EXPERT OPINION

1. Introduction
2. Pharmacokinetic and pharmacodynamic profile
3. Effects on pulmonary function
4. Effects on symptoms and use of rescue medication
5. Safety and tolerability
6. Expert opinion

Indacaterol: a new long-acting β_2-agonist in the management of chronic obstructive pulmonary disease

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Introduction: Bronchodilators represent the mainstay of symptomatic treatment for chronic obstructive pulmonary disease (COPD). The principal bronchodilator agents are β_2-agonists, anticholinergics and methylxanthines, used singly or in combination. Indacaterol is a novel long-acting β_2-agonist for maintenance bronchodilator treatment of airflow obstruction in patients with COPD, approved in December 2009 by the European Medicines Association, and recently by the US Food and Drug Administration. It is administered once daily and is delivered by means of a single-dose dry powder inhaler (SDDPI). In Europe, the recommended dose is 150 μg and the maximum dose is 300 μg, while in the US the recommended dose is 75 μg. Indacaterol shows evidence of a rapid onset of bronchodilation, and its bronchodilatory duration is sustained.

Areas covered: Numerous clinical studies have assessed the therapeutic effects of indacaterol in various physiologic parameters, as well as symptoms, disease progression, exacerbation rates, quality of life, safety and tolerability. This review summarises published evidence regarding the efficacy, tolerability and safety of indacaterol in regard to lung function and symptoms of COPD patients.

Expert opinion: Indacaterol, the novel once-daily β_2-agonist, has rapid and sustained bronchodilatory effect, showing excellent efficacy, tolerability and safety, as shown by all clinical trials so far.

Keywords: beta-agonists, bronchodilators, chronic obstructive pulmonary disease, indacaterol

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1. Introduction

Chronic obstructive pulmonary disease (COPD) affects > 5% of the adult population and represents the fourth leading cause of death worldwide, with a progressively increasing mortality and morbidity [1,2]. Approximately 2.75 million deaths per year are caused by COPD, and the number is expected to increase [3]. It is estimated that, by the year 2020, COPD will be the third leading cause of death and the fifth leading cause of disability worldwide [4,5]. COPD is also associated with increased economic burden, mainly due to its acute exacerbations [6].

Traditionally, understanding of the pathogenesis of COPD used to focus on the presence of chronic airflow obstruction, which is slowly progressive and irreversible; therefore, the main therapeutic approach was directed at relieving this. However, more recently it has been understood that airflow limitation is associated with an

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Box 1. Drug summary.

Drug name	Indacaterol
Phase	Launched
Indication	Chronic obstructive pulmonary disease
Pharmacology description	Long acting beta-2 adrenergic agonist
Route of administration	Inhalation powder (capsules)
Chemical formula	$C_{24}H_{28}N_2O_3$
Pivotal trial(s)	[28-30]

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abnormal inflammatory response, which appears to be responsible for the architectural distortion of the lung parenchyma, the mucociliary dysfunction and some systemic effects including skeletal muscle dysfunction, nutritional abnormalities, weight loss, cachexia, perturbations in the cardiovascular and nervous system, and skeletal effects such as osteoporosis [7,8]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifies COPD severity into four groups, and proposes proper treatment for each stage [3].

GOLD has established A-level evidence that i) bronchodilator medications are central to the symptomatic treatment of COPD; ii) the principal bronchodilator treatments are β_2-agonists, anticholinergics and methylxanthines, used singly or in combination; and iii) regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators [3].

The current pharmacological therapy for COPD is intrinsically limited in the reduction of the high mortality associated with progressive disease, as recently reported by the trial Towards a Revolution in COPD Health (TORCH) [9]. Indeed, TORCH has demonstrated that the reduction in mortality could not reach significance [9].

In the absence of available drugs preventing the evolution of the disease, the key aims for improving therapeutic outcomes are to reduce symptoms, especially dyspnoea; to improve exercise capacity; to reduce exacerbations and the potential need for hospitalisation; to enhance health status; and to improve quality of life [10]. In line with these, experts state that the management of a stable COPD patient includes several clear steps: reduction of exposure to risk factors by smoking cessation; optimising expiratory flow by means of bronchodilator drugs, such as long-acting β_2 agonists (LABAs) and anticholinergic agents; reducing pulmonary inflammation, most commonly by corticosteroids; and preventing and managing acute exacerbations [11,12]. In addition, there is accumulating evidence supporting the cardinal contribution of domiciliary oxygen treatment and pulmonary rehabilitation in improving the quality of life in patients developing exertional breathlessness. Surgical therapy (lung reduction for emphysematic patients) is reserved for more advanced disease, whereas noninvasive ventilatory support has shown clear utility in hypercapnic subjects [13].

Bronchodilators represent the cornerstone of pharmacological treatment for COPD, but adherence to treatment remains an important issue. Optimally, minimisation of dose frequency could improve adherence. LABAs represented a significant evolution in COPD management, for instance formoterol, which combines rapid onset and prolonged duration of action [14]. In December 2009, indacaterol, a LABA with 24-h duration of action (**Box 1**), was introduced into the European market for maintenance treatment of airflow obstruction in COPD patients, at a recommended dose of 150 µg and a maximum dose of 300 µg. Administration is achieved via the inhalation of the content of one capsule once a day, using the Onbrez® Breezhaler® inhaler (Novartis Pharmaceuticals UK Ltd). This inhalation has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD. The dose should only be increased on medical advice.

In July 2011, the FDA approved the use of indacaterol in the US, with the same indication (maintenance treatment of airflow obstruction in COPD patients) at a lower recommended dose (75 µg). Indacaterol is not indicated for the treatment of asthma. The aim of the present review is to summarise the current state of knowledge regarding the efficacy, safety and tolerability of inhaled indacaterol in the management of COPD, putting emphasis on the dosage schemes approved in European Union (150 and 300 µg). Our search strategy was based on the PubMed, EMBASE and Google scholar databases up to December 2011, using combinations of the following keywords: indacaterol, COPD, bronchodilators, treatment. It included all types of articles written in English.

2. Pharmacokinetic and pharmacodynamic profile

Inhaled indacaterol is a β_2-agonist with rapid onset and long duration of action. Its bronchodilator effect is maintained for 24 h. The sustained duration of action can be attributed to the high affinity for lipid raft domains within the membrane [15], while the rapid onset can be attributed to the high intrinsic efficacy at the receptor level [16]. Indeed, indacaterol has high intrinsic efficacy at the receptor level and does not act antagonistically to isoprenaline [17]. The potency and intrinsic efficacy of the new agent have been demonstrated in various *in vivo* and *in vitro* human or animal models [17-19]. Pharmacokinetics of indacaterol, as examined in patients with asthma, showed rapid absorption with maximum serum concentrations reached within 15 min in once-daily doses ranging between 600 and 2000 µg. The median time to reach peak serum concentrations of indacaterol was approximately 15 min after single or repeated inhaled doses in patients with COPD [20]. In addition, indacaterol 400 or 800 µg, administered once daily for 14 days in patients with mild asthma, was rapidly absorbed and mean elimination half-life was > 30 h [21].

Article highlights.

- Indacaterol is the only long acting β_2-agonist with duration of action of 24 h, providing the ability of a once-daily administration, which could enhance patients' adherence to treatment.
- Recommended doses in Europe are of 150 and 300 μg, but clinical trials have examined efficacy, safety and clinical outcomes in doses as high as 800 μg.
- Clinical trials have shown the efficacy of indacaterol in improving pulmonary function of COPD patients as well as the superiority vs placebo and the superiority or noninferiority vs other bronchodilators.
- Various doses of indacaterol result in clinical outcomes, such as symptoms, exacerbations, quality of life that are superior to placebo and at least as effective and in some cases superior to other long-acting bronchodilators.
- A safety and tolerability profile comparable to that of other long-acting bronchodilators has also been demonstrated by the clinical trials so far conducted.

This box summarises key points contained in the article.

The absolute bioavailability after an inhaled dose is on average 43%. The drug is detectable in serum at dose-dependent concentration, and a slight accumulation occurs after administration of multiple daily doses, which reaches a steady state within 12 – 14 h of treatment. Biliary exertion is the main elimination route of indacaterol and its metabolites [22].

3. Effects on pulmonary function

3.1 Indacaterol vs placebo

Indacaterol has proved more effective than placebo in improving various outcomes (**Table 1**). In a 28-day randomised, placebo-controlled trial in 163 moderate-to severe COPD patients, Beier *et al.* [23] observed a significant improvement in FEV_1 vs placebo on days 14 and 28 ($p < 0.01$) after indacaterol administration in supratherapeutic doses of 400 or 800 μg. Trough FEV_1 was also superior for both indacaterol groups vs placebo ($p < 0.001$).

In a dose-ranging study of indacaterol (50, 100, 200, and 400 μg) administered for 7 days in patients with COPD (FEV_1 > 40% of predicted values) [24], all indacaterol doses proved superior to placebo (and tiotropium 18 μg) on day 7. Likewise, in a crossover, double-blind, double-dummy study in 51 subjects with moderate-to-severe COPD who received either indacaterol (150, 300 or 600 μg) or placebo and formoterol (12 μg twice daily), trough FEV_1 (primary end point) was improved with all indacaterol doses as compared to placebo ($p < 0.001$) [25].

Beier *et al.* [26] compared the effect of 300 μg indacaterol vs placebo (and formoterol) on FEV_1 and resting inspiratory capacity (IC). At all time points between 5 min and 24 h, indacaterol led to significant increases of FEV_1 and IC in comparison to placebo ($p < 0.001$).

In a study comprising a dose-finding stage after 14 days of treatment and a stage evaluating efficacy and safety for 26 weeks of treatment, Barnes *et al.* [27] concluded that all indacaterol doses of (75, 150, 300, 600 μg) were superior over placebo in improving trough FEV_1 and FEV_1 – $AUC_{(1-4\ h)}$.

In a double-blind, double-dummy parallel-group study with duration of 1 year, the efficacy and safety of indacaterol 300 or 600 μg were compared with placebo and formoterol (12 μg twice daily) [28]. Trough FEV_1 at week 12 was increased by 170 ml ($p < 0.001$) after both doses of indacaterol, vs placebo; and this increase was maintained at week 52.

A 12-week double-blind study examined the efficacy and tolerability of 150 μg indacaterol administered by SDDPI vs placebo, using trough FEV_1 at week 12 as primary end point [29]. The superiority of indacaterol was demonstrated in trough FEV_1 at week 12 (130 ml vs placebo; $p < 0.001$), after one dose ($p < 0.001$), and in peak FEV_1 after one dose ($p < 0.001$) at week 12. Standardised AUC measurements were all significantly higher for indacaterol ($p < 0.001$) [29]. Donohue *et al.* [30], in a randomised, double-blind controlled trial of indacaterol 150 or 300 μg vs placebo (and open-label tiotropium) for 26 weeks, concluded that trough FEV_1 at week 12 was significantly increased with both indacaterol doses vs placebo by 180 ml.

Similarly, in another double-blind study with crossover design [31], patients received three of the following four treatment options for 14 days: indacaterol 150 or 300 μg, open-label tiotropium 18 μg and placebo, with a 14-day washout period between each treatment. Trough FEV_1 (primary efficacy end point) after 14 days of indacaterol 150 or 300 μg was significantly higher than with placebo by 170 and 150 ml, respectively ($p < 0.001$). Additionally, at 5 min post-dose on day 1, mean FEV_1 for both indacaterol doses was significantly higher than for placebo ($p < 0.001$).

Magnussen *et al.* [32] reported significantly higher trough FEV_1 by 200 ml ($p < 0.001$) after 14 days with indacaterol 300 μg, as compared to placebo. This difference was observed for both morning and evening indacaterol administration.

In a recent multicentre, randomised study enrolling > 1000 patients investigating the efficacy and safety of indacaterol 150 μg vs placebo (and salmeterol) [33], it was shown that indacaterol increased trough FEV_1 (primary end point) by 170 ml over placebo ($p < 0.001$) after 12 weeks. In a further randomised, multicentre, placebo-controlled, crossover study [34] comparing indacaterol 300 μg (once daily) with placebo (and open-label salmeterol 50 μg twice daily), trough FEV_1 on day 14 (primary end point) was 200 ml higher than placebo ($p < 0.001$), exceeding the prespecified minimum clinical significant difference of 120 ml. Additionally, indacaterol provided superior bronchodilation across the 24-h assessment period on days 1 and 14 ($p < 0.001$). In a 26-week extension to the 26-week study by Donohue *et al.* [30], an increase in trough FEV_1 was demonstrated in 415 moderate-to-severe

Table 1. Clinical trials examining the effect of indacaterol on pulmonary function.

Author	Design	Number of subjects enrolled	Primary end point	Results
Beier *et al.* [23]	Moderate-to severe COPD patients randomised to receive either indacaterol 400 μg or 800 μg or placebo	163 patients enrolled, 155 completed the study	Safety and tolerability (serum potassium, glucose, QTc interval, AEs: tremor, headache, nervousness) pre- and 30 min post-dose on days 1, 14, 28 [Secondary objective: bronchodilator efficacy (FEV_1, FVC, $FEF_{25-75\%}$) pre- and 30 min post-dose on days 1, 14, 28]	Improvement in FEV_1 at all post-baseline treatment points and trough FEV_1 with indacaterol 400 and 800 μg vs placebo ($p < 0.01$)
Rennard *et al.* [24]	COPD patients received indacaterol 50, 100, 200 or 400 μg or placebo or tiotropium 18 μg	635 patients enrolled	FEV_1 – AUC (22 – 24 h) on day 1	All indacaterol doses superior to placebo from 5 min to 24 h post-dose on days 1 and 7 and comparable or superior to tiotropium in FEV_1 – AUC from 0 – 4 h on day 1, and 0 – 4 h and 22 – 24 h on day 7/8 ($p < 0.05$)
Bauwens *et al.* [25]	COPD patients received indacaterol 150, 300 or 600 μg or placebo or formoterol 12 μg	51 patients completed the study	Changes in trough FEV_1	All indacaterol doses superior to placebo in trough FEV_1 improvement ($p < 0.001$). Indacaterol 300 and 600 μg superior to formoterol ($p < 0.05$ and $p < 0.01$, respectively)
Beier *et al.* [26]	COPD patients received either indacaterol 300 μg or placebo or formoterol 12 μg	30 patients completed the study	Mean maximal change from baseline in FEV_1 and IC	Increase in FEV_1 and resting IC at all time points between 5 min and 24 h vs placebo ($p < 0.001$). Indacaterol superior to formoterol in increasing FEV_1 at 8 ($p = 0.014$) and 24 h ($p = 0.003$) and IC from 4 to 24 h ($p < 0.05$)
Barnes *et al.* [27]	Dose-finding study enrolling moderate-to-severe COPD patients who received indacaterol 75, 150, 300 or 600 μg or placebo or formoterol or tiotropium. Selected doses were continued into the second, 26-week stage	801 patients participated	Selection of doses using pre-set efficacy criteria for trough FEV_1 on day 15 and early (1 – 4 h post-dose) bronchodilator effect on day 14, and all safety data. Selected doses had to exceed a threshold for clinical relevance or be superior to either tiotropium or formoterol, whichever was the highest value	All indacaterol doses superior to placebo in trough FEV_1 and FEV_1 – AUC (1 – 4 h) (dose-finding study)
Dahl *et al.* [28]	Moderate-to-severe COPD patients received indacaterol 300 or 600 μg or	1732 patients participated	Trough FEV_1 at week 12 [Secondary outcomes: TDI score, use of as-needed salbutamol,	Both indacaterol doses superior to placebo in trough FEV_1 increase (by 170 ml at week 12 vs

AE: Adverse event; AUC: Area under the curve; COPD: Chronic obstructive pulmonary disease; FEF: Forced expiratory flow; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; IC: Inspiratory capacity; QTc: QT corrected interval; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index.

Table 1. Clinical trials examining the effect of indacaterol on pulmonary function (continued).

Author	Design	Number of subjects enrolled	Primary end point	Results
	placebo or formoterol (12 μg) for 52 weeks		symptom-based measures recorded on diary cards, exacerbations, SGRQ score, BODE index, safety and tolerability]	placebo ($p < 0.001$), and by 100 ml vs formoterol ($p < 0.001$). The difference between formoterol and placebo diminished in week 52
Feldman *et al.* [29]	COPD patients received either indacaterol 150 μg or placebo	416 patients enrolled, 364 completed the study	Trough FEV_1 at week 12 [Secondary end points: trough FEV_1 after day 1, percentage of days with poor control]	Indacaterol superior to placebo in trough FEV_1 after 1 dose and in week 12 (increase by 130 ml, $p < 0.001$), in peak FEV_1 after 1 dose on day 1 and week 12, in standardised FEV_1 – AUC measurements
Donohue *et al.* [30]	Moderate-to-severe COPD patients received indacaterol 150 or 300 μg or placebo or tiotropium 18 μg	1683 patients enrolled	Trough FEV_1 at week 12 [Secondary end points: TDI score, SGRQ score, exacerbations, levels of potassium, glucose and QTc interval]	Both indacaterol doses increased trough FEV_1 vs placebo by 180 ml ($p < 0.001$) and 40 – 50 ml vs tiotropium ($p < 0.01$) These improvements were sustained at week 26 (160 – 180 ml vs placebo)
Vogelmeier *et al.* [31]	Patients received 3 of the 4 following options: indacaterol 150 or 300 μg, placebo or tiotropium 18 μg for 14 days with a 14-day washout period between treatments	169 patients enrolled, 153 completed the study	Trough FEV_1 after 14 days	Trough FEV_1 after both doses of indacaterol was statistically superior to placebo ($p < 0.001$). Mean FEV_1 5 min post-dose on day 1 was higher than placebo after both doses of indacaterol ($p < 0.001$). Trough FEV_1 after 14 days of indacaterol was numerically higher than with tiotropium, but did not meet the superiority criteria. Mean FEV_1 5 min post-dose on day 1 was significantly higher than with tiotropium ($p < 0.001$)
Magnussen *et al.* [32]	Moderate-to-severe COPD patients received indacaterol 300 μg administered either in the evening or in the morning or placebo or salmeterol 50 μg	96 patients enrolled, 83 completed the study	Trough FEV_1 after 14 days	Increase in trough FEV_1 with indacaterol versus placebo and salmeterol (200 ml vs placebo for indacaterol, morning and evening dosing (both $p < 0.001$), additionally evening dosing: 110 ml vs salmeterol, $p < 0.001$)
Kornmann *et al.* [33]	Moderate-to-severe COPD patients received either	1002 patients enrolled, 838 completed the study	Trough FEV_1 after 12 weeks	Indacaterol increased trough FEV_1 over placebo by 170 ml ($p < 0.001$) and by 60 ml over

AE: Adverse event; AUC: Area under the curve; COPD: Chronic obstructive pulmonary disease; FEF: Forced expiratory flow; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; IC: Inspiratory capacity; QTc: QT corrected interval; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index.

Table 1. Clinical trials examining the effect of indacaterol on pulmonary function (continued).

Author	Design	Number of subjects enrolled	Primary end point	Results
	indacaterol 150 μg or placebo or salmeterol			salmeterol at week 12 ($p < 0.001$)
LaForce *et al.* [34]	Moderate-to-severe COPD patients received indacaterol 300 μg or placebo or salmeterol 50 μg	68 patients enrolled, 61 completed the study	Trough FEV_1 after 14 days	Trough FEV_1 on day 14: 200 ml higher than placebo ($p < 0.001$). Superior bronchodilation across 24 h on days 1 and 14. Indacaterol more effective than salmeterol in FEV_1 in days 1 and 14 and in many post-baseline time points. Increased FEV_1 in comparison to salmeterol ($p < 0.05$) at many post-baseline time points
Chapman *et al.* [35]	Moderate-to-severe COPD received either indacaterol 150 or 300 μg or placebo for 52 weeks	415 patients included	Evaluation of long-term safety (secondary end points: trough FEV_1 at 52 weeks, exacerbations, SGRQ score)	Increase in trough FEV_1 vs placebo ≥ 170 ml at week 52 ($p < 0.001$)
O'Donnell *et al.* [36]	Two-period crossover study (3-week treatment, 3-week washout) indacaterol 300 μg vs placebo in moderate-to severe COPD patients	90 patients enrolled, 74 completed the study	Exercise endurance after 3 weeks of treatment	Higher exercise endurance (101 s vs placebo, $p < 0.001$), higher end-exercise IC and higher resting IC (75 min post-dose) with indacaterol on day 1 and after 3 weeks. Higher resting IC 60 min post-dose after 3 weeks
Korn *et al.* [38]	Moderate-to-severe COPD patients received either indacaterol 150 μg or salmeterol 50 μg	1123 patients enrolled, 1034 completed the study	FEV_1 – AUC (5 min – 11 h 45 min) at week 12 [Secondary end points: trough FEV_1 (mean of 23 h 10 min and 23 h 45 min post-dose) at week 12, FEV_1 and FVC measured over 24 h, TDI score and rescue medication use]	FEV_1 AUC (5 min – 11 h 45 min) and trough FEV_1 with indacaterol significantly higher than with salmeterol (57 and 60 ml, respectively; $p < 0.001$). Additionally, FEV_1 and FVC measured over 24 h at week 12 higher with indacaterol
Balint *et al.* [39]	Moderate-to severe COPD patients receiving indacaterol 150 or 300 μg, salbutamol 200 μg, salmeterol/fluticasone 50/500 μg, placebo	89 patients enrolled, 86 completed the study	FEV_1, 5 min post-dose	Both indacaterol doses were significantly superior to placebo ($p < 0.001$) and to salmeterol/fluticasone ($p = 0.003$) in 5-min post-dose FEV_1. Additionally, FEV_1 after both indacaterol doses was significantly higher than placebo ($p < 0.001$) at all post-dose time points. In comparison to salbutamol, FEV_1 was numerically higher

AE: Adverse event; AUC: Area under the curve; COPD: Chronic obstructive pulmonary disease; FEF: Forced expiratory flow; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; IC: Inspiratory capacity; QTc: QT corrected interval; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index.

Table 1. Clinical trials examining the effect of indacaterol on pulmonary function (continued).

Author	Design	Number of subjects enrolled	Primary end point	Results
Buhl *et al.* [40]	Moderate-to severe COPD patients randomised to receive indacaterol 150 μg and placebo vs tiotropium 18 μg and placebo	1598 patients enrolled, 1477 completed the study	Noninferiority of indacaterol to tiotropium in the effect of trough FEV_1 after 12 weeks of treatment	Noninferiority of indacaterol vs tiotropium. No difference in 'trough' FVC values. Higher FEV_1 values 5 min ($p < 0.001$), 30 min ($p < 0.001$) and 1 h ($p < 0.01$) post-dose in day 1 with indacaterol

AE: Adverse event; AUC: Area under the curve; COPD: Chronic obstructive pulmonary disease; FEF: Forced expiratory flow; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; IC: Inspiratory capacity; QTc: QT corrected interval; SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index.

COPD patients receiving indacaterol 150 or 300 μg for 52 weeks vs placebo (difference ≥ 170 ml) [35].

O'Donnell *et al.* [36] have conducted a double-blind, placebo-controlled, two-period crossover study comprising 74 moderate-to-severe COPD patients receiving either indacaterol 300 μg or placebo. The authors concluded that exercise endurance after 3 weeks of treatment was higher with indacaterol than with placebo by 111 s. On day 1, indacaterol was significantly superior to placebo for exercise endurance by 101 s. Additionally, indacaterol was superior to placebo in end-exercise IC on day 1 and after 3 weeks (by 190 and 280 ml, respectively) and in resting IC at 75 min post-dose on day 1 and 60 and 75 min post-dose after 3 weeks [36].

Recently, Beeh *et al.*, in a double-blind, placebo-controlled, two-period crossover study, evaluated the effect of indacaterol 300 μg on peak and isotime IC during constant load cycle ergometry in 24 patients with moderate-to-severe COPD. After 2 weeks of treatment, indacaterol showed significant improvement over placebo in peak and isotime IC (primary end points), as well as in resting IC, trough FEV_1, dyspnoea and exercise endurance time [37].

3.2 Indacaterol vs other β_2-agonists

3.2.1 Indacaterol vs salmeterol

In the study by Magnussen *et al.* [32], who compared the efficacy of indacaterol 300 μg, administered either in the evening or in the morning, vs salmeterol 50 μg and placebo, the difference between salmeterol and indacaterol in trough FEV_1 after 14 days was significant ($p < 0.001$), favouring indacaterol when the latter was administered in the evening (higher by 110 ml). After morning administration, trough FEV_1 was higher by 50 ml, but this difference was not significant (**Table 1**).

In a 2-week placebo-controlled, crossover study, the comparison between indacaterol 300 μg (once daily) and salmeterol 50 μg (twice daily) favoured indacaterol in terms of improved trough FEV_1 by 90 ml ($p = 0.011$). In addition, FEV_1 was better with indacaterol in comparison to salmeterol ($p < 0.05$) on days 1 and 14, as evidenced by many post-baseline time points, including the 5-min post-dose measurement [34]. Likewise, in another large, randomised, placebo-controlled trial recruiting > 1002 patients, indacaterol 150 μg increased trough FEV_1 at week 12 by 60 ml over salmeterol ($p < 0.001$) [33].

The superiority of indacaterol 150 μg vs salmeterol 50 μg was also demonstrated in 1034 patients with moderate-to-severe COPD who completed a randomised, parallel-group study [38]. At 12 weeks, FEV_1 AUC $_{(5\ min\ –\ 11\ h\ 45\ min)}$ (primary end point) for indacaterol was significantly higher in comparison to salmeterol ($p < 0.001$), as was trough FEV_1, by 60 ml ($p < 0.001$). Additionally, indacaterol was more efficacious than salmeterol in increasing FEV_1 and FVC over 24 h at week 12 [38].

In a multicentre, randomised, double-blind, placebo-controlled crossover study examining onset of action of indacaterol (150 and 300 μg) in COPD patients, assessed by 5-min post-dose FEV_1, indacaterol was superior to the combination of salmeterol–fluticazone (increase by 50 ml for the 150-μg dose, $p = 0.003$; increase by 70 ml for the 300-μg dose, $p < 0.001$) [39].

3.2.2 Indacaterol vs formoterol

In their crossover, double-blind, double-dummy study in COPD patients receiving different doses of indacaterol (150, 300 and 600 μg) vs formoterol (12 μg administrated twice daily) and placebo, Bauwens *et al.* [25] concluded that indacaterol was superior to formoterol at 600 and 300 μg ($p < 0.01$ and < 0.05, respectively) in terms of increasing trough FEV_1.

In another study published in the same year [26] comparing the effect of 300 μg indacaterol vs formoterol (and placebo) on FEV_1 and resting IC, it was also shown that indacaterol was more effective in increasing FEV_1 at 8 h ($p = 0.014$), and 24 h ($p = 0.003$) and in increasing IC from 4 to 24 h ($p < 0.05$).

At the dose-selection stage of the study by Barnes *et al.* [27], it was concluded that indacaterol 300 μg was superior over

formoterol and placebo in trough FEV_1; while in the largest study, with duration of 1 year, where the efficacy and safety of indacaterol 300 or 600 µg was compared with that of formoterol (12 µg twice daily) and placebo, it was concluded that trough FEV_1 at week 12 was increased by 100 ml ($p < 0.001$) after both doses of indacaterol vs formoterol [28].

3.3 Indacaterol vs anticholinergics

3.3.1 Indacaterol vs tiotropium

In a dose-ranging study assessing the efficacy and tolerability of indacaterol, followed by an open-label extension where patients received tiotropium 18 µg for 8 days, it was shown that FEV_1 – AUC for all indacaterol doses was comparable or superior to tiotropium at 0 – 4 h on day 1, and at 0 – 4 h and 22 – 24 h on days 7 and 8 [24].

In their dose-finding study, Barnes *et al.* [27] reported that all indacaterol doses (75, 150, 300, 600 µg) produced higher differences in trough FEV_1 and FEV_1 – $AUC_{(1-4\ h)}$ as compared to placebo than did open-label tiotropium; while at the same time, indacaterol doses (150 or 300 µg) increased trough FEV_1 vs tiotropium at week 12 by 140 ml, as Donohue *et al.* [30] demonstrated. Both differences exceeded the prespecified clinically important difference of 120 ml. The effects of both medications were maintained over the course of the study. A significant difference between indacaterol and tiotropium was observed in FEV_1 5 min post-dose on day 1, when the increase for both indacaterol doses vs placebo was 120 ml, while with tiotropium was 60 ml ($p < 0.001$) [30].

In the study by Vogelmeier *et al.* [31], after 14 days, trough FEV_1 with indacaterol 150 or 300 µg was higher than with tiotropium by 40 ml ($p = 0.043$) and 30 ml, respectively. Nevertheless, this difference did not meet the formal requirement for superiority, according to the design of the study. Additionally, at 5 min post-dose on day 1, mean FEV_1 for both indacaterol doses was significantly higher with indacaterol than tiotropium ($p < 0.001$) [31].

Finally, Buhl *et al.* [40], in a 12-week multicentre, randomised, parallel-group, blinded, double-dummy study in patients with moderate-to-severe COPD receiving either indacaterol 150 µg or tiotropium 18 µg, demonstrated the noninferiority of indacaterol vs tiotropium in trough FEV_1 after 12 weeks of treatment (1.44 l vs 1.43 l, respectively). No difference was noted between treatments in FVC values between 23 h 10 min and 23 h 45 min post-dose at week 12. On day 1, at 5 min after the first dose, FEV_1 was higher with indacaterol than with tiotropium ($p < 0.001$). This difference remained also significant after 30 min and 1 h post-dose. FVC followed a similar pattern.

4. Effects on symptoms and use of rescue medication

In addition to lung function, other parameters such as symptoms, exacerbations and quality of life are helpful in evaluating the efficacy of indacaterol in the management of COPD treatment. Recently published data (**Table 2**) have assessed clinical outcomes in COPD patients receiving various doses of indacaterol, comparing these outcomes with those of other treatment options.

Dahl *et al.* [28] concluded that indacaterol in high doses of either 300 or 600 µg were superior to placebo in all secondary end points of their study (days of poor control, St George's Respiratory Questionnaire [SGRQ] score, time to first exacerbations), but not superior to formoterol. Additionally, indacaterol increased Transition Dyspnoea Index (TDI) score and the differences between indacaterol and placebo were close to or exceeded the minimum clinically important difference. The difference between indacaterol and formoterol was significant only in week 12, as indacaterol reduced significantly vs formoterol the need of rescue medication ($p < 0.01$). Data from patients' diaries and BODE index scores also showed a significant improvement with indacaterol vs placebo [28].

Indacaterol 150 µg for 12 weeks resulted in a significant reduction by 22.5% ($p < 0.001$) of days of poor control and a reduction in use of rescue medication ($p < 0.001$) vs placebo in 416 COPD patients [29].

Similarly, indacaterol 150 µg for 12 weeks improved health status, as shown by the decrease in unadjusted mean SGRQ total score from baseline by more than the 4-point minimum clinically important difference, at all visits. A significant difference was also observed in SGRQ between indacaterol and salmeterol at week 12 ($p < 0.05$). Dyspnoea, as assessed by TDI, was improved with indacaterol compared with placebo ($p < 0.001$) [33].

Both doses of indacaterol (150 or 300 µg) for 26 weeks increased TDI ($p < 0.001$) and reduced SGRQ score ($p < 0.001$) in 1683 COPD patients recruited for a randomised, double-blind study [30]. Moreover, both doses were superior to tiotropium in reducing the requirement for rescue medication ($p < 0.001$), while the 300-µg dose was superior to tiotropium in improving the TDI score at weeks 4, 8 and 12.

Chapman *et al.* [35] demonstrated a significant reduction in COPD exacerbations and in as needed salbutamol use vs placebo ($p < 0.05$ and < 0.001, respectively) after 52 weeks of indacaterol use (150 or 300 µg). In addition, an improvement of health status was observed with a mean decrease in SGRQ score of > 4 units.

In a recently published, 12-week, randomised, parallel-group study, indacaterol 150 µg was superior to salmeterol 50 µg in TDI total score ($p < 0.001$) at week 12 [38]. The proportion of patients with a clinically important improvement (≥ 1 point) from baseline in total TDI score was significantly higher for indacaterol over salmeterol (OR 1.41, 95% CI 1.07 – 1.85, $p < 0.05$). The use of as-needed salbutamol during the 12-week study period was lower with indacaterol than with salmeterol. Patients on indacaterol treatment used fewer puffs/day ($p < 0.05$) and had a greater percentage of days with no rescue medication use ($p < 0.05$) [38].

Likewise, indacaterol 300 µg was associated with significant reduction in rescue medication use versus placebo, as assessed

Table 2. Clinical trials examining the effect of indacaterol on COPD symptoms and rescue medication.

Author	Design	Number of subjects enrolled	Primary end point	Results
Dahl *et al.* [28]	See **Table 1**	See **Table 1**	See **Table 1**	Both indacaterol doses more efficacious than placebo in days of poor control ($p < 0.05$ and $p < 0.001$), SGRQ score (both $p < 0.001$), but not better than formoterol. Indacaterol increased TDI score ($p < 0.001$). Diary data and BODE index: significant improvement with indacaterol vs placebo ($p < 0.001$ at week 52)
Feldman *et al.* [29]	See **Table 1**	See **Table 1**	See **Table 1**	Indacaterol more efficacious than placebo in reduction of days of poor control ($p < 0.001$) and in reduced use of rescue medication ($p < 0.001$)
Donohue *et al.* [30]	See **Table 1**	See **Table 1**	See **Table 1**	Both indacaterol doses for 26 weeks increased TDI score ($p < 0.001$) and decreased SGRQ score ($p < 0.01$) vs placebo
Magnussen *et al.* [32]	Indacaterol administered either in the evening or in the morning versus placebo and salmeterol	See **Table 1**	See **Table 1**	Indacaterol for 14 days produced significant improvement vs placebo in the percentage of nights without awakenings ($p < 0.01$), the percentage of days without symptoms ($p < 0.05$), and the percentage of days with ability to perform usual activities ($p < 0.05$). Indacaterol taken in the evening was more effective than salmeterol for percentage of nights with no awakenings ($p < 0.05$)
Kornmann *et al.* [33]	See **Table 1**	See **Table 1**	See **Table 1**	Decrease in mean SGRQ total score ($p < 0.001$) and improvement in TDI score ($p < 0.001$) with indacaterol vs placebo
Chapman *et al.* [35]	See **Table 1**	See **Table 1**	See **Table 1**	Significant reduction in rate of COPD exacerbations ($p < 0.05$) and in as-needed use of salbutamol with indacaterol 150 or 300 μg vs placebo ($p < 0.001$). Significant decrease in SGRQ score (> 4 units). Mean SGRQ total scores with both indacaterol doses were significantly higher at week 26 (150 μg, $p = 0.002$; 300 μg, $p = 0.025$) and week 44 ($p = 0.002$ for both doses)
O'Donnell *et al.* [36]	See **Table 1**	See **Table 1**	See **Table 1**	Indacaterol vs placebo produced significant reduction in number of puffs used daily ($p < 0.001$), during daytime ($p < 0.001$), or during night time ($p = 0.003$). Indacaterol was associated with an overall reduction in diary symptoms vs an increase with placebo
Korn *et al.* [38]	See **Table 1**	See **Table 1**	See **Table 1**	Indacaterol superior to salmeterol in TDI score in week 12 ($p < 0.001$), in the proportion of patients with clinically important improvement (OR 1.41. $p < 0.05$), and in the use of as-needed-salbutamol (less frequent with indacaterol, $p < 0.05$). Indacaterol

SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index.

Table 2. Clinical trials examining the effect of indacaterol on COPD symptoms and rescue medication (continued).

Author	Design	Number of subjects enrolled	Primary end point	Results
				was also associated with fewer puffs/day and greater percentage of days with no rescue medication
Buhl *et al.* [40]	See **Table 1**	See **Table 1**	See **Table 1**	Better TDI total scores at week 12 and higher possibility to achieve a clinically important improvement in dyspnoea with indacaterol than with tiotropium ($p < 0.001$). Additionally, reduced daily, daytime, and night-time use of rescue medication ($p < 0.001$) and higher proportion of days without rescue use ($p = 0.004$), with indacaterol

SGRQ: St George's Respiratory Questionnaire; TDI: Transition Dyspnoea Index.

by the number of puffs used daily ($p < 0.001$), or used during daytime ($p < 0.001$), or at night time ($p = 0.003$). The authors noted a 37% reduction from baseline in mean daily rescue use with indacaterol, versus a 3% increase with placebo. Additionally, indacaterol was associated with an overall reduction in diary symptoms over 3 weeks of treatment, compared with an increase with placebo [36].

Buhl *et al.* [40] compared indacaterol 150 µg with tiotropium 18 µg, in a 12-week randomised, double-dummy, blinded, parallel-group study, showing that TDI total scores at week 12 testified to a greater reduction in dyspnoea with indacaterol ($p < 0.001$) and that patients receiving indacaterol were more likely to achieve a clinically relevant improvement in dyspnoea (OR 1.49; $p < 0.001$). Additionally, patients' SGRQ total scores at week 12 depicted a better health status with indacaterol ($p < 0.001$), patients were also more likely to achieve a clinically relevant improvement (OR 1.43; $p < 0.001$). Indacaterol-treated patients reduced more their daily, daytime, and nocturnal use of rescue medication than tiotropium-treated patients ($p < 0.001$) and had a higher proportion of days without rescue use ($p = 0.004$) [38].

5. Safety and tolerability

In the first study on safety and tolerability of indacaterol in COPD (**Table 3**) [23], treatment duration was 28 days and indacaterol was administered in supratherapeutic doses of 400 and 800 µg. In this study, the overall incidence of adverse events (AEs) was similar for indacaterol and placebo groups, and no dose-related AE was observed. The most commonly reported AE was cough, reported by 14.7% in the 400-µg group and 28.4% in the 800-µg group. This was mild, tended to decline with duration of treatment, and never led to discontinuation of treatment. Additionally, no change in serum levels of potassium and glucose or mean QTc interval in ECG, pulse rate or blood pressure was observed [23].

In a study of the efficacy and tolerability of indacaterol at 50, 100, 200, and 400 µg, followed by an open-label extension where patients received tiotropium 18 µg for 8 days, Rennard *et al.* [24] demonstrated that the overall rate of AEs was similar across all indacaterol and placebo groups. The most frequently reported AEs were headache (in the range of 3.6 – 6.7% with indacaterol) and cough (2.9 – 12.4% with indacaterol vs 0.9% with placebo). Nevertheless, the incidence of cough decreased over the course of the study and was similar to placebo on day 7. The rate of other AEs was low, without significant differences between groups. Additionally, no significant differences were observed in the biochemical parameters (potassium and glucose) or in mean pulse rate, blood pressure or QTc interval [24].

Bauwens *et al.* [25] compared COPD patients receiving various indacaterol doses (150, 300 and 600 µg, administered as single doses) vs formoterol (12 µg administrated twice daily) and placebo. They found that all treatments were well tolerated and there was little effect on serum potassium, blood glucose, or QTc interval.

Later studies confirmed the excellent safety profile of indacaterol. In the study by Dahl *et al.* [28], which compared indacaterol 300 or 600 µg with placebo and formoterol (12 µg twice daily) over 52 weeks, deterioration of COPD and nasopharyngitis were the only AEs reported by 10% or more of the patients in all treatment groups. In addition, any case of cough occurring within 5 min of drug administration during clinical visits was recorded. This was observed in 19.1% of patients in both indacaterol groups, in 0.8% of patients of the formoterol group and 1.8% of patients of the placebo group. The cough typically started within 15 s of inhaling indacaterol, had a median duration of ≤ 12 s, and was not associated with bronchospasm. The presence of cough was not associated with any increase in discontinuation rates. Regarding ECG changes, an increase of QTc interval > 60 ms from baseline was observed in one patient

Table 3. Clinical trials examining the safety and tolerability of indacaterol.

Author	Design	Number of subjects enrolled	Primary end point	Results
Beier *et al.* [23]	See **Table 1**	See **Table 1**	See **Table 1**	No significant difference in overall incidence of AEs between indacaterol and placebo (35% for indacaterol 400 μg, 51% for 800 μg, 25% for placebo). No dose-related AEs. Most common AE was cough
Rennard *et al.* [24]	See **Table 1**	See **Table 1**	See **Table 1**	Overall incidence of AEs similar with all doses of indacaterol and placebo. Most common AEs were headache and cough
Bauwens *et al.* [25]	See **Table 1**	See **Table 1**	See **Table 1**	All indacaterol doses well tolerated. Little effect on serum potassium, blood glucose, QTc interval
Dahl *et al.* [28]	See **Table 1**	See **Table 1**	See **Table 1**	The only AEs reported in < 10% patients in any treatment group were deterioration of COPD and nasopharyngitis
Feldman *et al.* [29]	See **Table 1**	See **Table 1**	See **Table 1**	No significant differences between treatment groups in overall rate of AEs (300 μg 71%, 600 μg 65%, formoterol 65%, placebo 62%) Only AEs occurring at rate greater than 10% patients in all treatment groups were deterioration of COPD and nasopharyngitis
Donohue *et al.* [30]	See **Table 1**	See **Table 1**	See **Table 1**	Incidence of AEs was comparable in the 4 groups (66.6% for indacaterol 150 μg, 65.6% for indacaterol 300 μg, 67.2% for tiotropium, and 63.6% for placebo). In all groups COPD worsening was the most commonly reported AE
Vogelmeier *et al.* [31]	See **Table 1**	See **Table 1**	See **Table 1**	Overall incidence of AEs comparable between treatments. Most common AEs were cough, deterioration of COPD, nasopharyngitis
Kornmann *et al.* [33]	See **Table 1**	See **Table 1**	See **Table 1**	The proportion of patients with any AE was similar across treatment groups (51.2% for indacaterol 150 μg, 45.6% for salmeterol and 46.6% for placebo)
Chapman *et al.* [35]	See **Table 1**	See **Table 1**	See **Table 1**	AEs, mostly mild or moderate, occurred in 76, 77, and 68% of subjects receiving indacaterol 150 μg, indacaterol 300 μg, and placebo respectively. Serious AEs occurred in 10.4, 12.3, and 10.5%, respectively. No significant effects on ECG and levels of potassium and glucose
O'Donnell *et al.* [36]	See **Table 1**	See **Table 1**	See **Table 1**	Overall incidence of AEs was 22.9% for indacaterol 300 μg vs 27.4% for placebo. Most were mild or moderate in intensity while the most frequent AE was nasopharyngitis
Korn *et al.* [38]	See **Table 1**	See **Table 1**	See **Table 1**	Overall incidence of AEs was similar between indacaterol (33.8%) and salmeterol (33.5%). The most frequent

AE: Adverse event; COPD: Chronic obstructive pulmonary disease; ECG: Electrocardiogram.

Table 3. Clinical trials examining the safety and tolerability of indacaterol (continued).

Author	Design	Number of subjects enrolled	Primary end point	Results
				AEs were deterioration of COPD and headache
Buhl *et al.* [40]	See **Table 1**	See **Table 1**	See **Table 1**	AEs were reported for similar proportions in the 2 treatment groups (39.7% for indacaterol, 37.2% for tiotropium). COPD worsening (including exacerbations) was the most commonly reported AE (10.7% for indacaterol, 8.3% for tiotropium)
Khindri *et al.* [41]	Non-smoking healthy subjects were randomised to receive for 14 days indacaterol 150, 300 or 600 μg, placebo, or placebo/ moxifloxacin	404 patients enrolled; 388 completed the study	Change from baseline on day 14 in QTc	All indacaterol doses resulted in a mean prolongation of QTc < 5 msec. No dose-dependent relationship between indacaterol and QTc prolongation was established
Worth *et al.* [42]	Study incorporating data from three Phase III studies [28,30,33] Comparison between indacaterol 150, 300 or 600 μg, formoterol 12 μg, salmeterol 50 μg, tiotropium 18 μg, and placebo	The three studies enrolled totally 3517 moderate-to-severe COPD patients	Analysis of safety, based on pooled data from three Phase III studies (see **Table 1**)	No significant increase in cardiac and cerebrovascular AEs with either dose of indacaterol vs placebo, salmeterol, formoterol. No dose-dependent relationship was established

AE: Adverse event; COPD: Chronic obstructive pulmonary disease; ECG: Electrocardiogram.

of each indacaterol group and in one patient of the formoterol group. No patient had an absolute value > 500 ms. Low potassium concentrations (< 3 mmol/l) were recorded in two patients of each indacaterol group, while high glucose concentrations (9.9 mmol/l) were observed in 8% of the indacaterol 300 μg, 9% of the indacaterol 600 μg, 6.5% of the formoterol, and 7.5% of the placebo groups [28].

Feldman *et al.* [29] demonstrated that the overall rate of AEs was comparable between COPD patients receiving indacaterol 150 μg or placebo over 12 weeks. The most commonly reported AEs was deterioration of COPD (indacaterol 8.5%, placebo 12.2%) and cough (indacaterol 6.2%, placebo 7.3%). Additionally, serum potassium and glucose levels did not differ significantly between the two groups; and no patient had a prolongation of QTc interval > 500 ms in the ECG.

In a 2-week study, where patients received indacaterol 150 μg, indacaterol 300 μg, tiotropium 18 μg, or placebo, it was shown that the overall incidence of AEs was similar across all treatments [31]. Adverse events were mainly mild or moderate.

Recently, Chapman *et al.* [35], in a study whose primary objective was the evaluation of long-term safety of indacaterol, have reported an incidence of AEs of mainly mild-to-moderate intensity in 76, 77 and 68% in indacaterol 150 μg, 300 μg, and placebo, respectively. Serious AEs occurred in 10.4, 12.3 and 10.5%, respectively. No clinically significant effects on ECG findings (QTc interval) or on serum potassium, or plasma glucose were reported [35].

In a 12-week randomised study examining the efficacy of indacaterol 150 μg vs salmeterol 50 μg, Korn *et al.* [37] showed that the overall incidence of AEs was similar between groups (33.8% in the indacaterol group vs 33.5% in the salmeterol group). The majority of these events were mild or moderate. The most frequent were deterioration of COPD (4.5% for indacaterol, 5.7% for salmeterol) and headache (3.6% in both groups). The incidence of serious AEs was 3.6% for patients on indacaterol vs 2.8% for those on salmeterol. Clinically significant hyperglycaemia was reported at 2.9% in the indacaterol group vs 5.3% in the salmeterol group. Clinically significant hypokalaemia was only noted in one patient on indacaterol. Changes in heart rate or blood pressure were minimal, while prolongation of QTc interval was not observed [37].

In a recent study by Khindri *et al.* [41], the cardiac safety of indacaterol, assessed through changes in QTc interval, was

examined in 404 healthy, non-smoking subjects. Subjects received either indacaterol 150, 300 or 600 μg (supratherapeutic dose), placebo, or placebo–moxifloxacin (the latter was used to assess the sensitivity of the study, as it is known to be associated with an increase in QTc). The authors concluded that all doses of indacaterol resulted in a mean maximum prolongation of QTc that did not exceed 5 ms – indicating that indacaterol, across the investigated dose range, has no effects of concern on QTc. The longest prolongation of QTc (3.34 ms) was reported with the highest indacaterol dose (600 μg), but there was no clear relationship between indacaterol dose and QTc, due to the overlap between doses.

Interestingly, two pool analyses of cardiac and cerebrovascular safety data from patients enrolled in clinical trials have recently become available. Worth *et al.* [42] have incorporated data from patients enrolled in three Phase III studies [28,30,33] receiving indacaterol (150, 300 or 600 μg), formoterol 12 μg, salmeterol 50 μg, open-label tiotropium 18 μg or placebo with minimum study duration of 6 months. There was no significant increase in cardiac or cerebrovascular AEs with any dose of indacaterol vs placebo, nor with salmeterol or formoterol. Neither the incidence nor the relative risk increased with increasing dose of indacaterol. The incidence of ECG changes (increase in QTc > 60 ms from baseline, or absolute value > 500 ms) was low with all treatments. In a subgroup of patients examined by Holter monitoring, no difference in the development of arrhythmias was observed between patients on indacaterol and placebo [42]. Likewise, Donohue *et al.* [43] pooled data from 11 randomised double-blind clinical studies with minimum duration of 3 months, concluding that the adverse events were in most cases mild or moderate and the risk of serious adverse events was not increased vs placebo. COPD exacerbation rates were also reduced vs placebo. For all indacaterol doses (75, 150, 300 or 600 μg), the hazard ratios for major cardiovascular adverse events vs placebo were < 1 [43].

6. Expert opinion

According to the Global Initiative for COPD [3], long-acting bronchodilators are pivotal to symptom management in COPD, are prescribed on a regular basis to prevent or to reduce symptoms, and are more efficacious than short-acting bronchodilators. Moreover, their combined use may improve efficacy and reduce adverse effects, as compared to increasing the dose of a single bronchodilator.

Indacaterol is a novel, ultra-long-acting β_2-agonist bronchodilator, administered once daily with both rapid onset of action (within 5 min) and sustainable (24-h) efficacy in bronchodilation. Treatment with different doses of indacaterol has so far demonstrated its suitability for once-daily dosing, with a favourable safety and tolerability profile. The recommended dose is 150 μg once daily, while the maximum dose is 300 μg once daily. Data from recent clinical trials indicate that the new agent is superior to the LABAs salmeterol or formoterol (administered twice daily) and is at least as effective as the anticholinergic tiotropium (administered once daily) in terms of bronchodilation, clinical efficacy and safety [24-26,28,31,33,37-39]. In addition, in a recent cost–utility analysis, indacaterol 150 μg was superior to tiotropium and salmeterol, in view of its association with lower total costs and better outcomes [44].

So far, long-term clinical trials conducted in a large number of COPD patients have demonstrated the beneficial effects and the safety profile of indacaterol. Moreover, the 24-h duration of action and the once-daily treatment scheme indicate that indacaterol may be the treatment of choice in COPD – either alone or in combination with other treatment options, such as anticholinergics or inhaled corticosteroids. Thus, research should now focus on these treatment options, in order to examine the potential effects on different parameters of COPD management such as respiratory function, symptoms and exacerbations, as well as health-related quality of life and survival.

The major limitation is the short follow-up of patients receiving indacaterol, given that it has only recently been introduced to the market. Thus, there is a lack of current knowledge in terms of long-term effects on pulmonary function, amelioration of symptoms, reduction of exacerbations and cardiac safety beyond 1 year of follow-up.

In conclusion, indacaterol administration is favourable in COPD patients, as it is either comparable or superior to the rest of the currently existing treatment options. The introduction into the market of combination treatment schemes seems promising and may be anticipated to fulfil some hitherto unmet needs of COPD patients.

Declaration of interest

P Steiropoulos is an advisory board member of Novartis; a speaker for Novartis, Boehringer Ingelheim, Pfizer, AstraZeneca and Takeda; and is a grant recipient from GlaxoSmithKline. N Papanas has been an advisory board member of TrigoCare International; has participated in sponsored studies by Novo Nordisk and Novartis; received honoraria as a speaker for Novo Nordisk and Pfizer; and has attended conferences sponsored by TrigoCare International, Novo Nordisk, Sanofi-Aventis and Pfizer. D Bouros has received financial compensation by serving as an advisor to, acting as a speaker for and is a grant recipient from: Boehringer Ingelheim, Pfizer, AstraZeneca, Novartis, Actelion and InterMune.

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