMA), Umeclidinium and a long-acting beta-agonist (LABA), Vilanterol. Neither component is currently marketed as a single-ingredient inhalation product.

UMEC, the anticholinergic component, is a new molecular entity. VI, the LABA component, was recently approved in combination with fluticasone furoate (FF), an inhaled corticosteroid, as a combination product for COPD, Anoro (or Breo) Ellipta. UMEC/VI is supplied as a dry powder inhalation formulation administered by the Ellipta inhaler device.

Anoro (or Breo) Ellipta is the first once-daily product approved in the US that combines two long-acting bronchodilators in a single inhaler for the long-term maintenance treatment of



airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The FDA-approved strength is UMEC/VI 62.5 µg/25 µg 28.

The Phase III pivotal programme for Anoro (or Breo) Ellipta included seven clinical studies with almost 6,000 patients with COPD. To support the UMEC 62.5/VI 25 µg once daily dose for the proposed indication, GSK conducted a clinical program that included dose-ranging trials of varying duration for the individual components, two 6-month, placebo-controlled efficacy and safety trials, two 6-month, active-controlled efficacy and safety trials, and a 12-month safety trial. This clinical program focused primarily on efficacy, examining AE incidence, exercise endurance time and exertional dyspnea.



The four main efficacy trials of the pivotal program included a total of 4,733 patients treated with at least one dose of study drug, of which 842 patients received the proposed UMEC/VI 62.5/25 dose. The mean age was 63 years and 68% were male. Forty-nine percent were current smokers. At screening, 28% percent reported at least one exacerbation in the past year that required corticosteroids and/or antibiotics and approximately 10% reported a hospitalization in the past year due to an exacerbation. The majority of patients were categorized as GOLD Stage II (46%) or Stage III (43%). A total of 31% demonstrated reversibility to salbutamol alone, while 53% demonstrated reversibility after administration of salbutamol and ipratropium. The change from baseline in mean trough FEV1 at Day 169 was assessed as the primary endpoint in both the placebo- and active-controlled trials. UMEC/VI was compared to VI alone to assess the contribution of the UMEC component and to UMEC alone to assess the contribution of the VI component. In the placebo-controlled trials, a statistically significant difference was observed for the comparison of each of the active treatments against placebo (all p-values >0.001), demonstrating the efficacy of the monocomponents (UMEC 62.5, UMEC 125, and VI 25) and replicating the efficacy demonstrated for each individual component in the previous dose-ranging trials. A statistically significant difference was also observed for the comparison of both dose levels of UMEC/VI versus each of the individual components.

One of these studies, utilised a multicentre double-blind, placebo-controlled, parallel-group design, with a total of 1493 patients randomized (3:3:3:2) to 24 weeks of treatment with UMEC/VI 125/25µg, UMEC 125µg, VI 25µg, or placebo once-daily via dry powder inhaler. The primary efficacy endpoint was trough forced expiratory volume in one second (FEV1) on Day 169 (23–24 h post-dose). Additional lung-function, symptomatic and health-related quality of life endpoints were also assessed. Safety evaluations included adverse events, vital signs, electrocardiography and clinical laboratory measurements.

All active treatments significantly improved trough FEV1 vs placebo (0.124–0.238 L, all p<0.001). Improvements with UMEC/VI 125/25 µg were significantly greater than for UMEC

125 µg or VI 25 µg (0.079 L and 0.114 L; both  $p \leq 0.001$ ). Improvements for UMEC/VI 125/25 µg vs placebo were observed for the transition dyspnea index (1.0 unit;  $p < 0.001$ ), rescue albuterol use at Weeks 1–24 (-1.5 puffs/day) and St. George's Respiratory Questionnaire (-3.60 units,  $p < 0.001$ ). No safety signals were observed.

In conclusion once-daily UMEC/VI 125/25 µg was well tolerated and provided greater improvements in lung function, health status, and dyspnea scores compared with monotherapy components and placebo over 24 weeks. This study supports the use of UMEC/VI 125/25 µg for the maintenance treatment of COPD.

At the time of writing, no clinical data are available in asthma.

## 11. Triple Therapy

GOLD guidelines recommend that patients with severe or very-severe COPD with high risk of exacerbations also add an inhaled ICS to their bronchodilator regimen. In addition to dual fixed combination therapy, triple fixed combination therapies are being developed in COPD and asthma. Chiesi's glycopyrronium bromide + BDP/FF combination and Pearl Therapeutics's glycopyrronium bromide + Budesonide/FF product are both in Phase II/Phase III clinical development. No data are currently available for these triple therapies.

## 12. Conclusions

There is extensive evidence that treatment with LAMAs on a regular basis reduces COPD symptoms, decreases the frequency and severity of COPD exacerbations and improves both health status and exercise tolerance.

Newer and more selective LAMAs are in development with potentially unique efficacy and safety profiles and which are delivered via novel and hopefully easier to use inhaler devices.

There are some potential advantages with the novel LAMAs. Aclidinium bromide and Glycopyrrolate bromide achieve maximal bronchodilation on the first day of dosing or have a faster onset of action than tiotropium bromide, which may offer a faster improvement in symptom control. Furthermore, as some of these new drugs are suitable for once per day dosing there is the possibility to improve control of the early morning and nocturnal symptoms that patients with COPD often experience.

The safety reputation of LAMAs has been questioned with the safety results coming from the new tiotropium formulation (Respimat) clinical studies. Despite the clear efficacy shown with the Respimat formulation, post hoc pooled safety analyses showed an increased risk of serious cardiovascular effects particularly evident in patients with a history of cardiac arrhythmias. A large clinical trial specifically designed to investigate the safety of both tiotropium bromide formulations has shown that there was no significant difference among the Respimat 5 and 2.5 µg versus the Handihaler formulation with respect to death or the

first exacerbation. Patients with stable cardiac disease were included in the study, and there was no significant difference in mortality for those with a history of arrhythmia. The incidence of major cardiovascular adverse events was similar in the three study groups.

In order to improve patient compliance fixed combinations of double LABA/LAMA and triple ICS/LABA/LAMA are being developed. Clinical studies with these new combinations are very promising and preliminary efficacy and safety results are exciting.

As these new products become available in the clinical setting physicians will have a greater number of treatment options and consequently will be better equipped to prescribe the COPD treatment most appropriate for each individual patient.

### **13. About the Author**

Renato Testi graduated from the University of Padua with a degree in Chemistry, before gaining his MD from the University of Verona. After a couple of years at Padua University as an assistant in the Organic Chemistry Department, Renato joined Laboratory Glaxo S.p.A. (Italy) as Head of Chemistry from 1974 to 1979. In 1979 he moved to the Medical Department as a Medical Advisor, subsequently becoming Medical Respiratory Leader in the same company Glaxo Smith Kline SpA (Italy) from 1979 to December 2004. In this role Renato supported clinical development and marketing activities of several drugs in respiratory medicine.



In 2006, Renato became a Clinical Research Physician at Centro Ricerche Cliniche, Policlinico BG Roma, Verona focusing on performing medical activities and screening visits for volunteers involved in clinical trials in Phase I to III. Renato joined CROMSOURCE in 2010 as a Medical Monitor in the Clinical Research division. Here Renato has managed clinical trial activities, medical oversight and monitoring procedures for many international clinical trials in both asthma and COPD.

Renato continues practicing as a physician specialised in respiratory medicine, currently at Unit-Policlinico BG Roma, Verona University. Renato can be contacted at [renato.testi@cromsource.com](mailto:renato.testi@cromsource.com).

### **14. About CROMSOURCE**

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