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24-h bronchodilator efficacy of single doses of indacaterol in Japanese patients with asthma: A comparison with placebo and salmeterol

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KEYWORDS
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Summary
Background: Indacaterol is a novel, inhaled once-daily ultra-long-acting beta-2 agonist under development as a fixed-dose combination with an inhaled corticosteroid (ICS) for asthma treatment. This study evaluated the 24-h bronchodilator efficacy of indacaterol in Japanese patients with asthma.
Methods: Randomised, placebo-controlled, 5-period crossover study. Patients with persistent asthma (18–75 years, FEV_1 50–85% predicted, ≥12% and 200 mL FEV_1 reversibility) receiving ICS were randomised to double-blind single dose indacaterol 150, 300, or 600 μg or placebo, with open-label salmeterol 50 μg twice-daily for one day in the 5th period. Primary endpoint was FEV_1AUC_{22-24h}.
Results: Of 41 randomised patients (48.8% male; mean age: 47.8 years), 39 completed. All indacaterol doses showed significantly higher FEV_1AUC_{22-24h} than placebo ($P < 0.001$), with treatment–placebo differences of 180, 220, and 260 mL for indacaterol 150, 300, and 600 μg, respectively (salmeterol–placebo difference 170 mL; $P < 0.001$). For individual time-point FEV_1, all indacaterol doses were superior to placebo from 5 min to 24 h post-dose

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($P < 0.001$). Compared with salmeterol, all indacaterol doses were superior from 5 to 30 min ($P < 0.05$); in addition indacaterol 300 μg and 600 μg were superior at a number of subsequent time points. Changes in safety parameters with indacaterol were similar to placebo. All indacaterol doses were well tolerated.

Conclusion: Single dose indacaterol provided sustained 24-h bronchodilation with a faster onset of action than salmeterol and a good overall safety and tolerability profile in Japanese patients with asthma. These results are consistent with data from Caucasian populations.

Introduction

Worldwide, asthma affects people of all ages causing substantial debilitating symptoms and leading to a reduced quality of life.[1,2] Evidence from most studies, including longitudinal surveys, suggests that the prevalence of asthma has increased over the past decades in many parts of the world, including Japan.[3–7] Persistent asthma is most effectively controlled with inhaled corticosteroids (ICSs) administered daily on a long-term basis.[8] For patients with asthma not adequately controlled with a low-dose ICS alone, current treatment guidelines recommend the addition of a long-acting beta-2 agonist (LABA) to the existing ICS therapy.[7–10]

The goal of asthma management is to achieve and maintain control of symptoms — a major obstacle to which has been low patient adherence to medication plans.[11] A key factor contributing to poor adherence is a complicated or multiple treatment regimen, with simplified dosing regimens known to improve compliance.[11,12] Currently available inhaled LABAs (e.g., salmeterol and formoterol) have an approximately 12-h duration of action, necessitating twice-daily (bid) dosing to provide optimal clinical efficacy.[13,14] Thus the availability of a once-daily beta-2 agonist with a 24-h duration of action combined with a once-daily ICS could improve clinical outcomes in asthma by providing increased patient convenience and sustained bronchodilation.

Indacaterol is a novel, once-daily, inhaled, ultra-LABA under development as a fixed-dose combination with ICS for the treatment of asthma. In preclinical studies, indacaterol demonstrated a sustained bronchodilator and bronchoprotective effect, with a fast onset of action (comparable to salbutamol and formoterol) and greater cardiovascular safety margin than formoterol or salmeterol.[15,16] Furthermore, in earlier clinical studies involving mostly the Caucasian population, indacaterol showed effective 24-h bronchodilation, with a fast onset of action and a good overall safety and tolerability profile.[17–21] The present dose-ranging study was the first to investigate the 24-h bronchodilatory efficacy and safety of single doses of indacaterol 150, 300, and 600 μg delivered via a single-dose dry-powder inhaler (SDDPI) in Japanese patients with asthma. Given its similarity to a study conducted in a Caucasian population it helps to evaluate the ethnic sensitivity of the efficacy and safety of indacaterol.[21]

Methods

This was a Phase II, multicentre, randomised, double-blind, placebo-controlled, crossover, dose-ranging study conducted between November 2006 and November 2007 at 11 specialised allergy and respiratory care units in Japan (ClinicalTrials.gov registration no.: NCT00403754).[22] The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The study was approved by the institutional review board of each participating study centre, and all patients provided written informed consent before participating in the study.

Study population

The study recruited Japanese patients (aged 18—75 years) with a clinical diagnosis of asthma according to the 2006 Japanese asthma prevention and management guideline[7] (FEV_1 between 50% and 85% of the predicted normal value at screening, with ≥12% and 200 mL reversibility in FEV_1 within 30 min after inhalation of salbutamol 200 μg). In addition, patients must have received daily ICS treatment—defined as fluticasone propionate 200—800 μg (or equivalent)—in a stable regimen for at least 4 weeks before the screening visit (Visit 1).

Patients were excluded if they underwent hospitalization or emergency room treatment for an acute exacerbation of asthma in the 6 months before Visit 1, had respiratory disease other than asthma, had respiratory tract infection within 4 weeks before Visit 1, used tobacco products within 6 months before Visit 1, or had a smoking history of more than 10 pack-years. The other exclusion criteria included seasonal allergies that might cause deterioration of asthma; allergy to beta-2 agonists, sympathomimetics, and inhaled medications; ischemic heart disease; arrhythmia; uncontrolled hypertension; type 1 diabetes; cancer; and a prolonged QT interval.

Study design and treatments

The study comprised a 14-day screening period, four double-blind treatment periods (Visits 2—9), and an open-label treatment period (Visits 10 and 11) (Fig. 1). The visits on Day 1 and Day 2 of each treatment period were on consecutive days. Following screening, all eligible patients were randomised equally (at Visit 2), using a validated automated system, to one of four treatment sequences to receive a single dose of indacaterol 150, 300, and 600 μg or placebo via an SDDPI. Patients who completed the double-blind treatment period entered a single-day, open-label treatment period with salmeterol 50 μg bid delivered via the manufacturer's proprietary multidose dry-powder inhaler.