Respiratory Medicine (2011) 105, 719–726

available at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: A 12-week study

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Received 7 October 2010; accepted 6 February 2011
Available online 1 March 2011

KEYWORDS
beta2-agonist;
Bronchodilator;
COPD;
Indacaterol;
Salmeterol

Summary
Background: Indacaterol is a novel, inhaled once-daily ultra-long-acting β_2-agonist for the treatment of COPD.
Methods: This 12-week randomised, parallel-group study compared the efficacy of indacaterol 150 μg once-daily to salmeterol 50 μg twice-daily in patients with moderate-to-severe COPD. Assessments included FEV_1 standardised area under curve (AUC) from 5 min to 11 h 45 min at Week 12 (primary endpoint), 24-h trough FEV_1 (mean of 23 h 10 min and 23 h 45 min post-dose) at Week 12 (key secondary endpoint), FEV_1 and FVC measured over 24-h, transition dyspnoea index (TDI) and rescue medication use.
Results: Of 1123 patients randomised 92.1% completed. Mean ± SD age was 62.8 ± 8.78 years, post-bronchodilator FEV_1 51.8 ± 12.32% predicted, FEV_1/FVC 50.6 ± 9.54%. At Week 12, FEV_1 $AUC_{5\ min-11\ h\ 45\ min}$ for indacaterol was statistically superior ($p < 0.001$) to salmeterol (adjusted mean difference [95% CI] 57 [35, 79] mL), as was 24-h trough FEV_1 (60 [37, 83] mL, $p < 0.001$). Indacaterol also showed statistical superiority over salmeterol in terms of FEV_1 and FVC measured over 24-h at Week 12. For TDI at Week 12, the mean total score was statistically superior for indacaterol versus salmeterol (difference 0.63 [0.30, 0.97], $p < 0.001$), as was the percentage of patients with a clinically relevant (i.e., ≥1 point) change from baseline (69.4% vs 62.7%, $p < 0.05$). For rescue medication, patients on indacaterol used fewer puffs/day (difference −0.18 [−0.36, 0.00] puffs/day, $p < 0.05$) and had a greater percentage of days with no rescue use (difference 4.4 [0.6, 8.2], $p < 0.05$).

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doi:10.1016/j.rmed.2011.02.008

Conclusion: Once-daily indacaterol provided statistically superior bronchodilation with an improvement in breathlessness and rescue use compared with twice-daily salmeterol.
ClinicalTrials.gov NCT00821093

Introduction

Chronic obstructive pulmonary disease (COPD), is characterised by a progressive development of airflow limitation that is not fully reversible.[1,2] Current treatment guidelines, such as those from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), describe bronchodilators as the first-line therapy for patients with moderate, severe, and very severe COPD, with a preference for inhaled over oral therapy.[2] The algorithm for COPD maintenance treatment suggests that regular use of long-acting bronchodilators is more effective than treatment with short-acting bronchodilators.[2] The shift in treatment preference from short-acting bronchodilators with multiple dosing per day to long-acting bronchodilators with once- or twice-daily dosing and prolonged duration of bronchodilation has resulted in improved clinical outcomes for COPD patients.[3,4] The consequent reduction in dosing frequency not only simplifies disease management, but has the potential to improve patient adherence and compliance.[5] Until recently, the only available long-acting β_2-agonists (LABAs) were salmeterol and formoterol, both of which have a 12-h duration of action, and hence are used twice daily for maintenance therapy of COPD. Now the approval in the European Union of indacaterol, a once-daily ultra-long-acting β_2-agonist (ultra-LABA),[6] may further simplify COPD management. In previous placebo-controlled studies, indacaterol has demonstrated 24-h bronchodilation, with a fast onset of action on first dose, and a good overall safety and tolerability profile.[7–10]

When developing a new drug, it is useful to compare its efficacy and safety with that of other drugs in its class. The present study was therefore designed to compare indacaterol 150 μg once-daily with salmeterol 50 μg twice-daily over 12 weeks.

Methods

This was a 12-week, multi-centre, randomised, parallel-group, double-blind and double-dummy study. The study was approved by the Institutional Review Board or Independent Ethics Committee of each participating centre and was conducted in accordance with the ethical principles embodied in the Declaration of Helsinki (1989) and local applicable laws and regulations. All patients provided written informed consent prior to taking part in the study.

Selection of the study populations

The study enrolled male and female patients aged ≥40 years with moderate-to-severe COPD (according to the GOLD 2007 guidelines),[11] a smoking history of at least 10 pack years, and a post-bronchodilator forced expiratory volume in 1 s (FEV_1) ≥30% and <80% of predicted normal value and post-bronchodilator FEV_1/forced vital capacity (FVC) <70% at screening (the post-bronchodilator values were measured within 10–15 min after inhaling salbutamol 400 μg). Excluded were patients with a history of asthma or concomitant pulmonary disease; type I diabetes or uncontrolled type II diabetes; and cancer either active or a history with less than 5 years disease-free survival time. A COPD exacerbation or respiratory tract infection within 6 weeks prior to screening were also grounds for exclusion.

Study designs and treatments

The study comprised a pre-screening visit, a 14-day screening/run-in period and a 12-week treatment period. At the start of the 12-week treatment period, eligible patients were randomised in a ratio of 1:1 to receive either indacaterol 150 μg once-daily via single-dose dry powder inhaler (taken in the morning) or salmeterol 50 μg twice-daily (morning and evening) via the manufacturer's proprietary dry powder inhaler. Blinding was maintained by providing placebo matching both treatments.

Permitted concomitant medication included inhaled corticosteroids (ICS), if the dose and regimen were stable for 1 month prior to screening – the dose and regimen were also to remain stable throughout the study. Patients previously on fixed combinations of ICS and LABA were switched to the equivalent ICS monotherapy at a dose and regimen maintained throughout the study. Salbutamol was provided for use as needed (but not within 6 h before study assessments).

Assessments and variables

Efficacy

Spirometry was performed to measure FEV_1 and FVC at the following time points: 50 and 15 min pre-dose, and 5 min, 30 min, 1 h, 2 h, 3 h, 4 h, 8 h, 11 h 10 min and 11 h 45 min post-dose (on Days 1, 28 and 84), and 23 h 10 min and 23 h 45 min post-dose (on Days 2, 29 and 85, based on the time that the morning dose was taken on Days 1, 28 and 84).

The primary efficacy variable was time-standardised area under curve (AUC) of FEV_1 values between 5 min and 11 h 45 min after the morning dose at Week 12. An exploratory subgroup analysis of the primary variable by age, sex, smoking status, COPD severity (moderate or less versus severe or worse), ICS use, and SABA reversibility at screening was also performed.

The key secondary efficacy variable was trough FEV_1 (defined as the mean of the FEV_1 values at 23 h 10 min and 23 h 45 min following the morning dose) determined on Day 85. Trough FEV_1 was also determined after the first day and on Days 28, 29 and 84. Other secondary efficacy variables included standardised AUC 5 min–4 h, 5 min–8 h and 8 h–11 h 45 min of FEV_1 at Week 12, individual time point FEV_1 on Day 1/2 and at Week 12, and individual time point FVC measured at Week 12.