# Tolerability of indacaterol, a novel once-daily $\beta_2$-agonist, in patients with asthma: a randomized, placebo-controlled, 28-day safety study

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**Background:** Indacaterol is a novel, inhaled, once-daily $\beta_2$-agonist.

**Objective:** To investigate the safety and tolerability of indacaterol at doses of 400 and 800 $\mu$g/d.

**Methods:** Randomized, double-blind, placebo-controlled, parallel-group, multicenter, 28-day study. Patients with persistent asthma (forced expiratory volume in 1 second [$FEV_1$] $\geq$60% predicted, $\leq$1,600 $\mu$g of beclomethasone dipropionate or equivalent daily) received indacaterol, 400 $\mu$g (n = 59) or 800 $\mu$g (n = 59), or placebo (n = 26) once daily via a single-dose dry powder inhaler. Safety assessments were performed before and after dosing on days 1, 14, and 28, with particular attention to key $\beta_2$-agonist safety variables.

**Results:** A total of 144 patients were randomized, with 135 (93.8%) completing the study. Indacaterol was well tolerated: the incidence of adverse events (AEs) was similar between the active and placebo groups, and AEs, when they occurred, were mild or moderate for most (98.2%). There was no dose-response relationship between indacaterol and the incidence of AEs (400 $\mu$g, 40.7%; 800 $\mu$g, 37.3%; and placebo, 38.5%). Few AEs considered as $\beta_2$-agonist class effects occurred (none leading to withdrawal). Small differences between indacaterol and placebo in mean serum potassium ($\leq -0.29$ mmol/L) and glucose ($\leq$0.93 mmol/L) levels were occasionally statistically significant ($P < .05$) but not regarded as clinically meaningful**.** As expected for a $\beta_2$-agonist, there was some indication of a trend in QTc prolongation with increasing exposure (maximum mean change, 8.9 milliseconds; $P < .05$ vs placebo). Significant increases in $FEV_1$ ($P < .05$) were seen at all postbaseline time points for both indacaterol doses vs placebo, with indacaterol-placebo differences 30 minutes after dosing of 0.21 to 0.25 L and before dosing on days 14 and 28 (approximately 24 hours after the previous dose) of 0.15 to 0.23 L.

**Conclusion:** Indacaterol had a good overall safety profile and was well tolerated at both doses, with predose $FEV_1$ results on days 14 and 28 indicating 24-hour bronchodilator efficacy.

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## INTRODUCTION

Inhaled $\beta_2$-agonist bronchodilators are widely used in the treatment of patients with asthma and chronic obstructive pulmonary disease (COPD). Systemic absorption of these agents can lead to $\beta_2$-adrenoceptor–mediated cardiovascular effects, such as palpitations, tachycardia, changes in blood pressure, and electrocardiographic abnormalities,[1–3] together with adverse events (AEs), such as hypokalemia, hyperglycemia, headache, and skeletal muscle tremor.[1–4]

Indacaterol is a novel once-daily $\beta_2$-agonist that has demonstrated 24-hour bronchodilator efficacy together with a fast onset of action in patients with asthma and COPD.[5,6] Because indacaterol has a long duration of action, it is especially important to establish its safety profile. The primary objective of this study was to evaluate the safety and tolerability of 28 days of treatment with once-daily indacaterol, 400 and 800 $\mu$g (2–4 times the anticipated therapeutic dose at the planning of the study) compared with placebo. An exploratory analysis

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of spirometry results was included to evaluate bronchodilator efficacy.

## METHODS

### *Study Design*

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 144 adolescent and adult patients with persistent asthma. After a 14-day run-in phase to allow for adjustments to existing asthma therapy and evaluate asthma stability, patients were randomized in a 2:2:1 ratio to 28 days of treatment with indacaterol, 400 $\mu$g, indacaterol, 800 $\mu$g, or placebo (administered once daily in the morning between 7 AM and 11 AM via a single-dose dry powder inhaler). A follow-up visit was made 7 days after completion of treatment. A validated system was used that automated randomized assignment to treatment groups.

The design of the study was approved by the relevant institutional review boards and ethics committees and was performed in accordance with the Declaration of Helsinki (1964 and amendments), and all patients or their parent or legally acceptable representative gave written informed consent.

### *Inclusion and Exclusion Criteria*

The study included male and female patients aged 12 to 65 years diagnosed as having asthma who had been receiving daily treatment with an inhaled $\beta_2$-agonist and an inhaled corticosteroid, up to 1,600 $\mu$g of beclomethasone dipropionate (or equivalent), in a stable regimen for the past month. At screening, patients were required to demonstrate a forced expiratory volume in 1 second ($FEV_1$) of 60% or greater predicted and (at screening or recently documented) an increase in $FEV_1$ of 12% or greater over baseline $FEV_1$ within 30 minutes after inhalation of albuterol, 380 $\mu$g.[7] Patients were excluded if they had a smoking history of more than 10 pack-years, had used tobacco products within the previous 6 months, had been diagnosed as having COPD, had been hospitalized because of an acute asthma attack within 3 months before screening, or had a respiratory tract infection within 1 month before screening. Women of childbearing potential who were not using a reliable form of contraception were excluded.

The following medications were not allowed during the study and their use was discontinued with appropriate washout periods: fixed combinations of long-acting $\beta_2$-agonists and inhaled corticosteroids (24-hour washout), long-acting $\beta_2$-agonists (24 hours), parenteral and oral corticosteroids (3 months), theophylline and other xanthines (1 month), ipratropium bromide (24 hours), and tiotropium bromide (7 days). Anti-IgE therapy was not an exclusion criterion because the drug was not approved in Canada or Europe at the time of the study.

### *Concomitant Medication*

Patients taking long-acting $\beta_2$-agonists were switched to short-acting $\beta_2$-agonists for the run-in phase, and the corticosteroid component of any fixed combination therapy (inhaled corticosteroid and $\beta_2$-agonist) was replaced with an equivalent separate inhaler. Patients already taking inhaled corticosteroids from a separate inhaler continued to take their prestudy regimen. Albuterol was provided as rescue medication, but was not to be taken from 6 hours before a study visit until completion of spirometry, unless necessary. Other bronchodilator medication was not permitted.

The following medications for asthma and related conditions were permitted, provided treatment had been stable for at least 1 month before the study: nasal corticosteroids, antihistamines, cromones, ketotifen, leukotriene antagonists, and allergen immunotherapy for allergic rhinitis.

### *Study Assessments*

Safety assessments were performed on days 1, 14, and 28; hematological, blood chemistry, blood pressure, and electrocardiographic assessments were performed before and 60 minutes after dosing; spirometry was performed before and 30 minutes after dosing; and urinalysis was performed before dosing only. Physical condition was regularly monitored, and all AEs were monitored and reported. Spirometry included $FEV_1$, forced vital capacity (FVC), and forced expiratory flow between 25% and 75% of FVC. Particular attention was paid to key safety variables for $\beta_2$-agonists, namely, serum potassium level, blood glucose level, heart rate, blood pressure, QTc interval (calculated using the Fridericia and Bazett formulas: $QTc = QT/\sqrt{3RR}$ and $QTc = QT/\sqrt{RR}$, respectively, where RR denotes R-R interval), and AEs, such as tremor and headache. At each visit, patients were asked to estimate their daily use of short-acting inhaled $\beta_2$-agonist since the previous visit.

### *Statistical Analysis*

This was primarily a safety study, aimed at hypothesis generation rather than hypothesis testing, and, therefore, no formal sample size calculation was performed. It was planned to randomize 148 patients so that, with an assumed dropout rate of 10%, 133 patients would complete the study, approximately 106 of whom would have been exposed to indacaterol for 28 days. All safety analyses were performed on the safety population, which was defined as all randomized patients who received at least 1 dose of study medication. Adverse events were summarized for each treatment group. Laboratory data were summarized as absolute values and changes from baseline. Additional analyses were performed for serum potassium level, blood glucose level, QTc interval, and $FEV_1$ using an analysis of covariance (ANCOVA) model, with terms for country, treatment, and baseline values.

Analyses of $FEV_1$ using the previously described ANCOVA model were performed using data from the intention-to-treat population, which was defined as all randomized patients who received at least 1 dose of study medication and had at least 1 postdose $FEV_1$ measurement.

## RESULTS

### *Patients*

Patient recruitment commenced on February 17, 2004, and the study was completed on July 15, 2004, with patients