

# Indacaterol: a new once daily long-acting beta<sub>2</sub> adrenoceptor agonist

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**Introduction:** Indacaterol is a novel once daily long-acting beta agonist (LABA) developed for the treatment of chronic obstructive pulmonary disease (COPD) and asthma.

**Aims:** This review summarizes preclinical and clinical data of indacaterol, including all data generated during the phase II trial program, and further discusses the outlook and potential of the drug in the future treatment of COPD and asthma.

**Evidence review:** Clinical studies suggest that indacaterol produces rapid and sustained bronchodilation in COPD patients and asthmatics of different severities. Until now, clinical studies of up to 28 days' duration have been published that have confirmed the suitability of indacaterol for once daily dosing, along with a favorable overall safety and tolerability profile.

**Outcomes summary:** Indacaterol monotherapy has potential in COPD, where antiinflammatory treatment is not fully established and issues about a potential risk of LABA use causing excess mortality have not been raised. In addition, indacaterol represents an option for future combination therapies in both asthma and COPD. However, more data are required, particularly in COPD, to fully assess the therapeutic potential of indacaterol in improving symptoms, quality of life, exacerbation rates, disease progression, exercise capacity, and hyperinflation. The currently ongoing phase III clinical trial program will add knowledge in respect to many long-term efficacy outcomes and gather further safety and tolerability data in both asthma and COPD.

**Keywords:** indacaterol, long-acting beta agonist, asthma, COPD

## Core evidence outcomes summary for indacaterol in COPD and asthma

Outcome measure	Evidence	Implications
<b>Patient-oriented evidence</b>		
Tolerability	Clear	Overall incidence of adverse events similar to placebo and no dose-related increase in incidence Favorable tolerability profile and a wide therapeutic window
<b>Disease-oriented evidence</b>		
FEV <sub>1</sub>	Clear	Sustained and rapid improvement in lung function comparable to salbutamol and formoterol
FVC	Clear	Sustained and rapid improvement in lung function comparable to salbutamol and formoterol
Inspiratory capacity <sup>a</sup>	Moderate	Prolonged airway patency through sustained bronchodilation, which is an important factor reinforcing lung emptying and reduction of hyperinflation in COPD
<b>Note:</b> <sup>a</sup> COPD patients. <b>Abbreviations:</b> COPD, chronic obstructive pulmonary disease; FEV <sub>1</sub> , forced expiratory volume in 1 s; FVC, forced vital capacity.		

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## Introduction

An important step in simplifying the management of chronic airway diseases like asthma and chronic obstructive pulmonary disease (COPD) and improving the adherence with prescribed therapy is the attempt to reduce dose frequency to the minimum needed to maintain disease control. The incorporation of once daily dosing may represent a useful strategy to improve compliance and is also a regimen that may be preferred by most affected patients.<sup>1</sup>

Inhaled beta<sub>2</sub> adrenoceptor agonists are the most effective bronchodilators for the management of asthma. The Global Initiative for Asthma (GINA) guidelines recognize the role of long-acting beta<sub>2</sub> agonists (LABAs) for the optimal treatment of moderate-to-severe persistent asthma.<sup>2</sup> Currently available inhaled LABAs have durations of action of approximately 12 hours at recommended doses, necessitating twice daily dosing to provide optimal clinical efficacy.<sup>3</sup> The availability of a once daily beta<sub>2</sub> agonist could be expected to improve the treatment of asthma by providing patients with greater convenience and sustained benefit.

## Current therapy options

COPD is characterized by a progressive decline in lung function, however, current guidelines emphasize that the condition is both preventable and treatable. Bronchodilators are the cornerstone of treatment for all COPD severity stages. In more pronounced stages of airflow obstruction, the regular use of one or more long-acting bronchodilators is recommended.<sup>4</sup> These agents include the twice daily beta<sub>2</sub> agonists, formoterol and salmeterol, and the once daily anticholinergic, tiotropium. Long-acting bronchodilators may improve exercise tolerance<sup>5-7</sup> as a result of bronchodilation and reduction of both static and dynamic hyperinflation. Once daily anticholinergics have also been shown to produce clinically superior effects when compared to short-acting agents with multiple daily doses.<sup>8</sup> A single head-to-head comparison of the once daily bronchodilator tiotropium with twice daily salmeterol also indicates superior bronchodilation after 6 months of treatment.<sup>9</sup> Thus, it appears valid to speculate that a once daily beta<sub>2</sub> agonist as compared to twice daily agents will produce greater long-term benefit.

Indacaterol is a novel once daily beta<sub>2</sub> adrenoceptor agonist developed for the treatment of asthma and COPD. This review will give a summary of preclinical and clinical data including all data generated during the phase II clinical development.

## Pharmacology and preclinical data

Indacaterol is a beta<sub>2</sub> agonist bronchodilator in development for the treatment of asthma and COPD. Indacaterol is an almost full beta<sub>2</sub> agonist with high intrinsic efficacy. Unlike partial agonists, it does not exhibit antagonistic behaviour in the presence of isoprenaline.<sup>10</sup> Potency and intrinsic efficacy have been demonstrated in various models including recombinant receptors,<sup>11</sup> guinea pig trachea,<sup>11</sup> isolated human bronchus,<sup>10</sup> and human lung slices,<sup>12</sup> with a selectivity ratio for indacaterol of 28 and 22 against beta<sub>1</sub> and beta<sub>3</sub> receptors.<sup>11</sup> In these studies, a fast onset of action and longer duration of action versus formoterol and salmeterol was also demonstrated. Pharmacokinetic data taken during multiple-dose studies of indacaterol 400 or 800 mcg once daily for 14 days demonstrated rapid absorption and a mean elimination half life of >30 hours.<sup>13</sup> Likewise, in a single-dose study, doses between 600 and 2000 mcg were rapidly absorbed with maximum serum concentrations reached within 15 min.<sup>14</sup> All doses were well tolerated with a good safety profile, and were not associated with consistent or clinically relevant effects on systemic beta agonist mediated events.

## Clinical data

At the time of writing, more than 1700 patients with asthma or COPD have received indacaterol in various doses for up to 28 days of treatment during the phase II program.

## Efficacy

In both asthma and COPD, single doses of indacaterol produced significant and sustained 24-hour bronchodilation, with regard to trough forced expiratory volume in 1 s (FEV<sub>1</sub>) and forced vital capacity (FVC). In a study by Beeh et al<sup>15</sup> in asthmatics, the mean percentage increases in FEV<sub>1</sub> versus placebo with indacaterol 200 and 400 mcg delivered from a metered-dose inhaler (MDI) were, respectively, 7.6% and 14.9% at 30 min, and 7.5% and 10.4% at 21 hours postdose. Both doses were significantly superior to placebo in improving FEV<sub>1</sub> from 5 min to 25 hours, inclusively. These results were also confirmed in a subset of persistent asthmatics, where indacaterol 200 and 400 mcg increased FEV<sub>1</sub> by 0.17 L at 5 min (400 mcg) and 0.21 L at 10 min (200 mcg) compared with placebo.<sup>16</sup> Hence, early studies indicated that indacaterol not only had a long duration of action, but also a rapid onset comparable to that of salbutamol or formoterol.

In a 7-day dose-ranging study,<sup>17</sup> all doses of indacaterol (50, 100, 200, 400 mcg) either as a multiple-dose dry powder inhaler (MDDPI) or a single-dose dry powder inhaler (SDDPI) produced significant bronchodilation over placebo

at 22–24 hours postinhalation on days 1 and 7, respectively. Significant effects for all doses were already demonstrable at 5 min postdose on day 1. Of the doses evaluated, 200 mcg once daily appeared to be optimum as shown by trough FEV<sub>1</sub> 24 hours postdose on days 1 and 7. This was further supported by a multiple-dose, dose-ranging study by Kannies et al<sup>18</sup> and a 28-day safety study by Chuchalin et al.<sup>19</sup> Finally, indacaterol 200 mcg was also superior to salbutamol 200 mcg and salmeterol 50 mcg in a single-dose study in persistent asthmatics<sup>20</sup> Peak bronchodilation in these studies was observed between 2–4 hours postdose.

While indacaterol at different doses appears to produce effective bronchodilation in asthmatics, the further development of this drug for asthma was somewhat overshadowed by the renewed discussion about the long-term safety of LABAs in asthma, since published studies suggested an excess incidence of asthma-related mortality associated with the use of this class of drugs,<sup>21,22</sup> in particular when used as monotherapy. Although these findings have been criticized and debated,<sup>23</sup> the use of LABAs as monotherapy is nevertheless not recommended in current asthma guidelines, where this class of agent should only be prescribed together with an antiinflammatory agent, preferably an inhaled corticosteroid. Thus, the future of indacaterol as monotherapy for asthma remains questionable. However, when combined with a once daily inhaled corticosteroid (eg, mometasone) in a fixed-dose inhaler combination, such a product could considerably improve the current treatment options for asthma by at least improving therapy adherence and simplicity.

## COPD

Whereas the use of indacaterol monotherapy in asthma may be limited, there is clearly a sound rationale for its use in COPD, where guidelines recommend long-acting bronchodilators as first-line agents for patients with moderate, severe, and very severe disease stage. Thus, it is expected that the clinical development of indacaterol will have a strong focus on COPD.

Published data suggest that single doses of indacaterol produce rapid and sustained bronchodilation in patients with moderate to severe COPD. Rennard et al<sup>24</sup> conducted a dose-ranging study of once daily indacaterol 50, 100, 200, and 400 mcg for 7 days in COPD patients (prebronchodilator FEV<sub>1</sub> > 40% of predicted). While on day 1 both indacaterol 200 and 400 mcg improved FEV<sub>1</sub> by more than 120 mL (suggested as the minimal clinically important difference), all doses of indacaterol were superior to placebo on day 7, with trough FEV<sub>1</sub> values of 160–230 mL versus placebo. There

was also a clear dose response in this study. Moreover, the study incorporated an open-label comparison with tiotropium 18 mcg once daily for 7 days. Although not truly a direct, blinded comparison, the results of Rennard et al<sup>24</sup> suggested superior peak [area under the curve (AUC) at 0–4 hours post-dose] and trough (AUC 22–24 hours postdose) FEV<sub>1</sub> values for indacaterol 200 and 400 mcg on days 1 and 7. Similar observations were made in a study by Beier et al<sup>25</sup> although the primary endpoint of this study was safety. Nevertheless, using indacaterol 400 or 800 mcg versus placebo over 28 days' treatment duration, Beier et al<sup>25</sup> observed trough FEV<sub>1</sub> improvements of 230 and 210 mL for 400 and 800 mcg, respectively, on day 14, and 220 and 210 mL for 400 and 800 mcg, respectively, on day 28. Similar to observations in multiple-dose studies in asthmatics,<sup>18,26</sup> there was no evidence of bronchodilator tolerance over the time period studied (up to 28 days).

## Other endpoints

Particularly in COPD it is increasingly recognized that more patient-oriented clinical endpoints other than FEV<sub>1</sub> are of vital importance in the long-term evaluation of COPD therapies. These include quality of life, symptoms (eg, dyspnea), exacerbation rates, exercise tolerance and, finally, lung mechanics including static or dynamic hyperinflation.<sup>27</sup> For most of these variables, no data for indacaterol have been published so far, but it is expected that these will be addressed in the ongoing phase III clinical development program.

There is, however, a single study investigating the effect of single-dose indacaterol 300 mcg versus formoterol 12 mcg twice daily and placebo on resting hyperinflation (inspiratory capacity) in patients with COPD. In the study by Pascoe et al<sup>28</sup> indacaterol was superior to formoterol twice daily in improving FEV<sub>1</sub> at 8 and 24 hours postdose, and also had marked superiority in improving resting inspiratory capacity at all time points between 4 and 24 hours postdose.<sup>28</sup> These data support the concept of prolonged airway patency through sustained bronchodilation as an important factor reinforcing lung emptying and reduction of hyperinflation in COPD, as observed in studies with the once daily anticholinergic tiotropium.<sup>29</sup>

## Safety and tolerability

Safety studies with indacaterol were designed to address typically anticipated class effects from beta agonists due to systemic absorption of drug, potentially leading to tachycardia, palpitations, changes in electrocardiogram parameters (eg, QT prolongation), tremor, hypokalemia, increase in

blood glucose levels, or headache. Three trials primarily evaluating safety and tolerability of indacaterol have been published, two in asthma,<sup>19,26</sup> and one in COPD.<sup>25</sup> All three trials incorporated a treatment duration of 28 days. In the studies by Yang et al and Beier et al indacaterol at once daily doses of 400 and 800 mcg SDDPI was used, whereas Chuchalin et al evaluated indacaterol at doses of 200, 400, 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 and 800 mcg groups, respectively, in the study by Yang et al<sup>26</sup> in 8.1%, 17.1%, and 10.3% of patients in the indacaterol 600, 400, and 200 mcg groups, respectively, in the study by Chuchalin et al<sup>19</sup> and finally in 14.7% and 28.4% of patients in the 400 and 800 mcg groups, respectively, in the study by Beier et al<sup>25</sup>. This cough was, however, mild in severity, transient in nature and duration, and tended to decline with the duration of treatment. Further, treatment-associated cough did not lead to discontinuation of the study in any patients.

For the typical class effects of beta agonists, only modest effects were observed. While Yang et al<sup>26</sup> reported small changes in postdose serum potassium and glucose levels of asthmatic patients exposed to indacaterol 400 or 800 mcg, no effect on these parameters was observed in the study by Beier et al<sup>25</sup> using the same doses in COPD patients. However, in the study by Yang et al<sup>26</sup> only few patients had potassium or glucose levels outside the normal range. In the study by Chuchalin et al<sup>19</sup> in asthmatics, no effect of once daily indacaterol 200, 400, 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 min) with the 800 mcg dose (n = 59) on day 28 in the study by Yang et al<sup>26</sup> but these changes were numerically small and not clinically significant. Again, none of these effects were observed by Beier et al<sup>25</sup> in the study using indacaterol 400 and 800 mcg once daily in COPD patients.

Nevertheless, assuming that the doses of 400, 600, and 800 mcg represent suprathreshold doses (the selected dose for the phase III studies now appears to be 150 or 300 mcg once daily), the overall safety data imply a favorable tolerability profile and a wide therapeutic window. This conclusion is also supported by data from a single-dose

study using suprathreshold doses of indacaterol, salbutamol, and salmeterol, demonstrating a good overall safety profile of indacaterol.<sup>20</sup>

## Outcomes summary

Indacaterol is a novel once daily LABA developed for the treatment of obstructive airway disease, namely COPD and asthma. Clinical studies suggest that indacaterol produced rapid (within 5 min) and sustained (at least 24 hours) bronchodilation in patients with COPD and asthma of various severities. Exposure to a maximum of 28 days' treatment with different doses of indacaterol confirmed the suitability of the drug for once daily dosing, with a favorable overall safety profile, and lasting efficacy without evidence of development of tolerance. Early, open-label data indicate that indacaterol may be at least as effective as tiotropium in producing long-lasting bronchodilation. However, this needs to be investigated in well-controlled, fully blinded clinical trials. Interpretation of clinical data of indacaterol in asthma and COPD is somewhat complicated by the fact that several doses and different devices were studied (MDI, SDDPI, MDDPI). At present, the clinical trial registry lists the majority of ongoing studies with indacaterol at doses of 150 or 300 mcg once daily delivered by dry powder inhaler. Thus, it is anticipated that these doses will represent the marketed doses.

Clearly, there is more prospect for indacaterol monotherapy in COPD, where antiinflammatory treatment is not fully established and – in contrast to the ongoing discussion in asthma – issues about a potential risk of LABA use causing excess mortality have not been raised. In addition, indacaterol represents an attractive partner agent for future combination therapies, for example once daily fixed combination with an inhaled corticosteroid for both asthma and COPD, with an inhaled once daily anticholinergic bronchodilator in COPD (eg, “super”-Combivent<sup>TM</sup>), or even in a triple combination with an inhaled corticosteroid and long-acting anticholinergic for COPD.

However, more data are required, particularly in COPD, to fully assess the therapeutic potential of indacaterol in improving symptoms, quality of life, exacerbation rates, disease progression, exercise capacity, and hyperinflation. The currently ongoing phase III clinical trial program will add knowledge in respect to many long-term efficacy outcomes and gather further safety and tolerability data in both asthma and COPD.

## Disclosure

KMB and JB received compensation for serving on an advisory board for Novartis, Germany. Both have participated

as speaker in scientific meetings or courses organized and financed by various pharmaceutical companies (AstraZeneca, GSK, Boehringer, Novartis, Pfizer) in 2003, 2004, 2005, 2006, 2007, and 2008. KMB or JB have been reimbursed for travel expenses by Boehringer, Novartis, and Pfizer for attending and presenting at scientific conferences. The institution where KMB and JB are currently employed has received compensations for design and performance or participation in single or multi-centre clinical trials in 2004–2008 from several companies (Altana, AstraZeneca, Boehringer Ingelheim, Cytos, Novartis, GSK, Revotar Biopharmaceuticals, EpiGenesis, Corus Pharma, Almirall Prodesfarma, Merck Sharp & Dohme, Fujisawa, Pfizer, Medapharma).

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