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Indacaterol once-daily is equally effective dosed in the evening or morning in COPD

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Summary
Indacaterol is a novel, inhaled, long-acting β_2-agonist providing 24-h bronchodilation with once-daily (o.d.) dosing in patients with COPD.

In this double-blind, incomplete block crossover study, patients with moderate-to-severe COPD were randomised to receive three treatment cycles from: indacaterol 300 μg o.d. dosed PM or AM, salmeterol 50 μg twice daily or placebo, each for 14 days. Trough FEV_1 was measured 24 h after indacaterol, and 12 h after salmeterol.

Ninety-six patients (mean age: 64 years; post-bronchodilator FEV_1 57% predicted, FEV_1/FVC 55%) were randomised; 83 completed. After 14 days, the difference vs. placebo in trough FEV_1 for PM indacaterol was 200 mL ($p < 0.001$ [primary analysis]) and for AM indacaterol was 200 mL ($p < 0.001$). Compared with salmeterol, trough FEV_1 for PM indacaterol was 110 mL higher ($p < 0.001$), and for AM indacaterol was 50 mL higher (p = NS). Over 14 days, vs. placebo, both PM and AM indacaterol improved the % of nights with no awakenings (by 11.9 and 8.1 points; $p < 0.01$); the % of days with no daytime symptoms (by 6.7 and 5.5 points; $p < 0.05$); and the % of days able to perform usual activities (by 6.7 and 7.8 points; $p < 0.05$).

Indacaterol provided 24-h bronchodilation and improvement in symptoms regardless of whether taken regularly in the morning or evening.

Clinical trial registration: ClinicalTrials.gov NCT00615030.

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[f] Indacaterol: Appraising Uninterrupted Efficacy for Twenty-Four Hours.

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Introduction

Chronic obstructive pulmonary disease (COPD) is associated with rising morbidity and mortality, and is predicted to become the third leading cause of death worldwide by 2030.[1] Other co-morbid conditions are common (including cardiovascular)[2,3] these may not only impact the general health of COPD patients, but also disease management. With these challenges, pharmacologic intervention that offers ease of drug administration together with minimal side effects is of key concern in the effective management of COPD. Treatment guidelines, such as those from the Global Initiative for Chronic Obstructive Lung Disease (GOLD),[4] describe the use of bronchodilators including inhaled β_2-agonists as central to the symptomatic management of COPD, and regular treatment with long-acting bronchodilators (including long-acting β_2-agonists [LABAs]) as more effective and convenient than short-acting bronchodilators.

Indacaterol is a novel, inhaled once-daily (o.d.) LABA, that (at the time of preparation of this manuscript – August 2010) is approved in the European Union (EU) for the treatment of COPD. The recommended dose of indacaterol in the EU is 150 μg o.d.; the 300 μg dose has been shown to provide additional clinical benefit with regard to breathlessness, particularly for patients with severe COPD. In previous studies, the 24-h efficacy of indacaterol has been demonstrated following morning dosing. However, some patients – perhaps influenced by their lifestyles – may prefer a different dosing time. Further, in some cases clinicians may wish to recommend evening dosing, for example if a patient experiences nocturnal symptoms. It was therefore important to demonstrate, as part of its clinical development, that the efficacy of indacaterol was unaffected by dosing time. Consequently, this study was designed to compare the efficacy of indacaterol 300 μg dosed o.d. in the evening with that of placebo (primary efficacy variable). The study included two active comparators, indacaterol 300 μg dosed o.d. in the morning, and salmeterol 50 μg twice daily (b.i.d.).

Methods

This was a randomised, double-blind, double-dummy, placebo-controlled, incomplete block crossover study. It was conducted in accordance with the Declaration of Helsinki (1989), ICH Good Clinical Practice, and local applicable laws and regulations. Institutional review board or ethics committee approval was obtained for each participating study centre. All patients provided written informed consent prior to participating in the study.

Study population

The study population included male and female patients ≥40 years of age with moderate-to-severe COPD. Patients were to have a post-bronchodilator forced expiratory volume in 1 s (FEV_1) <80% and ≥30% of the predicted normal value, post-bronchodilator FEV_1/forced vital capacity (FVC) < 70% and a history of smoking of at least 20 pack years. Factors preventing entry to the study included recent respiratory tract infection or hospitalisation for COPD exacerbation, significant concomitant pulmonary disease, history of asthma, Type I or uncontrolled Type II diabetes, or any condition that might have compromised patient safety or compliance. Patients were also excluded if they had irregular day/night, waking/sleeping cycles (e.g., night shift workers).

Study design

The study included a pre-screening visit followed by a 14-day run-in period. During the pre-screening visit, patients were assessed for study eligibility, informed consent was obtained, and patients were transferred from prohibited to allowable COPD therapy. In the run-in period, the eligibility of patients was confirmed and baseline diary data were obtained. Eligible patients were then randomly allocated to one of 12 treatment sequences, each comprising three double-blind, 14-day treatment periods, with treatment periods separated by 14-day washout periods. In each treatment sequence, patients received three of the following four possible blinded treatments: indacaterol 300 μg o.d. administered in the evening (PM indacaterol) via a single-dose dry powder inhaler (SDDPI), indacaterol 300 μg o.d. administered in the morning (AM indacaterol) via SDDPI, salmeterol 50 μg b.i.d. via multi-dose dry powder inhaler, and placebo. Throughout the treatment periods, patients used both devices twice daily to maintain the blind. Patients were permitted to use inhaled corticosteroids at a dose and regimen to remain stable throughout the study, but only if they had had that regimen for one month prior to screening.

Efficacy assessments

On Day 1 of each treatment period, spirometry was performed at 50 and 15 min pre-dose, and at 5, 15, and 30 min, and 1 h post-dose in the morning and evening. In the evening of Day 14 of each period, spirometry was performed at 15 min pre-dose. In the morning and evening of Day 15, spirometry was performed at 23 h 10 min and 23 h 45 min post-dose, based on the time of morning and evening dosing on the previous day. Trough FEV_1 was calculated using data from assessments approximately 24 h after the two indacaterol Day 14 doses (i.e., in the morning of Day 15 for the AM regimen and the evening of Day 15 for the PM regimen), 12 h after each Day 14 salmeterol dose (i.e., in the evening of Day 14 and the morning of Day 15), and 24 h after each Day 14 placebo dose (i.e., in the morning and evening of Day 15), as illustrated in Fig. 1.

Outcomes

The primary efficacy variable was assessed by comparing the 24-h post-dose (trough) FEV_1 (mean of the FEV_1 measurements at 23 h 10 min and 23 h 45 min post-dose) of PM indacaterol with that of placebo after 14 days of treatment ('evening trough'). In addition, the difference in 'morning trough' FEV_1 post Day 14 dose between AM

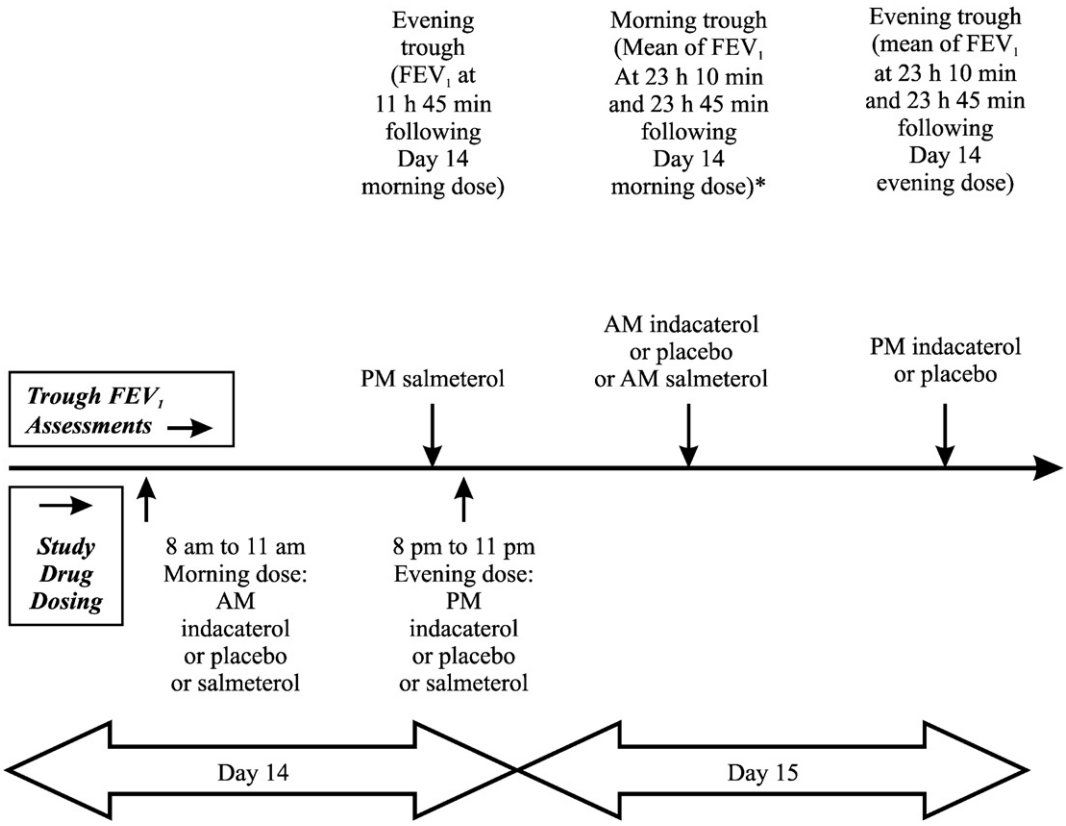

Figure 1 Trough FEV_1 assessments versus study drug dosing time. FEV_1: forced expiratory volume in 1 s; *: For salmeterol, this is equivalent to the mean of FEV_1 at 11 h 10 min and 11 h 45 min following Day 14 evening dose.

indacaterol and placebo was evaluated, as was the difference between PM indacaterol and AM indacaterol. The trough FEV_1 values for salmeterol (after morning and evening doses on Day 14) were also compared with indacaterol and placebo.

Other outcomes included assessment of FEV_1 at individual time points on Day 1 of each treatment period, and trough FVC measured after 14 days of treatment. Patients completed diaries twice daily to record the presence of symptoms; symptom scores were assessed at the end of each 2-week treatment period, to determine the percentage of nights with no night-time awakenings, the percentage of days with no daytime symptoms, and the percentage of days a patient was able to perform usual daily activities.

All adverse events (AEs) and serious AEs (SAEs) were evaluated in terms of severity, duration, and relationship to study drug. Safety was also assessed in terms of regular assessments of haematology, blood chemistry (including serum potassium and blood glucose), urine analysis, vital signs, and electrocardiogram data, with physical examinations conducted at the beginning and end of study.

The systemic exposure of indacaterol was determined by assessing the serum concentration of indacaterol in the morning and the evening at 30 min post-dose on Day 14 of each treatment period. A total volume of 3 mL of blood was drawn into a plain glass tube, left to clot at room temperature for 20 min, before being centrifuged for 10 min at approximately 2500 g. The resultant serum was assayed by liquid chromatography/tandem mass spectrometry, with a lower limit of quantification (LLOQ) of 10.0 pg/mL (expressed as base) using 200 μL of serum, with values below the LLOQ treated as zero. Serum levels were only included in data analysis when actual sampling time was recorded. The mean (standard deviation [SD]) serum concentration of indacaterol was compared between the morning and evening doses.

Sample size and statistical analysis

Assuming a standard deviation of 230 mL, as observed in previous indacaterol and formoterol studies, inflated by 10% to adjust for diurnal variation, 62 evaluable patients were required to detect a difference in trough FEV_1 of 120 mL between indacaterol 300 μg and placebo with 5% significance level (two-sided) and 90% power. Allowing a drop-out rate of 20%, a minimum sample size of 78 patients was chosen to provide 90% power for analysis of the primary endpoint.

Efficacy variables were analysed using data from the modified intention-to-treat (mITT) population, which included all randomised patients who received at least one dose of study drug. All safety analyses were performed on the safety population, which included all subjects who received at least one dose of the study medication.

The primary variable was analysed using an analysis of covariance (ANCOVA) model with patient as random effect, and period baseline FEV_1 (mean of values measured at 50

and 15 min prior to the first study drug administration on the morning of Day 1 in that period), period, treatment group, daytime (time of the day at which the FEV_1 measurements were taken: am, pm), and treatment by daytime interaction as fixed effects. All secondary efficacy analyses were performed on the mITT population using a similar ANCOVA model. Adjusted treatment differences were estimated along with the associated 95% confidence interval and two-sided *p*-values. Trough FVC data are presented as summary statistics only (change from baseline); confidence intervals were not calculated.

Results

This study was conducted at 13 centres in 3 countries (Germany, Spain, and France). The first patient was enrolled on January 22, 2008; the last patient completed on July 29, 2008.

Patient disposition, demographics, and baseline characteristics

A total of 125 patients were screened, with 96 randomised to the 12 treatment sequences, and 83 (86.5%) completing (Fig. 2). One patient, who did not receive study drug due to abnormal test procedure results, was excluded from the mITT and safety populations. All patients included in the mITT population were also included in the safety population ($n = 95$). All patients were Caucasian, with the majority male and a mean age of 64 years (Table 1). There was a wide range in duration of COPD, from newly-diagnosed patients up to 29.8 years.

Efficacy

For the primary efficacy endpoint, trough FEV_1 on Day 15, PM indacaterol 300 μg was superior to placebo ($p < 0.001$) with a difference of 200 mL, exceeding the pre-specified minimum clinically important difference of 120 mL (Fig. 3). The treatment−placebo difference in trough FEV_1 for AM indacaterol was also 200 mL ($p < 0.001$), with a difference between PM indacaterol and AM indacaterol of 10 mL (p = NS). There was a statistically significant difference in trough FEV_1 between PM indacaterol and salmeterol pm ($p < 0.001$). Although AM indacaterol was associated with a higher trough FEV_1 than salmeterol am, this difference did not reach statistical significance. The least squares mean values for trough FEV_1 after 14 days were 1.57, 1.56, 1.37, 1.36, 1.46, and 1.51 L for PM indacaterol, AM indacaterol, placebo pm, placebo am, salmeterol pm, and salmeterol am, respectively (all with standard errors of ±0.025L).

For individual time point FEV_1 values on Day 1, all active treatments were statistically superior to placebo at all post-

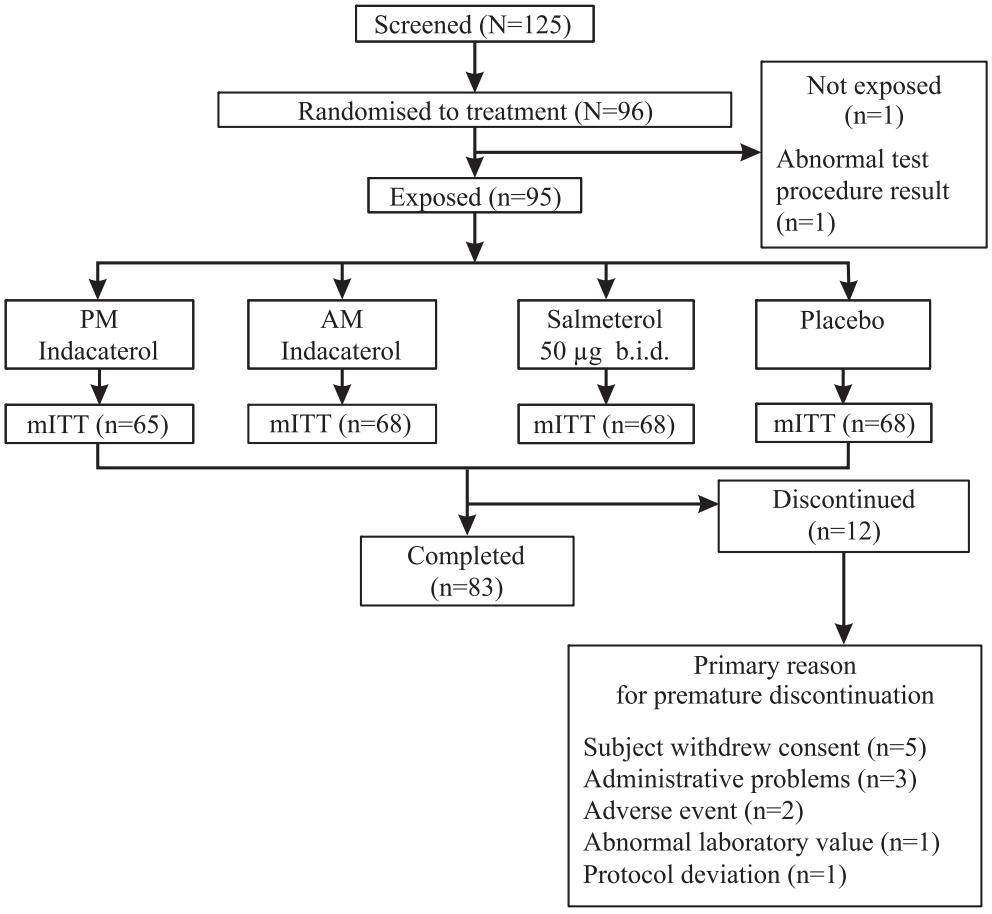

Figure 2 Patient disposition mITT: modified intent to treat.

Table 1 Demographic and baseline clinical characteristics.

	Total $N = 95$
Age (years), mean (SD)	64.1 (8.70)
Age group, *n* (%)	
40–64 years	53 (55.8)
≥65 years	42 (44.2)
Sex, *n* (%)	
Male	80 (84.2)
Female	15 (15.8)
Race, *n* (%): Caucasian	95 (100)
BMI (kg/m^2), mean (SD)	26.9 (4.52)
Duration of COPD (years), mean (SD)	8.9 (6.21)
Smoking history, *n* (%)	
Ex-smoker	53 (55.8)
Smoker	42 (44.2)
Estimated number of pack years, mean (SD)	47.3 (20.14)
FEV_1 (L), mean (SD)[a]	1.6 (0.44)
FEV_1 (% predicted), mean (SD)[a]	56.6 (13.68)
FEV_1/FVC (%), mean (SD)[a]	54.9 (8.34)
FEV_1 reversibility (%), mean (SD)[a]	12.6 (16.07)

SD: standard deviation; BMI: body mass index (weight in kilogram/height in square metres); FEV_1: forced expiratory volume in 1 s.
[a] Post-salbutamol.

exposure time points (Fig. 4; morning data not shown for PM indacaterol as this was prior to administration of study drug). At 5 min post-first dose, the treatment–placebo difference in FEV_1 for AM indacaterol was 150 mL, and for PM indacaterol was 140 mL (both $p < 0.001$ vs. placebo). The FEV_1 for both indacaterol regimens was numerically higher than that of salmeterol at all post-exposure time points, with statistical significance observed between AM indacaterol and salmeterol at all time points on Day 1 until the second salmeterol dose was taken.

Mean changes from baseline FEV_1 assessed in the evening of Day 14 (at 11 h 45 min after the time of morning dosing) and the morning of Day 15 (at 11 h 45 min after the time of Day 14 evening dosing) are shown in Fig. 5. Both indacaterol regimens provided similar bronchodilator efficacy, with changes from baseline that were higher than those with salmeterol or placebo.

Similar results were observed for trough FVC after 14 days dosing. In the analysis of evening trough FVC, the mean change from baseline for PM indacaterol was 220 mL, compared with 110 mL for salmeterol pm and 0 mL for placebo. For morning trough FVC, the mean change from baseline for AM indacaterol was 240 mL, compared with 170 mL for salmeterol am and 0 mL for placebo.

Over 14 days of treatment, compared with placebo, both indacaterol regimens significantly improved the percentage of nights with no awakenings, the percentage of days with no daytime symptoms, and the percentage of days able to perform usual activities (Table 2). Improvements in all of these analyses were consistently in favour of indacaterol (both regimens) over salmeterol, with the difference reaching statistical significance for PM indacaterol in the

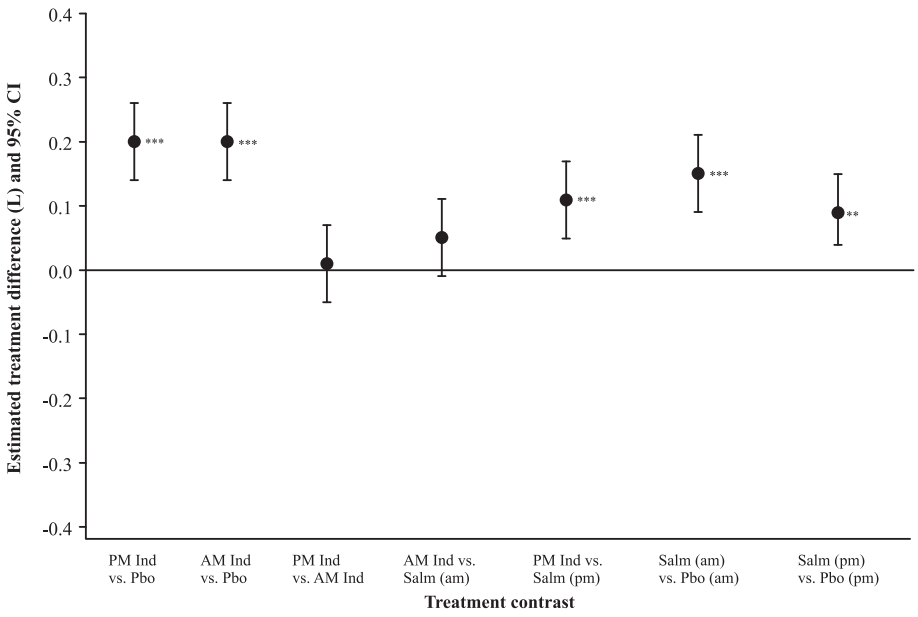

Figure 3 Estimated treatment differences and associated 95% confidence intervals of trough FEV_1 (L) after 14 days of treatment in mITT population Data presented are least squares mean treatment difference and 95% confidence interval. CI: confidence interval; FEV_1: forced expiratory volume in 1 s; **: $p < 0.01$; ***: $p < 0.001$; AM Ind: trough FEV_1 assessed 24 h after indacaterol morning dose on Day 14; Pbo: placebo; PM Ind: trough FEV_1 assessed 24 h after indacaterol evening dose on Day 14; Salm (am): trough FEV_1 assessed 12 h after salmeterol evening dose on Day 14; Salm (pm): trough FEV_1 assessed 12 h after salmeterol morning dose on Day 14.

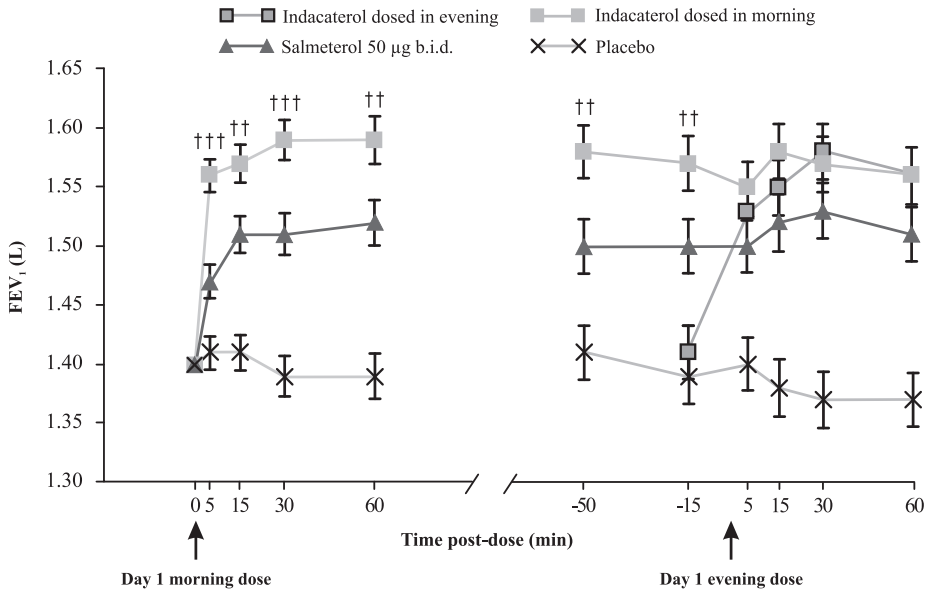

Figure 4 Least squares means of FEV_1 (L) post-period baseline on Day 1 in mITT population Data presented are least squares means ± standard error. ††: $p < 0.01$, †††: $p < 0.001$ vs. salmeterol. Treatment differences versus placebo were significant for indacaterol ($p < 0.001$) and salmeterol ($p < 0.01$) at each post-dose time point.

analysis of percentage of nights with no awakenings. There were no significant differences between the two indacaterol regimens.

Safety

The overall incidence of AEs was comparable between treatments (23.1, 25.0, 19.1, and 20.6% with indacaterol PM, indacaterol AM, salmeterol, and placebo, respectively); most AEs were mild or moderate in severity. Cough was the most frequently reported suspected drug-related AE with indacaterol treatment in this study (7.7 and 5.9% with PM and AM indacaterol, compared with 1.5% with salmeterol and 0% with placebo); all events were mild or moderate in intensity and transient in nature, and none resulted in treatment discontinuation. SAEs were reported in two patients — one of rib fracture during AM indacaterol treatment and another of lung cancer with brain metastasis reported during the follow-up period of PM indacaterol treatment; neither was suspected to be study drug-related. No death was reported during the study.

Class-related side effects of β_2-agonists include hypokalaemia, hyperglycaemia, increased pulse rate, and QTc interval prolongation. No notably low potassium values were reported in the study, and the incidence of notably high glucose levels was similar for all treatments, including placebo. No major effects on pulse rate or blood pressure were observed. One patient experienced QTc interval (Fridericia's) values >500 ms in both AM indacaterol and salmeterol treatment periods; these values were not the result of notable increases from baseline, and although the patient discontinued from the study due to an AE (anaemia, considered mild and not related to study medication), the high QTc interval values were not suspected related to study medication. The only increase in QTc interval from baseline >60 ms was in the placebo treatment group; the increase was not to a notable value.

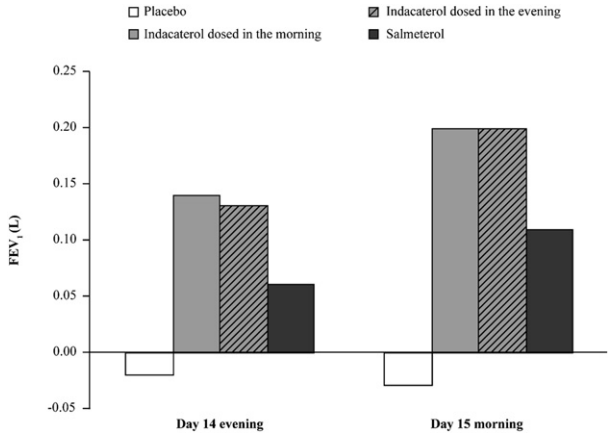

Figure 5 Mean difference from baseline in absolute FEV_1 (L) on Days 14 and 15 in mITT population Data presented are the mean (unadjusted) differences from baseline in absolute FEV_1 (L). The Day 14 evening timepoint is 15 min before the time of evening dosing (equivalent to 11 h 45 min after Day 14 morning dosing). The Day 15 morning timepoint is 11 h 45 min after the time of Day 14 evening dosing (equivalent to 23 h 45 min after Day 14 morning dosing). FEV_1: forced expiratory volume in 1 s.

Pharmacokinetics

A total of 112 samples were analysed for serum indacaterol levels, 57 from patients receiving AM indacaterol and 55 from patients receiving PM indacaterol. Four of these samples (3.6%) had indacaterol concentrations below LLOQ (three with AM indacaterol and one with PM indacaterol). The actual sampling times post-dose in the AM and PM groups compared well (mean ± SD of 0.55 ± 0.07

Table 2 Treatment contrasts of symptom scores (LSM ± SEM) over 14 days of treatment.

	Percent of nights with no night-time awakenings	Percent of days with no daytime symptoms	Percent of days able to perform usual daily activities
PM indacaterol 300 μg vs. placebo	11.9 ± 3.08***	6.7 ± 2.59*	6.7 ± 3.30*
AM indacaterol 300 μg vs. placebo	8.1 ± 3.07**	5.5 ± 2.58*	7.8 ± 3.29*
Salmeterol vs. placebo	5.4 ± 3.05	4.2 ± 2.57	3.5 ± 3.27
PM indacaterol 300 μg vs. salmeterol	6.5 ± 3.09*	2.5 ± 2.60	3.1 ± 3.33
AM indacaterol 300 μg vs. salmeterol	2.7 ± 3.08	1.3 ± 2.59	4.3 ± 3.30
PM indacaterol 300 μg vs. AM indacaterol 300 μg	3.8 ± 3.12	1.2 ± 2.61	−1.2 ± 3.34

LSM: least squares mean; SEM: standard error of the mean.
***$p < 0.001$; **$p < 0.01$; *$p < 0.05$.

and 0.53 ± 0.08 h post-dose, respectively) allowing direct comparison of the serum levels between the two groups. The mean ± SD serum concentration of indacaterol 30 min after AM indacaterol dosing on Day 14 was 465.2 ± 247.3 pg/mL, compared with 463.3 ± 246.1 pg/mL 30 min after PM indacaterol dosing.

Discussion

In this study, the clinically relevant treatment—placebo difference observed with indacaterol dosed in the evening (200 mL) was the same as that seen with indacaterol dosed in the morning. This treatment—placebo difference was well in excess of the value pre-specified as clinically significant (120 mL), as were the treatment—placebo differences at all post-exposure time points on Day 1. Furthermore, both indacaterol regimens were associated with an onset of action within 5 min of the first dose, and the two regimens resulted in similar changes from baseline in FEV_1 and in trough FVC after 14 days of dosing. One may conclude from this that the 24-h duration of bronchodilator efficacy of indacaterol is unaffected by the time of day at which the patients took their medication. Further, although there is some evidence of diurnal variation in the efficacy of indacaterol and salmeterol (as can be seen in the change from baseline data for FEV_1 on Days 14 and 15), after 14 days of dosing the two regimens of indacaterol provided consistent bronchodilator efficacy. For example, in the morning assessment on Day 15, the change from baseline FEV_1 data assessed approximately 12 h after indacaterol dosed in the evening was the same as that assessed approximately 24 h after indacaterol dosed in the morning.

In terms of the patient diary data, both indacaterol regimens provided statistically significant improvements in all endpoints compared with placebo. However, evening dosing of indacaterol was associated with a numerically greater improvement in nocturnal symptoms than morning dosing, reaching statistical significance compared with salmeterol. This suggests that it may be possible to personalise a regimen to the needs of an individual patient.

The 14-day treatment period was selected for this study as previous studies have shown that indacaterol reaches pharmacodynamic steady-state prior to this time[5,6] similarly in an earlier study the bronchodilator efficacy of salmeterol after 14 days of treatment was comparable to that seen after 1 year.[7] The efficacy of both indacaterol regimens in this study was consistently numerically greater than that of salmeterol twice daily — even at time points on the evening of Day 1 just after the second salmeterol dose had been taken, that were the equivalent of mid-way through the AM indacaterol dose interval. Similar results have been observed in two other studies comparing indacaterol and salmeterol — one of 26 weeks duration,[8] and the other a 14-day crossover design.[9] Of note, in the longer duration study there was no loss in bronchodilator efficacy with indacaterol on o.d. dosing for 26 weeks.[8]

Currently the only o.d. inhaled bronchodilator available is the long-acting muscarinic antagonist tiotropium. During its clinical development, the effect of tiotropium on the circadian variation of airway calibre was assessed, in a study comparing morning or evening dosing of tiotropium with placebo.[10] The bronchodilator results of the two tiotropium regimens were broadly comparable, with steady-state tiotropium—placebo differences in FEV_1 of 210 and 160 mL for the AM and PM regimens, respectively. Further, the investigators observed a circadian variation in lung function, with FEV_1 at its lowest in the early hours of the morning — perhaps helping to explain why patients are most likely to experience symptoms of their disease in the morning.[10] Although no studies have compared evening dosing of indacaterol with evening dosing of tiotropium, a number have compared morning dosing of the two bronchodilators. In one, for the primary endpoint (12 weeks) the trough FEV_1 for indacaterol 300 μg was 40 mL higher than that of open-label tiotropium ($p = 0.01$).[11] In a second study, the trough FEV_1 for indacaterol 300 μg was 30 mL higher than that of blinded tiotropium (p = NS).[12]

Both indacaterol regimens were well tolerated with a good overall safety profile and a low discontinuation rate. No notable differences were reported between the two active treatments and placebo in pulse rate, blood pressure, or QTc interval. In addition, the serum levels of indacaterol at 30 min post-inhalation were similar between the AM and PM treatments, indicating that systemic exposure is independent of the dosing time. This safety profile is consistent with that observed in previous studies, including a single-dose study with supratherapeutic doses up to 3000 μg,[13] and a study up to 52 weeks with doses of 300 μg or 600 μg o.d.[14]

Conclusion

These results have been obtained in a group of patients with moderate-to-severe COPD who would be suitable candidates for long-acting bronchodilator therapy. This

study, by confirming that indacaterol provides 24-h bronchodilator efficacy in both regimens, indicates that patients may be given the option of choosing a dosing time. Moreover the results suggest that once-daily indacaterol may be more effective than salmeterol dosed twice daily. The combination of once-daily dosing with choice of dosing time and fast onset of action may in turn help to enhance compliance.

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Disclosures

H Magnussen is the Managing Director of the Pulmonary Research Institute (PRI). PRI was funded by Novartis for conducting the study. H Magnussen attended several symposia sponsored by Novartis. C Verkindre has no conflict of interest pertaining to this study. D Jack, D Jadayel, M Henley, R Woessner, M Higgins, and B Kramer are employees of Novartis.

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References

1. WHO. World health statistics, http://www.who.int/whosis/whostat/2008/en/index.html; 2008. Date last accessed 04.06.10.
2. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005 Oct;**128**(4):2099—107.
3. Yeo J, Karimova G, Bansal S. Co-morbidity in older patients with COPD—its impact on health service utilisation and quality of life, a community study. *Age Ageing* 2006 Jan;**35**(1):33—7.
4. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Updated 2009, http://www.goldcopd.org.
5. Beier J, Chanez P, Martinot JB, Schreurs AJ, Tkacova R, Bao W, et al. Safety, tolerability and efficacy of indacaterol, a novel once-daily beta(2)-agonist, in patients with COPD: a 28-day randomised, placebo controlled clinical trial. *Pulm Pharmacol Ther* 2007;**20**(6):740—9.
6. 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**(4):4S.
7. Vestbo J, Pauwels R, Anderson JA, Jones P, Calverley P. Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. *Thorax* 2005 Apr;**60**(4):301—4.
8. Kornmann O, Dahl R, Centanni S, Dogra A, Owen R, Lassen C, et al. Once-daily indacaterol vs twice-daily salmeterol for COPD: a placebo-controlled comparison. *Eur Respir J*; 2010 doi:10.1183/09031936.00045810. Epub ahead of print Aug 6, 2010.
9. LaForce C, Aumann J, de Teresa Parreño L, Iqbal A, Young D, Owen R, et al. Sustained 24-h efficacy of once daily indacaterol (300 mug) in patients with chronic obstructive pulmonary disease: a randomized, crossover study. *Pulm Pharmacol Ther*; 2010 doi:10.1016/j.pupt.2010.06.005. Epub ahead of print 07.07.10.
10. Calverley PM, Lee A, Towse L, van Noord J, Witek TJ, Kelsen S. Effect of tiotropium bromide on circadian variation in airflow limitation in chronic obstructive pulmonary disease. *Thorax* 2003 Oct;**58**(10):855—60.
11. Donohue JF, Fogarty C, Lotvall J, Mahler DA, Worth H, Yorgancioglu A, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. *Am J Respir Crit Care Med* 2010;**182**:155—62.
12. Vogelmeier C, Ramos-Barbon D, Jack D, Piggott S, Owen R, Higgins M, et al. Once-daily indacaterol provides effective 24-hour bronchodilation in chronic obstructive pulmonary disease (COPD): a double-blind comparison with tiotropium. *Chest* 2009;**136**:4S.
13. Pascoe S, Reynolds C, Pleskow W, Perry S, Hmissi A, Brookman L. Safety and tolerability of single therapeutic and supratherapeutic doses of indacaterol in patients with chronic obstructive pulmonary disease (COPD). *Am J Respir Crit Care Med* 2007;**175**:A128.
14. Dahl R, Chung KF, Buhl R, Magnussen H, Nonikov V, Jack D, et al. Efficacy of a new once-daily long-acting inhaled beta2-agonist indacaterol versus twice-daily formoterol in COPD. *Thorax* 2010 Jun;**65**(6):473—9.