

Bronchodilator Efficacy of Single Doses of Indacaterol in Japanese Patients with COPD: A Randomised, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Background: Indacaterol is an investigational, novel, inhaled once-daily ultra-long-acting beta-2 agonist for the treatment of chronic obstructive pulmonary disease (COPD). This study evaluated the 24-h bronchodilatory efficacy and safety of indacaterol in Japanese patients with COPD.

Methods: This Phase-II, randomised, placebo-controlled, crossover study comprised four double-blind, single-dose treatment periods (washout between periods: 14-28 days). Japanese patients aged 40-75 years with moderate-to-severe COPD were randomised to receive single doses of indacaterol (150, 300, or 600 µg) or placebo via a single-dose dry-powder inhaler. Efficacy (primary endpoint: standardised FEV₁AUC_{22-24h}) and safety were assessed for 24 h post-dose in each treatment period.

Results: Of the 50 patients randomised (92% male; mean age, 67.2 years), 45 completed the study. Standardised FEV₁AUC_{22-24h} was significantly higher for all indacaterol doses as compared with placebo, with clinically relevant differences of 130, 160, and 170 mL for 150, 300, and 600 µg, respectively ($P < 0.001$). The improvement in FEV₁ was seen as early as 5 min post-dose with indacaterol and sustained for 24 h ($P < 0.001$ vs placebo at all time points). All indacaterol doses were well tolerated and showed no clinically meaningful effect on pulse rate, blood pressure, QTc interval, and laboratory parameters when compared with placebo.

Conclusions: In the Japanese COPD population studied, single doses of indacaterol (150, 300, and 600 µg) provided sustained 24-h bronchodilation, with onset of action within 5 min post-dose. All doses were well tolerated. These results are consistent with data from Caucasian populations.

KEY WORDS

beta2-agonists, bronchodilator, COPD, efficacy, indacaterol

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality

worldwide, accounting for a loss of approximately 30 million disability-adjusted life years in 2001.¹ The prevalence of COPD in Japan in adults aged ≥ 40 years is estimated to be at least 8.6%.² The increase in

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analysis, and interpretation of data. All authors substantially contributed in drafting and revision of the manuscript for important intellectual content and have read and approved the final manuscript.

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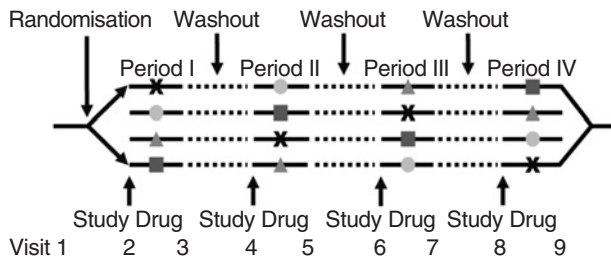


Fig. 1 Study design. (X) placebo, (○) indacaterol 150 µg, (△) indacaterol 300 µg, and (■) indacaterol 600 µg.

global COPD prevalence and mortality is anticipated to continue, with the disease being predicted to become the third leading cause of death worldwide, after heart disease and stroke, by 2020 (8.6% of all deaths).^{3,4}

COPD is characterised by airflow limitation caused by an abnormal inflammatory response in the lung. This airflow limitation is usually progressive and not fully reversible.⁵ According to the Guidelines for the Diagnosis and Treatment of COPD issued by the Japanese Respiratory Society (JRS),⁶ and the Global Initiative for Chronic Obstructive Lung Disease guideline for COPD Diagnosis, Management, and Prevention (GOLD)⁵ bronchodilators such as beta2-agonists and anticholinergics are central to the symptomatic management of COPD. By altering airway smooth muscle tone, bronchodilators improve expiratory flow, reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance.^{5,7,8} Regular use of long-acting bronchodilators has been shown to be more effective and convenient than treatment with short-acting bronchodilators.⁹⁻¹² Currently available inhaled long-acting beta2-agonists (LABAs), such as salmeterol and formoterol, induce bronchodilation that lasts for approximately 12 h and are administered twice daily.¹³⁻¹⁶

Indacaterol is a novel, once-daily, inhaled ultra-LABA¹⁷ currently in development for the treatment of COPD. The efficacy and safety of once-daily dosing of indacaterol in COPD patients have already been demonstrated in several studies that involved mostly the Caucasian population.¹⁸⁻²⁰ This is the first study evaluating the effect of indacaterol in Japanese patients with COPD, and 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.²⁰

The aim of the present randomised, double-blind, placebo-controlled study was to examine the 24-h bronchodilatory efficacy of a single dose of indacaterol 150, 300, and 600 µg, administered via a single-dose dry powder inhaler (SDDPI) in Japanese patients with COPD.

METHODS

This was a multicentre, randomised, double-blind, placebo-controlled, crossover, dose-ranging, Phase II study conducted between December 2006 and October 2007 at 11 specialised respiratory care units in Japan (ClinicalTrials.gov registration no.: NCT00403845).²¹ The study was approved by the institutional review board of each participating study centre and was conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice, applicable local regulations, and the ethical principles embodied in the Declaration of Helsinki. Written informed consent was obtained from each patient before their participation in the study.

STUDY POPULATION

Eligible for enrolment were male and female Japanese patients aged 40-75 years with clinically diagnosed COPD (according to the JRS Guideline for the Diagnosis and Treatment of COPD),⁶ a smoking history of ≥ 20 pack years, post-bronchodilator forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) <70%, and FEV₁ $\geq 30\%$ but <80% of predicted normal value at screening. Patients were excluded from the study if they had a history of heart failure, myocardial infarction, or asthma; had been hospitalised for a COPD exacerbation in the 6 months prior to screening; or had experienced a respiratory tract infection within 1 month prior to screening.

STUDY DESIGN AND TREATMENTS

The study comprised a 14-day screening period, during which patients were assessed for eligibility and monitored to ensure that they remained stable on their permissible COPD treatment. The screening period was followed by a randomised, double-blind treatment period (Fig. 1). At baseline, eligible patients were randomised equally to one of four treatment sequences (each with four double-blind treatment periods, with each patient receiving each of the four different treatments—one in each treatment period). Randomisation was performed using a validated system that automated the random assignment of the treatment sequences to randomisation numbers.

On Day 1 of each treatment period (Visits 2, 4, 6, and 8), patients received a single dose of indacaterol 150, 300, or 600 µg or placebo via an SDDPI (taken between 08:00 and 10:00 AM) according to the assigned treatment sequence. Each treatment period was separated by a washout period of 14-28 days. Treatment allocation was concealed from the patients, investigating staff, and the clinical trial team by using study drugs of identical packaging, labelling, schedule of administration, and appearance.

CONCOMITANT MEDICATION

Allowable therapy included the use of inhaled corticosteroids, provided the regimen had been stabilised for at least 1 month prior to the screening visit and the same regimen was continued for the duration of the study. The following medications could not be used prior to screening or administration of study drug on Day 1 in each treatment period for at least the minimum washout period specified, as indicated within the parentheses: the long-acting anticholinergic tiotropium (7 days), short-acting anticholinergics (8 h), short-acting beta₂-agonists (6 h), LABAs (48 h), and xanthine derivatives (48 h). Salbutamol was the only rescue medication permitted throughout the study, although the visits had to be rescheduled if it was taken within 6 h prior to the first spirometry measurements during that visit.

ASSESSMENTS

Efficacy and safety were assessed for 24 h post-dose in each treatment period. Efficacy was assessed by spirometry using the same model of spirometer (MICROSPIRO HI-201[®], Nihon Kohden Corporation, Tokyo, Japan) in all patients. FEV₁, FVC, and forced expiratory flow 25% to 75% (FEF_{25-75%}) were determined pre-dose (15 min prior to inhalation) and at 5, 15, and 30 min and 1, 2, 4, 8, 12, 22, 23, and 24 h post-dose. The primary efficacy outcome was the time-standardised area under the curve (AUC) of FEV₁ values measured between 22 and 24 h post-dose (FEV₁AUC_{22-24h}; L), calculated using the trapezoidal rule and adjusted for the area per time unit by using the scheduled time of measurements for FEV₁. Secondary efficacy outcomes included percent change in FEV₁ from baseline at individual post-dose time points; peak FEV₁ (defined as the maximum FEV₁ value recorded between 5 min and 4 h post-dose); standardised FEV₁AUC_{0-24h}, and individual time-point FEV₁, FVC, and FEF_{25-75%}.

Safety assessments involved recording of all adverse events (AEs) and serious adverse events (SAEs); monitoring of haematology and blood biochemistry at regular time points in each treatment period; urinalysis; and regular assessments of vital signs, electrocardiogram (ECGs), physical condition, and body weight.

SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSES

The three main treatment comparisons in this study were indacaterol 150 µg versus placebo, indacaterol 300 µg versus placebo, and indacaterol 600 µg versus placebo. A sample size of approximately 40 patients was estimated prior to the study, assuming a minimal clinically important difference of 120 mL between each indacaterol dose and placebo in terms of standardised FEV₁AUC_{22-24h},^{22,23} a standard deviation of

220 mL,¹⁸ a two-sided significance level of 10% (adjusted to 3.3% using a Bonferroni correction for the three main treatment comparisons), and a power of 85%. Allowing for a 15% dropout rate and with the number inflated to ensure balance across the treatment sequences, it was calculated that 48 patients were to be randomised.

The primary efficacy analysis was performed on a modified intention-to-treat (mITT) population, which included all randomised patients who received at least one dose of study drug and had post-randomisation efficacy data. Patients receiving only one treatment did not contribute to the analyses of treatment contrasts, although they remained in the population for the calculation of individual treatment means. All patients who received at least one dose of study drug were included in the safety population, which was used in the analysis of all safety variables. The safety population allowed for the inclusion of non-randomised patients who might have received the study drug in error. For both populations, patients were analysed according to the treatment received. Demographic and baseline characteristics were summarised for all patients in the safety population.

The primary efficacy variable, standardised FEV₁ AUC_{22-24h}, was calculated using the trapezoidal rule and was adjusted for the area per time unit by using the scheduled time of measurements for FEV₁. Treatment differences between each indacaterol dose and placebo were tested using analysis of covariance (ANCOVA), with patient, period, and treatment group modelled as fixed effects and period baseline FEV₁ as a covariate. Period baseline FEV₁ was defined as the value measured prior to the inhalation of study drug in each treatment period. Adjustment for multiple comparisons was made using a stepwise Dunnett test implemented via a closed test procedure. Similar ANCOVA models were used to analyse all secondary efficacy variables. Laboratory data for haematology, blood biochemistry, and urinalysis; ECG data; and measurements of vital signs were summarised descriptively by treatment group. The corrected QT interval was calculated from the QT and RR intervals using Fridericia's formula (QTcF).^{24,25} All tests of hypotheses used were two-tailed and interpreted at the 10% significance level (as this was a dose-ranging Phase II study). The data were analysed using SAS statistical software version 8.2 (or higher) for Windows (SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

PATIENT DISPOSITION, DEMOGRAPHICS, AND BASELINE CHARACTERISTICS

Out of 84 patients screened, 50 were randomised. The most common reason for failing to meet the eligibility criteria was unacceptable test results, mainly with respect to spirometry and laboratory findings

Table 1 Patient demographics and baseline characteristics (safety population)

Parameter	Statistic	Total (N = 50)
Age, years	Mean (SD)	67.2 (5.94)
	Range	48-75
Sex, n (%)		
Male		46 (92.0)
Female		4 (8.0)
Weight, kg	Mean (SD)	57.5 (10.05)
Body mass index, kg/m ²	Mean (SD)	21.6 (3.09)
Duration of COPD, years	Mean (SD)	2.9 (3.69)
	Range	0.02-17.03
FEV ₁ (post-bronchodilator) at screening, L	Mean (SD)	1.46 (0.395)
% predicted FEV ₁ (post-bronchodilator) at screening	Mean (SD)	53.2 (13.82)
	Range	31.3-77.8
FEV ₁ reversibility at screening, %	Mean (SD)	12.06 (9.62)
FVC (post-bronchodilator) at screening, L	Mean (SD)	3.07 (0.686)
FEV ₁ /FVC (post-bronchodilator) at screening, %	Mean (SD)	48.2 (11.28)
Smoking History, n (%)		
Ex-smoker		31 (62.0)
Current smoker		19 (38.0)
Smoking history, pack-years	Mean (SD)	60.3 (28.56)

COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation.

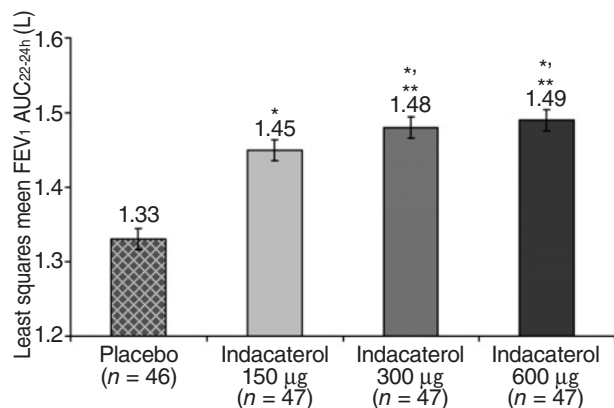


Fig. 2 Standardised FEV₁AUC_{22-24h} least squares means (±SE) (modified intent-to-treat population). AUC, area under the curve; FEV₁, forced expiratory volume in 1 second; SE, standard error. **P* < 0.001 vs. placebo; ***P* < 0.05 vs. indacaterol 150 µg.

(85% of patients). During the study, all patients were randomised, and no patient received the study drug in error; thus, the safety population was identical to the mITT population. Forty-five (90%) patients completed the study. Five patients discontinued prematurely; three withdrew consent (placebo: *n* = 1; indacaterol 150 µg: *n* = 2), one (indacaterol 150 µg) experienced an SAE (described later under the 'Safety' section), and one (indacaterol 600 µg) patient's condition no longer required any study medication.

Table 1 represents the demographics and baseline

clinical characteristics of all randomised patients. The mean age of all patients was 67.2 years. All patients were current or former smokers, and the majority (92%) of them were male. Mean duration of COPD was 2.9 years, and patients' post-bronchodilator % predicted FEV₁ at screening ranged from 31% to 78%, indicating a COPD severity of moderate-to-severe intensity according to the JRS COPD guidelines⁶ and the GOLD guideline.⁵

EFFICACY

For standardised FEV₁AUC_{22-24h}, all three indacaterol doses were statistically superior to placebo (*P* < 0.001), with all three doses exceeding the prespecified 120 mL criterion for minimal clinically important difference (130 [90% CI: 100, 160], 160 [130, 190], and 170 [140, 200] mL for the indacaterol 150, 300, and 600 µg doses, respectively; Fig. 2). The 300 and 600 µg doses of indacaterol showed similar bronchodilator efficacy, and both were statistically superior to the 150 µg dose (*P* < 0.05).

All indacaterol doses showed statistically significantly higher peak FEV₁ and significantly greater standardised FEV₁AUC_{0-24h} than placebo (*P* < 0.001) (Table 2). Serial measurements of FEV₁ over 24 h are shown in Figure 3. All indacaterol doses showed a statistically significantly higher FEV₁ than placebo (*P* < 0.001) at all post-dose time points. Indacaterol showed a fast onset of bronchodilation, with treatment-placebo differences in FEV₁ at 5 min post-dose being 110 (90% CI: 80, 130), 120 (100, 140), and 110 (90, 130) mL for the 150, 300, and 600 µg doses,

Table 2 Analysis of covariance of peak FEV₁ and standardised FEV₁AUC_{0-24h} (modified intent-to-treat population)

	Indacaterol			Placebo
	150 µg	300 µg	600 µg	
Peak FEV ₁ (L)				
<i>n</i>	48	47	48	47
Least squares mean (SE)	1.54 (0.009)*	1.57 (0.009)*,**	1.58 (0.009)*,**	1.42 (0.009)
Standardised FEV ₁ AUC _{0-24h} (L)				
<i>n</i>	47	46	47	45
Least squares mean (SE)	1.46 (0.009)*	1.49 (0.009)*,**	1.50 (0.009)*,**	1.32 (0.009)

AUC, area under the curve; FEV₁, forced expiratory volume in 1 second; SE, standard error.

P* < 0.001 vs placebo; *P* < 0.05 vs indacaterol 150 µg.

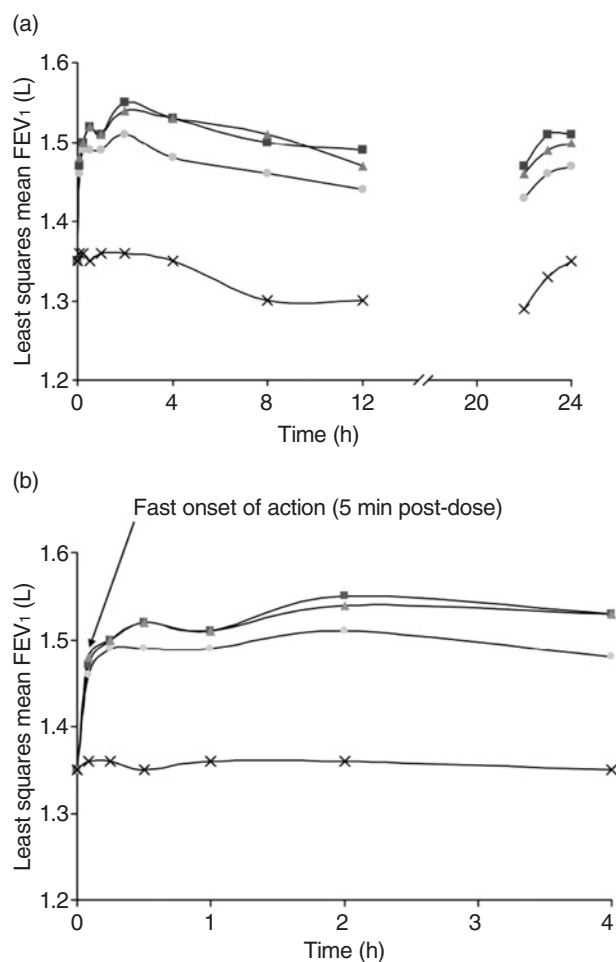


Fig. 3 Adjusted mean FEV₁ (a) over 24 h and (b) 0-4 h post-dose (modified intent-to-treat population). (x-x) placebo, (o-o) indacaterol 150 µg, (▲-▲) indacaterol 300 µg, and (■-■) indacaterol 600 µg. All doses of indacaterol were superior to placebo (*P* < 0.001) at all time points. Study drug was given between 08:00-10:00 AM on Day 1 (corresponding to time 0). FEV₁, forced expiratory volume in 1 second.

respectively. All indacaterol doses had statistically significantly higher FVC, FEF_{25-75%}, and percent change from period baseline in FEV₁ than placebo at

all post-dose time points (*P* < 0.001).

SAFETY

The overall incidence of AEs was 18.8% (9/48), 19.1% (9/47), and 25.0% (12/48) with indacaterol 150, 300, and 600 µg, respectively, as compared with 14.9% (7/47) with placebo (Table 3). The most common AE was cough (indacaterol 150 µg: *n* = 4 [8.3%]; 300 µg: *n* = 4 [8.5%]; 600 µg: *n* = 5 [10.4%]; placebo: *n* = 1 [2.1%]), and was mostly mild in severity and transient in nature, occurring just after inhalation of the study drug. One patient receiving indacaterol 150 µg experienced an SAE (subileus), which was not suspected to be study drug related and which resolved during follow up after study drug discontinuation. No death was reported during the study.

The overall incidences of hypokalaemia and hyperglycaemia are shown in Table 4. There were no clinically notable potassium values (minimum post-baseline value: <3.0 mmol/L) in any treatment group during the study. The incidence of clinically notable values in blood glucose levels (maximum post-baseline value: >9.99 mmol/L) for indacaterol 150 µg (two patients) and placebo (two patients) were similar and lower than that for indacaterol 300 µg (three patients) and 600 µg (four patients).

The incidence of abnormally high pulse rate (>90 beats/min) was lower with indacaterol treatments than that with placebo (Table 4). The incidences of abnormally decreased and elevated blood pressure findings were similar between indacaterol and placebo, with the exception of a higher incidence of elevated diastolic blood pressure (>90 mm Hg) with indacaterol treatments (10-17%) as compared with placebo (9%). Only one patient had a >60 ms change in QTcF from baseline, which was observed after administration of indacaterol 600 µg (Table 4). However, the increase was from 341 ms at baseline up to 403 ms at 4 h post-dose and up to 404 ms at 24 h post-dose, and was regarded by the investigator to have no clinical significance. No QTcF values above 500 ms were reported.

Table 3 Number (%) of patients with adverse events, overall and by primary system organ class (safety population)

Adverse events	Indacaterol			Placebo (N = 47)
	150 µg (N = 48)	300 µg (N = 47)	600 µg (N = 48)	
	<i>n</i> (%)			
Total	9 (18.8)	9 (19.1)	12 (25.0)	7 (14.9)
Primary system organ				
Respiratory, thoracic, and mediastinal disorders	4 (8.3)	6 (12.8)	6 (12.5)	2 (4.3)
Gastrointestinal disorders	1 (2.1)	1 (2.1)	1 (2.1)	1 (2.1)
Infections and infestations	0	0	2 (4.2)	1 (2.1)
Investigations	1 (2.1)	1 (2.1)	0	1 (2.1)
Musculoskeletal and connective tissue disorders	1 (2.1)	0	1 (2.1)	0
Nervous system disorders	0	0	2 (4.2)	0
Cardiac disorders	0	0	1 (2.1)	1 (2.1)
General disorders and administration site conditions	0	1 (2.1)	0	0
Injury, poisoning, and procedural complications	1 (2.1)	0	0	0
Metabolism and nutritional disorders	1 (2.1)	0	0	0
Vascular disorders	1 (2.1)	1 (2.1)	1 (2.1)	1 (2.1)

Table 4 Overall incidence of hypokalaemia, hyperglycaemia, abnormal values of pulse rate and blood pressure, and notable QTc values (safety population)

	Indacaterol			Placebo (N = 47)
	150 µg (N = 48)	300 µg (N = 47)	600 µg (N = 48)	
	<i>n</i> (%)			
Serum potassium: minimum post-baseline value [†]				
Below lower limit of normal range	1 (2.1)	0	2 (4.2)	0
Clinically notable [‡]	0	0	0	0
Blood glucose: maximum post-baseline value [†]				
Above upper limit of normal range	37 (77.1)	37 (78.7)	38 (79.2)	36 (76.6)
Clinically notable [‡]	2 (4.3)	3 (6.5)	4 (8.5)	2 (4.5)
Pulse rate: maximum post-baseline value [§]				
Above 90 bpm	8 (16.7)	9 (19.1)	8 (16.7)	10 (21.3)
Systolic blood pressure: maximum post-baseline value [¶]				
Above 140 mmHg	9 (18.8)	11 (23.4)	9 (18.8)	10 (21.3)
Diastolic blood pressure: minimum post-baseline value [¶]				
Above 90 mmHg	5 (10.4)	5 (10.6)	8 (16.7)	4 (8.5)
QTc interval (Fridericia's formula) ^{¶¶}				
Absolute values				
>450 ms (males)	0	1 (2.1)	0	0
>470 ms (females)	0	0	0	0
Change from baseline				
30-60 ms	2 (4.2)	0	0	0
>60 ms	0	0	1 (2.1)	0

[†]Measurement of serum potassium and blood glucose levels were taken pre-dose and at 15 min, 1 h, 4 h, and 24 h post-dose for each treatment.

[‡]Clinically notable values are those outside the following limits: potassium, <3 mmol/L; glucose, >9.99 mmol/L.

[§]Measurement of pulse rate was taken pre-dose and at 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, 22 h, 23 h, and 24 h post-dose for each treatment.

[¶]Measurement of blood pressure was taken pre-dose and at 15 min, 1 h, 4 h, 12 h and 24 h post-dose for each treatment.

^{¶¶}ECG was recorded pre-dose and at 1 h, 4 h, and 24 h post-dose for each treatment.

DISCUSSION

Clinical practice guidelines recommend treatment with one or more different classes of long-acting bronchodilators in patients with moderate-to-severe COPD.^{5,6} Poor adherence to treatment with long-acting bronchodilators may significantly hinder the attainment of optimal efficacy. Currently marketed LABAs, namely, formoterol and salmeterol, are both administered twice daily. Indacaterol is the first ultra-LABA with a once-daily dosing regimen. Once-daily regimens have advantages in terms of patient acceptability and convenience, and therefore improved adherence to therapy.^{26,27} The availability of an effective once-daily ultra-LABA could provide a useful addition to treatment options for COPD.

This study was designed to assess the bronchodilator efficacy and safety of single doses of indacaterol (150, 300, and 600 µg) in Japanese patients with COPD. A crossover design (rather than a parallel-group design) was chosen, because within-patient variability in FEV₁ was expected to be less than between-patient variability.

The primary efficacy analysis showed that all indacaterol doses were associated with statistically significantly greater standardised FEV₁AUC_{22-24h} than placebo, with differences exceeding the prespecified minimal clinically important difference of 120 mL^{22,23} (130, 160, and 170 mL for indacaterol 150, 300, and 600 µg, respectively); furthermore, the corresponding 90% CIs were relatively narrow, indicating the precision of the estimated differences. Although, all doses were associated with clinically relevant bronchodilation, indacaterol 300 and 600 µg provided similar values for FEV₁AUC_{22-24h}, and both were statistically superior to indacaterol 150 µg. This suggests that the efficacy of indacaterol might reach a plateau at a dose of 300 µg once daily.

The results of the primary analysis were supported by the other efficacy analyses, further indicating that all indacaterol doses had statistically significantly higher peak FEV₁ and greater standardised FEV₁ AUC_{0-24h} than that of placebo. All indacaterol doses showed improvement in FEV₁ as early as 5 min post-dose, which was thereafter sustained for 24 h, a finding similar to that observed in the Caucasian population.^{18,20}

Given the similar efficacy and safety demonstrated by indacaterol in Japanese and Caucasian patients, this is an indication that indacaterol is likely to be effective in the management of COPD regardless of a patient's ethnicity. This is an important consideration for any bronchodilator, as there is evidence of a possible relationship between ethnicity and clinical, physiological, and radiological phenotypes of COPD,^{28,29} which may impact a drug's efficacy.

In this study, for all treatment groups there was an increase in FEV₁ from 22 h to 24 h post-dose, a profile

similar to that seen in previous indacaterol studies in patients with COPD.^{18,20} Since this increase was also observed in the placebo group, this effect is likely due to diurnal variation in lung function, and not a true effect of indacaterol. Such diurnal variation is anticipated in patients with COPD, as sleep has negative effects on respiration and gas exchange.³⁰ It is of note, therefore, that the efficacy of indacaterol was maintained at these time points.

In terms of overall safety, all doses of indacaterol in this study were safe and well tolerated and showed a favourable safety profile in Japanese patients with moderate-to-severe COPD. Most of the AEs observed were expected in the patient population studied and were similar to those seen in previous studies of indacaterol conducted in the Caucasian population.^{18,19} Class-related side effects of inhaled beta₂-agonists include tachycardia, hypokalaemia, and hyperglycaemia, which are believed to be due to systemic absorption, resulting in the activation of beta-2 adrenoceptors located in various organs.³¹⁻³³ In the present study, there were no unexpected effects on clinical laboratory parameters, with no clear relationship between the incidence of hypokalaemia or hyperglycaemia and indacaterol dose. Furthermore, the incidences of abnormally high pulse rate or blood pressure was similar for both indacaterol and placebo. ECG evaluations showed no marked difference between the active treatments and placebo in terms of effects on the QT interval, with no relationship between notable QTc interval values and indacaterol dose. This favourable cardiac safety profile is important, given the high levels of cardiac comorbidities in patients with COPD.³⁴⁻³⁶ Longer-term safety studies of indacaterol are currently ongoing in the Japanese population.

In conclusion, once-daily dosing of indacaterol 150, 300, and 600 µg delivered via an SDDPI provided effective bronchodilation in Japanese patients with moderate-to-severe COPD, with sustained 24-h bronchodilator efficacy and a fast onset of action. These findings are similar to those observed in the Caucasian population, indicating the ethnic insensitivity of indacaterol. All doses of indacaterol were well tolerated with a good overall safety profile and showed no meaningful effects on the cardiovascular class-related side effects of beta₂-agonists in the Japanese population. Indacaterol could, therefore, be a useful treatment option for Japanese patients with COPD.

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