

# Bronchodilator efficacy and safety of indacaterol 150 µg once daily in patients with COPD: an analysis of pooled data

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**Background:** Indacaterol is an inhaled, once-daily long-acting  $\beta_2$ -agonist bronchodilator for regular use in patients with chronic obstructive pulmonary disease (COPD). As indacaterol is the first once-daily  $\beta_2$ -agonist to be developed, it is relevant to evaluate its bronchodilator efficacy, safety, and tolerability.

**Methods:** Data were pooled from three randomized, double-blind, clinical studies in patients with moderate-to-severe COPD treated with indacaterol 150 µg qd (n = 627) or placebo (n = 1021). Bronchodilator efficacy was assessed as trough (24-hour post-dose) forced expiratory volume in 1 second (FEV<sub>1</sub>) after 12 weeks (primary endpoint in individual studies) and FEV<sub>1</sub> measured serially post-dose. Rescue use of albuterol was monitored.

**Results:** At week 12, indacaterol increased trough FEV<sub>1</sub> by 160 mL compared with placebo ( $P < 0.001$ ), exceeding the 120 mL level prespecified as clinically important. FEV<sub>1</sub> during the first 12-hour post-dose at week 12 averaged 210 mL higher with indacaterol than with placebo ( $P < 0.001$ ). Patients receiving indacaterol recorded 53% of days without use of rescue albuterol, compared with 38% of days in the placebo group ( $P < 0.001$ ). Adverse events (mostly mild or moderate) were reported for 52% and 46% of patients receiving indacaterol and placebo, respectively, and serious adverse events for 4% and 5%. Worsening of COPD was the most frequent adverse event (10% indacaterol; 15% placebo). Indacaterol had little effect on pulse or blood pressure or measures of systemic  $\beta_2$ -adrenoceptor activity (blood glucose, serum potassium, and corrected QT interval).

**Conclusion:** Indacaterol was an effective bronchodilator and was well tolerated, with a good safety profile over 12 weeks of treatment. It should prove a useful treatment for patients with moderate-to-severe COPD.

**Keywords:** chronic obstructive pulmonary disease, tolerability, inhaled corticosteroids

## Introduction

Chronic obstructive pulmonary disease (COPD) is an obstructive pulmonary disease characterized by progressive resting and exertional dyspnea and is associated with major comorbidities.<sup>1</sup> In 2005, approximately 1 in 20 deaths in the United States was caused by COPD,<sup>2</sup> and COPD was reported to affect an estimated 6% of US adults in 2008,<sup>3</sup> with higher prevalence figures in higher-risk groups such as veterans (9%) and Medicare beneficiaries (11%).<sup>4,5</sup> However, COPD is often underdiagnosed and is relatively undertreated compared with other, less morbid, chronic conditions such as hypertension and hypercholesterolemia.<sup>6</sup>

According to current guidelines for the treatment of stable COPD, the regular use of long-acting bronchodilators is recommended for initial maintenance treatment of COPD.<sup>1</sup>

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These agents are either  $\beta_2$ -agonists administered twice daily (formoterol and salmeterol) or the once-daily anticholinergic, tiotropium. In the management of stable COPD, bronchodilator treatment improves forced expiratory volume in 1 second ( $FEV_1$ ) with a concomitant reduction in hyperinflation, and reduction in symptoms such as breathlessness (dyspnea).<sup>7</sup>

Indacaterol is a novel, inhaled, long-acting  $\beta_2$ -agonist providing 24-hour bronchodilation on once-daily dosing,<sup>8–10</sup> currently approved in many countries for the maintenance treatment of COPD. The purpose of this manuscript, using data pooled from the indacaterol clinical trial database, is to provide a comprehensive evaluation of the bronchodilator efficacy, safety, and tolerability of indacaterol 150  $\mu\text{g}$  compared with placebo in a large sample of patients with COPD. The 150  $\mu\text{g}$  dose was identified in the dose-ranging stage of a Phase II/III adaptive seamless design study as the lowest dose of indacaterol providing effective bronchodilation in COPD.<sup>11</sup> The data presented represent the results from the first 12 weeks of dosing in three registration studies with identical patient entry criteria. The 150  $\mu\text{g}$  dose of indacaterol was evaluated in two of the studies; only data from the placebo group in the third study (which assessed higher indacaterol doses) are included in the pooled dataset. All three studies are the subject of separate publications.<sup>8–10</sup>

## Methods

The study designs are described in detail in the individual publications.<sup>8–10</sup> All were randomized, double-blind, parallel-group comparisons of indacaterol and placebo prescribed once daily. One was a 12-week comparison of indacaterol 150  $\mu\text{g}$  and placebo;<sup>8</sup> one was a 6-month comparison of indacaterol 150  $\mu\text{g}$  and placebo (and indacaterol 300  $\mu\text{g}$  and tiotropium; not reported here)<sup>10</sup> and the third study, which contributed placebo data only to the present analysis, was a comparison of indacaterol 300 and 600  $\mu\text{g}$  qd, formoterol, and placebo.<sup>9</sup> Indacaterol 150  $\mu\text{g}$  and placebo were administered using identical single-dose dry-powder inhalers and were used daily each morning. All study protocols were approved by the independent ethics committee or institutional review board for each participating center. All patients provided written informed consent prior to participation.

The studies recruited patients aged  $\geq 40$  years with moderate-to-severe COPD and a smoking history of  $\geq 20$  pack-years. Patients had relatively stable COPD, and were excluded if they had a recent chest infection or had recently been hospitalized for a COPD exacerbation.

Other bronchodilator treatments were discontinued before the start of study treatment, apart from albuterol,

which patients could use as required. Patients were allowed to continue treatment with inhaled corticosteroids (ICS) during the study, providing they were using ICS at the time of screening; the dose and regimen were not altered for the duration of the study. Treatment with combination ICS and bronchodilators was replaced with the ICS component alone, at equivalent dose and regimen.

Spirometry was performed at screening, at baseline, and at regular clinic visits during the studies, according to recognized standards.<sup>12</sup> The primary efficacy outcome in each study was  $FEV_1$  measured at 'trough' (the mean of measurements taken at 23 hours and 10 minutes and 23 hours and 45 minutes post-dose) after 12 weeks of treatment. In each study, a difference between indacaterol and placebo of 120 mL in  $FEV_1$  was prespecified as a minimal clinically important difference. Spirometry was also performed at serial time points post-dose at clinic visits, including those at baseline and week 12. The patients' use of albuterol as rescue medication, recorded on daily diary cards, was a secondary efficacy outcome.

A secondary objective of the studies was to assess safety, including adverse events, electrocardiograms (ECGs) (measurement of corrected QT [QTc] interval), laboratory tests (measurement of blood glucose and serum potassium concentrations), and vital signs (blood pressure and pulse rate) measured at baseline and pre- and post-dose at week 12.

## Statistical methods

The methodology used for pooling the data was to include all available data from studies that were designed with identical or near-identical methods and patient entry criteria. Hence, data from the placebo treatment group of a study investigating higher doses of indacaterol (300 and 600  $\mu\text{g}$  qd)<sup>9</sup> were included in the pooled dataset. The primary endpoint, trough  $FEV_1$ , was analyzed using a mixed-model analysis of covariance (ANCOVA) with treatment as a fixed effect, and baseline  $FEV_1$  and  $FEV_1$  reversibility as covariates. Smoking status (current/ex-smoker), country, and study were included as fixed effects, and center nested within country as a random effect. Estimates of adjusted treatment effects and pairwise treatment differences from the ANCOVA are presented along with the associated 95% confidence intervals (CIs) and two-sided *P*-values. The percentage of days with no rescue use during the 12 weeks and the standardized area under the curve for  $FEV_1$  at week 12 (measured from 5 minutes to 11 hours and 45 minutes post-dose) were analyzed using the same mixed model, with the appropriate baseline measurement as covariates. No adjustment was made for multiple testing for the pooled analyses.

## Results

Table 1 shows the patients' demographic and clinical characteristics. Apart from a slightly higher proportion of men compared with women in the placebo group, the two treatment groups were well matched. Baseline prebronchodilator percent predicted FEV<sub>1</sub> was 49% in both treatment groups; post-bronchodilator (albuterol) values were also similar in the two groups (indacaterol 56%; placebo 55% predicted).

## Efficacy

### Spirometry

Trough FEV<sub>1</sub> (24 hours post-dose) was significantly higher with indacaterol compared with placebo both after the first dose and at week 12 (both  $P < 0.001$ ) (Figure 1). The difference of 160 mL at week 12 was one-third greater than the prespecified difference of minimal clinical importance (120 mL). After the first dose, trough FEV<sub>1</sub> was 100 mL greater with indacaterol than with placebo.

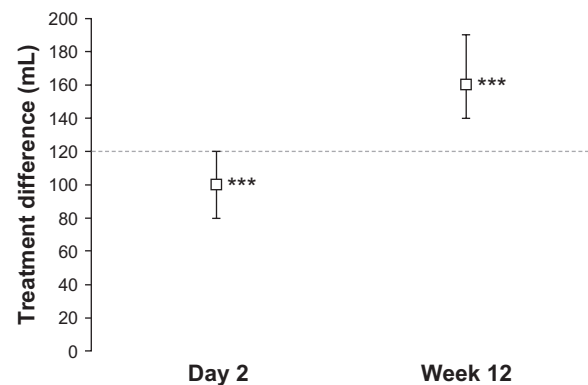
In terms of mean changes from baseline, the effects of indacaterol on trough FEV<sub>1</sub> equated to 130 mL (9.7%) after the first dose, and 150 mL (11.4%) at week 12 (Figure 2). Corresponding values with placebo treatment were 20 mL (1.5%) after the first dose and 10 mL (0.8%) at week 12.

**Table 1** Patient characteristics at baseline

	Indacaterol 150 µg N = 627	Placebo N = 1021
Age, years	63.2 (9.56)	63.6 (8.69)
Age ≥65 years, %	47	46
Sex, male/female, %	58/41	67/33
COPD severity, %		
Moderate or less	61	59
Severe or worse	39	41
Duration of COPD, years	6.8 (7.09)	6.8 (6.15)
ICS use, %	35	44
Smoking history		
Ex-/current smoker, %	53/47	55/45
Pack-years	50.0 (24.72)	50.6 (32.33)
FEV <sub>1</sub> pre-albuterol, L	1.33 (0.497)	1.35 (0.478)
FEV <sub>1</sub> pre-albuterol, % predicted	49.0 (14.54)	48.8 (13.99)
FEV <sub>1</sub> post-albuterol, L <sup>a</sup>	1.51 (0.510)	1.52 (0.497)
FEV <sub>1</sub> post-albuterol, % predicted <sup>a</sup>	55.5 (14.13)	55.0 (14.15)
FEV <sub>1</sub> /FVC post-albuterol <sup>a</sup>	0.53 (0.099)	0.53 (0.104)
FEV <sub>1</sub> reversibility, % <sup>b</sup>	15.9 (16.07)	14.8 (16.51)

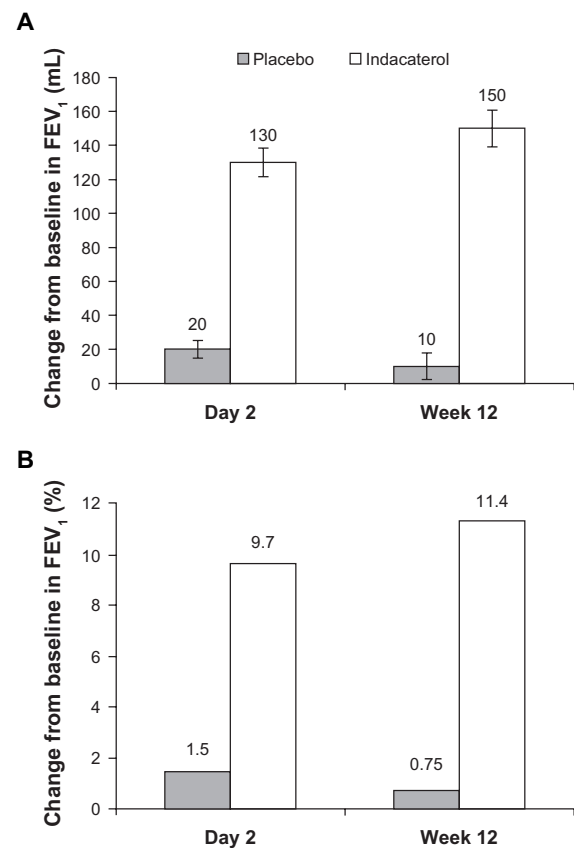
**Notes:** Data are mean (standard deviation) unless otherwise stated. <sup>a</sup>Post-albuterol measurements taken 30 minutes after patients inhaled albuterol 380 µg (four puffs); <sup>b</sup>Reversibility calculated as difference between pre- and post-albuterol values divided by the pre-albuterol value, expressed as a percentage.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroids.



**Figure 1** Trough forced expiratory volume in 1 second: differences between indacaterol and placebo treatment after first dose (measured on day 2) and after 12 weeks' treatment. Broken line indicates prespecified level of clinical importance. **Notes:** Data are least squares means and 95% confidence intervals. \*\*\*Denotes  $P < 0.001$  vs placebo.

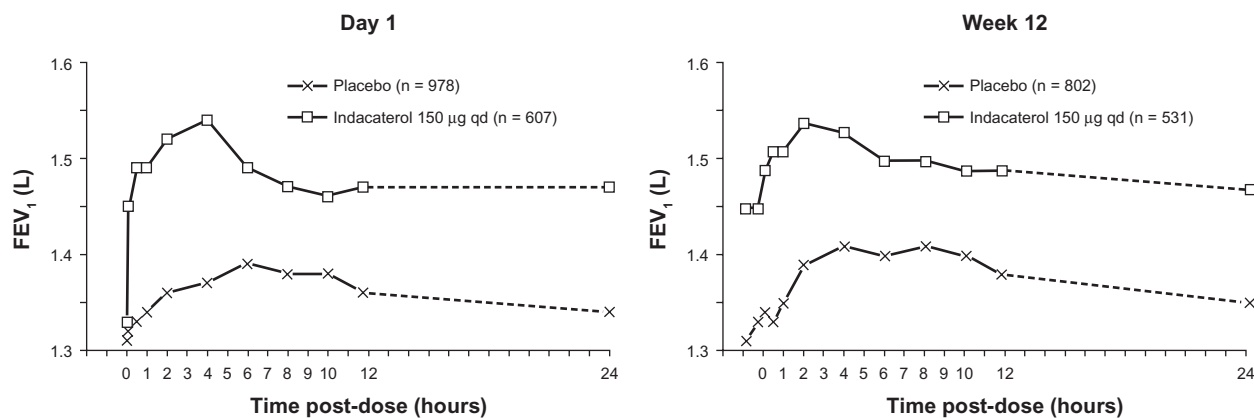
Serial post-dose measurements of FEV<sub>1</sub> after the first dose and at week 12 are shown in Figure 3. The analysis of the standardized area under the curve showed that FEV<sub>1</sub> was on average 210 mL (95% CI 150–280 mL) higher with indacaterol than with placebo during the first 12 hours post-dose ( $P < 0.001$ ).



**Figure 2** Trough FEV<sub>1</sub> after the first dose (day 2) and after 12 weeks of treatment, expressed as change from baseline (absolute (A) and percentage (B)).

**Note:** Data are unadjusted means ± standard error.

**Abbreviation:** FEV<sub>1</sub>, forced expiratory volume in 1 second.



**Figure 3** FEV<sub>1</sub> measured at serial time points post-dose on day 1 and week 12.

**Note:** Data are unadjusted means (error bars omitted for clarity).

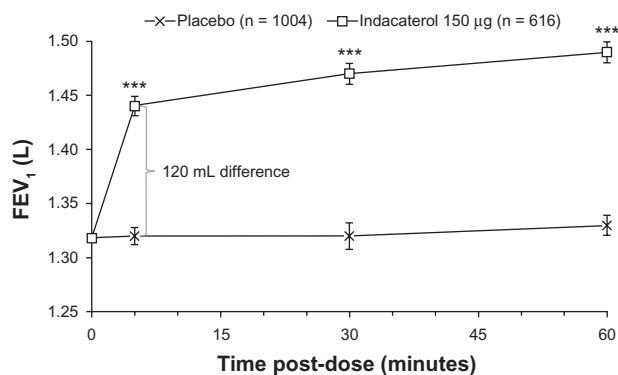
**Abbreviation:** FEV<sub>1</sub>, forced expiratory volume in 1 second.

Figure 4 illustrates the bronchodilator effect of treatment during the first hour following dosing on day 1. FEV<sub>1</sub> was significantly higher following indacaterol compared with placebo at each time point ( $P < 0.001$ ), with differences of 120 mL (5 minutes post-dose) and 150 mL (30 and 60 minutes post-dose).

Forced vital capacity (FVC) during treatment was evaluated in only one of the studies comparing indacaterol 150 µg qd with placebo.<sup>10</sup> Results after 12 weeks of treatment are shown in Figure 5,<sup>10</sup> demonstrating that indacaterol significantly increased FVC compared with placebo at each time point post-dose ( $P < 0.001$ ).

#### Days without use of rescue albuterol

Patients treated with indacaterol recorded no use of rescue albuterol on 52.7% of days, a 40% increase compared with the 37.7% rescue-free days among the placebo group (Figure 6).



**Figure 4** FEV<sub>1</sub> measured at serial time points up to 60 minutes post-dose on day 1.

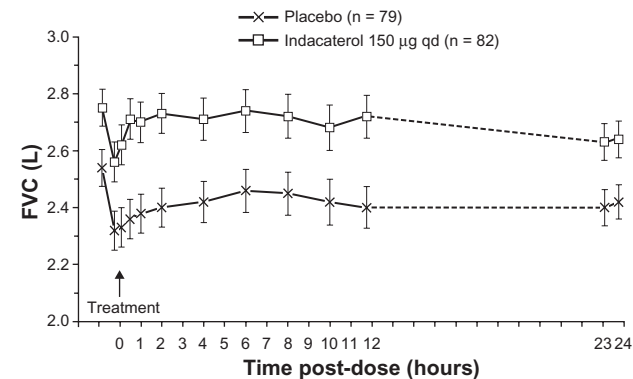
**Notes:** Data are least squares means  $\pm$  standard error. \*\*\*Denotes  $P < 0.001$  vs placebo.

**Abbreviation:** FEV<sub>1</sub>, forced expiratory volume in 1 second.

## Safety

### Adverse events

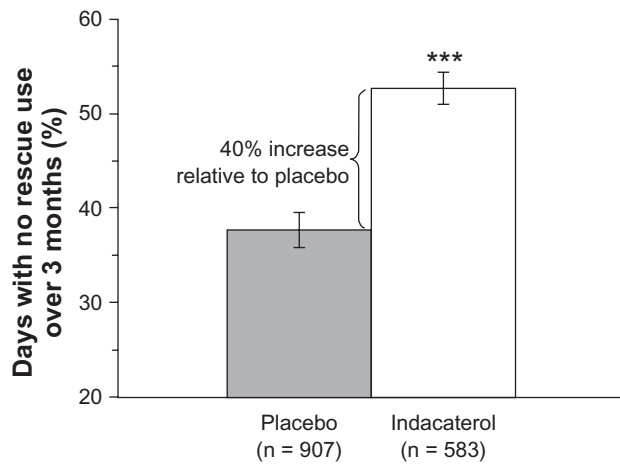
The incidence of (percentage of patients with) adverse events is shown in Table 2. In most cases (indacaterol 88%; placebo 87%), the adverse events were mild or moderate in severity. Comparing the two treatment groups, upper respiratory tract infection, headache, and muscle spasms were reported more frequently with indacaterol treatment than with placebo. For upper respiratory tract infection, all but one of the 33 cases (97%) during indacaterol treatment were mild or moderate, and none was considered to be related to the study drug. With indacaterol, headache was mild or moderate in most patients (26/28; 93%), and was considered related to the study drug in six patients (21%). The episodes of muscle spasms with indacaterol were generally mild or moderate (13/18; 72%), and were considered related to the study drug in six patients (33%). Only one of these cases (the episode of severe upper respiratory tract infection) was



**Figure 5** FVC measured at serial time points post-dose after 12 weeks in a single study.<sup>10</sup>

**Notes:** Data are least squares means  $\pm$  standard error. Differences between indacaterol and placebo were statistically significant ( $P < 0.001$ ) at each time point.

**Abbreviation:** FVC, forced vital capacity.



**Figure 6** Percentage of days with no use of rescue albuterol over 3 months of treatment.

**Notes:** Data are least squares means  $\pm$  standard error. \*\*\*Denotes  $P < 0.001$  vs placebo.

classified as a serious adverse event. Other events associated with  $\beta_2$ -agonist treatment were uncommon. Tremor occurred in one patient (0.16%) receiving indacaterol and in five receiving placebo (0.47%). Tachycardia was reported for five patients (0.80%) receiving indacaterol and five (0.47%) receiving placebo.

**Table 2** Adverse events overall and most commonly occurring ( $\geq 2\%$  of indacaterol treatment group) (3-month safety population)

	Indacaterol 150 µg (%) N = 627	Placebo (%) N = 1055
Patients with $\geq 1$ adverse event	51.7	46.3
COPD worsening	10.2	15.1
Cough	5.3	4.3
Upper respiratory tract infection	5.3	2.6
Nasopharyngitis	4.8	5.8
Headache	4.5	2.6
Muscle spasms	2.9	1.1
Diarrhea	2.4	1.5
Dyspnea	2.2	2.7
Back pain	2.1	1.7
Bronchitis	2.1	2.4
Dizziness	1.9	1.6
Nausea	1.9	1.4
Lower respiratory tract infection	1.8	2.2
Pharyngolaryngeal pain	1.8	0.8
Sinusitis	1.8	0.8
Urinary tract infection	1.8	1.2
Viral upper respiratory tract infection	1.6	1.5
Arthralgia	1.3	0.7
Influenza	1.3	0.8
Edema peripheral	1.1	0.4

**Abbreviation:** COPD, chronic obstructive pulmonary disease.

Overall, serious adverse events occurred in 33 (3.9%) and 47 (4.5%) of patients receiving indacaterol and placebo, respectively. The most common serious adverse event was “COPD worsening” (which includes disease progression and COPD exacerbations) (indacaterol, 0.6% of patients; placebo, 1.6% of patients). Two patients died during the 3-month treatment period, and both of them were in the placebo group.

The incidence of abnormal values for blood chemistries, vital signs, and ECG (QTc interval) is shown in Table 3. The one patient with a QTc interval  $> 500$  milliseconds also had a high baseline value (515 milliseconds) and a history of cardiac insufficiency, and was being treated with amiodarone, an anti-arrhythmic known to prolong QTc interval.

## Discussion

The studies that comprised the data for this analysis had identical entry criteria and followed the same methodologies. Despite their differing durations, the three studies shared a common primary efficacy outcome that was assessed at the same 12-week time point. The pooled dataset used here therefore provides a much larger database to report on the

**Table 3** Incidence of clinically notable values for blood glucose, serum potassium, blood pressure, pulse rate and QTc interval, recorded at any time post-baseline (3-month safety population)

	Indacaterol 150 µg n (%) N = 627	Placebo n (%) N = 1055
Blood glucose $> 9.99$ mmol/L (179.8 mg/dL)	34 (5.4)	49 (4.7)
Serum potassium $< 3$ mmol/L	0	3 (0.3)
Systolic blood pressure		
Low <sup>a</sup>	1 (0.19)	13 (1.23)
High <sup>b</sup>	4 (0.64)	15 (1.42)
Diastolic blood pressure		
Low <sup>c</sup>	4 (0.64)	7 (0.66)
High <sup>d</sup>	5 (0.80)	12 (1.14)
Pulse rate		
Low <sup>e</sup>	4 (0.64)	15 (1.42)
High <sup>f</sup>	0	5 (0.47)
QTc interval <sup>g</sup> absolute value		
$> 450$ (M) or $> 470$ (F) ms	20 (3.2)	33 (3.1)
$> 500$ ms	1 (0.2)	0
QTc interval <sup>g</sup> increase from baseline		
30–60 ms	48 (7.7)	59 (5.7)
$> 60$ ms	0	1 (0.1)

**Notes:** <sup>a</sup> $< 75$  mmHg, or  $\leq 90$  and decrease from baseline of  $\geq 20$  mmHg; <sup>b</sup> $> 200$  mmHg, or  $\geq 180$  and increase from baseline of  $\geq 20$  mmHg; <sup>c</sup> $< 40$  mmHg, or  $\leq 50$  and decrease from baseline of  $\geq 15$  mmHg; <sup>d</sup> $> 115$  mmHg, or  $\geq 105$  mmHg and increase from baseline of  $\geq 15$  mmHg; <sup>e</sup> $< 40$  bpm, or  $\leq 50$  bpm and decrease from baseline of  $\geq 15$  bpm; <sup>f</sup> $\geq 120$  bpm and increase from baseline of  $\geq 15$  bpm, or  $> 130$  bpm; <sup>g</sup>Calculated using Fridericia's formula.

**Abbreviation:** QTc, corrected QT interval.



efficacy, tolerability, and safety of indacaterol 150 µg qd. Once-daily dosing with indacaterol 150 µg provided a bronchodilator effect at 24 hours post-dose (trough FEV<sub>1</sub>) that was 160 mL greater than with placebo. This level of bronchodilation exceeded the 120 mL difference prespecified in the clinical studies as denoting clinical importance, and is also in excess of the 100–140 mL range that has been reported to be clinically significant in patients with COPD.<sup>13</sup> The bronchodilator effect of indacaterol on trough FEV<sub>1</sub> after the first dose was 100 mL greater than that observed with placebo.

Circadian variation in lung function is a normal process that also occurs in obstructive airway diseases, including COPD, and results in the lowest FEV<sub>1</sub> levels in the early hours of the morning.<sup>14–17</sup> In COPD, the normal early-morning decrease in FEV<sub>1</sub> is thought to be increased by the airflow obstruction in this disease and may be worsened by increased morning sputum production.<sup>18</sup> Reduced β<sub>2</sub>-adrenergic receptor stimulation due to decreased levels of endogenous catecholamines has also been proposed as a contributing factor.<sup>19</sup> It is therefore important to provide effective bronchodilation over the entire day, especially during the early morning. Treatment with a long-acting β<sub>2</sub>-agonist bronchodilator may represent an appropriate therapeutic approach. The early morning is also the time of day when symptoms are worse or the worst, and shortness of breath is often limiting for the patient's routine and daily activities in life.<sup>20</sup> Trough FEV<sub>1</sub> is a measure of early-morning efficacy of a long-acting β<sub>2</sub>-agonist, and the excellent bronchodilation still provided by indacaterol at this critical time of day may be helpful to COPD patients, facilitating improved levels of activity and resulting in improved quality of life.

The 160 mL difference in week 12 trough FEV<sub>1</sub> with indacaterol compared with placebo is similar or slightly better than previous reports of the effect of tiotropium in placebo-controlled studies (difference of 120–137 mL in trough FEV<sub>1</sub> for tiotropium compared with placebo).<sup>21–24</sup> Reported differences in trough FEV<sub>1</sub> between tiotropium and the twice-daily β<sub>2</sub>-agonist salmeterol are approximately 20–50 mL in favor of tiotropium.<sup>22,24,25</sup> Thus, indacaterol appears to have a greater effect on trough FEV<sub>1</sub> than other available long-acting bronchodilator treatments for COPD. The bronchodilator efficacy of indacaterol increased from the first dose to the measurements performed at the end of 12 weeks of treatment. In longer-term studies, the efficacy of indacaterol 150 µg qd was not reduced with repeated dosing for 6 or 12 months, showing persistence of bronchodilator response without tachyphylaxis.<sup>10,26,27</sup> In contrast, a decline

in bronchodilator effectiveness over time has been reported with both the twice-daily β<sub>2</sub>-agonists.<sup>28,29</sup>

The bronchodilator effect of indacaterol was also demonstrated in terms of its improvement of FVC. Effects on FVC generally reflect effects on FEV<sub>1</sub> but can also be useful in patients with COPD, specifically those with hyperinflation, to identify a therapeutic response in the absence of effects on FEV<sub>1</sub>.<sup>13</sup> This reduction in hyperinflation may represent an important mechanism through which indacaterol reduces symptoms in COPD.

A very important finding of this analysis is that treatment with indacaterol showed improvement in disease control, since the bronchodilation provided by indacaterol occurred in association with a 40% increase in rescue-free days compared with placebo. This reduction in the requirements for albuterol use for symptom relief suggests that patients receiving indacaterol were experiencing reduced symptoms.<sup>30</sup> Extrapolated to longer-term use, the difference in rescue use between treatments equates to 55 more days per year in which patients with moderate-to-severe COPD did not use albuterol while taking indacaterol, compared with those treated with a placebo.

While comparisons with placebo are a necessary step for approval of new treatments, it is relevant for practicing clinicians to judge the efficacy of a new treatment against other agents that are available for the treatment of COPD patients. Direct comparisons with other long-acting bronchodilators have been published recently. They show that indacaterol 150 µg qd had a bronchodilator effect similar to that of the once-daily anticholinergic, tiotropium, while providing greater improvements in symptoms and health status.<sup>31</sup> In comparison with the twice-daily β<sub>2</sub>-agonist, salmeterol, indacaterol proved to be a superior bronchodilator and had a greater effect in reducing dyspnea even though indacaterol-treated patients used less rescue medication.<sup>32</sup>

The overall frequency of adverse events and serious adverse events was similar between active and placebo treatments in the present analysis. The most common adverse event, "COPD worsening," occurred more often in the placebo group, which suggests a potential beneficial effect of indacaterol on COPD exacerbations. Those adverse events occurring more frequently with indacaterol were mostly mild or moderate, and indacaterol was well tolerated. The side effects of tremor and tachycardia that would be expected to result from β<sub>2</sub>-adrenergic stimulation were less common with indacaterol than with placebo. Muscle spasms were more common with indacaterol than with placebo (2.9% vs 1.1%), but these events were generally mild or moderate in severity.

The incidence of changes in glucose and potassium, and prolongation of QTc interval, were very low and similar with indacaterol and placebo treatments. Thus, in a large analysis of patients with COPD, therapy with indacaterol was well tolerated with a side-effect profile similar to placebo.

Adherence with treatment is often poor among patients with chronic respiratory diseases, including COPD.<sup>33–35</sup> Adherence in chronic diseases is reported to be inversely related to the number of doses per day, and poor adherence may contribute to the poor control of many medical disorders.<sup>36</sup> Once-daily dosing provides a simplified dosing regimen that should improve adherence and ensure more persistent medication use.<sup>37,38</sup> Thus, the development of an effective treatment for COPD with a simplified treatment regimen (eg, infrequent dosing, simple delivery), rapid onset of action and durable effect should improve patient adherence.<sup>39</sup>

## Conclusion

Consistent with international evidence-based treatment guidelines, the COPD patients included in the present analysis are appropriate candidates for regular maintenance treatment with one or more long-acting bronchodilators.<sup>1,7</sup> In view of its efficacy and the safety profile described in this report, once-daily indacaterol represents an appropriate treatment for patients with moderate-to-severe COPD.

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## Disclosure

Eugene Bleecker has performed clinical trials (all negotiated through Wake Forest University Health Sciences) with Actelion, Aerovance, AstraZeneca, Boehringer Ingelheim, Centocor, Ception, Genentech, GlaxoSmithKline, MedImmune, Novartis, and Pfizer. He has served as a consultant with Aerovance, AstraZeneca, Boehringer Ingelheim, Genentech, GlaxoSmithKline, Merck, and Pfizer. He has grant support from the following studies: Principal Investigator – R01 HL69167 – Genotype-Phenotype Interactions in Severe Asthma; Co-Principal Investigator – U10 HL74225 – Asthma Clinical Research Network (ACRN); Principal Investigator – U01 HL65889 – Pharmacogenetics of Asthma Treatment; Co-Principal Investigator – R01 HL087665 – Genome Wide Association for Asthma and Lung Function;

Co-Principal Investigator – K12 HL089992 – Scholars' Program for Genetics and Genomics of Lung Disease; Principal Investigator – R01091762 – SARP; Principal Investigator – HHSN268200900019C – Spiromics Clinical Center; Co-Principal Investigator – U10 HL098103 – Atlantic Coast Consortium for Asthma (ACC-A) AsthmaNet Clinical Site; Co-Principal Investigator – RC2 HL101487 – Linking Genetics, Genomics and Phenomics to Better Understand Asthma Severity; Co-Principal Investigator – R01 HL069116 – SARP Substudy, and Co-Investigator – RC2 HL101651 – The EVE Asthma Genetics Consortium: Building upon “GWAS.”

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Roger Owen and Benjamin Kramer are employees of Novartis, the manufacturers of indacaterol.

## Statement of authorship

RO and BK made substantial contributions to the conception and design of the individual studies from which the data were pooled for this analysis. ERB and TS were involved in the acquisition of data. RO was responsible for analysis of data. All authors were involved in the concept and design of this article and the interpretation of the data, and had full access to the primary study data. All authors revised the article critically for important intellectual content and gave their final approval of the version to be published.

## Note

ClinicalTrials.gov identifiers: NCT00463567, NCT00624286, and NCT00393458 (placebo data only).

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