Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Efficacy and safety of indacaterol 150 and 300 μg in chronic obstructive pulmonary disease patients from six Asian areas including Japan: A 12-week, placebo-controlled study

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ABSTRACT

Background and objective: **The efficacy and safety of indacaterol, a novel inhaled once daily ultra long-acting β_2-agonist was evaluated in COPD patients in six Asian countries/areas. This study was primarily designed to obtain the regulatory approval of indacaterol in Japan.**

Methods: **Moderate-to-severe COPD patients were randomized to indacaterol 150 μg, indacaterol 300 μg or placebo once daily. Efficacy variables: trough FEV_1 (average of 23 h 10 min and 23 h 45 min post-dose values), health status (St. George's Respiratory Questionnaire) and transition dyspnoea index at week 12. Safety/tolerability was evaluated.**

Results: **A total of 347 patients were randomized (96.5% male, mean (SD) age 66.7 (8.38) years, post-bronchodilator FEV_1% predicted: 53.7 (12.50)); 88.8% completed. The least squares means (LSM) trough FEV_1 at week 12 for indacaterol 150 μg, indacaterol 300 μg and placebo were 1.34 L, 1.37 L and 1.17 L, respectively, with differences versus placebo exceeding the pre-specified minimal clinically important difference of 0.12 L (0.17 L and 0.20 L for indacaterol 150 μg and 300 μg, respectively, both $P < 0.001$). The week 12 LSM transition dyspnoea index score was statistically superior for both indacaterol doses versus placebo (differences of 1.30 and 1.26, $P < 0.001$; both exceeding the minimal clinically important difference of 1). At week 12, both indacaterol doses provided statistically significant ($P \leq 0.005$) and clinically meaningful (≥4 units) improvements in LSM St. George's Respiratory Questionnaire total score versus placebo (differences: –4.8 and –5.7 units). Adverse events for indacaterol (49.1%, both doses) were lower than placebo (59.0%) and were mostly mild/moderate in severity; no deaths were reported.**

Conclusions: **Indacaterol provided clinically significant bronchodilation and improvements in dyspnoea and health status in Asian COPD patients.**

Key words: Asian population, bronchodilator, COPD, efficacy, indacaterol, safety.

SUMMARY AT A GLANCE

This placebo-controlled, parallel-group study evaluated the efficacy and safety of indacaterol in COPD patients from six Asian countries/areas. Trough FEV_1, health status, dyspnoea, and safety were evaluated. Significant bronchodilation and improvements in patient-reported outcomes indicate that indacaterol is a useful treatment option for Asian patients with moderate-to-severe COPD.

INTRODUCTION

The prevalence of COPD in the Asia-Pacific region in adults is approximately 6.3%.[1] Furthermore, the

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Conflict of interest statement: MK, SHL and L-WH declare that they have no conflicting interests with respect to this study. MI has previously served as a member of the scientific advisory board for GlaxoSmithKline KK, Nippon Boehringer Ingelheim, Novartis Pharma KK, and Astrazeneca KK. He has received lecture fees from GlaxoSmithKline KK, Astrazeneca KK, Nippon Boehringer Ingelheim, and Abbot Japan Co; unrestricted grants from GlaxoSmithKline KK, Nippon Boehringer Ingelheim, and Novartis Pharma KK. MI has received honoraria, consultancy fees, and/or research grants from GlaxoSmithKline KK, Nippon Boehringer Ingelheim, Novartis Pharma KK, Abbot Japan Co, and Astrazeneca KK. YF has acted as a paid consultant to Novartis Pharma KK and has previously served as a paid member of the scientific advisory board for Novartis Pharma KK. MH, NO, NP and BK are employees of Novartis.

Received 21 July 2011; invited to revise 16 August 2011, 18 September 2011; revised 14 September 2011, 7 October 2011; accepted 7 October 2011 (Associate Editor: David Hui).

Nippon COPD Epidemiology study found that the prevalence of airflow limitation in Japan (in adults ≥40 years) was 10.9%.[2]

Bronchodilators are central to the management of moderate, severe and very severe COPD.[3,4] Indacaterol is a novel, inhaled ultra long-acting β_2-agonist (LABA)[5] approved in more than 50 countries worldwide, including throughout the European Union, for the maintenance treatment of COPD at doses of 150 and 300 μg once daily (od). In studies mainly involving Caucasian COPD patients,[6–10] indacaterol demonstrated a 24-h duration of action with a rapid onset on first dose; the improvements in trough FEV_1 with both doses of indacaterol were sustained over 1 year.[6,7]

This was the first 12-week study designed to investigate the efficacy and safety of indacaterol (150 and 300 μg od) versus placebo in patients with moderate-to-severe COPD in six Asian countries/areas (Hong Kong, India, Japan, Korea, Singapore, and Taiwan). This study was primarily aimed to support the regulatory approval of indacaterol in Japan.

METHODS

This was a multicentre, randomized, double-blind, placebo-controlled, parallel-group study. It was approved by the independent ethics committees/institutional review boards of participating centres and was conducted according to the Declaration of Helsinki. Informed consent was obtained from each patient before enrolment.

Clinical Trials identifier: NCT00794157

Patients

Males and females aged ≥40 years with moderate-to-severe COPD (as per the GOLD[3] guidelines , 2005) and a smoking history of ≥20 pack-years were enrolled. Spirometry (post-bronchodilator) at screening was FEV_1 <80% and ≥30% predicted and FEV_1/FVC <70%. Patients with abnormal corrected QT (QTc) intervals, or who in the 6 weeks before screening had a respiratory tract infection or were hospitalized for a COPD exacerbation were excluded. Patients with a history of asthma indicated by (but not limited to) onset of respiratory symptoms (such as cough, wheezing, shortness of breath) suggestive of asthma prior to age 40 years, or a history of diagnosis of asthma were also excluded.

Study design

Patients were randomized (1:1:1) using a validated automated system to indacaterol 150 μg or 300 μg, or matching placebo via single-dose dry powder inhaler od for 12 weeks. Randomization was stratified for smoking status (current or ex-smoker).

Concomitant inhaled corticosteroids (ICS), as taken during screening, were permitted; however, the dose and regimen were to remain stable. Patients taking fixed dose ICS and LABA combinations were switched to the equivalent ICS monotherapy at the same dose and regimen throughout the study. Salbutamol was permitted as rescue medication. No other bronchodilators were permitted.

Assessments

The primary objective was to confirm the superiority of indacaterol 150 μg or 300 μg to placebo with respect to 24-h post-dose 'trough' FEV_1 (mean of FEV_1 measurements at 23 h 10 min and 23 h 45 min post-dose) after 12 weeks. Secondary assessments included: trough FEV_1 after 2, 4 and 8 weeks of treatment; individual time-point FEV_1 and FVC on day 1; and peak FEV_1 on day 1. Other efficacy variables (health status, diary card assessments, dyspnoea, rescue medication use), safety and tolerability were evaluated.

Spirometry equipment and spirometric testing were to be in accordance with American Thoracic Society/European Respiratory Society standards.[11] Spirometry assessments were conducted at 50- and 15-min predose and 30-min post-dose on day 1 and after 2, 4, 8 and 12 weeks, and at 23 h 10 min and 23 h 45 min post-dose at week 12. A subset of patients underwent additional serial spirometry assessments on day 1 at 5-min, 1-h, 2-h and 4-h post-dose; in addition to the individual time-point FEV_1 and FVC, these data were used to calculate peak FEV_1 on day 1.

Dyspnoea was assessed after 4, 8 and 12 weeks using the transition dyspnoea index (TDI), with a score of 1 point regarded as the minimum clinically important difference (MCID).[12] Health status at baseline and after 4, 8 and 12 weeks was assessed using the St. George's Respiratory Questionnaire (SGRQ), the MCID being 4 points.[13] The translations of baseline dyspnoea index/TDI and SGRQ instruments were culturally and linguistically validated by the developers. The versions used in this study were licensed directly from the developers. Patients recorded their daily clinical symptoms and use of rescue salbutamol on electronic patient diaries. Safety assessments included recording of all adverse events (AE) and serious AE (SAE) with their severity and relationship with the study drug, and regular assessments of vital signs and electrocardiograms.

Statistical methods

The primary endpoint, trough FEV_1 after 12 weeks, was analysed using a mixed model containing treatment, smoking status and country/area as fixed effects with the baseline FEV_1 measurement and FEV_1 reversibility at screening as covariates, and study centre nested within country/area as a random effect. Data were reported as least squares mean (LSM) treatment effects and SEM, and as LSM treatment contrasts with 95% confidence intervals. The superiority of both indacaterol doses versus placebo was determined after adjustment for multiplicity. Trough FEV_1 after 12 weeks was also analysed in subgroups according to age, smoking history, COPD disease severity, ICS use and country/area group ('Japan' and 'other countries/areas'). This last subgroup analysis

was prespecified in order to investigate the efficacy of indacaterol in Japanese patients; as a consequence, it was intended that more than 40% of patients would be recruited from sites in Japan. The primary endpoint was also analysed according to sex and country/area, although these data are not reported, as the numbers in some subgroups were too low to draw meaningful conclusions. Other efficacy variables and treatment comparisons were analysed without allowance for multiplicity.

Individual time-point FEV_1 and FVC, patient diary data (symptoms and rescue medication), and TDI and SGRQ total scores were analysed using similar mixed models. The percentages of patients achieving the MCID for TDI (a total score $\geq$1) and SGRQ (a decrease from baseline in total score of $\geq$4) were determined. In addition, the mean changes from baseline for individual time-point FEV_1 and FVC were calculated without adjustment for covariates.

Most of the safety data were analysed descriptively only, including the proportion of patients with notable values for serum potassium (<3 mmol/L), blood glucose (>9.99 mmol/L), pulse rate (>130 bpm, or $\geq$120 bpm and increase from baseline $\geq$15 bpm), diastolic blood pressure (>115 mm Hg, or $\geq$105 mm Hg and increase from baseline $\geq$15 mm Hg), systolic blood pressure (>200 mm Hg, or $\geq$180 mm Hg and increase from baseline $\geq$20 mm Hg) and QTc interval corrected with Fridericia's formula (QTcF) (a value >500 ms or a change from baseline >60 ms). The analyses of minimum post-baseline serum potassium, maximum post-baseline blood glucose, pulse rate, diastolic blood pressure, systolic blood pressure and QTc interval were performed using a similar mixed model analysis as specified for the primary efficacy variable (but excluding FEV_1 reversibility components from the model)

Efficacy data were analysed for the intention-to-treat population, comprising all randomized patients who received at least one dose of the study drug. The population for safety analysis comprised all patients who received at least one dose of study drug.

Sample size determination

A treatment difference between indacaterol and placebo of 0.12 L in trough FEV_1 was prespecified as MCID. Based on previous studies,[6,8,9] an SD of 0.225 L for trough FEV_1 was selected. A sample size of 89 evaluable patients in each treatment group was needed to detect a difference in trough FEV_1 of 0.12 L (between indacaterol 150 μg vs placebo and indacaterol 300 μg vs placebo) as statistically significant at the 2.5% significance level (two-sided) with 90% power. Assuming a drop-out rate of 20%, a total of 267 evaluable patients required 336 patients to be randomized.

RESULTS

This study involved 73 centres from the six participating countries/areas, and ran from November 2008 until October 2009. A total of 519 patients were screened, 347 were randomized, and 308 (88.8%) completed. Thirty-nine patients (11.2%) discontinued from the study (8.8%, 8.6% and 16.2% for indacaterol 150 μg, 300 μg and placebo, respectively). The most common reasons for discontinuation were AE (3.5%, 0.9% and 6.8%) and administrative problems (0.9%, 6.0% and 3.4%). Patient demographics and baseline clinical characteristics were well matched between the three treatment groups (Table 1).

Spirometry

The LSM trough FEV_1 at week 12 for indacaterol 150 μg, indacaterol 300 μg and placebo were 1.34 L, 1.37 L and 1.17 L, respectively, with differences versus placebo for both indacaterol doses exceeding the prespecified MCID (0.12 L) (Fig. 1). Similar results were observed in the age, smoking status, disease severity, ICS use subgroup analyses (Fig. 2a and b). In the country/area group analysis ('Japan' and 'other countries/areas'), differences versus placebo in both subgroups exceeded the MCID for both indacaterol doses. Trough FEV_1 values at weeks 2, 4 and 8 for indacaterol 150 μg and 300 μg were also significantly greater than for placebo ($P < 0.001$), with differences consistently exceeding the prespecified MCID (Fig. 1). Data for trough FEV_1 at week 12 were additionally analysed according to baseline reversibility to short-acting β_2-agonist (salbutamol 400 μg) in which patients were categorized into two subgroups—one with reversibility to salbutamol >12% and the second with $\leq$12% reversibility. Both indacaterol doses showed statistically significant bronchodilation ($P < 0.001$) compared with placebo in both subgroups with differences meeting and exceeding the prespecified MCID irrespective of baseline reversibility.

A total of 192 patients were included in the subset with additional spirometry measurements. In this subset, the LSM FEV_1 values for both indacaterol doses were significantly greater than for placebo (all $P < 0.001$) at all post-baseline time points on day 1, with differences that met or exceeded the MCID—including at 5-min post-dose on day 1 (unadjusted mean changes from baseline are shown in Fig. 3a). In the analysis of peak FEV_1 on day 1, both indacaterol doses were statistically superior to placebo ($P < 0.001$), with changes from baseline of 0.21 and 0.24 L for indacaterol 150 and 300 μg, respectively, compared with 0.03 L for placebo. In this subset, both indacaterol doses provided statistically superior FVC compared with placebo at all post-baseline time points (unadjusted mean changes from baseline are shown in Fig. 3b).

Dyspnoea

At week 12, the LSM TDI total scores for both indacaterol doses were significantly greater than placebo, with differences from placebo exceeding the MCID of 1 unit (Table 2). Similarly, TDI total scores were significantly greater with both indacaterol doses than

Table 1 Patient demographics and baseline clinical characteristics

	Indacaterol 150 μg (*N* = 114)	Indacaterol 300 μg (*N* = 116)	Placebo (*N* = 117)	Total (*N* = 347)
Age, years	66.4 (8.75)	67.1 (7.67)	66.5 (8.74)	66.7 (8.38)
Age group, *n* (%)				
≤65 years	46 (40.4)	43 (37.1)	41 (35.0)	130 (37.5)
>65 years	68 (59.6)	73 (62.9)	76 (65.0)	217 (62.5)
Male/female, %	96.5/3.5	97.4/2.6	95.7/4.3	96.5/3.5
Race (Asian), %	100	100	100	100
Country/area, *n* (%)				
Hong Kong	3 (2.6)	1 (0.9)	3 (2.6)	7 (2.0)
India	13 (11.4)	13 (11.2)	15 (12.8)	41 (11.8)
Japan	50 (43.9)	52 (44.8)	50 (42.7)	152 (43.8)
Korea	32 (28.1)	33 (28.4)	35 (29.9)	100 (28.8)
Singapore	0 (0.0)	2 (1.7)	0 (0.0)	2 (0.6)
Taiwan	16 (14.0)	15 (12.9)	14 (12.0)	45 (13.0)
Country/area group, %				
Japan	43.9	44.8	42.7	43.8
Other	56.1	55.2	57.3	56.2
Duration of COPD, years	4.2 (3.74)	3.4 (3.44)	3.9 (3.97)	3.9 (3.73)
Severity of COPD, *n* (%)				
Moderate	73 (64.0)	68 (58.6)	66 (56.4)	207 (59.7)
Severe	41 (36.0)	48 (41.4)	51 (43.6)	140 (40.3)
Ex-smoker/smoker, %	64.9/35.1	66.4/33.6	72.6/27.4	68.0/32.0
Smoking history, pack-years	51.7 (29.21)	54.0 (28.56)	49.7 (27.96)	51.8 (28.55)
ICS use, %	21.9	21.6	29.1	24.2
FEV_1, L[†]	1.46 (0.430)	1.41 (0.413)	1.38 (0.392)	1.41 (0.412)
FEV_1, % predicted[†]	55.2 (12.77)	53.7 (12.67)	52.3 (11.98)	53.7 (12.50)
FEV_1/FVC, %[†]	50.3 (10.55)	48.7 (9.61)	47.7 (10.41)	48.9 (10.22)
Reversibility to salbutamol, %	14.7 (12.88)	15.3 (14.86)	15.3 (12.58)	15.1 (13.44)
Rescue medication use, mean daily number of puffs	1.96	2.32	2.15	2.14
SGRQ	37.4 (17.85)	35.4 (16.03)	37.6 (18.23)	36.8 (17.37)
BDI	7.5 (2.14)	7.7 (2.30)	7.3 (2.48)	7.5 (2.31)

Data are mean (SD) unless otherwise stated.
[†] Post-salbutamol.
BDI, baseline dyspnoea index; ICS, inhaled corticosteroid; SGRQ, St George's Respiratory Questionnaire.

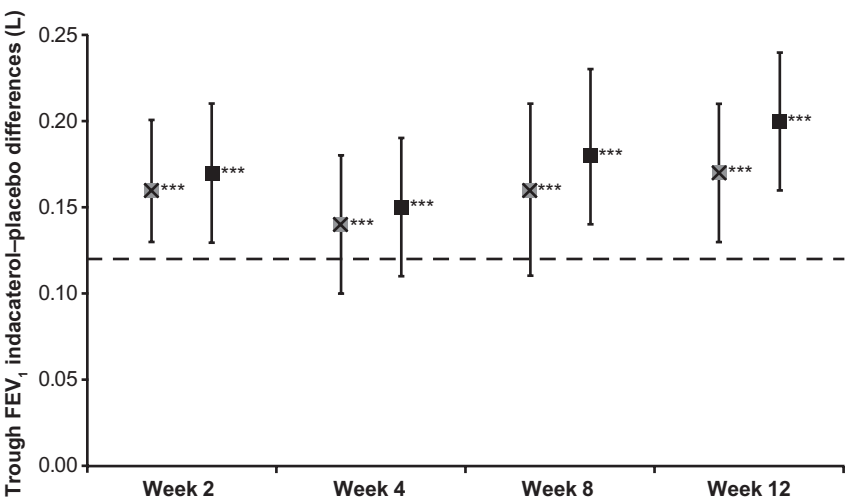

Figure 1 Least squares mean (95% confidence intervals) differences versus placebo for trough FEV_1 (L) after 2, 4, 8 and 12 weeks of treatment (intent-to-treat population). The dotted line indicates the prespecified level of clinical relevance. ***$P < 0.001$ versus placebo. (✖) indacaterol 150 μg; (■) indacaterol 300 μg.

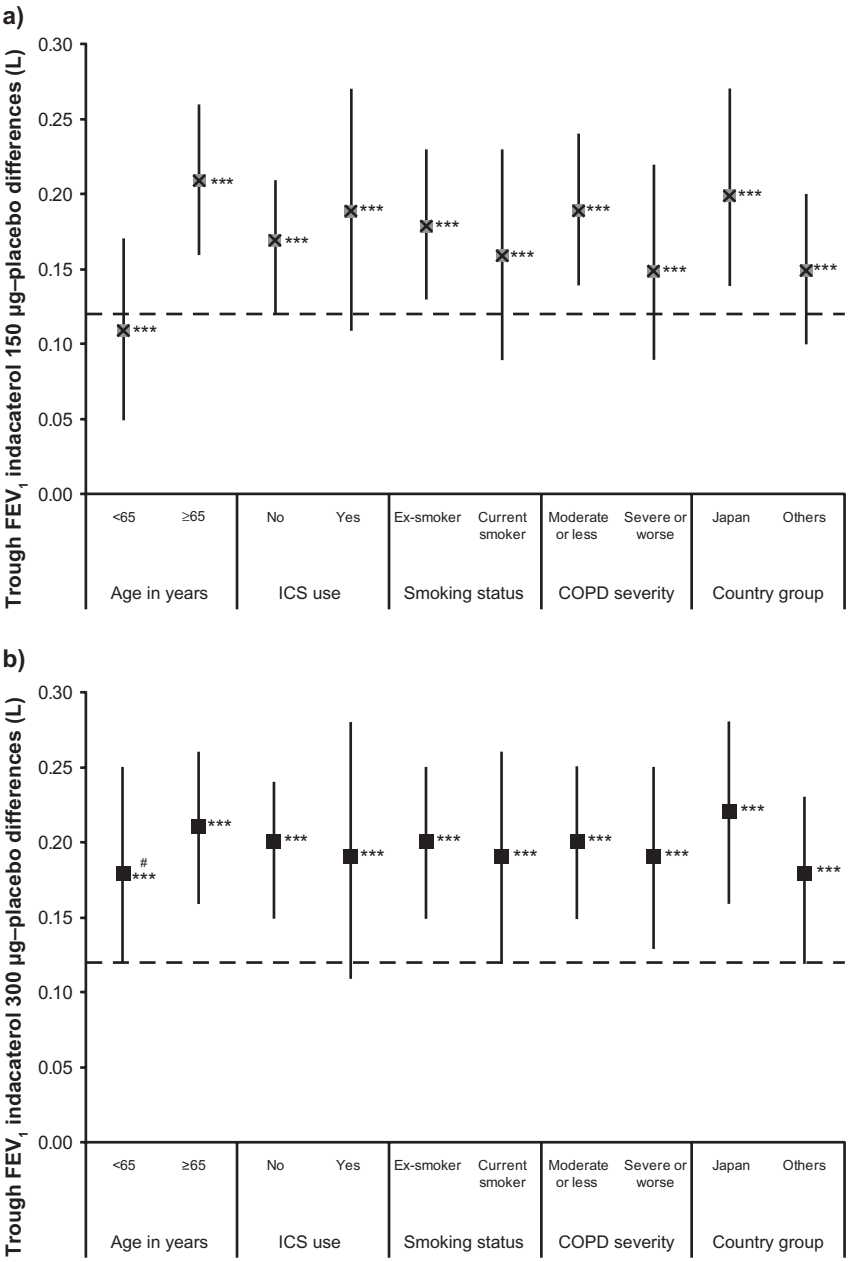

Figure 2 (a) Subgroup analyses: least squares mean (95% confidence intervals (CI)) differences versus placebo of trough FEV_1 (L) for indacaterol 150 µg (intent-to-treat (ITT) population). (b) Subgroup analyses: least squares mean (95% CI) differences versus placebo of trough FEV_1 (L) for indacaterol 300 µg (ITT population). The dotted line indicates the prespecified level of clinical relevance. Data following treatment with indacaterol and placebo at week 12. ICS, Inhaled corticosteroids. ***$P < 0.001$ versus placebo. (✕) indacaterol 150 µg; (■) indacaterol 300 µg.

placebo at weeks 4 ($P < 0.001$) and 8 ($P < 0.05$), though the differences did not exceed 1 unit at week 8 for either dose. Compared with placebo, a significantly larger proportion of patients in both indacaterol groups had a TDI total score ≥1 at weeks 4, 8 and 12 (placebo: 34.6–39.2%, indacaterol 150 µg: 48.2–61.1%, indacaterol 300 µg: 49.5–54.6%; $P < 0.05$ for both indacaterol doses vs placebo at all visits).

The TDI results in the subgroup of patients from Japan were broadly similar to the overall population, both in terms of LSM TDI total scores (Table 2) and the responder analysis (placebo: 22.7–25.0%, indacaterol 150 µg: 33.3–47.9%, indacaterol 300 µg: 34.0–41.7%).

Health status

The SGRQ total scores at week 12 were significantly lower (indicating improvement) than placebo for indacaterol 150 µg ($P = 0.005$) and indacaterol 300 µg

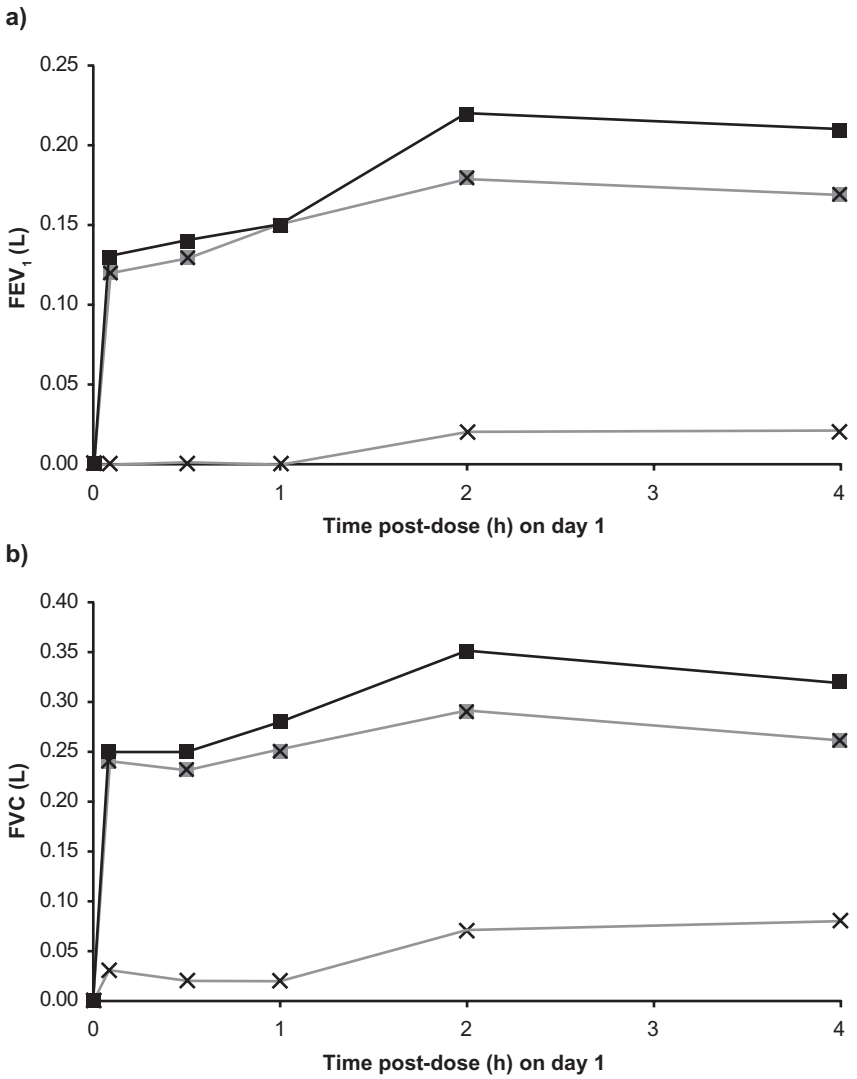

Figure 3 (a) Change from baseline in individual time-point mean FEV_1 (L) on day 1 (intent-to-treat (ITT) population). (b) Change from baseline in individual time-point mean FVC (L) on day 1 (ITT population). Values are unadjusted mean change from baseline. $P < 0.001$ for both indacaterol doses versus placebo at all post-baseline time points for FEV_1 and FVC (from least squares means). (✕—✕) indacaterol 150 μg; (■—■) indacaterol 300 μg; (✕—✕) placebo.

($P = 0.001$), with both differences exceeding the MCID. This improvement was consistent across all three components of the SGRQ, with scores for symptoms, activity and impacts all significantly lower for both indacaterol doses than placebo at week 12 (all $P < 0.05$) (Fig. 4).

The percentages of patients with a ≥4-unit improvement from baseline were consistently higher in indacaterol groups than placebo, although the difference only reached statistical significance for the 300 μg group at week 12 (Fig. 5a).

For the Japan subgroup, the differences from placebo in LSM SGRQ total score were higher than in the overall population, with both indacaterol doses exceeding the MCID versus placebo at all three visits (Table 2). In this subgroup, the proportion of patients with a ≥4-unit improvement from baseline was consistently higher than placebo for both indacaterol groups (Fig. 5b), with the difference reaching statistical significance for the 150-μg dose at week 12 and for the 300-μg dose at both weeks 8 and 12 (week 8: 51.1% vs 36.4%, $P = 0.017$; week 12: 55.3% vs 27.3%, $P < 0.001$).

Diary data

The percentages of 'nights with no night-time awakenings' ($P < 0.05$) and of 'days able to perform usual daily activities' ($P < 0.001$) were significantly greater for both indacaterol doses compared with placebo, with numerical improvements versus placebo in the percentage of 'days with no daytime symptoms' (Table 3).

Rescue medication use was low in all treatment groups (averaging <2.5 puffs/day). There were numerical improvements for both indacaterol doses versus placebo in most of the rescue medication parameters evaluated, although none reached statistical significance.

Safety

The overall incidence of AE was 49.1% with both indacaterol doses and 59.0% with placebo (Table 4). AEs were mostly mild to moderate in severity, the most common being COPD worsening (a term that

Table 2 Least squares mean (95% confidence intervals) treatment differences in TDI and SGRQ total scores at weeks 4, 8 and 12

	Indacaterol 150 μg versus placebo	Indacaterol 300 μg versus placebo	Indacaterol 300 μg versus Indacaterol 150 μg
TDI total score for the entire ITT population			
Week 4	1.16 (0.60, 1.71)***	1.22 (0.65, 1.79)***	0.06 (–0.50, 0.62)
Week 8	0.90 (0.21, 1.60)*	0.91 (0.21, 1.62)*	0.01 (–0.69, 0.70)
Week 12	1.30 (0.63, 1.97)***	1.26 (0.58, 1.94)***	–0.04 (–0.71, 0.63)
TDI total score for the Japan ITT population			
Week 4	1.40 (0.63, 2.16)***	1.07 (0.30, 1.85)**	–0.32 (–1.07, 0.42)
Week 8	1.03 (0.15, 1.90)*	0.88 (0.00, 1.76)	–0.15 (–1.00, 0.70)
Week 12	1.81 (0.85, 2.77)***	1.39 (0.42, 2.36)**	–0.42 (–1.36, 0.52)
SGRQ total score for the entire ITT population			
Week 4	–2.6 (–5.4, 0.3)	–3.4 (–6.2, –0.5)*	–0.8 (–3.6, 2.0)
Week 8	–2.1 (–5.2, 1.1)	–2.7 (–5.9, 0.5)	–0.6 (–3.8, 2.5)
Week 12	–4.8 (–8.2, –1.5)**	–5.7 (–9.2, –2.3)***	–0.9 (–4.2, 2.5)
SGRQ total score for the Japan ITT population			
Week 4	–4.8 (–8.4, –1.2)**	–4.5 (–8.2, –0.9)*	0.3 (–3.2, 3.7)
Week 8	–5.1 (–8.8, –1.3)**	–6.6 (–10.4, –2.8)***	–1.5 (–5.2, 2.2)
Week 12	–8.4 (–12.9, –3.8)***	–9.6 (–14.2, –5.1)***	–1.3 (–5.7, 3.1)

*$P < 0.05$, **$P < 0.01$, ***$P \leq 0.001$.
Data are least squares mean with 95% confidence intervals.
ITT, intent-to-treat; SGRQ, St. George's Respiratory Questionnaire; TDI, Transition Dyspnea Index.

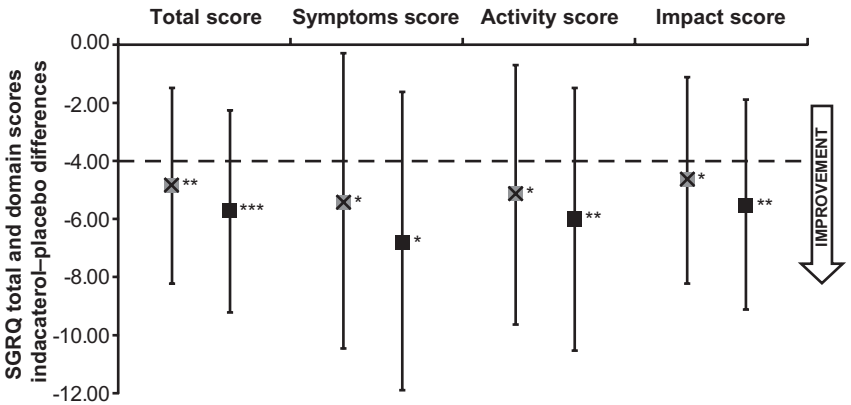

Figure 4 Least squares mean (95% confidence intervals (CI)) differences versus placebo in St. George's Respiratory Questionnaire (SGRQ) total and domain (symptoms, activity, impacts) scores at week 12 (intent-to-treat population). The dotted line indicates the MCID (≤–4.0 vs placebo). *$P < 0.05$ versus placebo; **$P < 0.01$ versus placebo; ***$P \leq 0.001$ versus placebo. (✕) indacaterol 150 μg; (■) indacaterol 300 μg.

includes exacerbations) followed by nasopharyngitis (Table 4). The incidence of SAE was low across all treatments (4/114 (3.5%), 2/116 (1.7%) and 6/117 (5.1%) for indacaterol 150 μg, 300 μg and placebo, respectively). No cardiac SAE was reported among patients taking indacaterol. The most frequently reported SAE was COPD worsening (two patients in each treatment group). No deaths were reported during the study.

The incidence of clinically notable glucose values for indacaterol 150 μg, indacaterol 300 μg and placebo was 11.4%, 9.5% and 6.8%, respectively. Many of these patients had blood glucose values at baseline that were either above normal or were clinically notable. The LSM of the maximum post-baseline blood glucose values were 7.81, 7.74 and 7.57 mmol/L for indacaterol 150 and 300 μg, and placebo, respectively, with no statistically significant differences between groups. Only one subject (0.9%) receiving placebo reported clinically notable serum potassium values. The LSM of the minimum post-baseline serum potassium values for indacaterol 150 μg, indacaterol 300 μg and placebo were 4.09, 4.11 and 4.06 mmol/L, with no statistically significant differences between treatments. No clinically notable pulse rates were observed with indacaterol 150 μg, indacaterol 300 μg and placebo. The LSM of the maximum post-baseline pulse rates for these treatments were 78.9, 80.0 and 79.8 bpm, respectively, with no statistically significant difference between treatments. One patient (0.9%) in the indacaterol 300 μg group reported a notable systolic blood pressure (SBP) value, while the incidence of notable high diastolic blood pressure (DBP) values was 2.7, 0.9 and 2.6% in the indacaterol 150 μg, indacaterol 300 μg and placebo groups, respectively. The LSM of the maximum post-baseline SBP and DBP values for indacaterol 150 μg, indacaterol 300 μg and placebo at the end of the study were 142.8, 142.7 and

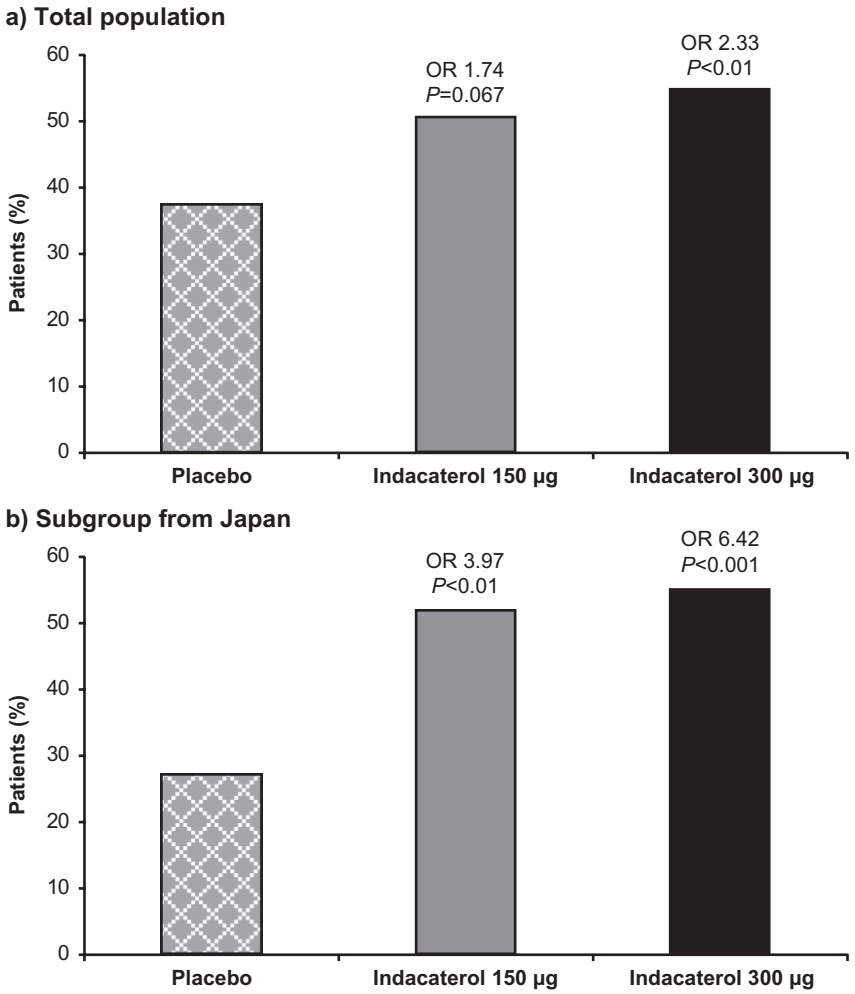

Figure 5 Percentage of patients achieving a clinically important improvement in St. George's Respiratory Questionnaire total score at week 12 (intent-to-treat (ITT) population). (a) Entire ITT population. (b) Japan ITT population. Significant differences (likelihood of achieving ≥4 units decrease from baseline) in odds ratios (OR). *P*-values are for comparisons between active and placebo treatments.

Table 3 Least squares mean (95% confidence intervals) treatment differences in percentage of nights with no awakenings, days with no daytime symptoms and days able to perform usual daily activities

Diary data	Indacaterol 150 µg versus placebo	Indacaterol 300 µg versus placebo	Indacaterol 300 µg versus Indacaterol 150 µg
Nights with no awakenings, %	7.5 (1.2, 13.8)*	7.9 (1.6, 14.2)*	0.4 (–5.8, 6.6)
Days with no daytime symptoms, %	1.9 (–2.7, 6.5)	2.5 (–2.1, 7.2)	0.7 (–3.9, 5.2)
Days able to perform usual daily activities, %	14.3 (7.3, 21.3)***	18.2 (11.2, 25.2)***	3.9 (–3.1, 10.8)

*$P < 0.05$, ***$P < 0.001$.
Data are least squares mean with 95% confidence intervals.

143.6 mm Hg, and 86.2, 85.3 and 87.5 mm Hg, respectively; the only statistically significant difference was a lower DBP with indacaterol 300 µg compared with placebo ($P < 0.05$). No QTcF interval values above 500 ms were reported, and the only patient (0.9%) with an increase from baseline >60 ms was in the placebo group. The LSM of the maximum post-baseline QTcF intervals for indacaterol 150 µg, indacaterol 300 µg and placebo were 421.3, 421.1 and 420.2 ms, respectively, with no statistically significant differences between treatments.

In previous studies, a proportion of patients receiving indacaterol have reported a short-lasting cough a few seconds after inhalation. In the current study, in addition to patients reporting cough as an AE, investigators were asked to record any instances of cough within 5 min of drug administration during clinic visits regardless of whether they considered it an AE. The average incidence of 'cough following inhalation' at any study visit was 14.6% with indacaterol 150 µg, 19.5% with indacaterol 300 µg and 1.5% with placebo. The cough started within 15 s of inhalation, with a median duration of 6–12 s. No patient discontinued or interrupted study treatment due to this, and there was no relationship with bronchospasm, exacerbation or any loss of efficacy or

Table 4 Adverse events (overall incidence and most commonly reported)

	Indacaterol 150 μg (*N* = 114) *n* (%)	Indacaterol 300 μg (*N* = 116) *n* (%)	Placebo (*N* = 117) *n* (%)
Patients with any adverse event(s)	56 (49.1)	57 (49.1)	69 (59.0)
COPD worsening	11 (9.6)	11 (9.5)	15 (12.8)
Nasopharyngitis	10 (8.8)	8 (6.9)	11 (9.4)
Upper respiratory tract infection	6 (5.3)	2 (1.7)	5 (4.3)
Cough	5 (4.4)	11 (9.5)	3 (2.6)
Pyrexia	4 (3.5)	0 (0.0)	2 (1.7)
Back pain	3 (2.6)	1 (0.9)	1 (0.9)
Headache	3 (2.6)	0 (0.0)	1 (0.9)
Non-cardiac chest pain	3 (2.6)	0 (0.0)	2 (1.7)
Constipation	2 (1.8)	4 (3.4)	1 (0.9)
Hypertension	2 (1.8)	0 (0.0)	5 (4.3)
Diarrhoea	1 (0.9)	1 (0.9)	3 (2.6)
Insomnia	1 (0.9)	0 (0.0)	3 (2.6)
Urticaria	1 (0.9)	3 (2.6)	1 (0.9)
Lower respiratory tract infection	0 (0.0)	2 (1.7)	3 (2.6)
Pneumonia	0 (0.0)	3 (2.6)	1 (0.9)

Most common events listed for ≥2% of patients in any group.

safety. The mechanism of this cough following inhalation is unknown.

DISCUSSION

This study was designed to assess and confirm the efficacy and safety of indacaterol 150 μg and 300 μg od in Asian patients with moderate-to-severe COPD. Indacaterol od showed sustained 24-h bronchodilation, with trough FEV_1 that was clinically and statistically significantly higher than with placebo at all visits. The onset of action of indacaterol was rapid following the first dose, with the FEV_1 being significantly higher with both doses than placebo at 5-min post-dose on day 1. Indacaterol demonstrated significant improvements versus placebo in other spirometry variables such as individual time-point FEV_1 and FVC at each scheduled post-baseline time point on day 1, supporting the benefit of indacaterol on bronchodilation in patients with moderate-to-severe COPD.

Previous indacaterol studies mainly involving Caucasian populations have shown that indacaterol 150 μg od significantly improved trough FEV_1 at 12 weeks by 0.13–0.18 L compared with placebo ($P < 0.001$),[8–10] and indacaterol 300 μg od showed improvements compared with placebo of 0.17–0.18 L ($P < 0.001$).[6,8] It is of note that the spirometry results in this all-Asian population study were consistent with these previous studies despite a number of differences in the demographic characteristics in the current study compared with the previous studies. In particular, the percentage of female patients recruited in this study (3.5%) was much smaller than in previous indacaterol studies (in which the proportion of female patients was 20–48%)—it is worth noting that in these previous studies the efficacy of indacaterol in males was broadly similar to the efficacy in females.[6,8–10,14,15] This could be due to historically very low smoking rates in Asian females (although this is now increasing, especially among women in their 20s and 30s)[16,17] and under-diagnosis of the disease,[2,18] both of which result in a lower prevalence of diagnosed COPD within females. The mean age of patients in the current study was slightly higher than in previous indacaterol studies—again perhaps related to underdiagnosis of this disease in younger patients.[2,18] The smoking history in the current study was similar to previous studies, yet the proportion of current smokers (32%) was lower (41–52%).[6,8–10] Finally, the proportion of patients using ICS (24%) was lower than in these previous studies (31–53%). It is important to emphasize here that patients with COPD can be reversible, which at times can make it difficult to differentiate from asthma. The investigators of this study have taken every effort to exclude asthma not only based on spirometric assessments but also the onset of respiratory symptoms suggestive of asthma prior to age 40 years and a prior diagnosis of asthma. It is thus highly unlikely that the randomized study population may have asthma or a mixed aetiology, even though they were relatively reversible. Furthermore, in this study, indacaterol demonstrated statistically ($P < 0.001$) and clinically relevant improvements versus placebo in lung function (trough FEV_1) in patients regardless of baseline reversibility.

In addition to improvements in lung function, both doses of indacaterol provided statistically significant ($P < 0.05$) and clinically relevant (i.e. ≥1 unit) improvements in dyspnoea compared with placebo. Such improvements versus placebo in dyspnoea were seen with indacaterol during previous studies of 6- (150 and 300 μg[8,10]) and 12-month (300 μg[6]) durations. TDI is an important measure of

efficacy because dyspnoea is a major clinical manifestation of COPD, and the improvement in TDI total scores indicates benefit from indacaterol. Furthermore, indacaterol provided a statistically significant ($P < 0.01$) and clinically meaningful improvement (i.e. ≥4 unit) in health status compared with placebo. The baseline SGRQ scores in the current study were lower (i.e. suggesting better health status at baseline) than in the previous indacaterol studies, perhaps a reflection of the different baseline characteristics of patients in the current study compared with the earlier studies—for example, one study found that health status (assessed by baseline SGRQ score) was better in male COPD patients than in female patients of matched age and disease severity.[19] It is interesting, therefore, that the improvements compared with placebo in the current study were broadly similar to the results of the previous studies.[10,13,16] Night-time awakenings,[20] daytime COPD symptoms[3] and impaired performance in daily activities[3] all have substantial impacts on a patient's ability to lead a normal life in patients with COPD. In this study, compared with placebo, both indacaterol doses caused significant improvements in the percentages of 'nights with no night-time awakenings' and of 'days able to perform usual daily activities' along with numerical (although not statistically significant) improvement in 'days with no daytime symptoms'. These improvements in a broad range of self-reported symptoms of daily living suggest that indacaterol could have a useful role in managing symptoms in COPD patients, and this may have contributed to the improvement in health status observed in this study.

Both indacaterol doses were well tolerated, with a lower incidence of AE than placebo. The incidences of β_2-agonist mediated adverse effects, pulse rate and blood pressure increases, QTc interval prolongations, and hypokalaemia and hyperglycaemia were low, with no meaningful differences between placebo and either indacaterol dose. Given the relatively short duration of the current study, definitive conclusions cannot be drawn on the safety of indacaterol from these data alone because a 12-week study may not identify all safety signals associated with an intervention. Data on the safety of indacaterol are available from longer term studies, including a 12-month study that recruited patients from Japan only,[21] and studies in Caucasian populations of up to 6-month[8] and 12-month[6] durations along with a pooled safety analysis.[22] These longer term studies provide supportive evidence of the safety of indacaterol. On the basis of these data, one cannot, of course, completely exclude the possibility of a safety signal with a very low incidence, although other long-term studies conducted with other LABA monotherapy in COPD have not identified any such signal.

In conclusion, indacaterol 150 μg and 300 μg od provided effective bronchodilation in patients with moderate-to-severe COPD in six Asian countries/areas, similar to previous indacaterol studies, together with improvements in health status and dyspnoea. The safety and tolerability profiles of both indacaterol doses were good and were consistent with the profiles observed in studies of up to 52-week duration.[6,7] Indacaterol can thus be a useful treatment option for Asian COPD patients.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the contribution of the late Professor Hisamichi Aizawa to this study and to the initial development of this manuscript. The authors also acknowledge the contribution of every member of the Indacaterol Asian COPD study group, the patients who took part in the study and the staff at the participating clinical centres. The authors thank Yuko Maruyama for her contribution to the conduct of this clinical trial, Ayako Sato for preparing the study report, and Dr Shaik Asma Sultana (Novartis) and David Young (Novartis) for their assistance in the preparation of the manuscript.

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