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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) FEV_1 (mean of FEV_1 at 23 h 10 min and 23 h 45 min post-indacaterol dose) after 14 days. FEV_1 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 FEV_1 (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 FEV_1 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 FEV_1 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.

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.

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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 ≥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