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Indacaterol, a novel inhaled β_2-agonist, provides sustained 24-hour bronchodilation in asthma

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ABSTRACT
This study examined the bronchodilator and safety profiles of single-dose indacaterol in intermittent or persistent asthma.

In this double-blind crossover study, 42 patients were randomised to receive single doses of indacaterol (50, 100, 200, 400 μg) or placebo, via HFA pMDI. The primary efficacy comparisons were the % changes in FEV_1 between indacaterol and placebo 30 minutes and 21 hours post-dose.

All doses resulted in prolonged bronchodilation, with indacaterol 200 and 400 μg meeting pre-specified efficacy criteria. The mean percentage increases in FEV_1 from placebo with indacaterol 200 and 400 μg were, respectively, 7.6% and 14.9% at 30 minutes, and 7.5% and 10.4% at 21 hours post-dose. At these doses, relative to placebo, changes in mean FEV_1 were statistically significant ($p<0.05$) from 5 minutes to 25 hours, inclusive. At 5 minutes, the geometric least squares mean values for FEV_1 were 3.08 and 3.22 L for the 200 and 400 μg doses, respectively, compared with 2.99 L for placebo (both $p<0.05$). At 24 hours after dosing, the baseline-adjusted geometric least square mean FEV_1 was 3.13, 3.11, 3.24 and 3.30L for indacaterol 50, 100, 200 and 400μg, respectively, and 2.98L for placebo. All treatments were well tolerated.

Once-daily indacaterol at doses of 200 and 400 μg provided sustained 24-hour bronchodilation, with a rapid onset, and a good tolerability and safety profile.

Word count: 219 (Limit 200 words)
KEYWORDS: Bronchodilators, FEV_1, indacaterol, long-acting β_2-agonist, once-daily, QAB149, asthma
Short title: Efficacy and safety of single-dose indacaterol (41 characters - limit 45 characters)

INTRODUCTION

Inhaled β_2-adrenoceptor agonists are the most effective bronchodilators for the management of asthma [1]. The Global Initiative for Asthma (GINA) guidelines recognise the role of long-acting β_2-agonists for the optimal treatment of moderate-to-severe persistent asthma [1]. Currently available inhaled long-acting β_2-agonists have durations of action of approximately 12 hours at recommended doses, necessitating twice-daily dosing to provide optimal clinical efficacy [2–5]. The availability of a once-daily β_2-agonist could be expected to improve the treatment of asthma, by providing patients with greater convenience and sustained bronchodilation.

Indacaterol is a β_2-agonist bronchodilator in development for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Pharmacologically, indacaterol is a nearly full β_2-agonist with a high intrinsic efficacy; unlike partial agonists, it does not exhibit antagonistic behaviour in the presence of isoprenaline [6]. Multiple-dose, dose-ranging studies in patients with asthma have shown that indacaterol provides effective bronchodilation with a fast onset of action (within 5 minutes) and which is sustained for at least 24 hours on once-daily dosing [7,8]. Pharmacokinetic data taken during a multiple-dose study of indacaterol 400 or 800 μg once daily for 14 days [9] demonstrated rapid absorption and a mean elimination half life of >30 hours. Likewise, in a single-dose study [10], doses between 600 and 2000 μg were rapidly absorbed with maximum serum concentrations reached within 15 minutes. All doses were well tolerated with a good safety profile, and were not associated with consistent or clinically relevant effects on systemic β-agonist mediated events [7–10].

The aim of the current study was to examine the bronchodilator profile of a range of indacaterol doses in patients with intermittent or persistent asthma.

METHODS

Design

This was a multicentre, randomised, double-blind, placebo-controlled, crossover, dose-ranging study. Patients were randomised to one of five crossover treatment sequences (Latin square design) to inhale a single dose of indacaterol 50, 100, 200 or 400 μg or placebo from a hydrofluoroalkane (HFA) pressurised metered-dose inhaler (pMDI) with a 5–14 day washout between treatment periods. At all treatment visits, patients were under continuous medical supervision from the first predose evaluation until 26 hours after administration of the study medication. Study medication was administered between 17.00 and 19.00 hours, and patients were allowed to sleep for 7 hours between approximately midnight and 07.00 hours.

The study received Institutional Review Board approval, and all patients gave written informed consent prior to the start of the study. The study was conducted according to Good Clinical Practice guidelines and in accordance with the Declaration of Helsinki (1964 and subsequent revisions).

Inclusion and exclusion criteria

Inclusion criteria were: male and females aged 18–65 years; a diagnosis of intermittent or persistent asthma [11]; use of daily treatment with an inhaled β_2-agonist, with or without an inhaled corticosteroid (up to 1,600 μg of beclometasone dipropionate, or equivalent); a stable regimen for at least 1 month prior to screening; a forced expiratory volume in one second (FEV_1) at screening between 60% and 85% of the predicted normal value [12] in the absence of short-acting β_2-agonist use for at least 6 hours and long-acting β_2-agonists for at least 48 hours prior; ≥15% FEV_1 reversibility over their baseline value within 30 minutes after inhalation of 400 μg (4 inhalations) of salbutamol in the afternoon or evening of the screening visit.

Exclusion criteria were: the presence of relevant pulmonary disease; use of tobacco products within 6 months before screening, or a smoking history of >10 pack-years; hospitalisation or emergency room treatment for acute asthma in the 3 months prior to screening or between screening and the start of the treatment period; a respiratory tract infection within 1 month prior to screening; abnormal blood glucose levels; QTc interval above 430 ms (males) or 450 ms (females) at screening, or a history of prolonged QTc interval.

Study treatment

Patients received a single dose of indacaterol 50, 100, 200 or 400 μg or placebo on each of five separate visits. The range of doses was chosen on the basis of results from an earlier study [10]. Study drug was administered by one inhalation from each of two HFA pMDIs (delivering indacaterol 50 or 200 μg or placebo).

Inhaled salbutamol only was permitted as rescue medication and was not to be taken within 6 hours prior to the start of a treatment period; if rescue salbutamol was needed during this period, the visit was rescheduled. Patients taking inhaled corticosteroids (up to 1,600 μg of beclometasone dipropionate or equivalent) continued to do so throughout the study. Inhaled long-acting β_2-agonists were allowed between treatment periods at recommended daily doses,

providing the dose remained fixed throughout the study, but had to be discontinued 48 hours prior to screening or study drug administration.

Treatments not permitted included fixed combinations of β_2-agonists and inhaled corticosteroids, parenteral or oral corticosteroids, theophylline or other xanthines, leukotriene antagonists, and oral or inhaled anticholinergics.

Assessments
Spirometry was conducted according to ATS standards [13] at all visits: predose and 5, 10, 20, 30 and 60 minutes post-dose, hourly from 2 to 6 hours post-dose, every 2 hours from 13 to 19 hours post-dose and hourly from 20 to 26 hours post-dose. The primary efficacy comparisons were the % changes in FEV_1 between indacaterol and placebo at 30 minutes and at 21 hours post-dose.

Secondary efficacy comparisons with placebo (both % change and absolute change) included the standardized areas under the curve (AUC) for FEV_1 0–6 hours, 13–24 hours and 0–24 hours post-dose. A summary table for FEV_1 at all timepoints is also provided together with ANCOVAs assessing treatment ratios in FEV_1 at each post dose timepoint.

Safety was assessed by monitoring and recording all adverse events, serious adverse events, haematology, blood chemistry, urinalysis, vital signs, electrocardiograms, spirometry and physical examination.

Statistical analyses
All efficacy variables were analysed for the intent-to-treat (ITT) population, which included all randomised patients. All safety variables were analysed for the safety population, which included all randomised patients who received at least one dose of study medication.

The primary comparisons were made using an analysis of covariance (ANCOVA) model for $\log(FEV_1)$, with patient as a random effect, period and treatment as fixed effects and $\log(\text{baseline } FEV_1)$ as covariate. If patients took rescue medication prior to the 30-minute post-dose evaluation, this value was excluded from the analysis. If a patient took rescue medication or withdrew between 13 and 21 hours post-dose, the 21-hour value was derived using last observation carried forward (LOCF). However, the 21-hour measurement was used in the analysis if it was lower than the last pre-rescue measurement. If a patient withdrew from the study prior to the 13-hour post-dose evaluation, the 21-hour value was not derived. For either timepoint, data missing for any other reason were imputed using linear interpolation.

ANCOVAs, similar to that used for the primary comparisons, were used for each of the AUC comparisons, with no adjustment for multiplicity.

Sample size calculation
An improvement of 12% in FEV_1 compared with placebo was defined as clinically relevant [13]. Assuming a within-patient variance of 0.011 for $\log [FEV_1]$, to detect an increase of 12% in FEV_1 a sample size of 35 was required. This sample size would provide an overall one-sided error rate of 2.1% and an overall power of 95.5%. It was expected that approximately 43 patients would be required to be recruited in order for 35 to complete.

Establishing optimal dose

The optimal dose was identified using three prespecified criteria. First, at both 30 minutes and 21 hours post-dose, an effective dose was one that was superior to placebo for FEV_1 at the 2.5% one-sided significance level and the upper limit of the 95% confidence interval (CI) for the treatment/placebo ratio was more than 1.12 (which corresponds to a clinically relevant increase of 12% improvement over placebo). Second, efficacy was to be determined from an estimation of the treatment difference between each pair of active doses. Third, the safety of each dose would be considered.

RESULTS

Patients

This study was carried out at three locations. Fifty patients were screened and 42 were randomised, all receiving at least one dose of study medication. Their demographics are shown in table 1. More than half of the patients had at least one concomitant disease at study start, most frequently related to allergic rhinoconjunctivitis, and 24 (57%) were using inhaled corticosteroids.

Forty patients (95%) completed all five treatments in the study. One patient discontinued because of a protocol violation (out of range FEV_1 at predose spirometry), and one, who later reported a previous history of a minor abnormality in a liver function test, because of mildly elevated bilirubin levels (suspected Gilbert's syndrome).

Efficacy

Indacaterol 50, 200 and 400 μg were superior to placebo for FEV_1 at both 30 minutes and 21 hours post-dose; indacaterol 100 μg was superior to placebo at 30 minutes, but not at 21 hours post-dose (fig. 1). Indacaterol 400 μg was the most effective dose, although the difference from the other indacaterol doses was not always statistically superior. The upper boundary of the 95% CI for the ratio with placebo exceeded 1.12 (corresponding to an increase of 12% over placebo) for indacaterol 200 and 400 μg at both timepoints (fig. 1). Therefore both the 200 and 400 μg doses met the first set of prespecified criteria for clinical efficacy.

FEV_1 at each post-dose timepoint is shown both as a summary table (table 2) and with ANCOVAs assessing treatment ratios (table 3). All indacaterol doses demonstrated higher mean FEV_1 values over the 26-hour assessment period compared with placebo (fig. 2, table 3). At the (first) 5-minute time point, significant improvements relative to placebo ($p<0.05$) were obtained for indacaterol 200 μg and 400 μg (Table 3), and sustained at each subsequent time point up to and including 25 hours (200 μg) and 26 hours (400 μg). Indacaterol 400 μg was statistically superior ($p<0.05$) to the other indacaterol doses at most timepoints (fig. 2). The highest mean differences in FEV_1 from placebo were reached at 2 to 3 hours post-dose.

Analysis of standardized AUC for FEV_1 at 0–6, 13–24 and 0–24 hours (table 4) demonstrated that all doses of indacaterol were superior to placebo ($p<0.05$), with the exception of the 100 μg dose at 13–24 hours. FEV_1 AUC for indacaterol 400 μg was statistically superior to all other doses ($p<0.05$) at 0–6 hours and 0–24 hours, and was superior to indacaterol 100 μg from 13–24 hours ($p<0.05$).

Safety and tolerability

All doses of indacaterol were well tolerated, with no serious adverse events experienced in any treatment sequence. The overall number of adverse events appeared to be dose-related (table 5). The most common adverse events were headache and cough, all episodes of which were mild-to-moderate apart from one severe headache with indacaterol 400 μg. There were no asthma-related adverse events.

Haematological and biochemical measurements fell within the normal ranges, and with one exception there were no clinically significant differences between treatments. One patient who had abnormally high values of creatinine kinase at the screening visit also had marked increases 6 hours post-dose whilst receiving indacaterol 100 μg, although the values returned to normal 13–26 hours post-dose. The incidence of newly occurring biochemical

abnormalities was low, with no clinically meaningful differences across treatments. There were minimal changes in mean potassium and glucose levels 6 hours post-dose, with no statistically significant or clinically meaningful differences between treatments (table 6).

There were no clinically significant differences in vital signs (including heart rate and blood pressure) or electrocardiogram abnormalities between treatments. For all treatments, the QTc interval decreased from predose to 15 minutes post-dose, with only minor changes at 6 and 24 hours post-dose. There were no clinically meaningful or statistically significant differences in mean QTc interval between indacaterol and placebo. No QTc interval increases of >60 ms from predose to post-dose were observed.

DISCUSSION

This study demonstrates that indacaterol provides sustained 24-hour bronchodilation when taken once daily. During this study, indacaterol was administered in the late afternoon (between 17.00 and 19.00), at a time when the upswing of diurnal variation in FEV_1 would have already occurred. Despite this, a rapid and sustained increase in FEV_1 was observed, with the rapid onset of action of indacaterol (within 5 minutes of dosing) comparable to that of the short-acting β_2-agonist salbutamol (approximately 2–3 minutes) [14]. In this study, the first timepoint (30 minutes post-dose) for one of the primary efficacy comparisons (% change in FEV_1 from placebo) was selected on the basis of the characteristics of salmeterol, which has a relatively slow onset of action, achieving a clinically meaningful effect at about 30 minutes post-dose [14]. The 30 minute timepoint was therefore used to assess if indacaterol was at least as fast in onset as salmeterol. The second timepoint for comparison (21 hours post-dose) was selected since this was considered to be the minimum requirement for a single dose of a drug that was to be given once a day.

All doses and placebo displayed a similar overnight decrease in FEV_1, as can be seen from the 6 and 13 hour measurements in fig. 2, consistent with circadian variation of lung function. Patients were allowed to sleep for approximately 7 hours during the test period (from midnight until 07.00) and this preserved the circadian variation in pulmonary function. Accentuation of the circadian variation of lung function is a recognised feature of asthma and an expression of bronchial hyperreactivity. It is influenced by diurnal changes in adrenaline, adenosine monophosphate, histamine and other inflammatory mediators, cortisol, vagal tone, body temperature, and lower airway secretions [15,16]. Other occurrences during sleep, such as the supine posture, sleep-associated reductions in lung volume, intrapulmonary pooling of blood and sleep-associated upper airway narrowing may also have influenced the early morning measurement [17]. Similar data have been shown in patients with mild asthma, in whom single doses of formoterol and salbutamol given in the morning significantly improved FEV_1 for at least 12 hours and moved the pattern of circadian variation in lung function to a higher FEV_1 level through the subsequent night, without actually influencing either the phase or amplitude of the variation over the 24-hour observation period [18].

The lung function data in this study demonstrate that there is a dose-dependent upward shift of the circadian pattern over the entire 26-hour period that FEV_1 was measured. Despite the preservation of the circadian pattern indacaterol doses provided trough FEV_1 values (*i.e.* 21 to 24 hours post-dose) that were superior to placebo. This confirms the sustained 24-hour bronchodilator efficacy of indacaterol (although only the 200 and 400 μg doses were statistically superior to placebo at all timepoints from 5 minutes to 24 hours post-dose). Since FEV_1 for all doses of indacaterol was greater than placebo at all timepoints, this provides evidence that the duration of action of indacaterol is dose-independent across the range tested, and may possibly be due to an intrinsic property of the molecule at the receptor level.

Besides indacaterol, other once-daily LABAs are being developed [19]. The convenience of once-daily dosing, together with sustained bronchodilation, will allow for better compliance, thus increasing the likelihood of medication adherence and asthma control. Improved clinical outcomes associated with prolonged bronchodilation have previously been shown when comparing twice-daily LABAs with regular short-acting β_2-agonist therapy [20,21]. In COPD, once-daily tiotropium is clearly superior to regular short-acting anticholinergic therapy for all relevant clinical outcomes [22].

Alongside the potential advantages of a once-daily LABA, one also needs to consider that the regular use of LABAs has been linked with the potential development of tolerance to bronchoprotective and bronchodilator effects. The pharmacological profile may favour indacaterol in this respect. In preclinical studies (relative to isoprenaline) indacaterol (73%) has more of a full agonist profile than the partial agonist salmeterol (38%) [23,24] and might therefore be expected to incur fewer problems of cross-tolerance to short-acting β_2-agonist rescue medication. Clinical studies to investigate these interactions as well as the potential for receptor down-regulation in humans have still to be carried out.

The regular use of the LABA salmeterol without concomitant anti-inflammatory treatment has been associated with an increased risk of asthma death [25]. The combination of LABA and ICS is currently considered as the gold standard for patients with moderate-to-severe persistent asthma [1]. Thus, it is anticipated that a once-daily LABA will be recommended to be combined with a once-daily ICS (e.g. ciclesonide or mometasone), either in free or fixed combination. A rapid onset of action of the bronchodilator component (as shown for indacaterol) in such combinations might be beneficial since it would also allow for use in acute situations, a strategy that has been successfully developed for fixed combinations of budesonide/formoterol [26,27]. Experiments using indacaterol in isolated human bronchus have demonstrated an onset of effect very similar to those of formoterol and salbutamol, the classic 'rescue' bronchodilator, in contrast to a more than two-fold slower onset for salmeterol [24]. Finally, another possible future use would be to combine treatment with a once-daily LABA with once-daily tiotropium (or other once-daily anticholinergic) in COPD. With distinct but complementary pharmacological modes of action [28], such a combination would be likely to provide additional therapeutic benefits in this indication [29].

Since the present study was limited to several single-dose exposures separated by at least 5 days, few conclusions can be drawn on the long-term safety of indacaterol. However, these results are consistent with those of a longer study, in which patients received indacaterol at up to 600 μg daily for 28 days [30]. A preliminary report of the systemic effects of indacaterol 1000 μg as a single dose (more than twice the upper dose used in this study) showed that the prolonged bronchodilation was not accompanied by a similar prolongation in the predictable β_2-adrenoceptor-mediated systemic effects. Plasma glucose, potassium, QTc and heart rate showed initial changes but all remained within normal levels. All of these values matched placebo levels sooner for indacaterol than the active comparator, salmeterol, given at a dose of 250 μg [31].

In conclusion, single 200 and 400 μg doses of indacaterol provided effective and sustained 24-hour bronchodilator control with a rapid onset of action (<5 minutes) and a good tolerability and safety profile. The convenience of once-daily dosing could lead to better compliance and may help to treat both daytime and nocturnal symptoms of asthma.

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Conflict of interest statement

K-M.B. received compensation for serving on an advisory board for Novartis, Germany. He has participated as a speaker in scientific meetings or courses organised and financed by various pharmaceutical companies (Boehringer, Novartis, Pfizer, Fujisawa, Merck, Sharpe & Dohme) in 2003, 2004 and 2005. He has received fees for speaking at a conference symposium sponsored by Novartis in 2005. The institution where K-M.B. is currently employed has received compensations for participating in multi-centre trials in 2004, 2005 and 2006 from several companies (AstraZeneca, Boehringer, Novartis, GlaxoSmithKline, Revotar, Biopharmaceuticals, EpiGenesis, Corus Pharma, Almirall Prodesfarma, Merck Sharpe & Dohme, Fujisawa). K-M.B. has been reimbursed for travel expenses by Novartis, Boehringer, Merck Sharp & Dohme and Pfizer for attending several conferences.
E.D. received grants in 2002; 2003 and 2004 for serving on an advisory board for GlaxoSmithKline; E.D. also received compensation during the period 2003-2005 from Altana Pharma, GlaxoSmithKline, SGSBiopharma and Novartis as research grants for participating in clinical trials. E.D. also received a grant from AstraZeneca to allow him to attend the ATS 2004 and from Altana Pharma to attend the ERS 2005 Congress.
FK has received compensation for the conduct of clinical trials or educational grants from GSK, Epigenesis, ALTANA, AstraZeneca, Allmiral Prodesfarma, Boehringer Ingelheim, Schering-Plough, Astellas, ONO
R.C. has been employed by Novartis since April 1996.
M.H. has been employed by Novartis since November 2001, and holds shares in the company.
At the time of the study and development of the manuscript A.V.A. was a full-time employee of Novartis and owned stock in the company.

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FIGURE 1. Estimates of % increases for FEV_1 of treatment groups compared with placebo with associated 95% confidence intervals (CI) at 30 minutes and 21 hours post-dose.

● = 400 µg vs placebo; ● = 200 µg vs placebo; ● = 100 µg vs placebo; ○ = 50 µg vs placebo.

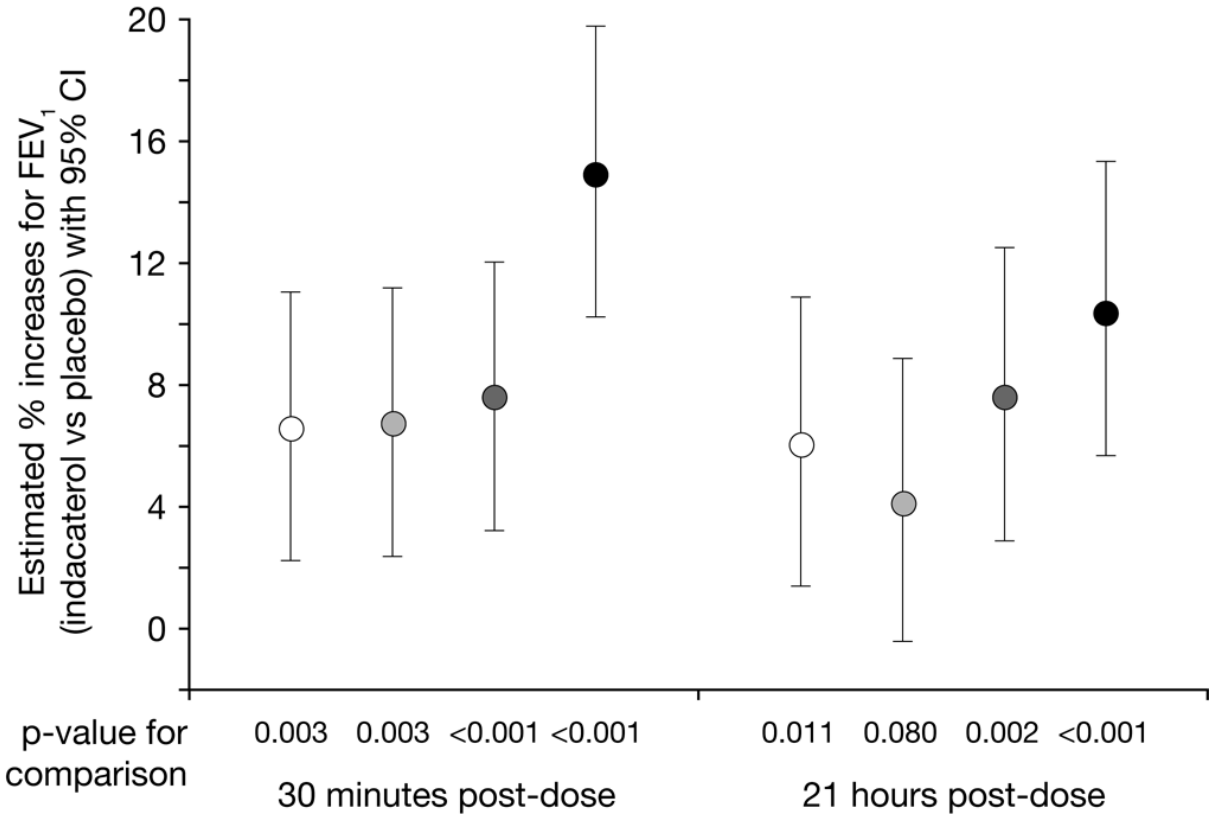

FIGURE 2. 26-hour profile of mean FEV_1. Indacaterol 400 µg was superior to placebo ($p<0.05$) at all post-dose timepoints; 200 µg superior to placebo ($p<0.05$) from 5 minutes to 25 hours post-dose (inclusive); 100 µg superior to placebo ($p<0.05$) from 10 minutes to 6 hours, 15 to 19 hours and 22 to 23 hours post-dose (inclusive); 50 µg superior to placebo ($p<0.05$) from 10 minutes to 6 hours and 15 to 25 hours post-dose (inclusive). □: indacaterol 50 µg (n=41);

■: indacaterol 100 µg (n=41); ■: indacaterol 200 µg (n=41); ■: indacaterol 400 µg (n=41); ▲: placebo (n=40). *: p<0.05 *versus* indacaterol 200 µg; †: p<0.05 *versus* indacaterol 100 µg; ‡: p<0.05 *versus* indacaterol 50 µg.

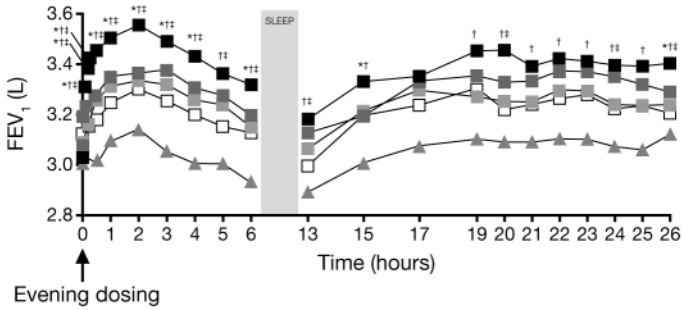

TABLE 1. Baseline demographics and disease characteristics

Variable	Total
Age (years), mean (range)	40.5 (24–64)
Sex, n (%)	
Male	36 (85.7)
Female	6 (14.3)
Race, n (%)	
Caucasian	42 (100.0)
Height (cm), mean (range)	179.3 (164–200)
Duration of asthma (years), mean (range)	21.31 (3.8–53.0)
FEV_1 (L)	
Mean (SD)	3.010 (0.596)
Range	1.78–4.32
FEV_1 (% predicted)[a]	
Mean (SD)	75.62 (7.11)
Range	59.6–85.6
FEV_1 reversibility (%)[b]	
Mean (SD)	25.20 (11.12)
Range	14.6–62.6
FVC (L)	
Mean (SD)	4.485 (1.001)
Range	2.49–6.71
Vital signs at screening	
SBP (mmHg), mean (SD)	124.9 (9.1)
Range	100–145
DBP (mmHg), mean (SD)	80.6 (6.9)
Range	60–95
Heart rate (bpm), mean (SD)	74.0 (9.6)
Range	50–96
ECG findings, n (%)	
Normal	35 (83.3)
Clinically insignificant abnormality	7 (16.7)
Clinically significant abnormality	0
At least one concomitant disease, n (%)	23 (54.8)

bpm: beats per minute; DBP: diastolic blood pressure; ECG: electrocardiogram; FEF: forced expiratory flow; FEV_1: forced expiratory flow in one second; FVC: forced vital capacity; SD: standard deviation; SBP: systolic blood pressure. [a]: Percent of increase of predicted FEV_1 is calculated using the QUANJER formula [22]. [b]: Percent increase in FEV_1 within 30 minutes after inhalation of salbutamol.

TABLE 2. Summary statistics of mean values for forced expiratory volume in one second (FEV_1) at selected timepoints (intent-to-treat population)

			Indacaterol			
Variable	**Timepoint**	**Placebo**	**50 µg**	**100 µg**	**200 µg**	**400 µg**
FEV_1 (L), mean	Predose	3.00	3.03	3.07	3.07	3.03
	5 min	3.04	3.13	3.19	3.18	3.31
	10 min	3.05	3.17	3.23	3.23	3.38
	20 min	3.03	3.15	3.25	3.25	3.42
	30 min	3.01	3.18	3.25	3.27	3.45
	21 hours	3.09	3.24	3.24	3.33	3.39
	22 hours	3.10	3.27	3.29	3.36	3.42
	23 hours	3.10	3.27	3.29	3.36	3.41
	24 hours	3.07	3.21	3.23	3.35	3.39
	25 hours	3.06	3.23	3.23	3.31	3.39
	26 hours	3.12	3.20	3.23	3.29	3.40

Placebo (n=40), indacaterol 50 µg (n=41), 100 µg (n=41), 200 µg (n=41), 400 µg (n=41).

TABLE 3. Comparisons of geometric least squares mean values for forced expiratory volume in one second (FEV_1) at selected timepoints (intent-to-treat population)

Variable	Timepoint	Placebo	Indacaterol			
			50 µg	100 µg	200 µg	400 µg
FEV_1 (L), geometric least squares mean[a]	5 min	2.99	3.07	3.07	3.08*	3.22*†
	10 min	3.00	3.11*	3.12*	3.12*	3.30*†
	20 min	2.98	3.10*	3.14*	3.14*	3.34*†
	30 min	2.93	3.13*	3.13*	3.16*	3.37*†
	21 hours	2.99	3.17*	3.11	3.22*	3.30*‡
	22 hours	3.02	3.20*	3.17*	3.25*	3.32*‡
	23 hours	3.01	3.20*	3.16*	3.25*	3.32*‡
	24 hours	2.98	3.13*	3.11	3.24*	3.30*‡#
	25 hours	2.96	3.16*	3.11	3.20*	3.30*‡
	26 hours	3.04	3.14	3.12	3.17	3.31*†

Placebo (n=40), indacaterol 50 µg (n=41), 100 µg (n=41), 200 µg (n=41), 400 µg (n=41).
*: $p<0.05$ *versus* placebo; †: $p<0.05$ *versus* indacaterol 50, 100 and 200 µg; ‡: $p<0.05$ *versus* indacaterol 100 µg; #$p<0.05$ *versus* indacaterol 50 µg. [a]: Analysed using the ANCOVA model $\log(FEV_1)$= patient + period + treatment + log[baseline (FEV_1)].

TABLE 4: Standardised area under curve (AUC) for forced expiratory volume in one second (FEV_1): adjusted geometric means (intent-to-treat population)

Variable	Time interval, hours post-dose	Placebo	Indacaterol 50 µg	Indacaterol 100 µg	Indacaterol 200 µg	Indacaterol 400 µg
FEV_1 (L)	0–6	2.9908	3.1469*	3.1409*	3.1967*	3.3602*†
	13–24	2.8018	3.1176*	3.0027	3.1852*	3.2965*‡
	0–24	2.9661	3.1098*	3.0982*	3.1605*	3.2725*†

Placebo (n=40), indacaterol 50 µg (n=41), 100 µg (n=41), 200 µg (n=41), 400 µg (n=41).
*: $p<0.05$ *versus* placebo; †: $p<0.05$ *versus* indacaterol 50, 100 and 200 µg; ‡: $p<0.05$ *versus* indacaterol 100 µg.

Analysed using the ANCOVA model log(stand AUC FEV_1)= patient + period + treatment + log[baseline (FEV_1)].

Table 5 Number (%) of patients with most frequent adverse events (>5% for any group) (safety population)

		Indacaterol			
	Placebo	50 µg	100 µg	200 µg	400 µg
No. of patients studied	40 (100)	41 (100)	41 (100)	41 (100)	41 (100)
No. of patients with an adverse event	6 (15.0)	8 (19.5)	11 (26.8)	14 (34.1)	15 (36.6)
Nervous system disorders					
Headache	1 (2.5)	3 (7.3)	5 (12.2)	5 (12.2)	7 (17.1)
Respiratory, thoracic and mediastinal disorders					
Cough	0	3 (7.3)	5 (12.2)	6 (14.6)	5 (12.2)

Patients may be counted more than once if they had more than one occurrence of an adverse event within different treatment periods.

TABLE 6. Adjusted mean serum potassium, blood glucose and heart rate at selected timepoints (safety population)

Time post-dose		Indacaterol			
	Placebo	50 µg	100 µg	200 µg	400 µg
Serum potassium, mmol/L					
15 minutes	4.31	4.27	4.29	4.33	4.33
6 hours	4.08	4.07	4.12	4.12	4.09
13 hours	4.29	4.33	4.29	4.28	4.27
24 hours	4.30	4.34	4.22	4.30	4.36
Blood glucose, mmol/L					
15 minutes	4.61	4.47	4.56	4.63	4.51
6 hours	5.03	5.21	5.10	5.22	5.07
13 hours	4.90	4.88	4.85	5.01	4.89
24 hours	5.04	4.93	4.94	5.02	5.15
Heart rate, bpm					
15 minutes	73.2	74.5	75.9	73.2	74.0
1 hour	72.4	73.1	73.2	72.4	73.8
3 hours	74.7	75.3	76.5	74.9	76.9
5 hours	73.0	72.8	75.6	73.7	73.8
13 hours	71.2	69.7	69.9	70.4	70.4
19 hours	73.5	73.2	74.0	72.5	74.5
24 hours	69.9	70.5	71.7	71.2	70.2

Placebo (n=40), indacaterol 50 µg (n=41), 100 µg (n=41), 200 µg (n=41), 400 µg (n=41). bpm: beats per minute