Tolerability of indacaterol, a novel once-daily β_2-agonist, in patients with asthma: a randomized, placebo-controlled, 28-day safety study

William H. Yang, MD*; Jean Benoit Martinot, MD†; Petr Pohunek, MD‡; Jutta Beier, MD§; Daniel Magula, MD¶; Ray Cameron, BSc (Hons)‖; Roger Owen, PhD‖; and Mark Higgins, MD‖

Background: Indacaterol is a novel, inhaled, once-daily β_2-agonist.

Objective: To investigate the safety and tolerability of indacaterol at doses of 400 and 800 μg/d.

Methods: Randomized, double-blind, placebo-controlled, parallel-group, multicenter, 28-day study. Patients with persistent asthma (forced expiratory volume in 1 second [FEV_1] $\geq$60% predicted, $\leq$1,600 μg of beclomethasone dipropionate or equivalent daily) received indacaterol, 400 μg (n = 59) or 800 μg (n = 59), or placebo (n = 26) once daily via a single-dose dry powder inhaler. Safety assessments were performed before and after dosing on days 1, 14, and 28, with particular attention to key β_2-agonist safety variables.

Results: A total of 144 patients were randomized, with 135 (93.8%) completing the study. Indacaterol was well tolerated: the incidence of adverse events (AEs) was similar between the active and placebo groups, and AEs, when they occurred, were mild or moderate for most (98.2%). There was no dose-response relationship between indacaterol and the incidence of AEs (400 μg, 40.7%; 800 μg, 37.3%; and placebo, 38.5%). Few AEs considered as β_2-agonist class effects occurred (none leading to withdrawal). Small differences between indacaterol and placebo in mean serum potassium (≤ -0.29 mmol/L) and glucose ($\leq$0.93 mmol/L) levels were occasionally statistically significant ($P < .05$) but not regarded as clinically meaningful**.** As expected for a β_2-agonist, there was some indication of a trend in QTc prolongation with increasing exposure (maximum mean change, 8.9 milliseconds; $P < .05$ vs placebo). Significant increases in FEV_1 ($P < .05$) were seen at all postbaseline time points for both indacaterol doses vs placebo, with indacaterol-placebo differences 30 minutes after dosing of 0.21 to 0.25 L and before dosing on days 14 and 28 (approximately 24 hours after the previous dose) of 0.15 to 0.23 L.

Conclusion: Indacaterol had a good overall safety profile and was well tolerated at both doses, with predose FEV_1 results on days 14 and 28 indicating 24-hour bronchodilator efficacy.

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INTRODUCTION

Inhaled β_2-agonist bronchodilators are widely used in the treatment of patients with asthma and chronic obstructive pulmonary disease (COPD). Systemic absorption of these agents can lead to β_2-adrenoceptor–mediated cardiovascular effects, such as palpitations, tachycardia, changes in blood pressure, and electrocardiographic abnormalities,[1–3] together with adverse events (AEs), such as hypokalemia, hyperglycemia, headache, and skeletal muscle tremor.[1–4]

Indacaterol is a novel once-daily β_2-agonist that has demonstrated 24-hour bronchodilator efficacy together with a fast onset of action in patients with asthma and COPD.[5,6] Because indacaterol has a long duration of action, it is especially important to establish its safety profile. The primary objective of this study was to evaluate the safety and tolerability of 28 days of treatment with once-daily indacaterol, 400 and 800 μg (2–4 times the anticipated therapeutic dose at the planning of the study) compared with placebo. An exploratory analysis

* Allergy and Asthma Research Centre, Ottawa, Ontario.
† Clinique Sainte-Elisabeth, Namur, Belgium.
‡ Charles University, 2nd Faculty of Medicine, Prague, Czech Republic.
§ Insaf Respiratory Research, Wiesbaden, Germany.
¶ Specialized Hospital of St Zoerardus Zobor, Nitra, Slovakia.
‖ Novartis Horsham Research Centre, Horsham, England.

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of spirometry results was included to evaluate bronchodilator efficacy.

METHODS

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 144 adolescent and adult patients with persistent asthma. After a 14-day run-in phase to allow for adjustments to existing asthma therapy and evaluate asthma stability, patients were randomized in a 2:2:1 ratio to 28 days of treatment with indacaterol, 400 μg, indacaterol, 800 μg, or placebo (administered once daily in the morning between 7 AM and 11 AM via a single-dose dry powder inhaler). A follow-up visit was made 7 days after completion of treatment. A validated system was used that automated randomized assignment to treatment groups.

The design of the study was approved by the relevant institutional review boards and ethics committees and was performed in accordance with the Declaration of Helsinki (1964 and amendments), and all patients or their parent or legally acceptable representative gave written informed consent.

Inclusion and Exclusion Criteria

The study included male and female patients aged 12 to 65 years diagnosed as having asthma who had been receiving daily treatment with an inhaled β_2-agonist and an inhaled corticosteroid, up to 1,600 μg of beclomethasone dipropionate (or equivalent), in a stable regimen for the past month. At screening, patients were required to demonstrate a forced expiratory volume in 1 second (FEV_1) of 60% or greater predicted and (at screening or recently documented) an increase in FEV_1 of 12% or greater over baseline FEV_1 within 30 minutes after inhalation of albuterol, 380 μg.[7] Patients were excluded if they had a smoking history of more than 10 pack-years, had used tobacco products within the previous 6 months, had been diagnosed as having COPD, had been hospitalized because of an acute asthma attack within 3 months before screening, or had a respiratory tract infection within 1 month before screening. Women of childbearing potential who were not using a reliable form of contraception were excluded.

The following medications were not allowed during the study and their use was discontinued with appropriate washout periods: fixed combinations of long-acting β_2-agonists and inhaled corticosteroids (24-hour washout), long-acting β_2-agonists (24 hours), parenteral and oral corticosteroids (3 months), theophylline and other xanthines (1 month), ipratropium bromide (24 hours), and tiotropium bromide (7 days). Anti-IgE therapy was not an exclusion criterion because the drug was not approved in Canada or Europe at the time of the study.

Concomitant Medication

Patients taking long-acting β_2-agonists were switched to short-acting β_2-agonists for the run-in phase, and the corticosteroid component of any fixed combination therapy (inhaled corticosteroid and β_2-agonist) was replaced with an equivalent separate inhaler. Patients already taking inhaled corticosteroids from a separate inhaler continued to take their prestudy regimen. Albuterol was provided as rescue medication, but was not to be taken from 6 hours before a study visit until completion of spirometry, unless necessary. Other bronchodilator medication was not permitted.

The following medications for asthma and related conditions were permitted, provided treatment had been stable for at least 1 month before the study: nasal corticosteroids, antihistamines, cromones, ketotifen, leukotriene antagonists, and allergen immunotherapy for allergic rhinitis.

Study Assessments

Safety assessments were performed on days 1, 14, and 28; hematological, blood chemistry, blood pressure, and electrocardiographic assessments were performed before and 60 minutes after dosing; spirometry was performed before and 30 minutes after dosing; and urinalysis was performed before dosing only. Physical condition was regularly monitored, and all AEs were monitored and reported. Spirometry included FEV_1, forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of FVC. Particular attention was paid to key safety variables for β_2-agonists, namely, serum potassium level, blood glucose level, heart rate, blood pressure, QTc interval (calculated using the Fridericia and Bazett formulas: $QTc = QT/\sqrt{3RR}$ and $QTc = QT/\sqrt{RR}$, respectively, where RR denotes R-R interval), and AEs, such as tremor and headache. At each visit, patients were asked to estimate their daily use of short-acting inhaled β_2-agonist since the previous visit.

Statistical Analysis

This was primarily a safety study, aimed at hypothesis generation rather than hypothesis testing, and, therefore, no formal sample size calculation was performed. It was planned to randomize 148 patients so that, with an assumed dropout rate of 10%, 133 patients would complete the study, approximately 106 of whom would have been exposed to indacaterol for 28 days. All safety analyses were performed on the safety population, which was defined as all randomized patients who received at least 1 dose of study medication. Adverse events were summarized for each treatment group. Laboratory data were summarized as absolute values and changes from baseline. Additional analyses were performed for serum potassium level, blood glucose level, QTc interval, and FEV_1 using an analysis of covariance (ANCOVA) model, with terms for country, treatment, and baseline values.

Analyses of FEV_1 using the previously described ANCOVA model were performed using data from the intention-to-treat population, which was defined as all randomized patients who received at least 1 dose of study medication and had at least 1 postdose FEV_1 measurement.

RESULTS

Patients

Patient recruitment commenced on February 17, 2004, and the study was completed on July 15, 2004, with patients

participating at 19 centers in 5 countries (Belgium, Canada, Czech Republic, Germany, and Slovakia). Of 179 patients screened, 144 were randomized. The demographics and baseline spirometry findings of the 3 treatment groups were broadly similar (Table 1). Most patients (135 [93.8%]) completed the study. Six patients withdrew because of AEs, 1 was withdrawn owing to a protocol violation (increased blood glucose level at the screening visit and at baseline), 1 was lost to follow-up and could not be located to complete the study, and 1 withdrew consent. The proportions of patients who used long-acting β_2-agonists before the study, and the use of short-acting β_2-agonists during the run-in phase, were comparable among groups (Table 1). During the study, the use of concomitant medication was similar between the indacaterol treatment groups; among placebo-treated patients, slightly fewer took inhaled corticosteroids, whereas the use of antihistamines and leukotriene inhibitors was slightly higher (Table 1).

Safety

In reviewing safety results, the placebo group was less than half the size of either active group (59 patients for each indacaterol group vs 26 in the placebo group). The incidence of AEs was similar among the 3 treatment groups (Table 2). The overall safety profile does not suggest any specific toxicity toward a major organ system. Only 1 event (an ectopic pregnancy in the indacaterol, 800 μg, group) was considered severe; this was not suspected to be related to the study drug. The most frequent class of AEs reported was respiratory, thoracic, and mediastinal disorders. These events were predominantly because of cough, reported by 10 (16.9%), 9 (15.3%), and 3 (11.5%) of the patients in the indacaterol, 400 μg, indacaterol, 800 μg, and placebo groups, respectively. Cough was mild or moderate, was frequently of short duration, occurred more often at the first dose of study medication than at subsequent visits, and did not seem to be related to bronchospasm. Other individual AEs with an incidence of 5% or greater in any treatment group were (for the indacaterol, 400 μg, indacaterol, 800 μg, and placebo groups, respectively) as follows: headache, 4 (6.8%), 0, and 0; tremor, 0, 4 (6.8%) (3 mild and 1 moderate), and 0; and nasopharyngitis, 2 (3.4%), 2 (3.4%), and 2 (7.7%). Mild palpitations were reported by 1 patient (1.7%) in each indacaterol group.

Five patients experienced serious AEs (2 in the indacaterol, 400 μg, group and 3 in the indacaterol, 800 μg, group), 4 of whom withdrew from the study as a result. Four of the serious

Table 1. Baseline Demographic and Disease Characteristics of All Randomized Patients[a]

Characteristic	Indacaterol, 400 μg (n = 59)	Indacaterol, 800 μg (n = 59)	Placebo (n = 26)
Age, y[b]	43.6 (12.4) [21.0–65.0]	43.5 (12.8) [12.0–64.0]	43.5 (14.5) [15.0–65.0]
Sex			
Male	28 (47.5)	31 (52.5)	9 (34.6)
Female	31 (52.5)	28 (47.5)	17 (65.4)
Race			
White	59 (100.0)	57 (96.6)	26 (100.0)
Other	0	2 (3.4)	0
Body mass index[c,d]	27.9 (5.3)	27.0 (5.2)	26.4 (5.4)
Asthma duration, y[b]	11.1 (8.5) [0.4–35.3]	15.0 (14.0) [0.4–54.3]	12.1 (11.9) [0.3–39.3]
FEV_1 % predicted[c]	81.5 (12.5)	78.5 (13.6)	84.4 (16.4)
FEV_1 reversibility, %[c]	18.2 (8.2)	19.1 (12.9)	15.8 (10.3)
Prior use of a long-acting β_2-agonist[e]	9 (15.3)	8 (13.6)	4 (15.4)
Prior use of an inhaled corticosteroid plus a long-acting β_2-agonist combination[e]	25 (42.4)	25 (42.4)	13 (50.0)
Albuterol use during run-in, puffs/day			
0	11 (18.6)	14 (23.7)	5 (19.2)
<1	12 (20.3)	14 (23.7)	6 (23.1)
1–2	16 (27.1)	16 (27.1)	7 (26.9)
3–6	16 (27.1)	12 (20.3)	8 (30.8)
>6	3 (5.1)	3 (5.1)	0
Concomitant medication			
Corticosteroid	58 (98.3)	59 (100.0)	22 (84.6)
Antihistamine	11 (18.6)	9 (15.3)	8 (30.8)
Leukotriene modifier	2 (3.4)	4 (6.8)	3 (11.5)

Abbreviation: FEV_1, forced expiratory volume in 1 second.

[a] Data are given as number (percentage) of each group unless otherwise indicated.

[b] Data are given as mean (SD) [range].

[c] Data are given as mean (SD).

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] Discontinued before the start of study drug treatment.

Table 2. Summary of Adverse Events in the Safety Population[a]

Primary system organ class	Indacaterol, 400 μg (n = 59)	Indacaterol, 800 μg (n = 59)	Placebo (n = 26)
Respiratory, thoracic, and mediastinal disorders	14 (23.7)	16 (27.1)	5 (19.2)
Infections and infestations	7 (11.9)	2 (3.4)	3 (11.5)
Nervous system disorders	4 (6.8)	5 (8.5)	0
General disorders and administration site conditions	1 (1.7)	2 (3.4)	0
Musculoskeletal and connective tissue disorders	0	2 (3.4)	0
Blood and lymphatic system disorders	1 (1.7)	0	0
Cardiac disorders	1 (1.7)	1 (1.7)	1 (3.8)
Eye disorders	1 (1.7)	0	0
Gastrointestinal disorders	0	1 (1.7)	1 (3.8)
Pregnancy, puerperium, and perinatal conditions	0	1 (1.7)	0
Psychiatric disorders	1 (1.7)	1 (1.7)	0
Renal and urinary disorders	1 (1.7)	0	1 (3.8)
Reproductive system and breast disorders	1 (1.7)	0	0
Skin and subcutaneous tissue disorders	1 (1.7)	1 (1.7)	0
Vascular disorders	1 (1.7)	1 (1.7)	0

[a] Data are given as number (percentage) of each group. The total number (percentage) of patients in each group who experienced adverse events is as follows: indacaterol, 400 μg, 24 (40.7%); indacaterol, 800 μ g, 22 (37.3%); and placebo, 10 (38.5%).

AEs were respiratory related: 1 patient in each indacaterol group had an event described as bronchospasm, associated with dyspnea and wheezing, both leading to use of the study drug being discontinued. The episodes of bronchospasm occurred shortly after dosing and were thought to be related to study drug. There was no clear link between the reported bronchospasm and decrease in FEV_1. One patient in the 400-μg group had an episode of hyperventilation; her medical history included hyperventilation, and the episode was attributed to underlying psychosomatic illness. One patient in the 800-μg group had an acute asthma attack, attributed to underlying disease progression, and discontinued use of the study drug; the attack occurred 16 days after the patient had, for undisclosed reasons, stopped taking her inhaled corticosteroid, and she made a complete recovery within a few days. The other serious AE was the ectopic pregnancy, which was diagnosed a week after a negative pregnancy test result; use of the study drug was discontinued when the patient underwent surgery. Two further (nonserious) events, both in the 800-μg group, led to withdrawal (asthma and cough, both moderate).

A small statistically significant ($P < .05$) difference was observed between the indacaterol and placebo treatment groups in mean serum potassium levels (Fig 1). Mean ± SE differences between the indacaterol, 800 μg, and placebo groups were −0.20 ± 0.076 mmol/L (day 1), −0.29 ± 0.079 mmol/L (day 14), and −0.18 ± 0.084 mmol/L (day 28). Only 1 patient, in the indacaterol, 800 μg, group, had a serum potassium level (3.4 mmol/L, at 1 time point) below the reference range (3.5–5.5 mmol/L). A statistically significant ($P < .05$) difference in mean blood glucose level was observed between the indacaterol and placebo groups 60 minutes after dosing on days 1 and 14 (these mean ± SE differences were 0.93 ± 0.22 and 0.77 ±0.23 mmol/L for the 800-μg dose, respectively), but not on day 28 (Fig 2). Blood

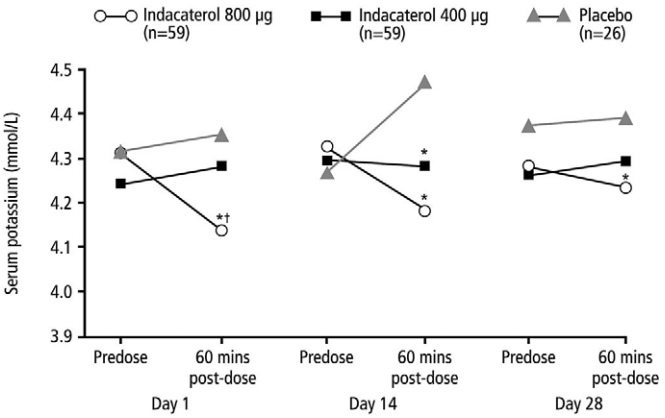

Figure 1. Mean serum potassium level over time in the safety population. The asterisk indicates significant differences ($P < .05$) vs placebo; dagger, significant differences ($P < .05$) vs indacaterol, 400 μg.

glucose levels greater than the reference range (3.33–7.77 mmol/L) were recorded for 3 (5.1%) of the patients in the indacaterol, 400 μg, group (9.27, 8.16, and 7.83 mmol/L, each at a single time point), 6 (10.2%) of the patients in the indacaterol, 800 μg, group (≤8.66 mmol/L, apart from 2 patients with notably high values), and 1 (3.8%) of the patients in the placebo group (15.37 mmol/L). Of the 3 patients with notably high (≥9.99 mmol/L) blood glucose levels, the placebo patient had a history of type 1 diabetes mellitus. Of the 2 patients in the 800-μg group, 1 had a high value at screening (9.71 mmol/L) and a history of diabetes mellitus; after the first dose of study drug, her blood glucose level increased from normal to 13.43 mmol/L and use of the drug was discontinued as a protocol violation. The other patient in the 800-μg group had high values before and after dosing at day 14 (10.55 and 11.99 mmol/L, respectively),

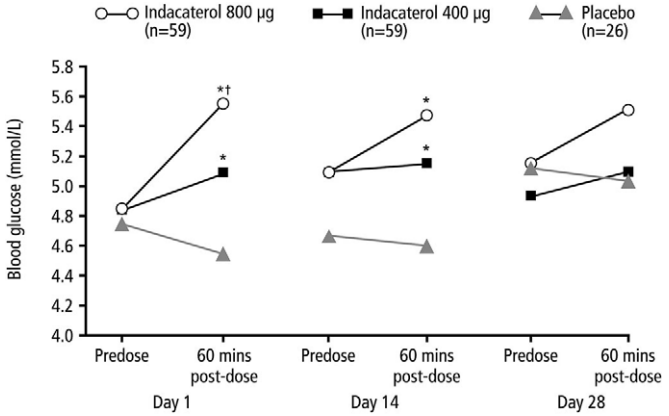

Figure 2. Mean blood glucose level over time in the safety population. The asterisk indicates significant differences ($P < .05$) vs placebo; dagger, significant differences ($P < .05$) vs indacaterol, 400 μg.

which had declined at the final visit (to 8.38 mmol/L predose and 7.94 mmol/L postdose); this patient completed the study uneventfully.

Using the Fridericia formula, there were statistically significant ($P < .05$) differences in mean QTc intervals compared with placebo for indacaterol, 400 μg, after dosing on day 1 (mean $\pm$ SE difference, 6.6 $\pm$ 3.2 milliseconds) and for indacaterol, 800 μg, after dosing on day 28 (mean $\pm$ SE difference, 8.9 $\pm$ 4.2 milliseconds) (Fig 3). No statistically significant difference was observed between indacaterol, 400 μg, and indacaterol, 800 μg, at any time point.

Notable QTc interval values were defined as absolute values of greater than 470 milliseconds for females or greater than 450 milliseconds for males and changes from baseline of 60 milliseconds or greater. Using the Fridericia formula, notable QTc interval values were recorded for 1 female patient in the indacaterol, 800 μg, group at most time points, including baseline (476 milliseconds at baseline, increasing up to 489 milliseconds after dosing). None of these values involved a notable increase in QTc interval, and there was little evidence of a treatment effect. This patient also had notable values using the Bazett formula. One female patient in the indacaterol, 800 μg, group had a notable increase in QTc interval (74 milliseconds after dosing on day 28), although the increase was not to a notable value (449 milliseconds). This patient also had a notable increase using the Bazett formula.

Using the Bazett formula, there were statistically significant differences ($P < .05$) in mean QTc intervals for both indacaterol groups compared with placebo, at all postdose time points. For the 400- and 800-μg groups, the mean $\pm$ SE differences were 8.7 $\pm$ 4.27 and 8.5 $\pm$ 4.25 milliseconds on day 1, 8.8 $\pm$ 4.38 and 11.0 $\pm$ 4.37 milliseconds on day 14, and 12.6 $\pm$ 5.06 and 18.5 $\pm$ 5.05 milliseconds on day 28, respectively.

Using the Bazett formula, notable QTc interval values were recorded for 3 patients in the indacaterol, 800 μg, group: 1 female patient at most time points, including baseline (from 477 milliseconds at baseline up to 489 milliseconds after dosing; this patient also had notable values using the Fridericia formula, previously described), and 2 male patients at isolated time points. None of these values involved a notable increase in QTc interval, and there was no evidence of a treatment effect. Notable increases in QTc interval occurred in 1 female patient in the indacaterol, 800 μg, group (maximum increase, 88 milliseconds) and in 1 female patient in the placebo group (68 milliseconds), although these increases were not to notable values (466 and 447 milliseconds, respectively). The patient in the 800-μg group also had a notable increase using the Fridericia formula.

No statistically significant difference in pulse rate was observed between indacaterol, 400 μg, and placebo. Statistically significant differences were observed between indacaterol, 800 μg, and placebo after dosing on day 14 (adjusted mean $\pm$ SE difference, 5.3 $\pm$ 2.2 beats/min; $P = .02$) and after dosing on day 28 (adjusted mean $\pm$ SE difference, 4.9 $\pm$ 1.9 beats/min; $P = .01$) (Fig 4). The small, but consistent, increase in pulse rate

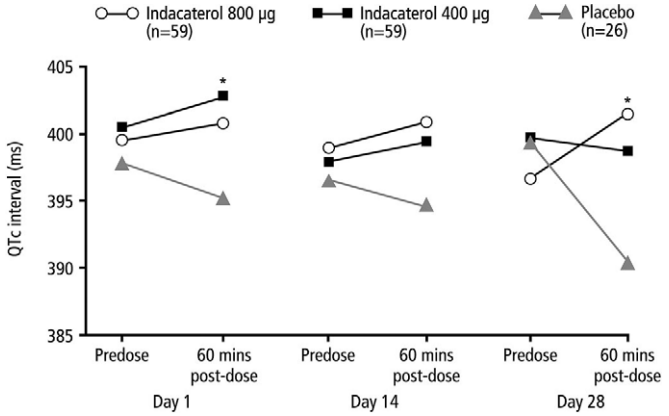

Figure 3. Mean QTc intervals (Fridericia formula) over time in the safety population. The asterisk indicates $P < .05$ vs placebo.

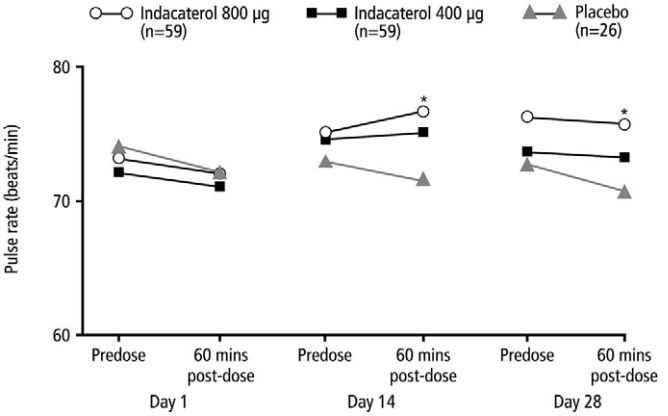

Figure 4. Mean pulse rate over time in the safety population. The asterisk indicates $P < .05$ vs placebo.

was also observed for the proportions of patients with a pulse rate of greater than 90 beats/min (10.2%, 16.9%, and 7.7% for indacaterol, 400 μg, indacaterol, 800 μg, and placebo, respectively). There was no statistically significant difference between treatment groups in mean systolic or diastolic blood pressure. There were no low systolic (<90 mm Hg) or diastolic (<50 mm Hg) values recorded. A number of patients had high blood pressure values: systolic, greater than 140 mm Hg (23.7%–25.4% with indacaterol and 30.8% with placebo); or diastolic, greater than 90 mm Hg (8.5%–10.2% with indacaterol and 7.7% with placebo). However, no drug-related trends or major differences vs placebo were observed.

Efficacy

Both indacaterol treatment groups demonstrated an improvement in FEV_1 at all postdose time points ($P < .05$) (Fig 5), with mean treatment-placebo differences of 0.21 to 0.24 L (adjusted for baseline values using the ANCOVA model). The bronchodilator effect was maintained during the study, with similar treatment-placebo differences 30 minutes after dosing (for 400 and 800 μg) of 0.23 and 0.24 L on day 14 and 0.22 and 0.24 L on day 28, respectively. In the same analysis, the predose FEV_1 measurements on days 14 and 28 for both indacaterol treatment groups were statistically superior ($P < .05$) to placebo, with adjusted mean indacaterol-placebo differences of 0.15 to 0.23 L. The bronchodilator efficacy of indacaterol was supported by FVC and forced expiratory flow between 25% and 75% of FVC data, in which the change from baseline observed with both indacaterol doses was consistently higher than the change from baseline observed with placebo.

Estimated albuterol use declined in all treatment groups from run-in levels and was comparable between groups. In the indacaterol, 400 and 800 μg, and placebo groups, 47.5%, 44.1%, and 42.3% of patients, respectively, reported no use of albuterol between days 1 and 14, and 45.8%, 55.9%, and 50.0%, respectively, reported no use between days 14 and 28.

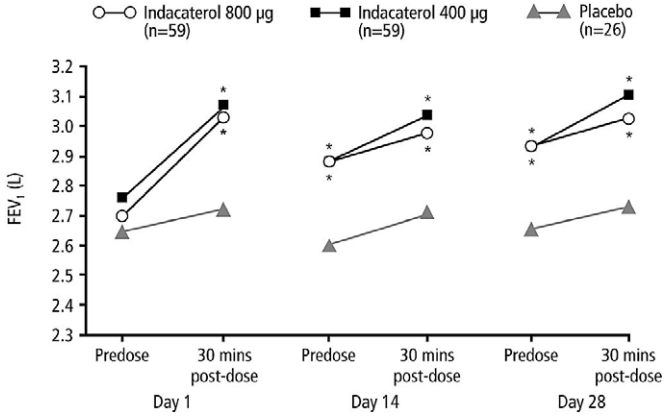

Figure 5. Mean forced expiratory volume in 1 second (FEV_1) over time in the safety population. The asterisk indicates $P < .05$ vs placebo.

DISCUSSION

The results of the present study demonstrate that once-daily treatment with indacaterol, 400 and 800 μg, is associated with a good overall safety and tolerability profile. These results provide evidence that indacaterol was well tolerated in a relevant clinical setting. Previous studies[8–10] have also demonstrated that patients comply better with, and prefer, therapies requiring less frequent dosing; therefore, indacaterol as a once-daily bronchodilator could represent an improvement over existing therapies.

The AEs resulting from systemic exposure to β_2-agonists include cardiovascular effects, such as tachycardia[2]; tremor and hypokalemia, mediated by skeletal muscle β_2-adrenoceptors[11,12]; and glycogenolysis and subsequent increases in blood glucose levels.[13] High doses of β_2-agonists have been reported to be associated with increases in blood glucose, decreases in serum potassium level, and AEs, such as tachycardia, tremor, and headache.[1–4]

In the present study, however, there was little evidence of drug-related hypokalemia with either dose of indacaterol, and although mean blood glucose levels were slightly higher in indacaterol-treated patients than in patients receiving placebo, these changes were well within expectations for the effects of a β_2-agonist. Few indacaterol-treated patients had serum potassium or blood glucose levels outside the normal reference range. In addition, there was a trend to a lesser effect on these variables by 4 weeks, compared with earlier time points, in keeping with previous observations with long-acting β_2-agonists.[14,15] The modest increase in mean pulse rate with the higher dose of indacaterol was also in line with expectations for an intervention of this type. Blood pressure readings in the indacaterol groups did not suggest any drug-related trends or major differences vs placebo. As expected for a β_2-agonist, there was some indication of a trend for mean QTc prolongation with increasing exposure. However, only 1 patient in the indacaterol, 800 μg, group exhibited a QTc (Fridericia) increase of greater than 60 milliseconds. Of the 2 formulas, the Fridericia formula has been shown to be superior to the Bazett formula when calculating QTc interval over a range of heart rates.[16] More important, few patients receiving indacaterol reported headache or tremor, AEs characteristic of β_2-agonists, and these were all mild apart from 1 case of moderate tremor.

Although cough was the most frequently reported AE, most episodes were mild and usually occurred after the first dose only. The episodes rarely continued beyond the day of the visit and only in 1 case (moderate) led to discontinuation of treatment. More important, the cough was not associated with bronchospasm.

The safety and tolerability of indacaterol demonstrated in the present study are consistent with previous studies[17,18] in patients with asthma receiving indacaterol doses up to 600 μg/d for 28 days or single doses up to 2,000 μg.

Although the present study was not primarily designed to evaluate efficacy, indacaterol improved FEV_1 relative to placebo at all postdose time points. The 24-hour duration of action of

indacaterol was demonstrated by the significantly higher predose FEV_1 values (approximately 24 hours after the previous dose), compared with placebo, at 14 and 28 days. There was no evidence of tolerance to the bronchodilator effects of indacaterol developing across 28 days, because all postbaseline results for indacaterol showed statistical significance over placebo and all postdose values were of a similar magnitude. These findings are consistent with the results of clinical studies[5,6,19,20] in patients with asthma and patients with COPD and support a once-daily dosing regimen. Interestingly, whereas some of the key safety variables (blood glucose level, serum potassium level, pulse rate, blood pressure, and QTc interval) were affected at 60 minutes after dosing, no statistically significant differences were observed between indacaterol and placebo in any of these variables approximately 24 hours after dosing (before dosing on days 14 and 28). It seems that the 24-hour bronchodilator action of indacaterol is not accompanied by a similarly prolonged effect on key safety variables.

In conclusion, the results of this study confirm that once-daily indacaterol has a good overall safety profile and is well tolerated and support the 24-hour bronchodilator efficacy of indacaterol observed in previous studies.

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Requests for reprints should be addressed to:
William H. Yang, MD
Allergy and Asthma Research Centre
707–1081 Carling Ave
Ottawa, ON K1Y 4G2, Canada
E-mail: wyang@yangmedicine.com