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Abediterol (LAS100977), a novel long-acting β_2-agonist: Efficacy, safety and tolerability in persistent asthma

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Summary
Background: Abediterol (LAS100977) is a novel, long-acting β_2-agonist, in development for the once-daily treatment of asthma in combination with mometasone. Here we report the results of a Phase IIa trial of single doses of abediterol added to ongoing maintenance therapy (inhaled corticosteroids) in patients with persistent mild-to-moderate asthma.
Methods: This was a randomised, double-blind, placebo- and active-comparator-controlled, five-way crossover study. Male patients (18–70 years) with a clinical diagnosis of persistent asthma received abediterol (5, 10 and 25 μg), salmeterol and placebo, on top of ongoing maintenance therapy. Lung function was determined using spirometry and whole body plethysmography. The primary efficacy endpoint was change from baseline in trough forced expiratory volume in 1 s (FEV_1) after a single dose.
Results: All three abediterol doses induced statistically significant increases in trough FEV_1 vs placebo and salmeterol. Improvements in other lung function parameters were also statistically significantly greater with all abediterol doses vs both placebo ($p < 0.0001$) and salmeterol ($p < 0.05$) than the first assessment at 5 min post-dose. These improvements were sustained to 36 h post-dose. The profile of treatment-emergent adverse events judged as related to abediterol was consistent with that seen after adrenergic stimulation and occurred exclusively in patients who received abediterol 10 μg or 25 μg.
Conclusions: This first-in-patient study revealed the potent, rapid and long-acting bronchodilatory effect of abediterol in patients with persistent mild-to-moderate asthma together with

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an overall good safety and tolerability profile. Further studies are now underway to establish the optimal efficacy—safety—tolerability profile for this compound.

Introduction

Asthma is a chronic, inflammatory respiratory disorder characterised by episodes of wheezing, breathlessness, chest tightness and coughing [1]. Asthma is thought to affect around 300 million individuals of all ages worldwide and is associated with a considerable morbidity burden and an increased risk for death [1].

Asthma management strategies aim to control daily symptoms and reduce the risk for asthma exacerbations. Current asthma guidelines recommend the use of long-acting bronchodilators such as long-acting β_2-agonists (LABAs) in conjunction with inhaled corticosteroids (ICS) for the management of patients with moderate-to-severe asthma [1,2]. This dual approach addresses both the daily symptomatic burden of moderate-to-severe asthma and the underlying inflammatory processes that are thought to increase the risk for episodic exacerbations. Currently available LABAs include salmeterol, formoterol, indacaterol (not approved for the treatment of asthma) and olodaterol. Whilst they are effective in terms of bronchodilation, there are safety concerns surrounding the use of LABA monotherapies in asthma, an approach which is thought to increase the risk for asthma-related adverse events [3]. Indeed, an FDA black box warning states that salmeterol and formoterol may only be used in combination with ICS in patients with asthma.

Abediterol (LAS100977) is a novel, potent and selective LABA, currently in clinical development for the once-daily treatment of chronic obstructive pulmonary disease (COPD) and asthma in combination with an ICS. The preclinical evaluation of this agent demonstrated a high potency and selectivity at the β_2-receptors, with a rapid onset of bronchodilation and long duration of action [4]. A Phase I, first-in-human, single-dose clinical trial, showed a potent bronchodilatory effect of abediterol at doses ranging from 5 μg to 50 μg [5], confirming preclinical data obtained with this compound. The safety and tolerability profile in healthy adults was encouraging with no treatment-emergent adverse events (TEAEs) reported at the lowest dose (5 μg) and a single case of moderate palpitations in the highest dose group (50 μg; all other TEAEs were mild in intensity). This paper reports data from an active comparator (salmeterol) and placebo-controlled proof-of-concept Phase IIa trial of single doses of abediterol (5 μg, 10 μg or 25 μg) added to ongoing maintenance therapy with ICS in a stable dose regimen in patients with mild-to-moderate persistent asthma.

Methods

This was a Phase IIa, randomised, double-blind, double-dummy, placebo- and active-comparator-controlled, five-way crossover study. The study was carried out in accordance with the Declaration of Helsinki (1964 and subsequent amendments) and with Good Clinical Practice and Good Laboratory Practice (1998) guidelines. The study was also conducted in line with European directives 2001/20/RC and 2005/29/EC.

Study subjects

The study included male patients aged 18—70 years with a clinical diagnosis of mild-to-moderate persistent asthma for at least 6 months prior to screening. Female patients did not take part in the current study as the requisite preclinical evaluations had not been completed at the time the study was initiated. Eligible patients were required to have a stable maintenance therapy of ICS during the 6 weeks prior to the screening visit, either alone or in combination with a short- or long-acting β_2-agonist. They were also required to have a forced expiratory volume in 1 s (FEV_1) between 60% and 85% of the predicted normal pre-bronchodilator value at screening, FEV_1 reversibility $\geq$12% and an absolute increase of at least 200 mL over baseline value following inhalation of 400 μg salbutamol. In addition, the pre-dose FEV_1 for each treatment period had to be within 80—120% of the pre-dose FEV_1 at screening. Exclusion criteria included a history of smoking during the previous 12 months and a $\geq$10 pack-years, the presence of clinically significant diseases, other than asthma, hospitalisation or emergency-room treatment for acute asthma in the 6 weeks prior to screening.

Study drug

After an initial screening and run-in period of up to 14 days, patients were randomised 1:1:1:1:1 to one of 5 treatment sequences during which they received once-daily abediterol (5, 10 and 25 μg), salmeterol 50 μg twice daily or placebo in addition to ongoing ICS maintenance therapy. Ongoing asthma medications were withdrawn during the run-in period, with the exception of ICS and rescue medication. All study drugs were delivered as dry powder for inhalation. Abediterol doses were administered in the morning as a single inhaled dose delivered via the Cyclohaler® device. Salmeterol was administered in twice daily (BID) inhaled doses, one in the morning and one in the evening, via the Accuhaler® device. A double-dummy approach was taken to maintain blinding as the study drugs were delivered in different inhalation devices and corresponding placebo treatments were administered using the Cyclohaler® and Accuhaler® devices. Each treatment period lasted 36 h, with a minimum 7-day washout period between consecutive treatments. Patients were properly washed out between each study period and asthma stability was re-checked. Patients were allowed to use their pre-existing long-acting bronchodilators during the washout periods, but these were withdrawn 72 h prior to the next treatment period. During treatment periods, only ICS and asthma rescue medication (100 μg/puff of salbutamol pressurised metered dose inhaler) were permitted; rescue medication was not permitted within 6 h prior to a study visit.