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Safety, tolerability and efficacy of indacaterol, a novel once-daily β_2-agonist, in patients with COPD: A 28-day randomised, placebo controlled clinical trial

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Abstract

In patients with chronic obstructive pulmonary disease (COPD) classified as moderate onwards, Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines recommend regular treatment with one or more long-acting bronchodilators, such as β_2-agonists or anticholinergics. In contrast to currently available long-acting β_2-agonists, which have a duration of action of 12 h, indacaterol has demonstrated effective 24-h bronchodilation on once-daily dosing. A double-blind, randomised, placebo-controlled study was conducted to compare the safety, tolerability and efficacy of indacaterol with that of placebo, over a 28-day period, in patients with moderate COPD (as defined by GOLD 2001 criteria; equivalent to moderate-to-severe COPD in the GOLD 2005 criteria).

Patients were randomised 2:2:1 to receive indacaterol 400 μg or 800 μg or placebo once-daily (between 07:00 and 11:00 h) via a single-dose dry-powder inhaler for 28 days. Assessments included monitoring of adverse events (AEs), blood chemistry (including serum potassium and blood glucose), vital signs (blood pressure and heart rate), electrocardiograms and spirometry.

One hundred and sixty-three patients were randomised, with 155 (95%) completing the study. There were no statistically significant differences between treatment groups in the overall incidence of AEs, with AEs reported by 35%, 51% and 25% of patients in the indacaterol 400 μg, 800 μg and placebo groups, respectively. The majority of AEs were mild or moderate in severity, and there were no study-drug related serious AEs. There were no statistically significant differences between indacaterol groups and placebo in mean pulse rate and QTc interval, and isolated statistically significant ($p<0.05$) treatment-placebo differences in mean blood pressure, blood glucose and serum potassium.

There was a statistically significant improvement in FEV_1 vs placebo at all post-baseline timepoints for both indacaterol treatment groups; 30 min post-dose, adjusted mean ± SE FEV_1 indacaterol-placebo differences were: Day 1, 220 ± 36 ml and 210 ± 36 ml; Day 14, 320 ± 50 ml and 270 ± 50 ml; Day 28, 260 ± 61 ml and 200 ± 61 ml for 400 and 800 μg, respectively (all $p<0.01$ vs placebo). Bronchodilation was still apparent after 24 h, with pre-dose (i.e. trough) adjusted mean ± SE FEV_1 indacaterol-placebo differences of: Day 14, 230 ± 44 ml and 210 ± 44 ml; Day 28, 220 ± 49 ml and 210 ± 49 ml for indacaterol 400 and 800 μg, respectively (all $p<0.0001$ vs placebo).

Once-daily indacaterol was well tolerated at doses up to 800 μg with a good overall safety profile. There was no statistical difference at any dose between the safety of indacaterol and placebo. Furthermore, this study supports the previously demonstrated 24-h bronchodilator efficacy of indacaterol.

Keywords: Indacaterol; β_2-agonist; Bronchodilation; Safety; Tolerability

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by progressive airway obstruction, resulting in airflow limitation that is only partially reversible [1]. COPD represents a major cause of morbidity and mortality worldwide and is therefore associated with high levels of social and economic burden [1]. The global initiative for chronic obstructive lung disease (GOLD), which provides physicians with guidance on appropriate management of COPD, recommends the implementation of a stepwise treatment plan to manage COPD [1]. Central to control of dyspnoea in COPD are bronchodilators, such as β_2-agonists: GOLD guidelines recommend regular treatment with one or more long-acting bronchodilators in patients with moderate-to-severe COPD [1]. Two long-acting β_2-agonists are currently available, formoterol and salmeterol, both of which have approximately 12-h durations of action at recommended doses and therefore must be taken twice daily [2–7]. The only once-daily bronchodilator available at present is the anticholinergic tiotropium, which has a duration of action of at least 24 h [8,9].

Indacaterol is a novel once-daily β_2-agonist being developed for the treatment of COPD and asthma. Preclinical study results suggest that indacaterol has a longer duration of action than either formoterol or salmeterol, with a rapid onset of action, and a potentially greater cardiovascular safety margin compared with formoterol or salmeterol, for a given degree of bronchodilator activity [10]. In clinical studies in patients with asthma, indacaterol has demonstrated effective 24-h bronchodilation with a rapid onset of action and was shown to be well tolerated with a good overall safety profile [11,12].

The primary objective of the current study was to compare the safety and tolerability of once-daily administration of two doses of indacaterol (400 and 800 μg) with that of placebo, over a 28-day period, in patients with moderate COPD. Particular attention was paid to the key safety parameters for this class of drug, namely serum potassium, blood glucose, heart rate, blood pressure, QTc interval and adverse events (AEs) such as tremor, headache and nervousness. A secondary objective was to explore the bronchodilator efficacy of indacaterol, in terms of the effects on lung function.

2. Methods

2.1. Design

This was a phase II, multinational, double-blind, randomised, placebo-controlled, parallel-group study in patients with COPD. Enrolled patients entered a 2-week run-in period and were subsequently randomised to receive 28 days of study treatment, with a 7-day follow-up period to monitor AEs after study-drug cessation. The study was conducted according to Good Clinical Practice Guidelines and in accordance with the Declaration of Helsinki (1964 and subsequent revisions). The study received Institutional Review Board approval, and all patients gave written informed consent prior to the start of the study.

2.2. Inclusion and exclusion criteria

Male and female patients aged 40–75 years with a diagnosis of moderate COPD as defined by the 2001 GOLD Guidelines [13] were eligible for enrolment, provided they had a smoking history of at least 10 pack-years and their forced expiratory volume in one second (FEV_1) was $<70\%$ of their forced vital capacity (FVC). In addition, patients were required to have an FEV_1 30–70% of the Quanjer predicted normal value [14], when measured after a washout period of at least 6 h during which no short-acting β_2-agonist was inhaled, and at least 24 h after the last use of a long-acting β_2-agonist.

Patients were excluded if they had a recent respiratory tract infection or COPD exacerbation, if they had a history of asthma (blood eosinophil count $>500/mm^3$ or an onset of symptoms prior to the age of 40 years), or if they had a significant unstable cardiovascular or metabolic comorbidity. Patients were also excluded if they had used any of the following: tiotropium bromide within 7 days of run-in or ipratropium bromide, inhalers combining inhaled corticosteroids and β_2-agonists, or long-acting β_2-agonists within 24 h of run-in.

2.3. Study treatment

Patients were randomised (2:2:1) to receive indacaterol 400 μg or 800 μg or placebo, once daily via a single-dose dry-powder inhaler. Treatments were administered in the morning (between 07:00 and 11:00 h) via sequential inhalation from two dry powder capsules, each delivering indacaterol 200 μg, 400 μg or placebo, respectively, per capsule. Dose selection was based on a previous study in patients with bronchial asthma where an effective dose was considered to be in the range of 200–400 μg [11]. The present study was therefore designed to examine the safety, tolerability and efficacy of doses considered up to approximately twice the anticipated therapeutic dose for asthma.

Inhaled salbutamol was provided as rescue medication to be used as needed throughout the run-in and treatment periods. Rescue salbutamol was not to be taken within 6 h of the start of a study visit unless necessary. Prior to the run-in period, those patients using long-acting β_2-agonists were permitted regular use of salbutamol for the duration of the run-in period, and for those using inhalers combining inhaled corticosteroids and β_2-agonists, the steroid component was replaced with equivalent inhaled corticosteroid monotherapy. Patients on inhaled corticosteroid monotherapy prior to run-in continued on their pre-study regimen. During the treatment phase, all patients received the same inhaled corticosteroid regimen as they received during the run-in period. Patients were not