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Sustained 24-hour efficacy of once daily indacaterol (300 µg) in patients with chronic obstructive pulmonary disease: A randomized, crossover study

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ABSTRACT

Purpose: Indacaterol is a novel, once daily, inhaled ultra-long-acting β_2 -agonist for the treatment of chronic obstructive pulmonary disease (COPD). Here we compared the 24-h spirometry profile of once daily indacaterol 300 µg with that of placebo and twice daily salmeterol 50 µg in patients with COPD.

Methods: This randomized, multicenter, placebo-controlled, crossover study comprised three 14-day treatment periods (with 14-day washouts). Patients (male/female ≥ 40 years) with moderate-to-severe COPD were randomized to receive double-blind indacaterol 300 µg or placebo once daily, or open-label salmeterol 50 µg twice daily. The primary outcome measure was 24-h post-dose (trough) FEV₁ (mean of FEV₁ at 23 h 10 min and 23 h 45 min post-indacaterol dose) after 14 days. FEV₁ was assessed at multiple time points on Days 1 and 14 of each treatment period. Safety and tolerability were also monitored.

Results: Of 68 randomized patients, 61 completed. Trough FEV₁ (primary endpoint) on Day 14 for indacaterol was 200 mL higher than placebo ($p < 0.001$), exceeding the prespecified minimum clinically important difference (120 mL), and was 90 mL higher than for salmeterol ($p = 0.011$). After Day 1, trough FEV₁ for indacaterol was 150 mL higher than placebo ($p < 0.001$). Indacaterol provided superior bronchodilation compared with placebo ($p < 0.001$) across the full 24-h assessment period on Days 1 and 14. In addition, on both days, indacaterol provided superior FEV₁ compared with salmeterol ($p < 0.05$) at many post-baseline time points, including 5 min post-dose. All treatments were well tolerated.

Conclusions: Once daily indacaterol 300 µg produced effective sustained 24-h bronchodilation from the first dose, an efficacy profile superior to placebo and twice daily salmeterol. Given its effective bronchodilation with once daily dosing, indacaterol is likely to be a useful treatment option for patients with moderate-to-severe COPD.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major (and increasing) cause of morbidity and mortality worldwide [1]. The condition is characterized by progressive airflow limitation and air trapping, resulting in hyperinflation. This hyperinflation reduces inspiratory capacity resulting in dyspnea and limitations in exercise capacity [2].

COPD treatment guidelines, including those from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [2], advocate the use of inhaled bronchodilators, including β_2 -agonists, at all COPD stages to improve expiratory flow and emptying of the lungs, thereby reducing hyperinflation at rest and during exercise [2]. Regular treatment with long-acting bronchodilators in symptomatic COPD patients has been shown to be more effective and convenient than treatment with short-acting bronchodilators [2]. Currently available inhaled long-acting β_2 -agonists (LABAs), such as salmeterol and formoterol, induce bronchodilation that lasts for approximately 12 h and are therefore administered twice daily [3–6].

Indacaterol is a novel, inhaled, ultra-LABA [7] for the treatment of COPD. In clinical trials, indacaterol has demonstrated 24-h

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¹ INTEGRAL – INdacaterol: Twenty four hours Efficacy duration usinG salmeteRol as Active control.

bronchodilation with once daily dosing, with a good overall safety and tolerability profile [8,9]. The majority of studies conducted thus far with indacaterol have incorporated relatively few spirometric assessments between 12 and 22 h post-dose. This study was therefore conducted to further characterize the 24-h lung spirometric profile of indacaterol 300 µg once daily in patients with moderate-to-severe COPD by incorporating multiple spirometric assessments across the full 24-h dosing interval.

2. Methods

This was a Phase III, randomized, multicenter, double-blind, placebo-controlled, crossover study conducted at specialized respiratory care centers in Belgium, Spain, and the US (ClinicalTrials.gov registration no.: NCT00622635) [10]. The study was approved by the institutional review board or the independent ethics committee of each participating study center and was conducted in accordance with the ethical principles embodied in the Declaration of Helsinki (1989) and applicable local regulations. Written informed consent was obtained from each patient before their participation in the study.

2.1. Patients

Male and female patients aged ≥ 40 years with a clinical diagnosis of moderate-to-severe COPD (as classified by the GOLD 2006 guidelines) [11], smoking history of at least 20 pack years, post-bronchodilator forced expiratory volume in 1 s (FEV_1) $< 80\%$ and $\geq 30\%$ of the predicted normal value and post-bronchodilator FEV_1 /forced vital capacity (FVC) $< 70\%$ at screening were eligible for enrolment in the study. Patients were excluded from the study if they had concomitant pulmonary disease, type I diabetes or uncontrolled type II diabetes, uncontrolled hypertension, unstable ischemic heart disease, or malignancy. Patients who had a history of asthma, had been hospitalized for a COPD exacerbation in the 6 weeks prior to screening or during the run-in period, or had experienced respiratory tract infection within 6 weeks prior to screening were also excluded.

2.2. Study design and interventions

The study comprised a pre-screening visit, a 14-day screening period, and three 14-day treatment periods. At the pre-screening visit, patients' ongoing COPD medications were reviewed and, if necessary, adjusted from prohibited to allowable COPD therapy. During screening, patients were assessed for eligibility and monitored to ensure that they remained stable on their permissible COPD treatment. At the baseline visit, eligible patients were randomized equally (using a validated system) to one of six treatment sequences (each with three treatment periods).

In each treatment period, patients received either double-blind indacaterol 300 µg once daily (qd) delivered via a single-dose dry powder inhaler (SDDPI), matching placebo qd, or open-label salmeterol 50 µg twice daily (bid) via a multi-dose dry powder inhaler according to the assigned treatment sequence. Each treatment period was separated by a washout period of 14 days.

2.3. Concomitant medication

Allowable therapy included the use of inhaled corticosteroids, provided the regimen had been stabilized for at least 1 month prior to the screening visit. The following medications could not be used after the screening visit: the long-acting anticholinergic agent

tiotropium, short-acting anticholinergics, short-acting β_2 -agonists, LABAs other than those used in this study, xanthine derivatives, parenteral or oral corticosteroids, and fixed-dose combinations of β_2 -agonists and inhaled corticosteroids. Albuterol was the only rescue medication permitted throughout the study, although visits had to be rescheduled if it was taken within 6 h prior to the pre-dose spirometry measurements during that visit.

2.4. Assessments and outcomes

2.4.1. Efficacy

On Days 1 and 14 of each treatment period, spirometry was conducted at -50 and -15 min pre-dose and at 5, 15, and 30 min and 1, 2, 3, 4, 5, 6, 8, and 10 h, 11 h 10 min, 11 h 45 min, 14 h, 20 h 10 min, 20 h 45 min, 22 h, 23 h 10 min, and 23 h 45 min post-dose. FEV_1 was assessed at all time points; inspiratory capacity was assessed at each time point, except 5 and 30 min post-dose. Spirometry was performed in accordance with the American Thoracic Society/European Respiratory Society standards [12].

The primary efficacy outcome was 24-h post-dose (trough) FEV_1 (mean of the FEV_1 measurements at 23 h 10 min and 23 h 45 min post-indacaterol dose, that is, 11 h 10 min and 11 h 45 min after the second of the twice daily doses of salmeterol) following 14 days of treatment. Secondary and exploratory outcomes included individual time point FEV_1 on Day 1 and Day 14, trough FEV_1 after 1 day of treatment, the mean of FEV_1 measurements at 11 h 10 min and 11 h 45 min post-dose (times representing the end of the dosing interval for the first salmeterol dose) as well as at 20 h 10 min and 20 h 45 min post-dose (times when patients would awaken and lung function would be at its lowest [13]) on Day 1 and Day 14, and inspiratory capacity on Day 1 and Day 14. All comparisons with (open-label) salmeterol were considered exploratory.

2.4.2. Safety

Adverse events (AEs) and serious AEs (SAEs) were recorded, along with evaluation of their severity, duration, and relationship to study drug. Other safety assessments included: urinalysis; regular monitoring of hematology, blood chemistry (including serum potassium and blood glucose), vital signs, and body weight; and assessment of corrected QT interval (QTc).

2.5. Sample size determination and statistical analysis

The patient numbers were chosen to provide at least 90% power for the primary endpoint (trough FEV_1 on Day 14) and 80% power for FEV_1 at each individual time point on Day 14; the relative sizes of the standard deviations implied that the latter condition was the limiting factor. Assuming a minimum FEV_1 difference from placebo of 120 mL for indacaterol for each time point over the 24-h post-dose period on Day 14, a standard deviation of 276 mL [14,15], a two-sided significance level of 5%, and a power of 80%, a sample size of approximately 44 patients was estimated prior to the study. This sample size implies at least 94% power for the primary objective. Allowing for a 15% dropout rate and with the number inflated to ensure balance across the treatment sequences, it was estimated that 54 patients were to be randomized (nine for each treatment sequence).

The primary efficacy analysis was performed on a modified intent-to-treat (mITT) population, which included all randomized patients who received at least one dose of study drug and had post-randomization efficacy data (the modification being that patients were analyzed according to the treatments received). All patients who received at least one dose of study drug were included in the

Table 1
Demographics and baseline clinical characteristics (safety population).

Characteristics	Participants (N = 68)
Age (years), mean (SD)	65.6 (9.03)
Sex, n (%)	
Male	52 (76.5)
Female	16 (23.5)
Race, n (%)	
Caucasian	65 (95.6)
Black	3 (4.4)
BMI (kg/m ²), mean (SD)	27.1 (5.54)
Duration of COPD (years), mean (SD)	9.3 (8.14)
Smoking history, n (%)	
Ex-smoker	43 (63.2)
Current smoker	25 (36.8)
Number of pack years, mean (SD)	49.2 (24.52)
Post-bronchodilator FEV ₁ (% predicted), mean (SD)	53.0 (13.37)
Post-bronchodilator FEV ₁ /FVC (%), mean (SD)	48.6 (10.50)
FEV ₁ reversibility (% increase), mean (SD)	13.4 (10.67)

SD = standard deviation; FEV₁ = forced expiratory volume in 1 s; FVC = forced vital capacity. Pack years = total years of smoking multiplied by cigarette packs smoked per day.

safety population, which was used in the analysis of all safety variables.

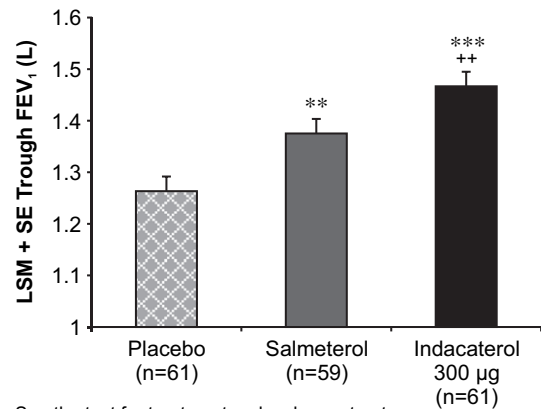
The primary efficacy variable was analyzed using a mixed model, with treatment group and period modeled as fixed effects, patient as a random effect, and period baseline FEV₁ as a covariate. Similar mixed effect models were used to analyze all the secondary and exploratory efficacy variables. The least squares means (LSM), i.e., means adjusted for the covariates in the model, of the treatment contrast for indacaterol 300 µg versus placebo were estimated along with the associated 95% confidence intervals and two-sided *p*-values.

AE and SAE data; laboratory data for hematology, blood biochemistry, and urinalysis; electrocardiogram (ECG) results; and measurements of vital signs were summarized descriptively by treatment group. The corrected QT interval was calculated from the QT and RR intervals using Fridericia's formula (QTcF) [16,17]. All tests of hypotheses used were two-tailed and interpreted at the 5%

Table 2
Treatment difference in FEV₁ (L) on Day 1 and Day 14 (modified intent-to-treat population).

	Comparison	LSM ± SEM	95% CI	<i>p</i> -value
24-h trough FEV ₁	Indacaterol – Placebo	0.15 ± 0.025	(0.10, 0.19)	<0.001
	Indacaterol – Salmeterol	0.04 ± 0.024	(–0.01, 0.09)	0.106
	Salmeterol – Placebo	0.11 ± 0.025	(0.06, 0.16)	<0.001
On Day 14 (primary endpoint)	Indacaterol – Placebo	0.20 ± 0.034	(0.13, 0.27)	<0.001
	Indacaterol – Salmeterol	0.09 ± 0.035	(0.02, 0.16)	0.011
	Salmeterol – Placebo	0.11 ± 0.035	(0.04, 0.18)	0.001
Mean of 11 h 10 min and 11 h 45 min post-dose	Indacaterol – Placebo	0.17 ± 0.022	(0.13, 0.22)	<0.001
	Indacaterol – Salmeterol	0.08 ± 0.022	(0.04, 0.13)	<0.001
	Salmeterol – Placebo	0.09 ± 0.022	(0.04, 0.13)	<0.001
On Day 14	Indacaterol – Placebo	0.21 ± 0.033	(0.15, 0.28)	<0.001
	Indacaterol – Salmeterol	0.11 ± 0.033	(0.04, 0.17)	0.001
	Salmeterol – Placebo	0.10 ± 0.034	(0.04, 0.17)	0.003
Mean of 20 h 10 min and 20 h 45 min post-dose	Indacaterol – Placebo	0.16 ± 0.024	(0.11, 0.21)	<0.001
	Indacaterol – Salmeterol	0.02 ± 0.023	(–0.03, 0.06)	0.519
	Salmeterol – Placebo	0.14 ± 0.024	(0.10, 0.19)	<0.001
On Day 14	Indacaterol – Placebo	0.20 ± 0.033	(0.13, 0.26)	<0.001
	Indacaterol – Salmeterol	0.06 ± 0.033	(–0.01, 0.12)	0.087
	Salmeterol – Placebo	0.14 ± 0.033	(0.08, 0.21)	<0.001

CI = confidence interval; FEV₁ = forced expiratory volume in 1 s; LSM = least squares mean; SEM = standard error of the mean.



See the text for treatment – placebo contrasts.
p* = 0.001; *p* < 0.001 vs placebo; ++*p* = 0.011 vs salmeterol.
Trough = average of 23 h 10 min and 23 h 45 min post-dose values; FEV₁ = forced expiratory volume;
LSM = least square means; SE = standard error.

Fig. 1. Least squares means trough FEV₁ (L) on Day 14 (modified intent-to-treat population).

significance level. The data were analyzed using SAS statistical software version 9.1.3 for Windows (SAS Institute Inc., Cary, North Carolina, USA).

3. Results

3.1. Patient disposition, demographics, and baseline characteristics

This study was conducted at 11 centers in 3 countries (6 in the USA, 3 in Belgium, and 2 in Spain). Out of 101 patients screened, 68 were randomized, and 61 (89.7%) completed the study. The most common reason for premature discontinuation was AE(s) (four patients), followed by withdrawal of consent (two patients) and abnormal test result(s) (one patient). Discontinuations were higher during treatment with salmeterol (*n* = 4) compared with indacaterol (*n* = 1) or placebo (*n* = 2).

The baseline demographics and clinical characteristics of all randomized patients are shown in Table 1. All patients were current or former smokers, and the majority were male.

3.2. Efficacy

3.2.1. Primary efficacy outcome: trough FEV₁ on Day 14, indacaterol vs placebo

For the primary endpoint, 24-h post-dose (trough) FEV₁ after 14 days of treatment, indacaterol was significantly superior to placebo, with the least squares mean (LSM) treatment difference between indacaterol and placebo being 200 mL (Fig. 1, Table 2). The mean (standard deviation [SD]) change from baseline to 24 h post-dose trough FEV₁ after 14 days of treatment was 180 (230) mL for indacaterol and –30 (200) mL for placebo.

3.2.2. Trough FEV₁ on Days 1 and 14

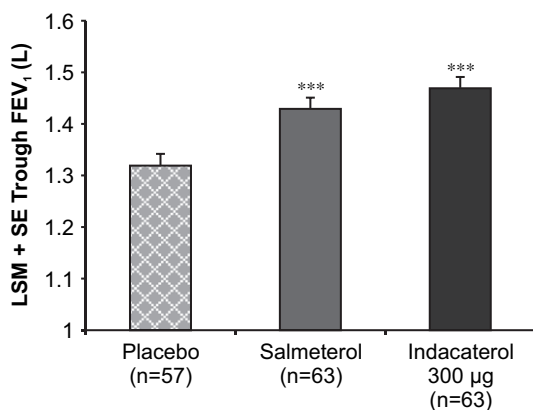
Indacaterol was also significantly superior to salmeterol for trough FEV₁ on Day 14 with the LSM difference between the two treatments being 90 mL (Table 2). In addition, salmeterol demonstrated significantly superior trough Day 14 FEV₁ results as compared with placebo (Table 2). After 1 day of treatment, the trough FEV₁ for both indacaterol and salmeterol was significantly superior to that of placebo, with the value for indacaterol being numerically higher than salmeterol (Fig. 2, Table 2).

3.2.3. Serial measurements of FEV₁ over 24 h

Serial measurements of FEV₁ over 24 h on Day 14 are shown in Fig. 3. Indacaterol was statistically superior to placebo at all post-baseline time points on both Day 1 and Day 14 ($p < 0.001$ at all time points, including 50 min and 15 min pre-dose on Day 14). In addition, on Day 14 indacaterol provided either numerically or statistically superior FEV₁ as compared with salmeterol at all time points (Fig. 3). On Day 1, the LSM treatment difference in FEV₁ between indacaterol and salmeterol was statistically significant at each post-dose time point up to and including 11 h 45 min, with the later time points showing numerical superiority of indacaterol over salmeterol.

3.2.4. Mean of FEV₁ values at 11 h 10 min and 11 h 45 min, and of 20 h 10 min and 20 h 45 min post-dose

On both Day 1 and Day 14, the LSM treatment difference in the mean of 11 h 10 min and 11 h 45 min post-dose FEV₁ measurements



See the text for treatment – placebo contrasts.

*** $p < 0.001$ vs placebo

Trough = average of 23 h 10 min and 23 h 45 min post-dose values; FEV₁ = forced expiratory volume;

LSM = least square means; SE = standard error.

Fig. 2. Least squares means trough FEV₁ (L) on Day 1 (modified intent-to-treat population).

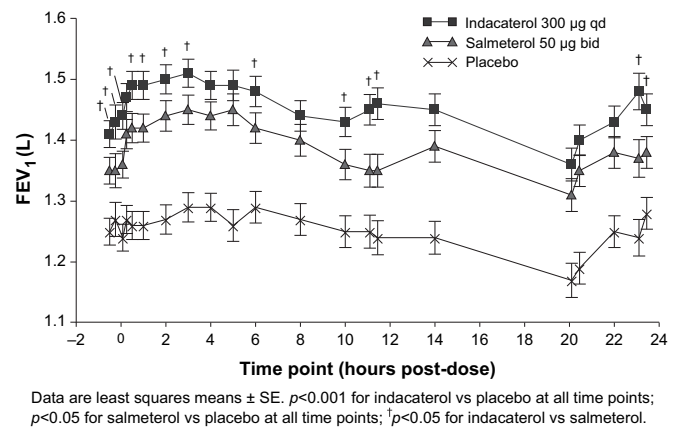


Fig. 3. Twenty-four-hour FEV₁ profile on Day 14 (modified intent-to-treat population).

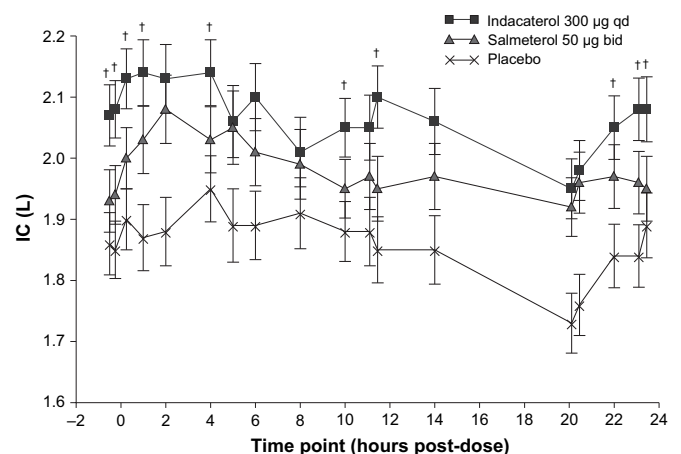
were statistically significant for indacaterol versus placebo, indacaterol versus salmeterol, and salmeterol versus placebo ($p < 0.001$ for all comparisons) (Table 2). Similarly, on both Day 1 and Day 14, the LSM treatment difference in the mean of 20 h 10 min and 20 h 45 min post-dose FEV₁ measurements was statistically significant for indacaterol versus placebo and salmeterol versus placebo ($p < 0.001$ for both comparisons) (Table 2). The value was higher for indacaterol than salmeterol on Day 14 ($p = \text{ns}$; Table 2).

3.2.5. Serial measurement of IC

The 24-h profile of inspiratory capacity measurements for all treatments on Day 14 are shown in Fig. 4. Data from the 3-h post-dose time point are excluded from the figure as one patient on indacaterol reported an out-of-range value (12.37 L). On both Day 1 and Day 14, the LSM treatment difference between indacaterol and placebo was statistically significant at all post-baseline time points. In addition, indacaterol was numerically or statistically superior to salmeterol at all post-baseline time points on Days 1 and 14.

3.3. Safety

The overall incidence of AEs was 25.8% (17/66), 15.4% (10/65), and 28.8% (19/66) with indacaterol, salmeterol, and placebo,



Data are least squares means \pm SE; Data on 3 hours post-dose is excluded, as one patient reported an out-of-range value. IC = inspiratory capacity

$p < 0.001$ for indacaterol vs placebo at all time points; $p < 0.05$ for salmeterol vs placebo from -15 min to 6 h, and from 11 h 45 min to 23 h 10 min inclusive; $p < 0.05$ for indacaterol vs salmeterol.

Fig. 4. Twenty-four-hour inspiratory capacity profile on Day 14 (modified intent-to-treat population).

Table 3
Adverse events overall and by primary system organ class (safety population).

	Indacaterol N = 66 n (%)	Salmeterol N = 65 n (%)	Placebo N = 66 n (%)
Patients with any AE(s)	17 (25.8)	10 (15.4)	19 (28.8)
Primary system organ class			
Respiratory, thoracic, and mediastinal disorders	7 (10.6)	2 (3.1)	6 (9.1)
Infections and infestations	5 (7.6)	4 (6.2)	5 (7.6)
Musculoskeletal and connective tissue disorders	4 (6.1)	1 (1.5)	4 (6.1)
Investigations	2 (3.0)	1 (1.5)	0
Nervous system disorders	2 (3.0)	0	3 (4.5)
Cardiac disorders	1 (1.5)	0	0
Gastrointestinal disorders	1 (1.5)	1 (1.5)	3 (4.5)
Reproductive system and breast disorders	1 (1.5)	1 (1.5)	0
Vascular disorders	1 (1.5)	1 (1.5)	0
General disorders and administration site conditions	0	0	2 (3.0)
Injury, poisoning and procedural complications	0	2 (3.1)	0
Psychiatric disorders	0	1 (1.5)	0
Renal and urinary disorders	0	0	1 (1.5)
Skin and subcutaneous tissue disorders	0	1 (1.5)	1 (1.5)

respectively (Table 3). The most frequently-reported AEs were cough for indacaterol (indacaterol: 3, 4.5%; salmeterol: 0; placebo: 1, 1.5%); rhinitis for salmeterol (indacaterol: 0; salmeterol: 2, 3.1%; placebo: 0); and back pain for placebo (indacaterol: 0; salmeterol: 0; placebo: 4, 6.1%). Only one AE was reported as severe (ligament sprain while on salmeterol).

Four patients discontinued due to AEs during the study. Two patients while on indacaterol treatment and one on the placebo experienced a COPD exacerbation and (as specified in the protocol) were discontinued from the study. In addition, one patient reported pneumonia while on placebo, leading to study drug discontinuation. None of these were suspected to be study drug related. No death was reported during the study.

There were no clinically notable potassium values (defined as a minimum post-baseline value of <3.0 mmol/L) with indacaterol or salmeterol during the study. One patient reported a clinically notable potassium value while on placebo. The incidence of clinically notable blood glucose levels (defined as a maximum post-baseline value of >9.99 mmol/L) for indacaterol (7/66, 10.6%) and salmeterol (5/65, 7.7%) was similar and lower than that for placebo (10/66, 15.2%). No patient had an abnormally high pulse rate (>130 bpm, or ≥ 120 bpm and increase from baseline ≥ 15 bpm). Only one patient had a >60 ms change in QTcF from baseline, which was observed after administration of salmeterol. No QTcF values >500 ms were reported.

4. Discussion

The majority of studies conducted so far with once daily indacaterol have incorporated relatively few spirometric assessments between 12 and 22 h post-dose. This has generally been done to permit patients to rest overnight and avoid the requirement for them to remain in the study center for a full 24-h period. This was the first study to evaluate the spirometric profile of indacaterol 300 μ g once daily in patients with COPD across the full 24-h dosing interval. In particular, the time points at 11 h 10 min and 11 h 45 min were included in this study to accurately evaluate spirometry assessments at the end of the dosing interval for the first salmeterol dose. Furthermore, the time points at 20 h 10 min and 20 h 45 min were included because it was anticipated that this would be the time during the dosing interval when lung function would be at its lowest (modeling the time when patients would awaken).

In this study, indacaterol demonstrated significantly superior bronchodilation compared with placebo at all post-dose time points throughout the full 24-h assessment period starting from the first post-baseline time point (5 min). The LSM treatment difference in trough FEV₁ between indacaterol and placebo after 14 days of treatment was 200 mL, which exceeded the set threshold of 120 mL for clinically relevant bronchodilation. In addition, trough FEV₁ was also statistically significantly higher for indacaterol versus placebo after 1 day of treatment. Some diurnal variation in lung function was observed, with the lowest values, as anticipated, measured at 20 h 10 min post-dose, perhaps because patients were allowed to rest during the 6 h interval between 14 and 20 h post-dose. In patients with COPD, sleep has negative effects on respiration and gas exchange [18], such that patients often wake in a state of hypoxia, with wheezing and shortness of breath. It is of note, therefore, that the efficacy of indacaterol was maintained at this time point.

The findings from this study are also noteworthy because they demonstrate the full 24-h efficacy of once daily indacaterol from the very first dose. This has also been observed in previous studies of indacaterol in patients with COPD [9,19] and is in contrast to the onset of action of salmeterol, which was more gradual. Other studies have also shown that salmeterol is associated with an onset of action of approximately 10–15 min [20], achieving peak bronchodilation approximately 2 h after administration [21]. The only other once-daily bronchodilator currently available is tiotropium, which also has a more gradual onset of action than indacaterol, with some sources suggesting that tiotropium may take 3–4 days to reach full pharmacological effect [22,23].

As salmeterol is a LABA recommended for twice daily use as regular maintenance therapy in COPD, a comparison between salmeterol and once daily indacaterol was of interest in this study. Although, given the open-label nature the salmeterol comparisons are initial exploratory findings, in subsequent blinded studies (including a 14-day crossover study and a 26-week parallel group study) similar FEV₁ differences between indacaterol and salmeterol were observed [24,25]. The open-label treatment design of salmeterol was selected for practical purposes in a study that, as a result of the multiple spirometry measurements, could potentially have high withdrawal rates. Salmeterol, if included in a double-blind manner, would require a double-dummy design with patients using both inhalers every day during the treatment periods. In contrast, the current design was much less complex for patients (as during the indacaterol and placebo periods they only used study medication once daily), so potentially contributing to the high study completion rate.

The 14-day time point was selected as primary endpoint in this study as previous studies have shown that indacaterol reaches pharmacodynamic steady-state prior to this time [8,26]. Likewise, in an earlier salmeterol study, bronchodilator efficacy after 2 weeks of treatment was comparable to that seen after 1 year [27]. In the current study, indacaterol was significantly superior to salmeterol after 1 and 14 days of treatment in terms of FEV₁ at most time points up to and including 11 h 45 min, with later time points favoring indacaterol and reaching statistical significance on Day 14 at 23 h 10 min and 23 h 45 min post-dose. Moreover, as evident from the 24-h lung function profile, use of indacaterol was associated with a reduction in the 'dipping' in lung function, seen in salmeterol treatment towards the end of the dosing interval. The results of this study therefore indicate that indacaterol dosed once daily has a bronchodilator profile that is consistently numerically superior to salmeterol dosed twice daily, and for most time points also statistically superior to salmeterol. Although this study assessed the efficacy of indacaterol for up to 14 days, other studies have examined its efficacy for up

to 52 weeks. In these studies, indacaterol demonstrated 24-h bronchodilation with no evidence of loss in efficacy on repeated once daily dosing, with statistical superiority to twice daily formoterol [26,28].

In COPD, LABAs act on peripheral airways to reduce air trapping within the lungs, thereby reducing lung volumes and improving hyperinflation and exercise capacity [2]. Inspiratory capacity has been shown to be a reliable indicator of the development of hyperinflation, a key determinant of dyspnea in patients with COPD [29]. Therefore, inspiratory capacity is a useful parameter when studying the effects of a bronchodilator. Improvements in inspiratory capacity with indacaterol, as observed in this study, suggest improvements in hyperinflation, which may in turn lead to improvements in patient-focused outcomes such as dyspnea. Similar improvements in inspiratory capacity have been observed with indacaterol in previous studies, with a single 300 µg dose of indacaterol having a greater effect on inspiratory capacity than formoterol 12 µg bid [30]. Further, in a 14-day cycle ergometry study, indacaterol 300 µg provided a statistically significant 317 mL improvement vs placebo in peak inspiratory capacity during exercise – indicating an improvement in dynamic hyperinflation [31]. This improvement was accompanied by a statistically significant 3.33 unit improvement vs placebo in the Transitional Dyspnea Index. The effect of indacaterol on inspiratory capacity during exercise is being investigated further in additional studies.

In terms of safety, all treatments in this study demonstrated good overall safety and tolerability profiles. The overall rate of AEs was comparable between indacaterol and placebo, with nearly all AEs reported in this study being mild or moderate in severity. In a 52-week study that compared indacaterol 300 and 600 µg once daily with formoterol and placebo, indacaterol was also well tolerated, with a safety profile that indicated minimal impact on QTc interval and systemic β₂-mediated events [28].

5. Conclusion

Indacaterol 300 µg once daily produced effective bronchodilation from the first dose, with efficacy compared with placebo that was sustained over 24-h. The efficacy of indacaterol was greater than that of open-label salmeterol administered twice daily. Indacaterol was generally well tolerated with a good overall safety profile. Indacaterol is therefore a useful alternative to the established bronchodilator therapies in patients with moderate-to-severe COPD. The sustained 24-h profile of indacaterol supports the convenience of once daily dosing.

6. Disclosure statement

Amir Iqbal, David Young, Roger Owen, Mark Higgins and Benjamin Kramer are employees of the study sponsor, Novartis. Craig LaForce has received fees for speaking for Novartis. Joseph Aumann and Luis de Teresa Parreño have no actual or potential conflict of interest. All authors contributed to the development of the manuscript, and approved the decision to submit the manuscript for publication.

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References

- [1] Calverley PM, Walker P. Chronic obstructive pulmonary disease. *Lancet* 2003;362:1053–61.
- [2] Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. At: <http://www.goldcopd.com>; 2009 [accessed 29.02.10].
- [3] Ulrik CS. Efficacy of inhaled salmeterol in the management of smokers with chronic obstructive pulmonary disease: a single centre randomised, double blind, placebo controlled, crossover study. *Thorax* 1995;50:750–4.
- [4] Boyd G, Morice AH, Pounsford JC, Siebert M, Plesis N, Crawford C. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1997;10:1696.
- [5] Cazzola M, Matera MG, Santangelo G, Vinciguerra A, Rossi F, D'Amato G. Salmeterol and formoterol in partially reversible severe chronic obstructive pulmonary disease: a dose-response study. *Respir Med* 1995;89:357–62.
- [6] Rossi A, Kristufek P, Levine BE, Thomson MH, Till D, Kottakis J, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. *Chest* 2002;121:1058–69.
- [7] Cazzola M, Matera MG, Lotvall J. Ultra long-acting β₂-agonists in development for asthma and chronic obstructive pulmonary disease. *Expert Opin Investig Drugs* 2005;14:775–83.
- [8] Beier J, Chanez P, Martinot JB, Schreurs AJ, Tkacova R, Bao W, et al. Safety, tolerability and efficacy of indacaterol, a novel once-daily β₂-agonist, in patients with COPD: a 28-day randomised, placebo controlled clinical trial. *Pulm Pharmacol Ther* 2007;20:740–9.
- [9] Rennard S, Bantje T, Centanni S, Chanez P, Chuchalin A, D'Urzo A, et al. A dose-ranging study of indacaterol in obstructive airways disease, with a tiotropium comparison. *Respir Med* 2008;102:1033–44.
- [10] ClinicalTrials.gov. NCT00622635. US National Institutes of Health. A crossover study to determine the 24-h lung function profile of indacaterol in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD), <http://clinicaltrials.gov/ct2/show/NCT00622635?term=NCT00622635&rank=1> [accessed 30.07.09].
- [11] Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. At: Revision. <http://www.goldcopd.com>; 2006 [accessed 12.11.09].
- [12] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
- [13] Teramoto S, Suzuki M, Matsui H, Ishii T, Matsuse T, Ouchi Y. Influence of age on diurnal variability in measurements of spirometric indices and respiratory pressures. *J Asthma* 1999;36:487–92.
- [14] Chuchalin AG, Tsoi AN, Richter K, Krug N, Dahl R, Luursemä PB, et al. Safety and tolerability of indacaterol in asthma: a randomized, placebo-controlled 28-day study. *Respir Med* 2007;101:2065–75.
- [15] Pearlman DS, Greos L, LaForce C, Orevillo CJ, Owen R, Higgins M. Bronchodilator efficacy of indacaterol, a novel once-daily β₂-agonist, in patients with persistent asthma. *Ann Allergy Asthma Immunol* 2008;101:90–5.
- [16] Morganroth J. Cardiac repolarization and the safety of new drugs defined by electrocardiography. *Clin Pharmacol Ther* 2007;81:108–13.
- [17] US Department of Health and Human Services, Food and Drug Administration. Guidance for industry. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs, <http://www.fda.gov/cder/guidance/6922fnl.pdf>; 2005 [accessed 10.11.08].
- [18] Urbano F, Mohsenin V. Chronic obstructive pulmonary disease and sleep: the interaction. *Panminerva Med* 2006;48:223–30.
- [19] Bauwens O, Ninane V, Van de Maele B, Firth R, Dong F, Owen R, et al. 24-hour bronchodilator efficacy of single doses of indacaterol in subjects with COPD: comparison with placebo and formoterol. *Curr Med Res Opin* 2009;25:463–70.
- [20] Kottakis J, Cioppa GD, Creemers J, Greefhorst L, Leclerc V, Pistelli R, et al. Faster onset of bronchodilation with formoterol than with salmeterol in patients with stable, moderate to severe COPD: results of a randomized, double-blind study. *Can Respir J* 2002;9:107–15.
- [21] Mahler DA, Donohue JF, Barbee RA, Goldman MD, Gross NJ, Wisniewski ME, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest* 1999;115:957–65.
- [22] Koumis T, Samuel S. Tiotropium bromide: a new long-acting bronchodilator for the treatment of chronic obstructive pulmonary disease. *Clin Ther* 2005;27:377–92.

- [23] van Noord JA, Smeets JJ, Custers FL, Korducki L, Cornelissen PJ. Pharmacodynamic steady state of tiotropium in patients with chronic obstructive pulmonary disease. *Eur Respir J* 2002;19:639–44.
- [24] Kornmann O, Luthra A, Owen R, Lassen C, Kramer B. Once-daily indacaterol provides superior bronchodilation, health status and clinical outcomes compared with salmeterol in patients with chronic obstructive disease (COPD): a 26-week placebo-controlled study. *Chest* 2009;136:152S.
- [25] Magnussen H, Verkindre C, Jack D, Jadayel D, Owen R, Higgins M, et al. Efficacy of indacaterol once-daily dosed either in the evening or morning in COPD patients. *Eur Respir J* 2009;34(Suppl. 53):E4361.
- [26] Rennard S, Chapman KR, Luthra A, Swales J, Lassen C, Owen R, et al. Once-daily indacaterol provides effective bronchodilation over 1 year of treatment in patients with chronic obstructive pulmonary disease (COPD). *Chest* 2009;136:4S.
- [27] Vestbo J, Pauwels R, Anderson JA, Jones P, Calverley P, on behalf of the TRISTAN study group. Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. *Thorax* 2005;60:301–4.
- [28] Dahl R, Chung KF, Buhl R, Magnussen H, Nonikov V, Jack D, et al. Efficacy of a new once-daily long-acting inhaled β_2 -agonist indacaterol versus twice-daily formoterol in COPD. *Thorax* 2010;65:473–9.
- [29] Taube C, Lehnigk B, Paasch K, Kirsten DK, Jorres RA, Magnussen H. Factor analysis of changes in dyspnea and lung function parameters after bronchodilation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2000;162:216–20.
- [30] Beier J, Beeh KM, Brookman L, Peachey G, Hmissi A, Pascoe S. Bronchodilator effects of indacaterol and formoterol in patients with COPD. *Pulm Pharmacol Ther* 2009;22:492–6.
- [31] Beeh KM, Khindri S, Eeg M, Drollmann AF. Effect of indacaterol maleate on dynamic lung hyperinflation in patients with COPD. *Eur Respir J* 2009;34 (Suppl. 53):E4357.