Long-term Safety and Efficacy of Indacaterol, a Long-Acting β2-Agonist, in Subjects With COPD

A Randomized, Placebo-Controlled Study

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Background

Indacaterol is an inhaled, long-acting β2-agonist providing 24-h bronchodilation with once-daily dosing in patients with COPD.

Methods

Subjects with moderate to severe COPD who completed a 26-week, randomized, double-blind study were eligible for enrollment in an extension, during which treatment with double-blind indacaterol, 150 or 300 µg once daily, or placebo was continued for a further 26 weeks. The primary objective was to evaluate the long-term safety of indacaterol. Efficacy end points included trough (24 h postdose) FEV₁ at 52 weeks, exacerbations, and health status (St. George Respiratory Questionnaire [SGRQ]).

Results

Four hundred fifteen subjects participated in the extension. Adverse events, mostly mild or moderate, occurred in 76%, 77%, and 68% of subjects receiving indacaterol, 150 µg; indacaterol, 300 µg; and placebo, respectively. Serious adverse events occurred in 10.4%,
12.3%, and 10.5%, respectively. Indacaterol had no clinically significant effects on ECG findings (corrected QT interval) or on serum potassium or plasma glucose levels. Indacaterol increased trough FEV₁ relative to placebo throughout the study (difference of ≥170 mL at week 52). No tolerance to its bronchodilator effect was detected. Indacaterol treatment was accompanied by significant reductions in COPD exacerbations (rate ratios compared with placebo, 0.62-0.64; P < .05) and as-needed albuterol use (1.2-1.4 puffs/d decrease, P < .001 compared with placebo). Health status improved with indacaterol treatment, with decreases from baseline in mean total SGRQ score generally > 4 units.

Conclusions

During 1 year of treatment, indacaterol was well tolerated and provided significant and well-maintained bronchodilation that was accompanied by improved clinical outcomes.

Trial registry

ClinicalTrials.gov; No.: NCT00677807; URL: www.clinicaltrials.gov

Abbreviations

ICS
inhaled corticosteroid

LABA
long-acting β₂-agonist

SGRQ
St. George Respiratory Questionnaire

The Bottom Line

How does this work advance the field?

A thorough characterization of safety is particularly relevant for a long-acting bronchodilator given recent interest in the safety of these agents in the treatment of COPD. This article reports the results of a 1-year, placebo-controlled study designed to evaluate the safety and tolerability of indacaterol, a once-daily, inhaled β₂-agonist bronchodilator for the treatment of COPD.

What are the clinical implications?

This study suggests that once-daily dosing of indacaterol at 150 µg and 300 µg may be a safe and well-tolerated treatment for patients with moderate to severe COPD. This treatment may reduce the need for albuterol as well as the number of COPD exacerbations.

Long-acting inhaled bronchodilators are recommended for the management of moderate and more severe COPD.[1] Currently available agents include the bid long-acting β₂-agonists (LABAs) formoterol and salmeterol and the once-daily anticholinergic tiotropium. Although long-acting bronchodilators are considered more effective and convenient than short-acting agents,[1] adherence to long-term treatment is poor among subjects with COPD, [2] [3] and symptoms remain limiting for many subjects.[4]

Indacaterol is an inhaled, once-daily, ultra-LABA that has been shown to be effective and well tolerated by subjects with COPD during 12 weeks of treatment. [5] [6] With any new treatment intended for long-term use, it is important to evaluate safety and to determine if efficacy remains unblunted with regular use. A thorough characterization of safety is particularly relevant for a long-acting bronchodilator, given the recent interest in the safety of these agents in the treatment of COPD. [7] [8] In addition, regulatory guidance requires long-term evaluation of the safety of a new treatment at the likely recommended doses. We report here on the long-term safety of indacaterol from a study in which subjects completing a 26-week core study could enter a study extension and continue double-blind treatment with
indacaterol, 150 or 300 µg, or placebo once daily for a further 26 weeks. The primary objective was to evaluate the 52-week safety of indacaterol; secondary evaluations included bronchodilator efficacy, exacerbations, and health status.

Materials and Methods

Subjects

Subjects enrolled in the extension had completed the 26-week core study. On entry to the core study, subjects had moderate to severe COPD with postbronchodilator FEV₁ < 80% and ≥ 30% predicted and postbronchodilator FEV₁/FVC < 70%,[9] were aged ≥ 40 years, and had a smoking history of ≥ 20 pack-years. Subjects were not eligible if they had a history of asthma or if they had experienced a respiratory tract infection or hospitalization for COPD exacerbation within the 6 weeks before the core study. Subjects provided signed informed consent before receiving any study treatment.

Study Design

In the core study, subjects were randomized (1:1:1:1) to double-blind treatment with indacaterol, 150 or 300 µg; placebo; or open-label tiotropium for 26 weeks.[10] In the extension, subjects who had previously been randomized to indacaterol, 150 µg; indacaterol, 300 µg; or placebo who had completed 26 weeks’ treatment and who consented to the extension continued their existing double-blind treatment for an additional 26 weeks. Data presented here are for the whole 52-week study period. The study design was approved by independent ethics committees or review boards at each center.

Study Medications

Subjects took indacaterol, 150 or 300 µg, or placebo via a single-dose dry powder inhaler each morning. Subjects were supplied with albuterol for use as needed; other bronchodilators were discontinued before the study. Treatment with fixed combinations of LABAs and inhaled corticosteroids (ICSs) was replaced with ICS monotherapy at equivalent doses and regimens prior to the core study. Subjects already on ICS monotherapy at the start of the core study could continue their ICS medication. ICS doses and regimens remained stable throughout the study.

Assessments and Outcome Measures

Following screening, subjects visited the clinic at day 1 and weeks 2, 4, 8, 12, 26, 36, 44, and 52. Adverse events were recorded at each visit, vital signs were monitored, and ECGs were obtained. A corrected QT interval was calculated using the Fridericia formula. Serum potassium and blood glucose levels were measured at 30 min and 1 h postdose at each visit.

The two key efficacy end points were “trough” FEV₁ (mean of measurements at 23 h 10 min and 23 h 45 min postdose) at 52 weeks and time to first COPD exacerbation. Spirometry was performed at intervals postdose at clinic visits according to recognized standards,[11] using the same equipment and technician per patient during the study whenever possible. The highest FEV₁ values from three acceptable maneuvers were recorded. A difference in trough FEV₁ of 120 mL between indacaterol and placebo was considered clinically relevant. COPD exacerbations were defined as onset or worsening of more than one respiratory symptom (dyspnea, cough, sputum purulence/volume, or wheeze) for > 3 consecutive days, plus intensified treatment (eg, systemic steroids, antibiotics, oxygen) and/or hospitalization or ED visit. Other efficacy end points were FEV₁ at other time points, albuterol use, rate of exacerbations, and St. George Respiratory Questionnaire (SGRQ) total score.[12]

Statistical Methods

Safety was analyzed for the safety population, comprising all subjects who received at least one dose of the study drug. Subjects were analyzed according to treatment received. Efficacy was analyzed for the intent-to-treat population, comprising all randomized subjects who received at least one dose of study drug, and subjects were analyzed according to their randomized treatment.

The key safety variables were analyzed using a mixed-model analysis of covariance, with treatment as a fixed effect and baseline value and reversibility as covariates, and smoking status and country as fixed effects. FEV₁, rescue use, and SGRQ scores were analyzed using a similar mixed model with appropriate baseline measurements as covariates. Missing observations were imputed where appropriate. Time to first exacerbation was analyzed using a Cox regression model, and exacerbation rates were analyzed using a Poisson regression model without imputation (a sensitivity analysis with imputation of an additional exacerbation for prematurely discontinuing subjects was also performed). Data are presented as least squares means with SE or, for pairwise treatment comparisons, with 95% CIs and associated P values. No adjustment was made for multiplicity, given the primary focus on safety.

Results

Subject Disposition and Baseline Characteristics
The disposition of subjects during the study is summarized in Figure 1. Across the treatment groups, similar proportions of subjects (144/325, 146/341, 125/294; 43%–44%) who had completed the core study entered the extension, although there was a higher dropout rate in the placebo group during the core study (31% [131/425], mainly because of adverse events, withdrawal of consent, and unsatisfactory therapeutic effect [10]). This resulted in fewer subjects on placebo (125) entering the extension compared with those receiving active treatments (144 and 146 subjects) (Fig 1). One subject on placebo, who recorded a date of last dose, had not taken treatment as specified and was, therefore, excluded from analysis. Baseline characteristics were generally similar across the treatment groups (Table 1). The total populations for the core and extension stages had similar overall characteristics.

**Figure 1** Disposition of subjects during the study.

**Table 1** Baseline (at Start of Core Study) Demographic and Clinical Characteristics of Subjects Entering the Extension

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Indacaterol, 150 µg (n = 144)</th>
<th>Indacaterol, 300 µg (n = 146)</th>
<th>Placebo (n = 124)</th>
<th>Total (N = 414)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>62.5 (9.52)</td>
<td>62.5 (9.00)</td>
<td>62.8 (9.18)</td>
<td>62.6 (9.21)</td>
</tr>
<tr>
<td>Male (female), %</td>
<td>60 (40)</td>
<td>59 (41)</td>
<td>65 (35)</td>
<td>61 (39)</td>
</tr>
<tr>
<td>Duration of COPD, y</td>
<td>6.8 (7.68)</td>
<td>6.7 (6.20)</td>
<td>6.6 (7.58)</td>
<td>6.7 (7.15)</td>
</tr>
<tr>
<td>Ex-smoker (smoker), %</td>
<td>49 (51)</td>
<td>52 (48)</td>
<td>49 (51)</td>
<td>50 (50)</td>
</tr>
<tr>
<td>Smoking history, pack-y</td>
<td>49.2 (24.61)</td>
<td>47.0 (24.56)</td>
<td>51.0 (26.57)</td>
<td>49.0 (25.18)</td>
</tr>
<tr>
<td>ICS use, %</td>
<td>34</td>
<td>34</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;, L</td>
<td>1.44 (0.462)</td>
<td>1.50 (0.491)</td>
<td>1.54 (0.517)</td>
<td>1.49 (0.490)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; % predicted</td>
<td>53.9 (13.69)</td>
<td>56.6 (14.62)</td>
<td>56.3 (14.83)</td>
<td>55.6 (14.38)</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/FVC [a]</td>
<td>0.52 (0.094)</td>
<td>0.53 (0.099)</td>
<td>0.54 (0.098)</td>
<td>0.53 (0.097)</td>
</tr>
<tr>
<td>Characteristic</td>
<td>Indacaterol, 150 µg (n = 144)</td>
<td>Indacaterol, 300 µg (n = 146)</td>
<td>Placebo (n = 124)</td>
<td>Total (N = 414)</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>--------------------------------</td>
<td>--------------------------------</td>
<td>------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Reversibility to albuterol, %</td>
<td>17.7 (18.08)</td>
<td>15.6 (17.26)</td>
<td>13.7 (14.55)</td>
<td>15.8 (16.83)</td>
</tr>
<tr>
<td>SGRQ total score [b]</td>
<td>46.0 (18.52)</td>
<td>45.3 (17.84)</td>
<td>45.0 (17.01)</td>
<td>45.3 (17.88)</td>
</tr>
<tr>
<td>Albuterol use, [b] puffs/d</td>
<td>3.3 (3.94)</td>
<td>3.1 (3.28)</td>
<td>2.8 (3.17)</td>
<td>3.1 (3.48)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) unless otherwise indicated. ICS = inhaled corticosteroid; SGRQ = St. George Respiratory Questionnaire.

a Postalbuterol.

b Intention-to-treat population.

Safety

The incidence and type of adverse events were generally comparable across study groups (76% and 77% of patients in the indacaterol treatment groups and 68% in the placebo group). The most common were COPD worsening and nasopharyngitis, occurring at a similar frequency across the treatment groups (24%-27% and 15%-18% of patients, respectively). Musculoskeletal disorders (muscle spasms, arthralgias, and musculoskeletal pain), headache, and cough were reported more frequently in the indacaterol groups than in the placebo group. For muscle spasms (8.3% and 2.7% of patients given indacaterol, 1.6% of those given the placebo), the majority of cases were mild or moderate (12/16, 75%), and 31% (5/16) were considered to be related to indacaterol treatment. For arthralgia (3.5% and 5.5% of patients given indacaterol), none of the cases was severe or considered to be related to indacaterol treatment. Similarly, the cases of musculoskeletal pain (3.5% and 5.5% of patients given indacaterol) were mostly mild or moderate (12/13, 92%), and none was considered related to treatment. For headache (10.4% and 4.8% of patients given indacaterol; 4.0% of those given the placebo), most cases were mild or moderate (20/22, 91%), and a minority (6/22, 27%) was considered related to treatment. For cough reported as an adverse event (11.8% and 10.3% of patients given indacaterol; 6.5% of those given the placebo), nearly all cases were mild or moderate (31/32; 97%), with 44% (14/32) considered related to treatment. None of these events was serious or led to discontinuation. The most frequently occurring adverse events (in ≥ 7.5% of either indacaterol group) are listed in e-Table 1.

Two subjects died, one in the placebo group and one in the indacaterol, 300 µg, group. Both deaths were due to myocardial infarction, and both were suspected to be related to study treatment. The subject who died after 231 days of treatment with indacaterol, 300 µg, was a 66-year-old Asian man with a smoking history of 55 pack-years and no other relevant medical history. The subject in the placebo group who died after 252 days in the study was a hypertensive 76-year-old Asian man with a smoking history of 50 pack-years. None of the other adverse events leading to treatment discontinuation (4/144 [2.8%], 2/146 [1.4%], and 7/124 [5.6%] of subjects in the indacaterol, 150 µg, indacaterol, 300 µg, and placebo groups, respectively) was considered to be related to study treatment.

Serious adverse events occurred in 10.4% (15/144) of subjects receiving indacaterol, 150 µg; 12.3% (18/146) receiving indacaterol, 300 µg; and 10.5% (13/124) receiving placebo. The only serious adverse event occurring in more than one subject was worsening of COPD (in 2.8% [4/144], 3.4% [5/146], and 2.4% [3/124] of subjects in the indacaterol, 150 µg; indacaterol, 300 µg; and placebo groups, respectively). Apart from the two deaths, none of the serious adverse events was considered to be related to study treatment.

Shifts in plasma potassium levels from normal to below normal (< 3.5 mmol/L) were uncommon in all treatment groups, whereas shifts in plasma glucose levels from normal to above normal (> 7.77 mmol/L) occurred slightly more frequently in the indacaterol treatment groups (Table 2). However, mean blood glucose level (mean of maximal values recorded at any assessment during treatment) did not differ significantly across the treatment groups (Table 2). Results for pulse rates and BP, and the incidence of corrected QT prolongation, were similar between the indacaterol and placebo groups (Table 2).

Table 2 -- Biochemistry, Vital Signs, and QTc Intervals (Fridericia Formula)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Indacaterol, 150 µg (n = 144)</th>
<th>Indacaterol, 300 µg (n = 146)</th>
<th>Placebo (n = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3.0 mmol/L</td>
<td>1 (0.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Variable</td>
<td>Indacaterol, 150 µg (n = 144)</td>
<td>Indacaterol, 300 µg (n = 146)</td>
<td>Placebo (n = 124)</td>
</tr>
<tr>
<td>------------------------------------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Shift from normal to below normal[a]</td>
<td>6 (4.2)</td>
<td>13 (8.9)</td>
<td>12 (9.7)</td>
</tr>
<tr>
<td>Minimum postbaseline, mmol/L</td>
<td>4.02 ± 0.03</td>
<td>4.00 ± 0.03</td>
<td>4.01 ± 0.04</td>
</tr>
<tr>
<td>Blood glucose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 9.99 mmol/L</td>
<td>15 (10.4)</td>
<td>19 (13.0)</td>
<td>10 (8.1)</td>
</tr>
<tr>
<td>Shift from normal to above normal[b]</td>
<td>38 (26.4)</td>
<td>42 (28.8)</td>
<td>27 (21.8)</td>
</tr>
<tr>
<td>Maximum postbaseline, mmol/L</td>
<td>7.75 ± 0.25</td>
<td>7.61 ± 0.24</td>
<td>7.24 ± 0.27</td>
</tr>
<tr>
<td>Pulse rate: high[c]</td>
<td>0</td>
<td>1 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Systolic BP: high[d]</td>
<td>1 (0.7)</td>
<td>2 (1.4)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Diastolic BP: high[e]</td>
<td>1 (0.7)</td>
<td>0</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>QTc interval</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute value &gt; 450/470 ms (men/women)[f]</td>
<td>10 (6.9)</td>
<td>9 (6.2)</td>
<td>11 (8.9)</td>
</tr>
<tr>
<td>Increase 30–60 ms</td>
<td>28 (19.4)</td>
<td>30 (20.5)</td>
<td>30 (24.4)</td>
</tr>
<tr>
<td>Increase &gt; 60 ms</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>1 (0.8)</td>
</tr>
</tbody>
</table>

Data are presented as No. (%) or mean ± SE. QTc = corrected QT.

- **a** < 3.5 mmol/L.
- **b** > 7.77 mmol/L.
- **c** > 130 beats/min, or ≥ 120 beats/min and ≥ 15 beats/min increase from baseline.
- **d** > 200 mm Hg, or ≥ 180 mm Hg and ≥ 20 mm Hg increase from baseline.
- **e** > 115 mm Hg, or ≥ 105 mm Hg and ≥ 15 mm Hg increase from baseline.
- **f** No patient had a value > 500 ms.

**Cough Following Study Drug Inhalation**

As distinct from reports of cough as an adverse event, investigators were asked to record any episodes of cough that occurred within 5 min of subjects inhaling the study drug at clinic visits. This was observed in an average of 18.3% (21-33 subjects per visit) and 23.6% (30-37 per visit) of subjects receiving indacaterol, 150 and 300 µg, and in 1.9% (0-4 per visit) of placebo subjects. In most cases, the cough started within 15 s of inhalation (18-36 subjects in the indacaterol treatment groups per visit, or 81%-100% of cases) and lasted for a median of 6 to 12 s. It was not associated with bronchospasm or exacerbations, nor with increased study discontinuation rates (no subject discontinued because of cough), and did not affect bronchodilator efficacy.

**Spirometry**

Trough FEV₁ at week 52 was significantly higher in the indacaterol groups relative to the placebo group, with differences of 170 mL (95% CI, 110-230) and 180 mL (95% CI, 120-240) (both P < .001) for the 150 µg and 300 µg doses, respectively (Fig 2). The changes from baseline in trough FEV₁ at week 52 were 120 mL (10%), 130 mL (10%), and -40 mL (-3%) with indacaterol, 150 µg; indacaterol, 300 µg; and placebo, respectively. The differences between indacaterol and placebo in trough FEV₁ were maintained at a similar level from week 2 to the end of the study, with differences of ≥ 160 mL compared with placebo for both doses at each time point (all P < .001) (Fig 2).
On day 1, at 5-min postdose, FEV₁ increased relative to placebo by 90 mL (95% CI, 40-140) with indacaterol, 150 µg, and by 100 mL (95% CI, 50-150) with indacaterol, 300 µg (both \( P < .001 \)). Significant bronchodilation at 5 min after dosing was maintained at all subsequent assessments, with differences compared with placebo of 150 to 290 mL with indacaterol, 150 µg, and 180 to 240 mL with indacaterol, 300 µg.

FEV₁ was also recorded as a safety variable in terms of the percentage of patients with a decrease in FEV₁ of ≥ 20% in the 30 min following the first dose. This was recorded for a small number of subjects (3/144 [2.1%] and 3/146 [2.0%] with indacaterol, 150 µg and 300 µg; 4/126 [3.2%] with placebo) and was not associated with cough following dosing in any subject.

### COPD Exacerbations, Albuterol Use, and Health Status

Exacerbation rates were low in all three treatment groups, but were significantly \( ( P < .05) \) lower in subjects receiving indacaterol, 150 µg (0.39 exacerbations/y) or indacaterol, 300 µg (0.38 exacerbations/y) compared with placebo (0.54 exacerbations/y). Rate ratios compared with placebo were similar with imputation but were not consistently significant (Table 3). There were too few events for time to first exacerbation to be evaluated. Hazard ratios compared with placebo of 0.82 (95% CI, 0.51-1.34) and 0.86 (95% CI, 0.53-1.39) for indacaterol, 150 µg, and indacaterol, 300 µg, respectively, suggested a trend toward improvement during indacaterol treatment but were not statistically significant (the study not being powered for such comparisons).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Indacaterol, 150 µg (n = 144)</th>
<th>Indacaterol, 300 µg (n = 146)</th>
<th>Placebo (n = 124)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without imputation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations/y</td>
<td>0.39</td>
<td>0.38</td>
<td>0.54</td>
</tr>
<tr>
<td>Rate ratio compared with placebo (95% CI)</td>
<td>0.64 (0.43–0.96)[a]</td>
<td>0.62 (0.42–0.92)[b]</td>
<td>…</td>
</tr>
<tr>
<td>With imputation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exacerbations/y</td>
<td>0.43</td>
<td>0.40</td>
<td>0.57</td>
</tr>
<tr>
<td>Rate ratio compared with placebo (95% CI)</td>
<td>0.67 (0.45–1.01)[c]</td>
<td>0.66 (0.44–0.98)[d]</td>
<td>…</td>
</tr>
</tbody>
</table>

\[a\] \( P = .029 \).  
\[b\] \( P = .018 \).  
\[c\] \( P = .054 \).  
\[d\] \( P = .042 \).
Over the 52 weeks, daily albuterol use decreased from baseline by 1.2 puffs (SE, 0.28) with indacaterol, 150 µg, and 1.4 puffs (SE, 0.27) with indacaterol, 300 µg, compared with 0.1 puffs (SE, 0.30) with placebo ($P < .001$ for both comparisons). The proportions of days without albuterol use were 56% and 59% with indacaterol, 150 µg, and indacaterol, 300 µg, respectively, both significant increases ($P < .05$) compared with placebo (46% of days without albuterol).

Total SGRQ scores improved with all treatments, including placebo, with decreases from baseline that generally exceeded the four-unit threshold for a clinically important improvement.[13] (Fig 3). The mean SGRQ total scores with both indacaterol doses were numerically higher than with placebo at all assessments, and significantly higher at week 26 (150 µg, $P = .002$; 300 µg, $P = .025$) and week 44 ($P = .002$ for both doses).

**Figure 3** Change from baseline in SGRQ total score. Data are presented as unadjusted means ± SE. Broken line shows the level of clinically important improvement (four units). *$P < .05$, **$P < .01$ compared with placebo, based on analysis of covariance of adjusted least squares means. SGRQ = St. George Respiratory Questionnaire.

**Discussion**

Long-term safety of a new treatment is important for subjects with COPD, who are often elderly, frequently have significant comorbidity, and are receiving multiple medications.[14], [15], [16] We can report good overall tolerability and safety with once-daily dosing of indacaterol, 150 µg and 300 µg, for 1 year in subjects with moderate to severe COPD. The overall incidence of adverse events was similar across the treatment groups, and the most commonly occurring events were related to COPD worsening and respiratory tract infections, as would be expected in a population of subjects with COPD.

There was a slight excess of the adverse events musculoskeletal disorders and headache with indacaterol; most events were mild or moderate, and none was serious or required treatment discontinuation. Similar findings have been reported for available LABAs such as salmeterol.[17] Unlike salmeterol, these side effects were not reported more commonly at higher doses in this or in previous studies of indacaterol at doses up to 600 µg once daily.[18], [19] In the earlier 1-year study,[19] muscle spasms (none severe or serious) were reported in 5% and 6% of patients taking indacaterol, 300 µg, and indacaterol, 600 µg, respectively. In other recent studies, [6], [10], [20] muscle spasms were reported in 0.2% to 3.1% of patients receiving indacaterol, 150 µg, or indacaterol, 300 µg, once daily. Muscle spasms and tremor are recognized β2-agonist class effects that occur at a very low incidence with indacaterol.

Reductions in serum potassium levels and increased blood glucose concentrations are recognized consequences of β2-adrenoceptor stimulation. We found no effect on serum potassium levels and a slightly increased incidence of elevated blood glucose levels with indacaterol. However, the mean values (means of the highest recorded value from all postbaseline measurements) did not differ significantly between either indacaterol dose or placebo.

Aside from cough as an adverse event, the study captured separately the incidence of cough occurring within 5 min of inhalation, which was observed in up to 24% of patients receiving indacaterol. This did not pose a safety concern because the cough was short in duration and was not associated with bronchospasm, higher dropout rates, or impaired efficacy. The mechanism for this cough has not been fully determined.

In terms of efficacy, once-daily indacaterol, 150 µg, and indacaterol, 300 µg, provided a significant and clinically relevant level of bronchodilation relative to placebo after 52 weeks of treatment.[21] Bronchodilation was maintained at a similar level throughout the study without any indication of tolerance. These findings confirm previous observations with indacaterol,[19] and contrast with the reported loss of bronchodilator efficacy over time with the twice-daily LABAs.[19], [22], [23], [24] Adherence, which is known to be poor among...
subjects with COPD, may be helped by once-daily dosing frequency. [21] , [3] The fast onset of action of indacaterol may also encourage adherence. Although this fast onset of effect might theoretically be evident only with the initial dose of long-term therapy with a once-daily bronchodilator, it might encourage compliance subsequently if it is evident to subjects who resume therapy after missed or delayed doses.

Although FEV₁ is useful in the diagnosis and assessment of severity of COPD, it does not reflect fully the burden of disease on subjects. [25] Clinical outcomes were, therefore, also assessed in the current study, although conclusions drawn from this analysis of the continuation study, which was not rerandomized, should be made with caution. Our data suggest that the sustained bronchodilator effect of indacaterol is associated with reductions in the use of as-needed albuterol and the rate of COPD exacerbations. The effect of indacaterol in this regard is noteworthy, because the number of events was relatively small and the magnitude of the effect (reduction by one-third compared with placebo) was larger than that seen in other studies assessing the effect of long-acting bronchodilators on COPD exacerbations. [26] , [27] , [28] , [29] , [30]

Health status, as measured by SGRQ, showed a marked improvement from baseline with indacaterol during the study, although differences compared with placebo were not consistently statistically significant. These findings may underestimate the clinical impact of indacaterol, because the higher discontinuation rate in the placebo group during the first 6 months of the study (a common observation in long-term placebo-controlled studies [31] ) may help explain the observed improvements from baseline health status with placebo. In an earlier 1-year study without a distinct “midpoint,” a clinically relevant difference between indacaterol and placebo in SGRQ total score was maintained for most of the study, and even increased over 52 weeks. [19] SGRQ was assessed in this study in order to include end points of efficacy in association with decreased as-needed albuterol use and reduced exacerbations. Indacaterol was well tolerated, and this study, along with previous reports, [19] supports the long-term safety of indacaterol.

Conclusions

Once-daily indacaterol provided effective and sustained bronchodilation when given for 1 year to subjects with moderate to severe COPD, in association with decreased as-needed albuterol use and reduced exacerbations. Indacaterol was well tolerated, and this study, along with previous reports, [19] supports the long-term safety of indacaterol.

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