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A dose-ranging study of indacaterol in obstructive airways disease, with a tiotropium comparison

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Summary
This dose-ranging study assessed the bronchodilator efficacy and tolerability of indacaterol, a novel once-daily inhaled β_2-agonist, in subjects clinically diagnosed with COPD. Comparative data with tiotropium were collected.
In the double-blind, core period of the study, 635 subjects with COPD (prebronchodilator $FEV_1 \geqslant 40\%$ of predicted and $\geqslant 1.0$ L; $FEV_1/FVC < 70\%$) were randomized to receive indacaterol 50, 100, 200 or 400 μg or placebo via multi-dose dry powder inhaler, or indacaterol 400 μg via single-dose dry powder inhaler, once daily for 7 days. After completing double-blind treatment and washout, a subset of subjects from each treatment group entered an open-label extension and received tiotropium 18 μg once daily for 8 days. The primary efficacy variable was the trough bronchodilator effect: standardized area under the FEV_1 curve between 22 and 24 h post-dose (FEV_1 AUC_{22-24h}) on Day 1.
Clinically relevant improvements *versus* placebo in FEV_1 AUC_{22-24h} were seen for 400 and 200 μg doses on Day 1 and all doses on Day 7. All indacaterol doses significantly ($P<0.05$) increased FEV_1 from 5 min to 24 h post-dose; the 400 and 200 μg doses were most effective. All doses were well tolerated. Indacaterol trough FEV_1 levels compared favorably with the improvement seen by Day 8 in subjects treated with tiotropium in the open-label extension. The results confirm that indacaterol has a 24-h duration of bronchodilator effect and a fast onset of action in COPD and suggest that indacaterol could be an effective once-daily inhaled

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β_2-agonist bronchodilator. Indacaterol demonstrated a good overall safety and tolerability profile.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible and is generally progressive. Bronchodilators, which can improve airflow, are central to symptom management of COPD. For subjects who experience symptoms on a regular basis, regular treatment with one or more long-acting bronchodilators is recommended.[1] For this purpose inhaled agents are recommended because of their greater therapeutic ratio and long-acting agents are preferred because of convenience and, more importantly, their ability to provide sustained bronchodilation through the day and night.

Two long-acting β_2-agonists are currently available, formoterol and salmeterol, which provide bronchodilation for approximately 12 h and are taken twice daily.[2] Both have been shown to be effective and well tolerated in the treatment of subjects with COPD.[3–5] Tiotropium, an anticholinergic agent with a duration of action of more than 24 h on once-daily dosing,[6] has also been shown to be effective in the management of subjects with COPD.[7] Compared with four-times-daily dosing with the anticholinergic ipratropium, once-daily dosing with tiotropium has delivered improvements in a range of outcomes, including dyspnea and exacerbations.[8] In chronic diseases like COPD, adherence to treatment improves as treatment regimens are simplified, for example by reduced dosing frequency.[9] This is an important consideration, since improved adherence to therapy has been demonstrated to be associated with improved outcomes in a range of chronic disease states, including asthma,[10] diabetes and hypertension.[11,12]

Indacaterol is a selective long-acting β_2-agonist in development for the treatment of COPD and in combination with an inhaled corticosteroid, asthma. Indacaterol has demonstrated 24-h bronchodilation on repetitive once-daily dosing in subjects with COPD and in asthma, together with a good overall safety profile.[13,14]

The primary objective of the current study was to find an indacaterol dose that is effective over 24 h and well tolerated in subjects with COPD. The study was extended to include a period of open-label treatment with tiotropium, to generate data for a within-subject comparison with the double-blind period of indacaterol treatment.

Methods

Design

The study consisted of two treatment periods. The core period was a 7-day, randomized, double-blind, placebo-controlled dose-ranging trial of indacaterol. This was followed by an 8-day tiotropium open-label extension period. The two periods were separated by a minimum of 7 days' washout.

In the core period, subjects were randomized using a validated automated system to receive indacaterol 50, 100, 200 or 400 μg once daily via multi-dose dry powder inhaler (MDDPI; Certihaler™),[i] indacaterol 400 μg once daily via a single-dose dry powder inhaler (SDDPI) or placebo via an SDDPI. The 400 μg SDDPI dose was included to allow reference to previous indacaterol studies where administration was via SDDPI. To maintain blinding, subjects inhaled treatment as two puffs from the MDDPIs (50, 100 or 200 μg of active drug or placebo) and one puff from the SDDPI (400 μg or placebo). In the extension (open-label) period, subjects received tiotropium bromide 18 μg once daily via the manufacturer's proprietary inhalation device. All daily doses were inhaled between 08:00 and 10:00 h.

The research protocol was approved by the relevant institutional review boards or ethics committees, and all subjects gave written informed consent.

Inclusion and exclusion criteria

The study included males and females aged 40–75 years, with a clinical diagnosis of COPD, a smoking history of at least 20 pack-years (current or past smokers); (pre-bronchodilator) FEV_1 at both the screening visit and the first study treatment visit $\geqslant$40% of the predicted normal value and $\geqslant$1.0 L (after a washout period, during which salbutamol had not been inhaled for at least 6 h, any other short-acting β_2-agonist had not been inhaled for at least 12 h and any long-acting β_2-agonist had not been inhaled for at least 24 h); and a pre-bronchodilator FEV_1/forced vital capacity (FVC) $<$70%.

Subjects were permitted to continue into the open-label period provided they had completed the core period, had at least one FEV_1 measurement in the period 22–24 h post-dose on Day 7 of the double-blind period, consented to continuing in the second period, and met the same spirometric inclusion criteria at the first visit of the open-label period.

Among those excluded from the study were: subjects who had been hospitalized for an exacerbation of their airways disease in the 6 months prior to the screening visit or between the screening and baseline visits; subjects with a history of asthma (e.g. blood eosinophil count $>$400/mm^3; onset of symptoms prior to age 40 years); those with seasonal or perennial allergic rhinitis; or subjects with a significant unstable cardiovascular or metabolic co-morbidity.

At the screening visit, subjects were trained to use the inhaler devices and given written instructions on how to use the SDDPI and MDDPI.

[i]The Certihaler was jointly developed by Novartis and SkyePharma AG and utilizes SkyePharma's proprietary formulation and device technologies, SkyeProtect™ and SkyeHaler™, respectively.

Concomitant medication

Inhaled salbutamol was permitted as rescue medication but was not to be taken within 6 h of the start of a study visit, unless necessary.

Subjects were not permitted to use the following medications prior to the screening visit (or start of the extension period) for at least the minimum washout period specified, or at any time during the study: tiotropium (7-day washout; other than as supplied in the extension period); short-acting anticholinergics (8 h); fixed combinations of β_2-agonists and inhaled corticosteroids (24 h); long-acting β_2-agonists (24 h); short-acting β_2-agonists, other than permitted (salbutamol) rescue medication (12 h); non-slow-release theophylline (72 h). Subjects were permitted to take oral modified-release theophylline, providing they had been stabilized for at least 1 month prior to screening.

Assessments and variables

Spirometry was performed pre-dose and at intervals post-dose on Days 1 and 7 (5, 10, 15, 30 min, 2, 3, 4, 22, 23 and 24 h on both days, and at 8 and 12 h post-dose on Day 7) of the core period, and pre-dose and at intervals post-dose on Days 1 and 8 (5, 10, 15, 30 min, 1, 2, 3 and 4 h on both days and at 22, 23 and 24 h on Day 8) of the open-label period.

The primary efficacy variable was the difference in standardized FEV_1 area under the curve (AUC) at 22–24 h post-dose (FEV_1 $AUC_{22–24\,h}$) on Day 1 (core period) between indacaterol (50, 100, 200 and 400 μg once daily delivered by MDDPI) and placebo.

Secondary efficacy variables in the core period were standardized FEV_1 $AUC_{22–24\,h}$ on Days 1 and 7 for comparisons other than the primary efficacy variable, peak FEV_1, and FEV_1, FVC, and forced expiratory flow between 25% and 75% of FVC ($FEF_{25–75\%}$) at each individual time point post-dosing. Secondary efficacy variables in the open-label extension period were standardized FEV_1 $AUC_{22–24\,h}$ on Day 8, and standardized FEV_1 $AUC_{0–4\,h}$ on Days 1 and 8.

Safety assessments during the core period consisted of monitoring and recording all adverse events and the regular monitoring of hematology, blood chemistry and urine, and the regular assessments of vital signs, electrocardiogram (ECG), spirometry and physical condition. During the open-label extension period, all adverse events were monitored and recorded, but no other safety assessments were performed.

Statistical analyses

All efficacy analyses were performed on the intention-to-treat (ITT) population, which included all subjects who were randomized to receive treatment. All safety analyses were performed on the safety population, which included all subjects who received at least one dose of trial medication.

The primary variables were analyzed using an analysis of covariance (ANCOVA) model, with treatment and center (nested within country) as fixed effects and baseline measurement as a covariate, where the baseline measurement was defined as the value measured before the first study drug administration on Day 1. The secondary efficacy variables and key laboratory variables (serum potassium and blood glucose) were analyzed using the same ANCOVA model applied to the primary variables.

The extension-period analysis included a series of within-subject pairwise comparisons, using data from the ITT population who entered the extension period. Thus, for the subset of subjects who continued in the extension period, their (indacaterol) data from the core period were compared with their (tiotropium) data from the extension period. An ANCOVA was performed with a model including treatment, subject and baseline FEV_1. For the indacaterol and placebo data, the baseline FEV_1 was defined as the value measured pre-dose on Day 1 of the core period. For the tiotropium data, the baseline FEV_1 was defined as the value measured pre-dose on Day 1 of the extension period. No testing for carry-over was performed because the washout period was deemed to be sufficient. For subjects who continued into the extension, data from Days 1 and 8 of the extension period were compared with data from Days 1 and 7 of the core period, to accommodate differences in half life of indacaterol and tiotropium.

The data were analyzed by statisticians at Novartis Pharma AG and Pharmaceutical Product Development, Inc.

Sample size

The sample size calculation was based on the primary efficacy assessment, FEV_1 $AUC_{22–24\,h}$ on Day 1 of treatment. A standard deviation of 350 mL was chosen for the sample size calculation, based on the assumption that the standard deviation would be greater than that observed at 12 h post-dose in previous studies in COPD owing to the longer exposure in the present study (22–24 h).[3,4] Taking into account previous data, the study was powered for a treatment difference of 150 mL between the indacaterol doses and placebo. Allowing for a 10% dropout rate, 110 subjects (with at least 99 evaluable subjects) per treatment arm were needed to achieve sufficient power to detect the defined treatment difference at a significance level of 0.05, based on a two-sample *t*-test. Therefore, 660 subjects (including the SDDPI reference group) were to be randomized to the study.

The estimated number of subjects needed to enter the extension period was based on the expected FEV_1 $AUC_{22–24\,h}$ on Day 8 of tiotropium treatment. A standard deviation of 250 mL was chosen for the sample size estimation, based on the results of previous studies. To detect a treatment difference of 150 mL in a within-subject comparison between individual treatment groups and tiotropium bromide with sufficient power, 32 subjects following each treatment sequence were needed. Assuming that subjects entering the extension period would be randomly selected, 260 subjects entering the open-label study would provide a high chance (>0.99) of having at least 32 subjects in any sequence.

Pharmacokinetic assessments

For pharmacokinetic assessments, venous blood samples were taken pre-dose, 15 min, 1 and 4 h post-dose; urine was

collected during the first 4 h after administration on the first and seventh day of treatment.

Serum was prepared from blood and stored at −20 °C until analysis. A 30 mL aliquot of the urine collection was stored at −20 °C until analysis. Indacaterol was determined by means of a validated LC\MS\MS method, with a lower limit of quantification of 0.05 ng/mL in serum and 0.1 ng/mL in urine. The area under the serum concentration–time curve of indacaterol between 0 and 4 h after inhalation ($AUC_{0-4\,h}$) was determined by the linear trapezoidal method.

Subjects were excluded from the pharmacokinetic analyses of serum data if samples were mislabelled, if the pre-dose serum concentration was greater than any post-dose concentrations, or if the concentration or sampling time information was missing. If the urine collection interval was shorter than 3.2 h or longer than 4.8 h on any given visit day, or if the post-dose urine data (volume or concentration) were missing, the subject's urinary excretion data ($Ae_{0-4\,h}$) were excluded from the urine pharmacokinetic analysis.

A linear model was used for analysis of logarithmically transformed $AUC_{0-4\,h}$ with treatment a fixed effect. The geometric mean and 90% confidence interval (CI) for $AUC_{0-4\,h}$ were determined for each dose. The AUC-to-dose relationship was investigated with a linear regression analysis of the logarithmic data set. Given the dose range tested in this study (i.e. an 8-fold increase), and assuming a 90% CI of 0.8–1.25 for the ratio of dose-normalized AUCs, dose proportionality would be concluded if the 90% CI of the slope of the regression line was completely within the range of 0.89–1.11.[15] For $Ae_{0-4\,h}$, the arithmetic mean and 90% CI were determined for each dose.

Results

In total, 1,170 subjects were screened; 635 subjects were randomized and treated between July and December 2004 at 102 centers in Belgium, Canada, Denmark, France, Germany, Italy, Netherlands, Norway, Peru, Russia, Sweden, Switzerland and USA. Most randomized subjects (98.1%) completed the core period of the study. Similarly, 97.8% of the 269 subjects in the extension period completed this period. Demographics and baseline characteristics of the subjects were broadly similar between treatment groups (Table 1). Most subjects (95%) were Caucasian. The most common COPD medications prior to the start of the study were inhaled β_2-agonist (31% of subjects) and inhaled β_2-agonist plus steroid (22%). Inhaled corticosteroids (without concomitant β_2-agonist) were taken by <2% of subjects. Ten patients continued use of theophylline during the study period.

Efficacy

Core study

All doses of indacaterol were superior to placebo ($P \leqslant 0.01$) for the primary efficacy variable, FEV_1 standardized $AUC_{22-24\,h}$ on Day 1, and on Day 7 (Figure 1). Improvements of ⩾120 mL relative to placebo were observed with indacaterol 200 and 400 μg (MDDPI and SDDPI) on Day 1, and with all doses on Day 7.

Serial FEV_1 measurements on Day 1 (Figure 2A) showed that all doses of indacaterol had a significantly greater effect than placebo ($P<0.05$) from 5 min to 24 h post-dose. The 24-h efficacy was maintained on Day 7, with all doses having a greater effect than placebo ($P<0.001$) at all time points. Indacaterol 400 μg (MDDPI or SDDPI) was superior ($P<0.05$) to 50 μg at all time points except 23 h post-dose. Values for FEV_1 measured pre-dose on Day 7 showed a statistically significant increase with all doses of indacaterol relative to placebo ($P<0.001$), with mean (95% CI) increases over placebo of 160 (100, 210), 160 (110, 220), 200 (150, 260), 230 (180, 290) and 220 (170, 280) mL for indacaterol 50, 100, 200 and 400 μg MDDPI and 400 μg SDDPI, respectively.

For FVC, all doses of indacaterol were statistically superior ($P<0.01$) to placebo at all time points up to 24 h post-dose on Days 1 and 7 (Figure 2B). Significant improvements in $FEF_{25-75\%}$ (results not shown) were achieved with indacaterol relative to placebo at several post-dose time points. The 400 μg SDDPI dose significantly increased $FEF_{25-75\%}$ at all time points on Days 1 and 7 apart from the 24-h measurement on Day 7.

The use of rescue medication during the core period was higher in the placebo group than in any of the active groups on both Day 1 (25% *versus* 11–23%) and Day 7 (24% *versus* 12–17%).

Indacaterol pharmacokinetics

In general, C_{max} was observed between 15 min and 1 h post-dose. There was high inter-subject variability with respect to serum and urine pharmacokinetic variables ($AUC_{0-4\,h}$, $Ae_{0-4\,h}$) (Table 2). This was most pronounced with the 50 μg dose on Day 1, where many serum and urine concentrations were below the limit of quantification.

The $AUC_{0-4\,h}$ of indacaterol increased with dose on Days 1 and 7. Over the eight-fold increase in dose, the model predicted an increase of $AUC_{0-4\,h}$ by a factor of 7.72 (90% CI: 4.88, 12.25) on Day 1 and 9.71 (90% CI: 6.40, 14.71) on Day 7, but formal dose-proportionality could not be concluded because the 90% CIs of the slope of the linear regressions were not included in the interval of 0.89–1.11. Geometric mean serum AUCs on Day 7 were 1.3–2.2-fold higher than those on Day 1 (Table 2). The $AUC_{0-4\,h}$ values were similar at the 400 μg dose level for indacaterol administered via the MDDPI and SDDPI devices.

Urinary elimination ($Ae_{0-4\,h}$) represented less than 1% of the dose regardless of the dose level and study day (Table 2).

Open-label crossover extension period

For FEV_1 AUC, all indacaterol doses (assessed during the core period but including only the subset of subjects in each dose group who continued in the extension) provided comparable or superior efficacy to tiotropium 18 μg (assessed during the open-label extension period) from 0–4 h on Day 1, and 0–4 h and 22–24 h on Day 7/8 (Figure 3). A similar ranking was seen for FEV_1 at individual post-dose time points (Figure 4A).

Table 1 Subject demographics and baseline characteristics.

	Indacaterol					Placebo $n = 107$	Open-label extension $n = 269$
	400 μg MDDPI $n = 110$	200 μg MDDPI $n = 105$	100 μg MDDPI $n = 105$	50 μg MDDPI $n = 103$	400 μg SDDPI $n = 105$		
Age (years), mean (SD)	61.6 (8.18)	60.8 (7.97)	61.5 (8.50)	60.9 (8.08)	62.1 (7.90)	60.6 (8.32)	60.0 (7.69)
Female sex, *n* (%)	29 (26.4)	37 (35.2)	33 (31.4)	38 (36.9)	37 (35.2)	37 (34.6)	95 (35.3)
Duration of COPD (years), mean (range)	6.7 (0.0–26.2)	7.3 (0.0–30.6)	7.6 (0.1–40.2)	7.1 (0.0–35.3)	7.0 (0.2–32.3)	6.9 (0.1–42.6)	6.7 (0.0–39.1)
Smoking history, *n* (%)							
Ex-smoker	46 (41.8)	47 (44.8)	48 (45.7)	43 (41.7)	51 (48.6)	40 (37.4)	96 (35.7)
Current smoker	64 (58.2)	58 (55.2)	57 (54.3)	60 (58.3)	54 (51.4)	67 (62.6)	173 (64.3)
Estimated pack years, mean (range)	47.2 (20–133)	46.0 (20–180)	47.7 (20–225)	47.0 (20–135)	47.7 (20–144)	43.6 (10–160)	48.3 (20–225)
Baseline spirometry							
Prebronchodilator FEV_1 (L), mean (range)	1.69 (0.90–3.57)	1.76 (0.89–3.81)	1.69 (1.05–3.06)	1.68 (1.00–3.57)	1.69 (0.76–3.18)	1.68 (1.00–2.91)	1.71 (0.98–3.81)
Prebronchodilator FEV_1 (% predicted), mean (range)	56.16 (40.49–95.01)	59.31 (37.54–101.03)	57.19 (31.34–96.39)	56.78 (39.81–99.44)	57.20 (39.58–92.38)	56.01 (31.79–97.65)	56.34 (37.54–96.39)
Post-bronchodilator FEV_1 (L), mean (range)	1.87 (0.80–3.54)	1.93 (1.04–4.00)	1.87 (1.00–3.50)	1.83 (1.06–3.78)	1.87 (0.84–3.70)	1.87 (1.05–3.37)	1.90 (0.96–4.00)
FEV_1 reversibility (%), mean (range)	11.40 (−11.11–49.56)	11.26 (−18.26–4.16)	10.84 (−21.61–3.93)	10.09 (−9.63–39.37)	10.88 (−12.78–6.01)	11.71 (−8.15–47.93)	11.44 (−38.85–49.56)

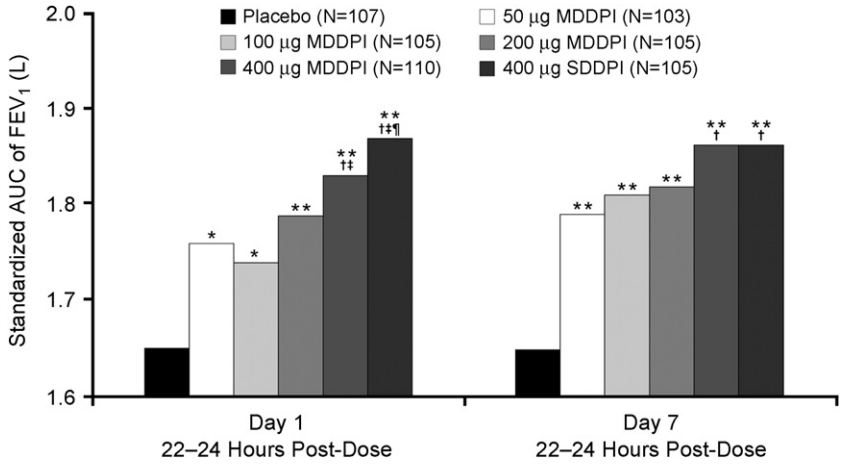

Figure 1 FEV_1 time-standardized AUC between 22 and 24 h post-dose on Days 1 and 7. $^{*}P<0.01$, $^{**}P<0.0001$ *versus* placebo; $^{\dagger}P<0.05$ *versus* 50 μg; $^{\ddagger}P<0.05$ *versus* 100 μg; and $^{\P}P<0.05$ *versus* 200 μg.

Post hoc efficacy analysis

To verify that the results were not influenced by data from subjects whose post-bronchodilator FEV_1 was normal (enrollment criteria for FEV_1 and FEV_1/FVC were based on pre-bronchodilator measurements), a post hoc analysis was carried out including only data from subjects with post-bronchodilator $FEV_1 \leqslant 80\%$ predicted. This analysis included 559 subjects (88% of all subjects), with 89, 93, 88, 97, 95 and 97 receiving indacaterol 50, 100, 200 and 400 μg MDDPI, and 400 μg SDDPI, and placebo, respectively. Of these subjects, 248 entered the extension phase.

In subjects with post-bronchodilator $FEV_1 \leqslant 80\%$, for indacaterol 50, 100, 200 and 400 μg MDDPI and 400 μg SDDPI, respectively, the adjusted mean (95% CI) standardized FEV_1 $AUC_{22-24\,h}$ values were increased relative to placebo by 110 (54, 160), 100 (46, 150), 160 (100, 210), 190 (140, 240) and 240 (170, 290) mL on Day 1 (the primary endpoint in the ITT analysis) and 150 (100, 210), 160 (110, 220), 170 (110, 230), 220 (160, 270) and 220 (160, 270) mL on Day 7 (all $p<0.001$ *versus* placebo). Figure 4 compares the 24-h FEV_1 profiles on Days 7/8 for the ITT population (subset of subjects in core and extension periods; Figure 4A) and for the subjects within this population with post-bronchodilator $FEV_1 \leqslant 80\%$ (Figure 4B).

Safety

The overall rate of adverse events in the core period was similar across treatment groups (including placebo), with the exception of the indacaterol 50 μg group, where the rate was lower (Table 3). The most frequent adverse events were headache and cough. The incidence of headache was comparable across treatment groups (3.6–6.7%) apart from a higher incidence (11.4%) in the 200 μg group. Cough (mild and short-lived) occurred at a higher frequency in the indacaterol groups compared with placebo (2.9–12.4% *versus* 0.9%) with evidence that this was a dose-related response. However, the incidence of cough decreased over the course of the study such that, by Day 7, the incidence with indacaterol was similar to that with placebo. The rate of other adverse events was low and there were no meaningful differences between treatment groups.

Two adverse events were classed as serious; both were considered unrelated to study drug. One subject receiving indacaterol 200 μg was hospitalized for investigation following the reporting of a pre-dose ECG suggestive of coronary artery disease. This was a pre-existing condition. The second serious adverse event was in a subject who suffered a pelvis fracture in the follow-up period after taking indacaterol 50 μg. Three subjects discontinued the study because of adverse events: one subject in the 400 μg MDDPI group had a COPD exacerbation; one in the 200 μg group with coronary artery disease as described above; and one subject in the 200 μg group had an episode of throat irritation.

There was no evidence of drug- or dose-related changes in hematology and no clinically relevant differences between groups in any of the biochemical variables measured. Mean post-dose serum potassium values did not differ significantly between treatment groups, apart from a difference in mean values for the 400 μg MDDPI dose versus placebo at a single time point (Day 1, 1 h). Post-dose values below normal were recorded for four, three, zero, six and seven subjects receiving indacaterol 50, 100, 200, 400 μg via MDDPI and 400 μg via SDDPI, respectively, and for one placebo subject.

For blood glucose, the only statistically significant differences between indacaterol and placebo were observed with the 400 μg SDDPI group, 1 h post-dose on Day 1 (adjusted mean [SE] 5.86 [0.111] and 5.34 [0.107] mmol/L for indacaterol and placebo, respectively), and 1 h post-dose on Day 7 (5.73 [0.129] and 5.24 [0.125] mmol/L). The only statistically significant differences between indacaterol groups were between 400 μg SDDPI and 50 μg MDDPI on Day 1 at 15 min (5.53 [0.078] and 5.23 [0.079] mmol/L, respectively) and on Day 1 at 1 h post-dose (5.86 [0.111] and 5.38 [0.110] mmol/L). Maximum post-dose values higher than normal were recorded for 22, 29, 17, 31 and 29 subjects on indacaterol 50, 100, 200, 400 μg MDDPI and 400 μg SDDPI, respectively, and for 23 placebo subjects.

There were no clinically significant differences in mean pulse rate or QTc interval between treatment groups, and no drug-related trends in systolic or diastolic blood pressure. There were no statistically significant differences in mean

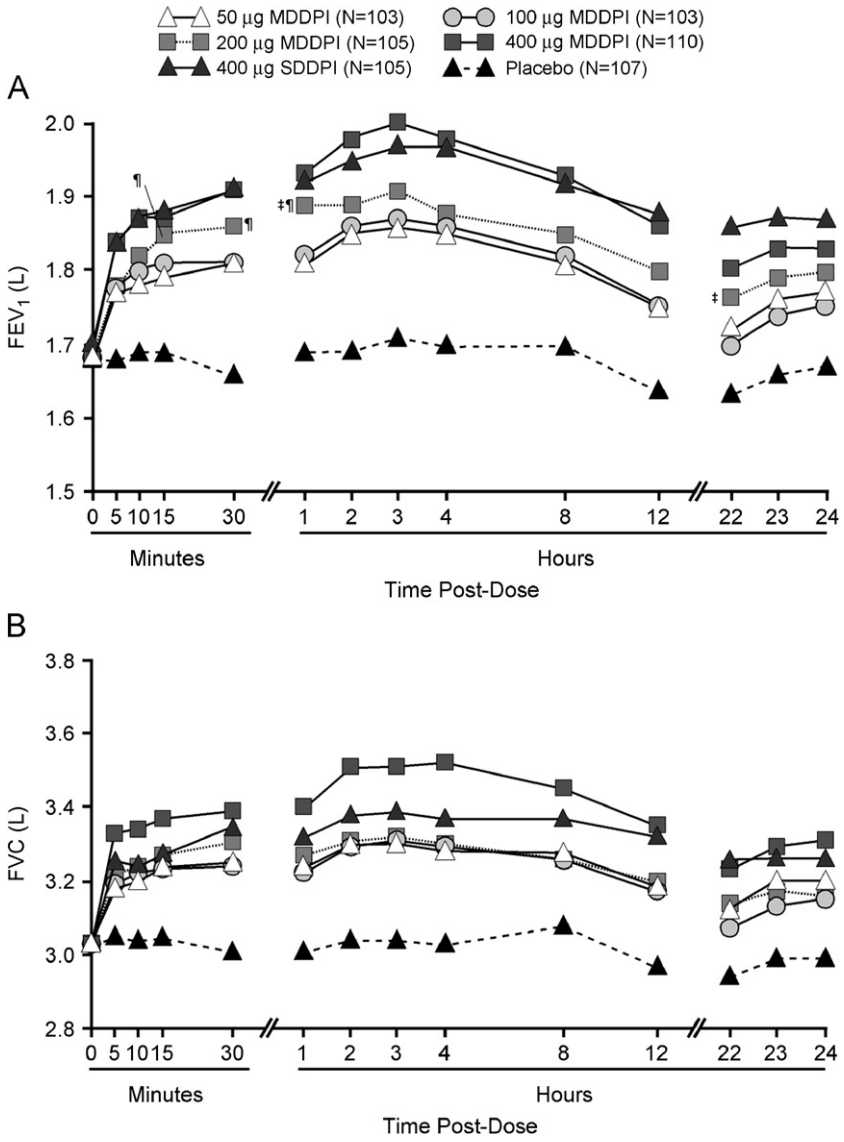

Figure 2 (A) Adjusted mean FEV_1 over 24 h on Day 1 (ITT population). All doses superior to placebo ($P<0.05$); 400 μg MDDPI and SDDPI superior to 100 μg and 50 μg at all timepoints ($P<0.05$); 400 μg MDDPI and 400 μg SDDPI superior to 200 μg ($P<0.05$) from 5 min to 12 h except 15 min and 1 h; $^{‡}P<0.05$ *versus* 100 μg; and $^{¶}P<0.05$ *versus* 50 μg. (B) Adjusted mean FVC over 24 h on Day 1 (ITT population). All doses superior to placebo ($P\leqslant0.005$); 400 μg MDDPI superior to 200, 100 and 50 μg at all timepoints ($P\leqslant0.05$) apart from one comparison (*versus* 200 μg at 22 h; $P=0.0567$); 400 μg SDDPI superior to 50 μg ($P<0.05$) at 5 and 30 min and 12 and 22 h; 400 μg SDDPI superior to 100 μg ($P<0.05$) at 30 min and 1, 8–24 h; and 400 μg SDDPI superior to 200 μg ($P<0.05$) at 8, 12, 22 and 24 h.

QTc interval between treatment groups, and no obvious differences in the number of subjects with notable QTc interval values or notable QTc interval increases. Fewer than 5% of subjects in any group had notably high values of QTc interval by Fridericia's formula. Two subjects, both in the 50 μg group, had increases >60 ms.

Discussion

The current study evaluated the bronchodilator effect of the novel selective β_2-adrenergic agonist indacaterol in subjects clinically diagnosed with COPD. Indacaterol resulted in significant bronchodilation with an onset within 5 min that peaked after 2–3 h and was maintained for 24 h after dosing with all doses evaluated. The magnitude of response compared favorably with that observed in subjects who, following washout, were subsequently treated with tiotropium. Indacaterol was well tolerated. These results suggest that indacaterol may be an effective once-daily β_2-agonist bronchodilator for use in the treatment of subjects with COPD.

There was a clear dose-response over the range tested. In the primary analysis, all indacaterol doses had a significantly greater effect than placebo on trough FEV_1 on Day 1, with the 200 and 400 μg doses exceeding the 120 mL suggested as the minimum clinically important difference for a bronchodilator in subjects with COPD.[16,17] Turning to the secondary comparisons of trough FEV_1, the 400 μg doses (via MDDPI or SDDPI), but not the 200 μg dose, were significantly more

Table 2 Geometric mean estimates and 90% CI for serum $AUC_{0-4\,h}$ and arithmetic means ± SD of urine elimination variable $Ae_{0-4\,h}$ per day, dose and device.

Day	Dose (μg)	Device	$AUC_{0-4\,h}$ (ng h/mL)			$Ae_{0-4\,h}$ (ng)	
			Geometric mean estimates*	Lower 90% CI*	Upper 90% CI*	Arithmetic mean	±SD
1	50	MDDPI	0.110 ($n = 12$)	0.078	0.155	47 ($n = 13$)	118
	100	MDDPI	0.226 ($n = 13$)	0.162	0.315	125 ($n = 13$)	310
	200	MDDPI	0.310 ($n = 22$)	0.241	0.400	146 ($n = 19$)	243
	400	MDDPI	0.920 ($n = 21$)	0.709	1.194	142 ($n = 15$)	80
	400	SDDPI	0.956 ($n = 23$)	0.745	1.226	188 ($n = 17$)	220
7	50	MDDPI	0.144 ($n = 19$)	0.108	0.192	110 ($n = 15$)	189
	100	MDDPI	0.407 ($n = 14$)	0.291	0.568	562 ($n = 13$)	1692
	200	MDDPI	0.687 ($n = 20$)	0.520	0.909	334 ($n = 20$)	451
	400	MDDPI	1.490 ($n = 20$)	1.127	1.970	589 ($n = 15$)	416
	400	SDDPI	1.532 ($n = 22$)	1.174	2.000	715 ($n = 15$)	638

*Obtained by anti-log of the least-square means and the 90% CI thereof from an ANOVA model of log $AUC_{0-4\,h}$ with treatment as fixed effect.

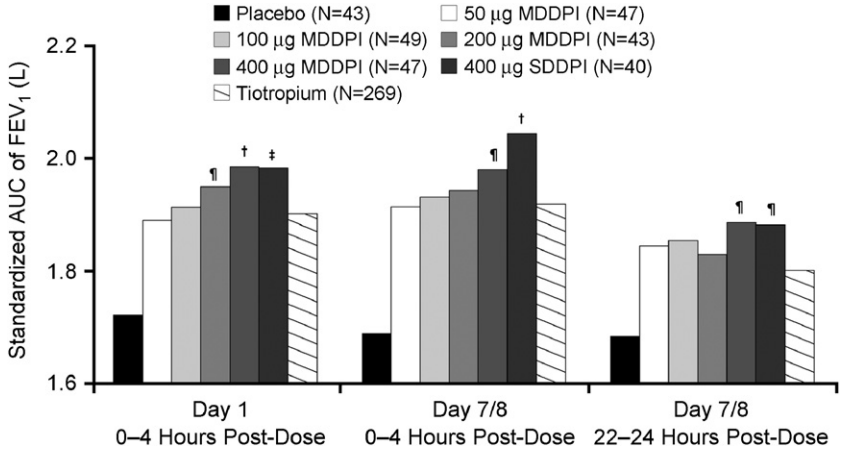

Figure 3 Adjusted mean time-standardized FEV_1 AUC obtained on Days 1 and 8 of treatment with tiotropium (open-label evaluation period) compared with data for the same subjects from Days 1 and 7 of double-blind treatment (core period; ITT population). $P < 0.0001$ tiotropium *versus* placebo at all timepoints; $^{\dagger}P \leqslant 0.001$ *versus* tiotropium; $^{\ddagger}P = 0.001$ *versus* tiotropium; and $^{\P}P < 0.05$ *versus* tiotropium.

effective than lower doses. A similar pattern was seen for trough FEV_1 on Day 7, with a generally greater magnitude of effect and a less clear-cut dose response. Both 400 μg doses exceeded the threshold for clinical relevance (210 mL difference *versus* placebo) and were significantly more effective than the lowest dose. It is suggested that the 400 μg dose was, overall, the most effective in this study.

The magnitude of the bronchodilator effect achieved with indacaterol compares favorably with that reported in other studies for salmeterol, formoterol and tiotropium.[3,5,18] While comparison between studies is problematic as different groups of subjects may respond differently, the current study also included a tiotropium treatment period. As expected, tiotropium was an effective bronchodilator. The comparisons between indacaterol and tiotropium should be interpreted carefully, since tiotropium was administered in an open-label fashion, and tiotropium was always administered in the second treatment period. Bearing these caveats in mind, among those who participated in the tiotropium treatment period, the bronchodilator response to indacaterol compared favorably with that observed with tiotropium in both the first 4 h and at 24 h after dosing.

This is the first study to compare once-daily inhaled β_2-agonist and anticholinergic bronchodilators. Although the study design results in an indirect comparison, our results suggest greater efficacy of the β_2-agonist. It will be interesting to see if this is confirmed in a study specifically designed to address this question, and in a larger group of patients with more severe disease. Previous studies are of limited help in understanding if one class of bronchodilator is superior to the other or if reported differences are due to differing durations of action, e.g. once-daily tiotropium was superior to four-times-daily ipratropium[19] or twice-daily salmeterol,[7,20] and twice-daily formoterol was superior to four-times-daily ipratropium.[3] Comparisons of the short-acting salbutamol and ipratropium showed little difference between the two bronchodilator classes, both inhaled four times daily[21] or via nebulizer three times daily.[22] In addition,

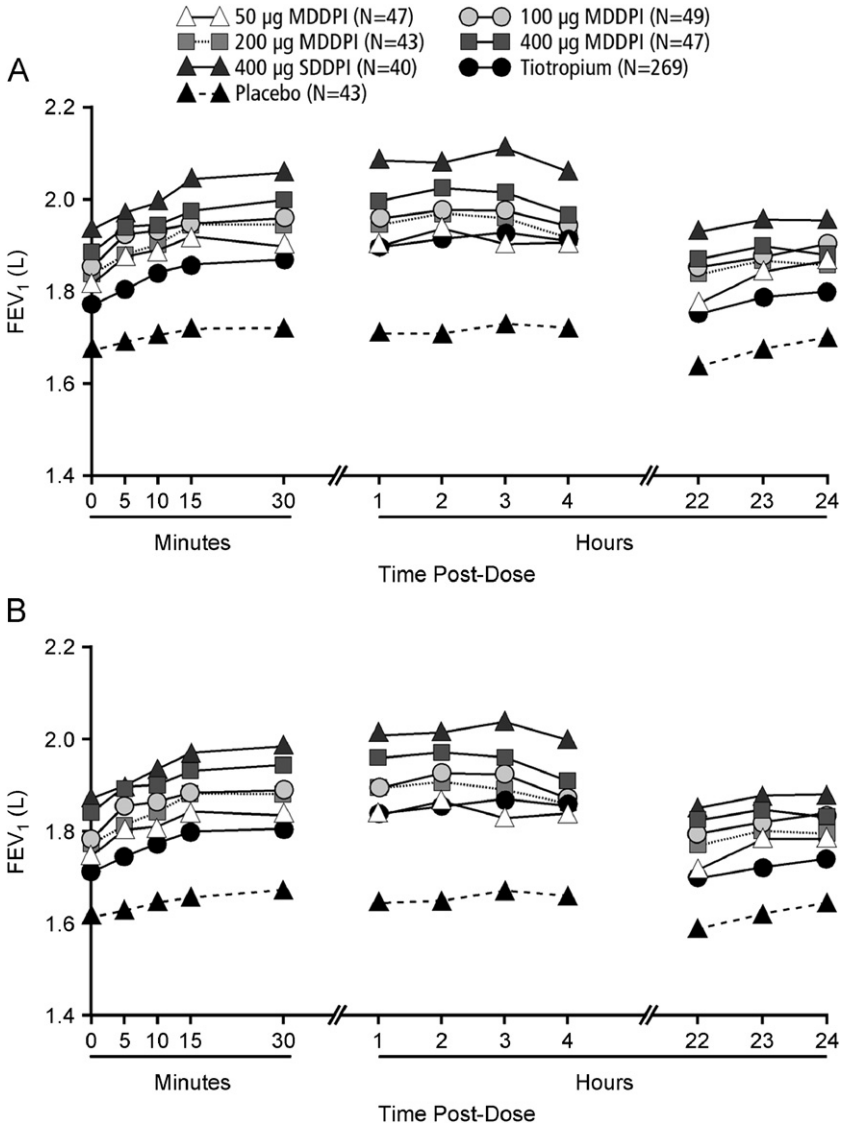

Figure 4 Adjusted mean FEV_1 on Day 7 of core period (indacaterol) and on Day 8 of the extension period (tiotropium) for: (A) the ITT population subset completing the extension period. 400 µg SDDPI superior ($P<0.001$) to tiotropium at all timepoints; 400 µg MDDPI superior ($P<0.01$) to tiotropium from 0–3 h and 22–24 h; 200 µg superior ($P<0.05$) to tiotropium from 0–30 min and 22–23 h post-dose; 100 µg superior ($P<0.05$) to tiotropium from 0–30 min and 22–24 h post-dose; 50 µg superior ($P<0.05$) to tiotropium at 5 min; and tiotropium superior to placebo ($P<0.001$) at all timepoints; and (B) for those in the same population with post-bronchodilator $FEV_1 \leqslant 80\%$ predicted. 400 µg SDDPI superior ($P<0.001$) to tiotropium at all timepoints; 400 µg MDDPI superior ($P<0.01$) to tiotropium from 0–3 h and 22–24 h; 200 µg superior ($P<0.05$) to tiotropium at pre-dose, and 15–30 min and 22–23 h post-dose; 100 µg superior ($P<0.05$) to tiotropium from 5–30 min and 22–24 h post-dose; and tiotropium superior to placebo ($P<0.001$) at all timepoints.

these studies generally compared the results in a single population. It is possible that some subjects may respond better to one class than another. Finally, these comparisons are all confounded by the variable response of subjects to a bronchodilator.[23,24] The apparent superiority of indacaterol over tiotropium in the present study may reflect a true pharmacological effect.

While the present study was primarily aimed towards studying subjects with moderate-to-severe COPD, we did not take specific steps to exclude subjects with mild COPD. Measures were taken to limit the inclusion of subjects with asthma, including asthma history, onset of symptoms prior to age 40 years and blood eosinophil count $>400/mm^3$, and a history of seasonal or perennial allergic rhinitis. As this was a dose-ranging study, we also set pre-bronchodilator lung function inclusion criteria at screening in order to provide sufficient potential to demonstrate a sizeable bronchodilator effect in order to help discriminate between indacaterol doses. It is noteworthy, therefore, that subjects with post-bronchodilator $FEV_1 \leqslant 80\%$ responded at least as well to indacaterol as did the overall population. While the overall bronchodilator effect was slightly blunted, the differences between indacaterol and placebo were maintained or even increased. Indeed, all differences for indacaterol relative to placebo for FEV_1 standardized $AUC_{22-24\,h}$ were higher for this sub-group than those observed in the ITT population. The

Table 3 Incidence of most frequent AEs (in >3% of patients in any group).

Primary system organ class	Indacaterol					
	400 μg MDDPI $n = 110$	200 μg MDDPI $n = 105$	100 μg MDDPI $n = 105$	50 μg MDDPI $n = 103$	400 μg SDDPI $n = 105$	Placebo $n = 107$
At least one adverse event	32 (29.1)	30 (28.6)	26 (24.8)	16 (15.5)	30 (28.6)	25 (23.4)
Respiratory, thoracic and mediastinal disorders	16 (14.5)	10 (9.5)	7 (6.7)	3 (2.9)	15 (14.3)	2 (1.9)
Nervous system disorders	8 (7.3)	13 (12.4)	10 (9.5)	7 (6.8)	10 (9.5)	10 (9.3)
Infections and infestations	4 (3.6)	1 (1.0)	7 (6.7)	1 (1.0)	1 (1.0)	4 (3.7)
Gastrointestinal disorders	3 (2.7)	1 (1.0)	4 (3.8)	1 (1.0)	2 (1.9)	3 (2.8)
General disorders and administration site conditions	2 (1.8)	2 (1.9)	2 (1.9)	2 (1.9)	1 (1.0)	4 (3.7)

Number (%) of subjects with AEs overall and by primary system organ class in the core period (safety population).

favorable comparison of indacaterol relative to tiotropium also held true for this subgroup, suggesting that the broader inclusion criteria applied to the overall population did not bias the results in favor of indacaterol.

Inhaled β_2-agonist bronchodilators have several class-related side effects due to systemic absorption. For β_2-selective agents, such as indacaterol, systemic side effects are likely due to activation of β_2-adrenoceptors, which are located in many tissues and may contribute to hyperglycemia, hyperkalemia, tachycardia and tremor.[25–28] In the current study, the only statistically significant effects observed were on blood glucose—and these changes were not felt to be clinically meaningful. Indacaterol demonstrated a good overall safety profile, with incidence of most adverse events similar to, or lower than, placebo. While all doses were well tolerated, there was an apparent dose-relation for cough. The cough was generally rapid in onset, mild in nature (often described as a 'tickle in the throat') and short-lived (e.g. 15 s in duration). The occurrence of cough did not persist with continued treatment, and by Day 7 the incidence of cough with indacaterol matched that of placebo.

The present study is very short and long-term studies will be necessary to demonstrate continued safety and efficacy. Bronchodilator efficacy is generally maintained over time with long-acting β_2-agonists in patients with COPD,[4,29] although diminution of bronchodilator efficacy has been described.[30] Studies will also be needed to investigate the phenomenon of cross-tolerance to the effects of rescue bronchodilators, which is a more clinically relevant form of tachyphylaxis.

After inhalation, indacaterol was rapidly absorbed. Serum exposure increased in relation to dose and was subject to slight accumulation during administration of multiple daily doses. Administration of a 400 μg dose using the SDDPI or MDDPI resulted in similar serum indacaterol levels, indicating that drug delivery characteristics are comparable between the two inhalation devices. Analysis of urine samples for indacaterol revealed that renal excretion plays a minor role in the elimination of indacaterol.

In summary, once-daily dosing of indacaterol provided effective 24-h bronchodilation and a fast onset of action in subjects with COPD, with a good overall safety and tolerability profile. The 400 μg dose of indacaterol, given via either device, appeared the most effective overall in this study, and was well tolerated. The comparison with tiotropium suggests that the bronchodilator efficacy of indacaterol is at least as good as tiotropium. The availability of an effective once-daily β_2-agonist bronchodilator could represent an important advance in the therapeutic armamentarium used to address COPD.

Conflict of interest and financial disclosure statement

SR has or has had a relationship with the following companies: Adams, Almirall, Altana, AstraZeneca, Bend, Biolipox, Centocor, Critical Therapeutics, Dey, GlaxoSmithKline, ICOS, Johnson & Johnson, Novartis, Ono Pharma, Parengenix, Pfizer, Roche, Sankyo, Sanofi, Schering-Plough, Talecris (consultancy and advisory board capacity); AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Otsuka, Pfizer (lecture capacity); Almirall, Altana, Astellas, Centocor, GlaxoSmithKline, Nabi, Novartis and Pfizer (industry support grant capacity).

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