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A randomised double-blind, placebo-controlled, long-term extension study of the efficacy, safety and tolerability of fixed-dose combinations of aclidinium/formoterol or monotherapy in the treatment of chronic obstructive pulmonary disease

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ABSTRACT

Introduction: Aclidinium bromide/formoterol fumarate (AB/FF) 400/12 μg efficacy and safety was demonstrated in two 6-month Phase III studies (AUGMENT and ACLIFORM) and a 12-month study in patients with moderate to severe chronic obstructive pulmonary disease (COPD). This Phase III, double-blind, placebo-controlled, 6-month AUGMENT extension investigated the long-term safety and tolerability of AB/FF 400/12 μg (NCT01572792).

Methods: Patients were randomised in AUGMENT (1:1:1:1:1) to twice-daily AB/FF 400/12 μg, AB/FF 400/6 μg, AB 400 μg, FF 12 μg or placebo. Patients completing AUGMENT were invited to continue the same treatment in the extension. Adverse events (AEs), major adverse cardiovascular events (MACE), laboratory tests, electrocardiograms and vital signs were recorded. Efficacy was assessed.

Results: Of 1322 patients completing AUGMENT, 921 enrolled and 780 completed the extension. AE incidence was low and comparable across treatment groups; most common were nasopharyngitis (range 4.8%–9.3%), urinary tract infection (range 4.1%–8.8%) and upper respiratory tract infection (range 2.7%–5.5%). Serious AEs (SAEs) and MACE were low (ranges 6.8%–7.7% and 0.5%–1.5%, respectively). Significant improvements in bronchodilation and dyspnoea were maintained over 52 weeks versus placebo. Trends towards improvements in other symptoms and health status were observed versus placebo and monotherapies. AB/FF combinations increased the time to first exacerbation by approximately 30% versus placebo ($p < 0.05$).

Conclusion: AB/FF 400/12 μg was well tolerated over 52 weeks with low incidences of AEs, SAEs and MACE that were comparable across treatment groups. Improvements in bronchodilation, symptoms and health status were maintained across 52 weeks.

Trial registration

Efficacy, Safety and Tolerability of Two Fixed Dose Combinations of Aclidinium Bromide/Formoterol Fumarate, Aclidinium Bromide, Formoterol Fumarate and Placebo for 28-Weeks Treatment in Patients With Moderate to Severe, Stable Chronic Obstructive Pulmonary Disease (COPD); NCT01572792.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive and treatable disease requiring long-term treatment with effective and well-tolerated bronchodilators. Current guidelines recommend treatment with inhaled long-acting bronchodilators (long-acting muscarinic antagonists [LAMAs] or long-acting β_2-agonists [LABAs]) for most patients with COPD [1]. For increased symptom control, it is recommended to combine two long-acting bronchodilators with complementary mechanisms of action (i.e. a LAMA and a LABA) [1]. LAMAs are thought to inhibit the muscarinic M_3-receptor (the primary receptor subtype that mediates airway smooth muscle contraction [2]), thereby reducing acetylcholine binding, leading to smooth muscle relaxation and bronchodilation; LABAs are primarily understood to stimulate β_2-adrenoceptors, leading to an increase in cyclic adenosine monophosphate via increases in adenylyl cyclase, thereby resulting in smooth muscle relaxation [3]. Several studies have shown that the combination of a LAMA and a LABA results in greater improvements in airflow and decreased use of rescue medication compared with either monotherapy [4–10]. Indeed, a number of LAMA and LABA combinations are now approved for use in patients with COPD [11–14]. This paper reports a long-term study of aclidinium bromide/formoterol fumarate (AB/FF) 400/12 μg, a LAMA/LABA combination therapy currently approved for COPD maintenance therapy in Europe and other territories, including Canada and Australia [11,15,16].

2. Methods

2.1. Study design

This 28-week, Phase III, double-blind, placebo- and active-controlled, long-term extension study (NCT01572792) was conducted in patients with moderate to severe COPD at 169 centres in the USA and Canada. The study was conducted from April 2012 to June 2013 in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidance on General Considerations for Clinical Trials and Good Clinical Practice. The protocol was approved by Institutional Review Boards and independent ethics committees; patients completed a randomised, double-blind, placebo-controlled lead-in trial and signed new written informed consent to participate in the extension study, equating to a total of 52 weeks of treatment.

Almirall, study personnel and study patients were blinded as to which treatment patients were receiving. All inhalers were identical from an external perspective; the only difference between them was that placebo did not contain active ingredient. Active ingredients had no perceptible taste, appearance, odour, or colour that could unmask the blinded design. Breaking the blind was done only in an emergency that required identification of the investigational product for the medical management of the patient.

Randomisation was carried out at the start of the 24-week lead-in study. A list of patient randomisation codes was generated by Statistical Programming at Forest Research Institute and implemented by using an interactive web response system. Patients were randomised (1:1:1:1:1) to 1 of 5 treatment groups:

- AB/FF 400/12 μg
- AB/FF 400/6 μg
- AB 400 μg
- FF 12 μg
- Placebo.

Treatment was administered twice daily (one puff, morning and evening) using the Genuair™/Pressair®[a] multidose dry powder inhaler. Patients who completed the 24-week treatment period of the lead-in study and met the eligibility criteria for the extension study were given the opportunity to enrol in the 28-week extension study during the final visit of the lead-in (Week 24); those who consented remained in the same treatment group. The final visit of the lead-in study (Week 24) was the first visit of this study, and there were 4 further study visits (Weeks 31, 38, 45 and 52, relative to the start of the lead-in study; Fig. 1). In addition, patients were contacted by phone at Weeks 27, 34, 41, 48 and 2 weeks after the final treatment administration to record adverse events (AEs) and exacerbations. The objectives of the extension study were to assess long-term safety and efficacy of AB/FF combination therapy compared with placebo and monotherapy components.

2.2. Patients

Detailed inclusion and exclusion criteria from the lead-in trial have been published previously [5]. Briefly, patients were male or female, ≥40 years of age with a smoking history of ≥10 pack-years and had a diagnosis of moderate to severe COPD according to Global initiative for chronic Obstructive Lung Disease 2011 criteria (post-bronchodilator forced expiratory volume in 1 s [FEV_1]/forced vital capacity ratio <70%; post-bronchodilator FEV_1 ≥30% and <80% predicted) [1].

Use of long-acting bronchodilators other than the investigative treatment was not permitted. Other COPD medications, such as theophylline, inhaled corticosteroids (ICS), oral or parenteral corticosteroids (≤10 mg/day or 20 mg every other day prednisone) were allowed if treatment was stable within 4 weeks of the lead-in trial start. Albuterol (108 μg/puff) or salbutamol (100 μg/puff) were the only rescue medications permitted during the study.

2.3. Treatment compliance

Patients recorded each dose of the experimental treatment (number of puffs) in an electronic treatment diary every morning and evening. Treatment compliance was calculated as total number of puffs divided by the expected number of puffs (two per day), multiplied by 100. For reporting purposes, patients were considered compliant if their treatment compliance was at least 75% and less than 110%.

2.4. Safety assessments

Safety assessments included recording of AEs, laboratory tests, 12-lead electrocardiograms (ECGs) and vital signs. AEs were recorded from the time the patient signed the consent form to 30 days after the last treatment dose. Exacerbation events were captured as efficacy endpoints and were therefore excluded from AE reporting. Major adverse cardiovascular events (MACE), defined in accordance with Food and Drug Administration guidance [17] (cardiovascular death, myocardial infarction and stroke) were adjudicated by a clinical outcomes committee of independent cardiologists.

2.5. Efficacy assessments

Pulmonary function was assessed using standard spirometry techniques. Changes in breathlessness during the study were evaluated using the Transition Dyspnoea Index (TDI). Exacerbations were assessed by healthcare resource utilisation (HCRU). Health-related quality of life was measured using the St George's Respiratory Questionnaire (SGRQ). Rescue medication use was recorded daily in an electronic diary. Daily respiratory symptoms were assessed using the Evaluating Respiratory Symptoms (E-RS)