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Original article

Indacaterol provides sustained 24 h bronchodilation on once-daily dosing in asthma: a 7-day dose-ranging study

Background: Indacaterol is a novel, once-daily β_2-agonist in development for the treatment of asthma and chronic obstructive pulmonary disease. Studies were required to determine optimal dose(s) for continuing investigation.
Objective: A dose-ranging study was undertaken to evaluate efficacy and safety of indacaterol.
Methods: A total of 436 patients with persistent asthma receiving inhaled corticosteroids were randomized to 7 days treatment with once-daily indacaterol 50, 100, 200, or 400 μg via multi-dose dry-powder inhaler (MDDPI; Certihaler™), indacaterol 400 μg via single-dose dry-powder inhaler (SDDPI), or placebo. Serial 24-h spirometry was performed on days 1 and 7. Vital signs, laboratory evaluations, and adverse events were monitored.
Results: All doses of indacaterol increased the mean time-standardized area under the curve of forced expiratory volume in 1 s (FEV_1) from 22 to 24 h postdose ($P \leq 0.001$ *vs* placebo) on days 1 and 7, with clinically relevant treatment-placebo differences of 240, 260, 350, 300, and 380 ml on day 1 and 230, 220, 320, 250, and 270 ml on day 7 for indacaterol 50, 100, 200, and 400 μg via MDDPI and 400 μg via SDDPI, respectively. All doses increased mean FEV_1 ($P < 0.05$ *vs* placebo) from 5 min to 24 h postdose on days 1 and 7. All doses were well tolerated. Most adverse events were mild-to-moderate in severity: most frequently reported were respiratory, thoracic, and mediastinal disorders.
Conclusion: Once-daily dosing with indacaterol provided sustained 24-h bronchodilation in patients with moderate-to-severe asthma, with a satisfactory overall safety profile. Indacaterol 200 μg appears the optimum dose, offering the best efficacy/safety balance.

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Key words: asthma; bronchodilator; efficacy; indacaterol; long-acting β_2-agonist.

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Inhaled β_2-agonists have an important role in the management of asthma-related symptoms (1). Currently available agents can be broadly divided into those with a short duration of bronchodilator action (2–4 h, e.g. albuterol) and the longer-acting (12 h) agents formoterol, which is also fast-acting, and salmeterol.

Asthma management guidelines (1) recommend that the latter are used as controller agents in conjunction with anti-inflammatory therapy, typically inhaled corticosteroids. In patients who require additional controller treatment in addition to a moderate dose of inhaled corticosteroids, such a regimen has been shown to offer better asthma control compared with the alternative step-up strategy of increasing the dose of inhaled corticosteroid (2, 3).

With chronic diseases such as asthma, patient adherence to medication plans is a major obstacle to successful management (4). One factor contributing to poor adherence is a complicated or multiple treatment regimen, and simplified dosing regimens are known to improve compliance (4, 5). To this end, a logical progression in the development of new asthma therapies is to extend the duration of action of existing classes of agents, as illustrated by inhaled corticosteroids that can be taken once daily such as mometasone or budesonide (6, 7). Similar research efforts are being made with the β_2-agonist class of bronchodilators.

Abbreviations: AUC, area under the curve; COPD, chronic obstructive pulmonary disease; $FEF_{25–75\%}$, forced expiratory flow between 25% and 75% of FVC; FEV_1 $AUC_{22–24h}$, FEV_1 standardized (with respect to time) AUC calculated between 22 and 24 h postdose; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ITT, intent-to-treat; LLN, lower limit of normal; MDDPI, multi-dose dry-powder inhaler; QTc, corrected QT interval; SDDPI, single-dose dry-powder inhaler; ULN, upper limit of normal.

Indacaterol is a novel β_2-agonist in development for once-daily administration in the treatment of asthma and chronic obstructive pulmonary disease (COPD). In previous studies, single doses of indacaterol provided sustained 24-h bronchodilation and were well tolerated, and a good overall safety profile was seen with once-daily dosing over 28 days (8, 9).

The present study was conducted to assess the bronchodilator efficacy of indacaterol in patients with persistent asthma and on stable doses of inhaled corticosteroids, investigating a range of doses given by multi-dose and single-dose dry powder inhalers (MDDPI and SDDPI). Safety and tolerability were also assessed.

Methods

Subjects

Patients aged 12–75 years were recruited with stable moderate-to-severe persistent asthma [forced expiratory volume in 1 s (FEV_1) ≥50% to ≤ 80% of the Quanjer predicted normal value (10), with a demonstrated FEV_1 increase of ≥15% over baseline within 30 min of inhaling albuterol 200 μg (ex-valve)], who were treated with inhaled corticosteroids at a dose of up to the equivalent of 1600 μg/day of beclometasone dipropionate (ex-valve). We excluded patients with COPD (11), a smoking history > 10 pack-years, current seasonal allergy, recent respiratory tract infection, or hospitalization or emergency room treatment for an asthma attack in the last 6 months. Pregnant women were excluded. Patients and/or their parents or guardians gave their written informed consent.

Patients receiving long-acting β_2-agonists as monotherapy were switched to a short-acting β_2-agonist, and patients on fixed-combination long-acting β_2-agonists and inhaled corticosteroids were switched to inhaled corticosteroid monotherapy and short-acting β_2-agonist as needed. Treatment with systemic corticosteroids, xanthines, and leukotriene antagonists or anticholinergics was not permitted during the study.

Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study consisting of a 2-week run-in, a baseline visit at which patients were randomized, and a 7-day study drug treatment period. Patients were assessed predose and up to 24 h postdose on day 1 and reassessed on day 7. The design was approved by the institutional review boards and the study was conducted in accordance with the declaration of Helsinki (1964 and updates).

Study treatment

Patients received indacaterol 50, 100, 200, or 400 μg, all via a MDDPI (Certihaler™*), indacaterol 400 μg via single-dose dry-powder inhaler (SDDPI), or placebo once daily in the morning, between 08:00 and 10:00, for 7 days. To maintain blinding, patients took three inhalations, one each from two MDDPIs and one from an SDDPI. Patients could take inhaled albuterol as rescue medication as required but not within 6 h of the start of each study visit, unless necessary.

Study assessments

Efficacy was assessed by spirometry [FEV_1, forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75\%}$)] performed on day 1, predose and at postdose time points of 5, 10, 15, and 30 min and 1, 2, 3, 4, 8, 12, 22, 23, and 24 h. Day 7 spirometry was performed at the same times excluding 8 and 12 h postdose. The highest of three FEV_1 and FVC measurements were recorded. The primary efficacy variable was the FEV_1 standardized (with respect to time) area under the curve (AUC) calculated between 22 and 24 h postdose on day 1 (FEV_1 $AUC_{22–24h}$), comparing the efficacy of each indacaterol dose *vs* placebo. Secondary efficacy variables included the FEV_1 $AUC_{22–24h}$ on day 7, and lung function variables at individual time points over the postdose period.

Safety was assessed by monitoring and recording adverse events, regular monitoring of hematology, blood chemistry, urine, vital signs and electrocardiograms, and regular physical examinations.

Statistical analyses

In total, 372 patients were to be evenly randomized between groups in order to attain 85% power to test for a treatment difference in FEV_1 of 300 ml, at a 0.05 significance level, allowing for a 10% dropout rate and based on an estimated between-patient standard deviation for FEV_1 of 520 ml at 21 h postdose.

All efficacy analyses were performed on the intent-to-treat (ITT) population, which was defined as all patients randomized to receive treatment. Safety analyses were performed on the safety population, defined as all patients who received at least one dose of study medication. An ANCOVA model was applied to the results of all efficacy variables, with terms for center, country, treatment, and baseline spirometry values. Adverse events that began after the start of study treatment and up to 7 days after the end were recorded. Laboratory data were summarized as absolute values and changes from baseline. The key laboratory variables of serum potassium and blood glucose were analyzed using the same ANCOVA model as above, and also by number of patients with serum potassium below the lower limit of normal (LLN, 3.5 mmol/l) at each time point, or with blood glucose above the upper limit of normal (ULN, 7.77 mmol/l) at each time point. Corrected QT interval (QTc), pulse rate, and blood pressure were analyzed also using the same ANCOVA model as above. QTc was calculated using Bazett's and Fridericia's formulae ($QTc = QT/\sqrt{RR}$ and $QTc = QT/\sqrt[3]{RR}$, respectively).

Results

Patients

Of 717 patients screened, 436 patients were randomized to receive indacaterol or placebo. (The most common reasons for failing to meet inclusion criteria were test results and asthma diagnosis/severity, i.e. FEV_1 > 80% or < 50% of predicted.) Their baseline demographics and background characteristics were broadly similar across the treatment groups (Table 1). The majority of patients were Caucasian (388; 89%) or black (38; 9%).

*The indacaterol Certihaler was jointly developed by Novartis and SkyePharma AG and utilizes SkyePharma's proprietary formulation and device technologies, SkyeProtect™ and SkyeHaler™, respectively.

Table 1. Patient demographics at baseline

	Indacaterol					
	MDDPI				SDDPI	
	400 μg	200 μg	100 μg	50 μg	400 μg	Placebo
Subjects, *n*	76	75	69	73	72	71
Age, years						
Mean (SD)	43.3 (14.98)	43.6 (16.17)	41.3 (15.40)	39.4 (16.61)	43.3 (16.17)	38.4 (15.47)
Range	14–75	13–70	13–74	12–74	13–72	12–73
Sex, *n* (%)						
Female	38 (50.0)	43 (57.3)	39 (56.5)	34 (46.6)	37 (51.4)	41 (57.7)
Male	38 (50.0)	32 (42.7)	30 (43.5)	39 (53.4)	35 (48.6)	30 (42.3)
Duration of asthma, years						
Mean (SD)	22.2 (13.50)	20.1 (13.30)	21.0 (12.62)	20.9 (12.74)	19.8 (12.07)	17.9 (11.38)
Range	1.0–59.2	0.6–51.3	0.4–49.2	2.0–58.2	0.5–60.2	1.0–50.1
FEV_1, l						
Mean (SD)	2.33 (0.635)	2.19 (0.557)	2.21 (0.689)	2.33 (0.569)	2.19 (0.599)	2.24 (0.514)
Range	0.96–3.66	1.28–3.25	1.17–3.91	1.23–3.58	1.15–3.62	1.46–3.47
FEV_1, % predicted*						
Mean (SD)	68.96 (8.689)	67.21 (8.676)	66.67 (8.886)	66.83 (8.544)	66.65 (9.772)	68.30 (8.855)
Range	50.53–80.28	50.41–81.82	50.66–79.11	50.14–79.58	42.90–80.40	49.74–80.74
FEV_1 reversibility, %*						
Mean (SD)	23.51 (8.256)	25.07 (9.572)	25.47 (10.531)	25.11 (10.044)	26.93 (14.782)	24.55 (9.017)
Range	14.36–53.77	14.52–62.50	14.94–61.03	13.59–57.56	14.41–91.10	14.49–61.69
Smoking history, *n* (%)						
Never smoked	62 (81.6)	65 (86.7)	50 (72.5)	62 (84.9)	57 (79.2)	60 (84.5)
Ex-smoker	14 (18.4)	10 (13.3)	18 (26.1)†	11 (15.1)	14 (19.4)†	11 (15.5)
Pack-years						
Mean (SD)	5.1 (3.05)	4.4 (3.06)	5.7 (3.28)	4.7 (3.23)	3.9 (2.43)	4.4 (2.80)
Range	1–10	1–9	1–10	1–10	1–8	1–9
ICS dose (μg/day) during study treatment						
Mean (SD)	816.0 (441.4)	889.4 (469.7)	836.5 (570.9)	816.4 (419.3)	769.3 (376.3)	874.4 (437.2)
Range	88–2000	100–2000	160–4000	176–2000	160–2000	80–2000

*Within 30 min of inhaling salbutamol 200 μg and †Group also includes one (1.4%) current smoker. FEV_1, forced expiratory volume in 1 s; MDDPI, multi-dose dry-powder inhaler; SDDPI, single-dose dry-powder inhaler; l, liters.

All randomized patients received at least one dose of study medication and therefore the ITT and safety populations were identical. Most randomized patients (431; 99%) completed the study. Five patients discontinued prematurely, four because of adverse events (see safety results) and one because of a protocol violation (noncompliance with the dosing schedule). Mean patient exposure to study medication was similar between treatment groups.

Efficacy

All doses of indacaterol resulted in statistically superior ($P < 0.0001$) adjusted mean FEV_1 $AUC_{22–24h}$ compared with placebo on day 1 (Fig. 1), with treatment–placebo differences of 240, 260, 350, 300, and 380 ml for indacaterol 50, 100, 200, and 400 μg via MDDPI and 400 μg via SDDPI, respectively. The only statistically significant ($P < 0.05$) differences between indacaterol doses were 200 μg *vs* 50 μg and 400 μg via SDDPI *vs* 50 μg and 100 μg. On day 7, the FEV_1 $AUC_{22–24h}$ for all doses of indacaterol remained statistically greater ($P \leq 0.0001$) than placebo, with differences ranging from 220 to 320 ml; no statistically significant differences were observed between indacaterol groups.

Statistically significant differences ($P < 0.001$) were seen in adjusted mean FEV_1 between placebo and all indacaterol doses at all time points on both days 1 and 7 (Figs 2 and 3). This included a statistically significant ($P \leq 0.0001$) effect of all doses *vs* placebo at the earliest postdose time point, 5 min, on both days, with treatment-placebo differences from 170 ml (50 μg) to 260 ml (both 400 μg doses) on day 1, and from 250 ml (100 μg) to 320 (200 μg) on day 7. Predose measurements on day 7 showed that FEV_1 was increased relative to placebo with all indacaterol doses (by 210–310 ml, $P < 0.001$).

Adjusted mean peak values for FEV_1 during the first 4 h postdose for active doses showed increases compared with placebo of 220–370 ml on day 1 and 300–430 ml on day 7 (all $P < 0$ .0001).

Forced vital capacity values were significantly higher ($P < 0.05$) with all doses of indacaterol relative to placebo at all time points on days 1 and 7, except at 4, 8, and 12 h postdose on day 1 for indacaterol 100 μg. Similarly, $FEF_{25–75\%}$ was statistically significantly greater than placebo ($P < 0.01$) with all doses of indacaterol at

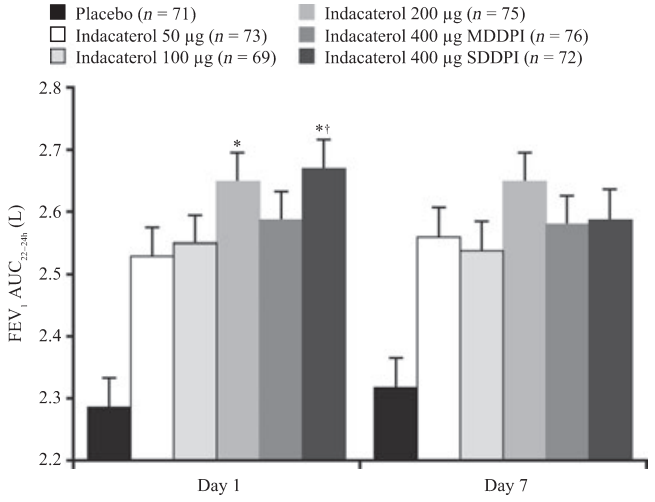

Figure 1. Adjusted mean (±SE) forced expiratory volume in 1 s (FEV_1) standardized (with respect to time) AUC calculated between 22 and 24 h postdose (FEV_1 $AUC_{22–24h}$) on day 1 and 7. Values with all indacaterol groups were significantly different ($P \leq 0.0001$) *vs* placebo; the day 1 value with the 400 µg SDDPI dose was significantly different ($P < 0.05$) *vs* 50 and 100 µg values.

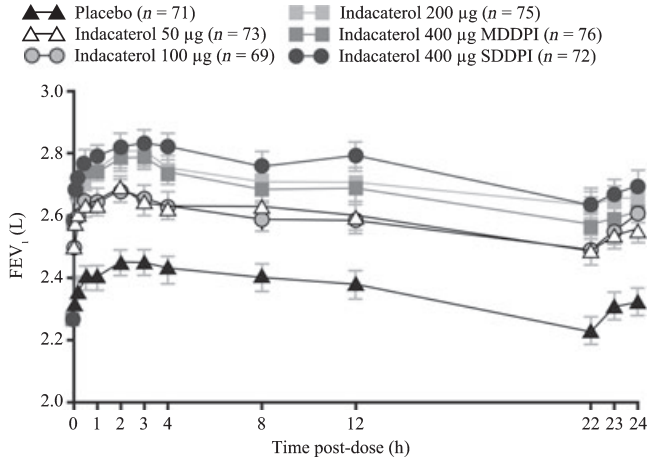

Figure 2. Adjusted mean (±SE) forced expiratory volume in 1 s (FEV_1) on day 1. All indacaterol doses had a significantly greater effect *vs* placebo ($P < 0.005$) at all time points postdose; indacaterol 400 µg MDDPI superior ($P < 0.05$) to 100 and 50 µg from 5 min to 4 h; indacaterol 200 µg superior ($P < 0.05$) to 100 and 50 µg from 5 min to 22 h, except at 30 min for 100 µg and at 8 h for 50 µg; indacaterol 400 µg SDDPI superior ($P < 0.05$) to 50 µg and 100 µg at all postdose time points except at 24 h for 100 µg.

all postbaseline time points; day 7 data are shown in Fig. 4.

Safety

Adverse events are summarized by primary system organ class in Table 2. The most frequently reported adverse

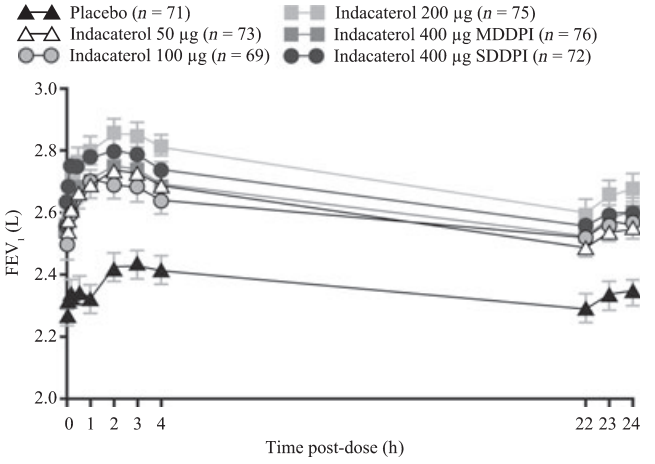

Figure 3. Adjusted mean (±SE) forced expiratory volume in 1 s (FEV_1) on day 7. All indacaterol doses had a significantly greater effect *vs* placebo ($P < 0.001$) at all time points pre- (time 0) and postdose; indacaterol 200 µg superior ($P < 0.05$) to 50 µg from 1 to 4 h and at 24 h; indacaterol 200 µg superior ($P < 0.05$) to 100 µg at 2–4 h and at 24 h; indacaterol 200 µg superior ($P < 0.05$) to 400 µg MDDPI from 3 to 4 h; indacaterol 400 µg SDDPI superior ($P < 0.05$) to 100 µg at 15 min and 2 h time points.

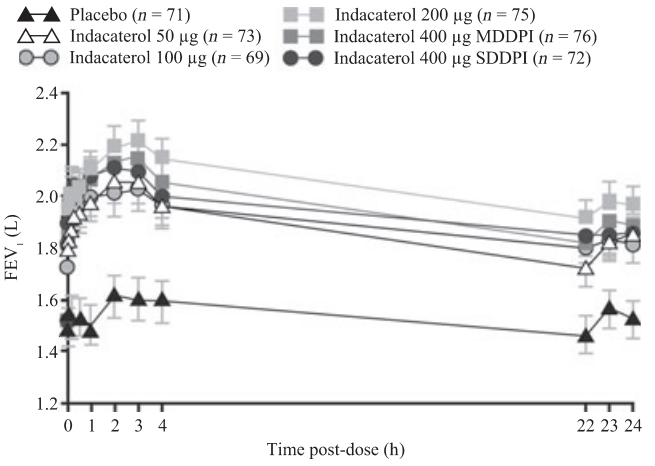

Figure 4. Adjusted mean (±SE) forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75\%}$) on day 7. All indacaterol doses had a significantly greater effect *vs* placebo ($P < 0.0001$) at all time points pre- (time 0) and postdose; indacaterol 200 µg had a significantly greater effect *vs* the 100 µg dose predose and *vs* the 50 µg dose at 22 h.

events were respiratory, thoracic, and mediastinal disorders. Other reported primary organ class adverse events did not show meaningful differences between treatment groups. Cough was the most frequent adverse event, reported by 11.0–33.3% of patients in the indacaterol treatment groups and by 1.4% of patients taking placebo. The incidence of cough was highest in the indacaterol 400 µg SDDPI group and appeared to be

Table 2. Adverse events (*n*, %) by primary system organ class

	Indacaterol					
	MDDPI				SDDPI	
	400 μg	200 μg	100 μg	50 μg	400 μg	Placebo
Subjects, *n*	76	75	69	73	72	71
At least one adverse event	32 (42.1)	26 (34.7)	18 (26.1)	20 (27.4)	36 (50.0)	17 (23.9)
Respiratory, thoracic, and mediastinal disorders	21 (27.6)	17 (22.7)	10 (14.5)	10 (13.7)	27 (37.5)	4 (5.6)
Nervous system disorders	9 (11.8)	5 (6.7)	5 (7.2)	7 (9.6)	0	5 (7.0)
General disorders and administration site conditions	3 (3.9)	2 (2.7)	1 (1.4)	2 (2.7)	1 (1.4)	0
Gastrointestinal disorders	2 (2.6)	0	3 (4.3)	0	2 (2.8)	2 (2.8)
Metabolism and nutrition disorders	2 (2.6)	0	0	0	0	0
Cardiac disorders	1 (1.3)	1 (1.3)	2 (2.9)	3 (4.1)	0	2 (2.8)
Ear and labyrinth disorders	1 (1.3)	0	0	1 (1.4)	0	0
Infections and infestations	1 (1.3)	3 (4.0)	0	1 (1.4)	1 (1.4)	1 (1.4)
Investigations	1 (1.3)	2 (2.7)	2 (2.9)	0	2 (2.8)	2 (2.8)
Musculoskeletal and connective tissue disorders	1 (1.3)	1 (1.3)	0	1 (1.4)	4 (5.6)	1 (1.4)
Psychiatric disorders	1 (1.3)	0	2 (2.9)	1 (1.4)	2 (2.8)	0
Endocrine disorders	0	0	0	0	1 (1.4)	0
Eye disorders	0	2 (2.7)	0	0	1 (1.4)	1 (1.4)
Immune system disorders	0	0	0	0	1 (1.4)	0
Injury, poisoning, and procedural complications	0	0	0	0	2 (2.8)	2 (2.8)
Skin and subcutaneous tissue disorders	0	1 (1.3)	1 (1.4)	0	1 (1.4)	0
Surgical and medical procedures	0	0	0	0	0	1 (1.4)*

*This patient had a surgical and medical procedures serious adverse event (ostectomy) that was 17 days after the last dose but within the reporting time window for serious adverse events. MDDPI, multi-dose dry-powder inhaler; SDDPI, single-dose dry-powder inhaler.

dose related. The majority of coughs occurred immediately after inhalation of study drug and resolved spontaneously shortly afterwards. At the treatment visit on day 1, cough was observed by the investigators in 11.0%, 10.1%, 13.3%, 18.4%, and 26.4% of patients receiving indacaterol 50, 100, 200, 400 μg MDDPI and 400 μg SDDPI, respectively, and in 1.4%, 0, 1.3%, 1.3% and 2.8% of patients in these respective groups on day 7. In most cases, the cough severity was mild (88%), and no patient had severe coughing. Of those patients reporting cough during the period up to 10 min postdose, three patients (one each from the 50, 200, and 400 μg groups) also had a decrease in FEV_1 (more than 200 ml or 10% drop from predose value). However, none of these patients reported concurrent wheeze, and there were no reports of bronchospasm as an adverse event during the study. Headache was the next most frequent adverse event, reported by 0–7.9% of patients in the indacaterol groups (and 2.8% of the placebo group), with an incidence unrelated to dose. There were no meaningful differences between treatment groups in the incidence of other adverse events.

The majority of adverse events were mild-to-moderate in severity. Only two patients had severe adverse events: one case of allergic rhinitis in the 200 μg group and one patient with severe palpitations, tachycardia, headache, vertigo, nausea, and insomnia in the 400 μg MDDPI group. The latter was suspected to be related to the study drug, and led to the patient withdrawing from the study. Three other patients withdrew from the study owing to adverse events, one of which (erythema, anxiety, nausea, and tachycardia), in the indacaterol 100 μg group, was suspected to be related to the study drug. One serious adverse event occurred (ostectomy, in a placebo patient, which was performed 17 days after the patient completed the treatment period) which was not suspected to be study drug related.

No consistent differences were observed between treatment groups in mean serum potassium levels, with the mean minimum postdose serum potassium values similar across treatment groups: group mean values were between 4.01 (placebo) and 4.10 mmol/l (indacaterol 50 μg). Few patients experienced serum potassium values below the LLN at each time point (0–6.3% of patients per treatment group). No patients had notably low values of serum potassium (below 3 mmol/l).

There were no consistent differences between treatment groups in mean blood glucose levels. Mean maximum values were significantly higher in the 400 μg groups (6.57 and 6.39 mmol/l via MDDPI and SDDPI, respectively) than in the 50 μg group (5.98 mmol/l) ($P < 0.05$), but neither value was significantly different from placebo

(6.21 mmol/l) and there was no clear dose relationship. Between 0% and 7% of patients per treatment group experienced a blood glucose value above the ULN at each individual time point. Although there was a tendency for more glucose elevations in the 400 μg MDDPI group, this was not consistent at every time point and there were no meaningful differences between the other treatment groups. Notably high values in (random) blood glucose levels (above 9.99 mmol/l) were seen for five patients in the 400 μg MDDPI group (6.6% of patients), for two patients in the 100 and 200 μg MDDPI and 400 μg SDDPI groups (2.9%, 2.7%, and 2.8% of patients, respectively), and for one patient in the 50 μg and placebo groups (1.4% of patients in both groups).

Differences between treatment groups in mean pulse rates were generally small, and occasional statistically significant differences between groups did not appear to be dose or time dependent. Compared with placebo, statistically significant ($P < 0.05$) differences were observed as follows: 2–4 beats/min higher at three (of 21) time points for 400 μg MDDPI; and 3 beats/min lower at one time point for 100 μg MDDPI and 400 μg SDDPI, and at two time points for 50 μg MDDPI. There were no consistent differences between treatment groups in the percentage of patients with readings >90 beats/min (Table 3).

Systolic and diastolic blood pressure readings showed no consistent trends in terms of mean values, changes from baseline or differences between treatment groups. There was no evidence of a drug-related effect on the number of patients experiencing blood pressure values outside the normal range (>90 and <140 mmHg for systolic pressure and >50 and <90 mmHg for diastolic pressure; Table 3). Between 88% and 99% of patients had normal systolic blood pressure values (>90 and <140 mmHg) over all time points. Systolic blood pressure <90 or >140 mmHg was experienced by fewer than 3% and 13% of patients, respectively, per treatment group at each time point. Diastolic blood pressure <50 or >90 mmHg was experienced by fewer than 3% and 11% of patients, respectively, per treatment group at each time point.

There were no trends in mean QTc interval values (Bazett's or Fridericia's) for any treatment group, with statistically significant differences between groups only observed at isolated time points. Two patients, one each in the indacaterol 50 and 400 μg MDDPI groups, experienced notable QTc interval values (Fridericia's; >450 ms for males and >470 ms for females; Table 3). The patient in the 50 μg group also had a notable increase in QTc interval (Fridericia's; >60 ms change from baseline); this patient had a predose QTc interval of 392 ms (Fridericia's) that increased to 473 ms at 1 h postdose.

There were no meaningful changes from baseline in hematological or biochemical variables.

Discussion

The significant effect with all doses of indacaterol relative to placebo for FEV_1 $AUC_{22–24h}$ (the primary efficacy variable) and for FEV_1 measured at all time points over 24 h, serves to demonstrate the sustained 24-h bronchodilator efficacy of indacaterol and supports the potential for a once-daily dosing regimen. Significant differences in FEV_1 compared with placebo were observed for all indacaterol groups by 5 min postdose on day 1. This pharmacodynamic profile is clearly distinct from currently available inhaled β_2-agonists: the rapid onset of action is similar to that of the short-acting agent albuterol and the longer-acting formoterol, but the duration of

Table 3. Incidences [*n* (%)] of notable values for pulse rate, blood pressure and QTc interval

	Indacaterol					
	MDDPI				SDDPI	
	400 μg	200 μg	100 μg	50 μg	400 μg	Placebo
Subjects, *n*	76	75	69	73	72	71
Pulse rate						
>90 beats/min	20 (26.3)	22 (29.3)	14 (20.3)	12 (16.4)	14 (19.4)	12 (16.9)
Systolic blood pressure						
<90 mmHg	0	1 (1.3)	0	1 (1.4)	2 (2.8)	4 (5.6)
>140 mmHg	15 (19.7)	15 (20.0)	14 (20.3)	13 (17.8)	15 (20.8)	14 (19.7)
Diastolic blood pressure						
<50 mmHg	2 (2.6)	0	1 (1.5)	0	0	1 (1.4)
>90 mmHg	9 (11.8)	14 (18.7)	6 (8.8)	10 (13.7)	10 (13.9)	9 (12.7)
QTc interval (Fridericia's formula)						
>450 ms (males)	1 (1.3)	0	0	1 (1.4)	0	0
>470 ms (females)	0	0	0	0	0	0
Change in QTc interval (Fridericia's formula; baseline to postdose)						
>60 ms	0	0	0	1 (1.4)	0	0

MDDPI, multi-dose dry-powder inhaler; SDDPI, single-dose dry-powder inhaler; QTc, corrected QT interval.

action is approximately four times that of albuterol (12) and double that of the long-acting β_2-agonists formoterol and salmeterol when used at recommended doses (13). Of the doses evaluated, indacaterol 200 μg once daily appeared to be the optimum dose, being the most effective based on trough FEV_1 (24 h postdose) on both days 1 and 7, and supported by the 24-h profiles on day 7 for both FEV_1 and $FEF_{25–75\%}$, with a satisfactory overall safety profile.

The selected range of doses may occupy a relatively flat part of the dose–response curve for the bronchodilator effect of indacaterol in asthma patients. A previous study investigating single indacaterol doses of 50, 100, 200, and 400 μg showed that increases in dose paralleled increases in FEV_1, with the 400 μg dose having the greatest effect (8). A recent 28-day study, although set up primarily to investigate safety, showed little difference between 200, 400, and 600 μg/day doses delivered via HFA-pMDI in their effect on trough (predose) and acute (30 min postdose) bronchodilation (9). A 7-day study of doses between 100 and 600 μg/day showed some evidence of optimal efficacy with the 200 μg dose (14). In the absence of a clear-cut dose–response relationship, the present data suggest that the 200 μg/day dose offers an acceptable balance of efficacy and tolerability.

Systemic absorption of β_2-agonists (especially at high doses) can cause predictable adverse effects including muscle tremor and metabolic effects such as hypokalemia and hyperglycemia (via skeletal muscle β_2-adrenoceptor stimulation), cardiac palpitations and tachycardia (cardiac β_2-adrenoceptors; response to peripheral vasodilation), and headache (peripheral vasodilation) (15–17). Administration of β_2-agonists via the oral and intravenous routes has been associated with cardiovascular adverse events, which has limited the use of such formulations in the treatment of obstructive airway diseases (18, 19). However, the predictable adverse events of β_2-agonists rarely present any problem when administered via inhalation (20–22). Any concerns with the introduction of the longer-acting β_2-agonist bronchodilators (e.g. formoterol) that these side effects would be more apparent than with the short-acting agents, e.g. albuterol and terbutaline, were allayed by comparative studies of equivalent high doses of the short- and longer-acting agents. These studies showed a lack of relationship between the size and duration of the unwanted systemic effect and the duration of bronchodilator effect; indeed, the longer-acting agents appeared to have a better safety profile (23–26). Furthermore, tolerance to these extrapulmonary effects occurs over time (27).

The results of the present study suggest that the sustained 24-h duration of action of indacaterol is not associated with any undue concerns in terms of its systemic effects at the range of doses investigated. No trends or consistent differences were observed between groups for the key safety variables of serum potassium, blood glucose, blood pressure, pulse rate, and QTc interval.

While future studies specifically investigating safety will include higher doses, the therapeutic dose(s) chosen for further investigation are likely to lie within the range evaluated here, and all of these were reasonably well tolerated. Cough was the only reported adverse event that had any relation to dose. While common, the cough was generally mild, transient, and self-limiting and did not prevent patients continuing in the study. In the very small proportion of patients who coughed following inhalation and who also had a decrease in FEV_1 in the 2 h postdose, there were no reports of concurrent wheeze and bronchospasm, suggesting that the postinhalation cough does not pose a problem for patient safety. The use of the different devices did not appear to affect the efficacy or safety of the 400 μg dose of indacaterol.

Overall, the current study has shown that once-daily indacaterol has sustained 24-h bronchodilator efficacy, with a rapid onset of action, and is tolerated acceptably well in patients with moderate-to-severe asthma. Further clinical investigation is warranted to establish if this useful profile of bronchodilator activity is accompanied by improved symptoms and better control of asthma.

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C. LaForce has a consultant arrangement and is on a speakers' bureau for Novartis. M. Alexander has a consultant arrangement with several pharmaceutical companies and has taken part in advisory boards on an *ad hoc* basis; he is on speakers' bureaux for several pharmaceutical companies. L. Fabbri reports having served as a consultant to and having been paid lecture fees by Altana Pharma, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp & Dohme; Novartis; Roche, and Pfizer. L. Fabbri has received grant support from these companies and from Menarini, Miat, Schering Plough, UCB, Italian Ministry of Health, and Italian Ministry for University and Research. R. Cameron, R. Owen, and M. Higgins are employed by Novartis, who sponsored the trial.

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