

# Long-acting $\beta$ -adrenoceptor agonists in the management of COPD: focus on indacaterol

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**Abstract:** Bronchodilators are the cornerstone of severe chronic obstructive pulmonary disease (COPD) treatment to improve airflow, symptoms, exercise tolerance, and exacerbations. There is convincing evidence that regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators. Long-acting  $\beta$ -2-agonists include the twice-daily drugs formoterol and salmeterol and, more recently, once-daily indacaterol. Studies with head-to-head comparisons of long-acting bronchodilators are scant, but novel data from controlled trials with the once-daily  $\beta$ (2)-agonist indacaterol indicate superior bronchodilation and clinical efficacy of indacaterol at recommended doses over twice-daily long-acting  $\beta$ (2)-agonists, and at least equipotent bronchodilation compared with once-daily tiotropium. The recent therapeutic developments in COPD underscore a shift from short-acting bronchodilators with multiple dosings per day to reduced dosing frequency and prolonged duration of action, including once-daily treatment, with more consistent effects on various clinical outcomes. This review summarizes relevant clinical data for twice-daily  $\beta$ -2-agonists in COPD, and further focuses on novel data for once-daily indacaterol, including head-to-head comparison trials.

**Keywords:** COPD, bronchodilators, salmeterol, indacaterol, formoterol, tiotropium, therapy, pharmacology

## Background: long-acting $\beta$ -agonists in the treatment of COPD

Current guidelines recommend long-acting bronchodilators as first-line maintenance therapy for moderate, severe, and very severe chronic obstructive pulmonary disease (COPD), with a preference for inhaled medications over oral theophyllines.<sup>1</sup> Until recently, the once-daily anticholinergic tiotropium and the twice-daily  $\beta$ (2)-agonists salmeterol and formoterol were the most widely used maintenance medications. Both classes of agents have been demonstrated to be effective and hold acceptable safety profiles. In December 2009, the first once-daily long-acting  $\beta$ -agonist indacaterol was approved by the European Medicines Agency, and indacaterol once daily was consequently introduced into the market. The availability of a once-daily inhaled  $\beta$ -2-agonist for the maintenance treatment of COPD somehow marks a trend in the recent therapeutic developments in COPD, indicating a shift from short-acting bronchodilators with multiple dosings per day to reduced dosing frequency and prolonged duration of action, including once-daily treatment. This change has been consistently associated with improvements in clinical outcomes of COPD patients. Alongside the introduction of new bronchodilators, longer duration of bronchodilation showed more consistent improvements in lung function and patient-centered outcomes,

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including airflow (forced expiratory volume in 1 second [FEV<sub>1</sub>]), hyperinflation, symptom control, dyspnea, quality of life, physical activity, and exacerbations.<sup>2,3</sup> Recent data from large-scale clinical trials may also indicate a beneficial effect of long-acting bronchodilators on disease progression<sup>4</sup> and even mortality in subsets of patients.<sup>5</sup> Finally, a reduction of dosing frequency for inhaled therapies will simplify the management of COPD, ultimately leading to improved patient adherence and compliance,<sup>6</sup> contributing to better clinical outcomes.<sup>7</sup> The aim of this review is to summarize relevant data and landmark studies comparing the efficacy of short- versus longer-acting bronchodilators in COPD, including new data for once-daily indacaterol.

## Clinical benefits of twice-daily long-acting $\beta$ -2-agonists in COPD

The long-acting  $\beta$ (2)-agonists (LABA) formoterol and salmeterol were licensed for the treatment of COPD over a decade ago. Both drugs have a duration of action of approximately 12 hours, requiring a twice-daily dosage.<sup>8,9</sup> Formoterol and salmeterol are more effective than short-acting bronchodilators in improving lung function (FEV<sub>1</sub>),<sup>10–13</sup> with improvements in symptoms for formoterol versus ipratropium,<sup>10</sup> but no consistent effect on exacerbations versus regular ipratropium for both.<sup>10,12,13</sup> In a study by Rennard et al<sup>13</sup> salmeterol 50 microgram (mcg) twice daily was also not superior to regular ipratropium in regard to improving symptoms, dyspnea, and exercise. To date, there are no conclusive data from comparative studies investigating the effects of salmeterol and formoterol head to head on relevant long-term outcomes in COPD.<sup>14</sup> As was already known from asthma trials, formoterol has a faster onset of bronchodilator action in COPD versus salmeterol.<sup>15,16</sup> Due to the lack of any further supporting data, current guidelines do not recommend any of these two twice-daily LABAs over the other for the maintenance treatment of COPD.

Both formoterol and salmeterol have been extensively studied as monotherapy for COPD as control arms in the pivotal studies investigating the efficacy of inhaled corticosteroids/LABA fixed-dose combination.<sup>17–20</sup> In these studies, LABA monotherapy was associated with numerous clinical improvements; however, as no regular short-acting bronchodilator comparator was investigated in any of these trials, the data do not allow any definite conclusion about the comparative efficacy of twice-daily versus short-acting  $\beta$ -agonists in COPD. Direct comparisons between twice-daily LABAs and the once-daily anticholinergic tiotropium in patients with COPD have generally been short term, with

one report of two combined studies of 6 months' duration.<sup>21</sup> In comparison with salmeterol, tiotropium provided greater improvements in lung function and symptoms,<sup>21,22</sup> whereas there was only a numerical reduction in exacerbations compared with salmeterol. A subsequent 12-week randomized, double-blind study versus salmeterol documented superior bronchodilation during 12-hour testing.<sup>23</sup> Formoterol provided similar bronchodilation to tiotropium 12 hours after inhalation, but the magnitude of effect was higher during the first 2 hours post-dose, consistent with a faster onset of bronchodilator action for formoterol.<sup>24</sup> A 6-month study comparing the combination of tiotropium and formoterol with single components and placebo reported no differences in outcomes of formoterol monotherapy versus tiotropium.<sup>25</sup> In general, the evidence level has not shown clear distinctions between twice-daily LABAs and tiotropium on more clinically oriented outcomes. Currently, an ongoing large-scale study will directly compare the effect of tiotropium with salmeterol on COPD exacerbations.<sup>26</sup>

## Indacaterol: once-daily $\beta$ -2-agonist with 24-hour duration of action

In December 2009, the once-daily LABA indacaterol was approved for the maintenance treatment of COPD in the European Union at a recommended dose of 150 mcg once daily and a maximum dose of 300 mcg once daily. Indacaterol is a partial  $\beta$ (2)-agonist with high intrinsic efficacy at the receptor level. Unlike other partial agonists, it does not exhibit antagonistic behaviour in the presence of isoprenaline ("near full agonist").<sup>27</sup> Potency and intrinsic efficacy have been demonstrated in various models, including recombinant receptors, guinea pig trachea, isolated human bronchus, and human lung slices, with a selectivity ratio for indacaterol of 28 and 22 against  $\beta$ <sub>1</sub> and  $\beta$ <sub>3</sub> receptors.<sup>27–29</sup> In these studies, a fast onset of action and longer duration of action versus formoterol and salmeterol were also demonstrated. Although the prolonged duration of action of indacaterol versus other lipophilic  $\beta$ (2)-agonists like salmeterol can potentially be explained by the higher affinity of indacaterol to lipid raft domains within the membrane,<sup>30</sup> its fast onset of action is related to the high intrinsic efficacy at the receptor level.<sup>31</sup> Pharmacokinetic data taken during multiple-dose studies of indacaterol 400 mcg or 800 mcg once daily for 14 days demonstrated rapid absorption and a mean elimination half life of >30 hours, whereas, in a single-dose study, doses between 600 mcg and 2000 mcg were rapidly absorbed with maximum serum concentrations reached within 15 minutes.<sup>32,33</sup> Steady state after inhalation was reached within 12 days of once-daily dosing.<sup>34</sup>

## Clinical data for once-daily indacaterol

At the time of writing, several thousands of patients with COPD have received indacaterol in various doses for up to 52 weeks of treatment during the Phase II and III clinical program. Early clinical studies suggested that indacaterol produces rapid (within 5 minutes) and sustained (for at least 24 hours) bronchodilation in patients with various degrees of airflow obstruction.<sup>35,36</sup> Further, a study by Beier et al<sup>37</sup> confirmed that a single dose of indacaterol 300 mcg provided a greater effect on airflow obstruction and resting hyperinflation (inspiratory capacity) in patients with COPD than twice-daily formoterol 12 mcg.<sup>37</sup>

In the randomized, controlled Phase III COPD trials investigating the effects of treatment with 150 mcg or 300 mcg indacaterol once daily for up to 52 weeks' duration, indacaterol effectively improved numerous clinical outcomes over placebo, including trough FEV<sub>1</sub>, symptom control, dyspnea, quality of life, and exacerbations.<sup>38–40</sup> However, the Phase III studies also incorporated several active comparator drugs, including the twice-daily LABAs formoterol and salmeterol and the once-daily anticholinergic tiotropium.

In a 2-week, open-label comparison study of indacaterol 300 mcg once daily versus salmeterol 50 mcg twice daily, trough FEV<sub>1</sub> on day 14 for indacaterol was 90 mL higher than for salmeterol ( $P = 0.011$ ). This was also accompanied by superior improvements in resting inspiratory capacity across a full 24-hour assessment period on day 14, reaching statistical significance at most post-dose timepoints.<sup>41</sup>

Compared with salmeterol 50 mcg twice daily, indacaterol 150 mcg once daily was superior in improving trough FEV<sub>1</sub> after 12 weeks and 26 weeks (differences +60 mL and +70 mL, respectively,  $P < 0.001$ ), quality of life, dyspnea, and need for additional rescue medication in a randomized, double-blind, comparison study.<sup>39</sup> Superior clinical efficacy of 150 mcg indacaterol once daily versus salmeterol twice daily was also confirmed in a double-blind, 12-week comparison study.<sup>42</sup>

A long-term comparison of indacaterol 300 mcg once daily over 52 weeks showed superior effects of indacaterol over formoterol 12 mcg twice daily on lung function (trough FEV<sub>1</sub>), dyspnea, and rescue medication usage.<sup>43</sup> In a pooled analysis, it appeared that 150 mcg indacaterol once daily also provided superior benefits on trough FEV<sub>1</sub> after 12 weeks of treatment versus formoterol 12 mcg twice daily, regardless of concomitant use of inhaled corticosteroids.<sup>44</sup>

During a 26-week randomized comparison trial, indacaterol 150 mcg or 300 mcg once daily was compared with

placebo and open-label tiotropium 18 mcg once daily over 26 weeks.<sup>45</sup> Trough FEV<sub>1</sub> at week 12 increased versus placebo by 180 mL with both indacaterol doses and by 140 mL with tiotropium (all  $P < 0.001$ ). At week 12 and week 26, there were also significant treatment differences between indacaterol at both doses and tiotropium (+40–50 mL favoring indacaterol), when tested for superiority ( $P < 0.05$ , all comparisons), although the interpretability of these data may be complicated by the fact that tiotropium was administered open label. Further clinically relevant improvements were observed with indacaterol versus placebo for dyspnea and health-related quality of life.

However, a fully (third-party) blinded, randomized, double-blinded, crossover clinical comparison of the effects of indacaterol 150 mcg and 300 mcg once daily versus tiotropium 18 mcg once daily or matching placebo proved noninferiority for both doses of indacaterol in regard to trough FEV<sub>1</sub> after 14 days of treatment compared with tiotropium 18 mcg, with mean trough FEV<sub>1</sub> values again favoring indacaterol 150 mcg (+50 mL vs tiotropium) and 300 mcg (+30 mL vs tiotropium). Although superiority was not proven statistically, these data nevertheless altogether indicate that indacaterol provides at least equipotent bronchodilation after 14 days compared with tiotropium.<sup>46</sup>

Finally, a further blinded comparison of indacaterol 150 mcg with tiotropium 18 mcg once daily showed comparable effects on trough FEV<sub>1</sub> after 12 weeks (1.44 L for indacaterol vs 1.43 L for tiotropium,  $P < 0.001$  for noninferiority), with additional benefits for indacaterol over tiotropium in regard to dyspnea, health-related quality of life, and rescue medication use.<sup>47</sup>

## Pooled analyses and subgroups

Pooled analyses, including some of the aforementioned clinical trials, were published during the American Thoracic Society 2010 annual meeting. These data demonstrated that indacaterol 150 mcg or 300 mcg once daily administered over 3–6 months provides significant and clinically meaningful improvement of symptoms, health-related quality of life, rescue medication use, and exacerbation rates in moderate-to-severe COPD patients.<sup>48,49</sup> Further, it was shown that longer-term beneficial effects of indacaterol were not dependent on age, concomitant inhaled corticosteroid use, and baseline bronchodilator reversibility.<sup>44,50,51</sup>

## Safety

Safety studies with indacaterol addressed the occurrence of adverse events and serious adverse events, cardiovascular

safety, and known class effects from  $\beta$ -agonists due to systemic absorption of drug, potentially leading to tachycardia, palpitations, changes in electrocardiogram parameters (eg, QT prolongation), hypokalemia, increase in blood glucose levels, and adverse events like tremor or headache.

## Phase II studies

Three multiple-dose Phase II trials primarily evaluating safety and tolerability of indacaterol have as yet been fully published, two in asthma<sup>52,53</sup> and one in COPD.<sup>54</sup> These three trials incorporated a treatment duration of 28 days. However, trials used different dosages of indacaterol, and indacaterol was delivered in a multiple-dose dry powder inhaler, which differs from the currently marketed single-dose dry powder inhaler device. In studies by Yang et al<sup>53</sup> and Beier et al<sup>54</sup> indacaterol at once-daily doses of 400 mcg and 800 mcg from single-dose dry powder inhaler was used, whereas Chuchalin et al<sup>52</sup> evaluated indacaterol at dosages of 200 mcg, 400 mcg, or 600 mcg daily.

In all studies, the overall incidence of adverse events was similar for active treatment and placebo groups, and there was no dose-related increase in the incidence of adverse events. The most common adverse event associated with indacaterol use was cough, which was reported in 16.9% and 15.3% of patients in the indacaterol 400 mcg and 800 mcg groups, respectively, in the study by Yang et al;<sup>53</sup> in 8.1%, 17.1%, and 10.3% of patients in the indacaterol 600 mcg, 400 mcg, and 200 mcg groups, respectively, in the study by Chuchalin et al;<sup>52</sup> and in 14.7% and 28.4% of patients in the 400 mcg and 800 mcg groups, respectively, in the study by Beier et al.<sup>54</sup> For the typical class effects of  $\beta$ -agonists, only modest effects were observed. Although Yang et al<sup>53</sup> reported small changes in postdose serum potassium and glucose levels of asthmatic patients exposed to indacaterol 400 mcg or 800 mcg, no effect on these parameters was observed in the study by Beier et al<sup>54</sup> using the same doses in COPD patients. In the study by Chuchalin et al<sup>52</sup> in asthmatics, no effect of once-daily indacaterol 200 mcg, 400 mcg, and 600 mcg on potassium and glucose levels was observed. In this study, there were also no changes in pulse rate, blood pressure, or mean QTc interval after 28 days' exposure to indacaterol. However, there was a small, statistically significant increase of the QTc interval (8.9 ms) and pulse rate (4.9 beats per minute) with the 800 mcg dose (n = 59) on day 28 in the study by Yang et al<sup>53</sup> but these changes were numerically small and not clinically significant. Again, none of these effects

was observed by Beier et al<sup>54</sup> in the study using indacaterol 400 mcg and 800 mcg once daily in COPD patients.

The effect of indacaterol at dosages up to 600 mcg once daily over 14 days on QTc values has been studied in a thorough QT study in healthy subjects. All doses of indacaterol had no effect on mean QTc values, and changes were within the regulatory safety margin.<sup>55</sup> Finally, inhalation of suprathreshold single doses of indacaterol up to 3000 mcg in COPD patients revealed only minor systemic effects.<sup>56</sup>

## Phase III trials

In a 12-week trial investigating 150 mcg indacaterol versus placebo for 12 weeks,<sup>40</sup> the incidence of any adverse event was comparable for indacaterol and placebo (indacaterol n = 104, 49.3%; placebo n = 96, 46.8%). There were no cardiac safety issues. No patient had a prolongation of the QTc interval beyond 500 msec absolute or >60 msec increase from baseline, and no increase of pulse rate was observed.

During a further 26-week comparison trial, the frequency of adverse events was comparable for indacaterol 150 mcg and 300 mcg with open-label tiotropium and placebo. Similarly, the overall proportion of patients with an increase in QTcF of 30–60 msec or >60 msec was low and comparable with tiotropium and placebo.<sup>57</sup>

Finally, during the large-scale comparator trial with indacaterol 300 mcg and 600 mcg versus formoterol 12 mcg twice daily and placebo over 1 year, adverse events and severe adverse events occurred in a similar frequency for both doses of indacaterol and placebo. Again, the overall proportion of patients with an increase in QTcF of 30–60 msec or >60 msec was low and comparable with formoterol and placebo. Further, indacaterol at both doses did not affect mean serum potassium at week 52, mean QTc values, or average pulse rate.<sup>43</sup>

Chapman et al<sup>38</sup> recently reported on the safety of indacaterol 150 mcg and 300 mcg once daily versus placebo during the 26-week extension phase of the 26-week open-label tiotropium comparison study, thereby providing data over a total duration of 52 weeks. In their analysis, adverse events occurred in 76%, 77%, and 68% of subjects receiving indacaterol 150  $\mu$ g, 300  $\mu$ g, and placebo, respectively, whereas serious adverse events occurred in 10.4%, 12.3%, and 10.5%, respectively. There were no clinically significant effects with indacaterol at both doses on QTc interval or potassium or glucose levels.

Finally, Worth et al<sup>58</sup> specifically reported on the cardiovascular and cerebrovascular safety of indacaterol 150 mcg and



300 mcg once daily versus placebo and comparator drugs salmeterol, formoterol, and tiotropium using Antiplatelet Trialists' Collaboration criteria for cardio-/cerebrovascular adverse events. Safety data were pooled from three clinical trials.<sup>39,43,45</sup> The risk of cardio-/cerebrovascular events was not significantly increased for indacaterol at both doses versus placebo, and the incidence of notable QTc interval changes (>60 ms versus baseline) was low with all treatments. In a subgroup of patients analyzed by Holter monitoring, there was no relevant effect of indacaterol versus placebo on the development of arrhythmias. Mortality was numerically lower with all active treatments than with placebo, with a 70% lower relative risk with indacaterol at both doses versus placebo ( $P = 0.054$ ).

In light of the approved recommended dose of 150 mcg and a maximal recommended dose of 300 mcg once daily, the overall safety data indicate a favorable tolerability profile and a broad therapeutic window for indacaterol.

## Summary

Bronchodilators are the cornerstone of treatment for all COPD severity stages, with a central role in the symptomatic management of COPD. They are given on an as-needed basis or on a regular basis to prevent or reduce symptoms and exacerbations. The principal inhaled bronchodilator treatments are  $\beta(2)$ -agonists and anticholinergics, used alone or in combination. There is broad evidence that regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators. New data from trials with the novel once-daily  $\beta(2)$ -agonist indacaterol indicate superior bronchodilation and clinical efficacy over twice-daily LABAs salmeterol and formoterol and at least equipotent bronchodilation as once-daily tiotropium. Therapeutic developments in COPD indicate a change shift from short-acting bronchodilators with multiple dosings per day to reduced dosing frequency and prolonged duration of action, including once-daily treatment.

## Disclosure

JB and KMB have both participated as speakers in scientific meetings or courses organized and financed by various pharmaceutical companies (AstraZeneca, Almirall, GSK, Boehringer, Novartis, Pfizer, Takeda) in 2006–2011. JB and KMB have also been reimbursed for travel expenses for attending and presenting at scientific conferences by various pharmaceutical companies. The institution where JB and KMB are currently employed has received reimbursement for design

and performance or participation in single or multi-centre clinical trials in 2004–2011 from various companies (Almirall, Altana, AstraZeneca, Boehringer Ingelheim, Cytos, Novartis, GSK, Revotar Biopharmaceuticals, EpiGenesis, Corus Pharma, Merck Sharp & Dohme, Fujisawa, Pfizer, Medapharma). JB and KMB have received compensations for serving on advisory boards for AstraZeneca, Almirall, Cytos, Boehringer Ingelheim, Novartis, and Revotar AG from 2006–2011.

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