Effect of indacaterol on exercise endurance and lung hyperinflation in COPD

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KEYWORDS
Indacaterol;
Exercise capacity;
Inspiratory capacity;
Bronchodilator agents

Summary
Background: Indacaterol is a novel, inhaled, once-daily ultra long-acting β2-agonist (ultra-LABA) for the treatment of COPD. This study investigated the effect of indacaterol on exercise endurance, and on lung hyperinflation during exercise and at rest in patients with moderate-to-severe COPD.

Methods: In this double-blind, placebo-controlled, two-period crossover study (3-week treatment, 3-week washout between treatments), patients were randomized to receive indacaterol 300 µg once-daily or matching placebo. The primary efficacy variable was exercise endurance time after 3 weeks of treatment, measured through constant-load cycle ergometry testing performed at 75% of the peak work rate in a screening incremental exercise test.

Results: Of 90 patients randomized (mean age: 62.8 years; post-bronchodilator FEV1: 61.2% predicted and FEV1/FVC: 51.6%), 74 completed the study. Pre-treatment exercise tolerance averaged 459 s. Improvement in exercise endurance time was higher with indacaterol 300 µg than with placebo both after the first dose (treatment difference: 101 s; \( p < 0.001 \)) and after 3 weeks (treatment difference: 111 s; \( p < 0.011 \)). In addition, indacaterol increased end-exercise inspiratory capacity (IC) versus placebo after 3 weeks (0.28 L, \( p < 0.002 \)). Significant improvements were also observed in resting IC (0.17 L, \( p = 0.002 \)), FEV1 (0.23 L, \( p < 0.001 \)) and FVC (0.26 L, \( p < 0.001 \)) with indacaterol compared with placebo at 75 min post-dose after 3 weeks.

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INABLE 1—Indacaterol: endurance, exercise-based, and lung evaluation 1.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a complex disease, characterized by a progressive decline in lung function, with both pulmonary and extra-pulmonary effects. One of the major consequences of COPD is expiratory flow limitation, leading to lung hyperinflation. Dynamic hyperinflation occurs during periods of increased ventilatory demand, particularly during exercise. Lung hyperinflation in turn reduces inspiratory capacity (IC), a lung volume measure that correlates with dyspnea and exercise tolerance in patients with moderate-to-severe COPD. Limitation in exercise capacity represents an important feature of COPD, and is one of the main factors to negatively impact patients’ quality of life.

In clinical practice, bronchodilators are recommended for symptomatic relief in COPD patients with all stages of severity. Bronchodilators, including long-acting β2-agonists (LABAs), have been shown to increase IC both at rest and during exercise in patients with COPD by reducing lung hyperinflation, with a resultant improvement in exercise capacity. Indacaterol is a novel, inhaled ultra-LABA providing 24-h bronchodilation with once-daily dosing in patients with COPD. Indacaterol has been approved in more than 50 countries worldwide, including throughout the European Union, for maintenance treatment of COPD at the doses of 150 and 300 μg once-daily. This study was designed to examine the impact of indacaterol 300 μg once-daily on exercise endurance time and lung hyperinflation in patients with moderate-to-severe COPD.

Methods

This was a phase III, randomized, multi-center, multinational, double-blind, placebo-controlled, two-period crossover study conducted at specialized respiratory care centers (ClinicalTrials.gov registration number: NCT00620022). Institutional review board or independent ethics committee approval was obtained at each participating study center. The study was conducted in accordance with the Declaration of Helsinki (1989) and local applicable laws and regulations. All patients provided written informed consent prior to their participation in the study.

Patients

Male and female patients aged ≥40 years, with a clinical diagnosis of moderate-to-severe COPD (according to GOLD 2005 guideline), marked by a post-bronchodilator forced expiratory volume in 1 s (FEV₁) <80% and ≥30% of the predicted normal value (i.e., Stage II or III) and a post-bronchodilator FEV₁/forced vital capacity (FVC) <70%, and a smoking history of at least 20 pack-years were eligible for enrollment in the study. Patients were excluded if they had been hospitalized for a COPD exacerbation in the 6 weeks prior to screening or during the run-in period, had experienced a respiratory tract infection in the 6 weeks prior to screening, experienced oxygen desaturation <80% during cycle exercise, or had contraindications to cardiopulmonary exercise testing including electrolyte abnormalities. Patients with concomitant pulmonary disease, type I diabetes or uncontrolled type II diabetes or with a history of asthma were also excluded, as were patients with a maximum work rate <20 W at screening.

Study design

The study comprised a pre-screening visit, a 14-day screening period, and two 3-week treatment periods. At the baseline visit, eligible patients were randomized equally to one of two treatment sequences to receive either indacaterol 300 μg once-daily in the first period followed by placebo in the second period, or to receive placebo in the first period followed by indacaterol in the second, each via a single-dose dry powder inhaler (SDDPI). Each treatment period was separated by a washout period of 3 weeks. Patients, investigators, clinic staff performing assessments, data analysts, and the sponsor’s trial team were blinded to treatment from the time of randomization until database lock.

Concomitant treatment

Daily inhaled corticosteroid (ICS) monotherapy was allowed, if the patient was using ICS on entry to the study, at a dose and regimen to remain stable throughout the study. Patients were not allowed to use the following medications: long- or short-acting anticholinergics, theophyllines or xanthine derivatives, parenteral or oral corticosteroids, and LABAs or short-acting β2-agonists other than those prescribed in the study. Patients using fixed combinations of ICS and LABA on study entry were switched to the equivalent ICS monotherapy at a dose and regimen maintained throughout the study. Salbutamol was available as a rescue medication throughout the study.

Assessments

The primary efficacy variable, exercise endurance time (in seconds) was measured through constant-load cycle ergometry testing at 75% of the maximum work rate (W_max) after 3 weeks of treatment. Period baseline for the exercise endurance test was defined as the pre-treatment exercise

Conclusion: In conclusion, indacaterol treatment improved the ability of patients with COPD to exercise. In addition, the improvements observed in resting and end-exercise IC indicate reductions in lung hyperinflation after 3 weeks treatment (ClinicalTrials.gov registration number: NCT00620022).

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time (in seconds) measured at a visit that took place 4–9 days prior to the scheduled start of each treatment period.

Cardiopulmonary exercise testing was performed using incremental and constant-load cycle ergometry. The cycle ergometer exercise test procedures commenced with a period of quiet breathing for at least 3 min, followed by pre-exercise resting measurement over a 30 s interval before commencing pedaling. At screening, patients underwent an incremental cycle ergometry test to determine their W\textsubscript{max} (defined as the greatest work rate that was maintained for ≥30 s at 50–70 rpm), with initial unloaded pedaling for 3 min followed by an immediate increase in work rate to 10 W and then by further increments of 10 W every minute until symptom limitation. For each constant-load cycle ergometer test, patients commenced 3 min unloaded pedaling at 50–70 rpm, followed by an immediate increase in work rate to 75% W\textsubscript{max}, with pedaling to continue until symptom limitation. The exercise endurance time was recorded as the duration of loaded pedaling, i.e., from the commencement of loaded pedaling to the symptom-limited endpoint where the patient indicated that they needed to stop exercise or could no longer maintain the required pedaling rate. Secondary efficacy variables included exercise endurance on Day 1, end-exercise IC and Borg CR10 scale outcomes on Day 1 and after 3 weeks of treatment. End-exercise IC measurements were collected from one maneuver performed immediately after the patient indicated that they could no longer continue loaded pedaling, preferably prior to lowering the load. The Borg CR10 scale was used to measure the level of dyspnea and leg discomfort during exercise, with assessments performed pre-exercise, and immediately upon completion of exercise.

Additional secondary efficacy variables included resting spirometry variables (IC, FEV\textsubscript{1} and FVC) at 75 min post-dose on Day 1 and at 60 min predose and 75 min post-dose (before commencing the exercise test) after 3 weeks of treatment. Spirometry was conducted according to American Thoracic Society (ATS)/European Respiratory Society (ERS) standards. Resting spirometry variables were determined from two separate sets of spirometer maneuvers — a set of IC maneuvers (with the mean value from three acceptable maneuvers recorded), and a set of forced expiratory maneuvers (for FEV\textsubscript{1} and FVC, with the highest values from three acceptable maneuvers recorded).

Patients' activity was assessed using a 120-h actigraphy device (Bodymedia SenseWear Armband device) worn for the final 5 days in each treatment period (the device was to be worn continually for this 5-day period, except that it was to be removed while bathing). Patient diaries were provided to patients for recording their daily clinical symptoms (overall, cough, wheeze, sputum and breathlessness, each assessed on a scale of 0–3) and rescue medication usage throughout the study. The mean total symptom scores and individual symptom scores for the patients were calculated over 3 weeks.

Safety assessments included recording of adverse events (AEs) and serious AEs (SAEs), along with evaluation of their severity, duration, and relationship to study drug. Other safety assessments included regular monitoring of vital signs, electrocardiograms (ECGs) and other standard clinical laboratory evaluations such as hematology, blood chemistry and urinalysis.

Statistical analysis

It was estimated that 70 patients were needed to complete the study, assuming a difference of 120 s between indacaterol and placebo in constant work rate exercise endurance time based on data from three studies with a standard deviation of 305.2 s (based on data from a previous for meterol study\textsuperscript{(5)}), a two-sided significance level of 5%, and a power of 90%. Allowing for a 15% dropout rate, it was calculated that 83 patients had to be randomized.

The efficacy variables were analyzed on the modified intent-to-treat (mITT) population, which included all randomized patients who received at least one dose of study drug. Missing values were not imputed; patients with efficacy measurements from only one treatment period were considered in the population for calculation of treatment means but were excluded for treatment contrasts. All safety analyses were performed on the safety population, which included all patients who received at least one dose of study drug.

The primary efficacy variable was analyzed using a mixed model, with treatment, period baseline exercise endurance time, and period as fixed effects, and patient as random effect. The least squares mean (LSM) adjusted treatment difference for indacaterol 300 μg versus placebo was estimated along with the associated 95% confidence interval and two-sided p-value. Secondary efficacy variables were analyzed using similar mixed models as used for the primary variable. AE and SAE data, laboratory data, electrocardiogram (ECG) results, and measurements of vital signs were summarized descriptively by treatment group.

Results

This study was conducted at 18 centers in 6 countries (Spain, Belgium, Italy, Denmark, Canada and USA). The first patient was enrolled in April, 2008; the last patient completed the study in January, 2009.

Patient disposition, demographics, and baseline characteristics

Of 114 patients screened, 90 were randomized and 74 (82.2%) completed the study. One randomized patient withdrew from the study prior to exposure to study drug. Of the 15 patients that withdrew after exposure to study drug, 14 withdrew due to adverse events; one patient withdrew consent.

The baseline demographics and clinical characteristics of all exposed patients are shown in Table 1. The majority of patients were male with a mean age of 63 years; 88 (98.9%) patients were Caucasian. The mean duration of COPD was 6.3 years, with the largest proportion of patients (76.4%) determined to have COPD of moderate severity. All calculations to determine the severity of COPD in patients at screening were performed at study centers. After database lock, COPD severity was derived using a standardized
after 3 weeks of treatment.

Exercise endurance time (seconds) on Day 1 and after 3 weeks of treatment, indacaterol 300 

g was significantly higher than placebo in patients with 

FEV1 <50% predicted (difference of 229 s; 95% CI: 31, 426, 

p = 0.024) and was numerically higher than placebo in patients with FEV1 ≥50% predicted (difference of 85 s; 95% 

CI: −10, 180, p = 0.078). In a second subgroup analysis according to smoking status at study entry, the exercise endurance time after 3 weeks with indacaterol was significantly higher than with placebo in current smokers (difference of 161 s; 

95% CI: 22, 299, p = 0.023) and was numerically higher than with placebo in ex-smokers (81 s; 95% CI: −25, 188, 

p = 0.132). On Day 1, indacaterol was also significantly superior to placebo for exercise endurance time, with an 

LSM treatment difference of 101 s (p < 0.001) (Fig. 1).

The most common reason for ceasing exercise in the indacaterol treatment group was muscle fatigue (53% of 

patients in the indacaterol group on Day 1 and 49% at Week 3); the most common reason in the placebo group was 

dyspnea (57% on Day 1 and 53% at Week 3). A greater proportion of patients with severe COPD discontinued due to 
dyspnea in both groups, although again this was more frequently quoted as the reason for discontinuation in the 

placebo group (73% and 73% on Day 1 and Week 3) than the 

indacaterol group (56% and 43%, respectively).

Other assessments during exercise
End-exercise IC was significantly higher with indacaterol 

than with placebo both on Day 1 and after 3 weeks, with 

LSM differences of 190 mL (p = 0.04) and 280 mL (p = 0.002), respectively (Fig. 2). For Borg CR10 scale 

outcomes, there were no significant differences at end-

exercise between indacaterol and placebo for either Borg 

CR10 exertional dyspnea or Borg CR10 leg discomfort on Day 

1 or after 3 weeks of treatment.

Resting spirometry assessments
Indacaterol treatment resulted in significant improvements 

versus placebo in resting IC at 75 min post-dose on Day 1 

(p < 0.001), and at 60 min predose (p = 0.004) and 75 min 

post-dose (p = 0.001) after 3 weeks of treatment (Table 2). 

The mean FEV1 and FVC values were also significantly 

higher (p < 0.001) for indacaterol versus placebo at all of 

these time points (Table 2).

Diary data and actigraphy
Indacaterol was associated with significant reductions in 

the use of rescue medication compared with placebo over 

the 3 weeks of treatment in terms of the number of puffs 

used daily (LSM treatment difference of −1.2, p < 0.001), 

the number of puffs used during daytime (LSM treatment 

difference of −0.7, p < 0.001) and the number of puffs 

used at nighttime (LSM treatment difference of −0.5, 

p = 0.003). Expressed as a change from baseline, there was a 

37% reduction from baseline in mean daily rescue use with 

indacaterol compared with a 3% increase from baseline 

with placebo. Use of indacaterol was also associated with 

an increase in the percentage of days when patients did not 

require rescue medication, with an indacaterol—placebo 

difference of 14.4 percentage points (p = 0.001).

Indacaterol treatment was associated with an overall 

reduction in diary symptoms over the 3 weeks of treatment 

(change from baseline in mean total symptom score of

Table 1 Patient demographics and baseline characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (N = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.8 (8.20)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>62 (69.7)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (30.3)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 (4.14)</td>
</tr>
<tr>
<td>Duration of COPD (years)</td>
<td>6.3 (5.87)</td>
</tr>
<tr>
<td>COPD severity (GOLD 2005), n (%)</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>4 (4.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>68 (76.4)</td>
</tr>
<tr>
<td>Severe</td>
<td>17 (19.1)</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV1 (L)</td>
<td>1.52 (0.470)</td>
</tr>
<tr>
<td>Post-bronchodilator FEV1 (L)</td>
<td>1.71 (0.492)</td>
</tr>
<tr>
<td>Post-bronchodilator FEV1 (%)</td>
<td>61.2 (12.36)</td>
</tr>
<tr>
<td>Range</td>
<td>32.3–84.5</td>
</tr>
<tr>
<td>Post-bronchodilator FEV1/FVC (%)</td>
<td>51.6 (10.51)</td>
</tr>
<tr>
<td>FEV1 reversibility (% increase)</td>
<td>13.1 (10.98)</td>
</tr>
<tr>
<td>Peak work rate in the incremental test (W)</td>
<td>91.8 (35.70)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>56 (62.9)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>33 (37.1)</td>
</tr>
<tr>
<td>Number of pack years</td>
<td>44.5 (18.71)</td>
</tr>
</tbody>
</table>

Data are mean (SD) unless otherwise specified. BMI, body mass index; SD = standard deviation; FEV1 = forced expiratory volume in 1 s; FVC = forced vital capacity.

calculation. This standardization resulted in 4 patients being re-classified as having mild COPD. The pre-treatment exercise endurance time in the constant work rate test averaged 459 s.

Efficacy

Exercise endurance time

For the primary efficacy variable, exercise endurance time 
after 3 weeks of treatment, indacaterol 300 μg was signifi-
cantly superior to placebo, with an LSM treatment differ-
ence of 111 s (95% CI: 27, 195, p = 0.011) (Fig. 1). In a 

subgroup analysis according to disease severity, the 

endurance time after 3 weeks of treatment with indaca-
terol was significantly higher than placebo in patients with 

FEV1 <50% predicted (difference of 229 s; 95% CI: 31, 426, 

p = 0.024) and was numerically higher than placebo in patients with FEV1 ≥50% predicted (difference of 85 s; 95% 

CI: −10, 180, p = 0.078). In a second subgroup analysis according to smoking status at study entry, the exercise endurance time after 3 weeks with indacaterol was significantly higher than with placebo in current smokers (difference of 161 s; 

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p = 0.132). On Day 1, indacaterol was also significantly superior to placebo for exercise endurance time, with an 

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difference of 14.4 percentage points (p = 0.001).

Indacaterol treatment was associated with an overall 

reduction in diary symptoms over the 3 weeks of treatment 

(change from baseline in mean total symptom score of

Figure 1 Exercise endurance time (seconds) on Day 1 and after 3 weeks of treatment.
In terms of patients’ activity level assessed via actigraphy, neither indacaterol nor placebo treatment had a significant effect during the third week of treatment. The LSM estimated average energy expenditure was 887 cal/day with indacaterol compared to 891 cal/day with placebo ($p = 0.879$); the LSM physical activity duration was 43.3 min/day and 46.2 min/day, respectively ($p = 0.564$).

Safety

The overall incidence of AEs was 22.9% (19/83) and 27.4% (23/84) with indacaterol and placebo, respectively (Table 3), the majority being mild or moderate in severity. The most frequently reported AE with both treatments was nasopharyngitis (7.2 and 7.1% with indacaterol and placebo, respectively). Of the patients discontinuing due to AEs, a relationship to study medication was suspected in one patient with indacaterol (erythema of the face, mild in severity) and three patients with placebo. Three patients while on indacaterol treatment and one patient on placebo experienced SAEs; none were suspected to be study drug related. No death was reported during the study.

The only notable pre-exercise vital sign changes over the 3-week treatment period were observed in one patient, who had a raised post-baseline diastolic blood pressure measurement (114 mmHg) while on placebo and a low measurement (40 mmHg) while on indacaterol. Clinically significant arrhythmias were noted in three patients; one patient had ventricular premature complexes noted during screening and at all visits during both treatment periods. For the other two patients (one patient with ventricular premature complexes and the other with unspecified arrhythmia), the abnormalities occurred during screening or placebo administration.

Table 2  Treatment difference between indacaterol and placebo groups in resting spirometry outcomes on Day 1 and after 3 weeks of treatment (modified ITT population).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Indacaterol—placebo comparison</th>
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<tbody>
<tr>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td></td>
<td>75 min post-dose</td>
</tr>
<tr>
<td>IC (L)</td>
<td>$0.20 \pm 0.038^{***}$</td>
</tr>
<tr>
<td></td>
<td>(0.13, 0.28)</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>$0.23 \pm 0.021^{***}$</td>
</tr>
<tr>
<td></td>
<td>(0.19, 0.27)</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>$0.30 \pm 0.044^{***}$</td>
</tr>
<tr>
<td></td>
<td>(0.21, 0.39)</td>
</tr>
</tbody>
</table>

Data are least squares means ± standard error (95% CI). **$p = 0.004$; ***$p \leq 0.001$. 

Discussion

This study was primarily designed to assess the effect of indacaterol 300 $\mu g$ once-daily on exercise endurance time in patients with moderate-to-severe COPD. Treatment with indacaterol resulted in a significant improvement in exercise endurance time, not only after 3 weeks but also after a single-dose, with the indacaterol–placebo treatment differences at both visits exceeding or meeting the minimum clinically relevant improvement of 101 s specified by Puente-Maestu and colleagues.17

To date, studies have been conducted to assess the effect of bronchodilators on exercise capacity using either constant work rate or incremental testing protocols. The constant work rate cycle ergometer test was selected in this study, as the protocol has been shown to be reliable and sensitive to detect patients’ response to bronchodilator interventions in COPD.14,18,19 Furthermore, the change in exercise capacity objectively measured in patients with COPD using a symptom-limited cycle ergometry test has been shown to correlate with changes in their health status.20 The overall improvement in exercise capacity achieved with indacaterol in the current study could be one of the explanations for the improved health status (assessed using the Saint George’s Respiratory Questionnaire) seen with indacaterol in long-term studies.8,9

Indacaterol also showed a significant improvement in end-exercise IC after 3 weeks of treatment, with a difference from placebo of 280 mL. IC, being an important indicator of lung hyperinflation, has been shown to be more closely related to exercise tolerance than other spirometric indices, including FEV1 and FVC.2 Reduced hyperinflation, may therefore be one of the reasons for improved exercise performance achieved following indacaterol treatment. In the present study, the Borg CR10 scale outcomes — exertional dyspnea and leg discomfort — were assessed at the symptom-limited end of exercise. Although the exercise
endurance time was longer for patients while receiving indacaterol than while receiving placebo, there were no statistically significant differences between treatments in Borg CR10 scores at the end of exercise. The results indicate that when patients received indacaterol they were able to endure constant work rate for longer before experiencing intolerable levels of exertional dyspnea and leg discomfort. These results are in line with those observed in a previous exercise endurance study, in which there were no statistically significant differences between tiotropium and placebo in terms of Borg exertional dyspnea assessed at the end of exercise, yet tiotropium was associated with a significant increase in exercise endurance time. To the best of our knowledge, no studies to date have demonstrated that pharmacological interventions alone can improve daily activity levels in patients with COPD – and in the current study, patients’ activity level measured using an actigraphy device showed no significant treatment effects. This finding could possibly be attributed to the lack of pulmonary rehabilitation in this study, since other studies have shown that daily activity levels are most effectively increased when (as recommended by treatment guidelines) bronchodilator pharmacotherapy is combined with pulmonary rehabilitation. However, the study was not powered to examine changes in activity levels; it would be interesting to examine the effect of indacaterol on activity levels in a larger, longer study.

Indacaterol provided significant improvements in resting IC (indacaterol—placebo differences of 140–200 mL). While these treatment—placebo differences were less than those observed in the previous tiotropium study (tiotropium—placebo differences of 210–250 mL), the tiotropium study recruited a larger proportion of patients with severe COPD. In contrast, approximately 76% of patients in the current study had moderate disease. Given differences in design between these two studies (parallel versus crossover), results should be compared with caution; however, patients with more severe disease are known to exhibit more air trapping than those with more moderate COPD, and as a consequence their exercise capacity is more likely to be limited by their ventilatory response. In such patients, a bronchodilator such as indacaterol could be predicted to provide a greater increase in exercise capacity than in patients with more moderate disease, whose exercise capacity is likely to be less limited by their lung function. Indeed, the improvement in exercise endurance time in the current study was particularly apparent in patients with more severe COPD (FEV₁ <50% predicted), who gained more benefit from indacaterol than did patients with more moderate COPD (FEV₁ ≥50% predicted). Indacaterol also provided improvements in other resting lung function assessments, including FEV₁, and FVC. Similar improvements in FEV₁ and FVC have been observed with indacaterol in previous studies.

No conclusions can be drawn about the dynamic shift of IC during exercise with indacaterol, as this would require an evaluation of lung function (and potentially Borg CR10 scores) at intervals throughout the exercise test. The inclusion of such evaluations would be valuable inclusions in future studies of indacaterol – at least in part as this would permit calculation of isotime responses. The indacaterol dose tested in the present study is the higher of the two doses currently approved (150 μg and 300 μg). Although the bronchodilator efficacy of the 150 μg dose has been demonstrated in a large number of studies, none of these included assessments of exercise capacity. As a consequence, it is difficult to speculate on the comparative efficacy of these two doses in terms of the efficacy parameters reported here.

There were no clinically relevant differences between indacaterol and placebo regarding AEs incidence and severity. The numbers of patients with SAEs, and that permanently discontinued study drug were very low; no deaths were reported during the study.

### Conclusion

In conclusion, indacaterol provided clinically meaningful improvements in exercise endurance with sustained reductions in lung hyperinflation both at rest and at the end of exercise.

### Acknowledgments

The authors thank the patients who took part and the staff at the participating clinical centers. This study was funded by Novartis Pharma AG, Basel, Switzerland. The authors would like to thank Lakshmi Kasthurirangan professional medical writer (Novartis) and David Young (Novartis) for their assistance in preparing the manuscript.

### Conflict of interest

Denis E O’Donnell has served on advisory boards for Boehringer Ingelheim, GlaxoSmithKline, Novartis, Nycomed and Pfizer; has received lecture fees from AstraZeneca,
Boehringer Ingelheim, GlaxoSmithKline and Pfizer; and has received industry-sponsored research grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Frostell Canada, Novartis and Pfizer. Richard Casaburi has served as consultant to advisory boards for Boehringer Ingelheim, Pfizer, Forest, AstraZeneca, Theratechnologies, Medtronics and Novartis. Los Angeles Biomedical Research Institute participated as an investigational site in this study under contract with Novartis. Walter Vincken has been a member of advisory boards for Altana/Nycomed, AstraZeneca, Boehringer Ingelheim/Pfizer, GlaxoSmithKline, Meda, MSD, Novartis and UCB; has given lectures for these pharmaceutical companies as well as for Abbott and Zambon; and has received research or educational grants from AstraZeneca, Boehringer Ingelheim/Pfizer, GlaxoSmithKline and Novartis. Luis Puente-Maestu has received fees for lectures by GlaxoSmithKline, ASTRA and Admirall-Prodesa pharma and MEDGRAPHICS (an exercise systems company) and was sponsored to attend to Respiratory meetings by Astra, GlaxoSmithKline, Esteve, Pfizer, Chiesi and Admirall. David Lawrence and Benjamin Kramer are employees of the study sponsor, Novartis Pharma AG. James Swales was employed by Novartis at the time of study conduct. All authors contributed to the development of the manuscript, and approved the decision to submit the manuscript for publication.

References