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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