

Efficacy of a new once-daily long-acting inhaled β_2 -agonist indacaterol versus twice-daily formoterol in COPD

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ABSTRACT

Background Indacaterol is a long-acting inhaled β_2 -agonist (LABA) for the treatment of chronic obstructive pulmonary disease (COPD). In previous studies, indacaterol provided 24 h bronchodilation on once-daily dosing with a fast onset of action. This study compared the efficacy and safety of indacaterol with the twice-daily LABA formoterol and placebo over 1 year.

Methods Patients with moderate to severe COPD were randomised to receive once-daily indacaterol 300 μ g (n=437) or 600 μ g (n=428), twice-daily formoterol 12 μ g (n=435) or placebo (n=432) for 52 weeks in a double-blind double-dummy parallel group study. The primary efficacy variable was forced expiratory volume in 1 s (FEV₁) measured 24 h postdose after 12 weeks (indacaterol vs placebo). Other outcomes included dyspnoea (transition dyspnoea index, TDI), use of as-needed salbutamol, symptom-based measures recorded on diary cards, exacerbations, health status (St George's Respiratory Questionnaire), BODE index (body mass index, obstruction, dyspnoea, exercise), safety and tolerability.

Results Indacaterol increased 24 h postdose FEV₁ after 12 weeks by 170 ml (both doses) versus placebo and by 100 ml versus formoterol (all p<0.001). These significant differences were maintained at 52 weeks.

Symptomatic outcomes were improved compared with placebo with all active treatments, and indacaterol was more effective than formoterol in improving TDI score and reducing the need for as-needed salbutamol.

Indacaterol was well tolerated and had a good overall safety profile, including minimal impact on QTc interval and systemic β_2 -mediated events.

Conclusions Once-daily indacaterol is an effective 24 h bronchodilator that improves symptoms and health status and confers clinical improvements over a twice-daily 12 h LABA as a treatment for patients with moderate to severe COPD.

Trial registration number NCT 00393458.

Current management guidelines for chronic obstructive pulmonary disease (COPD) provide a clear treatment algorithm for the maintenance treatment of COPD, recommending initial treatment with one or more long-acting bronchodilators for patients with moderate, severe and very severe disease, with the addition of inhaled corticosteroids (ICS) for patients who exacerbate frequently.¹ The long-acting bronchodilators currently available

include the twice-daily inhaled β_2 -agonists formoterol and salmeterol. It may be hypothesised that the sustained bronchodilation provided by a bronchodilator with a 24 h duration would reduce fluctuations in airway patency compared with twice-daily bronchodilators, and may improve clinical outcomes.

Indacaterol is a novel inhaled long-acting β_2 -agonist providing 24 h bronchodilation on once-daily dosing.^{2–4} This 1-year study was designed to provide efficacy and long-term safety information on indacaterol compared with placebo and formoterol. Our primary hypothesis was that indacaterol would have a greater effect than placebo on forced expiratory volume in 1 s (FEV₁) at 24 h post-dose ('trough') after 12 weeks.

METHODS

Patients

Subjects aged ≥ 40 years with a clinical diagnosis of moderate to severe COPD⁵ and a smoking history of ≥ 20 pack-years, with postbronchodilator (salbutamol 400 μ g) FEV₁ <80% and $\geq 30\%$ predicted and ratio of FEV₁ to forced vital capacity (FVC) <70% were enrolled in the study. Factors preventing study entry included respiratory tract infection or hospitalisation for COPD exacerbation within the previous 6 weeks, oral corticosteroids or change in ICS during the previous month, or history of asthma.

Study design

A 2-week run-in was followed by 52 weeks of double-blind treatment (see figure S1 in online supplement), with patients randomised to treatment (1:1:1:1) with stratification for smoking status (current/ex-smoker) using an automated interactive system. Data were collected from outpatient clinics and physicians' offices.

The study treatments were indacaterol 300 μ g and 600 μ g delivered once daily via single-dose dry powder inhaler (SDDPI), formoterol 12 μ g twice daily (the standard therapeutic dose) via its proprietary SDDPI and matching placebos to indacaterol and formoterol taken each morning (08:00–10:00; both devices) and evening (20:00–22:00; proprietary SDDPI only). Fixed-dose combinations of ICS plus long-acting β_2 -agonist were replaced by monotherapy ICS at an equivalent dose and regimen plus salbutamol as-needed. Patients on ICS monotherapy continued treatment

at a stable dose throughout the study. Patients were given salbutamol to use as-needed but were asked not to take it within 6 h before each visit. Other bronchodilators or corticosteroids were not allowed unless to treat a COPD exacerbation. Participating physicians were responsible for treating exacerbations.

Assessments

Patients visited the clinics on days 1, 2, 15, 29, 84, 85, 113, 168, 197, 253, 364 and 365. The visits on days 1 and 2, week 12 and week 52 were on consecutive days in order to provide a precise trough FEV₁ value which was based on the mean of two measurements taken 23 h 10 min and 23 h 45 min following the previous day's morning dose. At other visits the 15 min predose value was used as a 'trough' measurement. In a subset of patients, spirometry was performed serially over 24 h postdose. Patients were given a diary to record peak expiratory flow (PEF), symptoms, use of salbutamol, any change in concomitant medications and adverse events.

COPD exacerbations were defined as onset or worsening of more than one respiratory symptom (dyspnoea, cough, sputum purulence or volume or wheeze) for >3 consecutive days (based on diary cards or patients' reports of their health since the previous visit) plus documented proof of intensified treatment (eg, systemic steroids, antibiotics or oxygen) and/or hospitalisation or emergency room visit.

Health status (St George's Respiratory Questionnaire, SGRQ)⁶ and dyspnoea (baseline and transition dyspnoea indices, BDI/TDI⁷) were measured on day 1 and weeks 4, 8, 12, 24, 44 and 52. The modified Medical Research Council (mMRC) dyspnoea scale^{8,9} was measured on day 1, week 12 and week 52 followed by the 6-min walk test¹⁰ as components of the BODE (body mass index, obstruction (FEV₁, % predicted), dyspnoea, exercise) index.¹¹

Adverse events were recorded at each visit. ECG assessment, blood pressure and pulse rate measurements and blood sampling for haematology were performed at regular intervals.

Objectives and outcomes

The primary objective was to test the hypothesis that both indacaterol doses were superior to placebo in their effect on trough FEV₁ after 12 weeks. The important secondary efficacy outcomes were days of poor COPD control (a composite measure used in formoterol registration studies,^{12,13} defined as the number of days with a score of ≥ 2 on a 0–3 scale for at least two symptoms out of cough, wheeze, production/colour of sputum and breathlessness), SGRQ total score and time to first exacerbation. Other secondary efficacy outcomes included other spirometry, TDI scores and percentage of responding patients, exacerbation rates, BODE index and end points derived from diary data. Safety outcomes included the incidence of adverse events and clinically notable values for plasma potassium (<3.0 mmol/l) and blood glucose (≥ 9.99 mmol/l). QTc interval was calculated using the Fridericia formula.

Statistical methods

Efficacy results are presented for the modified intention-to-treat (ITT) population including all randomised patients who received at least one dose of study drug but excluding patients from six sites owing to non-conformance with good clinical practice. Safety results are presented for all patients who received at least one dose of study drug. All analyses presented here were preplanned.

The primary variable was analysed using a mixed model analysis of covariance (ANCOVA) with treatment as a fixed effect and baseline FEV₁ and FEV₁ reversibility as covariates. The

same model (with appropriate covariates) was used to analyse other efficacy variables. The results are presented as estimated adjusted treatment effects (least squares means) and treatment contrasts with 95% CIs and two-sided p values. For trough FEV₁ at weeks 12 and 52, SGRQ total score, TDI score and daily salbutamol use, missing values were replaced using last observation carried forward. Data were carried forward for a maximum of 11 weeks, and for trough FEV₁ no data were carried forward from before day 15. Exploratory analyses of week 12 trough FEV₁ values were performed in subgroups defined according to baseline age, disease severity, smoking history or ICS use. A hierarchical testing procedure to control type I error for multiplicity was used for the comparisons of indacaterol and placebo for the primary end point, then in turn for days of poor COPD control, SGRQ total score at week 12 and time to first COPD exacerbation. Other analyses were not adjusted for multiplicity.

Time to first COPD exacerbation was analysed using a Cox regression model with the assumption of proportional hazards checked with Schoenfeld residuals of treatment effects plotted against time. The number of COPD exacerbations over 52 weeks was analysed using a Poisson regression model with a sensitivity analysis to assess the impact of premature discontinuations by imputing an additional one exacerbation for these patients. Neither the Cox nor the Poisson regression model assumes normality. Normal distribution was assumed for efficacy and safety variables where ANCOVAs were performed. For the primary and important secondary variables (excluding exacerbations), the normality assumption was checked with a quantile–quantile plot of residuals for each treatment group.

All safety end points were summarised for the safety population.

Sample size

With a SD of 270 ml for trough FEV₁,^{12,13} 108 evaluable patients per group were needed to detect a 120 ml difference between indacaterol 300 μ g and placebo as significant at the 5% level (two-sided) with 90% power, with 84% power (due to the hierarchical testing) for the indacaterol 600 μ g versus placebo comparison. However, the plan for at least 300 patients per indacaterol dose group to provide a robust safety database provided 99% power for the primary comparisons.

RESULTS

Patients

Patient disposition is shown in figure 1, which shows that the ITT population was modified to exclude 129 patients (7.4% of randomised) before unblinding because of non-conformance with good clinical practice irrespective of treatment group, the main reasons for non-conformance being substandard spirometry, unsatisfactory completion of diary cards and health status questionnaires and inability to verify source data. Baseline data for all patients (safety population) are shown in table 1. Approximately 5% of patients were enrolled before an early protocol amendment stipulating postbronchodilator (rather than prebronchodilator) spirometry values as entry criteria and had baseline spirometry outside specified limits.

Spirometry

Trough FEV₁ at week 12 with both indacaterol doses was 170 ml higher than placebo ($p < 0.001$) and 100 ml higher than formoterol ($p < 0.001$) (table 2). Over the remainder of the study, significant differences versus placebo were maintained at a similar level for indacaterol, while the difference between formoterol and placebo diminished (table 2; figure 2). Analysis of

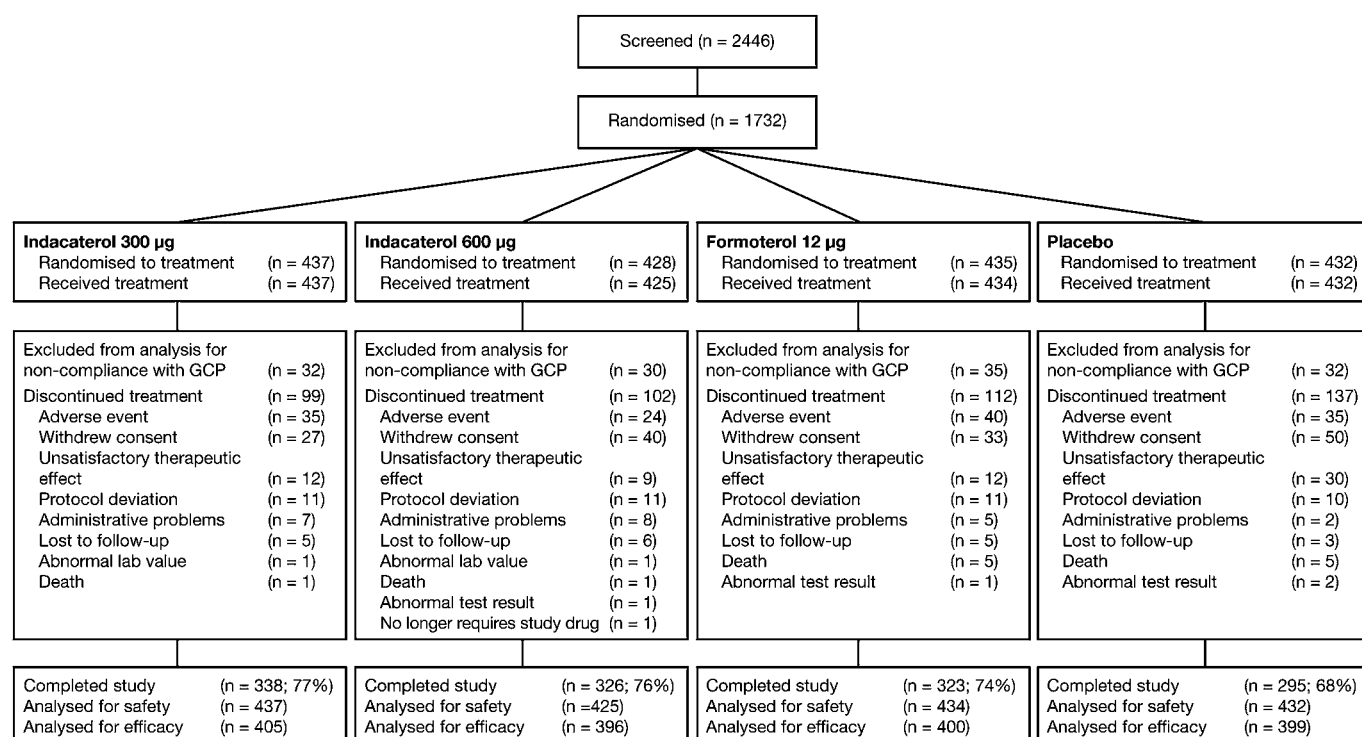


Figure 1 Patient flow through study.

trough FEV₁ at week 12 for the ITT population (ie, including patients from the centres excluded from the modified ITT analysis) is provided in table S1 in the online supplement.

Supportive analysis of the primary variable excluding any patients with protocol deviations (13–15% of patients across the groups, including those not meeting the postbronchodilator spirometry entry criteria; see table 1) showed similar results (not shown). The group mean values and differences between treatment and placebo groups in trough FEV₁ after 12 weeks were similar for subgroups of patients analysed according to age, COPD severity, smoking status and ICS use.

At 5 min postdose on day 1, compared with placebo FEV₁ increased by 130 ml (95% CI 110 to 150) with indacaterol 300 µg, by 150 ml (95% CI 140 to 170) with indacaterol 600 µg and by 140 ml (95% CI 120 to 160) with formoterol (all p<0.001 vs placebo). Serial measurements of FEV₁ showed a significant effect of indacaterol over placebo at each time point over 24 h postdose (figure 3). Other spirometry results are shown in the online supplement.

Clinical outcomes

Both indacaterol doses were superior to placebo for all secondary end points controlled for type I error (ie, days of poor control, SGRQ and time to first exacerbation; differences between indacaterol and formoterol for these end points were not statistically significant; tables 2 and 3, figure 4). Time to first COPD exacerbation was improved with all treatments, as shown by the HRs in table 3, although there were too few events to calculate event-free time. Exacerbation rate ratios were similar without imputation (table 3) and with imputation (not shown).

Both indacaterol and formoterol increased TDI scores, with the differences between indacaterol and placebo close to or exceeding the 1-point minimum clinically important difference^{14 15} (table 2). TDI scores were significantly higher with indacaterol than with formoterol at week 12 but not at week 52. At week 12, 63% and 58% of patients treated with indacaterol 300 and 600 µg, respec-

tively, had a clinically important increase of ≥ 1 in TDI score compared with 40% of patients given placebo (p<0.001) and 53% of patients treated with formoterol (p<0.01 for indacaterol 300 µg vs formoterol). Efficacy outcomes based on diary data and BODE index (table 2) were generally significantly improved with indacaterol and formoterol versus placebo, with significant differences between indacaterol and formoterol for use of as-needed salbutamol, nights without awakenings and PEF.

Safety

COPD worsening and nasopharyngitis were the only adverse events reported by >10% of patients in any treatment group (table 4). Most cases of COPD worsening were mild or moderate in severity (indacaterol 300 µg, 92%; indacaterol 600 µg, 91%; formoterol, 84%; placebo, 87%). All cases of nasopharyngitis were mild or moderate with indacaterol and formoterol.

Eight patients died during treatment and four during follow-up. Of the deaths during treatment, two were due to cardiac arrest (indacaterol 300 µg; placebo), one to multiorgan failure (formoterol), one to respiratory failure (formoterol) and four to sudden death (one formoterol; three placebo). The indacaterol-treated patient who died had discontinued treatment 3 days earlier owing to dyspnoea (suspected as related to treatment). The three deaths during formoterol treatment were considered unrelated to formoterol.

Tremor was reported in 0.2%, 1.9%, 1.2% and 0.5% of the indacaterol 300 µg, 600 µg, formoterol and placebo groups, respectively, and tachycardia in 0.9%, 0.7%, 0.5% and 1.2%, respectively. Two cases were severe (tremor in one patient receiving placebo and atrial tachycardia in one patient receiving indacaterol 600 µg).

In addition to patients reporting cough as an adverse event (table 4), investigators were asked to record any instances of cough occurring within 5 min of drug administration during clinic visits regardless of whether they considered it an adverse event. This was observed in an average of 19.1% of patients in

Table 1 Patient demographic data and other characteristics at baseline (safety population)

	Indacaterol 300 µg n = 437	Indacaterol 600 µg n = 425	Formoterol n = 434	Placebo n = 432
Age, years	64.0 (57.0, 71.0)	63.0 (57.0, 69.0)	64.0 (58.0, 69.0)	63.0 (57.5, 69.0)
Male sex, n (%)	351 (80.3)	327 (76.9)	348 (80.2)	352 (81.5)
BMI, kg/m ²	25.9 (23.3, 28.9)	26.0 (23.0, 29.7)	25.7 (22.9, 29.0)	26.4 (23.1, 30.0)
COPD severity, n (%) [*]				
At risk†	9 (2.1)	3 (0.7)	7 (1.6)	10 (2.3)
Mild†	2 (0.5)	6 (1.4)	7 (1.6)	10 (2.3)
Moderate	226 (51.7)	212 (49.9)	226 (52.1)	216 (50.0)
Severe	190 (43.5)	188 (44.2)	182 (41.9)	186 (43.1)
Very severe	9 (2.1)	15 (3.5)	10 (2.3)	9 (2.1)
ICS users, n (%)	243 (55.6)	226 (53.2)	221 (50.9)	224 (51.9)
Smoking history, pack-years	40.0 (30.0, 53.0)	40.0 (30.0, 58.0)	40.0 (30.0, 50.0)	43.0 (31.0, 53.5)
History of, n (%)				
CCV condition	80 (18.3)	93 (21.9)	88 (20.3)	82 (19.0)
Diabetes mellitus	33 (7.6)	39 (9.2)	37 (8.5)	50 (11.6)
Hypertension	227 (51.9)	204 (48.0)	213 (49.1)	216 (50.0)
Hyperlipidaemia	145 (33.2)	138 (32.5)	133 (30.6)	131 (30.3)
FEV ₁ , % predicted‡	51.5 (42.2, 62.9)	50.8 (41.2, 60.2)	52.5 (41.2, 63.1)	52.0 (41.9, 63.6)
FEV ₁ /FVC, %‡	50.7 (43.5, 59.5)	51.1 (43.8, 59.1)	51.2 (43.5, 59.0)	52.0 (44.1, 60.5)
Prebronchodilator FEV ₁ , l	1.29 (1.01, 1.58)	1.28 (0.98, 1.60)	1.30 (1.00, 1.62)	1.28 (1.00, 1.70)
Postbronchodilator FEV ₁ , l‡	1.44 (1.14, 1.78)	1.41 (1.11, 1.75)	1.47 (1.12, 1.80)	1.44 (1.12, 1.85)
Reversibility, %‡	9.8 (3.0, 18.3)	10.9 (3.8, 20.6)	10.1 (3.4, 18.3)	10.8 (4.7, 19.1)
SGRQ total score§	43 (32, 58)	44 (31, 56)	44 (32, 57)	43 (30, 57)
BDI total score§	6.0 (6.0, 8.0)	6.0 (5.0, 8.0)	6.0 (5.0, 8.0)	6.0 (5.0, 8.0)
6-min walking distance, m§	379 (300, 448)	370 (300, 447)	380 (300, 450)	390 (307, 444)
BODE index§	3.0 (2.0, 4.0)	3.0 (1.0, 4.0)	3.0 (1.0, 4.0)	3.0 (2.0, 4.0)

Data are median (upper and lower quartiles) unless stated otherwise.

^{*}COPD severity based on GOLD 2005 criteria.

†Patients enrolled before a protocol amendment of entry criteria stipulating postbronchodilator rather than prebronchodilator spirometry values.

‡Measured 30 min after salbutamol 400 µg inhalation. Reversibility was calculated as the difference between the prebronchodilator and postbronchodilator values of FEV₁ (in litres) as a percentage of the prebronchodilator value.

§Reported for the modified intention-to-treat population.

BDI, baseline dyspnoea index; BMI, body mass index; BODE index, body mass index, obstruction, dyspnoea, exercise; CCV, cardio- or cerebrovascular; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; SGRQ, St George's Respiratory Questionnaire.

both indacaterol groups, 0.8% of the formoterol group and 1.8% of the placebo group. The cough typically started within 15 s of inhaling indacaterol, had a median duration of 12 s or less, and was not associated with bronchospasm. Importantly, the presence of this cough was not associated with any increase in discontinuation rates.

An increase in QTc interval of >60 ms from baseline occurred in one patient (0.2%) in each of the indacaterol and formoterol groups and in no patient in the placebo group. No patient had an absolute value >500 ms. Serum potassium concentrations <3.0 mmol/l were recorded for two patients (0.5%) in each of the indacaterol 300 µg and placebo groups and not in the other two groups. Group mean values of serum potassium 1 h postdose at week 52 were not significantly different. Blood glucose concentrations of >9.99 mmol/l were recorded for 8.0%, 9.0%, 6.5% and 7.5% of the indacaterol 300 µg, 600 µg, formoterol and placebo groups, respectively. Group mean values of blood glucose 1 h postdose at week 52 were statistically significantly different for indacaterol 600 µg compared with placebo (5.86 vs 5.61 mmol/l, *p*=0.033).

DISCUSSION

This study provides clear evidence of effective 24 h bronchodilation with once-daily administration of indacaterol 300 or 600 µg. The effect of indacaterol on trough FEV₁ relative to placebo exceeded both the 120 ml level versus placebo that was

prespecified as clinically significant for this study and the 100–140 ml range proposed recently as a minimal important difference.¹⁷ Bronchodilator efficacy was independent of age, severity of airways obstruction and smoking status. Results for trough FEV₁ at week 12 were very similar when analysed for the ITT population, suggesting that the exclusion of patients from six sites for non-conformance with good clinical practice had little impact on efficacy outcomes.

The bronchodilator effect of indacaterol was accompanied by significant improvements compared with placebo in dyspnoea and health status (both by a clinically meaningful margin^{15 16}), time to first exacerbation, BODE index, use of as-needed salbutamol and symptom-based variables derived from diary data. Although this study was not primarily powered to detect significant differences between indacaterol and formoterol, indacaterol was more effective for several outcomes including bronchodilator efficacy. The 100 ml difference in trough FEV₁ between the two treatments after 12 weeks occurs in the early morning, a time that patients describe as worst for COPD symptoms.¹⁸ Among the clinical outcomes, differences favoured indacaterol over formoterol in dyspnoea score, use of as-needed salbutamol and nights without awakenings. Indacaterol had a greater effect than formoterol on SGRQ total score, although the difference did not reach statistical significance.

Table 2 Primary and additional efficacy outcomes

	Placebo (least squares mean, SE)	Difference vs placebo (least squares mean, 95% CI)		
		Indacaterol 300 µg	Indacaterol 600 µg	Formoterol
Trough FEV₁, l§				
After 1 day	1.31 (0.009)	+0.14 (0.11 to 0.16)***†	+0.17 (0.15 to 0.20)***†††	+0.11 (0.09 to 0.13)***
At week 12	1.31 (0.013)	+0.17 (0.13 to 0.20)***†††	+0.17 (0.13 to 0.20)***†††	+0.07 (0.04 to 0.10)***
At week 52	1.28 (0.017)	+0.16 (0.12 to 0.20)***†††	+0.15 (0.11 to 0.19)***†††	+0.05 (0.01 to 0.09)*
TDI score§				
At week 12	1.22 (0.185)	+1.17 (0.76 to 1.58)***†	+1.13 (0.71 to 1.54)***†	+0.72 (0.30 to 1.13)***
At week 52	1.57 (0.230)	+1.00 (0.53 to 1.47)***	+0.98 (0.51 to 1.46)***	+0.71 (0.24 to 1.19)**
Diary card data (over 52 weeks)				
Days of poor COPD control, %	38.3 (1.47)	-4.7 (-8.4 to -1.0)*	-8.3 (-12.0 to -4.6)***	-4.8 (-8.5 to -1.1)*
Change from baseline in mean daily inhalations of salbutamol as-needed	-0.02 (0.127)	-1.67 (-1.97 to 1.37)***†	-1.66 (-1.96 to -1.36)***†	-1.33 (-1.63 to 1.03)***
Days with no use of as-needed salbutamol, %	34.8 (1.88)	+23.6 (19.0 to 28.1)***††	+26.6 (22.0 to 31.2)***†††	+17.3 (12.2 to 21.9)***
Days with no daytime symptoms, %	6.2 (0.93)	+2.7 (0.3 to 5.1)*	+2.4 (0.0 to 4.8)	+2.9 (0.5 to 5.3)*
Days able to perform usual daily activities, %	34.1 (1.53)	+8.5 (4.6 to 12.5)***	+9.0 (5.0 to 13.0)***	+6.2 (2.3 to 10.2)**
Nights with no awakenings, %	67.5 (1.40)	+6.6 (3.1 to 10.1)***	+9.0 (5.5 to 12.4)***††	+4.2 (0.8 to 7.7)*
Change from baseline in morning (predose) PEF, l/min	1.7 (2.18)	+28.3 (22.8 to 33.8)***†††	+31.1 (25.6 to 36.7)***†††	+17.0 (11.5 to 22.6)***
Change from baseline in evening PEF, l/min	2.9 (2.20)	+24.6 (19.2 to 30.1)***†††	+28.3 (22.8 to 33.8)***†††	+15.7 (10.2 to 21.1)***
SGRQ total score§				
At week 12	41.3 (0.72)	-3.8 (-5.6 to -2.1)***	-4.1 (-5.9 to -2.3)***	-3.2 (-5.0 to -1.5)***
At week 52	41.3 (0.87)	-4.7 (-6.7 to -2.7)***	-4.6 (-6.6 to -2.6)***	-4.0 (-6.0 to -2.0)***
BODE index‡				
At week 12	2.67 (0.064)	-0.40 (-0.56 to -0.25)***	-0.24 (-0.40 to -0.08)**	-0.28 (-0.43 to -0.12)***
At week 52	2.90 (0.076)	-0.55 (-0.73 to 0.37)***	-0.49 (-0.68 to -0.31)***	-0.53 (-0.72 to -0.35)***

Data are least squares means.

*p<0.05, **p<0.01, ***p<0.001. Dagger symbols denote where significant treatment differences (not shown) occur vs formoterol (†p<0.05, ††p<0.01, †††p≤0.001).

‡Negative changes represent an improvement in the BODE index.

§Minimum clinically important differences are 120 ml (trough FEV₁), 1 point (TDI total score^{14 15}) and 4 points (SGRQ total score¹⁶).

BODE index, body mass index, obstruction, dyspnoea, exercise; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; PEF, peak expiratory flow; SGRQ, St George's Respiratory Questionnaire; TDI, transition dyspnoea index.

Indacaterol increased the time to first exacerbation and reduced the exacerbation rate relative to placebo; similar effects were seen with formoterol. Both treatments improved the BODE index, which correlates with risk of exacerbations.¹⁹ The low apparent rate of exacerbations and the effects of treatment need to be viewed cautiously since it is conceivable that some episodes were missed, owing perhaps to incomplete diary card reporting when patients were feeling particularly ill. A definition based only on documented treatment and/or hospitalisation, as used elsewhere,²⁰ might have increased the frequency of reporting.

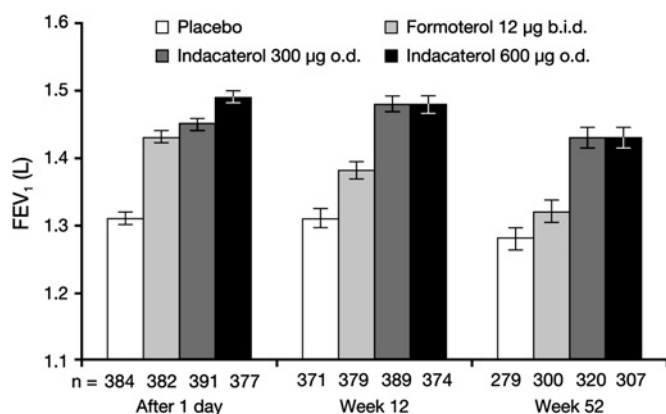


Figure 2 Trough forced expiratory volume in 1 s (FEV₁) after 1 day and at weeks 12 and 52 of treatment (modified intention-to-treat population). Data are least squares means ± SE. Between-treatment comparisons are shown in table 2.

Additionally, we recruited patients with relatively stable disease who were not required to have a history of frequent exacerbations. Appropriately designed and powered studies are under way to scrutinise the effect of indacaterol on exacerbations.

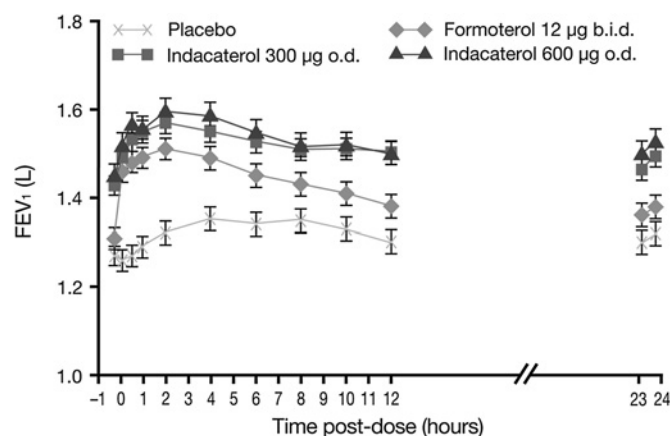


Figure 3 Serial measurements of forced expiratory volume in 1 s (FEV₁) from -15 min to 24 h postdose measured in subset with serial spirometry measurements (12 h serial spirometry subset) at week 12. Data are least squares means ± SE. Treatment differences: p<0.001 for indacaterol (both doses) vs placebo at each time point; p<0.05 for formoterol vs placebo at time points from 5 min to 11 h 45 min postdose; p<0.05 for indacaterol 300 µg vs formoterol at -15 min, 2 h and from 6 h to 23 h 45 min; p<0.05 for indacaterol 600 µg vs formoterol at all time points apart from 5 min postdose. Patient numbers at each time point are shown in table S3 in the online supplement.

Table 3 Analysis of time to first COPD exacerbation and exacerbation rates

	Indacaterol 300 µg	Indacaterol 600 µg	Formoterol	Placebo
Patients with a COPD exacerbation, n (%)	133 (32.8)	116 (29.3)	126 (31.5)	145 (36.3)
Event-free rate at month 12, % (95% CI)	63.1 (58.1 to 68.1)	66.7 (61.7 to 71.7)	65.0 (60.0 to 70.0)	57.0 (51.6 to 62.4)
HR vs placebo (95% CI)	0.77 (0.606 to 0.975)*	0.69 (0.538 to 0.882)*	0.77 (0.605 to 0.981)*	
Rate of exacerbations per year	0.60	0.57	0.56	0.74
Rate ratio vs placebo (95% CI)	0.82 (0.63 to 1.06)	0.74 (0.56 to 0.97)*	0.75 (0.58 to 0.99)*	

*p<0.05 vs placebo. Differences between indacaterol and formoterol not significant. COPD, chronic obstructive pulmonary disease.

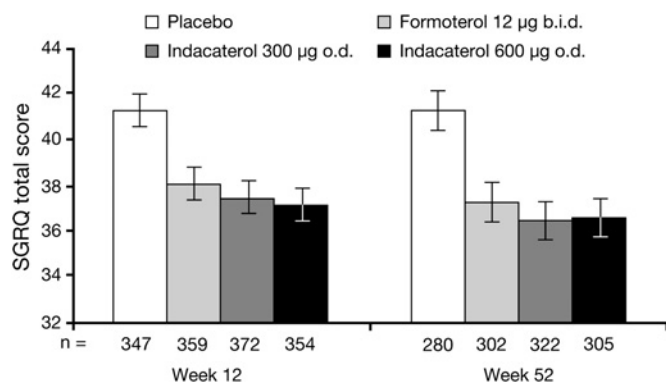


Figure 4 St George's Respiratory Questionnaire (SGRQ) total score at weeks 12 and 52. Data are least squares means ± SE. Between-treatment comparisons are shown in table 2.

The 12-week time point was chosen for the primary end point since this is the minimum period required to demonstrate efficacy on FEV₁ for purposes of formal drug registration, as well as to minimise the impact of patient dropout during the later stages of a 52-week study. Nevertheless, indacaterol maintained its significant bronchodilator effect during the study, while formoterol suffered from some loss in efficacy over 52 weeks. A previous 1-year study showed some loss of bronchodilator effect with formoterol at a higher dose of 24 µg twice daily,¹³ although other results showed no tolerance either at the same dose used

here¹³ or with nebulised formoterol 50 µg once daily.²¹ Compared with previous studies,^{12 13} formoterol had a lesser bronchodilator effect in the present study, perhaps because the older studies were in patients with higher mean FEV₁ reversibility of 17%. Nevertheless, the present double-blind comparison shows that indacaterol is the more effective bronchodilator and is similar or more effective for clinical outcomes. In addition, patient adherence to a once-daily dosing regimen may be better than with a twice-daily regimen since frequency of dosing has been shown to influence adherence.²²

The choice of indacaterol doses was based on previous short-term study results of bronchodilator efficacy and safety.²⁻⁴ Evaluating the two doses over 1 year was felt sufficient to determine if the higher dose had a better effect on the secondary efficacy outcomes. Subsequent clinical investigation has shown that doses of 150–300 µg once daily are effective.²³ However, it is important to know that a dose of 600 µg once daily (2–4 times the therapeutic dose) presented no safety concerns when given for a year. The overall incidence of adverse events was similar across the treatment groups and typical β₂-mediated adverse events were rare. Signs of systemic β₂-adrenoceptor activity were minimal, with no clinically meaningful differences between groups in mean serum potassium or blood glucose. Notable increases in QTc interval were observed very rarely and were not more common at the higher dose, suggesting that indacaterol has a very low potential for cardiac arrhythmogenicity. These properties point towards a good therapeutic ratio between efficacy and adverse event outcomes.

Table 4 Number (%) of patients with adverse events

	Indacaterol 300 µg n = 437	Indacaterol 600 µg n = 425	Formoterol n = 434	Placebo n = 432
Any adverse event	310 (70.9)	276 (64.9)	283 (65.2)	267 (61.8)
Events occurring in >5% of any group				
COPD worsening*	140 (32.0)	117 (27.5)	134 (30.9)	150 (34.7)
Nasopharyngitis	73 (16.7)	80 (18.8)	62 (14.3)	56 (13.0)
Cough	32 (7.3)	27 (6.4)	17 (3.9)	19 (4.4)
Upper respiratory tract bacterial infection	29 (6.6)	25 (5.9)	23 (5.3)	36 (8.3)
Lower respiratory tract infection	27 (6.2)	23 (5.4)	22 (5.1)	22 (5.1)
Muscle spasms	23 (5.3)	25 (5.9)	12 (2.8)	6 (1.4)
Adverse events leading to discontinuation	36 (8.2)	24 (5.6)	42 (9.7)	40 (9.3)
Events leading to discontinuation occurring in >0.5% of any group				
COPD worsening	5 (1.1)	4 (0.9)	17 (3.9)	17 (3.9)
Dyspnoea	4 (0.9)	2 (0.5)	1 (0.2)	3 (0.7)
Asthenia	3 (0.7)	0	0	0
Lower respiratory tract infection	2 (0.5)	1 (0.2)	4 (0.9)	1 (0.2)
Sudden death	1 (0.2)	0	0	3 (0.7)
Respiratory failure	0	0	4 (0.9)	1 (0.2)

*Including COPD exacerbations. COPD, chronic obstructive pulmonary disease.

Once-daily indacaterol, with its 24 h bronchodilator effect, improved several clinical outcomes to a greater extent than a twice-daily long-acting β_2 -agonist in patients with moderate or severe COPD who are candidates for long-acting bronchodilator therapy.¹ Indacaterol may prove useful as an alternative to established bronchodilators as initial regular therapy or, for those patients who require the added efficacy from combining two different agents, when added to a long-acting anticholinergic bronchodilator.¹ It can be concluded that once-daily indacaterol has significant value for patients with COPD, providing clinical benefits over twice-daily formoterol for 1 year without loss of effect and with a favourable safety profile.

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Competing interests DJ, PB, RO, MH and BK are employees of Novartis. RD has participated in advisory boards for Novartis, AstraZeneca, Boehringer-Ingelheim, Pfizer, ALK-Abello, UCB, Nycomed, Daiippon and ONO. KFC has received honoraria and research support from Novartis and has served on Novartis Advisory Boards. He also has similar relationships with GSK, Gilead, Merck and Boehringer-Ingelheim. RB has received reimbursement for attending scientific conferences and/or fees for speaking and/or consulting from Novartis. He also has similar relationships with AstraZeneca, Boehringer Ingelheim, GSK, Nycomed and Pfizer. The Pulmonary Department at Mainz University Hospital received financial compensation for services performed during participation in clinical trials organised by Novartis. HM has received fees for membership of advisory boards of various pharmaceutical companies (Altana, Boehringer Ingelheim, AstraZeneca) and for speaking (Boehringer Ingelheim, AstraZeneca, Chiesi, Altana). VN has no conflict of interest.

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REFERENCES

1. **Global Initiative for Chronic Obstructive Lung Disease (GOLD)**. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2008. <http://www.goldcopd.com> (accessed 24 Feb 2009).
2. **Rennard S**, Bantje T, Centanni S, *et al*. A dose-ranging study of indacaterol in obstructive airways disease, with a tiotropium comparison. *Respir Med* 2008;**102**:1033–44.
3. **Beier J**, Chanez P, Martinot JB, *et al*. Safety, tolerability and efficacy of indacaterol, a novel once-daily beta(2)-agonist, in patients with COPD: a 28-day randomised, placebo controlled clinical trial. *Pulm Pharmacol Ther* 2007;**20**:740–9.
4. **Bauwens O**, Ninane V, Van de Maele B, *et al*. 24-hour bronchodilator efficacy of single doses of indacaterol in subjects with COPD: comparison with placebo and formoterol. *Curr Med Res Opin* 2009;**25**:463–70.
5. **Global Initiative for Chronic Obstructive Lung Disease (GOLD)**. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2005. <http://www.goldcopd.com/GuidelinItem.asp?intId=1386> (accessed 24 Feb 2009).
6. **Jones PW**, Quirk FH, Baveystock CM, *et al*. A self-complete measure of health status for chronic airflow limitation. The St George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;**145**:1321–7.
7. **Mahler DA**, Weinberg DH, Wells CK, *et al*. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984;**85**:751–8.
8. **Mahler DA**, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988;**93**:580–6.
9. **Bestall JC**, Paul EA, Garrod R, *et al*. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999;**54**:581–6.
10. **American Thoracic Society**. ATS statement. Guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;**166**:111–17.
11. **Celli BR**, Cote CG, Marin JM, *et al*. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;**350**:1005–12.
12. **Dahl R**, Greefhorst LA, Nowak D, *et al*. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;**164**:778–84.
13. **Rossi A**, Kristufek P, Levine BE, *et al*. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. *Chest* 2002;**121**:1058–69.
14. **Witek TJ Jr**, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *Eur Respir J* 2003;**21**:267–72.
15. **Mahler DA**, Witek TJ Jr. The MCID of the transition dyspnea index is a total score of one unit. *COPD* 2005;**2**:99–103.
16. **Jones PW**. St George's respiratory questionnaire: MCID. *COPD* 2005;**2**:75–9.
17. **Cazzola M**, MacNee W, Martinez FJ, *et al*. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008;**31**:416–69.
18. **Partridge MR**, Karlsson N, Small IR. Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey. *Curr Med Res Opin* 2009;**25**:2043–8.
19. **Marin JM**, Carrizo SJ, Casanova C, *et al*. Prediction of risk of COPD exacerbations by the BODE index. *Respir Med* 2009;**103**:373–8.
20. **Wedzicha JA**, Calverley PMA, Seemungal TA, *et al*. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008;**177**:19–26.
21. **Donohue JF**, Hanania NA, Sciarappa KA, *et al*. Arformoterol and salmeterol in the treatment of chronic obstructive pulmonary disease: a one year evaluation of safety and tolerance. *Thorax* 2008;**63**:37–48.
22. **Bourbeau J**, Bartlett SJ. Patient adherence in COPD. *Thorax* 2008;**63**:831–8.
23. **Barnes PJ**, Pocock SJ, Magnussen H, *et al*. Integrating indacaterol dose selection in a clinical study in COPD using an adaptive seamless design. *Pulm Pharmacol Ther* 2010;**23**:165–71.