Efficacy and Tolerability of Indacaterol 75 μg Once Daily in Patients Aged ≥40 Years With Chronic Obstructive Pulmonary Disease: Results From 2 Double-Blind, Placebo-Controlled 12-Week Studies

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ABSTRACT

Background: Indacaterol is the first once-daily, long-acting, inhaled β_2-agonist bronchodilator for maintenance treatment of chronic obstructive pulmonary disease (COPD). Two studies (previously reported in a Congress abstract) were performed in 2010 to provide efficacy and tolerability data to support the application for approval in the United States of indacaterol 75 μg once daily, a dose lower than that previously investigated in most studies.

Objective: The primary objective was to evaluate the efficacy of indacaterol 75 μg once daily in terms of 24-hour post-dose ("trough") forced expiratory volume in the first second of respiration (FEV_1) compared with placebo after 12 weeks of treatment.

Methods: Patients with moderate to severe COPD were randomized to receive double-blind treatment with indacaterol 75 μg once daily (n = 163 and 159) or placebo (n = 160 and 159) for 12 weeks. In addition to trough FEV_1 after 12 weeks, rescue albuterol use, health status (St. George's Respiratory Questionnaire [SGRQ]), and tolerability were evaluated. Clinically relevant differences between active and placebo treatments were defined as ≥120 mL for trough FEV_1 and a decrease of ≥4 units in SGRQ total score.

Results: Of patients enrolled in the 2 studies, 54% were men, and 90% and 94% were white, with mean age 64 and 61 years. Mean duration of COPD was 7 years; smoking history was 52 pack-years; and 45% and 37% of patients were receiving inhaled corticosteroid therapy. At week 12, indacaterol demonstrated clinically relevant bronchodilator efficacy, increasing trough FEV_1 by ≥120 mL versus placebo ($P < 0.001$), with significant bronchodilation maintained at all time points from 5 minutes to 24 hours post-dose. Over 12 weeks, relative to placebo, in patients receiving indacaterol therapy, rescue albuterol use was reduced by 1.2 and 0.7 puffs per day ($P < 0.01$), and the percentage of rescue-free days was increased by 13.7 and 8.4 ($P < 0.01$). At week 12, the SGRQ total score differed in the indacaterol group versus the placebo group by −3.8 and −3.6, respectively ($P \leq 0.01$). Adverse events were reported for 49% and 45% of patients receiving indacaterol therapy, and for 46% and 41% receiving placebo.

Conclusions: Compared with placebo, indacaterol 75 μg once daily provided statistically significant and clinically relevant 24-hour bronchodilation and was well tolerated. In patients receiving indacaterol, the reduction in rescue albuterol use was statistically significant. Changes in health status also were statistically significant compared with placebo, although the differences of 3.6 and 3.8 units were below the predefined 4-unit level of clinical relevance. The results of these studies suggest that indacaterol 75 μg once daily is an effective maintenance treatment in patients with moderate to severe COPD. ClinicalTrials.gov identifiers: NCT01072448 and NCT01068600. (*Clin Ther.* 2011;33:1974–1984)

The study results were presented as a poster at the American Thoracic Society Annual Meeting, May 13–18, 2011, Denver, Colorado, and are also posted at www.novctrd.com.

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Key words: bronchodilator, chronic obstructive pulmonary disease, indacaterol.

INTRODUCTION

According to international disease management guidelines, bronchodilator medication is central to symptom management in chronic obstructive pulmonary disease (COPD), and regular treatment with one or more long-acting bronchodilators is recommended in patients with moderate and more severe COPD.[1]

Indacaterol is the first long-acting β_2-agonist bronchodilator providing 24-hour bronchodilation with once-daily dosing in patients with moderate to severe COPD. The efficacy and tolerability of indacaterol in COPD have been previously evaluated in placebo-controlled studies of 3- to 12-months' duration using treatment with once-daily doses of 150 and 300 μg,[2–6] which are the doses approved for use in countries outside the United States. A 75-μg once-daily dose has been approved in the United States for long-term maintenance treatment in patients with COPD.

Two identically designed placebo-controlled clinical studies have been conducted to investigate the efficacy and tolerability of a 75-μg once-daily dose of indacaterol given for 12 weeks. Using results from both of these studies, we report herein the bronchodilator efficacy and tolerability of indacaterol 75 μg once daily.

PATIENTS AND METHODS

Study Design

The 2 studies were randomized, double-blind, placebo-controlled studies of similar design. A 2-week run-in period during which baseline data were collected was followed by a 12-week treatment period during which efficacy and tolerability variables were measured. Both were multicenter studies conducted in the United States in respiratory outpatient clinics, physician's offices, and clinical research centers. Institutional review board approval was obtained at each participating center.

Patients

Patients with moderate to severe COPD (defined at that time using Global Initiative for Chronic Obstructive Lung Disease 2008 criteria[7]), aged ≥40 years and with a smoking history of ≥10 pack-years were enrolled in the studies. Their forced expiratory volume in the first second of respiration (FEV_1) at screening was <80% and ≥30% of predicted normal and FEV_1/forced vital capacity (FVC) was <70%, both measured after use of a bronchodilator (albuterol 90 μg x 4 puffs). Patients gave written informed consent before the start of any study-related procedures. Patients were not enrolled if they had a history of asthma or a recent (6 weeks before screening) exacerbation of COPD, or respiratory tract infection. Patients were recruited at routine physician visits. They were reimbursed for out-of-pocket expenses, but were not charged for any assessments or medications tested.

Treatments

Patients received indacaterol 75 μg once daily therapy via single-dose dry powder inhaler or matching placebo, administered at the same time each morning (8:00–11:00 AM). Albuterol was available for rescue use throughout the studies to relieve breakthrough symptoms. Any patient receiving inhaled corticosteroids (ICS) at baseline continued this therapy (or the ICS component alone if administered as a fixed combination with a bronchodilator) at an equivalent dose and regimen for the duration of the studies. The use of other bronchodilators was stopped before screening spirometry, with appropriate washouts (long-acting anticholinergics, 7 days; short-acting anticholinergics, 8 hours; long-acting β_2-agonists, 48 hours; short-acting β_2-agonists other than study rescue medication, 6 hours; and xanthines, 7 days).

Objectives, Assessments, and Outcome Measures

The primary objective was to evaluate the efficacy of indacaterol compared with placebo in terms of its effect on "trough" FEV_1 (mean of measurements made at 23 h 10 min and 23 h 45 min post-dose) after 12 weeks. A difference in trough FEV_1 of 120 mL between indacaterol and placebo was predefined as clinically relevant and is the midpoint of the 100- to 140-mL range suggested by a joint American Thoracic Society and European Respiratory Society task force as the minimal important difference.[8] During the studies, spirometry was performed according to recognized standards[9] and, insofar as possible, by the same personnel and using the same equipment for each patient. All study sites were supplied with the same make and model of spirometer (Vitalograph Ltd., Buckingham, England), and all persons performing spirometry were certified in the use of the supplied equipment before

use. The highest values of 3 acceptable maneuvers were recorded for each assessment. All spirometry assessments were reviewed centrally to ensure that procedures met the standards for acceptability and repeatability. Biomedical Systems (St. Louis, Mo) was responsible for spirometry assessments.

Secondary efficacy end points included other spirometric values (FEV_1 at successive time points post-dose and FVC), use of rescue albuterol recorded daily by patients, and health status assessed using the St. George's Respiratory Questionnaire (SGRQ), with a decrease of 4 units in total SGRQ score relative to placebo or baseline as the minimum clinically important difference. The total SGRQ score is a composite of scores in the symptoms, impacts, and activities domains.[10,11] Patients completed the questionnaires at study visits, and could ask questions but were undisturbed by study personnel. Questionnaires were completed before any other assessments to avoid influencing the responses. Culturally validated translations were licensed from the developer of the SGRQ instrument.

The studies also measured the effect of treatment on various clinical outcomes, which will be reported elsewhere, including dyspnea (as transition dyspnea index, the key secondary end point[12,13]) and other secondary or exploratory end points (SGRQ change from baseline scores and domain scores, percentages of patients achieving a clinically important change in transition dyspnea index and SGRQ scores, diary card symptom scores, and number of exacerbations). Exploratory analyses of trough FEV_1 after 12 weeks were conducted in patient subgroups classified according to smoking history, age, sex, race/ethnicity, COPD severity, use of ICS at baseline, body mass index, waist–hip ratio, and reversibility to albuterol at baseline. The tolerability evaluation included adverse events, vital signs (pulse and blood pressure), blood chemistry (blood glucose and serum potassium concentrations), and ECG (QTc interval, corrected using Fridericia's formula) at any time after baseline (measured pre-dose and 1 hour post-dose at day 1 and weeks 4, 8, and 12). Laboratory samples were processed centrally by Quintiles Laboratories Ltd. (Marietta, Georgia) and sent electronically to the studies' sponsor. ECG assessments were processed centrally by eResearch Technology Ltd. (Orton Southgate, Peterborough, England). All analyses were preplanned.

Randomization and Blinding

Treatment assignment was unbiased and concealed from patients and investigating staff. After confirming a patient's eligibility, investigators contacted an interactive voice response/web system that automatically and randomly assigned the patient number to a randomization number. These randomization numbers (not communicated to the caller) were linked to the treatment arms, which in turn were linked to medication numbers. A separate validated system automatically and randomly assigned medication numbers to study drug packs containing each of the study drugs. Randomization (1:1) was stratified according to smoking status (current or ex-smoker) and ICS use (yes or no).

The studies were double-blind, with patients, investigating staff, persons performing the assessments, and data analysts remaining blind to treatment from randomization to study completion (unless a patient emergency arose). Study drugs were identical in packaging, labeling, administration schedule, appearance, taste, and odor.

Statistical Methods

Two populations were defined for analysis. The full analysis population, used for analysis of all efficacy variables, comprised all randomized patients who received at least 1 dose of study drug, analyzed according to the treatment to which they were randomized. The safety population comprised all patients who received at least 1 dose of study drug, analyzed according to the treatment received.

The primary variable was analyzed using a mixed-model ANCOVA[14] containing treatment as a fixed effect, and baseline FEV_1, and FEV_1 before and after albuterol inhalation and before and after ipratropium inhalation (assessed at screening) as covariates. The model also included baseline smoking status, ICS use, and country as fixed effects, and center as a random effect. Missing values were imputed using the last observation carried forward (provided it was from week 4 or later). Similar models were used to analyze secondary and exploratory efficacy end points, with appropriate baseline measurements as covariates. No adjustment was made for multiplicity for the secondary analyses reported herein.

Results are given as least squares mean with SE for group mean values and 95% CI for differences between treatments. Descriptive summary data are also

Table I. Patient flow through studies. Values are given as number of patients (%).

Variable	Study 1		Study 2	
	Indacaterol Group	Placebo Group	Indacaterol Group	Placebo Group
Screened	755		597	
Randomized	323		318	
Allocated to treatment	163	160	159	159
Treated	163	160	159	159
Completed the study	144 (88.3)	130 (81.3)	148 (93.1)	142 (89.3)
Discontinued the study	19 (11.7)	30 (18.8)	11 (6.9)	17 (10.7)
Reason for discontinuation				
Adverse event	9	10	3	3
Withdrawal of consent	4	9	5	6
Protocol deviation	3	4	1	1
Unsatisfactory therapeutic effect	1	3	0	4
Loss to follow-up	1	1	1	2
Abnormal test result(s)	1	0	0	0
Abnormal laboratory value(s)	0	1	1	0
Administration problems	0	0	0	1
Death	0	2	0	0
Analyzed for efficacy	163	160	159	158

presented. Adverse events and other tolerability data are summarized descriptively.

The calculation of sample size (N = 326 randomized patients; n = 163 patients per treatment group) was based on the key secondary end point. This sample size gave >99% power to detect a difference of 120 mL for the primary objective, assuming an SD of 225 mL and a 2-sided significance level of 95%.

Statistical analysis was performed by DATAMAP GmbH (Freiburg, Germany).

RESULTS

The studies were conducted between January and July 2010. Results are given in the order Study 1 and Study 2.

Patients

Patient disposition is given in Table I. The studies and the treatment groups were generally well matched (Table II). There were, however, some small imbalances between and within studies. The proportion of patients with severe COPD was 43% in Study 1 and 38% in Study 2, and the proportion of ICS users was 45% in Study 1 and 37% in Study 2. The proportion of current smokers was 44% in Study 1 and 59% in Study 2. There were differences in FEV_1 before and after albuterol inhalation of approximately 40 to 50 mL between the placebo and indacaterol groups at baseline. In Study 2, the proportion of patients with moderate COPD was 69% in the indacaterol group and 55% in the placebo group.

Spirometry

In both studies, the results for the primary end point demonstrated the superiority of indacaterol over placebo, with differences in trough FEV_1 at week 12 of 120 mL (95% CI, 80–150 mL) and 140 mL (95% CI, 100–180 mL) (both, $P < 0.001$) (Figure 1). Results of the exploratory analyses of trough FEV_1 at week 12 in the subgroups are given in Table III. Indacaterol resulted in similar improvements in trough FEV_1 in patients with or without 12% albuterol reversibility, and increased trough FEV_1 by ≥100 mL more than with placebo in most of the patient subgroups assessed (Table III). Nearly all

Table II. Demographic and baseline characteristics. Data given as mean (SD) unless otherwise indicated.

	Study 1			Study 2		
Variable	Indacaterol Group (n = 163)	Placebo Group (n = 160)	All Patients (N = 323)	Indacaterol Group (n = 159)	Placebo Group (n = 159)	All Patients (N = 318)
Age, y	64 (8.3)	64 (9.4)	64 (8.9)	61 (9.8)	62 (9.9)	61 (9.8)
Sex, male/female, %	55/45	54/46	54/46	52/48	56/44	54/46
Race, %						
White	89	91	90	95	93	94
Black	6	6	6	4	6	5
Asian	3	2	3	–	–	–
Other	2	1	1	1	2	1
Duration of COPD, y	7 (6.3)	7 (6.4)	7 (6.4)	7 (6.1)	7 (6.1)	7 (6.1)
Severity of COPD, (GOLD 2008[7]), %						
Moderate	59	56	57	69	55	62
Severe or very severe	41	44	43	31	45	38
ICS use, yes/no, %	43/57	48/52	45/55	40/60	35/65	37/63
Ex-smoker/smoker, %	56/44	56/44	56/44	42/58	40/60	41/59
Smoking history, pack-years	53 (26.8)	51 (24.8)	52 (25.8)	52 (28.1)	52 (28.4)	52 (28.2)
FEV_1 % predicted, post-albuterol, %	54 (12.8)	53 (13.4)	54 (13.1)	56 (12.8)	54 (13.6)	55 (13.2)
FEV_1/FVC, post-albuterol, %	53 (9.5)	52 (10.6)	52 (10.1)	52 (10.3)	53 (9.9)	53 (10.1)
FEV_1, pre-albuterol, L	1.32 (0.463)	1.28 (0.500)	1.30 (0.481)	1.38 (0.533)	1.34 (0.525)	1.36 (0.529)
FEV_1, post-albuterol, L	1.49 (0.481)	1.46 (0.497)	1.47 (0.489)	1.59 (0.559)	1.52 (0.543)	1.56 (0.551)
FEV_1 reversibility, pre-/post-albuterol, %	15 (12.7)	17 (13.9)	16 (13.3)	18 (16.7)	16 (13.9)	17 (15.3)
Use of rescue albuterol, puffs/day*	4.6 (4.36)	4.7 (4.10)	–	4.7 (4.27)	4.5 (4.17)	–
Days without albuterol use,* %	24.9 (37.04)	19.1 (32.91)	–	23.2 (34.70)	23.3 (33.52)	–
Baseline SGRQ score	48.4 (18.60)(n=163)	49.7 (16.90)(n=160)	–	51.3 (18.36)(n=158)	50.3 (18.31)(n=157)	–

COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; FEV_1 = forced expiratory volume in the first second of respiration; FVC = forced vital capacity; GOLD = Global Initiative for Chronic Obstructive Lung Disease; SGRQ = St. George's Respiratory Questionnaire.
*Recorded during 2-week run-in period for patients included in efficacy analysis of these variables.

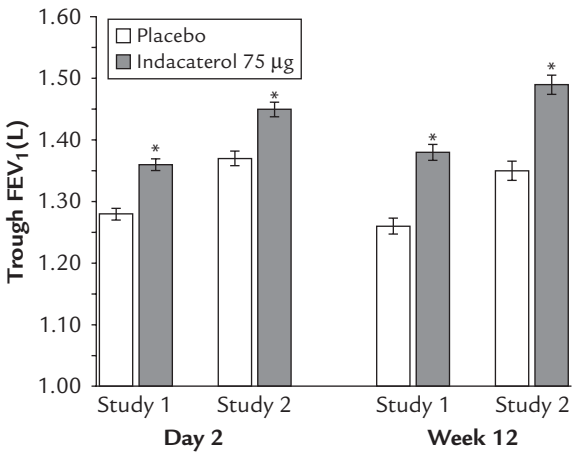

Figure 1. Trough forced expiratory volume in the first second of respiration (FEV_1) after the first dose (assessed pre-dose on the morning of day 2) and after 12 weeks of treatment (primary end point). Data represent least squares mean (SE). *$P <$ 0.001 versus placebo.

subgroups experienced a statistically significant benefit with indacaterol.

Indacaterol 75 μg had a rapid onset of effect on the first day of dosing. At 5 minutes post-dose on day 1, FEV_1 was 90 mL (95% CI, 70–100 mL) and 100 mL (95% CI, 80–120 mL) greater with indacaterol than with placebo (both, $P < 0.001$). Trough FEV_1 after the first dose of treatment was 80 mL (95% CI, 60–100 mL) and 80 mL (95% CI, 50–110 mL) greater with indacaterol than with placebo (both, $P < 0.001$) (**Figure 1**).

Unadjusted mean data for trough FEV_1 at week 12 showed an increase from baseline of 110 mL and 150 mL (10.4% and 13.0%) with indacaterol, and a change of 0 mL (−0.9%) for both studies with placebo.

The time course of the effect of indacaterol on FEV_1 after 12 weeks of dosing is shown in **Figure 2**. The curve shows that indacaterol resulted in a peak increase in FEV_1 over placebo of 170 to 190 mL at around 1 to 2 hours after dosing. Differences in FEV_1 between indacaterol and placebo were ≥110 mL at all time points assessed ($P < 0.001$). Similarly, FVC was increased with indacaterol compared with placebo at the same time points post-dose after 12 weeks of treatment ($P < 0.001$ for all indacaterol–placebo differences) (data not shown).

Use of Rescue Albuterol

Over the 12 weeks of treatment, in each of the studies, patients treated with indacaterol recorded a greater decrease from baseline in the use of rescue albuterol by 1.2 puffs per day and 0.7 puffs per day ($P < 0.001$), and used albuterol on 13.7% to 8.4% fewer days ($P < 0.01$), compared with those receiving placebo.

Health Status

Health status measured using the SGRQ total score changed with indacaterol by a statistically significant difference versus placebo at week 12 in both studies, with differences of −3.8 and −3.6 ($P \leq 0.01$) (**Figure 3**). The least squares mean total SGRQ scores at week 12 in the indacaterol and placebo groups were 43.4 and 47.2 in Study 1 and 45.9 and 49.5 in Study 2. The change at week 4 was statistically significant versus placebo in Study 1 ($P < 0.01$).

Tolerability

Adverse events were reported by 49% and 45% of patients in the indacaterol groups and by 46% and 41% in the placebo groups (**Table IV**). The most common event in each treatment group in both studies was COPD worsening, which occurred at a frequency of 9% with indacaterol therapy and 12% and 8% with placebo therapy. In the indacaterol treatment groups, headache occurred in 6% and 3% of patients, and nasopharyngitis in 5% and 6% of patients. In most cases, severity was mild or moderate (headache, 13/14; nasopharyngitis, 17/18). The frequency of cough as an adverse event with indacaterol therapy and placebo was 9.4% versus 3.1% in Study 2, and 4.3% versus 4.4% in Study 1. Tachycardia, tremor, and muscle spasms, events typically associated with β_2-adrenoceptor stimulation, occurred infrequently (<2%) with indacaterol therapy. No patients reported tremor, there was only 1 case of (mild) tachycardia. Most cases of muscle spasms were mild (4 mild cases and 1 moderate case with indacaterol; 1 mild with placebo).

Adverse events leading to withdrawal occurred in 8 and 3 patients in the indacaterol treatment groups, and in 11 and 3 patients in the placebo group (these numbers differ from those given in **Table I**, which lists primary reasons for withdrawal, whereas the adverse events described here were not necessarily

Table III. Indacaterol–placebo differences in effect on trough FEV_1 at 12 weeks in patient subgroups.* Data given as least squares mean and 95% CI.

	Study 1		Study 2	
Variable	No. of Patients (Indacaterol/Placebo)	Treatment Difference, mL	No. of Patients (Indacaterol/Placebo)	Treatment Difference, mL
Age, y				
<65	79/79	90 (40 to 140)	87/90	130 (70 to 180)
≥65	70/69	150 (90 to 200)	58/60	160 (100 to 230)
Sex				
Male	82/80	130 (80 to 180)	77/85	170 (110 to 230)
Female	67/68	110 (50 to 160)	68/65	110 (50 to 170)
Smoking history				
Ex-smoker	84/81	130 (80 to 180)	63/61	140 (80 to 210)
Current smoker	65/67	100 (50 to 160)	82/89	140 (90 to 200)
COPD severity (GOLD 2008[7])				
Moderate	88/80	140 (90 to 190)	103/84	160 (100 to 210)
Severe or very severe	61/68	90 (40 to 150)	42/66	130 (50 to 200)
Use of ICS				
No	86/77	140 (90 to 190)	90/97	180 (130 to 230)
Yes	63/71	100 (40 to 150)	55/53	70 (10 to 140)
Albuterol reversibility, %				
≤12	63/60	120 (60 to 180)	63/65	120 (60 to 190)
>12	86/88	120 (70 to 160)	82/85	160 (100 to 210)
BMI, kg/m^2				
Males, ≤30	55/58	140 (80 to 200)	59/49	180 (110 to 250)
Males, >30	27/22	90 (0 to 190)	18/36	170 (70 to 280)
Females, ≤30	42/48	120 (60 to 190)	42/45	130 (50 to 200)
Females, >30	25/20	80 (−10 to 180)	26/20	90 (−20 to 190)
Waist–hip ratio				
Males, <1.00	47/52	80 (20 to 150)	51/48	150 (80 to 230)
Males, ≥1.00	35/28	190 (110 to 270)	26/37	200 (110 to 290)
Females, <0.85	25/20	110 (10 to 200)	20/18	150 (30 to 270)
Females, ≥0.85	42/48	110 (40, 180)	48/45	100 (20 to 170)

BMI = body mass index; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in the first second of respiration; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroids.

*Evaluation of the Race/ethnicity subgroups not shown because of low patient numbers in the categories "Black," "Asian," and "Other."

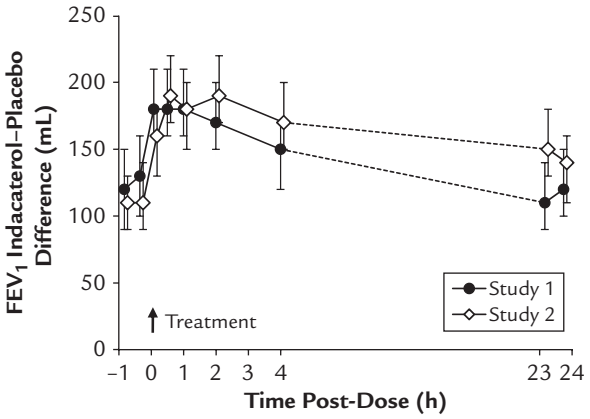

Figure 2. Indacaterol–placebo differences in forced expiratory volume in the first second of respiration (FEV_1) at post-dose time points (5 min to 4 h, 23 h 10 min, and 23 h 45 min) at week 12. Data represent least squares means and 95% CIs. All indacaterol–placebo differences were significant at $P < 0.001$.

the primary reason for withdrawal). The adverse events leading to withdrawal from indacaterol therapy were COPD worsening in 5 patients, dyspnea in 2, and sinusitis, viral upper respiratory tract infection, bronchitis, hemoptysis, osteoarthritis, mycosis fungoides, headache, and cerebrovascular accident in 1 patient each. The adverse events leading to placebo withdrawal were COPD worsening in 5 patients, pneumonia in 2, and sinusitis, bacterial upper respiratory tract infection, dyspnea, pulmonary mass, hemoptysis, lymphadenopathy, myocardial infarction, somnolence, aortic aneurysm rupture, hypotension, and limb-crushing injury in 1 patient each. Of these, the events considered by the investigators to be related to indacaterol therapy were moderate dyspnea and severe headache in 1 patient each, and with placebo were mild COPD worsening and moderate hypotension in 1 patient each.

Two patients in the placebo group died during Study 1, of myocardial infarction and aortic aneurysm, respectively. Serious adverse events were reported in 2.5% of indacaterol-treated patients (in both studies) and in 5.6% and 2.5% of patients given placebo. None of these events was suspected to be related to study treatment.

Results for vital signs and QTc interval are given in Table V. Notable values for pulse, blood pressure, and QTc interval were uncommon in both the indacaterol-treatment and placebo groups.

DISCUSSION

Treatment with indacaterol 75 μg once daily provided effective 24-hour bronchodilation. The effects of indacaterol on trough FEV_1 after 12 weeks (the primary end point of the studies) were superior to placebo by a statistically significant margin of 120 and 140 mL. These values for trough FEV_1 are within the range of 100 to 140 mL generally regarded as clinically relevant.[8] Measured 24 hours after the previous day's dosing, trough FEV_1 is a rigorous assessment of bronchodilator efficacy. Furthermore, the statistically and clinically significant effect of indacaterol at 24 hours demonstrates its sustained efficacy through to early morning, when symptoms of COPD tend to be most troublesome.[15,16]

The bronchodilator efficacy of indacaterol was generally maintained across the subgroups of patients evaluated in these predefined exploratory evaluations in both studies. There was some variation among subgroups in the magnitude of the difference versus placebo, with the smaller subgroups tending to show the most variable effects.

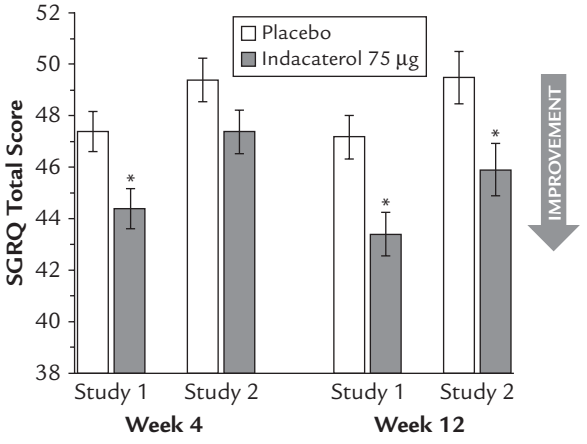

Figure 3. St. George's Respiratory Questionnaire (SGRQ) total score at weeks 4 and 12. Data represent least squares mean (SE). Week 4 data are without imputation. *$P \leq 0.01$ versus placebo.

Table IV. Overall and most commonly occurring adverse events (≥5% in either indacaterol treatment group). Data given as number (% of patients).

	Study 1		Study 2	
Variable	Indacaterol Group (n = 163)	Placebo Group (n = 160)	Indacaterol Group (n = 159)	Placebo Group (n = 159)
Any adverse event	80 (49.1)	74 (46.3)	71 (44.7)	65 (40.9)
COPD worsening	14 (8.6)	19 (11.9)	14 (8.8)	13 (8.2)
Headache	9 (5.5)	6 (3.8)	5 (3.1)	2 (1.3)
Urinary tract infection	9 (5.5)	2 (1.3)	1 (0.6)	4 (2.5)
Nasopharyngitis	8 (4.9)	2 (1.3)	10 (6.3)	3 (1.9)
Cough	7 (4.3)	7 (4.4)	15 (9.4)	5 (3.1)

COPD = chronic obstructive pulmonary disease.

The statistically significant bronchodilator effect of indacaterol on trough FEV_1 relative to placebo was observed as early as day 1 of treatment. Compared with placebo, indacaterol also demonstrated a statistically significant increase in FEV_1 at 5 minutes postdose on day 1.

The bronchodilator efficacy of indacaterol, compared with placebo, was also reflected in statistically significant increases in FVC. Improvement in FVC may be consistent with recruitment of additional lung volume, which may reflect reduced air trapping.

The level of use of a short-acting bronchodilator as rescue medication for treatment of breakthrough symptoms reflects the severity and/or frequency of COPD symptoms[15] and, thus, provides an indication of how well indacaterol therapy controls these symptoms. Compared with placebo, significant reductions in the use of rescue albuterol were observed

Table V. Number (%) of patients with notable values for pulse rate, blood pressure, and QTc interval (Fridericia's).

	Study 1		Study 2	
Variable	Indacaterol Group	Placebo Group	Indacaterol Group	Placebo Group
Pulse rate high*	0	0	0	1 (0.6)
Systolic blood pressure high†	0	1 (0.6)	2 (1.3)	1 (0.6)
Diastolic blood pressure high‡	1 (0.6)	3 (1.9)	5 (3.1)	1 (0.6)
QTc interval				
Absolute value >450/470 msec (males/females)	7 (4.3)	3 (1.9)	3 (1.9)	7 (4.4)
Absolute value >500 msec	0	0	0	0
Increase from baseline 30–60 msec	8 (4.9)	6 (3.8)	15 (9.4)	12 (7.5)
Increase from baseline >60 msec	0	0	0	0

*>130 beats/min, or ≥120 beats/min and ≥15 beats/min increase from baseline.
†>200 mm Hg, or ≥180 mm Hg and ≥20 mm Hg increase from baseline.
‡>115 mm Hg, or ≥105 mm Hg and ≥15 mm Hg increase from baseline.

with indacaterol therapy in both studies: patients receiving indacaterol reported a reduction of approximately 1 puff per day and an increase of 8 to 14 units in the percentage of days without recourse to albuterol.

Some small apparent differences in efficacy were observed between the 2 studies. Indacaterol therapy resulted in a slightly improved magnitude of FEV_1 effect in Study 2, although most CIs overlapped and the small differences were within the range of variability. Compared with patients enrolled in Study 1, those in Study 2 were somewhat younger (61 versus 64 years) and more had moderate COPD (59% versus 44%). Thus, it is possible that the Study 2 population had somewhat larger FEV_1 variability, as is typical in patients with moderate COPD compared with those with severe COPD. Such heterogeneity between the patient populations, as well as variability in the measurement of FEV_1 itself, in the 2 studies may have contributed to the differences.

Health status is often compromised in patients with COPD and, perhaps because of the multiple disabilities involved in COPD, provides important and complementary information in addition to spirometric assessments.[17] Health status is useful as a marker of disease severity and progression and of treatment efficacy.[18–22] The SGRQ instrument used in these studies measured disease-specific health status in terms of symptoms, impact of disease, and physical activity. Compared with placebo in the 2 studies, treatment with indacaterol 75 μg once daily provided consistent health status changes of 3.8 and 3.6 in SGRQ total scores, although these did not meet the 4-unit threshold for clinical significance.[11]

Treatment with indacaterol 75 μg once daily was well tolerated in both studies. Systemic effects of β_2-adrenoceptor stimulation were infrequent, without apparent differences from the placebo groups. Overall, the frequency of adverse events with indacaterol and placebo showed that indacaterol was well tolerated. For a treatment intended for regular long-term use in a population that includes a large percentage of patients who are elderly or have significant comorbid conditions, these findings are pertinent. Elsewhere, tolerability data for indacaterol in patients with COPD are reported for once-daily doses up to 600 μg[5,23] and with treatment over 1 year.[5,6]]

CONCLUSIONS

In this largely white clinical trial population of 641 patients aged ≥40 years with moderate to severe COPD, indacaterol 75 μg once daily provided statistically significant and clinically relevant 24-hour bronchodilation. Patients receiving indacaterol reported statistically significant reductions in rescue albuterol use. The changes in health status with indacaterol as measured using the SGRQ were statistically significant compared with placebo, although the differences of 3.6 and 3.8 units were below the predefined 4-unit level of clinical relevance. Indacaterol was well tolerated. The results of these studies suggest that indacaterol 75 μg once daily is an effective maintenance treatment in patients with moderate to severe COPD.

CONFLICTS OF INTEREST

Dr. Kerwin has received consulting fees from Dey Laboratories, Inc.; GlaxoSmithKline PLC, MAP Pharmaceuticals, Inc. (AstraZeneca PLC), and Sepracor, Inc. (Sunovion Pharmaceuticals); and speaking fees from AstraZeneca, GlaxoSmithKline, Merck & Co, Inc., and Teva Pharmaceutical Industries Ltd. Dr. Gotfried has received research grants from Novartis, GlaxoSmithKline, Boehringer Ingelheim Pharmaceuticals, Inc., Forest Laboratories, Inc., Pearl Therapeutics, Inc., and Teva Pharmaceutical Industries, and is a speakers bureau member for GlaxoSmithKline, Merck, Dey Laboratories, and Pfizer, Inc. Drs. Lawrence, Lassen, and Kramer are employees of Novartis, the sponsor of the studies, and have share options or shares in Novartis.

The studies were funded by Novartis, the manufacturer of indacaterol. Novartis was responsible for the design of the studies and analysis of the data and, in collaboration with the authors, was involved in interpretation and presentation of the data for this article. Data were recorded at participating clinical centers, and were maintained by Novartis.

Authorship was defined by the International Committee of Medical Journal Editors criteria for authorship (www.icmje.org). Drs. Lawrence, Lassen, and Kramer designed the studies; Drs. Kerwin and Gotfried contributed substantially to acquisition of data as investigators in the respective studies; Dr. Lawrence analyzed the study data; and all authors were involved in interpretation of the data, critical review of the manuscript, and approval of the final version for publication.

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