

First-in-Human Study of the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Abediterol (LAS100977), a Novel Long-Acting β_2 -Agonist

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Abstract

Here we report the results of a first-in-human study to evaluate the safety, tolerability pharmacokinetics, and pharmacodynamics of abediterol, a new β_2 -adrenergic agonist. Forty-eight healthy males aged 18–45 years received abediterol doses of 5, 10, 25, or 50 μ g, or placebo. Safety and tolerability assessments included adverse event reporting, pulse and blood pressure monitoring, 12-lead electrocardiograms, laboratory tests, and physical examination. Pharmacodynamic assessments included whole body plethysmography to determine the bronchodilatory effect by means of airway conductance and resistance. Blood and urine samples were obtained for pharmacokinetic analyses. Abediterol showed an overall good safety and tolerability profile in the dose range tested, consistent with the expected characteristics of a β_2 -adrenergic agonist. A dose-dependent increase of systemic treatment-emergent adverse events was observed, the most frequent being palpitations, tremor, nausea, and asthenia; most were mild in intensity and resolved without the need for intervention. Improvements in airway conductance (increase) and resistance (decrease) were greater for all doses of abediterol tested compared with placebo at all time-points up to 36 hours. This first-in-human study suggests a potent, rapid, and sustained bronchodilatory effect of abediterol in healthy male subjects. Lower doses are currently under investigation in patients with asthma and in patients with COPD.

Keywords

abediterol, asthma, COPD, long-acting β_2 -agonist, healthy adults

Asthma and chronic obstructive pulmonary disease (COPD) are both chronic, inflammatory respiratory diseases and are associated with a considerable morbidity burden and an increased risk for death. Asthma can affect individuals of any age and is thought to affect around 300 million people worldwide.¹ COPD is largely seen in older patients (>40 years of age) and is the fourth leading cause of death around the world.^{2,3}

Current guidelines advocate 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^{1,4} and the use of LABAs for the treatment of COPD either as monotherapies or in combination with a long-acting muscarinic agonist or ICS.² Currently available LABAs include twice-daily salmeterol and formoterol, and once-daily indacaterol, olodaterol, and vilanterol (in combination with fluticasone).

Abediterol (LAS100977) is a novel, once-daily, potent and selective LABA, currently in clinical development for the treatment of asthma and COPD in combination with ICS therapy. This agent has a low oral bioavailability ($\leq 8\%$) and high lung retention after intratracheal administration in preclinical species. In vitro studies

using human liver microsomes have shown that abediterol is extensively metabolized by mean of CYP3A4 and UGT1A1, leading to the formation of different oxidative metabolites and an O-glucuronide of the unchanged abediterol. The O-glucuronide is the main circulating metabolite in rats (Almirall, data on file). The preclinical properties of abediterol suggest it displays high potency and selectivity at the β_2 -receptors, with rapid onset and long duration of action.⁵ In cells overexpressing human β_2 -receptors and in isolated guinea pig trachea, abediterol showed sub-nanomolar affinity for the human β_2 -adrenoceptor. Further evaluations utilizing isolated human bronchi showed a potent relaxant activity (EC_{50} of $1.9 \text{ nM} \pm 0.4$), comparable to that of formoterol, with a duration of action similar to that of indacaterol.⁵

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This paper reports data from the first trial of abediterol in humans, which investigated the safety, tolerability, pharmacokinetics, and pharmacodynamics of single, escalating doses of abediterol (5, 10, 25, and 50 μg) in healthy male subjects.

Methods

This was a randomized, parallel, single-blind, placebo-controlled, single dose-escalation study conducted at a single center in Germany with the approval of the relevant Independent Ethics Committee (Dr. G. Hook [chair], Dr. T. Aleker, Dr. D. Luft, Dr. G. Maio, Dr. G. Mikus, Dr. B. Muller-Abicht, Dr. B. Rauch, Dr. E. Riedel, Dr. H. Weber, Dr. P. Knupfer). 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/EC and 2005/29/EC.

Study Subjects

Healthy adult males (aged between 18 and 45 years with a body mass index of 18.5–30 kg/m^2) were eligible to take part in the study. Systolic blood pressure (BP) was required to be between 100 and 140 mmHg, diastolic BP was required to be between 50 and 90 mmHg and heart rate was required to be between 45 and 90 beats per minute. Subjects were also required to be non-smokers or to smoke <5 cigarettes/day. Subjects were excluded if they had any clinically important abnormal physical findings or clinically relevant abnormalities on laboratory screening, abnormalities on screening electrocardiogram (ECG), a history of serious adverse reactions or hypersensitivity to any drug or of a contraindication to drugs pharmacologically related to the study drug. Subjects with a history of serious adverse reactions or hypersensitivity to any drug or contraindication to drugs pharmacologically related to the investigational product were excluded. In vitro studies showed that abediterol has a low potential to inhibit the metabolic clearance of concomitant drugs metabolized via the cytochrome P450 enzymes (Almirall, data on file). However, as a precaution, intake of any medication that could not be eliminated from the body (five elimination half-lives) before the administration of study drug was not permitted. Additional exclusion criteria were the presence of severe allergies or any type of chronic seasonal allergy, a history or evidence of substance abuse or mental retardation, having a common cold or viral infection at the time of the study or in the 4 weeks prior to starting the study, excessive coffee, tea or chocolate consumption (>6 cups per day on average) or a positive test for hepatitis B virus, hepatitis C virus, or

HIV. All subjects provided written informed consent to participate in the trial prior to any study procedure.

Subjects were not permitted to take any investigational medicinal agent during the 30 days prior to the first dose of study drug or during the course of the trial.

Study Drug

Subjects received abediterol or a placebo equivalent by oral inhalation. Study drug (or placebo) was delivered via inhalation of dry powder contained in hard capsules and administered using the Cyclohaler[®] (Almirall, S.A, Barcelona, Spain). Investigators were required to visually check that the capsule was empty after each administration. If residual powder was evident, the subject was required to inhale again from the device until the capsule was empty. The study was conducted with 6 groups of 8 subjects each (6 subjects randomized to receive study drug and 2 subjects randomized to receive placebo). Four dose levels were evaluated (5, 10, 25, and 50 μg) in an escalating and stepwise manner with progression to the next dose only when the previous dose level was confirmed as safe and well tolerated by a safety review committee. The dosing days of the different groups were separated by one week. Study drug was given in the morning of each test day and the duration of each observation period was 36 hours. Within 5 to 9 days of administration of the study drug a follow-up visit was performed.

The abediterol dose range for the current study was selected based on 4-week toxicity studies in dogs (nasal inhalation) and according to guidance issued by the US Food and Drug Administration.⁶ Based on these guidelines, the maximum recommended starting dose was 32.4 μg . Due to the high potency profile observed in vitro and in vivo studies, the starting dose chosen for the current study was 5 μg . The protocol provided the option to evaluate doses of 100 and 200 μg . However, after evaluation of the safety and tolerability data of the 50 μg group it was decided not to escalate the dose of study drug further and instead test again abediterol doses of 10 and 25 μg .

Assessments and Endpoints

Safety and tolerability were assessed by adverse event (AE) recording, 12-lead ECG, vital signs (pulse rate and blood pressure), laboratory tests (hematology, blood chemistry, coagulation, urinalysis), and physical examination throughout each 36-hour period following drug administration.

For each patient, 7 mL of blood was drawn for pharmacokinetic evaluation by venous puncture or indwelling venous catheter at pre-dose and 5, 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 18, 24, and 36 hours after study drug administration. The blood sampling time-frame was adapted and extended to the 36 hour period that

participants remained in the unit to collect the maximum pharmacokinetic information and to avoid overestimation of AUCs due to high extrapolated values from the past quantifiable concentration to infinity. Within 15 minutes of collection, blood samples were centrifuged at 2000 g at a temperature of 4 °C for 10 minutes. A volume of 2 mL of the supernatant was frozen and stored at –20 °C until analysis. Urine samples were collected at the following intervals: 0–4, 4–8, 8–12, 12–24, and 24–36 hours. The volume of diuresis was measured and aliquots of 10 mL of urine were frozen and stored at –20 °C until analysis. Abediterol plasma and urine concentrations were determined by two validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods using a multiple reaction monitoring and off-line solid-phase extraction. The lower limits of quantification were 2.5 and 100 pg/mL for plasma and urine, respectively.

The following pharmacokinetic parameters were evaluated: area under the concentration–time curve from time 0 to the last quantifiable time-point (AUC_{0-t}), area under the concentration–time curve from zero to infinity (AUC), maximum measured plasma concentration (C_{max}), time to maximal concentration (t_{max}), the elimination rate constant (λ_z) and half-life ($t_{1/2}$), total clearance from plasma (CL/f), apparent volume of distribution during the terminal phase (V_z/f), mean residence time (MRT), amount of unchanged drug excreted in the urine (A_e), and renal clearance (CL_R). The pharmacokinetic parameters were evaluated using a non-compartmental approach by least squares linear regression analysis of the terminal phase of the semilogarithmic concentration–time curve. The pharmacokinetic parameters were calculated according to standard methods using Kinetica software, version 4.2 (Thermo Scientific, Thermo Fisher Scientific, Inc., USA).

Pharmacodynamics were assessed by whole body plethysmography (sitting position) to determine specific airway conductance (sGaw) and airway resistance (Raw). For each endpoint, change and relative change from pre-dose were evaluated at 1, 2, 4, 6, 12, 24, and 36 hours after study drug administration. These data were used to derive normalized area under the curve at 24 hours (AUC_{0-24}) post-dose of sGaw and Raw. The normalized AUC between 12 and 24 hours (AUC_{12-24}) and the change from pre-dose in the normalized AUC over 24 hours of sGaw and Raw were also determined.

Statistical Analyses

Safety and tolerability data (AEs, vital signs, laboratory parameters, and ECG) and number of withdrawals are presented using descriptive statistics. For vital signs and ECG, changes from pre-dose, and for laboratory parameters changes from Day –1, were also analyzed.

Full descriptive statistics are given for all pharmacokinetic parameters.

All pharmacodynamic variables are presented using descriptive statistics. The evolution of sGaw and Raw for each treatment group was displayed in graphs showing the mean and 95% confidence interval (CI) at each time point of assessment (pre-dose and 1, 2, 4, 6, 12, 24, and 36 hours on Day 1). Normalized AUCs were calculated by means of the trapezoidal method, dividing by the corresponding time intervals. The analysis of all the pharmacodynamic variables and the pharmacokinetic parameters were performed on the per protocol (PP) population. All safety outcomes were analyzed using the safety population.

Results

Study Subjects

A total of 48 healthy male subjects took part in the study. Table 1 provides a summary of the baseline characteristics of the study population. All subjects completed the study as planned.

Safety and Tolerability

A total of 16 treatment-emergent AEs (TEAEs) were reported by 12 of the 48 subjects. Two TEAEs occurred in 2/12 subjects in the 10 µg dose group, 5 TEAEs in 4/12 subjects in the 25 µg group, 7 TEAEs in 4/6 subjects in the 50 µg group, and 2 TEAEs in 2/12 subjects in the placebo group. No TEAEs were reported by subjects who received the 5 µg dose of abediterol. Of the 14 TEAEs reported following abediterol administration, 13 were considered to be related to study treatment and included palpitations (7 subjects), tremor (4 subjects), nausea (1 subject), and asthenia (1 subject) (Supplementary Table 1). The remaining TEAE, palpitations reported by a subject who received 10 µg of abediterol, was not considered to be related to study treatment. Two further TEAEs, headache and increased triglycerides, were reported by subjects who received placebo. All TEAEs were of mild intensity except for one case of moderate palpitations reported by a subject in the 50 µg dose group. A dose-dependent

Table 1. Baseline Characteristics of the Study Population (Safety Population)

Characteristic	N = 48
Age, mean (SD) years	34 (7.6)
BMI, mean (SD) kg/m ²	25.5 (2.3)
Smoking history, n (%)	
Non-smokers	29 (60.4)
Current smokers, <5 cigarettes/day	19 (39.6)
Systolic BP, mean (SD) mmHg	129.7 (9.8)
Diastolic BP, mean (SD) mmHg	75.4 (7.9)
Pulse rate, mean (SD) beats/min	64.1 (11.0)
Heart rate, mean (SD) beats/min	63 (10.1)

BMI, body mass index; BP, blood pressure; SD, standard deviation.

increase in TEAEs was observed, with no TEAEs reported at the 5 µg dose. All TEAEs resolved without requiring any intervention and without sequelae. There were no deaths, serious AEs or withdrawals due to AEs observed during the study.

No clinically relevant changes in BP, laboratory data (including serum potassium and blood glucose) or physical examination were observed. No clinically relevant effects were noted on heart rate in subjects who received either 5 or 10 µg abediterol. A noticeable increase in heart rate compared with pre-dose was observed among subjects who received either the 25 or 50 µg doses that had not returned to pre-dose values at the 36 hour evaluation. Within the first 4 hours after dosing, during which subjects remained in a supine position, maximum heart rate mean values were reached at 3 hours for the 25 µg dose (mean heart rate of 75.5 bpm, mean change from pre-dose of 9.8 bpm) and at 4 hours for the 50 µg dose (mean heart rate of 81.3 bpm, mean change from pre-dose of 28.3 bpm). Abediterol doses of 5 and 10 µg showed similar mean values to placebo. Apart from an increase in heart rate observed with the two highest doses, in line with the measured increase in pulse rate, serial ECG recordings revealed normal findings throughout the study.

Pharmacokinetics

Table 2 summarizes the mean pharmacokinetic parameters for the four abediterol dose levels evaluated.

The mean plasma concentration profiles for abediterol determined in this study are shown in Figure 1.

With a lower limit of quantification of 2.5 pg/mL, abediterol was only measurable in plasma up to 1 hour in a

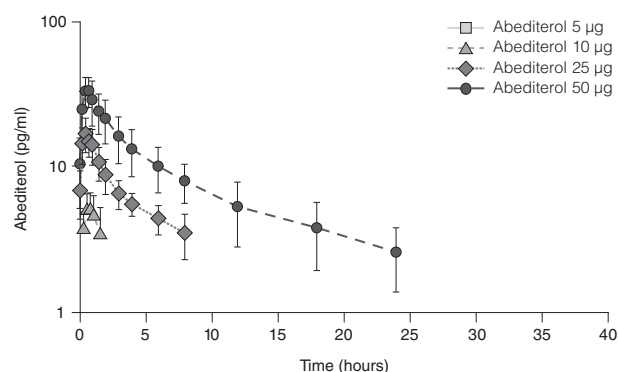


Figure 1. Mean plasma levels of abediterol in healthy male subjects after administration of 5, 10, 25 and 50 µg (logarithmic scale).

limited number of kinetic time-points after a dose of 5 µg, and up to 3 hours after a dose of 10 µg, being not possible at these doses the estimation of the elimination rate constant and the associated pharmacokinetic parameters. After single doses of 5 and 10 µg, peak plasma concentrations occurred between 0.5 and 1 hour reaching mean C_{max} values of 3.0 and 5.6 pg/mL with mean AUC_{0-t} values of 1.8 and 8.2 pg h/mL for 5 and 10 µg, respectively.

For the 25 and 50 µg dose groups the profiles were better defined, t_{max} occurred between 0.25 and 1 hour after inhalation with mean values of C_{max} of 17.2 and 34.6 pg/mL, respectively. Upon attaining C_{max} , plasma concentrations declined in a biexponential manner, with mean terminal $t_{1/2}$ values of 7.9 and 10.0 hours for the 25 and 50 µg doses, respectively. Abediterol showed high and aberrant physiological values for the CL/f and Vz/f suggesting a very low bioavailability. Mean residence

Table 2. Mean (SD) Pharmacokinetics of Single Dose Abediterol by Inhalation in Healthy Subjects (PP Population)

Parameter, units	Abediterol			
	5 µg (N = 6)	10 µg (N = 12)	25 µg (N = 12)	50 µg (N = 6)
C_{max} , pg/mL	3.0 (1.8)	5.6 (1.7)	17.2 (4.6)	34.6 (9.1)
t_{max} , h	0.7 (0.2)	0.6 (0.2)	0.5 (0.1)	0.7 (0.2)
$t_{1/2}$, h	—	—	7.9 (2.5)	10.0 (0.6)
λ_z , 1/h	—	—	0.0952 (0.028)	0.0695 (0.004)
AUC_{0-t} , pg h/mL	1.8 (1.0)	8.2 (4.0)	67.2 (22.6)	199 (78.1)
AUC, pg h/mL	—	—	105 ^a (31.6)	285 (4)
MRT, h	—	—	10.1 ^a (3.04)	12.2 (0.8)
CL/f , L/h	—	—	261 (92.7)	177 (20.6)
Vz/f , L	—	—	2771 ^a (605)	2562 (354)
Ae, ng	70.7 (82.4)	164 (129)	985 (664)	2413 (829)
CL_R , L/h	—	—	10.7 ^a (5.6)	10.4 (2.45)

^a% of AUC extrapolated (C_{last}/λ_z) > 20%.

Ae, amount of unchanged drug excreted in the urine; AUC, area under the concentration–time curve from 0 to infinity; AUC_{0-t} , area under the concentration–time curve from zero to the last quantifiable time-point; C_{last} , last recorded plasma concentration; CL/f , total clearance from plasma; CL_R , renal clearance; C_{max} , maximum plasma concentration; MRT, mean residence time; PP, per protocol; t_{max} , time to reach maximum concentration; $t_{1/2}$, elimination half-life; λ_z , terminal elimination rate constant; Vz/f , apparent volume of distribution during the terminal phase.

time, CL/f, Vz/f, or $t_{1/2}$ (for those doses where terminal elimination phase rate were accurately estimated) showed no apparent trends across doses, suggesting linear pharmacokinetic behavior.

A dose-proportional increase in C_{max} and a supra-dose-proportional increase in AUC_{0-t} were determined (Table 3 and Supplementary Table 2). Nevertheless, it should be noted that the very low plasma levels obtained at the 5 and 10 μ g doses and the below the limit of quantification concentrations at the 12 and 18 hour post-dose time-points after the dose of 25 μ g in comparison with the 50 μ g dose (measurable concentrations in general up to 24 hour) may have impacted the AUC estimation and therefore the dose-proportionality analysis.

Complete evaluation of urinary excretion for the 5 and 10 μ g doses was not possible due to the low urinary concentrations that were below the lower limit of quantification (100 pg/mL) in many of the urine samples corresponding to the relevant urine collection intervals from 0 to 24 hours. After inhalation of the 25 and 50 μ g doses, Ae mean values were 985 and 2413 ng, respectively, corresponding to 3.9% and 4.8% of the inhaled doses. A large proportion of the dose excreted in the urine was recovered within the first 12 hours post-dose. Figure 2 illustrates the mean cumulative excretion of abediterol following administration of 25 and 50 μ g doses. Renal clearance of abediterol was slightly higher than the glomerular filtration rate (7.5 L/h), with no trend for an increase or a decrease across doses.

Pharmacodynamics (Bronchodilation)

All abediterol doses increased sGaw mean values from pre-dose at all time-points over 36 hours; no increase was noted for placebo (Figure 3A). At 24 hours post-dose, all abediterol doses increased sGaw mean values by 0.208 to 0.247 1/kPa-sec compared with pre-dose (Table 2). sGaw normalized AUC_{0-24} was also increased from pre-dose with all doses of abediterol compared with placebo (Table 3). There was no clinically meaningful dose-

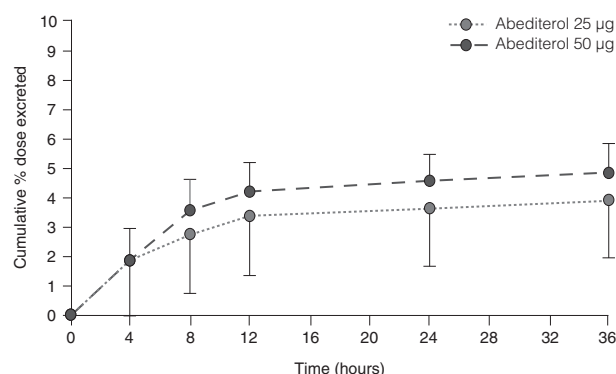


Figure 2. Mean cumulative urinary excretion profile (in % dose) of abediterol in healthy male subjects after administration of 25 and 50 μ g.

response relationship for abediterol on airway conductance.

All abediterol doses decreased Raw mean values from pre-dose at all timepoints over 36 hours (Figure 3B). No such decrease from pre-dose to 36 hours in Raw mean values was noted following placebo. At 24 hours post-dose, all abediterol doses decreased Raw mean values by -0.018 to -0.067 kPa sec/L versus pre-dose (Table 3). There was no decrease in Raw at 24 hours post-dose in subjects who received placebo. Raw mean values remained lower with all abediterol doses compared with placebo at all timepoints over 36 hours post-dose. All abediterol doses decreased Raw normalized AUC_{0-24} from the pre-dose value as opposed to placebo (Table 3). There was also no dose-response relationship for abediterol on airway resistance.

Discussion and Conclusions

The results of this Phase I, first-in-human study reveal that in healthy male subjects abediterol (5, 10, 25, and 50 μ g) is generally safe and well tolerated, increases airway conductance and decreases airway resistance for up to

Table 3. Mean (SD) Normalized AUC_{0-24} and Change from pre-dose at 24 hours for sGaw and Raw (PP population)

Parameter	Placebo (N = 12)	Abediterol			
		5 µg (N = 6)	10 µg (N = 12)	25 µg (N = 12)	50 µg (N = 6)
sGaw					
Normalized AUC _{0–24}	0.960 (0.260)	1.293 (0.296)	1.121 (0.200)	1.146 (0.179)	1.230 (0.206)
Change from pre-dose in normalized AUC _{0–24}	−0.014 (0.096)	0.175 (0.123)	0.348 (0.168)	0.247 (0.133)	0.243 (0.106)
Change from pre-dose at 24 hours	−0.056 (0.189)	0.247 (0.207)	0.233 (0.201)	0.208 (0.185)	0.212 (0.152)
Raw					
Normalized AUC _{0–24}	0.291 (0.079)	0.197 (0.033)	0.245 (0.063)	0.240 (0.061)	0.198 (0.064)
Change from pre-dose in normalized AUC _{0–24}	0.010 (0.027)	−0.026 (0.033)	−0.098 (0.078)	−0.044 (0.050)	−0.042 (0.030)
Change from pre-dose at 24 hours	0.035 (0.082)	−0.037 (0.039)	−0.067 (0.057)	−0.021 (0.104)	−0.018 (0.047)

AUC_{0-24} , area under the curve for 24 hours; PP, per protocol; Raw, airway resistance; SD, standard deviation; sGaw, specific airway conductance.

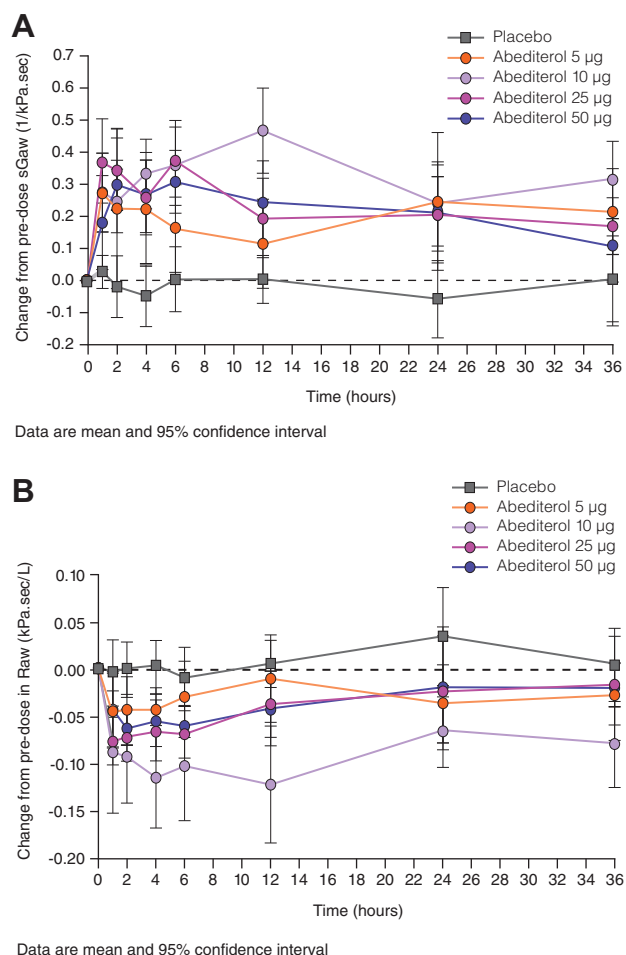


Figure 3. sGaw (Panel A) and Raw (Panel B) change from pre-dose over 36 hours (per-protocol population). PP, per protocol; Raw, airway resistance; sGaw, specific airway conductance.

36 hours after single doses. The results presented are consistent with the preclinical evaluation of this agent that indicated a rapid, potent, and sustained bronchodilatory effect in isolated human bronchi.⁵

The safety and tolerability profile across the dose range studied was consistent with the expected characteristics of β_2 -agonists and no additional or unexpected TEAEs were observed. The increase in heart rate and some specific TEAEs (tremor, palpitation) that were almost exclusively reported after administration of the higher doses (25 and 50 μ g) reflect the pharmacodynamic action of abediterol. Preclinical studies have shown that the potential for adverse cardiac side-effects is more significant with salmeterol than with abediterol.⁵ Our results support this observation in humans, with only a single case of moderate palpitations recorded in a subject who received abediterol 50 μ g.

No dose-response relationship was observed in any of the body plethysmographic parameters. This was not

unexpected given that this was a small clinical trial and was not powered to demonstrate a dose-response relationship. Another explanation may be that the dose range investigated in this trial was already beyond the ascending part of the dose-response curve, an assumption supported by the results of subsequent clinical trials as described further down. In any case, a clear bronchodilatory effect was observed for all dose levels investigated in this study. Together, these observations suggested that maximum bronchodilation may be achieved at lower doses, and have prompted evaluation of lower doses of abediterol in subsequent Phase II clinical trials.^{7,8} The Phase II study reported by Beier et al⁷ was conducted in 25 male patients with mild-to-moderate persistent asthma. At the time the study was initiated, data suggesting the potential for effective dosing <5 μ g were not available and patients received abediterol 5, 10, or 25 μ g, salmeterol or placebo with lung function monitored up to 36 hours post-dose. Consistent with the results presented here in healthy adults, all doses of abediterol were associated with statistically significant improvements in lung function compared with both placebo ($P < 0.0001$) and salmeterol ($P < 0.05$) from 5 minutes post-dose that were sustained to the 36 hour time-point. TEAEs were largely limited to abediterol 10 and 25 μ g and this, combined with a lack of obvious dose-effect relationship on lung function, prompted the evaluation of lower abediterol doses in a second Phase II study.⁸ In this subsequent study, abediterol 0.313, 0.625, 1.25, and 2.5 μ g doses were evaluated and compared with salbutamol and placebo in male and female patients with persistent asthma. Consistent with the results reported here and in the Phase IIa study,⁷ patients who received abediterol at these lower doses experienced rapid and sustained bronchodilation (change from baseline in peak forced expiratory volume in 1 second), with statistically significant benefits compared with placebo and a magnitude of effect comparable with salbutamol for all but the lowest abediterol dose. The tolerability profile at these lower doses was encouraging with most TEAEs reported as mild to moderate intensity, the most common being headache and nasopharyngitis.

To determine the effect of abediterol on airway conductance and resistance – parameters of direct relevance to patients requiring improved respiratory function – whole body plethysmography was performed. This technique is indicated by the AARC Clinical Practice Guidelines for the determination of the response to bronchodilators.⁹ The improvements in airway conductance and resistance observed in the current study with abediterol appear to be sustained to 36 hours post-dose. Previous studies with salmeterol demonstrated that whilst airway conduction was increased with doses from 25 to 200 μ g at 12 hours post-dose, values declined for all doses evaluated and remained statistically significantly different

from placebo only for the highest salmeterol dose (200 µg) at 24 hours post-dose.¹⁰

The results presented here show that over a broad dose range, abediterol produces potent, bronchodilatory activity in healthy male subjects that appears to be sustained for at least 24 hours post-dose, consistent with once-daily dosing in a clinical setting. The results of this study also suggest that body plethysmography in healthy subjects can be used as a suitable pharmacodynamic model to assess the potency and duration of action of a novel, inhaled LABA at an early stage of clinical development. Studies are in progress to examine the efficacy, safety, tolerability and pharmacokinetic profile of abediterol, and the impact it will have, in combination with ICS therapy, on the treatment of patients with asthma or with COPD.

Acknowledgment

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Declaration of Conflicting Interests

WT has no conflict to declare. EM, EJ, BS, GDM, and SR are employees of Almirall.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.