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REVIEW

Indacaterol, a Novel Inhaled, Once-Daily, Long-Acting Beta$_2$-Agonist for the Treatment of Obstructive Airways Diseases

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ABSTRACT

Indacaterol is a novel once-daily, long-acting beta$_2$-agonist developed for the treatment of chronic obstructive pulmonary disease (COPD) and asthma. The present review summarizes the preclinical and clinical data of indacaterol, including recent data from phase II and III trials. These clinical studies suggest that indacaterol produces rapid and sustained bronchodilation in patients with COPD, and asthma of different severities. Until now, clinical studies of up to 1-year's duration have been at least partially published, which have confirmed the suitability of indacaterol for once-daily dosing, along with a favorable overall safety and tolerability profile in the long-term treatment of COPD. Data on relevant outcomes in asthma are more limited, especially with regard to chronic treatment. Therefore, it appears that indacaterol monotherapy will have its therapeutic potential primarily in COPD, where anti-inflammatory treatment is not fully established and issues about a potential risk of long-acting beta$_2$-agonist use causing increased mortality have not been raised. As data from more advanced clinical trials have been published, a more complete picture of the full therapeutic potential of indacaterol in COPD has emerged, including patient-reported outcomes (eg, symptoms and quality of life) or additional pivotal outcomes (eg, exacerbation rates, disease progression, exercise capacity, and the development of hyperinflation). Finally, the pharmacological profile of indacaterol makes it an attractive partnering agent for future fixed-combination therapies in both asthma and COPD, eg, with once-daily inhaled corticosteroids or long-acting antimuscarinergic bronchodilators. The outlook and potential of indacaterol are further discussed.

Keywords: asthma; bronchodilator treatment; clinical trials; COPD; indacaterol; long-acting beta-agonists

INTRODUCTION

A reduction of dosing frequency for inhaled therapies to a required minimum is an important goal to eventually simplify the management of chronic airways diseases,

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such as chronic obstructive pulmonary disease (COPD) or asthma. Once-daily dosing of inhaled therapies has in the more recent past been proven to represent a useful strategy in improving compliance, eg, with the introduction of once-daily inhaled corticosteroids in asthma, or the once-daily bronchodilator tiotropium in COPD. Many patients who are chronically ill also prefer a once-daily regimen.[1]

While inhaled beta$_2$-agonists are the most effective bronchodilators for the management of asthma and their importance in the treatment of moderate-to-severe asthma in combination with inhaled corticosteroids is supported by current Global Initiative for Asthma (GINA) guidelines,[2] currently available inhaled long-acting beta$_2$-agonists (LABAs) have durations of action of approximately 12 hours at recommended doses, necessitating twice-daily dosing to provide optimal clinical efficacy.[3] The availability of a once-daily beta$_2$-agonist could be expected to improve the treatment of asthma by providing patients with greater convenience and sustained benefit.

In contrast to asthma, COPD is mainly caused by noxious inhalants, in particular cigarette smoke, and physiologically characterized by chronic, poorly reversible airflow obstruction, the presence of emphysema, and a progressive decline in lung function over time.[4] Current Global Initiative for Obstructive Lung Disease (GOLD) guidelines, however, 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.[4] These agents include the twice-daily beta$_2$-agonists formoterol and salmeterol, and the once-daily anticholinergic tiotropium. Long-acting bronchodilators may improve exercise tolerance[5-7] 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 with short-acting agents with multiple daily doses.[8] 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 with tiotropium.[9] Therefore, it appears valid to speculate that a once-daily, beta$_2$-agonist as compared with twice-daily agents will produce greater long-term benefit.

Indacaterol is a novel once-daily, beta$_2$-agonist developed for the treatment of asthma and COPD. This review will give a summary on preclinical and clinical data, including all data generated during the phase II and, more recently, phase III clinical development.

PHARMACOLOGY AND PRECLINICAL DATA

Indacaterol is a beta$_2$-agonist with high intrinsic efficacy at the receptor level. In preclinical and in-vitro models it behaves like an almost full agonist as it does not exhibit antagonistic behavior in the presence of isoprenaline.[10] Potency and intrinsic efficacy have been demonstrated in various models, including recombinant receptors, guinea pig trachea,[11] isolated human bronchus,[10] and human lung slices,[12] with a selectivity ratio for indacaterol of 28 and 22 against beta$_1$- and beta$_3$-receptors.[11] In these studies, a fast onset and longer duration of action of indacaterol compared with formoterol and salmeterol was also demonstrated.[10-12] Pharmacokinetic data taken during multiple dose studies of indacaterol 400 or 800 mg once daily for 14 days demonstrated rapid absorption and a mean elimination half-life of >30 hours.[13] Likewise, in a single dose study, doses between

600 and 2000 mg were rapidly absorbed with maximum serum concentrations reached within 15 minutes.[14] All doses were well tolerated with a good safety profile, and were not associated with consistent or clinically relevant effects on systemic beta$_2$-agonist-mediated events.

Clinical Data

At the time of writing, several thousands of patients with asthma or COPD have received indacaterol in various doses for up to 52 weeks of treatment during the phase II and III clinical programs.

Bronchodilator Efficacy in Asthma

In studies in asthmatics, single doses of indacaterol produced significant and sustained 24-hour bronchodilation with regard to trough forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). In a study by Beeh et al.[15] in asthmatics, the mean percentage increases in FEV_1 versus placebo with indacaterol 200 and 400 mg delivered from a metered dose inhaler were, respectively, 7.6% and 14.9% at 30 minutes, and 7.5% and 10.4% at 21 hours postdose. Both doses were significantly superior to placebo in improving FEV_1 from 5 minutes to 25 hours, inclusively. These results were also confirmed in a subset of persistent asthmatics, where indacaterol 200 and 400 mg increased FEV_1 by 0.21 liters at 10 minutes (200 mg) and 0.17 liters at 5 minutes (400 mg) compared with placebo.[16] Hence, early studies indicated that indacaterol not only had a long duration of action, but also a rapid onset comparable with that of salbutamol or formoterol.

In a 7-day dose-ranging study, all doses of indacaterol (50, 100, 200, 400 mg) either as a multiple dose dry powder inhaler or a single dose dry powder inhaler produced significant bronchodilation over placebo at 22-24 hours post-inhalation on days 1 and 7, respectively.[17] Significant effects on FEV_1 for all doses were already demonstrable at 5 minutes postdose on day 1. Of the doses evaluated, 200 mg once daily appeared to be optimum as shown by trough FEV_1 24 hours postdose on days 1 and 7. This was further supported by a multiple dose, dose-ranging study by Kanniess et al.[18] and a 28-day safety study by Chuchalin et al.[19] Finally, indacaterol 200 mg was also superior to salbutamol 200 mg and salmeterol 50 mg in a single dose study in persistent asthmatics.[20] Peak bronchodilation in these studies was observed between 2 and 4 hours postdose.

While indacaterol at different doses appears to produce effective bronchodilation in asthmatics, further development of this drug for asthma was somewhat overshadowed by renewed discussion about the long-term safety of LABAs in asthma, as published studies suggested an excess incidence of asthma-related mortality associated with the use of this class of drugs,[21,22] in particular when used as a monotherapy. Although these findings have been criticized and debated,[23] the use of LABAs as a monotherapy is nevertheless not recommended in current GINA asthma guidelines, where this class of agent should only be prescribed together with an anti-inflammatory agent, preferably an inhaled corticosteroid. Thus, the future of indacaterol as a 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 treatment adherence and simplicity.

Bronchodilator Efficacy in COPD

Whereas the use of indacaterol monotherapy in asthma may be limited, there is clearly

a sound rationale for its use in COPD, where, for example, GOLD guidelines recommend long-acting bronchodilators as first-line agents for patients with the moderate, severe, and very severe disease stage. Thus, it is reasonable that the clinical development of indacaterol this far has 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.[24] conducted a dose-ranging study of once-daily indacaterol 50, 100, 200, and 400 mg for 7 days in patients with COPD (prebronchodilator FEV_1 ≥40% of predicted). While on day 1 both indacaterol 200 and 400 mg improved FEV_1 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_1 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 mg once daily for 7 days. Although not truly a direct, blinded comparison, the results of Rennard et al.[24] suggested superior peak (area under the curve [AUC] at 0-4 hours postdose) and trough (AUC 22-24 hours postdose) FEV_1 values for indacaterol 200 and 400 mg on days 1 and 7. Similar observations were made in a study by Beier et al.,[25] although the primary endpoint of this study was safety. Nevertheless, using indacaterol 400 or 800 mg versus placebo over the duration of treatment (28 days), Beier et al.[25] observed trough FEV_1 improvements of 230 and 210 mL for 400 and 800 mg, respectively, on day 14, and 220 and 210 mL for 400 and 800 mg, respectively, on day 28 (all $P<0.0001$). Similar to observations in multiple dose studies in asthmatics,[19,26] there was no evidence of bronchodilator tolerance over the time period studied (up to 28 days).

Additional Outcomes, Comparison with Other Bronchodilators, and Long-Term Efficacy

Particularly in COPD it is increasingly recognized that more patient-oriented clinical endpoints other than FEV_1 are of vital importance in the long-term evaluation of COPD treatments. These include quality of life, symptoms (eg, dyspnea), exacerbation rates, exercise tolerance and, finally, lung mechanics including static or dynamic hyperinflation.[27] Data for indacaterol from phase III trials have at least been published as abstracts at recent conferences for most of these variables.

A study by Beier et al.[28] investigated the effect of single dose indacaterol 300 mg versus formoterol 12 mg twice daily and placebo on airflow obstruction and resting hyperinflation (inspiratory capacity) in patients with COPD. In this study, once-daily indacaterol was significantly superior to formoterol twice daily in improving FEV_1 at 8 and 24 hours postdose ($P=0.014$ and $P=0.003$, respectively), and also had marked superiority in improving resting inspiratory capacity at all time points between 4 and 24 hours postdose (all $P<0.05$). These single dose data have been replicated and extended by a study by Bauwens et al.[29] comparing the effect of single dose indacaterol at three different doses (150, 300, and 600 mg) and formoterol 12 mg twice daily on 24-hour trough FEV_1. In their study, all doses of indacaterol resulted in larger trough FEV_1 over formoterol and placebo, with once-daily indacaterol at 600 mg and 300 mg also being statistically significantly superior to twice-daily formoterol in terms of trough FEV_1 improvement.

In another placebo-controlled trial the effect of 14 days treatment with indacaterol 300 mg once daily on resting hyperinflation, dynamic hyperinflation and exercise tolerance was studied by Khindri et al.[30] Using a constant-workload cycling ergometry protocol, indacaterol reduced

static hyperinflation, dynamic hyperinflation during peak and isotime, exercise endurance time and exercise-induced dyspnea at days 1 and 14 of treatment.

These data clearly support the concept of prolonged airways 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.[31]

Feldman et al.[32] conducted a 12-week efficacy and safety study with 150 mg indacaterol once daily or matching placebo in 416 subjects with COPD. In their study, the difference in 24-hour trough FEV_1 after 12 weeks was 130 mL in favor of indacaterol over placebo ($P<0.001$). The study also tested a symptom-based endpoint termed COPD "days of poor control," defined as any day in the patient diary with a minimum score for at least two symptoms out of five (cough, wheeze, sputum production, sputum colour, breathlessness). Treatment with 150-mg indacaterol once daily resulted in 9% fewer of these days in comparison with placebo ($P<0.001$). Fogarty et al.[33] compared the bronchodilator effect of indacaterol 150 and 300 mg once daily over 26 weeks against placebo and open-label tiotropium in 1683 patients with COPD. Both indacaterol 150 mg and 300 mg produced clinically meaningful improvements in 24-hour trough FEV_1 versus placebo after 12 weeks (180 mL difference, both $P<0.001$) and 26 weeks (160 mL and 180 mL difference versus placebo for indacaterol 150 mg and 300 mg, respectively, both $P<0.001$). Data comparing indacaterol with open-label tiotropium in this study, however, were not reported in this abstract.

Recently, preliminary data from an indacaterol phase III 1-year trial have been released. The 1-year phase III program consisted of a large-scale randomized trial comparing indacaterol 300 mg and 600 mg once daily with 12 mg formoterol twice daily, and placebo. The primary endpoint of that trial was 24-hour trough FEV_1 after 12 weeks of treatment. Secondary outcomes included 24-hour trough FEV_1 at day 2 and week 52 of treatment, time to first COPD exacerbation and incidence of exacerbations, and percentage of COPD "days of poor control."[34-36] The data on the bronchodilator effects, including the primary endpoint, were reported by Dahl et al.[34] Both indacaterol 300 mg and 600 mg once daily resulted in clinically meaningful improvements in trough FEV_1 at week 12 (170 mL difference over placebo for both doses, $P<0.001$). Trough FEV_1 improvements versus placebo at day 2 were 140 mL and 170 mL for indacaterol 300 mg and 600 mg, respectively, and 160 mL and 150 mL at week 52 (all $P<0.001$), indicating that the bronchodilator effect of indacaterol at both doses was preserved over time.

In addition, once-daily indacaterol delayed the time to first COPD exacerbation (hazard ratios 0.77, $P=0.029$, and 0.69, $P=0.003$, versus placebo for indacaterol 300 mg and 600 mg, respectively), as reported by Buhl et al.[35] The mean number of exacerbations per patient over 52 weeks was 0.52 for indacaterol 300 mg, 0.48 for indacaterol 600 mg, and 0.58 for placebo (no *P* values given).

Finally, Nonikov et al.[36] presented data on COPD symptom control during the 1-year study. Indacaterol 300 or 600 mg once daily reduced COPD days of poor control versus placebo by 4.7% ($P=0.013$) and 8.3% ($P<0.001$), respectively. Studies by Buhl et al.[35] and Nonikov et al.[36] also reported data for formoterol twice daily. They showed a delay in time to first exacerbation by formoterol (hazard ratio 0.77, $P=0.034$). A numerical reduction in the mean total number of exacerbations per patient (0.46 versus 0.58 with placebo, no *P* value given) was also seen. Finally, there was a 4.8% reduction in COPD days of poor control ($P=0.012$ versus placebo).

These results indicate that indacaterol 300 mg is at least as effective, and indacaterol 600 mg may be even more effective than formoterol twice daily in preventing exacerbations and improving symptoms. However, none of the cited authors have presented data from direct comparisons of indacaterol once daily with formoterol twice daily.

SAFETY AND TOLERABILITY

Safety studies with indacaterol were designed to address typical anticipated drug class effects from beta$_2$-agonists due to systemic absorption of drug, potentially leading to tachycardia, palpitations, changes in echocardiogram parameters (eg, heart rate QT interval [QT] prolongation), tremor, hypokalemia, increase in blood glucose levels, or headache. An initial single dose study using supratherapeutic doses of indacaterol, salbutamol, and salmeterol in patients with asthma indicated a good overall safety profile of indacaterol in this regard.[20] Moreover, three trials primarily evaluating safety and tolerability of indacaterol have been fully published, two in asthma[19,26] and one in COPD.[25] All three trials incorporated treatment duration of 28 days. In the studies by Yang et al.[26] and Beier et al.[25] indacaterol at once-daily doses of 400 mg and 800 mg single dose dry powder inhaler were used, whereas Chuchalin et al.[19] evaluated indacaterol at doses of 200, 400, or 600 mg 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 mg and 800 mg groups, respectively, in the study by Yang et al.,[26] in 8.1%, 17.1%, and 10.3% of patients in the indacaterol 600, 400, and 200 mg groups, respectively, in the study by Chuchalin et al.,[19] and finally in 14.7% and 28.4% of patients in the 400 and 800 mg groups, respectively, in the study by Beier et al.[25] 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.

These studies demonstrate that for the typical class effects of beta$_2$-agonists, only modest effects were observed. While Yang et al.[26] reported small changes in postdose serum potassium and glucose levels of patients with asthma exposed to indacaterol 400 mg or 800 mg, no effect on these parameters was observed in the study by Beier et al.[25] using the same doses in patients with COPD. However, in the study by Yang et al.,[26] only few patients had potassium or glucose levels outside the normal range. In the study by Chuchalin et al.[19] in asthmatics, no effect of once-daily indacaterol 200, 400, and 600 mg on potassium and glucose levels was observed. In this study, there were also no changes in pulse rate, blood pressure, or mean corrected-QT after 28 days' exposure to indacaterol. However, there was a small, statistically significant increase of the corrected-QT interval with the 800 mg dose 60 minutes post-inhalation on day 28 (+8.9 ms, $P<0.05$; $n=59$) and a small increase in mean pulse rate for the 800 mg/daily 60 minutes post-inhalation on days 14 and 28 (+5.3 and +4.9 beats per minute, $P=0.02$ and $P=0.01$, respectively) in the study by Yang et al.,[26] but these changes were numerically small and not clinically significant. Again, none of these effects were observed by Beier et al.[25] in the study using indacaterol 400 and 800 mg once daily in patients with COPD.

Assuming that the dose of 800 mg represents a supratherapeutic dose (the selected doses for the phase III studies ranged between 150 and 600 mg once daily), the overall safety

data imply a favorable tolerability profile and a wide therapeutic window. This is supported by preliminary data from a 52-week phase III trial in 1732 patients with COPD randomized to treatment with either indacaterol 300 mg once daily, indacaterol 600 mg once daily, formoterol 12 mg twice daily, or placebo.[37] In this study, indacaterol at both doses did not affect mean serum potassium at week 52, mean corrected-QT values or average pulse rate, and the overall safety and tolerability profile was similar to placebo and formoterol.

SUMMARY AND CONCLUSIONS

Indacaterol is a novel once-daily LABA developed for the treatment of COPD and asthma. Clinical studies suggest that indacaterol produces rapid (within 5 minutes) and sustained (at least 24 hours) bronchodilation in patients with COPD, and asthma of various severities. Exposure to a maximum of 52 weeks' 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, measured by 24-hour trough FEV_1, and preliminary data of comparator trials with blinded formoterol twice daily also suggest equal or even superior efficacy of once-daily indacaterol over twice-daily formoterol. However, this needs to be further investigated in well-controlled, fully blinded clinical trials against tiotropium, and publication of full data from the formoterol comparator trials are awaited. Interpretation of clinical data of indacaterol in COPD is somewhat complicated by the fact that several doses and different devices were studied. At present, a clinical trial registry lists the majority of ongoing or completed studies with indacaterol at doses of 150, 300, or 600 mg once daily delivered by a single dose dry powder inhaler.[38] Thus, it is anticipated that one of these doses will represent the marketed doses, although even a flexible dosing regimen appears suitable.

Clearly, the main prospect for indacaterol monotherapy lies in COPD, where anti-inflammatory 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 has not been raised. The overall results from the clinical program, including preliminary data from a phase III trial over 52 weeks, overtly indicate that once-daily indacaterol at doses from 150 mg to 600 mg produces significant and clinically meaningful improvement in several important COPD outcome parameters, including 24-hour trough FEV_1, exacerbations, resting and dynamic hyperinflation, exercise capacity, and symptoms. Moreover, indacaterol represents an attractive partner agent for future combination treatment approaches; for example, once-daily fixed combination treatment with an inhaled corticosteroid for both asthma and COPD, with an inhaled once-daily anticholinergic bronchodilator in COPD, or even in a triple combination treament with an inhaled corticosteroid and long-acting anticholinergic for COPD.

However, more published data are required in COPD, to fully assess the treatment impact of indacaterol on various COPD outcomes, in particular, when compared with established drugs such as twice-daily LABAs, tiotropium and LABAs/inhaled corticosteroid fixed combinations. The ongoing clinical development program will add further knowledge in respect to many long-term efficacy outcomes and gather additional safety and tolerability data in both COPD and asthma.

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