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

J. Beier [a,*], R. Fuhr [b], E. Massana [c], E. Jiménez [c], B. Seoane [c], G. de Miquel [c], S. Ruiz [c]

[a] Institut für Atemwegsforchung (insaf), Villa Berg, Biebricher Allee 34, 65187 Wiesbaden, Germany
[b] PAREXEL International GmbH, Kilinkum Westend, Haus 17, D-14050 Berlin, Germany
[c] Almirall, R&D Centre, Laureà Miró, 408–410, 08980 Sant Feliu de Llobregat, Barcelona, Spain

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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

* Corresponding author. insaf Respiratory Research, Biebricher Allee 34, 65187 Wiesbaden, Germany. Tel.: +49 611 9854410; fax: +49 611 9854348.
E-mail addresses: j.beier@insaf-wi.de, jutta-beier@gmx.de (J. Beier).

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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.

Assessments and endpoints

Spirometry was performed before study drug administration (baseline) and at 5, 15 and 30 min, and at 1, 2, 3, 4, 6, 8, 12, 14, 23, 24 and 36 h post-dose. For spirometry, FEV_1, forced vital capacity (FVC), peak expiratory flow (PEF), and forced mid-expiratory flow (FEF_{25-75}) were determined. Body plethysmography was performed at baseline and at 1, 2, 4, 6, 12, 24 and 36 h post-dose to determine airway resistance (Raw) and specific airway conductance (sGaw).

The primary efficacy endpoint was change from baseline in trough FEV_1 after one day of treatment, expressed as the mean of the 23- and 24-h post-administration values. Secondary endpoints included the change from baseline in FEV_1, FVC, PEF, and FEF_{25-75}, Raw and sGaw.

Safety and tolerability assessments included reporting of adverse events, 12-lead electrocardiogram (ECG), physical examination, laboratory tests relating to safety evaluation, and recording of vital signs (pulse rate and blood pressure). Pharmacodynamic laboratory evaluations were conducted for serum potassium and glucose levels.

Statistical analyses

The analysis of the efficacy variables was performed on the per protocol (PP) population (those patients satisfying the main inclusion/exclusion criteria liable to affect the efficacy assessments, completed all treatment periods and did not present serious violations of the protocol) using a descriptive approach. The primary efficacy variable (change from baseline in trough FEV_1) and secondary efficacy variables were also analysed using Analysis of Covariance (ANCOVA) models for crossover designs. Missing data were not imputed and an observed cases (OC) approach was used. Safety and tolerability assessments, number of withdrawals and concomitant medication use were analysed descriptively for the safety population (all patients who received at least one dose of study drug).

Data were analysed using the SAS software (version 8.2).

Results

Patients

A total of 25 male patients with mild-to-moderate persistent asthma were enrolled and randomised to one of the 5 treatment sequences in this first-in-patient study. Table 1 provides a summary of the baseline characteristics of the study population. One patient was not included in the PP population due to the inhalation of rescue medication during treatment period 1 (considered a major protocol violation).

Table 1 Baseline characteristics of the study population (safety population).

Characteristic	$N = 25$
Age, mean (SD) years	44.2 (10.3)
BMI, mean (SD) kg/m^2	27.1 (2.5)
Smoking history, *n* (%)	
Non-smokers	20 (80)
Ex-smokers (8—20 cigarettes/day)	5 (20)
Duration of asthma (years)	21.7 (11.8)
Asthma category, *n* (%)	
60% to <80% predicted FEV_1	17 (70)
≥80% predicted FEV_1	8 (30)
FEV_1, mean (SD)	
Pre-salbutamol (L)	2.90 (0.45)
Pre-salbutamol % of predicted value	73.89 (6.75)
Change from pre-salbutamol (L)[a]	0.71 (0.31)
Percent of change from pre-salbutamol[a]	24.68 (10.85)

BMI, body mass index; FEV_1, forced expiratory volume in 1 s; SD, standard deviation.
[a] Reversibility defined as ≥12% increase in pre-salbutamol FEV_1 and a minimum absolute increase of 200 mL.

Efficacy

Primary endpoint

Single inhaled doses of abediterol (5 μg, 10 μg and 25 μg) induced statistically significant increases in trough FEV_1 compared with placebo and salmeterol (50 μg BID) (Fig. 1). At the first post-dose measurement (5 min post-dose) all abediterol doses (5 μg, 10 μg and 25 μg) statistically significantly improved lung function compared with placebo ($p < 0.0001$) and salmeterol ($p < 0.05$), and showed increases versus their respective baseline values that indicated a rapid onset of action (Fig. 2). At all doses tested, abediterol provided sustained bronchodilation for the entire 36-h duration of the study period. Increases in FEV_1 were observed at all timepoints and were statistically significantly greater than placebo ($p < 0.0001$) and salmeterol 50 μg BID ($p < 0.05$) (Fig. 3).

Secondary endpoints

The secondary lung function endpoints, change from baseline in FVC, PEF, and FEF_{25-75}, were also statistically significantly improved with all abediterol doses compared with placebo and salmeterol. All abediterol doses

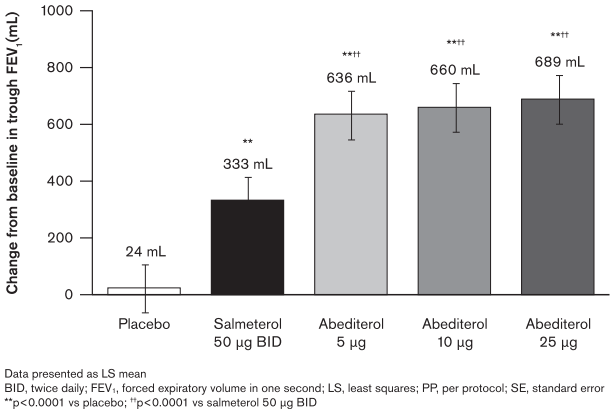
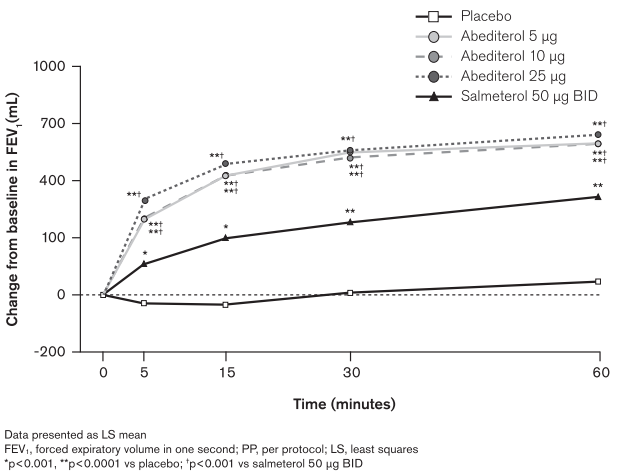


Figure 1 Change (SE) from baseline in trough FEV_1 after one day of treatment (PP population).



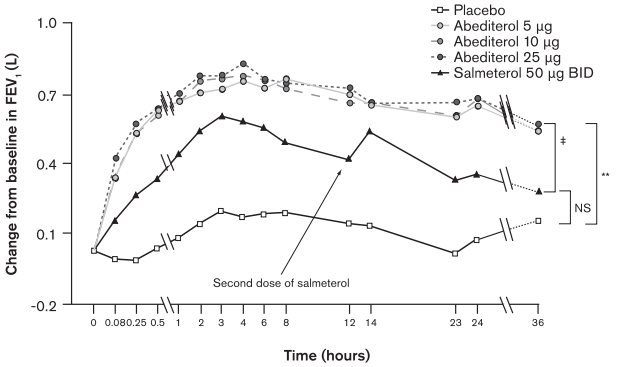
Data presented as LS mean
FEV_1, forced expiratory volume in one second; PP, per protocol; LS, least squares
*p<0.001, **p<0.0001 vs placebo; †p<0.001 vs salmeterol 50 µg BID

Figure 2 Change from baseline in FEV_1 0—60 min post-dose (PP population).

decreased mean Raw values from baseline starting at the first post-dose measurement (1 h post-dose) and at all remaining timepoints post-dose to 36 h (Fig. 4(A)). Compared with baseline, mean sGaw values increased with all abediterol doses starting at the first post-dose measurement (1 h post-dose) and at all remaining timepoints post-dose to 36 h (Fig. 4(B)). There were no dose—response relationships for abediterol from 5 µg to 25 µg on spirometry or body plethysmography parameters.

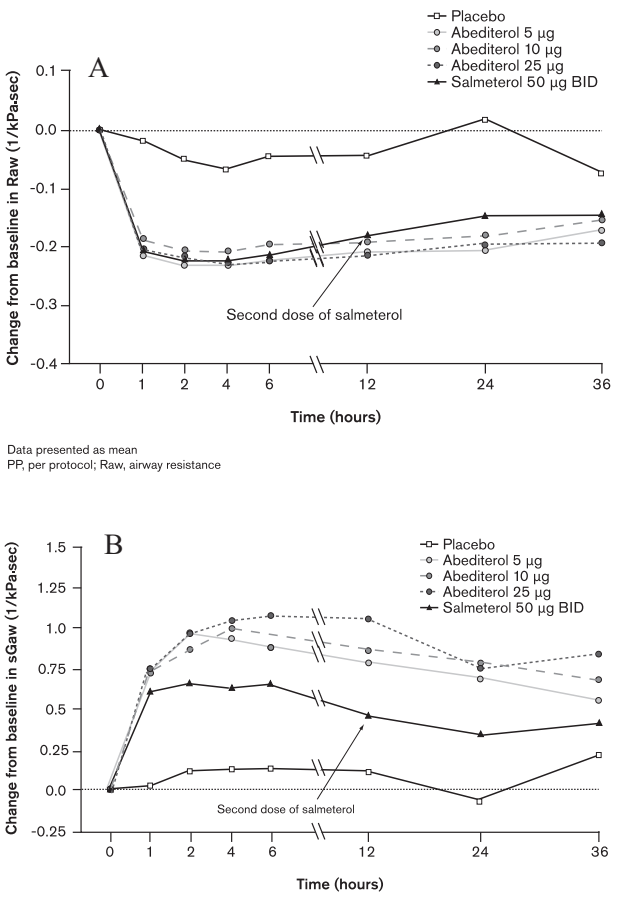
Safety and tolerability

Overall, 21 (84%) of the 25 patients who participated in the study reported 66 TEAEs. Of these, 8 were reported in the abediterol 5 µg group (20% of patients), 12 in the 10 µg group (36% of patients), 40 in the 25 µg group (68% of patients), 2 in the salmeterol group (8% of patients), and 4 in the placebo group (16% of patients). The most frequently reported drug-related TEAEs were tremor (17 episodes in 10 patients), restlessness (8 episodes in 6 patients) and nervousness (4 episodes in 4 patients), which were exclusively reported at the two highest doses of abediterol (10 µg and 25 µg) (Table 2). Only one drug-related TEAE



Data presented as mean
FEV_1, forced expiratory volume in one second; NS, not significant; PP, per protocol
**p<0.0001 (Abediterol [all doses] vs placebo at all time points);
†p<0.05 (Abediterol [all doses] vs salmeterol at all time points)

Figure 3 Change from baseline in FEV_1 over 36 h post-dose (PP population).



Data presented as mean
PP, per protocol; Raw, airway resistance

Data presented as mean
PP, per protocol; sGaw, specific airway conductance

Figure 4 Change from baseline in Raw (Panel A) and sGaw (Panel B) over 36 h post-dose (PP population).

(headache) was reported in the abediterol 5 µg group: single cases of headache were also reported in the 10 µg and 25 µg groups. All TEAEs were resolved by the end of the study.

Most TEAEs were mild or moderate in intensity. Four severe TEAEs were reported (one case each of vomiting, nausea, spinal osteoarthritis and headache); all of which were resolved by the end of the trial. The case of severe spinal osteoarthritis was classed as a serious TEAE and occurred in a patient receiving abediterol 10 µg; this event was not considered by the investigator to be related to study treatment. A dose-dependent increase in the occurrence of TEAEs was observed within the abediterol groups. No patients were withdrawn from the study due to TEAEs, and no deaths occurred.

Abediterol had no clinically relevant effects (as judged by the investigators) on physical examination, laboratory data, vital signs, or ECG outcomes. A non-clinically relevant increase in pulse and heart rate was observed at the two higher doses (10 µg and 25 µg). At 24 h post-dose the heart rate had returned to that observed at baseline for the 10 µg dose and remained elevated by around 7 beats per minute for the 25 µg dose. No clinically relevant increases in QTc Fridericia were determined for any abediterol dose. A slight prolongation for QTc Bazett was noted for the 10 µg and 25 µg doses. After the inhalation of all abediterol doses a

Table 2 TEAEs occurring in ≥1 patient in any treatment group considered to be related to study treatment (safety population).

	Number (%) of patients reporting treatment-related TEAEs				
	Placebo ($N = 25$)	Salmeterol 50 μg BID ($N = 25$)	Abediterol		
			5 μg ($N = 25$)	10 μg ($N = 25$)	25 μg ($N = 25$)
Any treatment-related TEAE	0 (0)	0 (0)	1 (4)	6 (24)	13 (52)
Tremor	0 (0)	0 (0)	0 (0)	2 (8)	10 (40)
Restlessness	0 (0)	0 (0)	0 (0)	1 (4)	6 (24)
Nervousness	0 (0)	0 (0)	0 (0)	2 (8)	2 (8)
Nausea	0 (0)	0 (0)	0 (0)	0 (0)	2 (8)
Tachycardia	0 (0)	0 (0)	0 (0)	1 (4)	1 (4)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)
Muscular weakness	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)
Dizziness	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)
Headache	0 (0)	0 (0)	1 (4)	1 (4)	1 (4)
Agitation	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)

BID, twice daily; TEAE, treatment-emergent adverse event.

trend towards a slight decrease versus baseline was recorded for serum potassium and a slight increase compared with baseline for serum blood glucose was observed. The effect on serum potassium was still present at the 36-h timepoint with the change from baseline ranging from −0.16 mmol/L for the 10 μg dose to −0.24 mmol/L for the 25 μg dose. The effect on glucose was not observed at either 24 or 36 h post-dose. The change from baseline at 12 h post-dose ranged from 10.8 mg/dL for the 10 μg dose to 15.1 mg/dL for the 25 μg dose. A slight decrease in serum potassium and a slight increase in serum glucose were also noted for salmeterol.

Discussion

The results reported here show that single inhaled doses of abediterol (5 μg, 10 μg and 25 μg) induce a marked bronchodilatory effect (lung function tests and body plethysmography) that is sustained over the complete observation period of 36 h post-dose. Abediterol demonstrated a rapid onset of action with all doses, exhibiting a statistically significantly greater improvement in lung function beginning at the first measurement timepoint (5 min post-dose) compared with both placebo and salmeterol for all abediterol doses. These latter results are consistent with preclinical results reported by Aparici and coworkers (2012) [4] that indicated a rapid and potent bronchodilatory effect for this agent in isolated human bronchi and a long duration of action. Taken together, the long duration of bronchodilatory action observed in preclinical evaluations [4] and in the clinical studies, either in this Phase II trial or in the Phase I study in healthy adults [5] support a once-daily dosing strategy for abediterol.

In this study, no dose—response relationship was identified in terms of lung function across the three doses of abediterol evaluated, suggesting that maximal efficacy had been achieved already with the lowest dose of 5 μg. The safety and tolerability profile of abediterol in the current study showed a dose—response relationship, was consistent with that expected after adrenergic stimulation and was observed at the two highest doses tested (10 μg and 25 μg); the profile for the abediterol 5 μg dose was favourable with a single case of a TEAE considered to be related to study drug (headache).

This was a first-in-patient study and at the time of the design of the trial the likely therapeutic dose range had not been confirmed, therefore a wide effective dose range was tested. Subsequent studies have shown that the optimal dose range to achieve effective bronchodilation with a good safety and tolerability profile is at the lower end of that evaluated in the current study [6]. In the Phase II study reported by Singh and coworkers (2013) [6], 62 male and female patients with persistent asthma received single doses of abediterol (0.313 μg, 0.625 μg, 1.25 μg and 2.5 μg), salbutamol or placebo in a 6-way cross-over trial. Consistent with the results reported here, patients who received abediterol experienced rapid, marked and sustained bronchodilation, with statistically significant benefits compared with placebo [6]; the safety and tolerability profile of abediterol in this Phase II study was favourable, with most TEAEs reported as mild to moderate in intensity, the most frequent being headache and nasopharyngitis. Together, these data support the favourable safety and tolerability of abediterol over a wide dose range from 0.313 μg to 25 μg.

In conclusion, abediterol showed a potent, rapid and long-acting bronchodilatory effect at all doses tested in patients with persistent mild-to-moderate asthma, as well as a good safety and tolerability profile. The promising results of this proof-of-concept evaluation have prompted further evaluations of abediterol for the treatment of asthma and COPD, both alone and in combination with ICS.

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