Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.5571-20
Intern Med 60: 2385-2394, 2021
http://internmed.jp

【 ORIGINAL ARTICLE 】

Real-world Safety and Efficacy of Indacaterol Maleate in Patients with Chronic Obstructive Pulmonary Disease: Evidence from the Long-term Post-marketing Surveillance in Japan

Tomoko Taniguchi, Dong Wang, Hajime Yoshisue, Makoto Nagasaki and Takayoshi Sasajima

Abstract:

Objective Evidence concerning the safety and efficacy of indacaterol maleate in a real-life setting is limited. The objective of this post-marketing surveillance was to evaluate the real-life safety and efficacy of indacaterol maleate in Japanese patients with chronic obstructive pulmonary disease (COPD).

Methods This was a 52-week post-marketing surveillance conducted between April 2012 and December 2018. The safety endpoints included the incidence of adverse events (AEs), serious adverse events (SAEs), and adverse drug reactions (ADRs). The efficacy endpoints included the physician-reported global evaluation of treatment effectiveness (GETE), change from baseline in the COPD assessment test (CAT) results, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and $\%FEV_1$ following 4, 12, 26, and 52 weeks of indacaterol administration.

Results Of the 1,846 enrolled patients, 1,726 were included in the safety and efficacy analyses. The mean age of the patients was 72.5 years old. Cough, pneumonia and COPD worsening were the most common AEs reported, while pneumonia (1.04%) was the most common SAE, and cough (1.68%) was the most common ADR. GETE showed that 69.70% of patients achieved an excellent/good/moderate response following indacaterol treatment. The CAT score decreased, and lung function parameters (FVC, FEV_1 and $\%FEV_1$) improved across all the COPD stages following treatment with indacaterol.

Conclusion Indacaterol showed a favorable safety and tolerability profile in Japanese patients with COPD without new safety signals observed in real-life settings. These findings demonstrated that indacaterol is an effective maintenance treatment in real-life practice for Japanese patients with COPD.

Key words: adverse events, COPD, COPD assessment test, indacaterol maleate, lung function, post-marketing surveillance, safety

(Intern Med 60: 2385-2394, 2021)
(DOI: 10.2169/internalmedicine.5571-20)

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and respiratory symptoms, including dyspnea, cough, and sputum production, resulting in increased morbidity and a poor quality of life (1). Globally, COPD affects more than 10% of subjects over 40 years old and became the third leading cause of death by 2010 (2). In 2016, the Global Burden of Disease Study and the World Health Organization reported COPD prevalence of 251 million worldwide (3). The disease accounts for approximately 5% of deaths worldwide with 3.17 million deaths reported in 2015 (3).

The NIPPON epidemiology study reported that, in Japan, the prevalence of COPD is 8.6% in people ≥40 years old (4). Higher prevalence rates of 10.3% and 22% were observed in patients ≥60 years old and those with a history of smoking or respiratory symptoms, respectively (5, 6). COPD is also associated with a significant economic and societal

Novartis Pharma K.K., Japan
Received: June 11, 2020; Accepted: January 5, 2021; Advance Publication by J-STAGE: February 22, 2021
Correspondence to Dr. Dong Wang, dong-1.wang@novartis.com

burden. The Continuing to Confront COPD survey, which estimated the economic impact of COPD across 12 countries, reported that the average annual cost per patient (the combined direct and indirect cost) with moderate-to-severe COPD is US$9,893 in Japan (7). The mean annual costs of healthcare resource use per patient in those <65 and ≥65 years old was reported to be US$4,389 and US$4,678, respectively, while the costs due to productivity loss were US $52,870 and US$30,187, respectively (5).

Bronchodilators, including long-acting β_2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs), remain the mainstay treatment options for the management of COPD (1). Indacaterol is the first approved LABA, providing 24-h bronchodilation with once-daily dosing in patients with COPD. Indacaterol induces bronchodilation through the activation of adenylyl cyclase resulting in increased intracellular calcium and direct relaxation of airway smooth muscles. It was approved by the European Medicines Agency at doses of 150 and 300 μg in 2009, followed by approval by the United States Food and Drug Administration and Japan's Ministry of Health, Labor and Welfare in 2011 at doses of 75 and 150 μg, respectively (8).

Several randomized studies performed in patients with moderate-to-severe COPD have shown that indacaterol improved the symptoms, lung function, and quality of life; reduced the use of rescue medications; and was well tolerated with an acceptable safety profile (9-13). The efficacy and safety of indacaterol have also been evaluated in Asian populations, including those in Japan (14, 15). However, these studies were performed with stringent inclusion/exclusion criteria that do not necessarily reflect the conditions in real-life practice. In addition, the majority of patients enrolled in a range of randomized controlled trials (RCTs) on indacaterol were from Western societies and showed marked phenotypic differences from their Asian counterparts (16). For example, Japanese patients tend to be older and have fewer exacerbations, fewer cardiovascular diseases and cardiac deaths, a lower average body mass index (BMI), and a more varied co-morbidity spectrum than Western patients (16, 17), suggesting the need to evaluate indacaterol use in Japanese patients with COPD.

Furthermore, some studies have reported that LABAs have the potential to increase the heart rate and can induce some class-related side effects, including palpitations, tremors, muscle spasm, and prolongation of the QTc interval (1, 18). However, limited evidence is available concerning the safety and efficacy of indacaterol maleate in a real-life setting in Japan.

This post-marketing surveillance was conducted to meet the local regulatory requirements and to evaluate the long-term safety in terms of adverse events (AEs), serious adverse events (SAEs), adverse drug reactions (ADRs), and efficacy of indacaterol maleate in Japanese patients with COPD.

Materials and Methods

Study design and patient population

This post-marketing surveillance was a 52-week multicenter, non-comparative, single-arm observational study conducted between April 2012 and December 2018 in accordance with the Good Post-Marketing Study Practice (19), with a protocol agreed upon in consultation with the Japanese Pharmaceutical and Medical Devices Agency (PMDA), and as such, informed consent was not mandated nor obtained.

Patients ≥18 years old with physician-diagnosed COPD with no prior use of indacaterol maleate and using it for the first time for the relief of COPD symptoms were included. Data on baseline demographics and clinical characteristics were collected at the start of indacaterol administration using case report forms (CRFs) with an electronic data capture system. Data on indacaterol administration, prior medications, and other concomitant therapies for COPD and related comorbidities/complications were also recorded in the CRFs.

Endpoints

The safety endpoints included the incidence of AEs, SAEs, and ADRs. An AE was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease occurring after the start of the study medication. The AEs suspected by the investigator to be related to the study medication were classified as ADRs. AEs and ADRs were monitored throughout the 52-week observation period. The ADRs of special interest (priority variables) were categorized as cardio- and cerebrovascular (CCV) events and post-inhalation cough. In addition to the analysis in the overall safety population, a subgroup analysis on the occurrence of ADRs by age category was also performed. AEs were classified based on the Medical Dictionary for Regulatory Activities (MedDRA/J) version 21.0 classification criteria (20).

The efficacy endpoints included assessment of symptoms by COPD assessment test (CAT), the lung function by forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and $\%FEV_1$ and a physician-reported global evaluation of treatment effectiveness (GETE). GETE was measured on a 5-point scale of "excellent," "good," "moderate," "poor," and "worsening," with scores of excellent and good considered to indicate an effective response (21). In this surveillance, a moderate GETE rating (slight improvement) was also considered to indicate an effective response. The CAT and lung function assessments were conducted at the start of indacaterol administration and at Weeks 4, 12, 26, and 52 following indacaterol treatment in the overall population and in patients classified by COPD stage.

Statistical analyses

Descriptive statistics were used to present the data of this

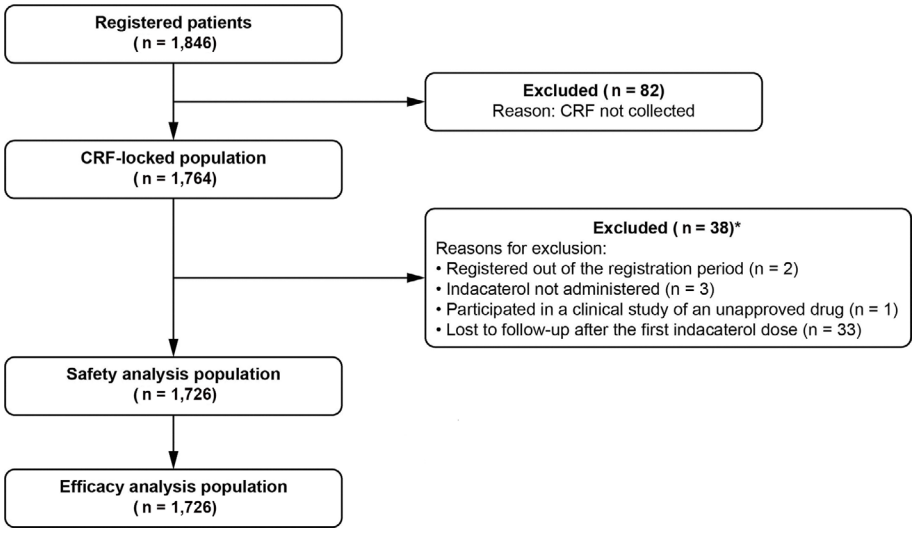

Figure 1. Patient disposition. *Patients with multiple reasons for exclusion from the safety analysis population and the efficacy analysis population were counted once for each of the reasons for exclusion. CRF: case report form

analysis. Categorical variables were presented as the frequency and respective percentage. Continuous variables were presented as the mean and standard deviation. The target sample size of 1,500 patients would provide 95% power to detect AEs occurring at an incidence of 0.2%. For comparisons among groups, a *t*-test was used for unpaired continuous data; Fisher's exact test was used for unpaired nominal data, and a paired *t*-test for paired continuous data for comparisons between two groups. The Mann-Whitney U test was used for the comparison of unpaired ordinal data of three or more groups (exception: Fisher's exact test was used when the analysis resulted in a 2×2 contingency). The level of significance was 5% in 2-tailed hypothesis tests. Analyses were performed using the Statistical Analysis Software (SAS) program, version 9.2 (SAS Institute, Cary, USA).

Two populations were defined for the analysis. The safety population excluded the patients lost to follow-up or who participated in a clinical study of an unapproved drug, who did not receive indacaterol during the observation period, or who did not register within the registration period (i.e., 14 days from the start of indacaterol administration). Patients with efficacy evaluation data that were missing or not recorded were excluded from the efficacy population. All patients in the safety analysis population were included in the efficacy analysis population.

Results

Patient disposition

In total, 1,846 patients were enrolled from 398 sites by the end of the investigation period (December, 2018), and the CRF data were locked for 1,764 of the enrolled patients. Of these, 38 patients were excluded, leaving 1,726 patients in the safety and efficacy analysis population (Fig. 1).

Demographics and clinical characteristics

The mean age of the population at the start of indacaterol administration was 72.5 years old. The majority of patients were men (84.76%), and elderly patients ≥65 years old accounted for 82.16% of the subjects. The mean COPD duration was 3.65 years. Patients with stage II accounted for a higher proportion (42.93%) than other COPD stages (22). Approximately 39.0% of patients were receiving a LAMA as a prior medication for COPD (Table 1).

Safety assessments

Incidence of AEs and SAEs

AEs occurred in 207 patients with an incidence of 11.99%. Cough, pneumonia, and COPD were AEs that occurred with an incidence of ≥1% in the safety population. SAEs occurred in 73 patients (4.23%), with pneumonia being the most common SAE (1.04%) (Table 2).

Incidence of ADRs and serious ADRs

ADRs were reported in 74 patients with an incidence of 4.29%. Cough was the most common ADR, with a reported incidence of 1.68%, followed by urticaria and supraventricular extra-systoles (0.29% and 0.23%, respectively). COPD exacerbation was a serious ADR reported in one patient that led to discontinuation of the treatment (Table 3).

Incidence of ADRs by age group

The risk ratio for ADRs in patients 75 to <85 years old compared with those in the age range of 65 to <75 years old was 0.5742 [95% confidence interval (CI): 0.3320-0.9929]. The most common ADRs in patients 75 to <85 years old were cough (0.96%), supraventricular extra-systoles (0.48%), and oropharyngeal pain (0.32%). There was no marked difference in the ADR incidence between patients 65 to <75 years old and younger patients (Table 4; Supplementary ma-

Table 1. Baseline Demographics and Clinical Characteristics (Safety Population).

Characteristic	Safety population (n=1,726)
Gender, n (%)	
Male	1,463 (84.76)
Female	263 (15.24)
Age, mean±SD, years	72.5±9.37
Age category, n (%)	
<45 years	18 (1.04)
≥45-<55 years	48 (2.78)
≥55-<65 years	242 (14.02)
≥65-<75 years	660 (38.24)
≥75-<85 years	624 (36.15)
≥85	134 (7.76)
Weight, mean±SD, kg (n=1,484)	57.81±10.932
BMI, mean±SD, kg/m^2(n=1,450)	21.96±3.559
Smoking history, n (%)	
Non-smokers	178 (10.31)
Current smokers	354 (20.51)
Ex-smokers	1,062 (61.53)
Unknown	132 (7.65)
COPD duration, mean±SD, years (n=890)	3.650±3.9365
COPD type, n (%)	
Emphysematous	1,280 (74.16)
Non-emphysematous	295 (17.09)
Not assessable	151 (8.75)
COPD stage [22]*, n (%)	
Stage I	411 (23.81)
Stage II	741 (42.93)
Stage III	353 (20.45)
Stage IV	96 (5.56)
Not assessable	125 (7.24)
Dyspnea severity†, n (%)	
Grade 0	149 (8.63)
Grade 1	586 (33.95)
Grade 2	359 (20.80)
Grade 3	169 (9.79)
Grade 4	51 (2.95)
Unknown	412 (23.87)
Comorbidities, n (%)	1,124 (65.12)
Bronchial asthma	267 (15.47)
CCV disorder	255 (14.77)
Renal disorder	36 (2.09)
Hepatic disorder	60 (3.48)
Others	1,009 (58.46)
Prior medications for COPD, n (%)	1,038 (60.14)
SAMA	5 (0.29)
LAMA	673 (38.99)
SABA	65 (3.77)
LABA	171 (9.91)
ICS	87 (5.04)
Corticosteroids (oral or injected)	37 (2.14)
ICS/LABA	136 (7.88)
LABA/LAMA	1 (0.06)
Others	463 (26.83)

*COPD stages were defined following the JRS Guidelines for the management of Chronic Obstructive Pulmonary Disease, Ver. 3. †Dyspnea severity was determined following the revised British Medical Research Council dyspnea scale.

BMI: body mass index, CCV: cardio- and cerebrovascular event, COPD: chronic obstructive pulmonary disease, ICS: inhaled corticosteroid, JRS: Japanese Respiratory Society, LABA: long-acting β_2-agonist, LAMA: long-acting muscarinic antagonist, SABA: short-acting β_2-agonist, SAMA: short-acting muscarinic antagonist, SD: standard deviation

Table 2. Incidence of Adverse Events and Serious Adverse Events (Safety Population, n=1,726).

System organ class Preferred term	Adverse events, n (%)	Serious adverse events, n (%)
Total	207 (11.99)	73 (4.23)
Infections and infestations	37 (2.14)	22 (1.27)
Pneumonia	21 (1.22)	18 (1.04)
Neoplasms benign, malignant and unspecified including cysts and polyps	14 (0.81)	11 (0.64)
Blood and lymphatic system disorders	1 (0.06)	1 (0.06)
Immune system disorders	2 (0.12)	-
Endocrine disorders	2 (0.12)	-
Metabolism and nutrition disorders	4 (0.23)	3 (0.17)
Psychiatric disorders	5 (0.29)	-
Nervous system disorders	10 (0.58)	6 (0.35)
Eye disorders	1 (0.06)	-
Cardiac disorders	35 (2.03)	9 (0.52)
Vascular disorders	7 (0.41)	3 (0.17)
Respiratory, thoracic and mediastinal disorders	79 (4.58)	24 (1.39)
Cough	29 (1.68)	-
COPD	18 (1.04)	10 (0.58)
Gastrointestinal disorders	19 (1.10)	5 (0.29)
Hepatobiliary disorders	3 (0.17)	1 (0.06)
Skin and subcutaneous tissue disorders	11 (0.64)	-
Musculoskeletal and connective tissue disorders	3 (0.17)	-
Renal and urinary disorders	8 (0.46)	2 (0.12)
Reproductive system and breast disorders	1 (0.06)	-
General disorders and administration site conditions	7 (0.41)	3 (0.17)
Investigations	13 (0.75)	-
Injury, poisoning and procedural complications	6 (0.35)	3 (0.17)

Multiple episodes of an event in the same patient were counted only once in the number of patients with the event. AEs were reported following the MedDRA/J version 21.0.

AEs are shown by preferred term for those occurring in ≥1% of the population.

AE: adverse events, COPD: chronic obstructive pulmonary disease

terial 1); however, older patients appear to have a reduced risk, reaching significance in the 75-to-<85-year-old age group.

Incidence of cardio- and cerebrovascular adverse events

In the safety population, CCV AEs occurred in 48 patients (2.78%), with supraventricular systoles and ventricular extra-systoles reported in 0.52% and 0.41% of patients, respectively (Supplementary material 2). CCV ADRs occurred in 16 (0.93%) patients. No CCV ADR was serious, as per investigator judgment. In patients with a history of CCV disorders, the incidence rates of CCV AEs and ADRs per 1,000-patient years were 74.68 and 37.06, respectively. The incidence rates of CCV AEs and ADRs were higher in patients with ≥2 CCV risk factors at baseline than in those with 0 or 1 CCV risk factor at baseline (Table 5).

Adverse drug reactions of cough

ADRs of cough occurred in 29 patients with an incidence of 1.68%. In more than half of these patients (16 patients), cough occurred within 5 minutes following indacaterol administration. In four of the patients, post-inhalation cough occurred following five minutes of indacaterol administration, while it was unknown in nine of the patients. No serious ADRs of cough were observed.

Efficacy assessments

Treatment response (GETE)

In total, 69.70% (95% CI: 67.47-71.86%) of patients receiving indacaterol achieved an effective response, based on GETE, in the overall efficacy population. A higher response rate was observed in patients with COPD stage I [72.75% (95% CI: 68.17-77.00%)], stage II [70.99% (95% CI: 67.57-74.23%)] and stage III [69.41% (95% CI: 64.31-74.17%)] than in those with stage IV [59.38% (95% CI: 48.87-69.29%)].

CAT score change from baseline

In the overall population, CAT score decreased (improvement in symptoms) following treatment with indacaterol. Decrease in the CAT score was seen by the first assessment at Week 4 and continued throughout the observation period until Week 52 (Fig. 2i). Similar to the overall population, a decrease in CAT score was observed irrespective of the disease severity at baseline (Fig. 2ii).

Lung function parameters

The mean FVC, FEV_1, and $\%FEV_1$ had improved following treatment with indacaterol by Week 4, and improvement continued until Week 52 in the overall population. Improvement in the lung function parameters (FVC, FEV_1, and %

Table 3. Incidence of Adverse Drug Reactions and Serious Adverse Drug Reactions (Safety Population, n=1,726).

System organ class Preferred term	Adverse drug reactions, n (%)
Total	74 (4.29)
Psychiatric disorders	1 (0.06)
Insomnia	1 (0.06)
Nervous system disorders	2 (0.12)
Dysgeusia	1 (0.06)
Hypoesthesia	1 (0.06)
Cardiac disorders	12 (0.70)
Supraventricular extra-systoles	4 (0.23)
Palpitations	3 (0.17)
Ventricular extra-systoles	3 (0.17)
Atrial fibrillation	1 (0.06)
Atrioventricular block first degree	1 (0.06)
Bundle branch block left	1 (0.06)
Left-ventricular hypertrophy	1 (0.06)
Vascular disorders	1 (0.06)
Hypertension	1 (0.06)
Respiratory, thoracic and mediastinal disorders	38 (2.20)
Cough	29 (1.68)
Oropharyngeal discomfort	3 (0.17)
Oropharyngeal pain	3 (0.17)
Dyspnea	2 (0.12)
Chronic obstructive pulmonary disease	1 (0.06)
Nasal discomfort	1 (0.06)
Gastrointestinal disorders	5 (0.29)
Abdominal pain upper	1 (0.06)
Constipation	1 (0.06)
Diarrhea	1 (0.06)
Dry mouth	1 (0.06)
Dyspepsia	1 (0.06)
Stomatitis	1 (0.06)
Skin and subcutaneous tissue disorders	8 (0.46)
Urticaria	5 (0.29)
Eczema	2 (0.12)
Rash	1 (0.06)
Musculoskeletal and connective tissue disorders	2 (0.12)
Muscle spasms	2 (0.12)
Renal and urinary disorders	1 (0.06)
Pollakiuria	1 (0.06)
General disorders and administration site conditions	1 (0.06)
Peripheral swelling	1 (0.06)
Investigations	6 (0.35)
Electrocardiogram QT prolonged	2 (0.12)
Blood pressure increased	1 (0.06)
Electrocardiogram abnormal	1 (0.06)
Electrocardiogram ST segment depression	1 (0.06)
Heart rate increased	1 (0.06)
Electrocardiogram T wave abnormal	1 (0.06)
System organ class Preferred term	**Serious adverse drug reactions, n (%)**
Total	**1 (0.06)**
Respiratory, thoracic and mediastinal disorders	1 (0.06)
COPD exacerbation	1 (0.06)

Multiple episodes of an event in the same patient were counted only once in the number of patients with the event. Adverse events were reported following the MedDRA/J version 21.0.

COPD: chronic obstructive pulmonary disease

Table 4. Incidence of ADRs by Age Category (Safety Population, n=1,726).

Items	Age category (years)					
	<45	≥45 to <55	≥55 to <65	≥65 to <75	≥75 to <85	≥85
Number of patients, n	18	48	242	660	624	134
Patients with ADRs, n (%)	1 (5.56)	3 (6.25)	13 (5.37)	35 (5.30)	19 (3.04)	3 (2.24)
Risk ratio	1.0476	1.1786	1.0130	Reference	0.5742	0.4222
95% CI	0.1518 to 7.2308	0.3761 to 3.6929	0.5453 to 1.8818	-	0.3320 to 0.9929	0.1318 to 1.3526
Type of ADR by System Organ Class, n (%)						
Psychiatric disorders	-	-	-	1 (0.15)	-	-
Nervous system disorders	-	1 (2.08)	-	-	1 (0.16)	-
Cardiac disorders	-	1 (2.08)	-	6 (0.91)	5 (0.80)	-
Vascular disorders	-	-	-	-	1 (0.16)	-
Respiratory, thoracic and mediastinal disorders	1 (5.56)	1 (2.08)	9 (3.72)	17 (2.58)	8 (1.28)	2 (1.49)
Gastrointestinal disorders	-	-	1 (0.41)	-	3 (0.48)	1 (0.75)
Skin and subcutaneous tissue disorders	-	-	2 (0.83)	5 (0.76)	1 (0.16)	-
Musculoskeletal and connective tissue disorders	-	-	-	2 (0.30)	-	-
Renal and urinary disorders	-	-	-	1 (0.15)	-	-
General disorders and administration site conditions	-	-	-	1 (0.15)	-	-
Investigations	1 (5.56)	-	1 (0.41)	3 (0.45)	1 (0.16)	-

Multiple episodes of an event in the same patient were counted only once in the number of patients with the event. Adverse events were reported following the MedDRA/J version 21.0.

ADR: adverse drug reaction, CI: confidence interval

Table 5. Incidence of CCV Adverse Events and Adverse Drug Reactions by Number of CCV Event Risk Factors (Safety Population, n=1,726).

	Adverse events		Adverse drug reactions	
	Patients with CCV/sample size (%)	Patients with CCV/PY (IR)	Patients with CCV/sample size (%)	Patients with CCV/PY (IR)
History of CCV diseases	18/309 (5.83)	18/241 (74.68)	9/309 (2.91)	9/243 (37.06)
CCV risk factors 0	2/106 (1.89)	2/86 (23.14)	1/106 (0.94)	1/86 (11.56)
CCV risk factors 1	9/497 (1.81)	9/406 (22.15)	2/497 (0.40)	2/410 (4.88)
CCV risk factors 2	17/376 (4.52)	17/301 (56.53)	6/376 (1.60)	6/303 (19.83)
CCV risk factors ≥3	12/310 (3.87)	12/241 (49.78)	5/310 (1.61)	5/243 (20.58)

CCV risk factors include previous history of CCV diseases, hypertension, hyperlipidemia, diabetes mellitus, BMI >30 kg/m^2, age ≥65 years and smoking. Patients with missing information were excluded from the analysis.

BMI: body mass index, CCV: cardio- and cerebrovascular events, IR: incident rate per 1000-PYs, PY: patient-year

FEV_1) was also observed across COPD stages compared with baseline (Supplementary material 3-5).

Discussion

This post-marketing surveillance assessed the long-term safety and efficacy of indacaterol maleate in a real-world setting in Japan and was completed during an eight-year re-examination period following its approval in 2011. The demographics and clinical characteristics, including more men, low BMI, and a higher proportion of patients with stage II disease (moderate COPD), are consistent with previous reports on COPD cohorts in Japan (5, 17). Considering the phenotypic differences between Japanese patients with COPD and those in Western countries, this surveillance has provided important information regarding the safety and efficacy of indacaterol in a large number of Japanese patients with COPD in a real-world setting.

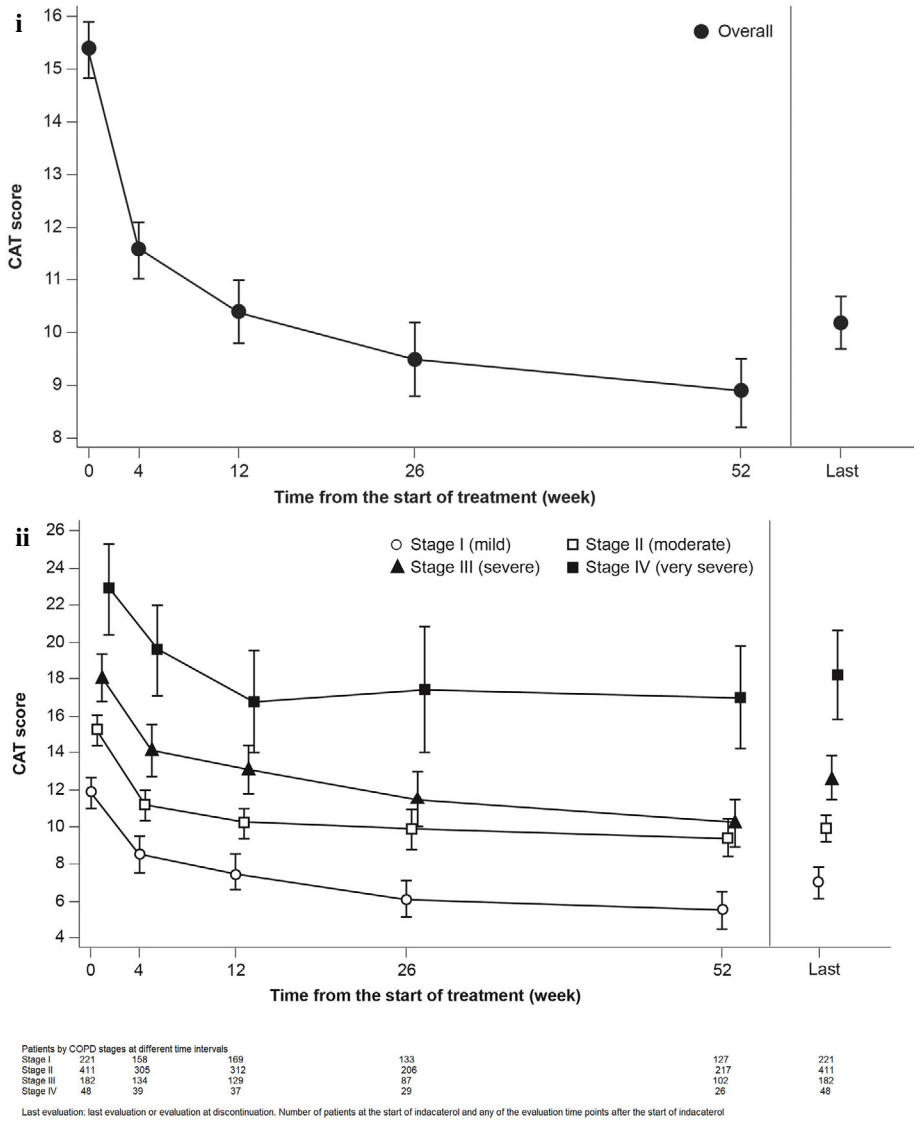

Figure 2. **(i) Change in the CAT score for the overall population (efficacy population); (ii) Change in the CAT score by COPD stage (efficacy population). Data presented are the mean (95% CI). Numbers of patients at the start of indacaterol and any of the evaluation time points after the start of indacaterol. CAT: COPD assessment test, CI: confidence interval, COPD: chronic obstructive pulmonary disease**

The safety findings of this prospective surveillance showed a lower incidence of AEs and SAEs than previously reported in randomized studies. In a 52-week randomized, long-term safety and efficacy study, the incidence of AEs and SAEs in patients receiving indacaterol 150 μg were 76% and 10.4%, respectively; in contrast, respective proportions of 68% and 10.5% of those receiving placebo experienced these events (9). A pooled analysis of 11 RCTs in patients with moderate-to-severe COPD also demonstrated that indacaterol has a comparable safety profile to that of placebo. The most common AEs reported in the analysis were COPD worsening, nasopharyngitis, and headache (23). A 12-week, randomized, placebo-controlled study across 6 Asian countries, including Japan, reported an AE incidence of 49.1% with both indacaterol doses of 150 and 300 μg, with COPD worsening being the most common AE, followed by nasopharyngitis (15). In this surveillance, we observed that 11.99% and 4.23% patients experienced AEs and SAEs, respectively. AEs were mostly mild to moderate in severity. Cough, pneumonia, and COPD worsening were the most common AEs reported by patients. This was in line with the 6-month, real world, INFLOW study, which reported a similar incidence of AEs (15% of all patients), with cough as the most common AE reported (4% of all patients) (24). Taken together, it is often difficult to extrapolate the results from RCTs consisting of a relatively small number of patients who were selected based on strict inclusion and exclusion criteria to diversified situations that could occur in a real-world setting. However, the observational nature of this surveillance enabled us to collect real-world data to assess safety and efficacy of indacaterol from a large number of patients in a naturalistic clinical setting who were not included in RCTs, including those with CCV risk, which was a key safety endpoint in this surveillance.

In this surveillance, it was observed that in over 50% of patients who experienced cough, symptoms occurred within 5 minutes post-administration of indacaterol. Cough was by far the most common ADR observed in this surveillance, but no ADRs were serious. One patient experienced a serious ADR (COPD exacerbation), which resulted in treatment discontinuation. Earlier clinical studies have also reported that a notable proportion of patients receiving indacaterol experience a short-lasting cough a few seconds after inhalation (18). A subgroup analysis of ADRs by age category showed the tolerability of indacaterol in all age groups. The risk ratio of ADRs in the elderly patients 75 to <85 years old was lower than in those 65 to <75 years old. However, due to the small number of patients with ADRs in this surveillance, it is difficult to disentangle the cause of a decrease in ADRs in the elderly patients 75 to <85 years old.

The class-related side effects of β_2-agonists include cardiac arrhythmias caused by an increased heart rate through β_2-adrenergic receptor stimulation, tremors, muscle spasms, hypokalemia, and prolonged QTc interval (18, 25). In this surveillance, 16 patients experienced CCV events, of which supraventricular systoles and ventricular extra-systoles were the most frequent, but none was serious. Pooled data of 4,635 patients receiving indacaterol or other bronchodilators reported that indacaterol was not associated with an increased risk of CCV AEs compared with placebo and other comparators (25). In this surveillance, the CCV incidence was higher in patients with ≥2 CCV risk factors at baseline than in those with 0 or 1 CCV risk factor at baseline, suggesting that careful monitoring of these patients during indacaterol treatment may be warranted. In a pooled analysis of clinical trials, Donohue et al. also noted that there is a relatively high presence of CCV risk factors in patients with moderate-to-severe COPD (23). Therefore, consideration of the presence of CCV risk factors should form part of the benefit-risk analysis of indacaterol treatment in these patients.

In this surveillance, CAT scores had improved by the first assessment at Week 4, and the improvement continued throughout the treatment period. This improvement in the CAT score was observed in the overall population and across all the COPD stages, even in patients with stage I (mild), the population that is rarely included in clinical trials of COPD. Similar improvement was observed in the lung function assessments, including FVC, FEV_1, and $\%FEV_1$. The findings observed in this surveillance are in agreement with earlier real-world studies in Japanese patients with COPD, which reported a similar improvement in the CAT score and FEV_1 following indacaterol administration (26).

The real-world INFLOW study reported that 76.8% of patients treated with indacaterol achieved a good or very good response as per the investigator-rated assessment of treatment effectiveness (24). It has also been reported that 44.4% of patients receiving indacaterol showed an improvement in their COPD condition based on physician's assessment by considering changes in symptoms and the lung function in a real-world clinical setting in South Korea (27). In this surveillance, 69.70% of patients achieved a good/excellent/moderate response in the overall efficacy population. A higher response was observed in patients with stage I (72.75%), and approximately 60% of patients with stage IV achieved this response. Although the severity of COPD patients and the criteria for effectiveness assessed by physicians were different among these three studies, indacaterol is considered an effective treatment for Japanese patients with COPD.

Interpretation of this surveillance needs to be done cautiously because this is a single-arm, non-interventional study without a placebo arm of patients not exposed to indacaterol. Caution also should be exercised in predicting which variables may have influenced the safety and efficacy of indacaterol. In addition, a common efficacy endpoint, such as COPD exacerbation, was not assessed in this surveillance. However, since Japanese patients with COPD tend to have fewer exacerbations than those in other countries (16, 17, 28), and more than 65% of patients were in stage I or II in this surveillance, the evaluation of the clinical symptoms, such as via a CAT, would be considered more meaningful in a clinical setting.

Despite these limitations, the low incidence of AEs along with proven efficacy suggests that indacaterol would be an effective treatment option for COPD patients in a real-life setting.

Conclusion

In conclusion, indacaterol demonstrated favorable safety and tolerability profile in Japanese patients with COPD without new safety signals observed in real-life settings. Treatment with indacaterol improved the CAT score and lung function, irrespective of disease severity, even in patients with stage I (mild). These findings are similar to those observed in the Caucasian population despite phenotypic differences, indicating the ethnic insensitivity of indacaterol. Indacaterol may therefore be an effective maintenance treatment in real-life practice for Japanese patients with COPD.

This post-marketing surveillance was in accordance with the Good Post-Marketing Study Practice (19), with a protocol agreed upon in consultation with the Japanese Pharmaceutical and Medical Devices Agency (PMDA), and as such, informed consent was neither mandated nor obtained.

Novartis is committed to sharing with qualified external researchers access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientificmerit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The trial data availability is according to the criteria and process described on www.clinicalstud ydatarequest.com

Author's disclosure of potential Conflicts of Interest (COI).

Tomoko Taniguchi: Employment, Novartis Pharma. Dong Wang: Employment, Novartis Pharma. Hajime Yoshisue: Employment, Novartis Pharma. Makoto Nagasaki: Employment, Novartis Pharma. Takayoshi Sasajima: Employment, Novartis Pharma.

Acknowledgement

The authors thank all the investigators and their patients who participated in this surveillance. The authors also thank Lakshmi Narendra Bodduluru, PhD and Chiranjit Ghosh, PhD for providing medical writing/editorial support.

References

1. Global Initiative for Chronic Obstructive Lung Disease - Global Initiative for Chronic Obstructive Lung Disease - GOLD [Internet]. 2019 [cited 2019 Nov 20]. Available from: https://goldcopd.org/
2. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet **380**: 2095-2128, 2012.
3. Chronic obstructive pulmonary disease (COPD) [Internet]. 2019 [cited 2019 Nov 20]. Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)
4. Fukuchi Y, Nishimura M, Ichinose M, et al. COPD in Japan: the Nippon COPD Epidemiology study. Respirology **9**: 458-465, 2004.
5. Igarashi A, Fukuchi Y, Hirata K, et al. COPD uncovered: a cross-sectional study to assess the socioeconomic burden of COPD in Japan. Int J Chron Obstruct Pulmon Dis **13**: 2629, 2018.
6. Minakata Y, Ichinose M. Epidemiology of COPD in Japan. Nihon Rinsho (Jpn J Clin Med) **69**: 1721-1726, 2011 (in Japanese, Abstract in English).
7. J Foo J, Landis SH, Maskell J, et al. Continuing to confront COPD international patient survey: economic impact of COPD in 12 countries. PloS One **11**: 2016.
8. Murphy L, Rennard S, Donohue J, et al. Turning a molecule into a medicine: the development of indacaterol as a novel once-daily bronchodilator treatment for patients with COPD. Drugs **74**: 1635-1657, 2014.
9. Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B; INDORSE Study Investigators. Long-term safety and efficacy of indacaterol, a long-acting β2-agonist, in subjects with COPD: a randomized, placebo-controlled study. Chest **140**: 68-75, 2011.
10. Donohue JF, Fogarty C, Lotvall J, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med **182**: 155-162, 2010.
11. Feldman G, Siler T, Prasad N, et al.; INLIGHT 1† study group. Efficacy and safety of indacaterol 150 μg once-daily in COPD: a double-blind, randomised, 12-week study. BMC Pulm Med **10**: 11, 2010.
12. Kornmann O, Dahl R, Centanni S, et al.; INLIGHT-2 (Indacaterol Efficacy Evaluation Using 150-μg Doses with COPD Patients) study investigators. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J **37**: 273-279, 2011.
13. Yorgancioglu A. Indacaterol in chronic obstructive pulmonary disease: an update for clinicians. Ther Adv Chronic Dis **3**: 25-36, 2012.
14. Kinoshita M, Lee SH, HANG LW, et al.; Indacaterol Asian COPD Study Investigators. 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. Respirology **17**: 379-389, 2012.
15. To Y, Kinoshita M, Lee SH, Hang LW, et al. Assessing efficacy of indacaterol in moderate and severe COPD patients: a 12-week study in an Asian population. Respir Med **106**: 1715-1721, 2012.
16. Nishimura M. Similarities and differences between East and West in COPD. Respirology **21**: 1340-1341, 2016.
17. Suzuki M, Makita H, Ito YM, Nagai K, Konno S, Nishimura M. Clinical features and determinants of COPD exacerbation in the Hokkaido COPD cohort study. Eur Respir J **43**: 1289-1297, 2014.
18. Metaxas EI, Balis E. The safety of indacaterol for the treatment of COPD. Expert Opin. Drug Saf **17**: 637-642, 2018.
19. Kumano S. GPSP: good post-marketing study practice. Nihon Yakurigaku Zasshi (Folia Pharmacol Japonica) **140**: 81-84, 2012 (in Japanese).
20. Meddra.org [Internet]. Available from: https://www.meddra.org/
21. Lloyd A, Turk F, Leighton T, Walter Canonica G. Psychometric evaluation of global evaluation of treatment effectiveness: a tool to assess patients with moderate-to-severe allergic asthma. J Med Econ **10**: 285-296, 2007.
22. Nagai A. Guidelines for the diagnosis and management of chronic obstructive pulmonary disease. Nihon Rinsho (Jpn J Clin Med) **69**: 1729-1734, 2011 (in Japanese, Abstract in English).
23. Donohue JF, Singh D, Kornmann O, Lawrence D, Lassen C, Kramer B. Safety of indacaterol in the treatment of patients with COPD. Int J Chron Obstruct Pulmon Dis **6**: 477, 2011.
24. Juvelekian G, El-Sorougi W, Pothirat C, et al. A real-world evaluation of indacaterol and other bronchodilators in COPD: the INFLOW study. Int J Chron Obstruct Pulmon Dis **10**: 2109, 2015.
25. Worth H, Chung KF, Felser JM, Hu H, Rueegg P. Cardio-and cerebrovascular safety of indacaterol vs formoterol, salmeterol, tiotropium and placebo in COPD. Respir Med **105**: 571-579, 2011.
26. Ohno T, Wada S, Hanada S, Sawaguchi H, Muraki M, Tohda Y. Efficacy of indacaterol on quality of life and pulmonary function in patients with COPD and inhaler device preferences. Int J Chron Obstruct Pulmon Dis **9**: 107, 2014.
27. Yum HK, Kim HR, Chang YS, Shin KC, Kim S, Oh YM. Safety and effectiveness of indacaterol in chronic obstructive pulmonary disease patients in South Korea. Tuberc Respir Dis **80**: 52-59, 2017.
28. Oishi K, Hirano T, Hamada K, et al. Characteristics of 2017 GOLD COPD group A: a multicenter cross-sectional CAP study in Japan. Int J Chron Obstruct Pulmon Dis **13**: 3901-3907, 2018.