Role of indacaterol in the management of asthma and chronic obstructive pulmonary disease

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Indacaterol is the first of a new category of inhaled β 2-agonists with a very long duration of action that allows for once-daily administration. The bronchodilation induced by indacaterol is more persistent than that caused by the current long-acting *β*2-agonists (LABAs; salmeterol and formoterol), and therefore, for this new compound, the word 'ultra-LABA' has been created. Indacaterol is an agonist with high intrinsic efficacy and a rapid onset (bronchodilation may reach a maximum after 5-30 min) similar to salbutamol and formoterol, but with a longer duration of action. The long-lasting bronchodilation up to 24 h has been largely demonstrated in several single-dose or short-term treatment studies with different doses of indacaterol. The increase in the forced expiratory volume in 1 s measured 24 h after indacaterol administration may reach up to 300 ml in asthma and 200 ml in chronic obstructive pulmonary disease (COPD). This long-lasting stabilization of the airway caliber may potentially translate into a reduced mechanical stress on the airways, and this might lead to a lower rate of exacerbations and other positive clinical consequences (improvement in exercise capacity and quality of life); these effects have not been confirmed yet with indacaterol. Long-term studies up to 52 weeks in COPD have confirmed these positive effects on patient-related outcomes. The comparison between indacaterol and other long-acting bronchodilators in COPD patients confirms that indacaterol has an efficacy profile similar and often better than that of LABAs or tiotropium. The safety profile is good and no relevant cardiovascular effects have been demonstrated in all clinical studies. Therefore, indacaterol has the characteristics for representing a new important resource for the treatment of COPD.

Keywords: asthma • chronic obstructive pulmonary disease • indacaterol • long-acting bronchodilator

Airway diseases (asthma and chronic obstructive pulmonary disease [COPD]) represent major problems for healthcare systems worldwide, owing to the increasing burden sustained by these diseases, which affect all age categories of the population. Recent data suggest that asthma prevalence is still increasing in both developed and developing countries [1], representing a disease with one of the highest morbidity rates and with high indirect costs [2], while COPD is a well-recognized primary cause of death [3] with a high burden due to the consumption of the health resources [4].

In these diseases, bronchodilation is a major objective of the treatment, because it is associated with positive consequences on symptoms, quality of life and disease progression. In asthma, regular inhaled bronchodilators are recommended when asthma symptoms and exacerbations are not controlled by inhaled corticosteroids alone [101], while in COPD they represent the first step in regular treatment in order to improve dyspnea and exercise tolerance [102].

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B2-agonists are one of the main bronchodilator drugs for both asthma and COPD. In the last 10 years, shortacting β 2-agonists (salbutamol, terbutaline and other less used compounds) have been largely substituted by longacting \beta2-agonists (LABAs; salmeterol or formoterol) for regular treatment. The introduction of this new category of bronchodilators represented a real advantage in the management of asthma and COPD, not only for the increase in the compliance to the treatment schedule (two administrations daily, instead of three-four administrations daily with the short-acting β 2-agonists), but also for a greater efficacy, probably owing to the more prolonged bronchodilation offered by LABAs, leading to a greater stability of the airway calibre [5]. Therefore, the change from short- to long-acting β2-agonists has represented a consistent improvement in the management of asthma and COPD.

Recently, a new category of β 2-agonists has been developed, with a consistently increased duration of action (up to 24 h) that allows for once-daily administration (termed 'ultra-LABA'). This increase in the duration of the bronchodilation may determine a further increase in the efficacy of this drug category, by means of a long-lasting stabilization of the airway calibre. These drugs may, therefore, have the potential for representing a consistent improvement in the pharmacologic treatment of airway diseases.

Among the different molecules that have been explored for their long-lasting bronchodilator efficacy [6], indacaterol is the first β 2-agonist with very long duration of action (>24 h) that has been approved in Europe for the management of COPD. It is prepared in a dry powder formulation in external space, delivered by a new device, Breezhaler[®], which has proven to be a low-resistance device suitable for use by patients with COPD of different severity and delivering a consistent and reproducible dose irrespective of disease severity and age [7]. The range of explored doses was from 50 to 800 µg, but the majority of the studies used doses from 200 to 600 µg. In the trade, capsules with 150 and 300 µg are now available.

This review summarizes the main preclinical and clinical data that have demonstrated the efficacy of this new molecule in asthma and COPD. Other reviews on this topic have recently been published [8,9], but, by contrast with the previous papers, our overview also includes data obtained from asthma patients in the short-term and dose-finding studies.

Pharmacology of indacaterol

Indacaterol is a β 2-agonist with high intrinsic efficacy, and it is characterized, in comparison with other β 2-agonists, by a very quick and long-lasting stimulation of the β 2-receptor. This characteristic seems related to the capacity to stimulate the β 2-receptor in a very short period of time, by diffusing in the pericellular fluid, and at the same time to dissolve in the lipid membrane (in particular in membrane areas termed 'raft domains', which are small lipid regions in close contact with signaling and effector membrane molecules), from which indacaterol may be released very slowly, therefore assuring it induces long-lasting stimulation of the β 2-receptor (Figure 1).

Many experimental studies on isolated bronchi and cells in the laboratory have confirmed the high intrinsic activity of this compound [10,11]. In these studies, indacaterol has been demonstrated to be a strong human β 2-adrenoceptor agonist in comparison with other β 2-agonists (Table 1) [12,13]. The functional selectivity profile of indacaterol for the β 2-adrenoceptor selectivity (this profile is similar to that of formoterol and salbutamol). In animal models, indacaterol induced protection against bronchoconstriction following 5-hydroxy-tryptamine for at least 24 h in guinea pigs, and the lowest increase in heart rate for a similar degree of antibronchoconstrictor activity was measured in Rhesus monkeys [12].

In a model of isolated human bronchi, indacaterol showed a potency and a maximum relaxing effect similar to that of formoterol and salmeterol, but did not show any antagonism with isoprenaline (in contrast to salmeterol, which may attenuate the efficacy of the addition of a full β -agonist such as isoprenaline), and had an onset of action similar to formoterol or salbutamol and faster than salmeterol; furthermore, duration of the smooth muscle relaxation *in vitro* was >12 h [13,14]. In addition, in other models, such as the inhibition of the IgE-dependent release of several chemical mediators from human lung mast cells, indacaterol was as efficacious as the full agonist isoprenaline, and showed a tendency to produce a lower desensitization than other β 2-agonists [15].

Short-term clinical studies

The first clinical studies have been performed in order to demonstrate the rapid-onset, very long-acting bronchodilation of indacaterol in comparison with placebo. The more frequently used model was the crossover study design of single administration or a few weeks treatment with indacaterol (at different doses) and placebo; the aim of these preliminary evaluations was also to find the best dose(s) of the drug to be studied in the long-term trials. Patients with asthma or with COPD have been enrolled in these studies. In some of them, comparators were included in the form of formoterol or salmeterol in a twice-daily administration, or tiotropium once-daily.

Indacaterol in asthma & COPD Review: Clinical Trial Outcomes

Studies in asthma

The studies performed in asthmatic patients have used a crossover study protocol on a relatively small number of subjects, and in some cases a parallel group study protocol on larger numbers of patients (Table 2) [16-24]. The main outcome used in many of the studies was the 'trough forced expiratory volume in 1 s [FEV,]'; the FEV, was measured at the end of the duration of action of the last (or the only) dose of indacaterol. This outcome has been validated in the assessment of tiotropium (the only bronchodilator drug, before indacaterol, with a proven 24-h activity), and in all studies reported in Table 2, indacaterol was significantly more effective than placebo on this outcome (sometimes expressed in different ways). The changes in FEV, in the studies on indacaterol in asthma were not only statistically significant, but also clinically significant, particularly with the highest doses of indacaterol (increase in FEV, over placebo up to 380 ml). In the study by La Force *et al.*, the increase in FEV, versus placebo was significant in all measurements performed between 5 min and 21-22 h after indacaterol administration, therefore confirming the rapid onset of action of this compound (Figure 2) [20]. In four studies, a comparator (another β 2-agonist) was included, sometimes in a open-label fashion; in all these studies, a significantly better effect of indacaterol versus the comparator was shown with regard to the duration of bronchodilation (for all comparators) and the rapid onset of action (for salmeterol). Extensive side effects were reported in all studies, and in greater detail in some of these [17,19,21,23].

Studies in COPD

Studies performed in COPD, as single-dose administration and short-term treatment, are summarized in Table 3 [25-34]. In addition, the majority of these studies used the crossover study design and compared different doses of indacaterol in a single-dose model or

in parallel groups of patients. The range of doses used in these trials was 75 to 800 μ g, and the main aim was to verify the long-lasting duration (up to 24 h) of the bronchodilation. In all studies, trough FEV₁ (or other similar measurements) was always significantly better than placebo, and often also better than comparators; the mean increase in trough FEV₁ was approximately 200 ml, which is clinically significant when considering the baseline FEV₁ value (between 51 and 57% predicted) of the COPD patients



Figure 1. The β 2-adrenoreceptor on the cell membrane, and the double effect of indacaterol. Rapid-onset and long-term effect mediated by the high lipophility and the deposition in the raft domains with ultra-slow release. (A) Lipophilic activity (long duration of action). (B) Hydrophilic activity (rapid onset of action). (C) Retained in raft domain of lipid membrane. (D) Ultra-slow release from cell membrane. Adapted from [9].

included in the trials (Figure 3). In some studies, the onset of action was also tested, again showing the rapid onset of the bronchodilation (in the first 5 min, the increase in FEV₁ may reach up to 250 ml). In the studies that enrolled a high number of patients treated for a few days or weeks [26,28,33,34], side-effects were reported and good safety profiles on many clinical (headache and cough), cardiovascular (pulse rate, blood pressure and QTc) and biochemical indices (serum potassium, blood glucose and hematology) were demonstrated in COPD patients.

Effects on small airways

Additional results have been reported with regard to changes in indices of small airway involvement both

in vitro models.						
	E _{max} ⁺ (% isoprenaline)	E _{max} *				
		Resting tone	Precontraction with histamine	Precontraction with carbachol		
Isoprenaline	98 ± 1	-	-	-		
Indacaterol	73 ± 1	77 ± 5	84 ± 7	77 ± 4		
Formoterol	90 ± 1	94 ± 1	86 ± 4	84 ± 2		
Salmeterol	38 ± 1	74 ± 4	57 ± 15	29 ± 6		
Salbutamol	47 ± 1	84 ± 4	79 ± 7	53 ± 8		
[†] On cAMP production from transfected cells [12]. [†] On isolated human bronchi [13].						

Table 1. Comparison of the intrinsic efficacy of the different β 2-agonists in some *in vitro* models.

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Table 2. Main short-term studies on the efficacy of indacaterol in asthma.							
Study (year)	No. pts (FEV ₁ % predicted at screening, all prebronchodilator)	Study design	Duration/ doses (µg)	Main outcome ^t	Comparator [†]	Ref.	
Beeh (2007)	42 (76)	СО	SD (50, 100, 200, 400)	FEV_1 30 min (+7–15% vs placebo), FEV_1 21 h (+4–10% vs placebo)	Placebo	[16]	
Brookman (2007)	20 (Part A) and 19 (Part B) (≥60)	СО	SD (200 [Part A], 1000 [Part B])	FEV ₁ AUC 0–24 h (+11.8 l/h vs placebo, +8.8 vs salbutamol [Part A] and +11.9 l/h vs placebo [Part B])	Placebo Salbutamol Salmeterol (all open-label)	[17]	
Chuchalin (2007)	156 (79)	PG	28 days (200, 400, 600)	FEV_1 24 h (≥166 ml vs placebo)	Placebo	[18]	
Kanniess (2008)	115 (72)	СО	7 days (100–600)	FEV ₁ AUC 22–24 h on day 7 (+80–160 ml)	Placebo Formoterol (twice- daily for 1 day, open-label)	[19]	
La Force (2008)	436 (68)	PG	7 days (50–400)	FEV_1 AUC 22–24 h on day 1 (+240–380 ml vs placebo) and day 7 (+220–320 ml vs placebo)	Placebo	[20]	
La Force (2009)	45 (72)	СО	SD (150, 300, 600)	FEV ₁ 24 h (+110–220 ml)	Placebo Formoterol (twice- daily for 1 day, open-label)	[21]	
Pearlman (2008)	25 (70)	СО	SD (200, 400)	Mean FEV ₁ over 24 h (+90–400 ml vs placebo)	Placebo	[22]	
Sugihara (2010)	41 (67)	СО	SD (150, 300, 600)	FEV ₁ AUC 22–24 (+180–260 ml vs placebo) (+130 ml vs formoterol)	Placebo Salmeterol (twice- daily for 1 day, open-label)	[23]	
Yang (2007)	144 (81)	PG	28 days (400, 800)	$FEV_1 24$ (+150–230 ml vs placebo), $FEV_1 30$ min (+210–240 ml vs placebo)	Placebo	[24]	
⁺ Significantly di [‡] Significantly di	fferent from placebo or other cor fferent on some outcomes.	nparators, co	onsidering the highest do	ose of indacaterol.			

AUC: Area under curve; CO: Crossover; FEV,: Trough forced expiratory volume in 1 s; PG: Parallel group; SD: Single dose.

in asthma and COPD. A significant improvement in lung volumes (forced vital capacity [FVC] and inspiratory capacity [IC]) and in expiratory flow at low lung volumes (FEF25-75) in comparison with placebo and also in some studies with other bronchodilators (salmeterol and formoterol) has been reported in many shortterm or single-dose studies in asthmatic and COPD patients [19,20,22,23,26-33] and also in a few long-term studies [35]. Since the reduction of static and dynamic lung hyperinflation both in asthma and COPD have been associated with an improvement in dyspnea and exercise tolerance, this effect might explain the positive consequences of the bronchodilation (particularly at lower airway levels) in terms of clinical outcomes. However, this point requires more mechanistic studies linking bronchodilation to improvement in exercise tolerance, particularly in COPD.

Long-term clinical studies

Long-term (\geq 3 months) studies on the efficacy and safety of indacaterol have only been performed in COPD (Table 4) [35–39]. After the preliminary observations, the development program was addressed to the long-term treatment of COPD, considering that in this disease bronchodilators represent the first choice of the treatment, and that in this disease many unmet needs are still present. These studies led to the approval by the EMA of indacaterol as a drug for COPD.

Significant bronchodilation was observed following administration of the first dose of indacaterol, with efficacy sustained over the full 12-week treatment period with respect to placebo in patients with moderate-to-severe COPD [35]. Trough FEV₁ after 12 weeks of treatment (the primary end point) exceeded the placebo value by more than 120 ml. The value of 120 ml was

chosen because it is higher than the 100 ml described by Donohue as a difference that patients can perceive [40], and is the midpoint of the 100–140 ml range proposed as a minimal clinically important difference [41]. A statistically significant improvement in FEV₁ for indacaterol versus placebo was also observed at all individual post-baseline time points on day 1 and at week 12, with improvements versus placebo for FEV₁ AUCs between 5 min and 1 h, 5 min and 4 h, and 1 and 4 h postdose, demonstrating a sustained 24-h duration of action of indacaterol on once-daily dosing.

β2-adrenoceptor downregulation following chronic dosing with LABAs may result in the development of tolerance to the bronchodilator effects of LABAs [42]. Moreover, several studies showed reduced efficacy over time for β2-agonists, including salmeterol, both on bronchodilation properties [43] and on the protection from bronchoconstriction induced by allergen challenge [44]. No apparent loss in efficacy for bronchodilation properties over the 12 weeks of treatment was demonstrated, with indacaterol-placebo differences maintained from day 29 (the first trough assessment in that study after indacaterol is known to have reached a steady state) to week 12 in terms of trough FEV₁ [38], confirming results from another study that also lasted up to 1 year [39].

An original study has considered a two-stage design by which the first stage provided a robust validation of the dose selection [26] or efficacy evaluation in the second stage [35]: 1683 patients with moderate-tosevere COPD were randomized to double-blind indacaterol 150 or 300 mg or placebo, or open-label tiotropium 18 mg, all once-daily, for 26 weeks. The primary efficacy outcome was trough FEV, at 12 weeks. Additional analyses (not adjusted for multiplicity) included transition dyspnea index (TDI), and health status (St George's Respiratory Questionnaire [SGRQ]). The statistically significant and clinically relevant effects on trough FEV, at 24 h postdose (180 ml above placebo at week 12) demonstrate the suitability of this agent for once-daily dosing. The 40- to 50-ml difference in trough FEV, for indacaterol beyond that achieved with the established bronchodilator tiotropium, is similar to the increase that tiotropium had previously achieved over twice-daily

β2-agonists (Figure 4) [45,46]. Indacaterol maintained its bronchodilator efficacy over time, with efficacy (in terms of the primary end point) also retained in subgroups of patients divided according to baseline age, inhaled corticosteroids (ICS) use, and smoking status. Both indacaterol doses improved dyspnea (TDI) over placebo by margins that were generally close to the onepoint difference regarded as clinically relevant [47], but the indacaterol 300 µg dose was the only treatment that consistently exceeded this threshold. The improvement in dyspnea may be explained by reduced hyperinflation, which in turn may allow patients a greater activity and an improved health status [48,49], as indirectly proven by the effects of indacaterol on the IC at rest [29]. The study was not powered for exacerbations, especially in view of the low overall rate of exacerbations in the study (annual exacerbation rate of 0.72 in the placebo arm of this study).

It may be hypothesized that the sustained bronchodilation provided by a bronchodilator with a 24 h duration would reduce fluctuations in airway patency compared with twice-daily bronchodilators, and may improve clinical outcomes. The Indacaterol: Value in COPD: Longer Term Validation of Efficacy and Safety (INVOLVE) study was designed to provide efficacy and



Figure 2. Increase in FEV_1 during the first 4 h and between 22 and 24 h after 7-day treatment with placebo or indacaterol in different doses in patients with asthma. FEV_1 : Trough forced expiratory volume in 1 s. Reproduced with permission from [20].

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Table 3. Main short-term studies on the efficacy of indacaterol in chronic obstructive pulmonary disease.								
Study (year)	No. pts (FEV ₁ % predicted at screening)	Study design	Duration/ doses (µg)	Main outcome ⁺	Comparator [‡]	Ref.		
Balint (2010)	89 (54 ^s)	СО	SD (150, 300)	$FEV_1 5 min (+100-120 ml vs placebo)$ (+30 ml vs salbutamol) (+50 ml vs SFC)	Placebo Salbutamol SFC	[25]		
Barnes (2010)	801 (53)	PG	14 days (75–600)	$FEV_1 24$ h after 14 days (+150–210 ml vs placebo), FEV_1 AUC 1–4 h after 14 days (+200–280 ml vs placebo)	Placebo Tiotropium (open-label), Formoterol	[26]		
Bauwens (2009)	51 (51 ^s)	СО	SD (150, 300, 600)	FEV_1 24 h (+140–180 ml vs placebo) (+50 ml vs formoterol)	Placebo Formoterol (twice-daily for one day)	[27]		
Beier (2007)	163 (53")	PG	28 days (400, 800)	FEV_1 24 h (+210–230 ml vs placebo), FEV_1 30 min (+210–320 ml vs placebo)	Placebo	[28]		
Beier (2009)	30 (56 [§])	СО	SD (300)	Mean FEV ₁ over 24h (p < 0.0001 vs placebo at all assessed timepoints, and vs formoterol at $8-24$ h)	Placebo Formoterol (twice-daily for one day)	[29]		
Kato (2010)	50 (53 [§])	СО	SD (150, 300, 600)	$FEV_1 AUC 22-24 h (+130-170 ml vs placebo)$	Placebo	[30]		
La Force (2010)	68 (53 [§])	СО	14 days (300)	$FEV_1 24$ h after 14 days (+200 ml vs placebo) (+90 ml vs salmeterol)	Placebo Salmeterol (open-label)	[31]		
Magnussen (2010)	96 (57 [§])	СО	14 days (300 am–pm)	$FEV_1 24$ h after 14 days (+200 ml vs placebo) (+50 ml vs salmeterol)	Placebo Salmeterol	[32]		
Rennard (2008)	635 (571)	PG	7 days (50–400)	FEV_1 22–24 on day 1 (+80–170 ml vs placebo) (+60 ml vs tiotropium)	Placebo Tiotropium (open-label; 8-day extension)	[33]		
Vogelmeier (2010)	169 (57 [§])	СО	14 days (150, 300)	$FEV_1 24$ h after 14 days (+150–170 ml vs placebo) (+50 ml vs tiotropoium [#])	Placebo Tiotropium	[34]		
'Significantly different from placebo or other comparator, considering the highest dose of indacaterol. 'Significantly different on some outcomes.								

[§]Postbronchodilator.

¹Prebronchodilator.

*For indacaterol 150 μg

AUC: Area under curve; CO: Crossover; PG: Parallel group; SD: Single-dose; SFC: Salmeterol-fluticasone combination.

long-term safety information on the once-daily dosing indacaterol compared with placebo and the twice-daily dosing formoterol in a 52-week time period [37]. The primary hypothesis was that indacaterol would have a greater effect than placebo on FEV, at 24 h postdose (trough FEV,) after 12 weeks: 1732 patients with moderate-to-severe COPD were randomized to receive oncedaily indacaterol 300 or 600 µg, twice-daily formoterol 12 µg or placebo for 52 weeks in a double-blind, double-dummy, parallel-group study, to measure FEV, 24 h postdose after 12 weeks, and also clinical findings such as TDI, use of as-needed salbutamol, symptom-based measures recorded on diary cards, exacerbations, health status (SGRQ), BODE index (body mass index, obstruction, dyspnea, exercise), safety and tolerability. Indacaterol increased 24 h postdose FEV, after 12 weeks by 170 ml (both doses) versus placebo (p < 0.001) (Figure 4). These

significant differences were maintained at 52 weeks; symptomatic outcomes were improved, compared with placebo, with all active treatments, and indacaterol was significantly more effective than formoterol in reducing the need for as-needed salbutamol.

Another long-term study compared the bronchodilator effect 24 h after the dose of indacaterol and 12 h after the previous evening dose of salmeterol on trough FEV_1 [36]. This effect was significantly higher with indacaterol than with salmeterol at weeks 12 and 26 (Figure 4). The difference in trough effect with indacaterol of 170–180 ml relative to placebo after 12 and 26 weeks exceeded the prespecified 120 ml active-placebo difference, a value of the midpoint of the range accepted as clinically important [41], and there was no loss of bronchodilator effect over the course of the study. In summary, indacaterol also showed a persistent significant bronchodilation in long-term studies, with no risk of tolerance. This effect was linked to clinical effects on dyspnea, use of as-needed salbutamol, symptom-based measures recorded on diary cards, and health status (SGRQ). To evaluate effects of indacaterol on exacerbation rates, other studies powered for this outcome are still required.

Comparison with other long-acting bronchodilators in COPD

In the same way as the twice-daily β 2-agonist bronchodilators were shown to be more effective treatments for COPD patients than more frequently dosed short-acting bronchodilators [50], indacaterol, the once-daily β 2-agonist, might generally be more effective than a twice-daily agent. In deciding whether to use a new drug, it is clearly useful to know how the efficacy and safety of indacaterol may compare with other bronchodilators, using studies of suitable design and appropriate duration.

Comparison with formoterol

Due to the similar pharmacologic characteristic (short onset of action), the main comparator of indacaterol once-daily was formoterol, in a twice-daily administration.

The main short-term study exploring the comparison between indacaterol and formoterol [27] was a crossover, double-blind, double-dummy study comparing a range of a single doses of indacaterol (150, 300 and 600 µg) with placebo and the daily therapeutic dose of formoterol (two 12 µg doses 12 h apart, in 51 patients with moderate-to-severe COPD. The 24-h trough FEV (primary end point; mean) was 1.46 l with indacaterol 600 μ g (p < 0.001 vs placebo; p < 0.01 vs formoterol; p < 0.05 vs indacaterol 150 µg), 1.45 l with indacaterol $300 \ \mu g \ (p < 0.001 \ vs \ placebo; p < 0.05 \ vs \ formoterol),$ 1.42 l with indacaterol 150 μ g (p < 0.001 vs placebo), 1.41 l with formoterol (p < 0.001 vs placebo) and 1.28 l with placebo. All treatments were well tolerated and there was little effect on serum potassium, blood glucose or QTc interval.

In the INVOLVE study, efficacy and long-term safety information on the once-daily dosing with indacaterol were compared with placebo and the twice-daily dosing of formoterol in a 52-week time period [37]. Indacaterol increased 24 h postdose FEV₁ after 12 weeks by 100 ml versus formoterol (all p < 0.001), maintaining these significant differences at 52 weeks; indacaterol was significantly more effective than formoterol in reducing the need for as-needed salbutamol.

Since it is well known that other spirometric measures such as IC may correlate better than FEV_1 with clinical indices [51], a study compared indacaterol once-daily dosing, with the twice-daily bronchodilator formoterol

on IC [29]: 30 patients with moderate-to-severe COPD (FEV₁/FVC 49%; FEV₁: 56% predicted) inhaled three treatments (two in randomized sequence followed by open-label formoterol) on separate study days: a single dose of indacaterol 300 µg, matching placebo, and two doses of formoterol 12 µg 12 h apart. Indacaterol and formoterol increased FEV₁ and IC at all time points relative to placebo (p < 0.001). Peak effects on FEV₁ were similar, while indacaterol had a greater effect on peak IC (31 vs 23% from predose; p = 0.034). Indacaterol had a greater effect than formoterol on FEV₁ at 8 h (1.47 vs 1.39 l; p = 0.014) and 24 h (1.44 vs 1.35 l; p = 0.003), and on IC from 4 to 24 h (differences of 0.13–0.19 l; p < 0.05). At 24 h, indacaterol and formoterol increased FEV₁ by 17.7 and 7.5%, respectively, from predose.

In summary, once-daily indacaterol is as effective as two doses of formoterol, but after a long period of treatment, from 12 until 52 weeks, it improves symptoms and health status and confers clinical improvements over the twice-daily formoterol in patients with moderate-to-severe COPD. Moreover, the greater effect of indacaterol than formoterol on IC may translate into improved long-term clinical outcomes.

Comparison with salmeterol

Another long-term study compared the bronchodilator effect 24 h after the dose of indacaterol and 12 h after the previous evening dose of salmeterol on trough FEV, [36].



Figure 3. Trough FEV₁ mean values (± standard error) after 14-day treatment with indacaterol 150 and 300 μ g, in comparison with placebo and tiotropium in patients with chronic obstructive pulmonary disease. FEV₁: Trough forced expiratory volume in 1 s. Reproduced from [34].

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Table 4. Main long-term studies on the efficacy of indacaterol in chronic obstructive pulmonary disease.							
Author (study)	No. pts (FEV ₁ % predicted at screening, all postbronchodilator)	Duration/doses (µg)	Main outcome'	Comparator [*]	Ref.		
Donohue (INHANCE)	1683 PG (56)	26 weeks (150, 300)	$FEV_1 24 h at 12 weeks + 180 ml vs placebo, + 140 ml vs tiotropium$	Tiotropium (open-label)	[35]		
Kornmann (INLIGHT 2)	1002 PG (53)	26 weeks (150)	$FEV_1 24 h at 12 weeks + 170 ml vs placebo, + 60 ml vs salmeterol$	Salmeterol	[36]		
Dahl (INVOLVE)	1732 PG (52)	52 weeks (300, 600)	$FEV_1 24 h at 12 weeks + 170 ml vs placebo, + 100 ml vs formoterol$	Formoterol	[37]		
Feldman (INLIGHT 1)	416 PG (55)	12 weeks (150)	$FEV_1 24 h at 12 weeks + 130 ml vs placebo$		[38]		
Rennard (INDORSE)	414 PG (56)	52 weeks (150, 300)	$FEV_1 24 h at 52 weeks + 170 ml and + 180 ml (for both doses) vs placebo$		[39]		
[†] Significantly differe [†] Significantly differe FEV.: Trough forced	ent from placebo. ent on some outcomes. I expiratory volume in 1 s: PG: Para	allel aroup.					

This effect was significantly higher with indacaterol than with salmeterol at weeks 12 and 26. The difference in trough effect with indacaterol of 170–180 ml relative to placebo after 12 and 26 weeks exceeded the clinically important 120 ml value for active-placebo difference [41]

and there was no loss of bronchodilator effect over the course of the study, while this did not occur with salmeterol [43]. The additional efficacy of 50–60 ml provided by indacaterol over salmeterol is similar to the margin provided by once-daily tiotropium over salmeterol [45].



Figure 4. Comparison between indacaterol 150 µg and tiotropium (open-label) versus placebo at 12 weeks; indacaterol 150 µg and salmeterol 50 µg twice-daily, versus placebo, at 12 and 26 weeks, and indacaterol 300 µg and formoterol 12 µg twice-daily at 12, 26 and 52 weeks.

*p < 0.001 versus placebo; **p < 0.001 versus the other drug. Adapted from [35–37].

Across the range of outcomes evaluated, once-daily indacaterol 150 µg was more effective than placebo and, in most cases, more effective than twice-daily salmeterol [36]. Indacaterol-treated patients reported improved health status (as measured by SGRQ) relative to placebo, by a margin that was close to (week 4) or exceeded (weeks 8, 12 and 26) the minimum clinically important difference for this measure, with significant difference with salmeterol at week 12. The effect of indacaterol and salmeterol on dyspnea followed a similar pattern. Both treatments were more effective than placebo, with indacaterol reaching statistical significance versus salmeterol at weeks 4 and 12. Indacaterol also allowed patients more days without rescue salbutamol and to undertake usual activities compared with salmeterol and particularly with placebo [36].

In the attempt to compare the onset of action of indacaterol in COPD, single doses of indacaterol, salbutamol 150 and 300 µg, or salmeterol/fluticasone 50/500 µg, or placebo were administered in 89 moderate-to-severe COPD patients, in a multicenter, randomized, doubleblind, placebo-controlled, crossover study measuring FEV, at 50 and 15 min predose and at 5, 15 and 30 min, and at 1 and 2 h postdose [25]. FEV, at 5 min postdose with both indacaterol doses was higher than salbutamol (10 and 30 ml for indacaterol 150 and 300 µg, respectively) and significantly higher than salmeterol-fluticasone (50 ml; p = 0.003 and 70 ml; p = 0.001, respectively). The numbers of patients with an FEV, increase of at least 12% and 200 ml at 5 min postdose were 16 (18.8%), 24 (27.6%), 20 (23.3%), 8 (9.1%) and 3 (3.4%) for indacaterol 150 and 300 µg, salbutamol 200 µg, salmeterol-fluticasone 50/500 µg and placebo, respectively.

Therefore, once-daily treatment with indacaterol 150 μ g has a significant and clinically relevant bronchodilator effect over 24 h postdose, and improves health status and dyspnea to a greater extent than twice-daily salmeterol 50 μ g. Moreover, a single dose of indacaterol 150 and 300 μ g demonstrated a fast onset of action similar to that for salbutamol and faster than that for salmeterol–fluticasone combination.

Comparison with tiotropium

Some studies were made comparing tiotropium and indacaterol. The first study had the primary objective to find an indacaterol dose that was effective over 24 h and well-tolerated in subjects with COPD, but a period of open-label treatment with tiotropium was included, to generate data for a within-subject comparison with the double-blind period of indacaterol treatment [33]. A total of 635 COPD patients with a prebronchodilator FEV₁/FVC <70% and prebronchodilator FEV₁ at both the screening visit and the first study treatment visit

≥40% predicted and ≥1.0 l after a washout period for bronchodilator treatment, were randomized in double-blind fashion to use placebo, 50, 100, 200 or 400 µg/die of indacaterol for 7 days; 269 subjects continued into the open-label period, after completing the core period, to use tiotropium for 8 days. This study demonstrated efficacy of indacaterol on FEV₁, especially at 200–400 µg/day, similar to the effect of tiotropium.

In the Indacaterol and Tiotropium: Measuring Efficacy (INTIME) study, in an incomplete-block, multidose, three-period, crossover design, 169 patients (mean age 65 years) received three of four treatments with indacaterol 150 µg, indacaterol 300 µg, tiotropium 18 µg and placebo, each once-daily for 14 days, maintaining blinding of patients and investigators [34]. The primary efficacy variable was trough FEV, at 24 h postdose after 14 days. Trough FEV, after 14 days with indacaterol 150 and 300 µg was statistically and clinically superior to placebo, with differences (95% CI) of 170 ml (120-220) and 150 ml (100-200), respectively (both p < 0.001). For this end point, both doses of indacaterol not only met the criterion for noninferiority compared with tiotropium, but also achieved numerically higher values, with (not significant) differences versus tiotropium of 40 and 30 ml for indacaterol 150 and 300 µg, respectively. Interestingly, at 5 min postdose on day 1, the mean FEV, for both indacaterol doses was significantly higher than placebo (p < 0.001) and tiotropium (by 80 ml for both doses; p < 0.001). Adverse events were reported by similar proportions of patients in the different groups of patients, from 28.3 to 31.4%.

The Indacaterol (Versus Tiotropium) to Help Achieve New COPD Treatment Excellence (INHANCE) study evaluated the effect of placebo or indacaterol 150 or 300 µg/day in comparison with placebo and openlabel tiotropium for 26 weeks on FEV, in 1683 subjects with moderate-to-severe COPD [35]. Indacaterol was as effective as tiotropium on bronchodilation, and it was at least as effective as tiotropium in improving clinical outcomes for patients with COPD, as seen by TDI, health status (SGRQ) and exacerbations. The 40- to 50-ml difference in trough FEV, for indacaterol beyond that achieved with the established bronchodilator tiotropium, is similar to the increase that tiotropium had previously achieved over twice-daily β2-agonists (Figure 4) [45,46]. The design of the INHANCE study was limited by the inability to blind the tiotropium treatment, raising the possibility of bias in comparing the indacaterol results with those of tiotropium: in fact, the effect of tiotropium on trough FEV, (140 ml vs placebo) in this study was very close to previously reported differences (140 or 120-150 ml vs placebo) in studies using blinded tiotropium.

In conclusion, once-daily indacaterol provided clinically and statistically significant 24-h bronchodilation, at least as effective as tiotropium, with a faster onset of action (within 5 min) on the first day of dosing.

Influence of concomitant ICS on efficacy of indacaterol treatment

To investigate the effects of concomitant ICS treatment on efficacy and safety of indacaterol in COPD, data were pooled from three randomized, double-blind, placebo-controlled studies of indacaterol in patients with moderate-to-severe COPD, each including prespecified analyses of efficacy and safety according to baseline ICS use. Data were only reported for the first 3 months [52]. Patients received indacaterol 150 µg (n = 627), indacaterol 300 µg (n = 821), formoterol 12 µg twice-daily (n = 522), tiotropium 18 µg once-daily (n = 415; openlabel) or placebo (n = 1021) for up to 12 months, but data were only reported for the first 3 months, evaluating FEV, at 24 h postdose at 12 weeks. At screening, ICS were used by 43% of patients. For ICS nonusers/users respectively, mean FEV, (postalbuterol) was 1.56/1.43 1 (55.9/52.4% predicted), and COPD was severe or very severe in 43/48% of patients. Indacaterol demonstrated significant differences versus placebo of >120 ml in trough FEV, at week 12 in each subgroup of ICS use. One or both doses of indacaterol had significantly greater effects than formoterol and tiotropium in each subgroup. Hazard ratios versus placebo for time to first COPD exacerbation showed a significant effect of indacaterol in non-ICS users (150 µg; 0.47 [p = 0.001]; 300 μ g; 0.64 [p < 0.05]) and a smaller nonsignificant effect in ICS users (0.77 and 0.72 for 150 and 300 µg, respectively). Adverse events in ICS nonusers/users respectively occurred in 47/61% of patients treated with indacaterol 150 µg, 48/51% with indacaterol 300 µg, 41/48% with formoterol, 52/62% with tiotropium, and 47/45% with placebo.

Therefore, indacaterol was an effective bronchodilator irrespective of concomitant ICS use. The significant effect of indacaterol on COPD exacerbations in ICS nonusers reinforced the appropriateness of indacaterol as first-line maintenance treatment for COPD patients.

Safety data

Adverse events have been accurately monitored in all short- and long-term studies, and the conclusions are that the safety profile of indacaterol, at the doses used in these studies, may be considered good.

In asthma studies, no significant difference in the occurrence of biochemical, electrocardiographic (heart rate or QTc), cardiovascular and clinical events between indacaterol (up to the maximum dose used in these studies) and placebo or comparators were reported, confirming the safety profile of indacaterol in these short-term studies in asthmatics [18,24].

The INHANCE study showed that indacaterol had an acceptable cardiovascular tolerability profile and was not generally associated with adverse changes in QTc interval [35]. Similar proportions of patients in all groups had increases in QTc interval of 30-60 ms and >60 ms. In the Indacaterol Efficacy Evaluation Using 150 ug Doses With COPD Patients (INLIGHT)2, OTc interval increases from baseline of >60 ms were recorded for two patients, one each in the indacaterol and salmeterol groups [36]. In INVOLVE, similar low occurrence of QTc change from baseline >60 ms was recorded in both indacaterol and formoterol groups [37]. In the Indacaterol: Double-Blind 1-Year Safety Evaluation (INDORSE) study, over 52 weeks, indacaterol showed a profile of action on QTc similar to placebo [39]. The INLIGHT 1 study was performed to evaluate the efficacy of indacaterol in 416 COPD subjects treated with indacaterol 150 µg for 12 weeks; no subject showed QTc >500 ms [38]. Furthermore, in the INTIME study no patient had an abnormally high pulse rate and the proportion of patients with newly occurring or worsening QTc interval (Fridericia's) >450 ms (males) or >470 ms (females) was lower during treatment with indacaterol 150 μ g (2.5%) compared with indacaterol 300 μ g (4.9%), tiotropium (5.0%) and placebo (4.1%). No patient had a maximum post-baseline increase in Fridericia's QTc of >60 ms or an absolute value >500 ms [34].

A higher prevalence of cough (reported as an immediate reaction to the inhalation of indacaterol) has been reported in many studies. Symptoms are of short duration, and do not seem to be associated with other components of the inhaled powder. However, the symptoms were not so severe to cause withdrawal from the treatment.

In conclusion, indacaterol did not show significant adverse effects on the cardiovascular system, paralleling the good safety profile on other organs (Table 5).

Potential for indacaterol use in the airway diseases & future development

The data published on indacaterol (the first ultra-LABA) in asthma and COPD have extensively documented the efficacy of this drug in term of bronchodilation. While data on asthma are limited to short-term studies, data on COPD have also evaluated the long-term efficacy of this drug. In effect, the use of LABA is strongly different in asthma and COPD: while in asthma, LABA always need to be used in association with inhaled corticosteroids (LABA monotherapy is strongly discouraged for the risk of severe asthma exacerbations and death) [53], in COPD LABA may be used as first-line therapy with no relevant risk of adverse side effects. This point underlines the need of always performing an accurate differential diagnosis between asthma and COPD in all patients with airway obstruction.

This long-lasting stabilization of the airway calibre may potentially translate to a reduced mechanical stress on the airways, and this might lead to a lower rate of exacerbations and other positive clinical consequences (improvement in exercise capacity and quality of life). These points have been well demonstrated with other long-acting bronchodilators (salmeterol, formoterol and tiotropium), and underline the positive consequences of a strong bronchodilation on other more clinically relevant outcomes of airway diseases. This needs to be confirmed with indacaterol.

The comparison with the existing long-acting bronchodilators (formoterol, salmeterol and tiotropium) has demonstrated that indacaterol has some advantages in comparison with LABA (probably owing to the greater duration of action and the similar rapid-onset effectiveness of a full β 2-agonist like formoterol) and a similar efficacy than tiotropium. This point suggests that indacaterol has the potential to represent the first-choice bronchodilator in COPD, a characteristic currently of tiotropium rather than of the current LABA. Future long-term, double-blind studies of comparison between indacaterol and tiotropium may help in the decision on which is the first bronchodilator to be recommended for the pharmacologic treatment of COPD.

Future perspective

Some points still need to be investigated before a clear position of the use of indacaterol in asthma and COPD may be defined. In asthma, the efficacy of a combination of indacaterol with a once-daily inhaled corticosteroid (e.g., mometasone or ciclesonide) should be

Table 5. Adverse events in the most important studies investigating indacaterol.								
Study (year)	Duration	No. patients	Comparison (µg)	Any AEs (%)	QTc (%)	Most frequent AEs	Ref.	
INTIME (2010)	14 days	169	I 150 I 300 TIO Placebo	31.4 29.5 28.3 28.5	2.5 ⁺ 4.9 5.0 4.1	Cough COPD worsening Nasopharyngitis	[34]	
INHANCE (2010)	26 weeks	1683	I 150 I 300 TIO (open-label) Placebo	66.6 65.6 67.2 63.6	0.2 [*] 0.2 0.5 0.7	COPD worsening URTI Nasopharyngitis Cough Headache	[35]	
INLIGHT 2 (2010)	26 weeks	1002	I 150 Salm Placebo	51.2 45.6 46.6	0.3 [*] 0.3 0	COPD worsening Nasopharyngitis URTI LRTI	[36]	
INVOLVE (2010)	52 weeks	1732	I 300 I 600 Form Placebo	70.9 64.9 65.2 61.8	0.2 [*] 0.2 0.2 0	COPD worsening Nasopharyngitis URTI Cough LRTI	[37]	
Rennard <i>et al.</i> (2008)	7 days	635	I 50 I 100 I 200 I 400 Placebo	15.5 24.8 28.6 29.1 23.4	<5⁺ <5 <5 <5 <5	Headache Cough	[33]	
INLIGHT 1 (2010)	12 weeks	416	I 150 Placebo	49.3 46.8	0* 0	COPD worsening Cough	[38]	
INDORSE (2009)	52 weeks	414	I 150 I 300 Placebo	77.1 76.7 68.5	6.9 ⁺ 6.2 8.9	COPD worsening Nasopharyngitis Cough	[39]	
[†] QTc Fridericia's criteria (>450 male, >470 female). [†] QTc change >60 ms vs baseline.								

AE: Adverse event; COPD: Chronic obstructive pulmonary disease; Form: Formoterol; I: Indacaterol; Salm: Salmeterol; TIO: Tiotropium.

demonstrated, in comparison with the currently available ICS/LABA combinations. In COPD, the efficacy of indacaterol plus tiotropium versus single bronchodilators should be demonstrated, as well as the efficacy of a combination between indacaterol and an inhaled corticosteroid in comparison with the currently available ICS/LABA combinations. A preliminary crossover 7-day study in 154 patients with COPD has shown that a combination of indacaterol plus glycopyrronium (a new long-acting anticholinergic drug) improved trough FEV₁ by 117–123 ml on indacaterol alone [54].

In any case, indacaterol represents the first of a new category of bronchodilators that we expect will contribute to better management of the chronic airway diseases.

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Executive summary

- Indacaterol is the first of a new category of inhaled β2-agonists with very long duration of action (up to 24 h), which allows a once-daily administration.
- Indacaterol is a β2-agonist with high intrinsic efficacy and a rapid onset effect (bronchodilation may reach a maximum after 5–30 min) similar to salbutamol and formoterol, but with a longer duration of action.
- The long-lasting bronchodilation up to 24 h has been demonstrated in several single-dose or short-term treatment trials with different doses of indacaterol. The increase in the FEV₁ measured 24 h after indacaterol administration may reach up to 300 ml in asthma and 200 ml in chronic obstructive pulmonary disease (COPD). The rapid onset of action (better than salmeterol and tiotropium) has been confirmed in serial spirometry.
- Long-term studies up to 52 weeks in COPD have confirmed the efficacy in terms of improvement in trough FEV₁, and also the positive effects on patient-related outcomes (dyspnea, quality of life and exacerbation rate).
- The comparison between indacaterol and other long-acting bronchodilators in COPD patients confirms that indacaterol has an efficacy profile similar to, and often better than, that of long-acting β2-agonists or tiotropium.
- The safety profile is good, and no relevant cardiovascular effects have been demonstrated in all clinical studies.
- Indacaterol has the characteristics for representing a new important resource for the treatment of COPD.

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