Indacaterol in chronic obstructive pulmonary disease: an update for clinicians

Arzu Yorgancioglu

Ther Adv Chronic Dis

[2012] 3(1) 25–36

DOI: 10.1177/

2040622311426204

© The Author(s), 2012.

Reprints and permissions:

<http://www.sagepub.co.uk/journalsPermissions.nav>

Abstract: Bronchodilation is the cornerstone of chronic obstructive pulmonary disease (COPD) management and is based on regular treatment with one or more long-acting β_2 agonists (LABAs). A novel bronchodilator, indacaterol, satisfies the requirements of an efficacious LABA: it has a relatively longer duration of action compared with existing LABAs and a fast onset of action. This review is a presentation of data on indacaterol with respect to its molecular characteristics as well as comparisons with other long-acting bronchodilators. Data from 12 relevant trials show that once-daily indacaterol provides significant, consistent and clinically important improvements in lung function (forced expiratory volume in 1 second), significant improvements in breathlessness and health status at least as good as or better than tiotropium, salmeterol and formoterol, and reduction in requirement for relief medication compared with tiotropium, salmeterol and formoterol.

Keywords: chronic obstructive pulmonary disease, indacaterol, long-acting beta agonist

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the major causes of morbidity and mortality in the world despite the many treatment modalities available. Airflow limitation plays the central role in leading the symptoms in COPD and bronchodilation is the cornerstone of COPD symptom management [GOLD, 2010]. The pharmacological management of patients with moderate, severe and very severe COPD is based on regular treatment with one or more long-acting β_2 agonists (LABAs), either the once-daily anticholinergic drug, tiotropium, or one of the twice-daily LABAs, formoterol or salmeterol. COPD is a heterogeneous disease: for optimal management all aspects of a patient must be taken into account. Choice of bronchodilator should depend on the availability and individual response in terms of symptom relief and side effects [GOLD, 2010].

Although LABAs remain the cornerstone of COPD management, there is still room for improvement: there are patients who remain symptomatic [GOLD, 2010]. Evidence shows that current LABAs can be improved upon. Ideally, there is a need for a new LABA that could include the properties mentioned in Table 1 [Cazzola *et al.* 2011].

In December 2009, the first once-daily LABA, indacaterol, was approved by the European Medicines Evaluation Agency (EMA) and, consequently, introduced into the market in many countries [Beeh and Beier, 2010]. This review looks at the different characteristics of this novel agent with respect to Table 1 and also compare it with other LABAs.

Molecular properties of indacaterol

LABAs are highly lipophilic compounds. This characteristic helps to prolong their duration of action since they dissociate more slowly than short-acting β_2 agonists from fat-soluble tissues in the lung. Ultra-LABA is the term used to describe a variety of new β_2 adrenoreceptor agonists that have a more prolonged half life thus facilitating once-daily administration [Roig *et al.* 2009; Battram *et al.* 2006].

Indacaterol satisfies the requirements of an efficacious LABA with relatively longer duration of action compared with existing LABAs (24-hour sustained bronchodilator efficacy) and fast onset of action. These are due to the molecular characteristics of indacaterol as described below [Cazzola *et al.* 2011].

Correspondence to:
Arzu Yorgancioglu, MD
Celal Bayar University,
School of Medicine,
Department of
Pulmonology, Manisa,
Turkey
arzuyo@hotmail.com

Table 1. Properties of a novel long-acting β_2 agonist (LABA) for chronic obstructive pulmonary disease (adapted with permission from Cazzola *et al.* 2011).

1. Longer duration of action (compared with existing LABAs):
true 24-hour sustained bronchodilator efficacy allowing once-daily dosing.
2. Fast onset of action.
3. Superior efficacy compared with existing LABAs.
4. Favourable safety and tolerability profile.

The chemical structure of indacaterol (previously known as QAB149) may be described as 5-[(R)-2-(5,6-Diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1*H*-quinolin-2-one. It is a novel, chirally pure inhaled β_2 adrenoceptor agonist with a more rigid, compact and shorter tail than salmeterol. It was discovered in a program to specifically identify compounds with a duration of action compatible with once-daily dosing in humans, combined with a fast onset of action and an increased therapeutic index compared with the available inhaled β_2 adrenoceptor agonists (Figure 1) [Battram *et al.* 2006].

Indacaterol is a partial agonist although, relative to isoprenaline, it has more of a full agonist profile (73%) than the partial agonist salmeterol (38%). That onset of action correlates closely with intrinsic efficacy. It has twofold higher intrinsic activity than salbutamol or salmeterol [Cazzola and Matera, 2008; Battram *et al.* 2006]. The potency and intrinsic efficacy of indacaterol have been demonstrated in various models such as recombinant receptors, guinea-pig trachea, isolated human bronchus and human lung slices [Beeh and Beier, 2009]. These studies revealed the following: indacaterol behaves as a high-efficacy β_2 adrenoceptor agonist with an onset of action (30 ± 4 min) that is not significantly different from that of formoterol and salbutamol but is significantly faster than that of salmeterol; indacaterol has a significantly longer duration of action (529 ± 99 min) than both formoterol and salmeterol; indacaterol and formoterol have a higher intrinsic efficacy than salbutamol and salmeterol [Cazzola *et al.* 2011]. In the conscious guinea pig, when given intratracheally as a dry powder, indacaterol inhibits 5-hydroxytryptamine-induced bronchoconstriction for at least 24 hours, whereas salmeterol, formoterol and salbutamol have durations of action of 12, 4 and 2 hours, respectively [Battram *et al.* 2006]. When given *via*

nebulization to anaesthetized rhesus monkeys, all of the compounds dose-dependently inhibit methacholine-induced bronchoconstriction, although indacaterol produces the most prolonged bronchoprotective effect and induces the lowest increase in heart rate for a similar degree of antibronchoconstrictor activity (Figure 2) [Battram *et al.* 2006].

In conclusion, the preclinical profile of indacaterol suggests that this compound has a superior duration of action compatible with once-daily dosing in human, together with a fast onset of action and an improved cardiovascular safety profile over marketed inhaled β_2 adrenoceptor agonists [Cazzola *et al.* 2011; Battram *et al.* 2006].

The faster onset and longer duration of action of indacaterol may be related to lipid membrane interaction. Higher partitioning of indacaterol into the microenvironment of the receptor and its faster membrane permeation is likely to contribute to its faster onset and longer duration of therapeutic action [Cazzola *et al.* 2011]. A striking difference was observed for the effect of indacaterol and salmeterol on membrane fluidity. While indacaterol did not alter membrane fluidity, salmeterol drastically increased it. This increase may affect receptor function and reduce the intrinsic efficacy of the salmeterol [Cazzola *et al.* 2011].

Lipid rafts, cholesterol-enriched membrane lipid microdomains, are areas of cell membranes where β_2 adrenoceptors are held together in close contact with signalling molecules and effectors. They act as 'assembly sites' (scaffolds), concentrating the key components of cell signalling (i.e. β_2 agonist, β_2 adrenergic receptor and G protein) by restricting their movement in the membrane. Clustering of receptors and effectors into signalling platforms in lipid rafts may contribute to the efficacy and selectivity of signal transduction [Cazzola *et al.* 2011; Pontier *et al.* 2008]. It has also been suggested that lipid rafts in airway smooth muscle might play a role in the long duration of action of indacaterol. Indacaterol has twofold higher affinity for raft microdomains compared with salmeterol, and this might contribute to the difference in duration of action [Cazzola *et al.* 2011].

After inhalation, indacaterol is rapidly absorbed into the systemic circulation with a median time to maximum concentration ($T_{\max}$) of 15 min. It

Figure 1. Chemical structures of indacaterol, salmeterol and formoterol [adapted with permission from Battram *et al.* 2006].

has linear and dose-proportional pharmacokinetics (PK), and steady state is reached within 12 days of once-daily dosing at doses of 150, 300 and 600 mg [Cazzola *et al.* 2011].

Clinical efficacy

The efficacy of indacaterol in the maintenance treatment of COPD in adults has been assessed in 12 large, randomized, double-blind, parallel-group, placebo-controlled, multicentre phase III trials, as summarized in Table 2.

Short-term trials

The first five studies in Table 2 (INSURE [Balint *et al.* 2010], B2318 [Beeh *et al.* 2009], INTIME [Vogelmeier *et al.* 2010], INTEGRAL [La Force *et al.* 2011] and INABLE 1 [O'Donnell *et al.* 2011]) are short-term studies, either single dose or 14 or 21 days' duration showing the acute effect of indacaterol on forced expiratory volume in 1 second (FEV₁) which is due to the rapid onset of action of the molecule and comparing indacaterol with placebo, salmeterol or tiotropium.

INSURE [Balint *et al.* 2010] was a single-dose study showing that in COPD, single doses of indacaterol 150 and 300 mg demonstrate a fast onset

of action similar to that for salbutamol and faster than that for salmeterol plus fluticasone.

INTIME [Vogelmeier *et al.* 2010] compared the bronchodilator efficacy of indacaterol with tiotropium for 14 days in 169 patients and found that indacaterol was at least as effective as tiotropium, with a faster onset of action (within 5 min) on the first day of dosing. Indacaterol at doses of both 150 and 300 µg given once daily, resulted in clinically relevant 24-hour bronchodilation in patients with moderate-to-severe COPD and demonstrated a good overall safety and tolerability profile. This study has showed that the bronchodilator efficacy of indacaterol appeared to be at least comparable with that of tiotropium, with a faster onset of action.

The INTEGRAL [La Force *et al.* 2011] study aimed to provide evidence to characterize the 24-hour lung function profile of indacaterol and also to compare it with salmeterol 50 µg twice daily. The secondary objective was to measure inspiratory capacity (IC) at individual timepoints on days 1 and 14 for the study. For individual timepoint IC, indacaterol was superior to placebo at all post-baseline timepoints on both day 1 and day 14 ($p < 0.001$). In addition, indacaterol IC

Figure 2. Effect of β_2 adrenoceptor agonists on methacholine-induced bronchoconstriction and baseline heart rate in the anaesthetized rhesus monkey. A, dose-response curves. The bronchoprotective effect and heart rate changes were measured 5 min after commencement and at the end of the drug application, respectively. Animal numbers are indicated in parentheses. B, effect over time for indacaterol ($n=6$), formoterol ($n=9$), salmeterol ($n=6$), and salbutamol ($n=4$) at doses chosen to give 80% of maximal bronchoprotection for indacaterol, formoterol and salbutamol or a dose to give just maximal bronchoprotection for salmeterol. Data are shown as mean $\pm$ SEM. Significance, $p < 0.05$, indicated by * is against the respective control values [adapted with permission from Battram *et al.* 2006].

measurements were statistically superior to salmeterol at many timepoints.

B2318 and INABLE (B2311) studies provided data on the effect of indacaterol on dynamic and static hyperinflation, respectively [O'Donnell *et al.* 2011; Beeh *et al.* 2009] comparing indacaterol with placebo alone. The primary objective of the INABLE trial was to evaluate the effect of indacaterol 300 μ g for 21 days (3 weeks) on exercise endurance. Exercise endurance time was measured through constant-load cycle ergometry testing (at 75% W_{max}). Additional efficacy assessments included exercise endurance time on day 1, trough IC and trough FEV₁ measured at rest (60 minutes predose),

peak IC measured at exercise completion after 21 days of treatment ('end-exercise IC'), and use of rescue medication (albuterol [salbutamol]) throughout the study. Safety and tolerability were also monitored. Patients receiving indacaterol 300 μ g once daily had a significant improvement in exercise endurance compared with placebo, after the first treatment on day 1 and day 21 (Week 3). Exercise endurance was increased by 1.68 minutes (101 seconds), compared with placebo, on day 1 and by 1.85 minutes (111 seconds) on day 21 (week 3) [O'Donnell *et al.* 2011].

The results of the three studies mentioned above [La Force *et al.* 2011; O'Donnell *et al.* 2011; Beeh *et al.* 2009] showed that indacaterol

Table 2. Indacaterol clinical trials.

Trial	Indacaterol dosage	Comparators	Duration	Number of patients
Trials (single dose, 14 days, 21 days)				
INSURE [Balint <i>et al.</i> 2010].	150/300 µg od	Placebo; salbutamol 200 µg; salmeterol/fluticasone 50/500 µg	Single-dose crossover	89
B2318 [Beeh <i>et al.</i> 2009].	300 µg od	Placebo	14 days (crossover study)	25
INTIME [Vogelmeier <i>et al.</i> 2010].	150/300 µg od	Tiotropium 18 µg od (3rd party-blinded); placebo	14 days (crossover study)	169
INTEGRAL [La Force <i>et al.</i> 2011].	300 µg od	Placebo; salmeterol 50 µg bid (open label)	14 days (crossover study)	68
INABLE 1 [O'Donnell <i>et al.</i> 2011].	300 µg od	Placebo	21 days (crossover study)	90
Trials (12 weeks)				
INLIGHT 1 (B2346) [Feldman <i>et al.</i> 2010].	150 µg od	Placebo	12 weeks	416
INTENSITY [Buhl <i>et al.</i> 2011].	150 µg od	Tiotropium 18 µg od (blind)	12 weeks	1593
INSIST [Korn <i>et al.</i> 2011].	150 µg od	Salmeterol 50 µg bid	12 weeks	1123
Trials (26-52 weeks)				
INHANCE [Barnes <i>et al.</i> 2010; Donohue <i>et al.</i> 2010].	150/300 µg od	Placebo; tiotropium 18 µg od (open label)	26 weeks	1683
INLIGHT 2 [Kornmann <i>et al.</i> 2011].	150 µg od	Placebo; salmeterol 50 µg bid	26 weeks	998
INVOLVE [Dahl <i>et al.</i> 2010].	300/600 µg od	Placebo; formoterol 12 µg bid	52 weeks	1728
INDORSE [Chapman <i>et al.</i> 2011].	150/300 µg od	Placebo	52 weeks	414

bid, twice daily; od, once daily.

provided effective sustained 24-hour bronchodilation and improved measures of dynamic hyperinflation and exercise tolerance compared with salmeterol and placebo.

Twelve-week trials

Table 2 shows the three 12-week studies (INLIGHT 1 [Feldman *et al.* 2010], INTENSITY [Buhl *et al.* 2011] and INSIST [Korn *et al.* 2011]) with indacaterol that were designed to investigate whether the effects observed with indacaterol in the short-term studies persist.

The INLIGHT 1 (B2346) study [Feldman *et al.* 2010] provides 12-week efficacy and safety data for indacaterol 150 µg comparing it with placebo alone.

The main objective of the INTENSITY trial [Buhl *et al.* 2011] was to demonstrate the non-inferiority of indacaterol *versus* tiotropium with respect to trough FEV₁ but secondary objectives included efficacy evaluations of dyspnoea

(transition dyspnoea index [TDI]), health status (St George's Respiratory Questionnaire [SGRQ]) and rescue albuterol use and safety (adverse events, laboratory findings, vital signs, and ECG) for 12 weeks. Trough FEV₁ at week 12 was 1.44 l with indacaterol and 1.43 l with tiotropium. The treatment difference was 0 ml (95% confidence interval [CI] -20 to 20 ml). This demonstrated noninferiority of indacaterol to tiotropium ($p < 0.001$). TDI total scores showed a significantly greater reduction in dyspnoea with indacaterol than with tiotropium. At baseline, the use of as-needed albuterol was 3.8 puffs/day for the patients in the indacaterol group and 3.6 puffs/day for those randomized to tiotropium. Indacaterol-treated patients reduced their use of rescue albuterol more than those receiving tiotropium and had a higher proportion of days without any rescue use.

The INSIST study [Korn *et al.* 2011] compared indacaterol 150 µg and salmeterol over 12 weeks. Indacaterol was statistically superior to salmeterol for the primary endpoint, FEV₁

standardized area under the curve ($AUC_{5 \text{ min to } 11 \text{ h } 45 \text{ min}}$) at week 12, with an adjusted mean difference of 60 (95% CI 40–80) ml. The percentage of patients with a clinically important improvement (≥ 1 point) from baseline in TDI total score at week 12 was statistically higher ($p < 0.05$) for indacaterol (69.4%) than salmeterol (62.7%). Compared with salmeterol, patients on indacaterol had a greater percentage of days with no rescue medication use (difference of 4.4 days [least squares mean]; 95% CI 0.6–8.2; $p < 0.05$) and used fewer puffs/day of rescue medication (difference of -0.18 ; 95% CI -0.36 to 0.00 ; $p < 0.05$) over the 12-week study.

Thus, the three 12-week studies described above showed that the effect of indacaterol on pulmonary function and clinical outcomes persisted over 3 months and was superior to salmeterol and at least effective as tiotropium (and with a faster onset of action).

Longer-term trials

The last four trials (INHANCE [Barnes *et al.* 2010; Donohue *et al.* 2010], INLIGHT 2 [Kornmann *et al.* 2011], INDORSE [Chapman *et al.* 2011] and INVOLVE [Dahl *et al.* 2010]) are relatively long-term studies showing the positive effects on exacerbations and quality of life and comparing indacaterol with placebo, salmeterol, formoterol or tiotropium.

The INHANCE study [Barnes *et al.* 2010] was a multicentre, double-blind, randomized, placebo and active controlled, adaptive and seamless, parallel-group study design consisting of two stages. The first stage was a 14-day dose selection stage including four indacaterol doses (75, 150, 300 and 600 μg once daily), formoterol 12 μg twice daily, open-label tiotropium 18 μg once daily and placebo. In stage 2, indacaterol 150 and 300 μg were compared with placebo and open-label tiotropium during the remainder of the 26-week study ($n = 1683$) [Donohue *et al.* 2010]. The primary objective was to compare the efficacy of indacaterol with that of placebo based on measurement of trough FEV_1 at week 12. Secondary outcomes were the effect on dyspnoea score (TDI), health related quality of life (SGRQ), rescue use and the number of exacerbations.

Trough FEV_1 at week 12 increased *versus* placebo by 180 ml with both indacaterol doses and by 140 ml with tiotropium (all $p < 0.001$ *versus* placebo) and tiotropium *versus* placebo at all

timepoints; $p < 0.05$ for indacaterol 300 mg *versus* tiotropium at -50 , -15 and 5 minutes, 2 hours, 4 hours, and 23 hours 10 minutes (Figure 3) [Donohue *et al.* 2010]. TDI increased with both indacaterol doses (1.00/1.18, $p < 0.001$) (Figure 4) [Donohue *et al.* 2010].

SGRQ total score decreased (23.3/22.4, $p < 0.01$); corresponding results with tiotropium were 0.87 ($p < 0.001$) for TDI and -1.0 (p value not significant) for SGRQ total score [Yorgancıoğlu *et al.* 2009]. The incidence of adverse events, low serum potassium, high blood glucose and prolonged QTc interval was similar across treatments. Both treatment arms were effective in providing 24-hour bronchodilation, and indacaterol was at least as effective as tiotropium in its effect on symptoms and health status [Donohue *et al.* 2010; Yorgancıoğlu *et al.* 2009].

INLIGHT 2 [Kornmann *et al.* 2011] is another 6-month study comparing indacaterol 150 μg with placebo and salmeterol 50 μg . Mean trough FEV_1 at week 12 (the primary endpoint) was 170 ml higher in patients receiving indacaterol, compared with placebo ($p < 0.001$), exceeding the prespecified 120 ml level of clinical significance. Mean trough FEV_1 at week 12 was also 60 ml higher in patients receiving indacaterol than in those receiving salmeterol ($p < 0.001$). The percentage of patients achieving a clinically important improvement in SGRQ total score at week 12 was higher in the indacaterol group (57.9%), compared with the salmeterol (46.8%) and placebo (39.1%) groups. Patients receiving indacaterol had a greater chance of achieving a clinically relevant improvement in quality of life than those receiving placebo or salmeterol. The odds ratio (OR) for indacaterol *versus* placebo was 2.41 (95% CI 1.69–3.42), $p < 0.001$, and the OR for indacaterol *versus* salmeterol was 1.59 (95% CI 1.12–2.25), $p = 0.009$.

The 52-week INVOLVE trial (B2334) [Dahl *et al.* 2010] provides further efficacy data for the 300 μg indacaterol dose (including additional safety data at 600 μg for 1 year) as well as a comparison with formoterol. Trough FEV_1 values were significantly higher in the indacaterol group than in the formoterol group (1.48 *versus* 1.38 l at 12 weeks, $p < 0.001$ for indacaterol *versus* formoterol). Differences *versus* placebo in trough FEV_1 for indacaterol 300 μg were greater than those for formoterol after 1 day (140 *versus*

Figure 3. Serial measurements of forced expiratory volume in 1 second [FEV₁]. Treatment differences for FEV₁: $p < 0.05$ for indacaterol (both doses) [with permission from Donohue *et al.* 2010].

110 ml, $p < 0.05$ for indacaterol *versus* formoterol), at week 12 (170 *versus* 70 ml, $p < 0.001$ for indacaterol *versus* formoterol) and at week 52 (160 *versus* 50 ml, $p < 0.001$ for indacaterol *versus* formoterol) [Dahl *et al.* 2010]. Benefits associated with indacaterol use were apparent as early as day 2 and were sustained through 52 weeks (Figure 5) [Dahl *et al.* 2010].

Although the INVOLVE study was not specifically designed to investigate the effect of indacaterol compared with formoterol on exacerbations, and patients were not specifically selected to have a history of exacerbations, exacerbations occurred in 133 (32.8%), 126 (31.5%) and 145 (36.3%) patients in the indacaterol 300 µg, formoterol and placebo groups, respectively. Cox regression analysis of time to first COPD exacerbation showed statistical improvement for indacaterol 300 µg and formoterol *versus* placebo, with hazard ratios of 0.77 ($p = 0.029$) and 0.77 ($p = 0.034$), respectively. Indacaterol was more effective than formoterol in improving TDI score and reducing the need for as-needed albuterol, was well tolerated and had a good overall safety profile, including minimal impact on QTc interval and systemic β_2 -mediated adverse events [Dahl *et al.* 2010].

The INDORSE (B2335SE) study was a 6-month extension of INHANCE (B2335S) and was

specifically designed to evaluate the long-term efficacy and safety of indacaterol 150 and 300 µg compared with placebo [Chapman *et al.* 2011]. Among patients participating in INDORSE, indacaterol 150 and 300 µg once daily resulted in significant improvements in FEV₁ compared with placebo throughout the 52 weeks of the study (all $p < 0.001$). The differences between indacaterol 300 µg and placebo exceeded the threshold for a clinically important difference (120 ml) at all timepoints from day 1 to week 52, while differences between indacaterol 150 µg and placebo exceeded the threshold at all timepoints from day 15 to week 52 [Chapman *et al.* 2011]. Indacaterol 150 and 300 µg once daily resulted in statistically significant reductions in use of rescue medication as well as significant reductions in exacerbation rates, compared with placebo, during the 52 weeks of the INDORSE study [Rennard *et al.* 2009].

Results from the 12 clinical trials showed that that once-daily indacaterol provided significant, consistent and clinically important improvements in lung function (FEV₁), significant improvements in breathlessness and health status at least as good as or better than tiotropium, salmeterol and formoterol, and a reduction in the requirement for relief medication compared with tiotropium, salmeterol and formoterol.

Figure 4. (a) Transition dyspnoea index (TDI) total score and (b) the proportions of patients with a clinically important improvement from baseline in TDI total score (>1 point) (intention-to-treat population). Data for TDI total score are least squares means with 95% confidence intervals. ** $p < 0.01$ and *** $p < 0.001$ versus placebo; † $p < 0.05$; †† $p < 0.01$; ††† $p < 0.001$ versus tiotropium [with permission from Donohue *et al.* 2010].

Pooled analyses

A pooled analysis of results was performed at 3 months from three long-term studies (INHANCE, INLIGHT 1 and INVOLVE) [Siler *et al.* 2010] to look at the efficacy of indacaterol 150 µg once daily, indacaterol 300 µg once daily, placebo, open-label tiotropium 18 µg once daily and formoterol 12 µg twice daily and evaluate outcomes. The pooled population consisted of 3406 men and women with entry criteria of moderate-to-severe COPD. In the 3-month pooled analyses, indacaterol 150 and 300 µg once daily

provided significant improvement *versus* placebo over a range of clinical outcomes that are relevant to assessing benefit in COPD patients, including: improvement in health status as demonstrated by SGRQ total score; increase in percentage of days without rescue medication use; and reduction in rate of COPD exacerbations. Both indacaterol doses were significantly superior to open-label tiotropium in terms of percentage of days with no rescue medication use and SGRQ total score. Patients receiving indacaterol were least likely to experience an exacerbation over

Figure 5. Trough forced expiratory volume in 1 second (FEV₁) after 1 day and at weeks 12 and 52 of treatment (modified intention-to-treat population). Data are least squares means $\pm$ SE [with permission from Dahl *et al.* 2010].

3 months, with the rate of exacerbations decreased for each of the indacaterol doses *versus* placebo [Siler *et al.* 2010].

A 6-month pooled analysis of the efficacy of indacaterol 150 µg once daily, indacaterol 300 µg once daily, placebo, open-label tiotropium 18 µg once daily and formoterol 12 µg twice daily was conducted to evaluate outcomes from the three long-term studies (INHANCE, INLIGHT 2 and INVOLVE) [Dunn *et al.* 2010]. The pooled population consisted of 4088 men and women with entry criteria of moderate-to-severe COPD.

Compared with salmeterol, patients on indacaterol had a greater percentage of days with no rescue medication use (difference of 4.4 days [least squares mean]; 95% CI 0.6–8.2; $p < 0.05$) and used fewer puffs/day of rescue medication (difference of -0.18 ; 95% CI -0.36 to 0.00 ; $p < 0.05$) over the 12-week study. Indacaterol-treated patients reduced their use of rescue albuterol more than those receiving tiotropium and had a higher proportion of days without any rescue use [Dunn *et al.* 2010]. The percentage of patients with an improvement from baseline in TDI total score of at least 1 (minimal clinically important change) was highest with indacaterol 150 and 300 µg. The OR *versus* placebo for improvement of ≥ 1 unit were 1.49 for open-label tiotropium, 2.02 for formoterol, 1.79 for

salmeterol, and 1.91 and 2.69 for indacaterol 150 µg and 300 µg, respectively. Both doses of indacaterol (150 and 300 µg) resulted in clinically relevant changes from baseline in mean SGRQ total score that exceeded the minimum clinically important difference (≥ 4 units). Improvements in SGRQ score were numerically greater with indacaterol than with open-label tiotropium, with a statistically significant difference for the comparison between indacaterol 150 µg and open-label tiotropium ($p < 0.01$) [Jones *et al.* 2011].

A pooled analysis of the efficacy and safety of indacaterol assessed at month 3 in subgroups divided according to inhaled corticosteroid (ICS) use (ICS users and nonusers) has also been performed. Overall, the proportion of patients with exacerbations was higher in ICS users than in nonusers. Hazard ratios *versus* placebo for time to first COPD exacerbation showed a significant effect of indacaterol in nonusers (150 µg, 0.47 [$p = 0.001$]; 300 µg, 0.64 [$p < 0.05$]) and a smaller nonsignificant effect in ICS users (0.77 and 0.72 for 150 and 300 µg, respectively). The significant effect of indacaterol *versus* placebo on COPD exacerbations in nonusers indicates that indacaterol is an appropriate first-line maintenance treatment for COPD patients [Decramer *et al.* 2010]. In the subgroups divided by age (< 65 and ≥ 65 years of age), indacaterol provided clinically significant

Table 3. The incidence of cardiovascular and cerebrovascular (CCV) adverse events (AEs) in the 6-month safety population [with permission from Worth *et al.* 2011].

	Indacaterol 150 µg	Indacaterol 300 µg	Formoterol 12 µg	Salmeterol 50 µg	Open-label tiotropium	Placebo
Number of patients	746	853	556	333	415	1185
Total patient years	331.04	379.31	227.49	149.79	180.23	487.41
Number of CCV AEs	46	56	28	19	33	54
Number of patients with CCV AEs, n (%)	39 (5.2)	43 (5.0)	22 (4.0)	16 (4.8)	24 (5.8)	41 (3.5)
Relative risk versus placebo of experiencing ≥1 CCV AE (95% CI)	1.51 (0.98–2.32)	1.46 (0.96–2.22)	1.14 (0.69–1.90)	1.39 (0.79–2.44)	1.67 (1.02–2.73)	
p value	0.061	0.090	0.585	0.255	0.044	

Indacaterol 150 µg once daily *versus* placebo and salmeterol 50 µg twice daily (6 months); indacaterol 150 µg and 300 µg once daily *versus* placebo, and tiotropium 18 µg once daily (6 months); indacaterol 300 µg once daily *versus* placebo and formoterol 12 µg twice daily (1 year); CI, confidence interval.
AE, adverse event; CI, confidence interval; CCV, cardiovascular and cerebrovascular.

bronchodilation on day 1 compared with placebo regardless of age [Buhl *et al.* 2010].

Safety issues

The overall incidence of adverse events in the INDORSE study (up to week 52) was 77%, 77% and 69% in patients receiving indacaterol 150 µg once daily, indacaterol 300 µg once daily and placebo, respectively [Chapman *et al.* 2011]. The most frequent adverse event (COPD worsening, nasopharyngitis and cough) occurred in similar percentages of patients across the three treatment groups. Cough following inhalation with indacaterol was not considered to be a safety concern.

In phase III clinical studies, healthcare providers observed during clinic visits that on average 17–20% of patients experienced a sporadic cough that occurred usually within 15 seconds following inhalation and typically lasted for 5 seconds (about 10 seconds in current smokers). It was observed with a higher frequency in females than in males and in current smokers than in exsmokers. This postinhalation cough was generally well tolerated and did not lead to any patient discontinuing from the studies at the recommended doses (cough is a symptom in COPD and only 6.8% of patients overall reported cough as an adverse event). There is no evidence that cough experienced following inhalation is associated with bronchospasm, exacerbations, deteriorations of disease or loss of efficacy [Chapman *et al.* 2011].

Few patients discontinued due to adverse events in the indacaterol 150 µg once daily (2.8%) and 300 µg once daily (1.4%) groups, with a higher incidence in the placebo group (5.6%). Serious adverse events (SAEs) occurred in 10%, 13% and 11% of patients receiving indacaterol 150 µg once daily, indacaterol 300 µg once daily and placebo, respectively. The most frequent SAEs (respiratory/thoracic/mediastinal disorders, infections and infestations, and cardiac disorders) occurred in similar percentages of patients across the three treatment groups. There were two deaths due to cardiac disorders (both myocardial infarctions; one with indacaterol 300 µg and one with placebo) [[author, insert reference]].

Table 3 shows the incidence of cardiovascular and cerebrovascular (CCV) adverse events in the 6-month safety population. There was no significant increase in the risk for CCV adverse events with indacaterol compared with placebo, nor with formoterol or salmeterol. Tiotropium was associated with an increased relative risk *versus* placebo ($p < 0.05$). Neither the incidence nor the relative risk increased numerically with increasing dose of indacaterol [Worth *et al.* 2011].

In all studies designed to investigate whether indacaterol has the same tolerability of LABAs already in the market, indacaterol was well tolerated at all doses and with a good overall safety profile [Cazzola *et al.* 2011; Chapman *et al.* 2011].

The good overall tolerability profile of indacaterol is further supported by the high level of compliance to treatment and by the very low drop-out rate. Both doses of indacaterol demonstrated a good overall safety profile, with no clinically relevant differences between treatment groups in any of the cardiovascular or biochemical variables assessed [Beier *et al.* 2007].

There could be several limitations of this review at this timepoint. One is the lack of trials comparing indacaterol with LABA/ICS combinations particularly for patients with moderate and severe COPD. The second is that none of the studies were specifically designed to investigate the effect of indacaterol on exacerbations; however, *post hoc* analyses were performed. Future studies are needed for a better definition of the role of indacaterol in COPD management.

Conclusions

In conclusion, data from clinical trials show that once-daily indacaterol improves lung function at least as effectively as tiotropium, and better than salmeterol or formoterol. It also improves clinical outcomes such as breathlessness, health-related quality of life, reduction in need for rescue medication and it has faster onset of action than other LABAs. It has a good overall tolerability profile and is associated with a high level of compliance (very low drop-out rate). The author proposes that indacaterol could be a better option for the first-line treatment of COPD than other existing therapies and that future studies will better define its place in COPD therapy.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Arzu Yorgancıoğlu has received honoraria for speaking and consulting, and/or financial support for clinical trials and attending meetings from AstraZeneca, Boehringer Ingelheim, Pfizer, Chiesi Farmaceutici, GSK, MSD, Novartis, Pfizer and Sanovel.

References

Balint, B., Watz, H., Amos, C., Owen, R., Higgins, M. and Kramer, B. (2010) Onset of action of indacaterol in patients with COPD: comparison with salbutamol

and salmeterol-fluticasone. *Int J Chron Obstruct Pulmon Dis* 5: 311–318.

Barnes, P.J., Pocock, S.J., Magnussen, H., Iqbal, A., Kramer, B., Higgins, M. *et al.* (2010) Integrating indacaterol dose selection in a clinical study in COPD using an adaptive seamless design. *Pulm Pharmacol Ther* 23: 165–171.

Batram, C., Charlton, S.J., Cuenoud, B., Dowling, M.R., Fairhurst, R.A., Farr, D. *et al.* (2006) In vitro and in vivo pharmacological characterization of 5-[(R)-2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one (indacaterol), a novel inhaled β_2 adrenoceptor agonist with a 24-h duration of action. *J Pharmacol Exp Ther* 317: 762–770.

Beeh, K.M. and Beier, J. (2009) Indacaterol: a new once daily long-acting β_2 adrenoceptor agonist. *Core Evidence* 4: 37–41.

Beeh, K.M. and Beier, J. (2010) The short, the long, and the “ultra-long”: why duration of bronchodilator action matters in chronic obstructive pulmonary disease. *Adv Ther* 27: 150–159.

Beeh, K.M., Khindri, S., Eeg, M. and Drollmann, A.F. (2009) Effect of indacaterol maleate on dynamic lung hyperinflation in patients with COPD. *Eur Respir J* 34(Suppl. 53): E4357.

Beier, J., Chanez, P., Martinot, J.B., Schreurs, A.J., Tkáčová, R., Bao, W. *et al.* (2007) Safety, tolerability and efficacy of indacaterol, a novel once-daily β_2 -agonist, in patients with COPD: a 28-day randomised, placebo controlled clinical trial. *Pulm Pharmacol Ther* 20: 740–749.

Buhl, R., Dunn, L.J., Disdier, C., Lassen, C., Amos, C., Henley, M. *et al.* on behalf of the INTENSITY study investigators. (2011) Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. *Eur Respir J* [ePub ahead of print].

Buhl, R., Mahler, D.A., Owen, R., Lassen, C. and Kramer, B. (2010) Indacaterol Provides Effective Bronchodilation in Patients with COPD Irrespective of Age. European Respiratory Society.

Cazzola, M., Calzetta, L. and Gabriella Matera, M. (2011) β_2 -adrenoceptor agonists: current and future direction. *Br J Pharmacol* 163: 4–17.

Cazzola, M., Calzetta, L. and Matera, M.G. (2008) Novel long-acting bronchodilators for COPD and asthma. *Br J Pharmacol* 155: 291–299.

Chapman, K.R., Rennard, S.I., Dogra, A., Owen, R., Lassen, C. and Kramer, B. (2011) Long-term safety and efficacy of indacaterol, a novel long-acting β_2 -agonist, in subjects with COPD: a randomized, placebo-controlled study. *Chest*, DOI: 10.1378/chest.10-1830.

Dahl, R., Chung, K.F., Buhl, R., Magnussen, H., Nonikov, V., Jack, D. *et al.* for the INVOLVE (INdacaterol: Value in COPD: Longer Term Validation of Efficacy and Safety) Study Investigators.

- (2010) Efficacy of a new once-daily LABA, indacaterol, versus the twice-daily LABA formoterol, in COPD. *Thorax* 65: 473–479.
- Decramer, M., Donohue, J., Owen, R., Lassen, C. and Kramer, B. (2010) Indacaterol Provides Effective Bronchodilation in Patients with COPD Regardless of Concomitant ICS Use. European Respiratory Society.
- Donohue, J.F., Fogarty, C., Lötvall, J., Mahler, D.A., Worth, H., Yorgancioglu, A. *et al.* for the INHANCE study investigators. (2010) Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. *Am J Respir Crit Care Med* 182: 155–162.
- Dunn, L.J., Buhl, R., Lassen, C., Henley, M. and Kramer, B. (2010) Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD. *Chest* 138: 719A.
- Feldman, G., Siler, T., Prasad, N., Jack, D., Piggott, S., Owen, R. *et al.* INLIGHT 1 study group. (2010) Efficacy and safety of indacaterol 150 µg once-daily in COPD: a double-blind, randomised, 12-week study. *BMC Pulm Med* 10: 11.
- GOLD. (2010) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, Updated 2010, available at: <http://www.goldcopd.com/>.
- Jones, P.W., Mahler, D.A., Gale, R., Owen, R. and Kramer, B. (2011) Profiling the effects of indacaterol on dyspnoea and health status in patients with COPD. *Respir Med* 105: 892–899.
- Korn, S., Kerwin, E., Atis, S., Amos, C., Owen, R. and Lassen, C. for the INSIST study group. (2011) Indacaterol once-daily provides superior efficacy to salmeterol: a 12-week trial. *Respir Med* 105: 719–726.
- Kornmann, O., Dahl, R., Centanni, S., Dogra, A., Owen, R., Lassen, C. *et al.* for the INLIGHT-2. Indacaterol Efficacy Evaluation Using 150-µg Doses with COPD Patients study investigators. (2011) Once-daily indacaterol vs twice-daily salmeterol for COPD: a placebo-controlled comparison. *Eur Respir J* 37: 273–279.
- La Force, C., Aumann, J., Parreño, L.D., Iqbal, A., Young, D., Owen, R. *et al.* on behalf of the INTEGRAL study investigators. (2011) Sustained 24-hour efficacy of once-daily indacaterol (300 µg) in patients with chronic obstructive pulmonary disease: a randomized, crossover study. *Pulm Pharmacol Ther* 24: 162–168.
- O'Donnell, D.E., Casaburi, R., Vincken, W., Puente-Maestu, L., Swales, J., Lawrence, D. *et al.* for the INABLE 1 study group. (2011) Effect of indacaterol on exercise endurance and lung hyperinflation in COPD. *Respir Med* 105: 1030–1036.
- Pontier, S.M., Percherancier, Y., Galandrin, S., Breit, A., Galés, C., Bouvier, M. *et al.* (2008) Cholesterol-dependent separation of the β_2 -adrenergic receptor from its partners determines signaling efficacy. Insight into nanoscale organization of signal transduction. *J Biol Chem* 283: 24659–24672.
- Rennard, S.I., Chapman, K.R., Luthra, A., Swales, J., Lassen, C., Owen, R. *et al.* (2009) Once-daily indacaterol provides effective bronchodilation over 1 year of treatment in patients with chronic obstructive pulmonary disease (COPD). *Chest* 136: 4S–f.
- Roig, J., Hernando, R. and Mora, R. (2009) Indacaterol, a novel once daily inhaled β_2 -adrenoreceptor agonist. *Open Respir Med J* 3: 27–30.
- Siler, T., Williams, J., Yegen, U., Owen, R., Lassen, C. and Kramer, B. (2010) The effect of once-daily indacaterol on health-related quality of life, rescue medication use, and exacerbation rates in patients with moderate-to-severe COPD: a pooled analysis of three months of treatment. *Am J Respir Crit Care Med* 181: A4430.
- Vogelmeier, C., Ramos-Barbon, D., Jack, D., Piggott, S., Owen, R., Mark Higgins, M. *et al.* for the INTIME study investigators. (2010) Indacaterol provides 24-hour bronchodilation in COPD: a placebo-controlled blinded comparison with tiotropium. *Respir Res* 11: 135.
- Worth, H., Chung, K.F., Felser, J.M., Hu, H. and Rueegg, P. (2011) Cardio- and cerebrovascular safety of indacaterol vs formoterol, salmeterol, tiotropium and placebo in COPD. *Respir Med* 105: 571–579.
- Yorgancıoğlu, A., Mahler, D., Iqbal, A., Owen, R., Higgins, M., Kramer, B. *et al.* (2009) Indacaterol once-daily improves health-related quality of life in COPD patients: a 26-week comparison with placebo and tiotropium. *Eur Respir J* 34(Suppl. 53): 346S.