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A randomised, placebo-controlled, Phase II, dose-ranging trial of once-daily treatment with olodaterol, a novel long-acting β_2-agonist, for 4 weeks in patients with chronic obstructive pulmonary disease

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KEYWORDS
Olodaterol;
COPD;
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Once-daily

Summary
Background: Olodaterol is a novel long-acting β_2-agonist (LABA) with ≥24-h duration of action in preclinical and clinical studies.
Objective: This Phase II, multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose-finding study evaluated four doses of once-daily olodaterol over 4 weeks in patients with chronic obstructive pulmonary disease (COPD), based on efficacy, safety and pharmacokinetic parameters.
Methods: Patients received olodaterol inhalation solution or placebo via Respimat® Soft Mist™ inhaler once daily for 4 weeks. Pulmonary function testing was performed pre-dose (trough) and up to 3 or 6 h post-dose, depending on visit. Primary end point was change from baseline in trough forced expiratory volume in 1 s (FEV_1) after 4 weeks' treatment. Secondary end points included change from baseline in peak FEV_1 and FEV_1 area under the curve from 0 to 6 h.

Abbreviations: AE, adverse event; AUC_{0-6}, area under the curve from 0 to 6 h; COPD, chronic obstructive pulmonary disease; C_{max}, maximum concentration; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; gCV, geometric coefficient of variation; LABA, long-acting β_2-agonist.

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Results: 405 patients with COPD were randomised and assigned to treatment. Mean baseline post-bronchodilator FEV_1 was 1.50 L (54% predicted). All olodaterol doses provided statistically significant increases in trough FEV_1 compared to placebo (2 μg: 0.061 L [$p = 0.0233$]; 5 μg: 0.097 L [$p = 0.0003$]; 10 μg: 0.123 L [$p < 0.0001$]; 20 μg: 0.132 L [$p < 0.0001$]). A clear dose—response relationship was demonstrated regarding pulmonary function; the two highest olodaterol doses (10 and 20 μg) formed the plateau of the dose—response curve. All olodaterol doses were well tolerated, with no dose-dependent safety effects.
Conclusion: Once-daily olodaterol demonstrated 24-h bronchodilator efficacy, confirming its potential as a once-daily LABA for the management of COPD.
Trial registration: ClinicalTrials.gov: NCT00452400.

Introduction

Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity, mortality and health-care costs, with an estimated 65 million people worldwide experiencing moderate to severe disease activity according to World Health Organization estimates [1]. COPD is characterised by persistent and progressive airflow limitation, and is associated with chronic and progressive dyspnoea, cough and sputum production [2]. Treatment guidelines recommend the use of long-acting bronchodilators, such as long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists, for the maintenance treatment of patients with COPD when symptoms are not adequately controlled with short-acting agents [2]. The introduction of LABAs with a duration of action of ~12 h, nearly two decades ago, provided patients with superior bronchodilator efficacy and improved outcomes compared to that of shorter-acting agents [3,4]. Recently, several LABAs with a duration of action of ~24 h have been developed, providing the potential for once-daily pharmacotherapies that could offer improved treatment adherence as well as the opportunity for combination with other once-daily drugs such as tiotropium [5—8].

Olodaterol, which belongs to this new generation of LABAs, is characterised by enantiomeric purity, a high β_2-receptor selectivity and a near full agonist response at the human β_2-adrenoceptor *in vitro* [9]. In preclinical animal studies, olodaterol shows a rapid onset of action and inhibits acetylcholine-induced bronchospasms in anaesthetised guinea pigs and dogs [10]. Moreover, this bronchoprotective effect was demonstrated to last >24 h in both models [10].

This study is part of a series of trials designed to establish the optimum dose and treatment regimen for olodaterol in patients with COPD. An initial single-dose study demonstrated effective bronchodilation over 24 h for a range of olodaterol doses (2, 5, 10 and 20 μg) in a dose-dependent manner [11].

The primary objectives of this Phase II study were, therefore, to confirm the 24-h bronchodilator efficacy of olodaterol after once-daily administration in patients with COPD over an extended 4-week treatment period and to determine the most appropriate dose for the Phase III studies. The Phase III studies have now been performed and demonstrated the efficacy and tolerability of olodaterol 5 and 10 μg [12—15]. Additional objectives of this Phase II study were to evaluate the safety and tolerability of olodaterol as well as systemic pharmacodynamic and pharmacokinetic parameters.

Methods

Patients

Patients were enrolled if they met the following inclusion criteria: aged ≥40 years with a diagnosis of COPD [16]; current or ex-smokers with a smoking history of >10 pack-years; a post-bronchodilator forced expiratory volume in 1 s (FEV_1) of ≥30% and <80% of predicted normal; and a post-bronchodilator FEV_1/forced vital capacity (FVC) <70%. Key exclusion criteria were: a history of asthma; a history of myocardial infarction (within 1 year); clinically relevant cardiac arrhythmia; marked prolongation of QT/QTc interval (QTc interval >450 ms); regular use of daytime oxygen therapy; and use of β-adrenergic antagonists (β-blockers).

Study design

This was a Phase II, 4-week, multi-dose, multicentre, multinational, randomised, double-blind, placebo-controlled, parallel-group study registered with ClinicalTrials.gov (NCT00452400). Following an initial screening phase, patients entered a 2-week baseline period to ensure clinical stability (Fig. 1).

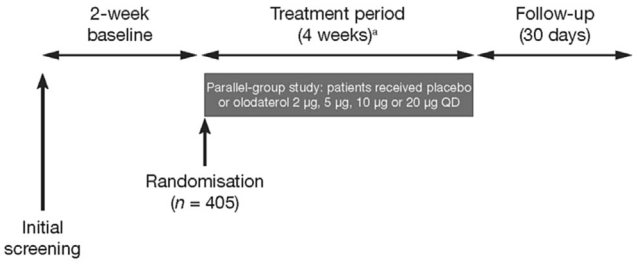

Figure 1 Study design.