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# Blinded 12-week comparison of once-daily indacaterol and tiotropium in COPD

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Abstract [200 words]

Two once-daily (od) inhaled bronchodilators are available for the treatment of COPD: the $\beta_2$-agonist indacaterol and the anticholinergic tiotropium. This blinded study compared the efficacy of these two agents, and assessed their safety and tolerability.

Patients with moderate-to-severe COPD were randomized to treatment with indacaterol 150 µg od (n=797) or tiotropium 18 µg od (n=801) for 12 weeks.

After 12 weeks, the two treatments had similar overall effects on 'trough' (24 h post-dose) $FEV_1$. Indacaterol-treated patients had greater improvements in transition dyspnoea index (TDI) total score (least squares means 2.01 vs 1.43; $p<0.001$) and St George's Respiratory Questionnaire (SGRQ) total score (least squares means 37.1 vs 39.2; $p<0.001$; raw mean change from baseline –5.1 vs –3.0), and were significantly more likely to achieve clinically relevant improvements in these end-points (odds ratios for indacaterol vs tiotropium of 1.49 for TDI and 1.43 for SGRQ, both $p<0.001$).

Adverse events were recorded for 39.7% and 37.2% of patients in the indacaterol and tiotropium treatment groups, respectively; the most frequent adverse events were COPD worsening, cough and nasopharyngitis.

Both bronchodilators demonstrated spirometric efficacy. The two treatments were well tolerated with similar adverse event profiles. Compared with tiotropium, indacaterol provided significantly greater improvements in clinical outcomes.

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Key words: chronic obstructive pulmonary disease; indacaterol; tiotropium

[3463 words]

## Introduction

Bronchodilators are central to the symptomatic management of patients with COPD [1]. While short-acting bronchodilators are useful for acute symptom relief as needed, the inhaled long-acting bronchodilators are recommended as first-line maintenance treatment for patients with moderate or more severe COPD on the basis of long-term improvements that can be achieved in clinical outcomes such as dyspnoea, health status and exacerbations [1]. Two once-daily inhaled bronchodilators are now available: the anticholinergic, tiotropium, and, more recently, indacaterol, a long-acting (24 h) $\beta_2$-agonist. Indacaterol is approved for use in many countries, including the EU, at doses of 150 and 300 μg once daily.

Two clinical studies comparing indacaterol with tiotropium have been reported to date. In a 26-week study, Donohue and colleagues demonstrated that indacaterol was at least as effective as tiotropium as a bronchodilator and was similarly or more effective for a number of symptomatic and health status end-points. Tiotropium treatment was not blinded in that study [2]. A short-term blinded comparison of indacaterol with tiotropium supported Donohue and colleagues' finding of similar bronchodilator efficacy [3]. Both studies were placebo-controlled. The present investigation is the first blinded study designed with the primary end-point of comparing indacaterol with tiotropium; the aim was to demonstrate that indacaterol had a similar, and potentially superior, efficacy profile compared with tiotropium over 12 weeks of treatment. Safety and tolerability were also assessed.

# Methods

## Patients

The study enrolled male and female adults aged at least 40 years, with a diagnosis of moderate to severe COPD (post-bronchodilator [salbutamol 400 μg] $FEV_1$ <80% and ≥30% predicted; $FEV_1$/FVC <70%) [4] and a smoking history of ≥10 pack-years. Patients with a history of asthma, or a recent COPD exacerbation or respiratory infection, were not included. The patients gave their written informed consent before any study procedure was performed.

## Study design

This was a 12-week, multicentre, randomized, parallel-group, blinded, double-dummy study. The protocol was approved by the institutional review boards or ethics committees at each of the participating centres (respiratory out-patient clinics, physician's offices and clinical research centres).

## Study medications

Following a 2-week run-in, patients were randomized to treatment with indacaterol 150 μg taken once daily (od) via single-dose dry powder inhaler (Onbrez® Breezhaler®; Novartis, Basel, Switzerland) or tiotropium 18 μg od via its proprietary single-dose dry powder inhaler (Spiriva® HandiHaler®; Boehringer Ingelheim, Ingelheim, Germany). Patients receiving indacaterol also took placebo via the inhaler used for tiotropium, and patients receiving tiotropium took placebo via the inhaler used for indacaterol. Blinding was achieved by specifying that study medications were dispensed by a third party not involved in other aspects of the study.

Patients were also given a short-acting $\beta_2$-agonist (salbutamol) to use as required to relieve symptoms. Apart from study treatments, no other bronchodilator use was permitted. Long-acting bronchodilators were discontinued prior to the run-in with an appropriate washout (7 days for tiotropium and theophylline; 2 days for salmeterol or formoterol). Patients previously receiving inhaled corticosteroid (ICS) monotherapy continued this treatment unchanged; any patients on a fixed-dose ICS and $\beta_2$-agonist combination were switched to the ICS component at equivalent dose and regimen.

## Objectives, assessments and outcome measures

The primary objective was to demonstrate non-inferiority of indacaterol to tiotropium in their effect on 'trough' $FEV_1$ (mean of 23 h 10 min and 23 h 45 min post-dose measurements) after 12 weeks of treatment. For each assessment, three acceptable manoeuvres were performed and the highest values of $FEV_1$ and FVC recorded. Spirometry was performed according to recognized standards [5], with the same personnel and equipment for each patient during the study as far as possible. All sites were supplied with the same make and model of spirometer (Vitalograph), and all persons performing spirometry testing were certified in the use of the supplied equipment before use. In addition, all spirometry assessments were reviewed centrally to ensure the manoeuvres met the standards for acceptability and repeatability.

If non-inferiority for trough $FEV_1$ was shown, the comparison was also to be tested for superiority of indacaterol to tiotropium. Secondary end-points were as follows. $FEV_1$ and FVC were measured at other time points. Dyspnoea was assessed by the transition dyspnoea index (TDI) total score at week 12 ($\geq$1 point is a clinically relevant change from baseline) [6,7]. Health status was assessed by St George's Respiratory

Questionnaire (SGRQ) score after 12 weeks (≥4 units is a clinically relevant change from baseline) [8–10]. The use of as-needed ('rescue') salbutamol over 12 weeks was recorded daily by patients in an electronic diary. The diary was also used to record the percentages of days with no COPD symptoms, nights with no awakenings and days of usual activities.

Safety and tolerability were assessed by adverse events and the incidence of notable values for vital signs, Fridericia's correction of QT interval (QTc interval) measured from ECGs, reduced levels of serum potassium (<3.0 mmol/L) and elevated blood glucose (>9.99 mmol/L) measured at any time post-baseline (blood samples were taken pre-dose and ECG and vital signs measured 30 min post-dose after 4 and 12 weeks).

## Randomization and blinding

Patients were randomized in a 1:1 ratio, and stratified by smoking status (current/ex-smoker). The order of use of the inhalers was randomly assigned. The assigned study treatment was dispensed to patients by a third party who was not otherwise involved in the study. Patients, who were blinded to treatment assignment, self-administered their treatment at each visit. Investigators, study staff performing the assessments and data analysts were blinded and did not observe the actual treatment patients took at clinic visits.

## Statistical methods

Three patient populations were defined for analysis. The full analysis (intention-to-treat) population comprised randomized patients who received at least one dose of study drug, and was analysed according to the allocated treatment group. The per-protocol population included patients in the full analysis population who did not have major

protocol deviations and was analysed according to treatment received. The safety population comprised patients who received at least one dose of study drug, analysed according to treatment received.

The primary variable was analysed using a mixed-model analysis of covariance (ANCOVA), with treatment, smoking status and country as fixed effects, centre nested within country as a random effect, and baseline $FEV_1$, $FEV_1$ reversibility components (assessed at screening) and ICS use as covariates. Missing values were imputed by carrying forward the last observation. Results are presented as least squares means (LSM) with standard errors for group mean values and the 95% confidence intervals for the difference between treatments. Non-inferiority of indacaterol to tiotropium was demonstrated if the 95% confidence interval for the mean $FEV_1$ difference of indacaterol minus tiotropium was entirely to the right of (higher than) −55 mL in the per-protocol population. If non-inferiority was determined, superiority could be demonstrated in the full analysis population if (in the full analysis population) $p<0.05$ (two-sided) and the 95% CI was entirely to the right of 0 mL. In a pre-planned analysis, the primary variable was also compared in subgroups of patients categorized according to their baseline age, sex, smoking history, COPD severity, ICS use and salbutamol $FEV_1$ reversibility.

The secondary variables were analysed using a mixed model similar to that used for the primary end-point, although for the full analysis set, with appropriate baseline measurements as covariates and without adjustment for multiplicity. Values for missing TDI and SGRQ total scores were imputed by carrying forward the last observation. The proportions of patients achieving a clinically important improvement in TDI total scores and SGRQ total scores were analysed using a logistic regression model with terms for

treatment, smoking status and country as fixed effects and centre nested within country as a random effect, and with $FEV_1$ reversibility, ICS use and baseline dyspnoea index (BDI) or SGRQ scores as covariates. Results are given as estimated adjusted odds ratios with 95% confidence intervals and two-sided p-values. Results were also summarized as unadjusted (raw) mean changes from baseline. Data for the exploratory variables of diary records (percentages of days with no COPD symptoms, nights with no awakenings and days of usual activities) were summarized and not analysed statistically.

Previous study results provided an assumed treatment difference (indacaterol−tiotropium) of 40 mL for trough $FEV_1$ at Week 12 [2], with a standard deviation of 225 mL [2,11,12]. A sample size of 666 evaluable patients per treatment group was needed to detect this difference as statistically significant at the 5% level (two-sided) with 90% power. This sample size provided >99% power for detecting non-inferiority at the 2.5% significance level (one-sided), assuming a non-inferiority margin of 55 mL (this being half the confidence interval associated with the published treatment difference between tiotropium and placebo [13]). An assumed drop-out rate of 15% gave a minimum sample size of 1568 patients.

## Results

The disposition of the patients is shown in Table 1, with baseline demographics and other characteristics presented in Table 2. Most patients (95%) were Caucasian. Most patients had moderate (62%) or severe COPD (37%). All calculations to determine the severity of COPD in patients at screening were performed at study centres. After database lock, COPD severity was derived using a standardized statistical calculation. This resulted in one patient (in the tiotropium group) being re-classified as having mild

COPD, 13 as having very severe COPD (five in the indacaterol group and eight in the tiotropium group), and two as having a post-bronchodilator $FEV_1$/FVC ratio ≥70% (both in the indacaterol group).

## Spirometry

Trough $FEV_1$ at Week 12 was 1.44 L with indacaterol and 1.43 L with tiotropium. The confidence intervals for the rounded treatment difference (0 mL; 95% CI −20, 20 mL) in the per-protocol population met the pre-defined criteria for non-inferiority ($p<0.001$). Subsequent criteria for superiority in terms of trough $FEV_1$ at Week 12 were not met. The corresponding raw mean changes from baseline in trough $FEV_1$ were 130 mL (11.1%) and 120 mL (10.6%) with indacaterol and tiotropium, respectively.

Trough $FEV_1$ at Week 12 in patient subgroups of the intent-to-treat population, analysed according to baseline age, sex, smoking history, COPD severity, ICS use and salbutamol reversibility, are shown in **Table 3**.

A formal calculation of trough FVC was not made. However, for FVC values at 23 h 10 min and 23 h 45 min post-dose at Week 12 (the two time points used in determination of trough $FEV_1$), there was no difference between treatments, with values of 2.83 and 2.84 L for indacaterol and tiotropium at 23 h 10 min, and 2.89 and 2.90 L at 23 h 45 min post-dose.

At 5 minutes after the first dose on Day 1, $FEV_1$ (least squares mean) was 70 mL (95% CI 60, 80) higher with indacaterol than with tiotropium ($p<0.001$). The least squares mean treatment difference remained statistically significant at 30 min (30 mL [95% CI 20, 40], $p<0.001$) and 1 h (20 mL [95% CI 0, 30], $p<0.01$) post-dose. FVC followed a similar pattern, and was significantly higher with indacaterol than with tiotropium at post-dose time points of 5 min (120 mL [95% CI 100, 140], $p<0.001$), 30 min (40 mL

[20, 70], p<0.001), 1 h and 2 h (both 30 mL [10, 60], p<0.05). The adjusted between-treatment differences at 5 min post-dose at Week 12 (10 mL in $FEV_1$, 20 mL in FVC) were not statistically significant, since the immediate bronchodilator effect occurred when the previous doses of treatment were still providing effective bronchodilation, as illustrated by the raw mean change from baseline data in Figure 1.

## Clinical outcomes: symptoms, health status and diary card data

TDI total scores at Week 12 showed a greater reduction in dyspnoea with indacaterol than with tiotropium (2.01 [SE 0.178] and 1.43 [SE 0.178] points, respectively; p<0.001 for the treatment difference of 0.58). Similarly, patients taking indacaterol were significantly more likely (odds ratio 1.49; p<0.001) to achieve a clinically relevant improvement in dyspnoea (Figure 2).

SGRQ total scores at Week 12 demonstrated better health status with indacaterol than with tiotropium (37.1 [SE 0.56] and 39.2 [SE 0.55] units, respectively; treatment difference −2.1, p<0.001). Raw mean changes (improvements) from baseline were −5.1 [SD 12.06] with indacaterol and −3.0 [SD 11.64] with tiotropium. The analysis of the proportion of patients with a clinically relevant improvement in SGRQ total score (≥4 units) showed that this was statistically significantly more likely to be achieved with indacaterol than with tiotropium treatment (odds ratio 1.43; p<0.001) (Figure 2).

Indacaterol-treated patients reduced their daily, daytime and night-time use of rescue salbutamol more than those receiving tiotropium (p<0.001) and had a higher proportion of days without any rescue use (p=0.004) (Table 4). Diary data showed that during the 12-week study the indacaterol- and tiotropium-treated patients had, respectively, increases from baseline of 2.0 and 1.9 in the percentage of days with no daytime COPD

symptoms, 7.5 and 4.6 in the percentage of nights with no awakenings, and 6.2 and 3.1 in the percentage of days able to undertake usual activities.

## Safety

Adverse events were reported for similar proportions of patients in the two treatment groups (Table 5), with the most common events generally reflecting the typical disease characteristics of COPD. The incidence of COPD worsening was 10.7% with indacaterol and 8.3% with tiotropium; most cases were mild or moderate in severity with both treatments (92% [78/85] with indacaterol and 89% [59/66] with tiotropium). Serious adverse events occurred in 2.8% of indacaterol-treated patients and in 3.8% of the tiotropium treatment group. The system organ class most commonly affected was 'respiratory, thoracic and mediastinal', reported in 1.0 and 1.3% of the indacaterol and tiotropium groups, respectively (most of these events were COPD worsening, which includes exacerbations). The only other system organ class with ≥1.0% of patients affected in either group was 'infections and infestations' (generally respiratory tract infections), reported in 0.9% and 1.0% of the indacaterol and tiotropium treatment groups, respectively.

Two patients died during the study, both in the tiotropium treatment group. One 62-year-old man with a medical history of hypertension died of cardiac arrest due to arrhythmia. The other was a 65-year-old man who died of septic shock due to bilateral nosocomial pneumonia. Neither death was suspected to be related to treatment.

There was little difference between treatment groups for vital signs, plasma potassium and blood glucose and QTc intervals. Few patients in either group had notable values (Table 6).

## Discussion

This study has demonstrated similar efficacy of indacaterol and tiotropium on trough $FEV_1$ after 12 weeks of treatment, with statistical tests establishing non-inferiority of indacaterol compared with tiotropium. Indacaterol had a significantly greater bronchodilator effect than tiotropium during the first hour following dosing. Statistically significantly better results for indacaterol versus tiotropium for the clinical outcomes of dyspnoea, use of as-needed salbutamol and health status were observed.

The magnitude of differences detected as statistically significant varies depending on the size of the study. It is therefore necessary to make a judgement on the clinical relevance of differences between the treatments for the clinical outcomes assessed. This judgement must necessarily be subjective, since reported minimal clinically important differences (MCID) and clinically relevant changes were derived on the basis of differences versus placebo or changes from baseline, not differences between two active treatments [7,9,10].

Dyspnoea and health status are among the most important and robust clinical outcomes in clinical COPD research [14]. Dyspnoea is the most disabling symptom for COPD patients [15]. TDI is a widely used, multidimensional instrument that measures breathlessness related to activities of daily living, and reflects changes in dyspnoea over time and/or in response to treatment [16]. The TDI total scores recorded here indicate clinically relevant improvements from baseline in dyspnoea with both treatments, but the additional effect of indacaterol (difference of 0.58 over an established bronchodilator) represents a degree of relief of breathlessness during activities of daily living that may benefit patients with COPD. In addition, patients treated with

indacaterol had a 49% greater likelihood of experiencing a clinically relevant improvement compared with those receiving tiotropium.

The SGRQ assesses changes over time in health status in patients with COPD. The accepted MCID for this measure is a reduction in total score of 4 units from baseline [10], with a tolerance range of 2.4–5.6 [14]. The mean change for indacaterol exceeded the MCID in this study (−5.1 change from baseline). The result for tiotropium (−3.0 from baseline) is similar to previous reports over longer periods (−3.3 at 6 months [17] and −2.3 to −3.3 units over 4 years [18]), although other, smaller studies have reported changes from baseline of 4 units at 6 months [19]. The additional improvement of more than 2 units following treatment with indacaterol seen in this study is close to the tolerance range limit of 2.4 reported by Cazzola and colleagues and is likely to represent a perceptible difference in patients' health status. Compared with tiotropium, indacaterol-treated patients had a 43% greater likelihood of achieving a clinically relevant improvement in health status.

Patients with COPD are usually given a short-acting bronchodilator with a fast onset (e.g. salbutamol) to use to relieve acute symptoms, e.g. exertional dyspnoea. The level of use is reported to correlate with COPD symptoms [20]. Measuring a patient's use of 'rescue' medication reflects the effectiveness of maintenance COPD treatment in achieving clinical control. A greater reduction in rescue use with indacaterol over tiotropium was seen (more than half a puff per day), with patients on indacaterol experiencing an additional 5% of days when no rescue use was needed. This would equate to an additional 17.5 days per year with no requirement for rescue use.

Overall, the effects on clinical outcomes in the present study (indacaterol–tiotropium differences of 0.58 points in TDI total score, −2.1 units in SGRQ total score and −0.54

puffs/day of salbutamol, all $p<0.001$) are of a similar order to those previously reported for tiotropium in comparison with salmeterol (differences at 6 months of 0.78 in TDI total score, −1.6 in SGRQ total score, but no difference in rescue use) [21]. Analogously, indacaterol may represent a further therapeutic advance over tiotropium. The present results also support and extend those of a previous 6-month study of indacaterol versus tiotropium in which tiotropium was administered unblinded [2]. The closely similar effect of treatments on trough $FEV_1$ indicates that this study is a comparison of equipotent bronchodilator doses and demonstrates true superiority of indacaterol in its effect on clinical outcomes. Indacaterol had statistically significantly greater effects on dyspnoea, rescue salbutamol use and health status. However, the mechanistic reasons for these differences are not obvious. There may be differences between indacaterol and tiotropium in their effect on overall lung volume, despite the similarity of FVC results, and it would be interesting to compare effects on inspiratory capacity. The two drugs may have differential bronchodilator effects on small airways, possibly due to regional variation in airway distribution of muscarinic and adrenergic receptors [22], leading to differing non-bronchodilator effects on lung ventilation and pulmonary haemodynamics [23]. A range of non-bronchodilator, generally anti-inflammatory effects has been postulated for long-acting $\beta_2$-agonists in COPD [24], although the clinical relevance of these remains to be established. In terms of $FEV_1$, it seems likely that the similar magnitude of response achieved with indacaterol and tiotropium represent the full bronchodilator potential of $\beta_2$-agonists and anticholinergics, respectively, and that further improvements will be possible by combining both therapeutic principles, ideally as a fixed combination [25].

The small differential in bronchodilator effect in patient subgroups of differing disease severities may also reflect mechanistic differences between the two bronchodilators, or may reflect shortcomings in $FEV_1$ as a single measure of treatment effect in a heterogeneous condition such as COPD [15]. While potentially interesting, the actual differences of 30–40 mL are very small and well below the 100–140 mL level of clinical relevance [14]. Elsewhere, indacaterol has been reported to have a similar effect in patients with differing COPD severities [12].

The present study has advantages over previous reported comparisons of indacaterol and tiotropium, being larger and more robustly blinded than the previous 6-month study with unblinded tiotropium [2], and larger and longer than the previous 2-week double-blind study [3]. In terms of blinding of the present study, study drugs were dispensed by a third party who was not otherwise involved in the study and, because this was a parallel-group study, no patient received both active and placebo tiotropium.

The improvements in clinical outcomes observed during treatment with indacaterol were obtained without any increase in side-effects or other safety signals compared with tiotropium. Comparable safety of these two treatments was also observed in the previous 6-month open-label comparison [2], and indacaterol has previously demonstrated an acceptable tolerability and safety profile with the 300 μg and the above-therapeutic 600 μg doses given for up to 1 year compared with placebo [12]. These results overall present a reassuring safety profile for this new bronchodilator.

In conclusion, we believe that indacaterol may provide more symptomatic benefit than tiotropium and, as such, extends the therapeutic options for patients with COPD.

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**Table 1.** Disposition of patients (n, %)

| | Indacaterol | Tiotropium | Total |
|---|---|---|---|
| Screened | – | – | 2558 |
| Randomized | 797 (100.0) | 801 (100.0) | 1598 (100.0) |
| Exposed | 794 (99.6) | 799 (99.8) | 1593 (99.7) |
| Completed | 737 (92.5) | 740 (92.4) | 1477 (92.4) |
| Discontinued | 60 (7.5) | 61 (7.6) | 121 (7.6) |
| Adverse event(s) | 31 (3.9) | 27 (3.4) | 58 (3.6) |
| Subject withdrew consent | 8 (1.0) | 7 (0.9) | 15 (0.9) |
| Protocol deviation | 8 (1.0) | 11 (1.4) | 19 (1.2) |
| Administrative problems | 5 (0.6) | 4 (0.5) | 9 (0.6) |
| Abnormal test procedure result(s) | 3 (0.4) | 0 (0.0) | 3 (0.2) |
| Abnormal laboratory value(s) | 2 (0.3) | 4 (0.5) | 6 (0.4) |
| Lost to follow-up | 2 (0.3) | 3 (0.4) | 5 (0.3) |
| Unsatisfactory therapeutic effect | 1 (0.1) | 3 (0.4) | 4 (0.3) |
| Death | 0 (0.0) | 2 (0.2) | 2 (0.1) |
| Analysed for safety | 794 (99.6) | 799 (99.8) | 1593 (99.7) |
| Analysed for efficacy (full analysis set) | 794 (99.6) | 799 (99.8) | 1593 (99.7) |
| Analysed for efficacy (per-protocol set) | 599 (75.2) | 624 (77.9) | 1223 (76.5) |

**Table 2.** Demographics and baseline characteristics

| | Indacaterol N=794 | Tiotropium N=799 |
|---|---|---|
| Age (years) | 63.6 (8.60) | 63.4 (8.29) |
| Male/female (%) | 70/30 | 67/33 |
| Duration of COPD, years | 7.0 (6.01) | 7.0 (6.32) |
| ICS use, % | 54 | 56 |
| Ex-smoker/smoker, % | 55/45 | 56/44 |
| Smoking history, pack-years | 43.2 (20.87) | 41.8 (19.81) |
| $FEV_1$ post-bronchodilator, L | 1.53 (0.459) | 1.52 (0.447) |
| $FEV_1$ reversibility, % | 14.1 (12.63) | 13.7 (13.44) |
| $FEV_1$ % predicted (post-bronchodilator) | 54.6 (12.80) | 54.3 (12.81) |
| $FEV_1$/FVC post-bronchodilator | 51.0 (9.38) | 51.2 (9.42) |
| Use of as-needed salbutamol, puffs/day | 3. 8 (3.74) | 3.6 (3.51) |
| BDI score | 6.8 (2.2) | 6.8 (2.23) |
| SGRQ score | 42.3 (17.60) | 42.7 (18.04) |

Data are mean (SD) unless otherwise stated.

**Table 3.** Trough $FEV_1$ at Week 12 in all patients (primary endpoint) and in patient subgroups divided according to baseline age, sex, smoking history, COPD severity, ICS use and salbutamol reversibility

| | Indacaterol mean (SE) | Tiotropium mean (SE) | Indacaterol−tiotropium difference, mean (95% CI) | p-value for non-inferiority | p-value for superiority |
|---|---|---|---|---|---|
| *All patients (per-protocol population):* | | | | | |
| | 1.44 (0.010) | 1.43 (0.010) | 0.00 (−0.02, 0.02) | <0.001 | 0.850 |
| *Patient subgroups (intent-to-treat population):* | | | | | |
| Age (years): | | | | | |
| <65 | 1.44 (0.011) | 1.45 (0.011) | 0.00 (−0.03, 0.02) | <0.001 | 0.774 |
| ≥65 | 1.44 (0.012) | 1.43 (0.012) | 0.01 (−0.02, 0.04) | <0.001 | 0.420 |
| Sex: | | | | | |
| Male | 1.44 (0.010) | 1.44 (0.010) | 0.00 (−0.02, 0.02) | <0.001 | 0.987 |
| Female | 1.44 (0.015) | 1.43 (0.014) | 0.01 (−0.03, 0.04) | <0.001 | 0.659 |
| Smoking status | | | | | |
| Ex-smoker | 1.45 (0.011) | 1.46 (0.011) | −0.01 (−0.04, 0.01) | <0.001 | 0.409 |
| Current smoker | 1.44 (0.012) | 1.42 (0.012) | 0.02 (−0.01, 0.05) | <0.001 | 0.177 |
| COPD severity: | | | | | |
| Moderate or less | 1.45 (0.011) | 1.42 (0.011) | 0.03 (0.01, 0.05) | <0.001 | 0.013 |
| Severe or very severe | 1.42 (0.014) | 1.47 (0.013) | −0.04 (−0.07, −0.01) | 0.215 | 0.007 |
| ICS use: | | | | | |
| No | 1.46 (0.012) | 1.44 (0.012) | 0.02 (−0.01, 0.04) | <0.001 | 0.244 |
| Yes | 1.43 (0.011) | 1.44 (0.011) | −0.01 (−0.03, 0.02) | <0.001 | 0.495 |
| Reversibility to salbutamol: | | | | | |
| ≤12% | 1.43 (0.012) | 1.42 (0.012) | 0.01 (−0.02, 0.03) | <0.001 | 0.631 |

| | | | | | |
|---|---|---|---|---|---|
| >12% | 1.46 (0.013) | 1.46 (0.013) | 0.00 (−0.03, 0.03) | <0.001 | 0.948 |

**Table 4.** Use of as-needed salbutamol ('rescue') over 12 weeks

| | Indacaterol (mean, SE) | Tiotropium (mean, SE) | Difference (mean, 95% CI) | p-value for difference |
|---|---|---|---|---|
| Change from baseline in mean daily number of rescue puffs | −1.40 (0.097) n=740 | −0.85 (0.097) n=747 | −0.54 (−0.75, −0.33) | <0.001 |
| Change from baseline in mean daytime number of rescue puffs | −0.90 (0.063) n=722 | −0.59 (0.063) n=732 | −0.32 (−0.45, −0.19) | <0.001 |
| Change from baseline in mean night-time number of rescue puffs | −0.52 (0.043) n=729 | −0.28 (0.042) n=742 | −0.24 (−0.34, −0.14) | <0.001 |
| Percentage of days with no rescue use | 46.1 (1.65) n=725 | 41.4 (1.64) n=738 | 4.8 (1.5, 8.0) | 0.004 |

**Table 5.** Adverse events overall and most commonly occurring (≥2% of patients)

| | Indacaterol (n=794) | Tiotropium (n=799) |
|---|---|---|
| Any adverse event (% of patients) | 315 (39.7) | 297 (37.2) |
| COPD worsening (including exacerbations) | 85 (10.7) | 66 (8.3) |
| Cough | 37 (4.7) | 27 (3.4) |
| Nasopharyngitis | 36 (4.5) | 37 (4.6) |
| Headache | 24 (3.0) | 24 (3.0) |
| Influenza | 19 (2.4) | 16 (2.0) |
| Bronchitis | 16 (2.0) | 7 (0.9) |

**Table 6.** Proportions of patients with notable values for plasma potassium, blood glucose, pulse rate, blood pressure and QTc interval (Fridericia's)

| | Indacaterol | Tiotropium |
|---|---|---|
| Plasma potassium <3.0 mmol/L | 0/778 | 0/776 |
| Blood glucose >9.99 mmol/L | 26/778 (3.3) | 20/776 (2.6) |
| Pulse rate – high[†] | 2/792 (0.3) | 0/799 |
| Systolic blood pressure – high[‡] | 7/792 (0.9) | 5/799 (0.6) |
| Diastolic blood pressure – high[§] | 6/792 (0.8) | 13/799 (1.6) |
| QTc interval | | |
| Absolute value >450/470 ms (males/females) | 23/793 (2.9) | 25/799 (3.1) |
| Absolute value >500 ms | 0/793 | 1/799 (0.1) |
| Increase 30–60 ms | 36/788 (4.6) | 48/794 (6.0) |
| Increase >60 ms | 2/788 (0.3) | 0/794 |

[†]>130 bpm, or ≥120 bpm and ≥15 bpm increase from baseline; [‡]>200 mmHg, or ≥180 mmHg and ≥20 mmHg increase from baseline; [§]>115 mmHg, or ≥105 mmHg and ≥15 mmHg increase from baseline.

**Figure 1.** Change from baseline in (a) $FEV_1$ and (b) FVC measured up to 4 h post-dose on Day 1. Data are unadjusted means ±SE.

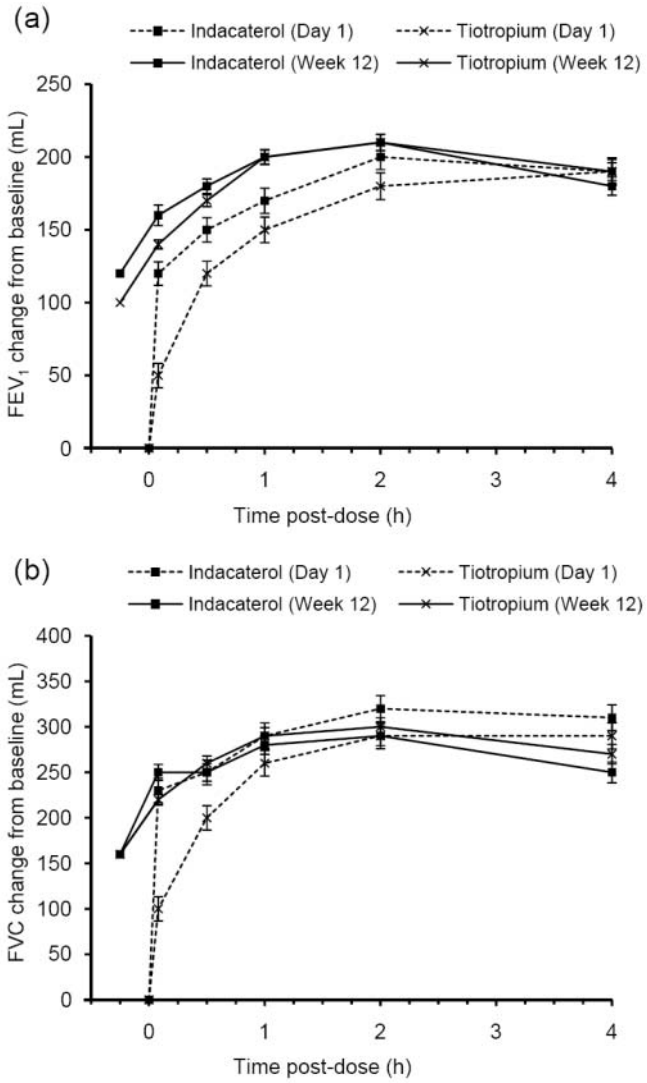

**Figure 2.** Odds ratios for differences between indacaterol and tiotropium in proportions of patients with or exceeding the minimal clinically important difference for TDI total score and SGRQ score. ***p≤0.001, indacaterol vs tiotropium.