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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

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Abstract

In patients with chronic obstructive pulmonary disease (COPD) classified as moderate onwards, Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines recommend regular treatment with one or more long-acting bronchodilators, such as β_2-agonists or anticholinergics. In contrast to currently available long-acting β_2-agonists, which have a duration of action of 12 h, indacaterol has demonstrated effective 24-h bronchodilation on once-daily dosing. A double-blind, randomised, placebo-controlled study was conducted to compare the safety, tolerability and efficacy of indacaterol with that of placebo, over a 28-day period, in patients with moderate COPD (as defined by GOLD 2001 criteria; equivalent to moderate-to-severe COPD in the GOLD 2005 criteria).

Patients were randomised 2:2:1 to receive indacaterol 400 μg or 800 μg or placebo once-daily (between 07:00 and 11:00 h) via a single-dose dry-powder inhaler for 28 days. Assessments included monitoring of adverse events (AEs), blood chemistry (including serum potassium and blood glucose), vital signs (blood pressure and heart rate), electrocardiograms and spirometry.

One hundred and sixty-three patients were randomised, with 155 (95%) completing the study. There were no statistically significant differences between treatment groups in the overall incidence of AEs, with AEs reported by 35%, 51% and 25% of patients in the indacaterol 400 μg, 800 μg and placebo groups, respectively. The majority of AEs were mild or moderate in severity, and there were no study-drug related serious AEs. There were no statistically significant differences between indacaterol groups and placebo in mean pulse rate and QTc interval, and isolated statistically significant ($p<0.05$) treatment-placebo differences in mean blood pressure, blood glucose and serum potassium.

There was a statistically significant improvement in FEV_1 vs placebo at all post-baseline timepoints for both indacaterol treatment groups; 30 min post-dose, adjusted mean ± SE FEV_1 indacaterol-placebo differences were: Day 1, 220 ± 36 ml and 210 ± 36 ml; Day 14, 320 ± 50 ml and 270 ± 50 ml; Day 28, 260 ± 61 ml and 200 ± 61 ml for 400 and 800 μg, respectively (all $p<0.01$ vs placebo). Bronchodilation was still apparent after 24 h, with pre-dose (i.e. trough) adjusted mean ± SE FEV_1 indacaterol-placebo differences of: Day 14, 230 ± 44 ml and 210 ± 44 ml; Day 28, 220 ± 49 ml and 210 ± 49 ml for indacaterol 400 and 800 μg, respectively (all $p<0.0001$ vs placebo).

Once-daily indacaterol was well tolerated at doses up to 800 μg with a good overall safety profile. There was no statistical difference at any dose between the safety of indacaterol and placebo. Furthermore, this study supports the previously demonstrated 24-h bronchodilator efficacy of indacaterol.

Keywords: Indacaterol; β_2-agonist; Bronchodilation; Safety; Tolerability

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by progressive airway obstruction, resulting in airflow limitation that is only partially reversible [1]. COPD represents a major cause of morbidity and mortality worldwide and is therefore associated with high levels of social and economic burden [1]. The global initiative for chronic obstructive lung disease (GOLD), which provides physicians with guidance on appropriate management of COPD, recommends the implementation of a stepwise treatment plan to manage COPD [1]. Central to control of dyspnoea in COPD are bronchodilators, such as β_2-agonists: GOLD guidelines recommend regular treatment with one or more long-acting bronchodilators in patients with moderate-to-severe COPD [1]. Two long-acting β_2-agonists are currently available, formoterol and salmeterol, both of which have approximately 12-h durations of action at recommended doses and therefore must be taken twice daily [2–7]. The only once-daily bronchodilator available at present is the anticholinergic tiotropium, which has a duration of action of at least 24 h [8,9].

Indacaterol is a novel once-daily β_2-agonist being developed for the treatment of COPD and asthma. Preclinical study results suggest that indacaterol has a longer duration of action than either formoterol or salmeterol, with a rapid onset of action, and a potentially greater cardiovascular safety margin compared with formoterol or salmeterol, for a given degree of bronchodilator activity [10]. In clinical studies in patients with asthma, indacaterol has demonstrated effective 24-h bronchodilation with a rapid onset of action and was shown to be well tolerated with a good overall safety profile [11,12].

The primary objective of the current study was to compare the safety and tolerability of once-daily administration of two doses of indacaterol (400 and 800 μg) with that of placebo, over a 28-day period, in patients with moderate COPD. Particular attention was paid to the key safety parameters for this class of drug, namely serum potassium, blood glucose, heart rate, blood pressure, QTc interval and adverse events (AEs) such as tremor, headache and nervousness. A secondary objective was to explore the bronchodilator efficacy of indacaterol, in terms of the effects on lung function.

2. Methods

2.1. Design

This was a phase II, multinational, double-blind, randomised, placebo-controlled, parallel-group study in patients with COPD. Enrolled patients entered a 2-week run-in period and were subsequently randomised to receive 28 days of study treatment, with a 7-day follow-up period to monitor AEs after study-drug cessation. The study was conducted according to Good Clinical Practice Guidelines and in accordance with the Declaration of Helsinki (1964 and subsequent revisions). The study received Institutional Review Board approval, and all patients gave written informed consent prior to the start of the study.

2.2. Inclusion and exclusion criteria

Male and female patients aged 40–75 years with a diagnosis of moderate COPD as defined by the 2001 GOLD Guidelines [13] were eligible for enrolment, provided they had a smoking history of at least 10 pack-years and their forced expiratory volume in one second (FEV_1) was $<70\%$ of their forced vital capacity (FVC). In addition, patients were required to have an FEV_1 30–70% of the Quanjer predicted normal value [14], when measured after a washout period of at least 6 h during which no short-acting β_2-agonist was inhaled, and at least 24 h after the last use of a long-acting β_2-agonist.

Patients were excluded if they had a recent respiratory tract infection or COPD exacerbation, if they had a history of asthma (blood eosinophil count $>500/mm^3$ or an onset of symptoms prior to the age of 40 years), or if they had a significant unstable cardiovascular or metabolic comorbidity. Patients were also excluded if they had used any of the following: tiotropium bromide within 7 days of run-in or ipratropium bromide, inhalers combining inhaled corticosteroids and β_2-agonists, or long-acting β_2-agonists within 24 h of run-in.

2.3. Study treatment

Patients were randomised (2:2:1) to receive indacaterol 400 μg or 800 μg or placebo, once daily via a single-dose dry-powder inhaler. Treatments were administered in the morning (between 07:00 and 11:00 h) via sequential inhalation from two dry powder capsules, each delivering indacaterol 200 μg, 400 μg or placebo, respectively, per capsule. Dose selection was based on a previous study in patients with bronchial asthma where an effective dose was considered to be in the range of 200–400 μg [11]. The present study was therefore designed to examine the safety, tolerability and efficacy of doses considered up to approximately twice the anticipated therapeutic dose for asthma.

Inhaled salbutamol was provided as rescue medication to be used as needed throughout the run-in and treatment periods. Rescue salbutamol was not to be taken within 6 h of the start of a study visit unless necessary. Prior to the run-in period, those patients using long-acting β_2-agonists were permitted regular use of salbutamol for the duration of the run-in period, and for those using inhalers combining inhaled corticosteroids and β_2-agonists, the steroid component was replaced with equivalent inhaled corticosteroid monotherapy. Patients on inhaled corticosteroid monotherapy prior to run-in continued on their pre-study regimen. During the treatment phase, all patients received the same inhaled corticosteroid regimen as they received during the run-in period. Patients were not

permitted to use any of the following medications during the run-in or treatment periods: tiotropium bromide, ipratropium bromide, combination formulations of β_2-agonists and inhaled corticosteroids, long-acting β_2-agonists or short-acting β_2-agonists (other than salbutamol as above). Patients were permitted to use theophyllines during the study in recommended and constant dose regimens, providing treatment had been stabilised for at least 1 month prior to the start of the run-in period. However, such medication was to be withheld on the morning of scheduled clinic visits until after completion of the last spirometry measurement at those visits.

2.4. Assessments

Safety assessments included monitoring of AEs throughout the study and regular monitoring of haematology, blood chemistry (with particular attention to serum potassium and blood glucose), urinalysis, vital signs and electrocardiograms (ECGs). Efficacy assessments included the monitoring of lung function throughout the study.

On Days 1, 14 and 28 of study treatment, the results of the following assessments were recorded pre- and 60 min post-dose: haematology, blood chemistry (including serum potassium and blood glucose), urinalysis, pulse rate, systolic and diastolic blood pressure, and ECGs. Both Bazett's formula ($QTc = QT/\sqrt{RR}$) and Fridericia's formula ($QTc = QT/\sqrt[3]{RR}$) were used to calculate QTc interval.

Spirometry (FEV_1, FVC and forced expiratory flow [$FEF_{25–75\%}$]) was assessed pre- and 30 min post-dose on Days 1, 14 and 28. Pulmonary function tests were evaluated with the use of calibrated spirometry. All pulmonary function testing was performed according to European Respiratory Society standards with the patients in a sitting position. Tests were performed at the same time of day under standard conditions by the same technician in order to ensure consistent technique. Three technically acceptable measurements were performed for each patient and the highest value was used in the analyses. The change and percentage increase in FEV_1 from baseline were compared across the treatment groups. In addition, the use of rescue medication was examined on Days 1, 14 and 28 by asking the patient to provide an estimate of average daily use since the last visit. Records of study medication use, dosages administered and intervals between visits were kept during the study; patients were asked to return all unused medication at the end of the study.

2.5. Statistical analyses

Adverse events which began or worsened between starting study treatment and the end of follow-up were summarised. The incidences of tremor, headache and nervousness, which are recognised AEs for the class of drug, were presented with 95% confidence intervals (computed as exact 95% confidence intervals based on the binomial distribution) for each treatment group.

Key variables (serum potassium, blood glucose, pulse rate, systolic and diastolic blood pressure, QTc interval and FEV_1) were analysed using a two-way analysis of covariance (ANCOVA) model, with country and treatment as factors and the baseline value of the variable as a covariate. The country effect was treated as fixed and interactions or other effects were not investigated. This type of model provided comparisons between treatment groups at each timepoint while adjusting appropriately for any baseline differences in the variable of focus (note that for all variables analysed in this way there were no significant differences at baseline between active groups and placebo). In each case, the ANCOVA model did not employ repeated measures, but rather applied at each timepoint separately.

Spirometry data other than FEV_1 (i.e. FVC and $FEF_{25–75\%}$) were summarised over time, with no additional statistical analyses prespecified. Salbutamol rescue medication was summarised by the average daily number of puffs used between visits, again with no additional statistical analyses pre-specified. Safety variables were analysed using results from the safety population (all randomised patients who received at least one dose of study medication), whereas exploratory efficacy analyses were performed using results from the intent-to-treat population (all randomised patients who received at least one dose of study medication and had at least one post-dose FEV_1 measurement).

3. Results

3.1. Patient characteristics

Patients were recruited from 22 centres in five countries: Belgium, Germany, France, the Netherlands and Slovakia. In total, 253 patients were screened, of whom 163 met the inclusion criteria and were randomised to study treatments; 155 (95%) completed the study. All randomised patients received at least one dose of the study drug. Of the eight patients who did not complete the study, five withdrew because of protocol violations, 2 withdrew because of AEs (see later for further details) and one patient withdrew consent. Patients were almost exclusively Caucasian (99.4%), aged 40–75 years, with a mean duration of COPD of 7 years (Table 1).

Baseline patient demographics, lung function and salbutamol use were well balanced, with no statistically significant differences between treatment groups. Although mean FEV_1 reversibility appeared to be relatively high (mean values ranging between 11.2% and 12.7%), patients with a history of asthma had been excluded from the study. Compliance to treatment was high and similar among treatment groups, with patients in the indacaterol 400 and 800 μg and placebo groups receiving treatment for a

Table 1
Patient demographics and baseline characteristics

Variable	Indacaterol 400 μg ($n = 68$)	Indacaterol 800 μg ($n = 67$)	Placebo ($n = 28$)
Age (years)			
Mean (SD)	59.6 (8.5)	61.2 (8.9)	61.1 (7.0)
Range	41.0–75.0	40.0–75.0	50.0–74.0
Age category (years), *n* (%)			
40–65	47 (69.1)	44 (65.7)	19 (67.9)
66–75	21 (30.9)	23 (34.3)	9 (32.1)
Sex, *n* (%)			
Male	54 (79.4)	51 (76.1)	22 (78.6)
Female	14 (20.6)	16 (23.9)	6 (21.4)
Race, *n* (%)			
Caucasian	68 (100)	66 (98.5)	28 (100)
Oriental	0	1 (1.5)	0
Height (cm), mean (SD)	172.5 (7.5)	171.9 (8.0)	172.4 (7.2)
Weight (kg), mean (SD)	81.4 (17.4)	76.6 (17.9)	78.5 (18.2)
Body mass index, kg/m^2 (SD)	27.3 (5.3)	25.8 (5.2)	26.2 (4.9)
Smoking history, *n* (%)			
Ex-smoker	43 (63.2)	34 (50.7)	16 (57.1)
Current smoker	25 (36.8)	33 (49.3)	12 (42.9)
COPD duration (years), mean (range)			
Mean (SD)	7.3 (6.58)	6.5 (5.94)	7.4 (6.14)
Range	0–28.4	0.2–31.3	1.6–27.2
FEV_1% predicted, mean (SD)	52.1 (10.4)	53.8 (11.0)	53.9 (12.0)
FEV_1% reversibility, mean (SD)	12.7 (10.3)	11.5 (9.7)	11.2 (10.2)
Salbutamol use during run-in phase[a] (puffs/day), *n* (%)			
Missing	0	1 (1.5)	0
None	12 (17.6)	11 (16.4)	3 (10.7)
<1	11 (16.2)	9 (13.4)	4 (14.3)
1–2	12 (17.6)	15 (22.4)	9 (32.1)
3–6	23 (33.8)	24 (35.8)	6 (21.4)
>6	10 (14.7)	7 (10.4)	6 (21.4)

No statistically significant differences between treatment groups.
[a]i.e. between screening and the first treatment visit.

mean ± SD of 27.0 ± 4.7, 26.9 ± 4.5 and 27.1 ± 2.8 days, respectively.

3.2. Safety

The overall AE profile did not suggest any specific toxicity towards a major organ system, and the majority of AEs experienced were mild or moderate in severity. There were no statistically significant differences between treatment groups in the overall AE incidence, with AEs reported by 35.3% (95% CI: 24.1%, 47.8%), 50.7% (38.2%, 63.2%) and 25.0% (10.7%, 44.9%) of patients taking indacaterol 400 and 800 μg and placebo, respectively (Table 2). The most frequent AEs were typical of this patient population (respiratory, thoracic and mediastinal [excluding infections]). Of the AEs that could be considered to be β_2-agonist class effects, there was one case of tremor reported in each of the indacaterol treatment groups and five patients (7.5%) in the 800 μg group reported headache.

The difference between treatment groups in the incidence of AEs was largely due to an increased incidence of cough in the indacaterol groups, reported by 10 (14.7%) and 19 (28.4%) patients in the indacaterol 400 and 800 μg groups, respectively, compared with no patients in the placebo group. The majority of cough events were of mild severity, with onset associated with the initial dose of study medication. The incidence of cough declined at subsequent visits, such that at the final dosing visit (Day 28) no patients in any treatment group coughed after study drug administration.

Three patients (4.4%) in the indacaterol 400 μg group and two (7.1%) in the placebo group (compared to no patients in the indacaterol 800 μg group) experienced an exacerbation of their COPD. One of the events in the indacaterol 400 μg group was classified as a serious AE; this occurred 1 week after the patient finished taking study medication. One of the other patients in the indacaterol 400 μg group withdrew from the study as a result of an exacerbation. None of the COPD exacerbations was considered related to study drug treatment.

Table 2
Number (%) of patients with AEs overall and by primary system organ class (Safety population)

	Indacaterol 400 μg *n* (%)	Indacaterol 800 μg *n* (%)	Placebo *n* (%)
Patients studied			
Total no. of patients	68	67	28
Total no. with AEs	24 (35.3)	34 (50.7)	7 (25.0)
Primary system organ class			
Respiratory, thoracic and mediastinal disorders[a] (excl. infections)	17 (25.0)	20 (29.9)	4 (14.3)
Infections and infestations	4 (5.9)	5 (7.5)	3 (10.7)
Gastrointestinal disorders	3 (4.4)	2 (3.0)	0
Ear and labyrinth disorders	2 (2.9)	0	0
Nervous system disorders	2 (2.9)	6 (9.0)	1 (3.6)
General disorders and administration site conditions	1 (1.5)	3 (4.5)	0
Psychiatric disorders	1 (1.5)	2 (3.0)	0
Skin and subcutaneous tissue disorders	1 (1.5)	1 (1.5)	1 (3.6)
Vascular disorders	1 (1.5)	0	0
Cardiac disorders	0	1 (1.5)	0
Hepatobiliary disorders	0	1 (1.5)	0
Investigations	0	1 (1.5)	1 (3.6)
Musculoskeletal and connective tissue disorders	0	2 (3.0)	0
Renal and urinary disorders	0	1 (1.5)	0

[a]The category of respiratory, thoracic and mediastinal disorders included: chronic obstructive airways disease, exacerbated; cough; dry throat; dyspnoea; dyspnoea, exertional; epistaxis; rhinitis seasonal; throat irritation.

One other AE led to discontinuation. This also occurred in the indacaterol 400 μg group, in which a patient developed a severe throat irritation which was considered to be related to study medication.

3.3. Cardiovascular safety

Pulse rate and blood pressure results are shown in Table 3. There were no statistically significant differences in pulse rate between indacaterol and placebo groups at any timepoint. Mean pulse rate was significantly lower in the indacaterol 400 μg group compared to the indacaterol 800 μg group at 60 min post-dose on Day 14 ($p = 0.015$), and pre-dose on Day 28 ($p = 0.022$; Table 3). High pulse rates (i.e. >90 b.p.m.) were observed in 14.7%, 14.9% and 17.9% of patients in the indacaterol 400 and 800 μg and placebo groups, respectively; no patient had a low pulse rate (i.e. <40 b.p.m.).

The only statistically significant difference between groups in mean systolic blood pressure was seen with indacaterol 800 μg compared with placebo 60 min post-dose on Day 14 ($p = 0.003$; Table 3). For mean diastolic blood pressure, the only statistically significant differences were between indacaterol 400 μg and placebo 60 min post-dose on Day 14 ($p = 0.048$) and between indacaterol 400 and 800 μg pre-dose on Day 28 ($p = 0.029$).

There was no statistically significant difference between treatments in mean QTc interval at any timepoint using either formula (Table 4). Using Bazett's formula, only one patient taking indacaterol 800 μg and one patient taking placebo had an increase in QTc interval >60 ms from baseline. Using Fridericia's formula, one patient in the indacaterol 400 μg group and three in the 800 μg group had QTc interval values above the normal range, and one patient in the 800 μg group had an increase in QTc interval >60 ms from baseline.

3.4. Laboratory variables and haematology

Post-dose on Day 1, but not on subsequent visits, mean serum potassium was significantly lower in the indacaterol 800 μg group compared to the indacaterol 400 μg ($p = 0.031$) and placebo groups ($p = 0.029$; Table 5). One patient in the indacaterol 800 μg group experienced at one timepoint a post-baseline value of 3.4 mmol/l that occurred pre-dose on Day 28.

The only statistically significant difference between groups in mean blood glucose was between indacaterol 800 μg and placebo pre-dose on Day 14 ($p = 0.009$; Table 5). Blood glucose values above the normal range (i.e. >7.7 mmol/l) were reported by five (7.4%), ten (14.9%) and six (21.4%) patients in the indacaterol 400 and 800 μg and placebo groups, respectively.

There was no evidence of any drug- or dose-related effects on the majority of the standard haematological tests in any treatment group, and no haematology-related AEs were reported.

3.5. Efficacy

There was a marked improvement in FEV_1 in both indacaterol treatment groups at all visits, with a statistically significant improvement vs placebo at all post-baseline timepoints ($p < 0.01$) (Fig. 1). Since the pre-dose

Table 3
Cardiovascular assessments (safety population)

	Indacaterol 400 μg ($n = 68$)	Indacaterol 800 μg ($n = 67$)	Placebo ($n = 28$)
Pulse rate (b.p.m.), mean (SD)			
Pre-dose, Day 1 (baseline)	75.0 (13.30)	75.4 (10.04)	76.1 (11.42)
1 h post-dose, Day 1	71.1 (9.96)	72.8 (10.25)	70.2 (8.92)
Pre-dose, Day 14	74.2 (11.96)	75.5 (9.85)	76.4 (14.24)
1 h post-dose, Day 14	71.2 (10.54)†	74.4 (8.88)	71.1 (11.88)
Pre-dose, Day 28	73.4 (12.44)†	76.7 (10.62)	76.2 (10.31)
1 h post-dose, Day 28	72.2 (11.46)	74.2 (8.93)	75.9 (10.09)
Maximum post-baseline	78.7 (12.08)	81.5 (9.84)	80.8 (12.14)
Systolic blood pressure (mmHg), mean (SD)			
Pre-dose, Day 1 (baseline)	129.9 (15.02)	130.6 (17.05)	133.2 (14.21)
1 h post-dose, Day 1	130.8 (15.60)	128.0 (15.02)	134.3 (14.11)
Pre-dose, Day 14	129.7 (16.43)	129.2 (17.59)	133.9 (22.05)
1 h post-dose, Day 14	129.6 (15.94)	126.0 (15.74)*	136.0 (19.38)
Pre-dose, Day 28	132.0 (16.77)	128.8 (17.09)	132.4 (15.61)
1 h post-dose, Day 28	129.6 (15.82)	126.1 (15.50)	131.1 (11.77)
Maximum post-baseline	139.2 (15.30)	137.5 (16.60)	144.4 (16.73)
Diastolic blood pressure, (mmHg), mean (SD)			
Pre-dose, Day 1 (baseline)	79.9 (10.53)	78.7 (10.04)	81.5 (9.73)
1 h post-dose, Day 1	80.4 (9.77)	77.5 (9.04)	80.5 (8.57)
Pre-dose, Day 14	79.2 (11.43)	78.5 (8.88)	81.4 (12.32)
1 h post-dose, Day 14	77.7 (11.01)*	77.1 (8.01)	82.2 (9.63)
Pre-dose, Day 28	80.5 (11.47)†	76.5 (9.02)	79.2 (10.16)
1 h post-dose, Day 28	78.5 (10.14)	75.5 (9.31)	79.3 (8.39)
Minimum post-baseline	74.0 (9.41)	71.9 (8.23)	75.2 (9.48)

*$p < 0.05$ vs placebo.
†$p < 0.05$ vs indacaterol 800 μg.

Table 4
Mean (SD) QTc interval values (using both Bazett's and Fridericia's formulae) (safety population)

	Indacaterol 400 μg ($n = 68$)	Indacaterol 800 μg ($n = 67$)	Placebo ($n = 28$)
QTc interval (Bazett's; ms), mean (SD)			
Pre-dose, Day 1 (baseline)	411.9 (20.15)	416.7 (23.16)	419.4 (22.29)
1 h post-dose, Day 1	408.0 (22.31)	413.1 (23.31)	412.0 (21.11)
Pre-dose, Day 14	412.8 (21.53)	414.9 (26.81)	418.3 (22.54)
1 h post-dose, Day 14	408.9 (21.54)	416.8 (23.17)	414.2 (21.86)
Pre-dose, Day 28	412.1 (19.94)	416.7 (22.75)	421.7 (27.60)
1 h post-dose, Day 28	410.6 (22.39)	411.7 (26.56)	418.1 (22.69)
Maximum post-baseline	424.8 (20.39)	431.8 (20.92)	433.7 (21.51)
QTc interval (Fridericia's; ms), mean (SD)			
Pre-dose, Day 1 (baseline)	401.0 (19.11)	403.1 (19.27)	406.7 (22.01)
1 h post-dose, Day 1	400.8 (20.39)	403.0 (19.22)	404.0 (19.21)
Pre-dose, Day 14	401.8 (19.92)	402.0 (22.60)	404.4 (19.16)
1 h post-dose, Day 14	400.5 (20.67)	404.5 (19.93)	406.2 (21.24)
Pre-dose, Day 28	400.5 (16.45)	402.1 (19.33)	407.8 (24.44)
1 h post-dose, Day 28	401.1 (19.22)	399.2 (22.98)	406.1 (19.65)
Maximum post-baseline	412.6 (19.20)	416.3 (18.30)	419.3 (20.34)

No statistically significant difference between any treatment group at any timepoint.

FEV_1 assessment on Days 14 and 28 was approximately 24 h after inhalation of the previous dose of study medication, this was effectively the 'trough' value, and provided evidence of the duration of action of indacaterol. Pre-dose adjusted mean ± SE FEV_1 improvements compared with placebo on Day 14 were 230 ± 44 ml and 210 ± 44 ml for indacaterol 400 and 800 μg, respectively ($p < 0.0001$ vs placebo for both). Corresponding values on

Table 5
Mean (SD) serum potassium and blood glucose (Safety population)

	Indacaterol 400 μg ($n = 68$)	Indacaterol 800 μg ($n = 68$)	Placebo ($n = 28$)
Serum potassium (mmol/l), mean (SD)			
Pre-dose, Day 1 (baseline)	4.41 (0.414)	4.46 (0.332)	4.42 (0.378)
1 h post-dose, Day 1	4.49 (0.449)	4.41 (0.361)*,†	4.55 (0.371)
Pre-dose, Day 14	4.44 (0.425)	4.36 (0.314)	4.45 (0.324)
1 h post-dose, Day 14	4.44 (0.367)	4.39 (0.417)	4.54 (0.307)
Pre-dose, Day 28	4.45 (0.436)	4.40 (0.372)	4.42 (0.362)
1 h post-dose, Day 28	4.45 (0.409)	4.40 (0.353)	4.42 (0.360)
Minimum post-baseline	4.21 (0.352)	4.16 (0.287)	4.19 (0.244)
Blood glucose (mmol/l), mean (SD)			
Pre-dose, Day 1 (baseline)	5.29 (1.424)	5.10 (1.165)	5.28 (1.203)
1 h post-dose, Day 1	5.37 (1.274)	5.35 (1.447)	5.04 (0.986)
Pre-dose, Day 14	5.36 (1.128)	5.02 (1.142)*	5.78 (1.983)
1 h post-dose, Day 14	5.39 (1.361)	5.14 (0.674)	5.24 (1.425)
Pre-dose, Day 28	5.25 (1.129)	5.33 (1.299)	5.43 (1.223)
1 h post-dose, Day 28	5.31 (1.424)	5.27 (0.883)	5.19 (0.940)
Maximum post-baseline	6.17 (1.667)	6.17 (1.672)	6.15 (2.004)

Central laboratory lower limit of normal for serum potassium was 3.5 mmol/l, and upper limit of normal for blood glucose was 7.77 mmol/l.
*$p < 0.05$ vs placebo.
†$p < 0.05$ vs indacaterol 400 μg.

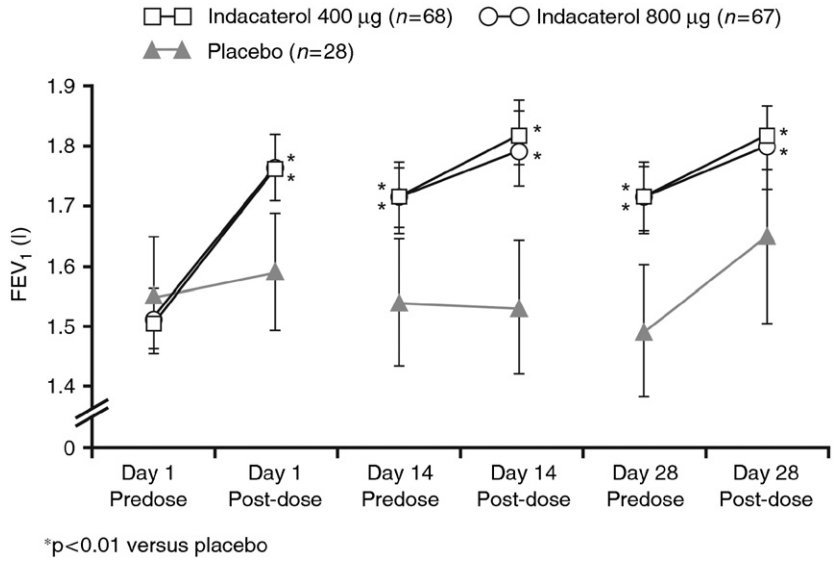

Fig. 1. Mean (±SEM) FEV_1 over time (safety population).

Day 28 were 220±49 and 210±49 ml ($p < 0.0001$ vs placebo for both).

At 30 min post-dose, adjusted mean±SE FEV_1 improvements compared with placebo for indacaterol 400 and 800 μg, respectively, were: Day 1, 220±36 ml and 210±36 ml ($p < 0.0001$ vs placebo for both); Day 14, 320±50 ml and 270±50 ml ($p < 0.0001$ vs placebo for both); Day 28, 260±61 ml ($p < 0.0001$ vs placebo) and 200±61 ml ($p = 0.001$ vs placebo).

Indacaterol, but not placebo, demonstrated statistically significant improvements in FEV_1 from baseline to 30 min post-dose on Days 1, 14 and 28. Post-dose adjusted mean (95% confidence interval) improvements from baseline in FEV_1 (in ml) for indacaterol 400 and 800 μg and placebo, respectively were: Day 1, 260 (220, 300), 240 (200, 280), 30 (−30, 90); Day 14, 320 (270, 370), 270 (210, 320), 0 (−90, 80); Day 28, 320 (260, 380), 260 (200, 320), 60 (−40, 160). The mean percentage increase in FEV_1 from baseline was consistently higher for the indacaterol treatment groups vs placebo at each post-dose timepoint, with the highest proportion of patients with increases >17% from baseline in the 400 μg group (30 min post-dose on Day 28, 44

Table 6
Mean (SD) FVC and $FEF_{25–75\%}$ (Safety population)

	Indacaterol 400 μg ($n = 68$)	Indacaterol 800 μg ($n = 67$)	Placebo ($n = 28$)
FVC (l), mean (SD)			
Pre-dose, Day 1 (baseline)	3.04 (0.748)	2.98 (0.687)	3.01 (0.699)
30 min post-dose, Day 1	3.40 (0.818)	3.29 (0.782)	3.08 (0.658)
Pre-dose, Day 14	3.27 (0.793)	3.24 (0.770)	2.99 (0.676)
30 min post-dose, Day 14	3.39 (0.859)	3.35 (0.787)	2.99 (0.690)
Pre-dose, Day 28	3.25 (0.807)	3.20 (0.795)	2.92 (0.728)
30 min post-dose, Day 28	3.36 (0.835)	3.26 (0.848)	3.14 (0.919)
$FEF_{25–75\%}$ (l/sec), mean (SD)			
Pre-dose, Day 1 (baseline)	0.64 (0.288)	0.68 (0.305)	0.72 (0.385)
30 min post-dose, Day 1	0.79 (0.385)	0.85 (0.369)	0.70 (0.354)
Pre-dose, Day 14	0.75 (0.328)	0.79 (0.356)	0.70 (0.360)
30 min post-dose, Day 14	0.82 (0.380)	0.83 (0.395)	0.70 (0.399)
Pre-dose, Day 28	0.78 (0.333)	0.80 (0.387)	0.72 (0.358)
30 min post-dose, Day 28	0.83 (0.383)	0.86 (0.404)	0.81 (0.430)

[71.0%], 30 [48.4%] and 3 [13.0%] patients in the indacaterol 400 and 800 μg and placebo groups, respectively, demonstrated FEV_1 increases from baseline $>17\%$).

At all post-baseline timepoints, mean FVC and $FEF_{25–75\%}$ were greater than baseline in both indacaterol groups; values in the placebo group were below baseline at a number of post-baseline timepoints (Table 6). In all groups, the number of patients who required rescue salbutamol medication decreased over the course of the study. According to patient estimates, the number of patients not using salbutamol increased from 18% to 60% in the indacaterol 400 μg group from 16% to 42% in the indacaterol 800 μg group, and from 11% to 36% in the placebo group.

4. Discussion

The present study showed that in patients with COPD, once-daily indacaterol at doses up to 800 μg per day had a good safety profile, was well tolerated and demonstrated 24-h bronchodilation. As 800 μg represents 2–4 times the therapeutic dose suggested by earlier studies [15], these results imply that the therapeutic window for indacaterol may be wide. Although the population of this study was originally defined as having moderate COPD, following an update of the GOLD criteria, these patients would now be classified as having moderate-to-severe COPD [1]. Current GOLD Guidelines recommend the use of long-acting bronchodilators for the treatment of patients with COPD classified as moderate onwards, therefore indacaterol, as a novel long-acting β_2-agonist, has the potential to extend the options available for the treatment of such patients [1]. Salmeterol and formoterol, the two currently available long-acting β_2-agonists, are recommended to be used twice daily as they have approximately 12-h durations of action at recommended doses [2–7]. Previous studies have shown that patients prefer once-daily dosing regimens over twice-daily regimens [16], which suggests the possibility of improved patient compliance with once-daily indacaterol. In addition, tiotropium, the only once-daily bronchodilator available at present, has been shown to provide superior improvements in lung function and health-related quality of life when compared to four-times-daily dosing with the short-acting anticholinergic ipratropium [8,9].

Overall, indacaterol was well tolerated in the current study with no statistically significant differences between treatment groups in the overall incidence of AEs. There was no indication of a relation between the incidence of individual AEs and dose. The only exceptions were the higher number of headaches reported in the indacaterol 800 μg group and the higher incidence of cough in both indacaterol groups compared with placebo. The fact that no patients receiving placebo reported cough may be partly the result of chance, since fewer patients received placebo than indacaterol owing to the 2:2:1 randomisation. However, most of the episodes of cough were mild in severity and occurred after the first inhalation of study medication, with incidence declining at subsequent visits such that no patients coughed after study drug administration on the final visit. The incidence of cough is therefore not expected to affect the overall tolerability of indacaterol. The characteristics of the cough have been investigated further in other studies: It is of short duration (typically lasting less than 2 min post-dose) and is not associated with bronchospasm. These results will be included in future publications. There were no serious AEs considered to be related to the study drug, and only one patient discontinued because of an AE suspected of being related to indacaterol. In addition, AEs typical of the β_2-agonist class were generally mild in severity and low in overall incidence, although, as expected, they occurred in the indacaterol treatment groups more frequently than with placebo. The good overall tolerability profile of indacaterol is further supported by the high level of

compliance to treatment in this study, and by the very low drop-out rate. In addition, both doses of indacaterol demonstrated a good overall safety profile, with no clinically relevant differences between treatment groups in any of the cardiovascular or biochemical variables assessed.

This study was designed primarily to investigate the safety and tolerability of indacaterol and therefore was not powered to allow definitive conclusions about efficacy. However, exploratory analyses showed statistically superior increases in FEV_1 for both indacaterol doses compared with placebo, at all post-baseline timepoints, including pre-dose (or trough). This suggests that tolerance to the bronchodilator effects of indacaterol did not develop over 28 days. These results are consistent with those previously observed for indacaterol in a 28-day study in patients with asthma, in which there was no loss of efficacy over the duration of the study [12]. In the current study, clinically relevant improvements in FEV_1 were apparent pre-dose on Days 14 and 28, approximately 24 h after the previous dose, demonstrating the 24-h duration of action of indacaterol and supporting the appropriateness of a once-daily dosing regimen. This sustained efficacy has been demonstrated previously in a study in patients with asthma in which single doses of indacaterol as low as 200 μg provided 24-h bronchodilator efficacy [11]. Further to the spirometry results, the greater reduction in rescue medication use reported in the indacaterol groups may also reflect improved control of dyspnoea with indacaterol.

Long-acting β_2-agonists administered at higher than recommended doses have previously been associated with changes in heart rate, QTc interval and serum potassium and glucose levels, in patients and healthy volunteers [17–23]. The current study was therefore specifically designed to monitor and assess changes in these variables. There were no clinically relevant differences in serum potassium or blood glucose observed between groups, with isolated statistically significant differences only recorded at two timepoints, both with indacaterol 800 μg. Over the duration of the study, there were no clinically significant effects on pulse rate or blood pressure and no statistically significant differences between indacaterol groups and placebo in mean QTc intervals. Both doses of indacaterol therefore demonstrated a favourable clinical cardiovascular safety profile, supporting data from a previous study in patients with asthma in which indacaterol doses as high as 600 μg were not associated with cardiovascular adverse effects [12]. Overall, the current study does not raise any concerns over the effect of indacaterol on these specific safety variables.

In conclusion, the present study demonstrates that the novel once-daily β_2-agonist indacaterol is well tolerated at doses up to 800 μg with a good overall safety profile. Furthermore, these results support the previously demonstrated 24-h bronchodilator efficacy of once-daily indacaterol.

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