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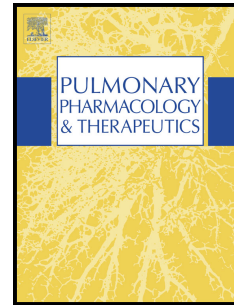
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Bronchodilator effects of indacaterol and formoterol in patients with COPD

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ABSTRACT

Background Resting inspiratory capacity (IC) reflects static hyperinflation in chronic obstructive pulmonary disease (COPD). This study compared the effects of formoterol and indacaterol, a novel once-daily ultra-long-acting β_2 -agonist (or ultra-LABA), on resting IC and forced expiratory volume in 1 second (FEV₁).

Methods Thirty patients with COPD (mean FEV₁/FVC 0.49, mean FEV₁ 56% predicted) each inhaled three treatments (two in randomized sequence followed by open-label formoterol) on separate study days: a single dose of indacaterol 300 μ g, matching placebo, and two doses of formoterol 12 μ g 12 h apart.

Results Indacaterol and formoterol increased FEV₁ and IC at all time points relative to placebo ($p < 0.001$). Peak effects on FEV₁ were similar, while indacaterol had a greater effect on peak IC (31% vs 23% from pre-dose; $p = 0.034$). Indacaterol had a greater effect than formoterol on FEV₁ at 8 h (1.47 vs 1.39 L; $p = 0.014$) and 24 h (1.44 vs 1.35 L; $p = 0.003$), and on IC from 4 to 24 h (differences of 0.13–0.19 L; $p < 0.05$). At 24 h, indacaterol and formoterol increased FEV₁ by 17.7% and 7.5%, respectively, from pre-dose.

Conclusions This study discriminated between the effects on IC and FEV₁ of once-daily indacaterol and twice-daily formoterol. The greater effect of indacaterol on IC may translate into improved long-term clinical outcomes.

KEYWORDS: bronchodilation; chronic obstructive pulmonary disease; forced expiratory volume in 1 second; formoterol; indacaterol; inspiratory capacity

INTRODUCTION

Current guidelines emphasize that chronic obstructive pulmonary disease (COPD) is both preventable and treatable, while acknowledging that the condition is characterized by a progressive decline in lung function¹. Bronchodilators are the cornerstone treatment for all COPD severity stages. In more pronounced stages of airflow obstruction, the regular use of one or more long-acting bronchodilators is recommended. These agents include the twice-daily β_2 -agonists, formoterol and salmeterol, and the once-daily anticholinergic, tiotropium. Long-acting bronchodilators may improve exercise tolerance²⁻⁴ as a result of bronchodilation and reduction of both static and dynamic hyperinflation.

The diagnosis and severity staging of COPD and measurement of response to therapy are based on objective measures of lung function, i.e. forced expiratory volume in 1 second (FEV₁) and the ratio of FEV₁ to forced vital capacity (FVC). However, there is evidence that acute changes in resting FEV₁ do not correlate with improvements in exertional dyspnoea and exercise capacity and vice versa^{5,6}. Other spirometric measures such as inspiratory capacity (IC) may correlate better with these measures of clinical response⁵. Resting IC represents the limit for inspiratory volume expansion following exhalation during tidal breathing, and therefore indirectly infers functional residual capacity, i.e. the degree of hyperinflation. Moreover, a decrease in IC during exercise indicates dynamic hyperinflation, assuming that total lung capacity remains constant. Finally, an increased resting IC is a better predictor of exercise tolerance in COPD than other lung function variables, e.g. FEV₁⁵.

Indacaterol is a novel inhaled ultra-long-acting β_2 -agonist (ultra-LABA) being investigated for once-daily use in subjects with COPD^{7,8}. Improved clinical benefits have been demonstrated with the long-acting anticholinergic tiotropium once-daily versus short-acting ipratropium four-times daily⁹, and one of the proposed underlying mechanisms for this observation may be a prolonged effect of long-acting bronchodilators on lung emptying, by improving IC and reducing resting hyperinflation. The objective of the present exploratory study was to compare the response in FEV₁ and IC between single doses of indacaterol and matched placebo, with the recommended daily dose of formoterol (12 μ g twice daily) as an active control. Safety and tolerability were also assessed.

METHODS

Patients (inclusion/exclusion criteria)

The study enrolled males and females aged 40–80 years, with a clinical diagnosis of COPD according to GOLD recommendations¹⁰ and a smoking history of at least 10 pack-years. Spirometric criteria were a post-bronchodilator FEV₁ ≥40% predicted at screening and ≥1.0 L; FEV₁ reversibility of ≥5% to salbutamol 400 µg (after an appropriate bronchodilator washout period: no use of short-acting bronchodilators for 6 h, no long-acting β₂-agonists for 48 h, and no tiotropium for 72 h); and a post-bronchodilator ratio of FEV₁/FVC <0.7.

Patients were allowed to continue taking inhaled corticosteroids, provided a regimen of regular use had been stable for at least 1 month previously. Similarly, patients could continue use of short-acting β₂-agonists, provided the washout period of at least 6 hours prior to dosing visits could be adhered to. Apart from inhaled corticosteroids, patients refrained from using concomitant medication on the study dosing day until after assessments had been completed the following day.

The following medications were not allowed throughout the whole study period: tiotropium (a 72 h washout), long-acting β₂-agonists other than study medications (48 h washout), and systemic corticosteroids (1 month washout).

Study design

The study was a multicentre, placebo-controlled, randomized crossover design comparing indacaterol, matching placebo and formoterol in patients with mild-to-severe COPD. The study was conducted at three sites: insaf Respiratory Research Institute, Wiesbaden, Germany; Chiltern's Clinical Research Unit (CCRU), Slough, UK, and Cyncron (ex-Medicon Clinical Pharmacology) A/S, Copenhagen, Denmark.

Following a maximum 28-day screening period patients were randomly assigned to receive single doses of either indacaterol (300 µg via a single-dose dry powder inhaler [SDDPI]) or matching placebo (SDDPI) in a cross-over fashion in the morning under double-blind conditions. Following this, all patients received open-label formoterol 12 µg administered twice, morning and evening, via a single-dose dry powder inhaler device (Aerolizer™, Novartis).

Each treatment period was separated by a 4–7 day washout. Patients could receive allowable COPD medications and prescribed salbutamol (as needed) during washout periods.

All patients received appropriate training in inhaler device use and spirometry manoeuvre techniques prior to receiving treatment.

The study was approved by the internal review board or ethics committee at each centre and the three respective health authorities, and conducted according to the Declaration of Helsinki. Each subject gave written informed consent before randomization.

Study assessments

Spirometry measures included IC (mean of three reproducible manoeuvres) and FEV₁ (best of three reproducible manoeuvres) that were performed at each visit (pre-dose; and 5 min, 30 min, 1 h, 2 h, 4 h, 6 h, 8 h, 23 h 30 min and 24 h post-dose). Spirometry was not assessed between 8 and 23 h post-dose for logistical reasons. Spirometry equipment and performance of spirometric testing was conducted in accordance with American Thoracic Society and European Respiratory Society joint recommendations and standards¹¹.

The primary efficacy variable in this study was a comparison between FEV₁ and IC in terms of the mean maximal change from baseline following single doses of indacaterol and matched indacaterol placebo with two doses (b.i.d. regimen) of formoterol as an active control. Secondary endpoints were comparisons among indacaterol, formoterol and matched indacaterol placebo of: (1) percent predicted FEV₁ time course change; and (2) mean maximal change in IC time course change. Inspiratory capacity manoeuvres were performed prior to forced measurements to avoid any influence of forced exhalations on resting hyperinflation¹¹. Safety assessments included recording of all reported adverse events and serious adverse events.

Statistical analysis

The efficacy analyses included all randomized subjects who received at least one dose of study drug and had at least one post-baseline assessment of FEV₁. The safety population included all subjects who received at least one dose of study drug.

Exploratory analyses were used to assess the relationship between IC and FEV₁. Comparison of peak and trough FEV₁ and IC between indacaterol and placebo treatments was conducted using a mixed linear model with period, treatment and treatment period effects as fixed effects and subject as a random effect. Comparisons between formoterol versus placebo and formoterol versus indacaterol were conducted using a t-test on peak FEV₁.

Data are presented as least squares means (LSM) and the significance of between-treatment differences was determined using analysis of covariance (ANCOVA), with baseline (pre-dose values), subject and treatment as factors. For formoterol the baseline value was pre-first dose.

This study was an exploratory study and no sample size computation was performed. A sample size of 30 patients was pre-specified and had at least 80% power to detect a difference of 0.22 L between the mean levels of FEV₁ at 24 h after the morning dose for indacaterol and placebo. This assumes a common within-subject standard deviation of 0.292 L using a paired t-test at 5% significance level.

RESULTS

Patients

As planned, 30 subjects were randomized. Demographic and baseline characteristics are shown in **Table 1**. All subjects were Caucasian. No patient withdrew from the study.

Efficacy

Spirometry data were available for all 30 subjects on the formoterol treatment day, for all but one subject at the 23.5 and 24 h time points on the indacaterol day, and for all but one subject at 6 and 8 h and two subjects at 23.5 and 24 h on the placebo day, the reasons for missing measurements being administration of rescue medication, or concomitant medication for shortness of breath.

FEV₁, IC and FVC over time

Baseline (pre-dose) mean (SD) FEV₁ values for each treatment were 1.19 (0.328) L for indacaterol, 1.28 (0.319) L for placebo, and 1.29 (0.311) L for formoterol. Respective IC values were 1.89 (0.540) L, 2.00 (0.607) L and 2.01 (0.558) L.

FEV₁ was significantly greater at all assessment time points (5 min to 24 h) following treatment with indacaterol ($p < 0.0001$) or formoterol ($p < 0.001$) compared with placebo

(**Figure 1**). At 5 min post-dose, adjusted mean FEV₁ increased by 0.22 L relative to placebo with both indacaterol and formoterol. Mean FEV₁ for indacaterol was significantly greater than for formoterol at 8 h and 24 h. At 24 h, respective adjusted mean (SE) values were 1.44 (0.029) and 1.35 (0.028) L, a mean (SE) difference of 0.09 (0.029) L (p=0.003). These values reflect unadjusted mean (SD) changes from pre-dose of 17.7 (15.02)% with indacaterol and 7.5 (12.94)% with formoterol at the 24 h time point.

IC was significantly greater at all time points (5 min to 24 h) following treatment with indacaterol (p<0.0001) or formoterol (p<0.001) compared with placebo (**Figure 2**). Indacaterol had a numerically greater effect than formoterol at all time points, with differences that were significant (at 4 h to 24 h; p<0.05) or were close to significance (at 30 minutes to 2 h; p=0.059 to p=0.069). The effects of indacaterol and formoterol on FEV₁ and IC in terms of percentage change from pre-dose values are compared in Figure 3.

In terms of FVC, for indacaterol and formoterol, respectively, the percent increases from pre-dose were 19.4% and 14.3% at 5 min post-dose, 24.2% and 17.5% at peak effect (1–2 h post-dose), and 16.4% and 6.6% at 24 h post-dose. Analysis of covariance of FVC was not planned or performed.

Peak FEV₁ vs peak IC

Peak effects on FEV₁ and IC as percentages of pre-dose values are shown in **Table 2**. While the effect of indacaterol and formoterol on peak FEV₁ was of a similar order (32% vs 28% increase from pre-dose, respectively), the two bronchodilators varied in their effect on peak IC and indacaterol had a significantly greater effect (31% increase from pre-dose with indacaterol vs 23% with formoterol, p=0.034).

Safety

Adverse events according to body system and preferred term are shown in **Table 3**. Cough was the most common adverse event, occurring most frequently following indacaterol, and was suspected to be related to treatment. There were no serious adverse events reported during the study, and no discontinuations due to adverse events.

DISCUSSION

The primary objective of this study was to compare and contrast indacaterol, placebo and formoterol in terms of their effects on two measures reflecting the airflow limitation of COPD, namely FEV₁ and resting IC. Comparing peak effects, indacaterol and formoterol had similar effects on FEV₁, whereas indacaterol had a significantly greater peak effect than formoterol on IC, although additional work is needed to determine clinical relevance. This pattern is reflected in the profile of relative effects over 24 hours, where indacaterol was superior to formoterol for FEV₁ towards the end of formoterol's 12-h duration of bronchodilator effect. At 8 h following the morning dose, FEV₁ increased from pre-dose by 20% with indacaterol and 11% with formoterol. At 24 h following the morning dose of indacaterol (i.e. 12 h after the second formoterol dose), the 18% increase in FEV₁ compared favourably with the increase of 8% 12 h following the second dose of formoterol. For IC, indacaterol had a significantly greater effect than formoterol during most of the post-dose period.

These results are unlikely to be the result of underlying differences in treatment period baseline lung function, since pre-dose measures of FEV₁ and IC were consistent between treatments. The choice of doses is another possible factor that may partly account for the present results. However, the formoterol dose was chosen as the commercially available therapeutic dose, the indacaterol dose is within the range previously shown to provide effective bronchodilation over 24 h¹² and an approximate equivalence between the effects of formoterol and the chosen indacaterol dose on FEV₁ (the differences at the later time points reflecting their differing durations of effect) was demonstrated (as shown in Figure 3). Nevertheless, the comparative results between indacaterol and formoterol need to be interpreted with a degree of caution, given the open-label nature of the latter treatment, and the results of this exploratory study should be confirmed using appropriate blinding and a double-dummy comparative design.

Previous studies have demonstrated the 24-h bronchodilator efficacy of indacaterol in subjects with COPD^{7,8}; this is the first comparison with formoterol. In addition to the potential advantages of greater convenience for the patient of once-daily versus twice-daily dosing, the superior bronchodilator efficacy at time points when formoterol's effect is tailing off may be reflected in a smoother and more sustained control of symptoms and, importantly, peripheral lung emptying under resting conditions, which may be reflected by the superior effect of indacaterol on trough IC at 24 h post-dose. This is also the first study to report on the effect of indacaterol on

IC, which was significantly greater than placebo throughout the 24-h post-dose period. The effect was significant as early as 5 min post-dose and remained significant at 24 h post-dose.

Previous studies of up to 8 weeks in duration have shown significant (pre-dose) effects on resting IC at trough after treatment with tiotropium (differences vs placebo ranging from 0.10 L [$p < 0.05$] to 0.22 [$p < 0.001$])^{4,13,14} and salmeterol/fluticasone (0.23 L vs placebo; $p \leq 0.008$) but not salmeterol (0.11 L vs placebo)¹⁵. It has been suggested that a bronchodilator-induced increase in resting IC of the order of 0.3 L, or 15–17% of baseline value, is clinically meaningful in terms of important improvements in exercise endurance and exertional dyspnoea¹⁶. In the present study indacaterol increased IC by 0.30–0.45 L relative to placebo, and by 15–25% from pre-dose values, during the 24-h study period. Other studies comparing the acute effects of formoterol and salmeterol on IC have suggested that formoterol has a greater effect than salmeterol 1–2 h post-dose, reflecting its faster onset of action^{17,18}. The present data show that indacaterol may provide a greater effect than formoterol in the early hours post-dose and at trough.

Lung IC has been shown to correlate significantly with increased exercise endurance and with reduced dyspnoea during exercise^{5,19}. It has been shown that the reduction in breathlessness during exercise and improved exercise tolerance are closely related to the bronchodilator-induced change in IC at rest, regardless of the change in resting FEV₁²⁰. Furthermore, though not tested here, increases in IC were shown to correlate much better than increased FEV₁ with patients' perceptions of improved symptoms²¹. Measurement of IC may therefore be useful in predicting the beneficial effects of bronchodilator therapy on dyspnoea and exercise tolerance.

In terms of the data from the present study, IC appears to be a more sensitive measure than FEV₁ in discriminating between the effects of indacaterol and formoterol on the airflow limitations of subjects with COPD. It is hoped that these early observations will translate into a beneficial effect on exercise capacity and associated breathlessness in subjects with COPD, and results of further studies in which these endpoints will be specifically evaluated are awaited.

In conclusion, indacaterol proved an effective and well tolerated bronchodilator in this population of subjects with moderately severe COPD. Both indacaterol (single dose) and formoterol (twice daily) had a significant bronchodilator effect in patients with COPD, measured either by FEV₁ or IC. The results of this exploratory study suggest

that indacaterol had the greater effect on IC compared with formoterol, which may translate into more marked benefits on other clinical endpoints.

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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 2007 (based on an April 1998 NHLBI/WHO Workshop). At: <http://goldcopd.com>. Last accessed 9 December 2007.
2. Neder JA, Fuld JP, Overend T, Thirlwell J, Carter R, Stevenson R, Ward SA. Effects of formoterol on exercise tolerance in severely disabled patients with COPD. *Respir Med* 2007; 101: 2056-2064.
3. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. *Eur Respir J* 2004; 24: 86-94.
4. Maltais F, Hamilton A, Marciniuk D, Hernandez P, Sciruba FC, Richter K, Kesten S, O'Donnell D. Improvements in symptom-limited exercise performance over 8 h with once-daily tiotropium in patients with COPD. *Chest* 2005; 128: 1168-1178.
5. O'Donnell DE, Lam M, Webb KA. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1999; 160: 542-549.
6. Calverley PM, Burge PS, Spencer S, Anderson JA, Jones PW. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. *Thorax* 2003; 58: 659-664.

7. Beier J, Chanez P, Martinot J-B, Schreurs AJR, Tkáčová R, Bao W, Jack D, Higgins M. 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* 2007;20(6):740-749.
8. Rennard S, Bantje T, Centanni S, Chanez P, Chuchalin A, D'Urzo A, Kornmann O, Perry S, Jack D, Owen R, Higgins M. A dose-ranging study of indacaterol in obstructive airways disease, with a tiotropium comparison. *Respir Med* 2008; 102:1033-1044.
9. Vincken W, van Noord JA, Greefhorst AP, Bantje TA, Kesten S, Korducki L, Cornelissen PJ. Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J* 2002;19: 209-216.
10. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2005 (based on an April 1998 NHLBI/WHO Workshop). At: <http://goldcopd.com>. Last accessed 9 September 2007.
11. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J* 2005; 26: 319-338.
12. Rennard S, Bantje T, Centanni S, Chanez P, Chuchalin A, D'Urzo A, Kornmann O, Perry S, Jack D, Owen R, Higgins M. A dose-ranging study of indacaterol in obstructive airways disease, with a tiotropium comparison. *Respir Med* 2008; in press.
13. O'Donnell DE, Flüge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, Make B, Magnussen H. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004; 23: 832-840.
14. Celli B, ZuWallack R, Wang S, Kesten S. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. *Chest* 2003; 124: 1743-1748.
15. O'Donnell DE, Sciruba F, Celli B, Mahler DA, Webb KA, Kalberg CJ, Knobil K. Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. *Chest* 2006; 130: 647-656.

16. Laveneziana P, O'Donnell, DE. The role of spirometry in evaluating therapeutic responses in advanced COPD. *Disease Management & Health Outcomes* 2007; 15: 91–100.
17. Bouros D, Kottakis J, Le Gros V, Overend T, Della Cioppa G, Siafakas N. Effects of formoterol and salmeterol on resting inspiratory capacity in COPD patients with poor FEV₁ reversibility. *Curr Med Res Opin* 2004; 20: 581-586.
18. Di Marco F, Milic-Emili J, Boveri B, Carlucci P, Santus P, Casanova F, Cazzola M, Centanni S. Effect of inhaled bronchodilators on inspiratory capacity and dyspnoea at rest in COPD. *Eur Respir J* 2003;21: 86-94.
19. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; 164: 770-777.
20. Boni E, Corda L, Franchini D, Chirolì P, Damiani GP, Pini L, Grassi V, Tantucci C. Volume effect and exertional dyspnoea after bronchodilator in patients with COPD with and without expiratory flow limitation at rest. *Thorax* 2002; 57: 528-532.
21. Taube C, Lehnigk B, Paasch K, Kirsten DK, Jorres RA, Magnussen H. Factor analysis of changes in dyspnea and lung function parameters after bronchodilation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000; 162: 216-220.

Table 1. Baseline demographic and clinical characteristics at screening.

Variable	Statistic	Total n=30
Age (years)	Mean (SD)	65 (7.5)
	Range	51–78
Sex	Male n (%)	16 (53)
	Female n (%)	14 (47)
Height (cm)	Mean (SD)	171 (6.5)
Weight (kg)	Mean (SD)	77 (15.0)
FEV ₁ pre-bronchodilator (L)	Mean (SD)	1.29 (0.317)
	Range	0.80–2.12
FEV ₁ post-bronchodilator* (L)	Mean (SD)	1.53 (0.348)
	Range	1.19–2.58
FEV ₁ reversibility (%)	Mean (SD)	23.0 (12.01)
	Range	(8.1–48.8)
FEV ₁ (% predicted) (post-bronchodilator* values)	Mean (SD)	56.3 (11.37)
	Range	40.5–84.6
FVC (L) (post-bronchodilator*)	Mean (SD)	3.20 (0.862)
	Range	1.86–5.82
FEV ₁ /FVC (post-bronchodilator)	Mean (SD)	0.49 (0.099)
	Range	0.31–0.67
IC (L) (pre-bronchodilator)	Mean (SD)	1.87 (0.549)
	Range	1.03–3.68

*30 minutes after inhalation of salbutamol.

FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; IC = inspiratory capacity; L = litre; SD = standard deviation

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Table 2. Comparison of peak effect on FEV₁ and IC (as % increase from pre-dose value)

		Indacaterol n=30	Placebo n=30	Formoterol n=30
FEV ₁ , % increase	Mean	32.3 ^a	8.0	27.9 ^a
	(95% CI)	(26.4, 38.3)	(5.5, 10.4)	(23.6, 32.1)
IC, % increase	Mean	31.2 ^{a,b}	8.8	22.9 ^a
	(95% CI)	(23.7, 38.7)	(5.3, 12.3)	(18.2, 27.7)

^ap<0.001 vs placebo; ^bp<0.05 vs formoterol

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Table 3. Adverse events, n (%)

Body system	Adverse event	Indacaterol n=30	Placebo n=30	Formoterol n=30
Any		11 (36.7)	4 (13.3)	1 (3.3)
General and administration site	Chest discomfort	1 (3.3)	1 (3.3)	0
Infections and infestations	Nasopharyngitis	0	1 (3.3)	0
Musculoskeletal and connective tissue	Back pain	1 (3.3)	1 (3.3)	1 (3.3)
	Myalgia	1 (3.3)	0	0
Nervous system	Headache	0	0	1 (3.3)
Respiratory, thoracic and mediastinal	Cough	6 (20.0)	1 (3.3)	0
	Dry throat	1 (3.3)	0	0
	Dyspnoea	2 (6.7)	2 (6.7)	0

Figure 1. FEV₁ (adjusted means, \pm SE) over 24 hours post-dose. n=30 for each treatment. p<0.0001 for indacaterol vs placebo at all time points. p<0.0001 for formoterol vs placebo (5 min to 8 h); p<0.001 (23.5 h and 24 h). p=0.014 and p=0.003 for indacaterol vs formoterol at 8 h and 24 h, respectively. ■ = indacaterol; □ = formoterol; ▲ = placebo

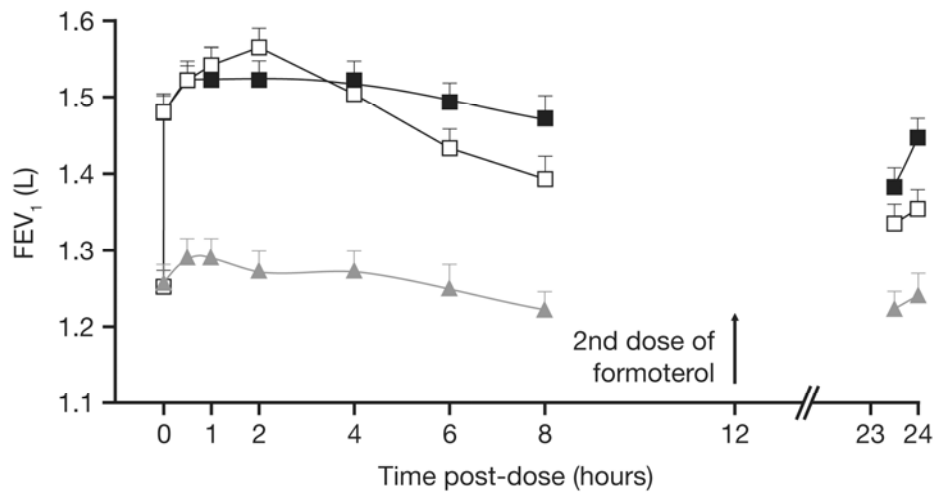
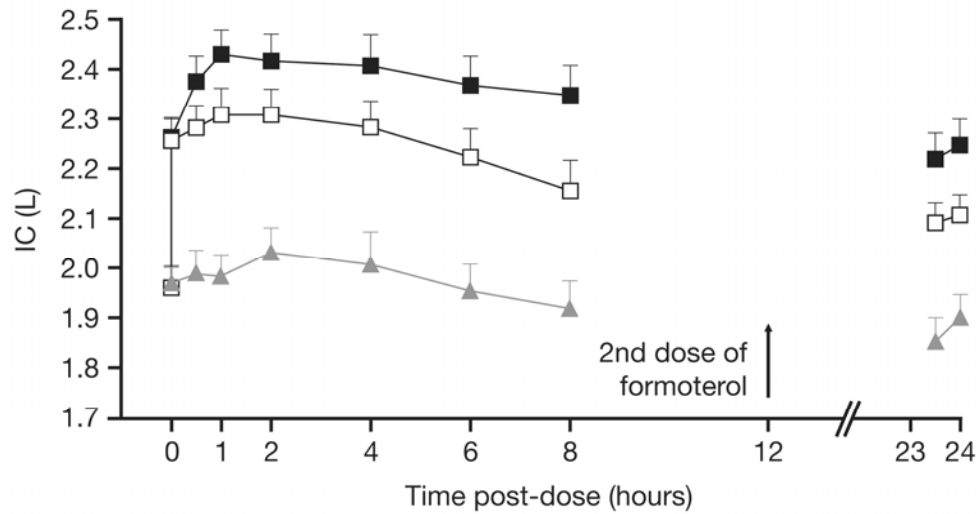
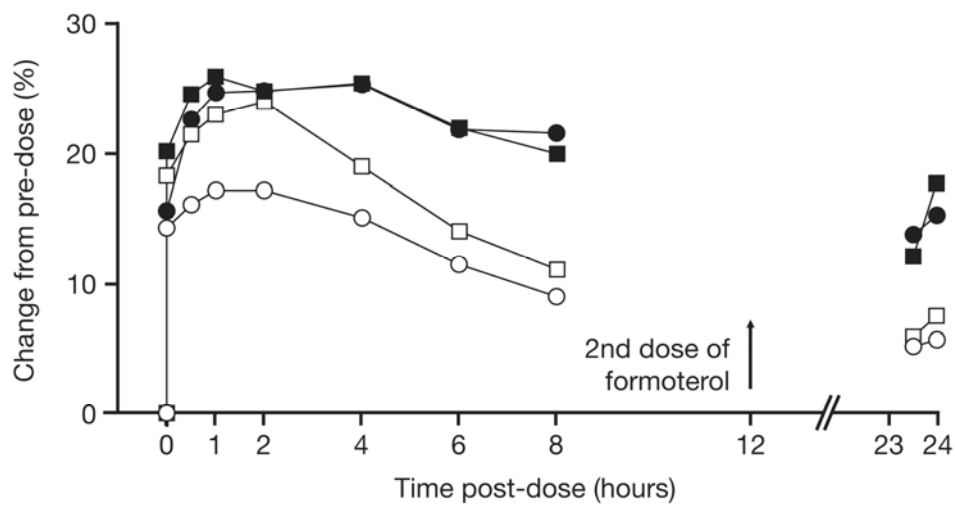


Figure 2. Inspiratory capacity (least squares means, \pm SE) over 24 hours post-dose. n=30 for each treatment. $p < 0.0001$ for indacaterol vs placebo at all time points. $p < 0.0001$ for formoterol vs placebo (5 min to 6 h); $p < 0.001$ (8 h and 23.5h); $p < 0.01$ (24 h). $p < 0.05$ for indacaterol vs formoterol (4h to 24h). ■ = indacaterol; □ = formoterol; ▲ = placebo



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Figure 3. Comparison of effects of indacaterol and formoterol on FEV₁ and IC as % change in unadjusted mean values from pre-dose. Error bars omitted for clarity. n=30 for each treatment. ■ = indacaterol (FEV₁); ● = indacaterol (IC); □ = formoterol (FEV₁); ○ = formoterol (IC)



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Variable	Statistic	Total n=30
Age (years)	Mean (SD)	64.8 (7.50)
	Range	51–78
Sex		
Male	n (%)	16 (53.3)
Female	n (%)	14 (46.7)
Height (cm)	Mean (SD)	170.7 (6.53)
Weight (kg)	Mean (SD)	76.8 (14.95)
FEV ₁ pre-bronchodilator (L)	Mean (SD)	1.29 (0.317)
	Range	0.80–2.12
FEV ₁ post-bronchodilator* (L)	Mean (SD)	1.53 (0.348)
	Range	1.19–2.58
FEV ₁ reversibility (%)	Mean (SD)	23.0 (12.01)
	Range	(8.1–48.8)
FEV ₁ (% predicted) (post-bronchodilator* values)	Mean (SD)	56.3 (11.37)
	Range	40.5–84.6
FVC (L) (post-bronchodilator*)	Mean (SD)	3.20 (0.862)
	Range	1.86–5.82
FEV ₁ /FVC (post-bronchodilator)	Mean (SD)	0.49 (0.099)
	Range	0.31–0.67
IC (L) (pre-bronchodilator)	Mean (SD)	1.87 (0.549)
	Range	1.03–3.68

*30 minutes after inhalation of salbutamol.

FEV₁ = forced expiratory volume in 1 second; FVC = forced vital capacity; IC = inspiratory capacity; L = litre; SD = standard deviation

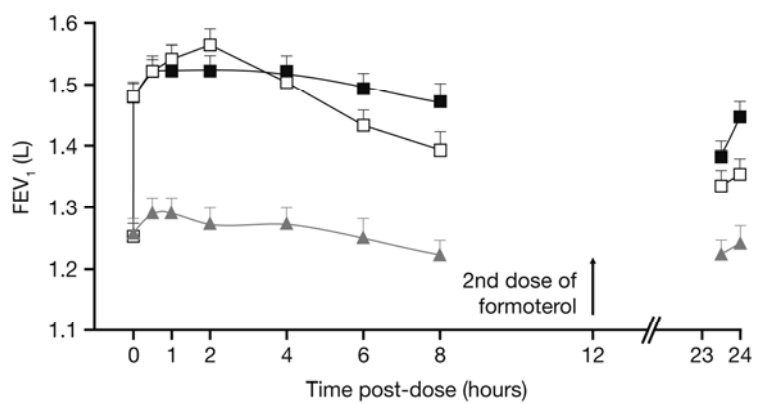
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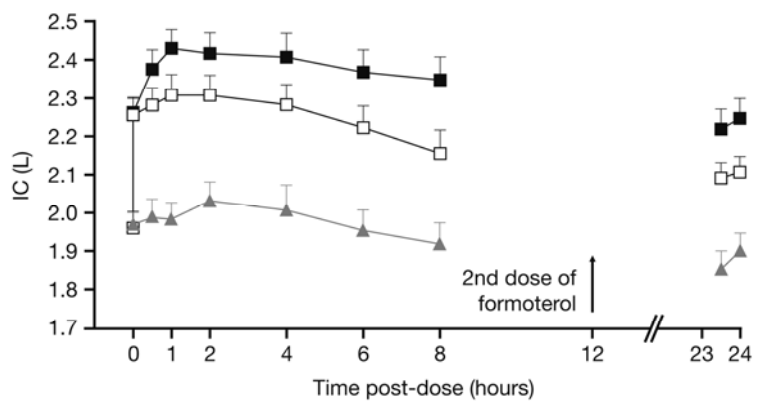
		Indacaterol n=30	Placebo n=30	Formoterol n=30
FEV ₁ , % increase	Mean	32.32 ^a	7.95	27.86 ^a
	(95% CI)	(26.35, 38.30)	(5.49, 10.40)	(23.59, 32.14)
IC, % increase	Mean	31.20 ^{a,b}	8.82	22.91 ^a
	(95% CI)	(23.72, 38.69)	(5.31, 12.34)	(18.17, 27.65)

^ap<0.001 vs placebo; ^bp<0.05 vs formoterol

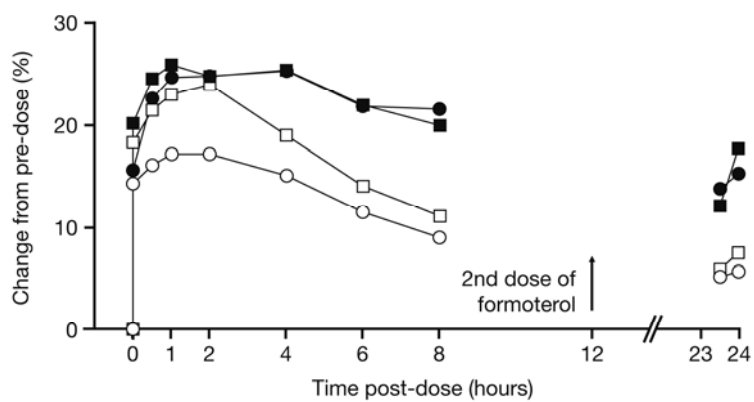
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Body system	Adverse event	Indacaterol n=30	Placebo n=30	Formoterol n=30
Any		11 (36.7)	4 (13.3)	1 (3.3)
General and administration site	Chest discomfort	1 (3.3)	1 (3.3)	0
Infections and infestations	Nasopharyngitis	0	1 (3.3)	0
Musculoskeletal and connective tissue	Back pain	1 (3.3)	1 (3.3)	1 (3.3)
	Myalgia	1 (3.3)	0	0
Nervous system	Headache	0	0	1 (3.3)
Respiratory, thoracic and mediastinal	Cough	6 (20.0)	1 (3.3)	0
	Dry throat	1 (3.3)	0	0
	Dyspnoea	2 (6.7)	2 (6.7)	0





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