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Once-daily indacaterol vs twice-daily salmeterol for COPD: a placebo-controlled comparison

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Abstract [200 words]

Indacaterol is a novel, inhaled, once-daily, ultra-long-acting β_2-agonist bronchodilator, recently approved in Europe for the treatment of COPD. This study set out to investigate the efficacy and safety of indacaterol compared with placebo and the twice-daily β_2-agonist, salmeterol, as an active control.

Patients with moderate-to-severe COPD were randomized to 6 months' double-blind treatment with indacaterol 150 µg once daily, salmeterol 50 µg twice daily or placebo. Primary efficacy endpoint was trough (24 h post-dose) forced expiratory volume in 1 s (FEV_1) after 12 weeks.

1002 patients were randomized and 838 (84%) completed the study. Indacaterol increased trough FEV_1 at Week 12 by 170 mL over placebo ($p<0.001$), and by 60 mL more than salmeterol ($p<0.001$). Both active treatments improved health status (St George's Respiratory Questionnaire) and dyspnoea (transition dyspnoea index) compared with placebo, with differences between them favouring indacaterol. Safety profiles were similar across the treatment groups and both indacaterol and salmeterol were well tolerated.

Once-daily treatment with indacaterol 150 µg has a significant and clinically relevant bronchodilator effect over 24 h post-dose, and improves health status and dyspnoea to a greater extent than twice-daily salmeterol 50 µg. Indacaterol should prove a useful additional treatment for patients with COPD.

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Chronic obstructive pulmonary disease (COPD) is estimated to affect 10% of the world's population aged 40 years and over, and prevalence is expected to continue to increase over coming years [1,2]. Regular treatment with one or more long-acting inhaled bronchodilators is an important and recommended element in managing the symptoms of patients with COPD [3]. These agents are administered twice-daily (the β_2-agonists formoterol and salmeterol) or once-daily (the anticholinergic tiotropium). Indacaterol is an inhaled ultra-long-acting β_2-agonist bronchodilator that has demonstrated 24-h efficacy on once-daily administration, and was recently approved in the European Union at two doses, 150 and 300 μg once daily, for use in the maintenance treatment of patients with COPD.

In deciding whether to use a new agent, it is clearly useful to know how the efficacy and safety of indacaterol compare with other long-acting bronchodilators using studies of suitable design and appropriate duration. The present study is one of a series of studies designed to compare indacaterol with currently available long-acting bronchodilators. The other studies were a 6-month comparison of indacaterol 150 and 300 μg with tiotropium [4] and a 1-year comparison of indacaterol 300 μg with formoterol [5]. The present study compares indacaterol 150 μg once-daily with salmeterol 50 μg twice-daily over 6 months.

METHODS

The study was approved by the ethics committees or institutional review boards of participating centres, and was conducted in respiratory out-patient clinics, physician's offices and clinical research centres.

Patients

The study enrolled males and females aged ≥40 years with a clinical diagnosis of moderate-to-severe COPD [6] and a smoking history of ≥20 pack-years. Spirometry at screening was FEV_1 <80% and ≥30% predicted and FEV_1/FVC <0.7, measured within 30 min of inhaling salbutamol 400 μg. Patients with a history of asthma were excluded. All patients gave their written informed consent.

Study design

Following a 2-week run-in and screening period during which baseline variables were assessed and concomitant medication stabilized, patients were randomized to receive double-blind treatment with indacaterol 150 μg once daily via single-dose dry powder inhaler (taken in the morning), salmeterol 50 μg twice daily (morning and evening) via its proprietary dry powder inhaler or placebo for 26 weeks. Placebos matching both active treatments were used to maintain blinding.

Patients were permitted concomitant medication with inhaled corticosteroids (ICS), if dose and regimen were stable for 1 month prior to screening. Dose and regimen were to remain stable throughout the study. Patients previously on fixed combinations of ICS and long-acting β_2-agonist were switched to the equivalent ICS monotherapy at a dose and regimen maintained throughout the study. Salbutamol was provided for use as needed (but not within 6 h before study assessments).

Objectives, assessments and outcome measures

The primary objective was to confirm the superiority of indacaterol 150 μg over placebo with respect to 24-h post-dose 'trough' FEV_1 after 12 weeks. Trough FEV_1 was defined as the average of the values at 23 h 10 min and 23 h 45 min following the previous day's morning dose, and was also determined on Day 2 and Week 26. Spirometry was also performed at intervals up to 1 h post-dose at each clinic visit. Secondary objectives were to compare the effect of indacaterol versus salmeterol and salmeterol versus placebo on trough FEV_1 at Week 12, and to evaluate the effect of treatment (all comparisons) on FEV_1 at other time points, on other efficacy outcomes (health status, diary card assessments, dyspnoea), and on safety and tolerability.

Health status was assessed by St George's Respiratory Questionnaire (SGRQ) [7], which patients completed at baseline and at Weeks 4, 8, 12 and 26. The minimum clinically important difference (MCID) was 4 points in SGRQ total score [8]. Dyspnoea was assessed at baseline as the baseline dyspnoea index (BDI) and at Weeks 4, 8, 12 and 26 as the transition dyspnoea index (TDI) [9], with a change of 1 point regarded as the MCID [10]. Patients recorded their symptoms, pre-treatment peak expiratory flow (PEF) morning and evening and use of as-needed salbutamol on diary cards, completed daily. A composite measure of 'days of poor COPD control' was based on an endpoint used in formoterol registration studies [11,12], and was defined as 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. The effect of indacaterol relative to placebo on SGRQ score at Week 12 and on percentage days of poor COPD control were pre-defined important secondary endpoints.

At each clinic visit, adverse events were recorded, vital signs were monitored and ECGs recorded. The QT interval was calculated using Fridericia's correction. Blood samples were taken at each visit pre- and 1 h post-dose for haematology and blood chemistry. Clinically notable laboratory values were specified for reduced serum potassium (<3.0 mmol/L) and elevated blood glucose (>9.99 mmol/L). Investigators were asked to record any events they observed within 5 minutes of drug administration at clinic visits, including cough (as distinct from reports of cough as an adverse event).

Statistical methods

Patients were randomly allocated to treatment in a 1:1:1 ratio (with stratification for smoking status) using an automated system. Blinding was maintained from randomization until database lock unless any patient emergencies arose.

Efficacy variables were analysed using a mixed-model analysis of covariance containing treatment as a fixed effect with the appropriate baseline measurement and baseline FEV_1 reversibility as covariates, smoking status and country as fixed effects and centre nested within country as a random effect. To handle the issue of multiplicity, the primary and important secondary efficacy variables were analysed in hierarchical fashion, i.e. the primary efficacy variable, then SGRQ total score at 12 weeks, then percentage of days of poor COPD control (all for superiority of indacaterol vs placebo). Other efficacy variables and treatment comparisons were analysed without allowance for multiplicity. Results of the analysis of covariance are expressed as (adjusted) least squares means with associated 95% confidence intervals for the treatment contrasts. Raw mean (non-adjusted) data are also presented for the changes from baseline in TDI and SGRQ scores.

Efficacy data were analysed for the intention-to-treat (ITT) population, comprising all randomized patients who received at least one dose of study drug. The population for the safety analysis comprised all patients who received at least one dose of study drug.

Sample size determination

A treatment difference between indacaterol and placebo of 120 mL in trough FEV_1 was pre-specified as a clinically important difference for COPD patients. Based on this, and a standard deviation of 270 mL for trough FEV_1 based on previous data [11,12], a sample size of 108 evaluable patients in each treatment group was needed to detect this difference as statistically significant at the 5% significance level (two-sided) with 90% power. The criterion for the sample size decision also targeted 90% power for the symptomatic endpoint, percentage of COPD days of poor control, which (assuming a standard deviation of 28% [11,12]) required 259 evaluable patients per treatment group to detect an 8% difference as statistically significant at the 5% significance level (two-sided). This, being the larger number, defined the sample size. Assuming a 15% drop-out over the first 12 weeks of treatment, the resulting target sample size of 324 patients per treatment group would provide >99% power for the primary endpoint.

RESULTS

The study involved 142 centres in 15 countries, and patients were treated between November 2007 and January 2009. Of 1518 patients screened, 1002 were randomized, of whom 838 (84%) completed the study. Discontinuations were more common from the placebo arm, owing mainly to lack of therapeutic effect and withdrawal of consent

(table 1). Table 2 shows demographic data and disease characteristics for the treated patients.

Spirometry

Figure 1 shows the differences between active treatments and placebo for trough FEV_1 at Day 2, Week 12 and Week 26. Differences vs placebo were significant for both indacaterol and salmeterol at all assessments ($p<0.001$), with trough FEV_1 significantly greater with indacaterol than with salmeterol at Weeks 12 and 26 (by 60 mL and 70 mL, both $p<0.001$). As changes from baseline, trough FEV_1 at week 12 increased by 150 mL (13%) with indacaterol and by 90 mL (8%) with salmeterol, and decreased by 30 mL (0.7%) with placebo. Indacaterol maintained a clinically significant increase over placebo during the course of the study, with an increase from 130 mL at 24 h following the first dose to 170 mL at Week 12 and 180 mL at Week 26; the salmeterol–placebo difference was smaller and did not increase with length of treatment (120, 110 and 110 mL at Day 2, Week 12 and Week 26, respectively).

Five minutes after the first dose on Day 1, FEV_1 increased over placebo by 110 mL (95% CI 90, 130) with indacaterol and by 60 mL (95% CI 40, 80) with salmeterol ($p<0.001$ for both vs placebo), with an advantage for indacaterol over salmeterol of 50 mL (95% CI 30, 70; $p<0.001$). An advantage of 60–100 mL for indacaterol over salmeterol ($p<0.01$) at the 5 min post-dose time point was observed at all remaining clinic visits.

Health status, symptoms and use of as-needed salbutamol

The unadjusted mean SGRQ total score with indacaterol decreased (i.e. improved health status) from baseline by more than the 4-point minimum clinically important difference at all visits (fig. 2). The adjusted mean SGRQ total score was significantly

lower than placebo with indacaterol (differences of −3.6, −4.1, −6.3 and −5.0 at Weeks 4, 8, 12 and 26; all $p<0.001$) and salmeterol (−2.5, −3.6, −4.2 and −4.1 at Weeks 4, 8, 12 and 26; all $p<0.01$) throughout the study. The difference between indacaterol and salmeterol was significant at ($p<0.05$) Week 12, the specified time point for SGRQ as an important secondary variable.

The percentages of patients with a clinically important improvement from baseline in SGRQ total score of ≥4 units, and the odds ratios versus placebo for the likelihood of achieving this improvement, are shown in table 3. The difference between indacaterol and salmeterol was significant at Week 12 (odds ratio 1.59 [95% CI 1.12, 2.25]; $p<0.01$).

The percentage of days of poor COPD control over 26 weeks was a mean of 34.1% (SE 1.82) with both indacaterol and salmeterol, compared with 38.1% (SE 1.85) with placebo; the reductions from placebo were not statistically significant either for indacaterol (−4.0% days, 95% CI −8.0, 0.1; $p=0.058$) or salmeterol (−4.0% days, 95% CI −8.1, 0.1; $p=0.057$). Compared with salmeterol, indacaterol-treated patients used less as-needed salbutamol, had higher morning PEF and experienced more days able to undertake usual activities (table 4). Figure 3 shows the unadjusted mean change from baseline in TDI total score at Weeks 4, 8, 12 and 26. Adjusted mean total score was higher than placebo with both salmeterol ($p<0.05$) and indacaterol ($p<0.001$) at all visits. The mean differences versus placebo were numerically larger with indacaterol than with salmeterol, significantly so at Weeks 4 (0.95 vs 0.55; $p<0.05$) and Week 12 (1.45 vs 0.90; $p<0.05$). The percentage of patients with a clinically important improvement in TDI total score of ≥1 unit at Weeks 4, 8, 12 and 26 were 39.5–45.7% with placebo, 48.7–53.6% with salmeterol and 56.6–60.5% with

indacaterol. Odds ratios for the likelihood of achieving this improvement were significant for indacaterol over placebo at each time point (2.26, 1.71, 2.79 and 1.87 at Weeks 4, 8, 12 and 26, respectively; all $p<0.001$), while the odds ratio for salmeterol versus placebo was significant only at Weeks 12 and 26 (2.13 and 1.90; $p\leq0.001$).

Safety

Table 5 shows the overall incidence of adverse events and those reported most frequently. Those events that might be considered to be typically β_2-adrenoceptor-mediated were seldom reported (tremor, one patient in each of the indacaterol and salmeterol groups; tachycardia, one patient treated with indacaterol). The proportions of patients with serious adverse events were similar across the groups: 7.8%, 5.7% and 8.8%, for placebo, salmeterol and indacaterol, respectively. Among these, the most common categories affected were 'respiratory, thoracic and mediastinal' (including COPD worsening) and 'infections and infestations' (including respiratory tract infections). The incidence of bacterial and viral upper respiratory tract infections as adverse events was higher with indacaterol although most cases (23/24) were mild or moderate.

Four deaths occurred, three during treatment and one during the 30-day follow-up period. None was considered related to treatment. The deaths occurred in one patient in the indacaterol group (cardiac arrest) and three on placebo (cardio-respiratory arrest; multi-organ failure; COPD exacerbation).

Clinically notable values for blood glucose (>9.99 mmol/L) were recorded for 5.8% of indacaterol-treated patients, 9.0% of salmeterol-treated patients, and 6.3% of the placebo group. Clinically notable serum potassium values of <3.0 mmol/L were

recorded for 0.3%, 0.6% and 0% of the indacaterol, salmeterol and placebo groups, respectively.

QTc interval increases from baseline of >60 ms were recorded for two patients, one each in the indacaterol and salmeterol groups. The indacaterol patient with the >60 ms increase also had a notable high value (557 ms) at the time. His baseline value was at the higher end of normal (433 ms) and he had a number of medical problems that became apparent during the study (jaundice, adenocarcinoma, alcoholism).

As an adverse event, cough was reported by 2.4% of indacaterol-treated patients, similar to the 2.7% of salmeterol patients and lower than the 3.9% of placebo patients. In contrast, investigators observed cough following inhalation of study drug in an average of 17.6% (indacaterol), 0.9% (salmeterol) and 2.5% (placebo) of patients per visit. In the majority of cases, this cough started within 15 s of inhalation, and had a median duration of 12 s. The cough was not associated with bronchospasm, increased study discontinuation rates, or loss of bronchodilator efficacy. Only two patients withdrew from the study because of cough, neither of whom was receiving indacaterol.

DISCUSSION

Similar to the way in which the twice-daily β_2-agonist bronchodilators were shown to be more effective treatments for COPD patients than more frequently dosed short-acting bronchodilators [5,13], in this 6-month comparison a once-daily β_2-agonist was generally more effective than a twice-daily agent. Comparing the bronchodilator effect 24 h after the dose of indacaterol and 12 h after the previous evening's dose of salmeterol, trough FEV_1 was significantly higher with indacaterol than with salmeterol at all visits during the 6-month period. The difference in trough effect with

indacaterol of 170–180 mL relative to placebo after 12 and 26 weeks exceeded the pre-specified 120 mL clinically important active–placebo difference (a value at the mid-point of the range accepted as clinically important [14]), and there was no loss of bronchodilator effect over the course of the study. Salmeterol had a smaller effect at these times and did not achieve the 120 mL trough FEV_1 threshold for a difference versus placebo.

The effect of salmeterol on trough FEV_1 was similar to that observed in other studies [15–17]. The additional efficacy of 50–60 mL provided by indacaterol over salmeterol is similar to the margin provided by once-daily tiotropium over salmeterol [15]. The choice of trough FEV_1 as a primary endpoint is relevant to COPD patients, given that the early morning is when COPD patients report symptoms to be at their worst and they have difficulty accomplishing activities [18]. Morning PEF was also higher with indacaterol compared with salmeterol. The additional improvement in airflow with indacaterol at this time, both before and just after dosing, may help patients start to undertake their morning activities. The effects of indacaterol monotherapy on morning lung function appear similar to previous findings with combined bronchodilator treatment [19].

Across the range of outcomes evaluated, once-daily indacaterol 150 μg was more effective than placebo and, in most cases, more effective than twice-daily salmeterol. Indacaterol-treated patients reported improved health status (as measured by SGRQ) relative to placebo, by a margin that was close to (Week 4) or exceeded (Weeks 8–26) the MCID for this measure. Salmeterol had a lesser but still significant effect. The effect of indacaterol and salmeterol on dyspnoea followed a pattern similar to that of the health status results. Both treatments were more effective than placebo, with

indacaterol reaching statistical significance versus salmeterol at Weeks 4 and 12. This was observed even though salmeterol had a larger effect on dyspnoea [13,15,16,21] and health status [15,22] than in previous studies. Reasons for the differences are unclear and do not appear to be due to differences in COPD severity. The effects of indacaterol on these endpoints were consistent with those seen at the 6-month time point in other studies [4,5]. Breathlessness is considered the most disabling symptom for the COPD patient [20], and a sustained reduction in dyspnoea is an important finding for indacaterol. Indacaterol also allowed patients more days without recourse to salbutamol use and able to undertake usual activities compared with salmeterol.

FEV_1 was chosen as the primary endpoint in order to meet regulatory requirements for a clinical study aimed to support registration of a bronchodilator treatment for COPD. The timing of the primary endpoint (12 weeks) also reflected regulatory standards. It may be more relevant to everyday clinical practice to focus on a clinical outcome such as dyspnoea, and the focus on FEV_1 may have reduced the power to investigate the effect of indacaterol on those other endpoints. The study was not powered sufficiently to detect the small reductions in 'days of poor COPD control' that occurred with indacaterol and salmeterol as statistically significant versus placebo. This instrument, although used previously [11,12], has not been validated, and relies on accurate completion of daily diaries. However, the other key secondary variable, SGRQ total score, was robust in showing a marked treatment effect.

Safety and tolerability were similar across the treatment groups, and the greater efficacy and duration of bronchodilator effect of indacaterol was not reflected in any increase in β_2-mediated effects relative to salmeterol. Similar observations were made in a 1-year study employing higher doses (300 μg and 600 μg) of indacaterol [5].

Although bacterial and viral URTI were more frequent with indacaterol treatment, other similar adverse events (e.g. 'URTI', 'rhinitis') occurred more frequently with placebo. In the 1-year study of indacaterol 300 μg and 600 μg [5], bacterial URTI was observed in approximately 6% of patients in both indacaterol groups, compared with 8% in the placebo group. The event rate per patient-year for the overall category 'infections and infestions' was less than 1 in all treatment groups in the present study. An acceptable safety profile is especially important for a treatment designed for chronic use by COPD patients, who tend to be elderly and often have co-morbidities, the most important being cardiovascular conditions, lung cancer and osteoporosis [23–25].

Cough immediately following indacaterol inhalation has been reported previously [26,27], and the observation of cough incidence following inhalation of study drug (as distinct from the recording of cough as an adverse event) was therefore pre-specified in the present study. The cough following inhalation was fairly common but did not appear troublesome to patients. It did not result in any loss of efficacy (comparison of the change from baseline in trough FEV_1 showed similar or greater increases in patients who coughed compared with those who did not), nor was it associated with bronchoconstriction or withdrawal from the study.

This and other comparative studies show that indacaterol is a more effective bronchodilator than salmeterol and the other twice-daily β_2-agonist, formoterol [5], and that it may prove to be at least as effective as the once-daily anticholinergic bronchodilator, tiotropium [4]. They also show that indacaterol improved health status and reduced dyspnoea versus placebo and was better than, or at least as effective as, the currently available bronchodilator agents in respect of improving clinical

outcomes [4,5]. The findings of early-morning bronchodilation with sustained reduction in dyspnoea and improved health status are important for the lives of patients with COPD and suggest that once-daily indacaterol will be a useful additional option for treating this disabling condition.

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TABLE 1 Disposition of patients (n, %) during the study

	Indacaterol	Salmeterol	Placebo
Randomized	333 (100.0)	334 (100.0)	335 (100.0)
Treated	330 (99.1)	333 (99.7)	335 (100.0)
Completed	289 (86.8)	284 (85.0)	265 (79.1)
Discontinued	44 (13.2)	50 (15.0)	70 (20.9)
Primary reason for premature discontinuation			
Adverse event(s)	18 (5.4)	16 (4.8)	13 (3.9)
Protocol deviation	9 (2.7)	11 (3.3)	13 (3.9)
Subject withdrew consent	8 (2.4)	12 (3.6)	22 (6.6)
Abnormal lab value(s)	2 (0.6)	1 (0.3)	2 (0.6)
Abnormal test procedure result(s)	2 (0.6)	1 (0.3)	1 (0.3)
Lost to follow-up	2 (0.6)	5 (1.5)	2 (0.6)
Unsatisfactory therapeutic effect	1 (0.3)	2 (0.6)	15 (4.5)
Administrative problems	1 (0.3)	1 (0.3)	0
Death	1 (0.3)	0	3 (0.9)
Patient's inability to use the device	0	1 (0.3)	0
Intention-to-treat population	330 (99.1)	333 (99.7)	335 (100.0)
Safety population	330 (99.1)	333 (99.7)	335 (100.0)

TABLE 2 Demographics and baseline characteristics

	Indacaterol (N=330)	Salmeterol (N=333)	Placebo (N=335)
Age, years	63 (8.7)	63 (9.2)	64 (8.6)
Male/female, %	72/28	75/25	77/23
Duration of COPD, years	6.5 (5.7)	6.4 (5.7)	6.6 (5.8)
Ex-smoker/smoker, %	54/46	54/46	55/45
Smoking history, pack-years	40 (17.0)	40 (16.7)	41 (18.9)
ICS use, %	45	46	40
FEV_1, L[a]	1.5 (0.49)	1.5 (0.49)	1.5 (0.47)
FEV_1, % predicted[a]	54 (14.0)	53 (13.6)	53 (14.2)
FEV_1/FVC[a]	0.5 (0.10)	0.5 (0.10)	0.5 (0.11)
Reversibility to salbutamol, %	12 (15.3)	11 (13.9)	13 (16.4)
SGRQ total score	43 (18.6)	44 (18.4)	44 (18.1)
BDI score	6.8 (2.1)	6.6 (2.2)	6.6 (2.0)
Salbutamol use, puffs/day	3.2 (3.6)	3.1 (3.4)	3.2 (3.2)

Data are mean (SD) unless otherwise stated. SGRQ = St George's Respiratory Questionnaire. BDI = baseline dyspnoea index.

[a]Post-salbutamol.

TABLE 3 Health status responder analysis: percentage of patients achieving minimal clinically important difference (MCID) in SGRQ score (≥4-point increase) and odds ratios versus placebo for likelihood of achieving the MCID

Week	Placebo	Indacaterol			Salmeterol		
	%	%	Odds ratio (95% CI)	p<	%	Odds ratio (95% CI)	p<
4	38.9	46.9	1.48 (1.04, 2.11)	0.05	46.0	1.46 (1.02, 2.09)	0.05
8	41.5	53.9	1.78 (1.26, 2.51)	0.001	48.7	1.45 (1.03, 2.05)	0.05
12	39.1	57.9	2.41 (1.69, 3.42)	0.001	46.8	1.52 (1.06, 2.16)	0.05
26	38.0	52.8	1.96 (1.37, 2.81)	0.001	48.6	1.72 (1.19, 2.48)	0.01

Odds ratios and p-values are for comparisons between active and placebo treatments.

TABLE 4 Symptom-related outcomes and PEF over 26 weeks

	Placebo	Indacaterol	Salmeterol
Change from baseline in as-needed salbutamol use, puffs/day	−0.3 (0.16)	−1.3 (0.16)***	−1.2 (0.16)***
Days with no as-needed salbutamol use, %	42.2 (2.59)	59.7 (2.58)***†	54.7 (2.58)***
Change from baseline in morning PEF, L/min	−0.8 (2.74)	25.3 (2.72)***†††	15.2 (2.73)***
Change from baseline in evening PEF, L/min	−2.3 (2.82)	23.4 (2.80)***†††	12.7 (2.80)***
Nights with no awakenings, %	65.3 (1.64)	71.6 (1.61)***	70.8 (1.62)**
Days with no daytime symptoms, %	6.2 (1.13)	10.5 (1.11)**	8.9 (1.11)*
Days able to perform usual activities, %	34.8 (1.77)	42.5 (1.75)***†	38.2 (1.75)

Data are least squares means (SE). Significant differences between treatments: *p<0.05, **p<0.01, **p<0.01, ***p<0.001 vs placebo. †p<0.05, †††p<0.001 vs salmeterol.

Patient numbers evaluated for the different outcomes were 301–304 for placebo, 306–310 for indacaterol and 303–310 for salmeterol.

TABLE 5 Adverse events (overall incidence and most commonly reported[a])

	Indacaterol N=330 n (%)	Salmeterol N=333 n (%)	Placebo N=335 n (%)
Patients with any adverse event(s)	169 (51.2)	152 (45.6)	156 (46.6)
COPD worsening	60 (18.2)	51 (15.3)	65 (19.4)
Nasopharyngitis	24 (7.3)	29 (8.7)	21 (6.3)
Upper respiratory tract infection, bacterial	14 (4.2)	3 (0.9)	5 (1.5)
Upper respiratory tract infection, viral	10 (3.0)	3 (0.9)	7 (2.1)
Lower respiratory tract infection	9 (2.7)	13 (3.9)	8 (2.4)
Back pain	7 (2.1)	12 (3.6)	6 (1.8)

[a]Most common events listed for ≥3% of patients in either indacaterol or salmeterol groups.

FIGURE 1. Differences between active treatments over placebo for trough FEV_1 (***p<0.001 vs placebo; †††p<0.001 for treatment difference for indacaterol vs salmeterol). Dotted line shows pre-specified 120 mL clinically important difference vs placebo. Data are least squares means with 95% CI. Patient numbers analysed at Day 2, Week 12 and Week 26, respectively, were 317, 320 and 300 (indacaterol), 320, 317 and 291 (salmeterol), and 321, 316 and 274 (placebo).

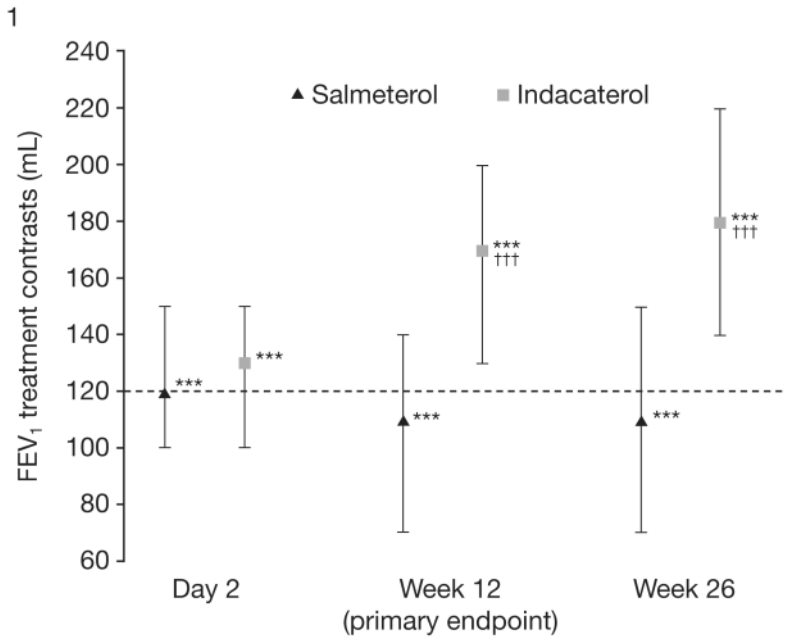

FIGURE 2. Changes from baseline in SGRQ total score. Data are unadjusted means ±SE. Patient numbers analysed at Weeks 4, 8, 12 and 26 were, respectively, 311, 304, 309 and 299 (indacaterol), 302, 300, 301 and 292 (salmeterol), and 298, 294, 294 and 274 (placebo).

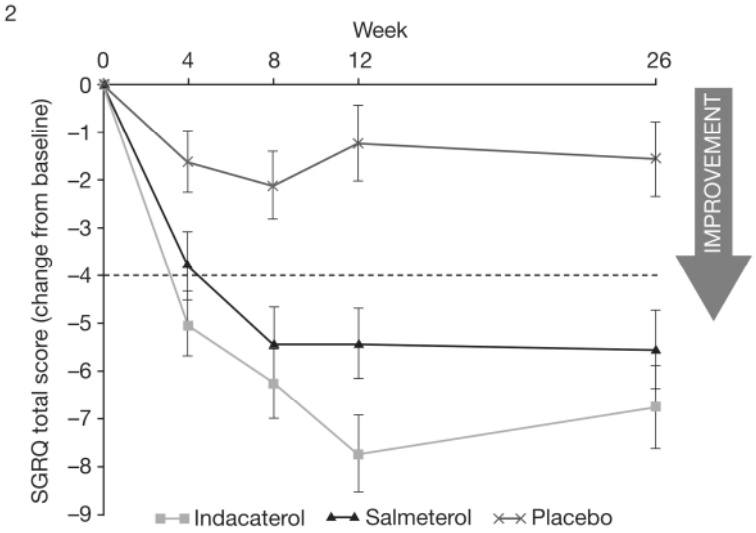

FIGURE 3. Changes from baseline in TDI total score. Data are unadjusted means ±SE. Patient numbers analysed at Weeks 4, 8, 12 and 26 were, respectively, 309, 300, 303 and 297 (indacaterol), 298, 292, 296 and 289 (salmeterol), and 295, 282, 286 and 272 (placebo).