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 (FEV1), and %FEV1 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, FEV1, and %FEV1) 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 Advance Publication)
(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
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 (FEV1), and %FEV1, 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
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 Inc. 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 18, 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. 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 Ta-
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/m² (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 (%)**                            |                             |
| Bronchial asthma                                    | 1,124 (65.12)               |
| CCV disorder                                        | 267 (15.47)                 |
| Renal disorder                                      | 255 (14.77)                 |
| Hepatic disorder                                    | 36 (2.09)                   |
| Others                                              | 60 (3.48)                   |
| **Prior medications for COPD, n (%)**               |                             |
| SAMA                                                | 1,038 (60.14)               |
| LAMA                                                | 5 (0.29)                    |
| SABA                                                | 673 (38.99)                 |
| LABA                                                | 65 (3.77)                   |
| ICS                                                 | 171 (9.91)                  |
| Corticosteroids (oral or injected)                  | 87 (5.04)                   |
| ICS/LABA                                            | 37 (2.14)                   |
| LABA/LAMA                                           | 136 (7.88)                  |
| Others                                              | 1 (0.06)                    |
| **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 β₂-agonist, LAMA: long-acting muscarinic antagonist, SABA: short-acting β₂-agonist, SAMA: short-acting muscarinic antagonist, SD: standard deviation
ble 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 extrasystoles reported in 0.52% and 0.41% of patients, respectively (Supplementary Table 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 in symptoms following treatment with indacaterol by Week 4, and improvement continued until Week 52 in the overall population. Improvement in the lung function parameters (FVC, FEV1, and %FEV1) had improved following treatment with indacaterol by Week 4, and improvement continued until Week 52 in the overall population.

### 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

AE: adverse events, COPD: chronic obstructive pulmonary disease
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)                      |
| Dysesthesia                       | 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.
FEV₁) was also observed across COPD stages compared with baseline (Supplementary Figs. 1-3).

### 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.

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-agonists include cardiac arrhythmias caused by an increased heart rate through β-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, FEV₁, and %FEV₁. 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 FEV₁ 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.

**Conclusions**

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.

**Author’s disclosure of potential Conflicts of Interest (COI).**
Tomoko Taniguchi: Employment, Novartis Pharma K.K. Dong Wang: Employment, Novartis Pharma K.K. Hajime Yoshisue: Employment, Novartis Pharma K.K. Makoto Nagasaki: Employment, Novartis Pharma K.K. Takayoshi Sasajima: Employment, Novartis Pharma K.K.

**Acknowledgement**
All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript. All authors contributed to the interpretation of the data and the writing and reviewing of all drafts of the manuscript. All authors approved the final version to be published and agree to be accountable for all aspects of this work.

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 (Novartis Healthcare Private Limited, India) for providing medical writing/editorial support, which was funded by Novartis, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Funding source: This study was supported by Novartis Pharma AG, Basel, Switzerland

Disclosures

Tomoko Taniguchi, Dong Wang, Hajime Yoshisue, Makoto Nagasaki and Takayoshi Sasajima are the employees of Novartis Pharma K.K., Tokyo, Japan

Compliance with Ethics Guidelines

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.

Data sharing

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 scientific merit. 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.clinicalstudiesdatarequest.com

Disclaimer

This paper has not been published or presented at national or international meetings, in part or in its entirety, and is not under consideration by another journal.

References

1. Global Initiative for Chronic Obstructive Lung Disease - Global Initiative for Chronic Obstructive Lung Disease - GOLD. Global Initiative for Chronic Obstructive Lung Disease - GOLD [Internet]. 2019 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). Who.int [Internet]. 2019 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. Japanese journal of clinical medicine 69: 1721-1726, 2011.
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: 1655-1677, 2014.
9. Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B; INDOMERE 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. Respiratory medicine 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: 1209-1297, 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 yakuigaku zasshi. Folia pharmacologica Japonica 140: 81-84, 2012.
20. Meddra.org [Internet]. Available from: https://www.meddra.org/site/s/default/files/page/documents/meddra-j_adjunct_file_0.pdf
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. Japanese journal of clinical medicine 69: 1729-1734, 2011.
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. Juvelikian G, El-Sorougi W, Pothirat C, et al. A real-world evaluation of indacaterol and other bronchodilators in COPD: the INLIGHT study. Int J Chron Obstruct Pulmon Dis 10: 2109, 2015.
25. Wootth P, Chung KE, 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.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).