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Safety and tolerability of indacaterol in asthma: A randomized, placebo-controlled 28-day study

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Summary

The safety and tolerability of indacaterol, a novel once-daily β_2 -agonist bronchodilator with a fast onset of action, were assessed in 156 asthma patients in a multicentre, randomized, double-blind, placebo-controlled study. Patients received indacaterol 200, 400 or 600 μg or placebo once daily for 28 days. Adverse events (AEs), laboratory assessments, vital signs, electrocardiograms, spirometry and physical examinations were monitored. Indacaterol pharmacokinetics were assessed.

There was no evidence of dose-related increases in AE incidence or clinically significant hypokalaemia or hyperglycaemia in indacaterol-treated patients. Mean pulse rate changes were minor in any group, with maximum 1-h post-dose changes from baseline of -3.7 , -3.3 and -2.2 bpm for indacaterol 200, 400 and 600 μg , respectively, and -2.9 bpm for placebo. Mean QTc interval was similar between groups; change from baseline >60 ms occurred in only two patients. Mean FEV₁ increased after the first indacaterol dose; baseline-adjusted pre-dose (trough) values remained ≥ 166 mL higher than placebo at all subsequent visits, supporting a 24-h bronchodilator effect. Pre-dose (but not post-dose) serum indacaterol concentrations indicated a slight trend for accumulation.

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Once-daily indacaterol 200–600 µg has a favourable therapeutic index. It is well tolerated, and is not associated with any adverse cardiac or metabolic effects, while providing effective 24-h bronchodilation.

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Introduction

Inhaled β_2 -agonists are the most effective bronchodilators for the prevention and relief of bronchoconstriction associated with asthma, and therefore have an important role in managing asthma symptoms.^{1–3} Long-acting β_2 -agonists, such as salmeterol and formoterol, have 12-h durations of action, and their recommended use is in combination with inhaled corticosteroids (ICS) in patients with moderate or severe persistent asthma.¹

Selective β_2 -agonists were developed to minimize the β_1 -mediated chronotropic effects that were associated with the non-selective agents such as isoprenaline. β_2 -receptors are also present in myocardial tissue, and the occurrence of tachycardia and palpitations has been associated with the use of selective β_2 -agonists, especially at higher doses. Other dose-limiting β_2 -mediated side effects include skeletal muscle tremor, hyperglycaemia and hypokalaemia.⁴ Thus, an important property of a new β_2 -agonist is to provide effective bronchodilation at a dose that is not associated with these side effects and to have a wide safety margin with higher doses.

Indacaterol is a novel once-a-day and fast-acting β_2 -agonist in development for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Preclinical data suggest that, for a given degree of bronchodilator activity, indacaterol has a greater cardiovascular safety margin than formoterol or salmeterol.⁵ In-vivo guinea pig studies with indacaterol have demonstrated a sustained bronchodilator and bronchoprotective effect, and a rapid onset of action (comparable to salbutamol and formoterol).⁵

The aim of the current study was to assess the safety and tolerability of indacaterol 200, 400 and 600 µg compared with placebo, dosed once daily over 28 days in patients with asthma. The 200 µg dose was selected as a potentially therapeutic dose based on the results of a previous Phase I study.⁶ Particular attention was paid to the predictable pharmacological effects of a β_2 -agonist on serum potassium, blood glucose, heart rate, blood pressure, QTc, and occurrence of tremor, headache and nervousness.

Methods

Design

This was a Phase II, multicentre, randomized, double-blind, placebo-controlled, parallel-group study in adolescents and adults with asthma. Patients enrolled in the study entered a 14-day run-in phase. Study treatment was then given for 28 days, with follow-up for a further 7 days to assess asthma stability and adverse events after treatment cessation. Patients attended the study centre on five occasions: at the start of the run-in phase; at the start of the double-blind

treatment phase, after 14 and 28 days of treatment, and at the 7-day follow-up.

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.⁷

Inclusion and exclusion criteria

Male and female patients aged 13–75 years with asthma diagnosed according to GINA 2002 guidelines⁸ were enrolled if they were receiving daily treatment with an inhaled β_2 -agonist with or without inhaled corticosteroids at a dose of up to 1600 µg beclometasone dipropionate (or equivalent), in a regimen that had remained stable for at least the past month, and their forced expiratory volume in 1 s (FEV₁) was at least 60% of the predicted normal value,⁹ with at least 12% reversibility within 30 min after inhalation of 400 µg (2 × 2 inhalations) of salbutamol (either demonstrated at screening or documented within the prior 6 months).

Pregnant or breastfeeding women or women of childbearing potential not using reliable contraception were excluded. Patients with COPD, current or recent smokers or those with a smoking history of >10 pack-years were excluded. Patients were also excluded if they had been hospitalized or received emergency treatment for asthma in the last 3 months, or if they had a respiratory tract infection in the last month, or concomitant pulmonary disease. Other exclusion criteria included abnormal blood test or electrocardiogram (ECG) results, and any clinically significant condition that could compromise patient safety or conduct of the study.

Study treatment

Patients were randomized using a validated automated system in the ratio 1:1:1:1 to receive indacaterol 200, 400 or 600 µg or placebo once daily by inhalation from hydrofluoroalkane (HFA) metered dose inhalers (pMDIs). To ensure blinding, indacaterol and placebo devices were identical in appearance.

Inhaled salbutamol was permitted as rescue medication. Patients who had been using long-acting β_2 -agonists prior to the study were instructed to use salbutamol on a regular basis for the duration of the run-in phase and as needed during the randomized treatment phase. The steroid component of combination (inhaled corticosteroid and β_2 -agonist) therapy was replaced with the equivalent monotherapy inhaled corticosteroid. Those patients on “monotherapy” inhaled corticosteroid continued on the pre-study steroid regimen. Patients could use nasal corticosteroids, antihistamines, cromones, ketotifen and leukotriene antagonists, provided that treatment had been stable for 1 month prior to the study. Desensitization therapy for rhinitis

was permitted, provided that treatment had been stable for the previous 3 months.

Assessments

Safety was assessed, as the primary objective, by recording all adverse events, regular monitoring of haematology, blood chemistry and urinalysis, vital signs, electrocardiograms (ECGs), spirometry, and physical examinations.

On Days 1, 14 and 28, pre-dose and 60 min post-dose (the estimated time of maximum systemic exposure [C_{max}] to indacaterol post inhalation), assessments were made in the following order: ECG, diastolic and systolic blood pressure, and blood samples (non-fasting) for laboratory evaluation. ECG and blood pressure were assessed after the patient had rested in the sitting position for at least 5 min. Electrocardiographic events of rate, rhythm, conduction activation and repolarization were derived from standardized 12-lead ECGs. Both Bazett's and Fridericia's formulae were used to calculate the QTc interval. Blood samples were analysed at a central laboratory (BARC [Bio Analytical Research Corporation], Ghent, Belgium) and ECGs were reviewed by a single cardiologist (at ERT [eResearch Technology], Peterborough, UK) for purposes of standardization.

Spirometry was performed before and 30 min after dosing on Days 1, 14 and 28. At the Days 14 and 28 visits, patients were asked to estimate their mean daily use of salbutamol over the past 14 days.

Pharmacokinetic assessments

Systemic exposure to indacaterol was assessed, with venous blood samples taken pre-dose and 60 min post-dose (at the same time as those for blood chemistry/haematology) on Days 1, 14 and 28 of treatment. The aims of the pharmacokinetic evaluations were to investigate the possible dose relationship and whether serum accumulation of indacaterol would occur.

Blood (3 mL) was drawn into a plain polypropylene tube, and a serum sample was prepared and stored at -20°C before analysis by validated liquid chromatography/tandem mass spectrometry (LC/MS/MS), with a lower limit of quantification for indacaterol of 0.05 ng/mL. Intra-assay accuracy was accepted when calibrations were within $\pm 20\%$ of nominal values and reproducibility of the method was within $\pm 15\%$ for a set of six quality control samples.

Statistical methods

As this study was a hypothesis-generating rather than hypothesis-testing study, no formal sample size calculation was performed. To generate sufficient safety and tolerability data to justify the commencement of large-scale studies with indacaterol, approximately 100 patients were to be exposed to indacaterol for 28 days. Therefore, assuming a 10% dropout rate and taking into account that 25% of patients would be randomized to placebo, 148 patients were to be enrolled. Safety variables were summarized or analysed for the safety population, which consisted of all randomized patients who received at least one dose of study medication. Adverse events were defined

as those that started or worsened after initiation of study medication. Serum potassium, blood glucose, pulse rate, diastolic and systolic blood pressure, QTc interval and FEV₁ were analysed using an analysis of covariance (ANCOVA) model with centre, treatment and baseline value as covariates. All analyses were performed using SAS/STAT software (Version 8 of the SAS System for Unix, SAS Institute Inc., Cary, NC, USA).

For the pharmacokinetic data, separate statistical analyses were conducted for each indacaterol dose as well as for the pre-dose and post-dose measurements. Patients were excluded from the analysis if Day 14 or 28 data were missing because of study discontinuation, or if there was no sample or insufficient sample for analysis. Data were analysed using a mixed linear model in which the day was a fixed effect and the subject was a random effect. This was stratified by dose and time (pre-dose or post-dose); the difference in arithmetic means and corresponding 90% confidence intervals (CIs) were determined for each dose and time point. The concentration–dose relationship was investigated with a linear regression analysis.

Results

Patients

Patients were recruited at 18 centres in four countries (Denmark [five centres], Germany [four], the Netherlands [six] and Russia [three]). Of 191 patients screened, 156 patients were randomized between February and July 2003. All randomized patients received at least one dose of study drug, although five patients did not complete the study (Fig. 1). Demographic and baseline characteristics were well balanced between the treatment groups (Table 1).

Adverse events

Most adverse events were mild, with only one described as severe—a tendon rupture in a patient receiving indacaterol 400 μg . As expected in this population, respiratory-related disorders were the most frequent adverse events, followed by nervous system disorders and infections (Table 2). There was no indication of a dose-related increase in the incidence of adverse events in any body system, although in general patients on indacaterol had slightly higher incidences of respiratory and nervous system disorders than those on placebo. The most frequent adverse event was nasopharyngitis (15% in the indacaterol 200 μg group). Headache was reported in three (7.7%), five (12.8%), zero, and two (5.4%) patients in the placebo and indacaterol 200, 400 and 600 μg groups, respectively. Tremor was reported by two (5.4%) patients in the indacaterol 600 μg group, and there were no reports of nervousness. Cough occurred at a higher frequency in patients receiving indacaterol compared with placebo, experienced by one (2.6%), four (10.3%), seven (17.1%) and three (8.1%) patients in the placebo and indacaterol 200, 400 and 600 μg groups, respectively. The majority of coughing events were considered as being of mild severity.

There were no serious adverse events in any patients receiving indacaterol. One placebo recipient was hospitalized

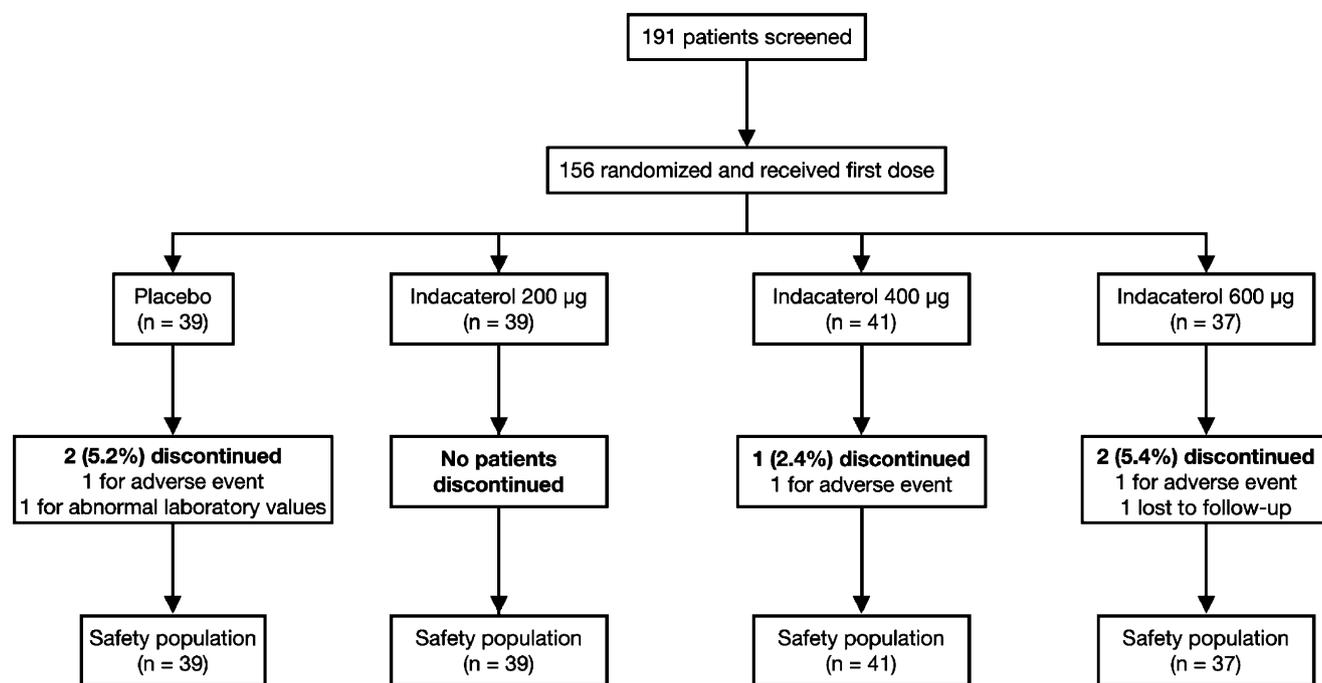


Figure 1 Flow of patients during the study.

because of hypoglycaemia. One patient discontinued because of cough (indacaterol 400 µg) and two because of asthma exacerbations (one placebo and one indacaterol 600 µg); these events were of moderate severity and not considered to be related to the study drug by the investigator.

Laboratory values and biochemistry

There was no evidence of any drug or dose-related effects on the standard haematological tests in any treatment group.

A reduction in serum potassium is considered to be one of the dose-limiting β_2 -mediated side effects. No indacaterol dose was associated with statistically significant reductions in mean serum potassium *versus* placebo at any time point (Fig. 2a). The only statistically significant between-treatment comparison was an increase of 0.21 mmol/L on day 1 post-dose between the indacaterol 200 and 400 µg groups ($p = 0.01$). At the same time point, an increase of 0.15 mmol/L was observed between indacaterol 200 and 600 µg groups ($p = 0.05$, regarded as not clinically significant). No further significant comparisons between treatment groups in potassium levels were noted, suggesting that the isolated statistically significant Day 1 post-dose differences were a random finding. There were no clinically significant changes in mean serum potassium levels and no evidence of drug-related hypokalaemia. Individual serum potassium levels remained above the lower limit of normal (3.5 mmol/L), with the exception of post-dose measurements in the indacaterol 400 µg group on Day 1 (one patient, 3.3 mmol/L), Day 14 (one patient, 3.4 mmol/L) and Day 28 (two patients, both 3.3 mmol/L).

An increase in blood glucose is considered to be one of the dose-limiting β_2 -mediated side effects. There were no

statistically or clinically significant differences in mean blood glucose values between the treatment groups (Fig. 2b), and no evidence of drug- or dose-related hyperglycaemia. Individual blood glucose levels remained below the upper limit of normal (7.77 mmol/L), except for three patients (four episodes) in the placebo group (maximum of 8.82 mmol/L, post-dose on Day 1), one patient (one episode) in the indacaterol 200 µg group (8.99 mmol/L, post-dose on Day 1), three patients (11 episodes) in the indacaterol 400 µg group (maximum of 10.8 mmol/L, post-dose on Day 1), and one patient (four episodes) in the indacaterol 600 µg group (maximum of 10.2 mmol/L, pre-dose on Day 14).

One patient in the placebo group was withdrawn at the request of the study sponsor because of elevated creatinine kinase values that were elevated prior to dosing.

There was no evidence of either a drug- or dose-related effect in any of the other biochemical variables measured.

Vital signs

Mean pulse rate and blood pressure changes were minimal, with no statistically significant differences between treatment groups (although for diastolic blood pressure post-dose on Day 1 the difference between indacaterol 400 and 200 µg was $p = 0.05$, regarded as not clinically significant; Table 3). Overall, 16 patients had isolated pre- or post-dose readings of pulse rates >90 bpm (three, four, four and five, in the placebo and indacaterol 200, 400 and 600 µg groups, respectively). The maximum individual post-baseline pulse rates observed in each treatment group were: placebo, 100 bpm; indacaterol 200 µg, 107 bpm; 400 µg, 102 bpm; 600 µg, 97 bpm. The greatest individual increase from baseline in the indacaterol 600 µg group was 25 bpm (from 71 to 96 bpm), compared with an increase of 31 bpm seen in the placebo group (from 60 to 91 bpm).

Table 1 Baseline demographics and disease characteristics (all randomized patients).

	Placebo	Indacaterol		
		200 µg	400 µg	600 µg
Median age (yr) (range)	45.0 (20–67)	50.0 (22–67)	49.0 (18–73)	52.0 (20–71)
Sex, n (%)				
Male	20 (51.3)	17 (43.6)	20 (48.8)	19 (51.4)
Female	19 (48.7)	22 (56.4)	21 (51.2)	18 (48.6)
Race, n (%)				
Caucasian	38 (97.4)	39 (100)	40 (97.6)	37 (100)
Other	1 (2.6)	0	1 (2.4)	0
Median BMI (kg/m ²) (range)	26.8 (18.1–37.7)	26.8 (20.1–41.1)	25.5 (19.5–37.6)	25.4 (19.1–33.7)
Smoking history, n (%)				
Never smoked	33 (84.6)	29 (74.4)	35 (85.4)	28 (75.7)
Ex-smoker	6 (15.4)	10 (25.6)	6 (14.6)	9 (24.3)
Median asthma duration (yr) (range)	18.0 (3–62)	13.0 (3–41)	15.0 (1–48)	16.0 (1–48)
FEV ₁ pre-salbutamol (L)				
Mean (SD)	2.6 (0.74)	2.6 (0.84)	2.6 (0.79)	2.6 (0.65)
FEV ₁ % predicted (%)				
Mean (SD)	77.0 (11.68)	81.3 (12.85)	79.0 (13.33)	80.1 (12.25)
FEV ₁ reversibility (%)				
Mean (SD)	19.4 (11.50)	15.4 (6.40)	18.3 (9.32)	17.8 (7.80)
Salbutamol use, n (%) ^a				
None	1 (2.6)	1 (2.6)	0	0
< 1 puff/day	11 (28.2)	9 (23.1)	6 (14.6)	4 (10.8)
1–2 puffs/day	7 (17.9)	10 (25.6)	9 (22.0)	15 (40.5)
3–6 puffs/day	16 (41.0)	17 (43.6)	19 (46.3)	13 (35.1)
> 6 puffs/day	4 (10.3)	2 (5.1)	7 (17.1)	5 (13.5)
Prior/concomitant asthma medications				
Long-acting β ₂ -agonist ^b	11 (28.2)	13 (33.3)	13 (31.7)	13 (35.1)
Inhaled corticosteroids ^c	32 (82.1)	34 (87.2)	39 (95.1)	29 (78.4)

Placebo (n = 39); indacaterol 200 µg (n = 39); 400 µg (n = 41); 600 µg (n = 37).

BMI: body mass index; FEV₁: forced expiratory volume in 1 s.

^aAverage daily use estimated by investigator based on patient information during run-in.

^bDiscontinued at the start of the run-in.

^cStarted prior to randomization and continued throughout treatment period.

Table 2 Number (%) of patients with adverse events by treatment group (safety population).

	Placebo	Indacaterol		
		200 µg	400 µg	600 µg
Total no. of patients studied	39	39	41	37
Total no. with adverse events	13 (33.3)	16 (41.0)	17 (41.5)	15 (40.5)
Primary system organ class				
Infections and infestations	4 (10.3)	7 (17.9)	1 (2.4)	1 (2.7)
Respiratory, thoracic and mediastinal disorders	4 (10.3)	7 (17.9)	9 (22.0)	7 (18.9)
Nervous system disorders	3 (7.7)	6 (15.4)	2 (4.9)	4 (10.8)
General disorders and administration site conditions	1 (2.6)	2 (5.1)	3 (7.3)	0
Gastrointestinal disorders	0	1 (2.6)	0	2 (5.4)
Investigations	1 (2.6)	1 (2.6)	0	0
Musculoskeletal and connective tissue disorders	1 (2.6)	1 (2.6)	2 (4.9)	2 (5.4)
Cardiac disorders	0	0	1 (2.4)	1 (2.7)
Immune system disorders	1 (2.6)	0	0	0
Injury, poisoning and procedural complications	0	0	2 (4.9)	1 (2.7)
Metabolism and nutrition disorders	1 (2.6)	0	0	0
Skin and subcutaneous tissue disorders	1 (2.6)	0	0	3 (8.1)

Data are presented as n (%).

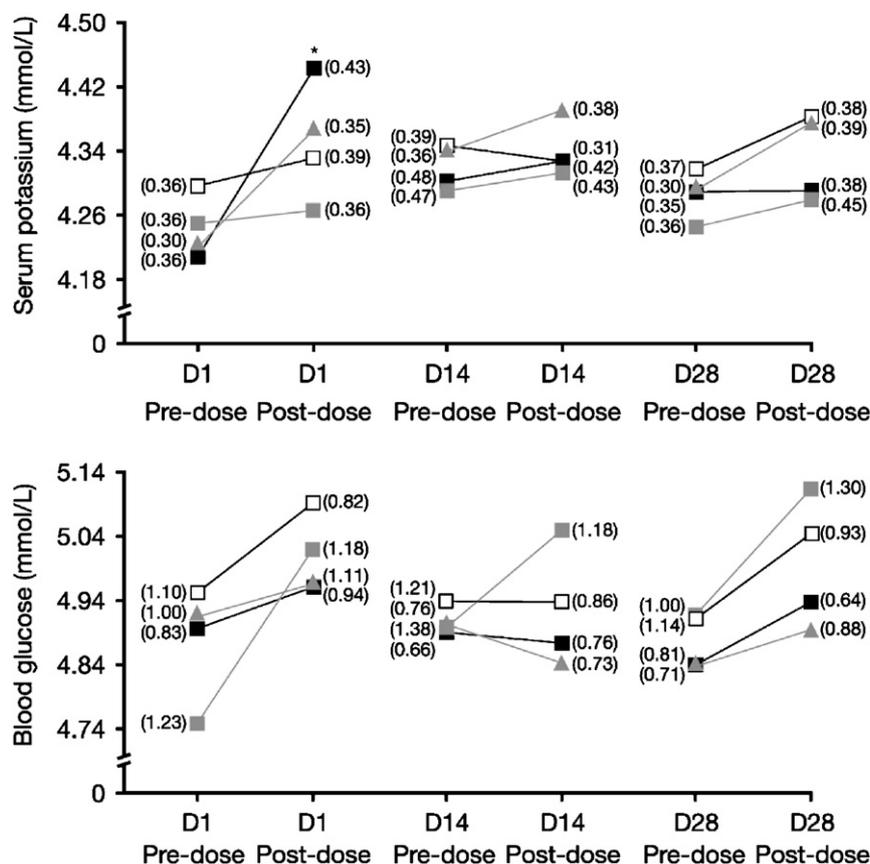


Figure 2 (a) Mean (SD) serum potassium over time. (b) Mean (SD) blood glucose over time. ■: indacaterol 200 µg ($n = 39$); ■: indacaterol 400 µg ($n = 41$); □: indacaterol 600 µg ($n = 37$); ▲: placebo ($n = 39$). * $p = 0.01$ versus indacaterol 400 µg.

Although a significant proportion of patients had pre- and post-dose systolic blood pressure values > 140 mmHg, there were no drug-related trends or major differences between the indacaterol and placebo groups. Similarly, although some patients had elevated pre- and post-dose diastolic values, no trends were apparent, and no low values (< 50 mmHg) were seen.

ECG

There were no differences in mean QTc interval between any of the treatment groups (Fig. 3) and only one patient (indacaterol 400 µg) had a notable value (male; 451 ms; Bazett's formula) during treatment. Notable changes from baseline in QTc interval (> 60 ms) occurred in one patient in the indacaterol 200 µg group (both formulae), and one patient in the 600 µg group (Bazett's formula only) but did not exceed the upper limit of normal (430 ms for males, 450 ms for females; Table 4). Although using Bazett's formula resulted in a higher incidence of QTc interval prolongation between 30 and 60 ms compared with placebo, this was not confirmed with Fridericia's formula, and there was no evidence of a dose-related increase in QTc interval values (Table 4). Twelve patients on indacaterol treatments had QTc interval increases ≥ 30 ms from baseline according to Fridericia's formula, none of which exceeded the upper limit of normal. In eight of these cases, the values were not notable compared with screening values. Of the remaining

patients, three were receiving the lowest dose (200 µg) and one was receiving indacaterol 400 µg. Overall, no clinically relevant effect on QTc interval was observed for indacaterol in the dose range studied.

FEV₁ and salbutamol use

In the placebo group there was a slight but gradual decline in mean FEV₁ over the course of the study (Fig. 4). In contrast, mean trough pre-dose FEV₁ increased after the first dose of indacaterol and remained above baseline at all post-baseline time points, with no evidence of a clinically relevant reduction in bronchodilator efficacy over time. Adjusting for baseline FEV₁ values, there was a difference of at least 166 mL between placebo and any indacaterol group in mean trough pre-dose FEV₁.

Post-dose FEV₁ (measured at 30 min) was statistically superior to placebo ($p < 0.05$) with all indacaterol doses on each assessment day. The difference relative to placebo was in excess of 220 mL for all post-dose FEV₁ measurements apart from on Day 1 for indacaterol 200 µg. Overall, a decrease in FEV₁ of > 200 mL from baseline occurred in approximately half of the placebo group (18 patients; 46%), compared with five (13%), three (7%) and three (8%) patients for indacaterol 200, 400 and 600 µg, respectively. None of these patients treated with indacaterol had cough or other signs of bronchial irritation associated with the FEV₁ decrease.

Table 3 Cardiovascular assessments (safety population).

	Placebo	Indacaterol		
		200 µg	400 µg	600 µg
Mean pulse rate (bpm) (SD)				
Pre-dose, Day 1 (baseline)	69.0 (10.49)	70.5 (9.50)	71.3 (11.26)	69.3 (9.25)
Post-dose, Day 1	66.1 (9.39)	66.8 (9.49)	68.1 (9.33)	67.1 (12.35)
Pre-dose, Day 14	69.5 (9.46)	70.7 (11.36)	70.5 (10.46)	70.7 (10.81)
Post-dose, Day 14	66.8 (8.60)	67.5 (8.59)	68.5 (10.34)	68.9 (11.00)
Pre-dose, Day 28	69.8 (11.24)	70.9 (11.62)	71.5 (9.86)	72.6 (12.33)
Post-dose, Day 28	67.3 (7.80)	67.8 (10.95)	68.0 (11.23)	68.9 (10.65)
Mean systolic blood pressure (mmHg) (SD)				
Pre-dose, Day 1 (baseline)	129.5 (17.80)	127.5 (15.10)	126.3 (12.22)	126.0 (15.54)
Post-dose, Day 1	128.8 (16.33)	128.3 (13.13)	125.9 (11.87)	126.9 (14.94)
Pre-dose, Day 14	128.1 (14.06)	128.8 (13.53)	125.2 (12.79)	126.7 (14.64)
Post-dose, Day 14	129.4 (16.54)	130.1 (14.28)	126.2 (12.80)	126.6 (15.38)
Pre-dose, Day 28	128.0 (17.15)	129.6 (13.20)	126.3 (12.69)	126.2 (11.67)
Post-dose, Day 28	128.4 (17.10)	130.7 (14.60)	125.8 (12.74)	127.7 (14.11)
Mean diastolic blood pressure (mmHg) (SD)				
Pre-dose, Day 1 (baseline)	79.1 (8.85)	79.9 (9.76)	79.7 (7.72)	78.0 (8.32)
Post-dose, Day 1	79.0 (6.76)	80.4 (7.83)	77.8 (8.52)	78.1 (10.52)
Pre-dose, Day 14	78.7 (10.06)	80.9 (8.35)	78.4 (9.44)	79.8 (7.57)
Post-dose, Day 14	79.2 (9.63)	79.7 (8.84)	79.4 (8.55)	77.4 (9.96)
Pre-dose, Day 28	77.2 (11.00)	80.6 (8.11)	80.2 (8.93)	78.8 (7.70)
Post-dose, Day 28	79.1 (10.95)	80.3 (7.92)	79.5 (8.69)	76.7 (8.72)

Placebo ($n = 39$); indacaterol 200 µg ($n = 39$); 400 µg ($n = 41$); 600 µg ($n = 37$).

No statistically significant differences were observed in mean pulse rate, mean systolic or diastolic blood pressure (although for diastolic blood pressure post-dose on Day 1 the difference between indacaterol 400 and 200 µg was $p = 0.05$, regarded as not clinically significant).

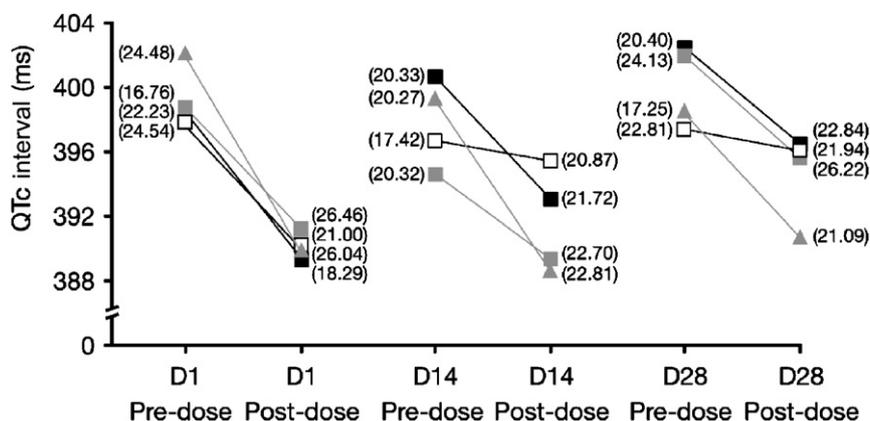


Figure 3 Mean (SD) QTc intervals (Bazett's) over time. ■: indacaterol 200 µg ($n = 39$); ▣: indacaterol 400 µg ($n = 41$); □: indacaterol 600 µg ($n = 37$); ▲: placebo ($n = 39$).

Daily use of salbutamol decreased during the study in all treatment groups (Table 5). There was evidence for a trend of decreased use of salbutamol with increasing dose of indacaterol.

Pharmacokinetic assessments

From the indacaterol 200, 400 and 600 µg groups, 39, 41 and 36 patients, respectively, provided evaluative data. There

was high inter-subject variability in the pre-dose sample results as trough levels approached the limit of quantification of the assay (0.05 ng/mL). Variability within the post-dose results was acceptable. Mean pre-dose and post-dose serum concentrations increased with indacaterol dose on all days (Fig. 5). The differences in pre-dose arithmetic means (and 90% CIs) between Day 28 and Day 14 were 0.002 (−0.007, 0.012), 0.024 (0.002, 0.045) and 0.035 (0.018, 0.052) ng/mL for indacaterol 200, 400 and 600 µg, respectively, indicating a trend for slight accumulation of

Table 4 Notable QTc intervals and changes by treatment (safety population).

	Placebo	Indacaterol		
		200 µg	400 µg	600 µg
<i>Patients with notable values, n (%)</i>				
Bazett's formula				
Male (>450 ms)	0	0	1 (2.4)	0
Female (>470 ms)	0	0	0	0
Change ^a < 30 ms	36 (92.3)	32 (82.1)	34 (82.9)	28 (75.7)
Change ^a 30–60 ms	3 (7.7)	6 (15.4)	7 (17.1)	8 (21.6)
Change ^a > 60 ms	0	1 (2.6)	0	1 (2.7)
Fridericia's formula				
Male (>450 ms)	0	0	0	0
Female (>470 ms)	0	0	0	0
Change ^a < 30 ms	36 (92.3)	34 (87.2)	38 (92.7)	33 (89.2)
Change ^a 30–60 ms	3 (7.7)	4 (10.3)	3 (7.3)	4 (10.8)
Change ^a > 60 ms	0	1 (2.6)	0	0

Placebo ($n = 39$), indacaterol 200 µg ($n = 39$), 400 µg ($n = 41$), 600 µg ($n = 37$).

^aChange from baseline to worst (highest) post-baseline value.

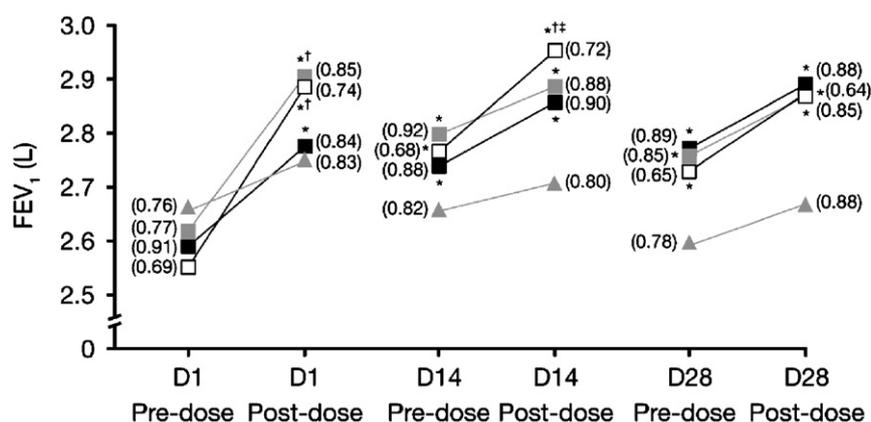


Figure 4 Mean (SD) forced expiratory volume in one second (FEV₁) over time. ■: indacaterol 200 µg ($n = 39$); ◐: indacaterol 400 µg ($n = 41$); □: indacaterol 600 µg ($n = 37$); ▲: placebo ($n = 39$). * $p < 0.05$ versus placebo; † $p < 0.05$ versus indacaterol 200 µg; ‡ $p < 0.05$ versus indacaterol 400 µg.

Table 5 Daily salbutamol use between visits and by treatment (safety population).

Period	Average puffs/day since last visit	Placebo	Indacaterol		
			200 µg	400 µg	600 µg
Screening to Day 1	None	1 (2.6)	1 (2.6)	0	0
	< 3 puffs/day	18 (46.2)	19 (48.7)	15 (36.7)	19 (51.4)
	≥ 3 puffs/day	20 (51.3)	19 (48.7)	26 (63.4)	18 (48.6)
Days 1–14	None	6 (15.4)	10 (25.6)	12 (29.3)	16 (43.2)
	< 3 puffs/day	21 (53.8)	28 (71.8)	23 (56.1)	17 (45.9)
	≥ 3 puffs/day	11 (28.2)	1 (2.6)	6 (14.6)	2 (5.4)
Days 14–28	None	5 (12.8)	10 (25.6)	12 (29.3)	18 (48.6)
	< 3 puffs/day	25 (64.1)	27 (69.2)	24 (58.5)	16 (43.2)
	≥ 3 puffs/day	7 (17.9)	2 (5.1)	4 (9.8)	1 (2.7)

Data are presented as n (%). Placebo ($n = 39$); indacaterol 200 µg ($n = 39$); 400 µg ($n = 41$); 600 µg ($n = 37$).

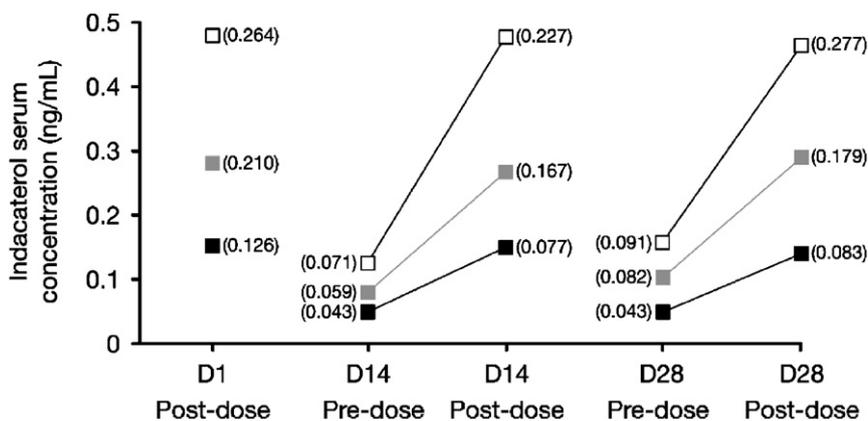


Figure 5 Mean (SD) indacaterol serum concentrations. ■: indacaterol 200 µg ($n = 39$); ■: indacaterol 400 µg ($n = 41$); □: indacaterol 600 µg ($n = 36$).

indacaterol over time. However, accumulation could not be concluded from the analysis of the corresponding post-dose values, where differences between Day 14 and Day 28 were -0.013 ($-0.038, 0.012$), 0.013 ($-0.035, 0.061$) and -0.016 ($-0.061, 0.028$), for indacaterol 200, 400 and 600 µg, respectively.

Although exposure to indacaterol increased with increasing dose, the limited sampling strategy did not allow conclusions regarding dose-proportionality. The linear regression returned adjusted coefficients of determination (adjusted R^2) of 0.26 and 0.29 pre-dose on Days 14 and 28, respectively, and 0.30, 0.39 and 0.33 post-dose on Days 1, 14 and 28, respectively, indicating that the variability in the data was too high to allow for assessment of dose-proportionality.

Discussion

This was a safety study, the objective of which was to examine the effect of indacaterol, at doses up to 600 µg, on key safety variables commonly associated with β_2 -agonist use. The results support a favourable safety profile of indacaterol in patients with asthma. The frequency of adverse events was low and indacaterol was not associated with adverse cardiovascular effects at doses of up to 600 µg once daily for 28 days. These findings confirm and extend the results of a single-dose, dose-ranging study in patients with asthma,¹⁰ and provide clinical confirmation of the favourable pre-clinical findings on the cardiovascular safety profile of indacaterol.⁵ The reduction of asthma symptoms associated with bronchospasm during the use of the long-acting β_2 -agonists formoterol and salmeterol, when given twice daily, is well established.¹ A selective β_2 -agonist that can provide safe and effective 24-h bronchodilation with once-daily dosing extends the treatment options for many patients with asthma, as well as potentially contributing to patient compliance, especially among adolescents and children.^{11,12}

The very low incidence of predictable pharmacological side effects such as tremor, headache, nervousness, nausea and tachycardia, together with negligible effects on QTc interval, blood glucose and serum potassium, over a wide range of doses suggests a favourable therapeutic index for indacaterol. Changes in heart rate, QTc interval and plasma

potassium and glucose levels have been reported in patients and healthy volunteers receiving the long-acting β_2 -agonists salmeterol^{13–15} and formoterol^{16–19} at higher doses than indicated for clinical use. In this study doses of up to 600 µg once daily for 28 days were not associated with an increase in side effects.

It might be considered somewhat unusual that there were no changes in key safety variables for the higher doses of indacaterol in this study, except for occasional changes in serum potassium. This may be because doses used were simply not high enough to have an impact on these safety variables despite all indacaterol doses achieving clinically relevant differences in FEV₁ of >200 ml *versus* placebo at most post-dose time points. In a subsequent study, higher doses of indacaterol (800 µg) demonstrated effects on serum potassium and blood glucose; however, these changes were considered to be not clinically meaningful.²⁰ At a higher single dose of 1000 µg, indacaterol had a good safety profile and was not associated with sustained systemic adverse effects; mean heart rate and QTc interval remained within normal ranges following administration.²¹

Hypoxemia due to respiratory insufficiency is a key problem in asthma, particularly during acute severe exacerbations, and results in adverse cardiovascular effects, including prolongation of the QTc interval.^{22,23} A potential effect on QTc interval is applicable to all β_2 -agonists, particularly in the context of the use of high doses of rescue β_2 -agonist such as salbutamol, as may be used during episodes of sudden worsening, which are likely to have an additive effect on prolongation of the QTc interval.²⁴ The relatively wide therapeutic margin observed for the effect of indacaterol and a dose-related but modest effect at several multiples of the likely therapeutic dose in patients with asthma,²¹ together with the results of the present study, provide reassurance at this stage of the drug's development that the effect of indacaterol would have no greater significance than for any other LABA. However, since patients with congenital ECG abnormalities are routinely excluded from clinical studies such as this, the effect of β_2 -adrenergic agonists on QTc interval deserves further careful examination in view of the finding of an independent association between asthma and an increased risk of cardiac events in subjects with the long QT syndrome,²⁵ suggesting a possible genetic linkage underlying the two diseases.

As this was a safety study, efficacy data were collected as a secondary objective. The FEV₁ results from the current study support the efficacy of indacaterol and are consistent with the previous report of a 24-h duration of action in patients with intermittent or persistent asthma, which also demonstrated a rapid (<5 min) onset of effect.¹⁰ In the current study, pre-dose FEV₁ values on Days 14 and 28 were effectively trough values, which provide further supportive evidence that indacaterol has 24-h bronchodilator efficacy.¹⁰ The reductions in salbutamol use also support the efficacy of indacaterol.

Another important aspect of the safety and tolerability of long-acting β_2 -agonists in asthma is the question of tolerance to the bronchodilator and bronchoprotective effects, and to potential cross-tolerance to the bronchodilating effect of "rescue" β_2 -agonists. Although these are recognized phenomena,^{26,27} tolerance appears to be less of a long-term clinical problem, at least in so far as that worsening symptoms and increasing use of rescue medication are not features of continuing use.^{28,29} Attenuation of systemic β_2 -adrenoceptor mediated effects has also been observed.^{30,31} Pharmacologically, indacaterol behaves as a nearly full agonist at the β_2 -adrenoceptor in vitro,^{5,32} and this profile may lessen the risk of cross-tolerance to short-acting β_2 -agonists. Additionally, a lack of tachyphylaxis to the bronchoprotective effect of indacaterol against 5-HT challenge was observed in a guinea pig model.⁵ In the present study, there was no reduction in bronchodilator efficacy over time with indacaterol: mean FEV₁ increased following the first dose, and the adjusted trough pre-dose values remained at least 166 mL higher than placebo at both subsequent visits. However, since the pre-treatment β_2 -agonist washout period was only 6 h (and therefore insufficient to allow the receptors to recover to an untreated state), no conclusions about tachyphylaxis can be made.

The safety and efficacy results of the current study are supported by those of a study with similar design, albeit in patients with COPD. In this study, indacaterol demonstrated good tolerability and overall safety profile at doses up to 800 μ g.³³

The pharmacokinetic analysis showed that indacaterol exposure increased with increasing dose, but dose-proportionality could not be concluded from this sparse data set. Comparison of trough levels on Days 14 and 28 at the different doses suggested a slight trend for accumulation.

In conclusion, the results of this study suggest that indacaterol has a wide therapeutic index—it is well tolerated, is neither associated with adverse cardiac effects nor clinically significant changes in β_2 -mediated systemic effects, and provides effective 24-h bronchodilation on once-daily dosing. If these findings are substantiated in large-scale, controlled clinical trials, indacaterol may represent a significant improvement in selective β_2 -agonist safety and efficacy.

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