

[ORIGINAL ARTICLE]

Real-world Safety and Efficacy of Indacaterol/ Glycopyrronium in Japanese Patients with Chronic Obstructive Pulmonary Disease: A 52-week Post-marketing Surveillance

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Abstract:

Objective To evaluate the long-term safety and efficacy of indacaterol/glycopyrronium (IND/GLY) in patients with chronic obstructive pulmonary disease (COPD) in a real-world setting in Japan.

Methods This 52-week, multicentre, post-marketing surveillance conducted in Japan between December 2013 and August 2019 included patients using IND/GLY for the first time to relieve airway obstructive disorder-related symptoms. Safety outcomes included the incidence of adverse events (AEs), serious AEs (SAEs), adverse drug reactions (ADRs), and serious ADRs during the 52-week period. The incidence of priority variables, including cardiovascular/cerebrovascular (CCV) AEs, β -adrenergic-related or anticholinergic AEs and cough, was also assessed. Safety outcomes were also evaluated in elderly patients. Efficacy outcomes included a physician's global assessment, COPD assessment test (CAT) and lung function test.

Results Of the 1,167 patients registered, 1,108 were included in the safety and efficacy analysis. In the safety analysis population, the incidence of AEs was 13.54%, that of SAEs was 4.69%, that of ADR was 3.61%, and that of serious ADRs was 0.36% over 52 weeks. CCV AEs, β -adrenergic-related and anticholinergic AEs and cough were reported as 2.62%, 1.99% and 0.63%, respectively. The physician's global assessment showed that the overall response rate at the last assessment was 74.19%. The mean (95% confidence interval) CAT scores decreased from the start of treatment to Week 52 with IND/GLY [-6.9 (-7.8 to -6.1)]. The lung function (FEV₁ and FVC) improved over time from the start of IND/GLY to Week 52.

Conclusion IND/GLY demonstrated a good long-term safety profile in a real-world setting in Japanese patients with COPD, with beneficial effects in terms of the lung function and symptoms in clinical use.

Key words: anticholinergic, cardiovascular, cerebrovascular, COPD, indacaterol/glycopyrronium, post-marketing surveillance

(Intern Med 61: 789-800, 2022)

(DOI: 10.2169/internalmedicine.7845-21)

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease characterised by persistent respiratory symptoms (such as dyspnoea, cough and/or sputum production) and airflow limitation that is due to airway and/or alveolar abnormalities caused by significant exposure to noxious particles, mainly from tobacco smoke or gases (1). The global prevalence of COPD was reported to be around 251

million cases in 2016 (2). By 2030, COPD is projected to be the third leading cause of death worldwide (3). The NIPPON COPD epidemiology (NICE) study reported that the prevalence of COPD in Japan was 8.6% in subjects \geq 40 years old (4); however, in subjects with a smoking history or some respiratory symptoms, the prevalence of COPD is 22% (5). The NICE study estimated that 5.3 million Japanese patients \geq 40 years old are afflicted by COPD (4, 5).

The Global Initiative for Chronic Obstructive Disease (GOLD 2020) and Japanese Respiratory guidelines (JRS 3rd

edition) recommend bronchodilators, i.e. short-acting β_2 -agonists (SABA), long-acting β_2 -agonists (LABA) and long-acting muscarinic antagonists (LAMA), as the mainstay pharmacological treatment for stable COPD, to be chosen in a stepwise manner depending on the patient's disease severity and their responsiveness to treatment (1, 6). Regular use of LABA or LAMA is recommended for moderate or relatively severe COPD. However, in patients not adequately controlled with monotherapy or with severe symptoms, two or more bronchodilators may be combined (1, 6).

Indacaterol/glycopyrronium (IND/GLY) is a once-daily fixed-dose combination of indacaterol maleate (IND, a LABA) and glycopyrronium bromide (GLY, a LAMA), delivered via the Breezhaler[®] device, approved as a maintenance bronchodilator therapy to relieve symptoms in patients with COPD (7). IND/GLY was approved based on data from the Phase III IGNITE clinical trial programme comprising 11 studies, with more than 10,000 patients across 52 countries, which established its efficacy and safety profile in patients with COPD (7). In Japan, IND/GLY was approved in 2013 for the "relief of airway obstructive disorder-related symptoms in COPD (chronic bronchitis, emphysema), requiring combined use of a LABA and a LAMA".

Several large randomised clinical trials (RCTs) demonstrated the safety and efficacy of IND/GLY in patients with COPD, which also included patients from Japan (7, 8). However, RCTs on COPD are designed to determine the efficacy and safety of an intervention under standardised conditions with strict selection criteria, especially excluding those with comorbidities such as cardiovascular diseases. As a result, patients recruited in RCTs may not necessarily represent those encountered in real-life situations (9). In addition, the majority of patients enrolled in RCTs of IND/GLY were from Western societies, showing marked phenotypic differences from their Asian counterparts (10). Despite numerous RCTs represented by those included in the IGNITE programme, limited data are currently available on the safety and efficacy of IND/GLY in COPD patients in a real-life setting (11, 12).

At approval, the Ministry of Health, Labour and Welfare identified the further need to assess the long-term safety of IND/GLY in elderly patients, cardiovascular/cerebrovascular (CCV) events, β -adrenergic stimulation-related or anticholinergic adverse events (AEs), and the occurrence of cough. This post-marketing surveillance was conducted to evaluate the long-term safety in terms of AEs, serious AEs (SAEs), adverse drug reactions (ADRs) and efficacy of IND/GLY in Japanese patients with COPD.

Materials and Methods

Study design

This 52-week multicentre, observational study was conducted between December 2013 and August 2019 in accordance with the Good Post-marketing Study Practice (GPSP)

guidance, as directed by the Japanese Pharmaceutical and Medical Devices Agency (PMDA). The protocol of this surveillance was agreed upon in consultation with the PMDA, and as such, informed consent from the patients was not mandated nor obtained.

This post-marketing surveillance was conducted in 309 sites across Japan and used a central patient registration system. Investigators or sub-investigators registered patients by filling in the registration forms using the electronic data capture (EDC). Details of all registered patients were recorded from the start of IND/GLY treatment to the completion/discontinuation of the observation period (12 weeks and 52 weeks) in the case report form (CRF) using EDC. Patients who were diagnosed with COPD and prescribed IND/GLY for the first time for the relief of airway obstructive disorder-related symptoms were included.

Study variables

Patient demographics and characteristics

The patient demographics and disease characteristics, such as age, body mass index (BMI), type of COPD, COPD stage (JRS guideline), dyspnoea severity (grade), prior COPD medications, complications, medical history and smoking status, were recorded.

Safety

Safety endpoints included the incidence of AEs, ADRs, SAEs and serious ADRs during the 52-week observation period. The AEs suspected by the investigator of being related to the study medication were classified as ADRs. The incidence of ADRs was also assessed by age subgroups.

The incidence of priority variables, which included CCV AEs, β -adrenergic-related AEs, anticholinergic AEs and cough, were also assessed. For CCV AEs and ADRs, the incidence per 1,000 patient-years was evaluated based on the number of CCV disorder risk factors that were present. CCV risk factors were predefined as the following seven factors: history of CCV disorder, hypertension, hyperlipidaemia, diabetes mellitus, BMI of >30 kg/m², age ≥ 65 years old and a current smoking status. The safety was evaluated in the safety analysis population, which included patients whose CRFs were locked and excluded those meeting the criteria described in Supplementary material 1.

Efficacy

Efficacy endpoints included the physician's global assessment, COPD assessment test (CAT) and lung function test (spirometry). The physician's global assessment (global impression of change) evaluated changes in the global clinical impression of patients on a 5-point scale ("excellent", "good", "moderate", "poor" and "worsening") from the start of IND/GLY treatment. "Excellent", "good" and "moderate" were defined as response, whereas "poor", "worsening" and "not assessable" were considered to indicate a non-response. CAT scores and the lung function [forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC)] were assessed at the start of IND/GLY treatment and at Weeks 4, 12, 26 and 52 as well as at the last assessment time point.

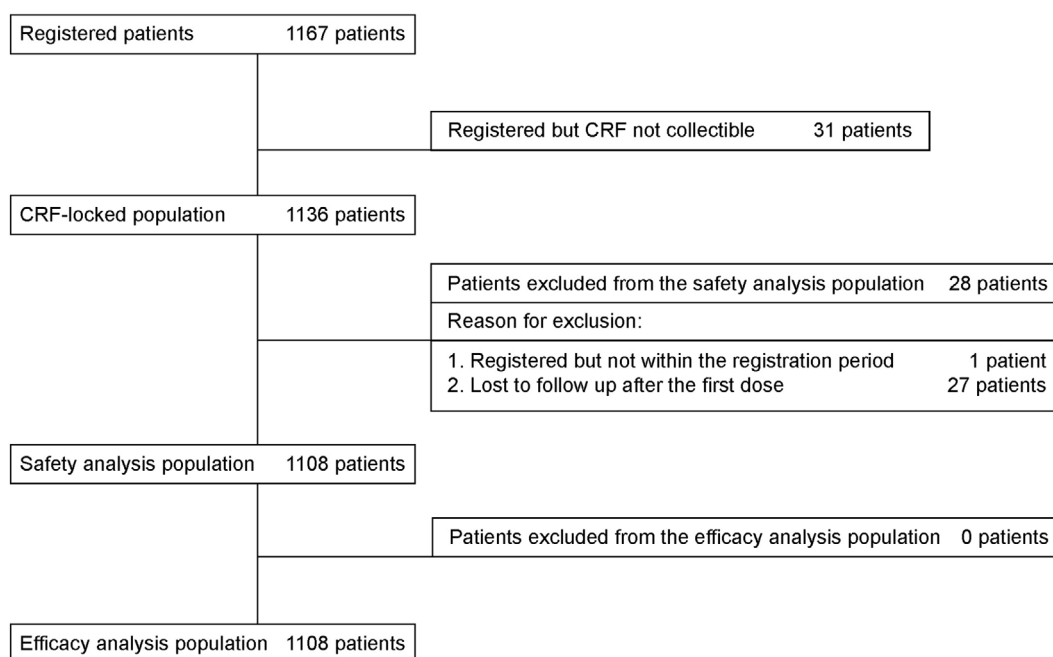


Figure 1. Patient disposition. CRF: case report form

Changes over time in CAT scores was evaluated in the overall efficacy analysis population and by subgroups of COPD stages, body weight, BMI, dyspnoea severity and elderly versus non-elderly populations.

The efficacy variables were analysed using the efficacy analysis population, which included all patients in the safety analysis population but excluded those meeting the efficacy analysis exclusion condition, as described in Supplementary material 2

Statistical analyses

A sample size of 1,000 patients (safety analysis population) was considered adequate for this post-marketing surveillance, which would provide for an adequate number of patients in different age groups, thereby allowing the safety of IND/GLY in elderly patients to be evaluated by segmented age groups (e.g. 10-year age groups). With a target sample size of 1,000 patients in this post-marketing surveillance of IND/GLY, 214 patients 0-49 years old, 79 patients 50-59 years old, 249 patients 60-69 years old and 458 patients ≥ 70 years old (1,000 patients in total) were expected to be registered, assuming that the registered population would reflect the same distribution as the numbers of Japanese patients with COPD in these age groups reported in the NICE study (4). AEs were evaluated from the start date of IND/GLY to the “maximum observation period (52 weeks) +30 days”, referred to as the safety analysis period. For patients who discontinued/dropped out, the safety analysis period was considered from the start date of IND/GLY to “last date of IND/GLY administration+30 days”. The incidence of AEs, SAEs, ADRs and serious ADRs are summarized and evaluated by system organ class (SOC) and preferred term (PT). Multiple episodes of a PT in an SOC were counted

only once in the number of patients within the SOC. Regarding the lung function (FEV₁, FVC) and CAT evaluations, summary statistics were calculated for the respective assessment time points (at the start of IND/GLY; at Weeks 4, 12, 26 and 52 of IND/GLY treatment; and at the last assessment) and presented as the change over time in the mean along with the 95% confidence interval (CI). Patients who skipped or interrupted IND/GLY treatment for 30 days or longer were considered to have discontinued treatment, and their details were recorded in the discontinuation field.

Results

Study population

In total, 1,167 patients were registered for this study, and CRFs of 1,136 registered patients were locked (Fig. 1). Of the 1,136 patients with locked CRFs, 28 were excluded from the analysis (27 patients were lost to follow-up, and 1 patient registered outside the registration period). Therefore, the safety analysis set consisted of 1,108 subjects. A total of 392 patients (35.38%) discontinued this study. The most common reasons for discontinuation were “stopped returning before completion” (n=133, 12.00%), “patient’s/family’s wish” (n=98, 8.84%) and “hospital change” (n=61, 5.51%).

Patient demographics and baseline characteristics are presented in Table 1. The mean [\pm standard deviation (SD)] age of patients at the start of IND/GLY was 73.2 \pm 10.01 years (median age, 74.0 years old). Elderly patients (≥ 65 years old) accounted for a majority (n=814, 73.47%) in the study. Most patients had stage II COPD, followed by stage III and stage I. Prior use of LAMA was reported in nearly 34% of patients. The most common comorbid conditions included

Table 1. Patient Demographics and Baseline Characteristics (Safety Dataset).

Characteristics	Total number of patients (N=1,108)
Age, years	
Mean±SD	73.2±10.01
Median (min-max)	74.0 (29.0-98.0)
Men	900 (81.23)
Weight, kg	
Mean±SD	58.12±11.703
Median (min-max)	57.90 (30.0-120.8)
BMI, kg/m ²	
Mean±SD	22.23±3.907
Median (min-max)	21.970 (12.86-42.00)
Smoking status, n (%)	
Never smoker	176 (15.88)
Ex-smoker	604 (54.51)
Current smoker	226 (20.40)
COPD duration, years,	
Mean±SD	4.37±4.604
Median (min-max)	2.750 (0.00-15.83)
<1 year, n (%)	158 (14.26)
≥1 to <3 years, n (%)	105 (9.48)
≥3 years, n (%)	245 (22.11)
Unknown/not recorded	600 (54.15)
COPD stage*	
Stage I (mild)	223 (20.13)
Stage II (moderate)	444 (40.07)
Stage III (severe)	242 (21.84)
Stage IV (very severe)	68 (6.14)
Dyspnoea severity, (grade) [†]	
0	99 (8.94)
1	454 (40.97)
2	341 (30.78)
3	174 (15.70)
4	40 (3.61)
Prior experience with inhaled muscarinic antagonists, n (%)	512 (46.21)
Prior use of β_2 agonists	536 (48.38)
Complications, n (%)	
Bronchial asthma	220 (19.86)
CCV disorder	171 (15.43)
Hepatic disorder	34 (3.07)
Prior medication for COPD, n (%)	665 (60.02)
SAMA	6 (0.54)
LAMA	372 (33.57)
SABA	30 (2.71)
LABA	277 (25.00)
ICS	62 (5.60)
OCS.CSI	21 (1.90)
LABA/ICS	97 (8.75)
LABA/LAMA	1 (0.09)
Others	295 (26.62)

*JRS Guidelines for the Management of COPD (version 4) (Please refer to Supplementary material 5 for disease staging). [†]As per British Medical Research Council (MRC) dyspnoea scale revised. BMI: body-mass index, CCV: cardiovascular/cerebrovascular, COPD: chronic obstructive pulmonary disease, CSI: corticosteroid injection, ICS: inhaled corticosteroid, LABA: long-acting β_2 -agonist, LAMA: long-acting muscarinic antagonist, OCS: oral corticosteroid, SABA: short-acting β_2 -agonist, SAMA: short-acting muscarinic antagonist

Table 2. Adverse Events and Serious Adverse Events (Safety Analysis Population).

	Total number of patients (N=1,108)	
	Adverse events, n (%)	Serious adverse events, n (%)
Patients experiencing adverse events	150 (13.54)	52 (4.69)
Infections and infestations	27 (2.44)	12 (1.08)
Neoplasms benign, malignant and unspecified	6 (0.54)	6 (0.54)
Blood and lymphatic system disorders	3 (0.27)	2 (0.18)
Metabolism and nutrition disorders	3 (0.27)	-
Nervous system disorders	7 (0.63)	1 (0.09)
Ear and labyrinth disorders	1 (0.09)	-
Cardiac disorders	26 (2.35)	12 (1.08)
Vascular disorders	4 (0.36)	2 (0.18)
Respiratory, thoracic and mediastinal disorders	78 (7.04)	24 (2.17)
Gastrointestinal disorders	12 (1.08)	2 (0.18)
Hepatobiliary disorders	2 (0.18)	1 (0.09)
Skin and subcutaneous tissue disorders	5 (0.45)	-
Musculoskeletal and connective tissue disorders	5 (0.45)	1 (0.09)
Renal and urinary disorders	9 (0.81)	1 (0.09)
Reproductive system and breast disorders	1 (0.09)	-
General disorders and administration site conditions	7 (0.63)	6 (0.54)
Investigations	4 (0.36)	-
Injury, poisoning and procedural complication	2 (0.18)	-

System organ class (SOC): shown in the order of international consensus. Multiple episodes of an event [preferred term (PT)] in the same patient are counted only once. MedDRA/J version 22.0.

CCV disorders (15.43%) and diabetes mellitus (10.83%). The mean (\pm SD) duration of IND/GLY total administration was 272.2 \pm 135.68 days (median, 365.0 days).

Safety outcomes

Incidence of AEs and SAEs

Overall, 150 (13.54%) patients experienced AEs with long-term treatment of IND/GLY (up to 52-week observation; Table 2). The most frequently reported AEs by SOC (up to the third-highest incidence) were respiratory, thoracic and mediastinal disorders (7.04%), infections and infestations (2.44%) and cardiac disorders (2.35%). The most frequently reported AEs by PT were COPD (4.87%), pneumonia (1.08%) and palpitations and cough (0.63% each).

In total, 52 (4.69%) patients reported SAEs with IND/GLY during this study (Table 2). The most common SAEs (up to the third-highest incidence) by SOC were respiratory, thoracic and mediastinal disorders (2.17%), cardiac disorders and infections and infestations (1.08% each). The most common SAEs by PT were COPD (1.44%), pneumonia (0.90%) and malignant lung neoplasm (0.36%). The incidences of all AEs and SAEs by PTs are described in Supplementary material 3.

Incidence of ADRs and serious ADRs

In this surveillance, the incidence of ADRs was 3.61% (Table 3). The most common ADRs were dysuria and cough (0.45% each), palpitations (0.36%) and constipation and urinary retention (0.27% each). ADRs occurred most frequently up to 4 weeks from the start of IND/GLY, with an incidence of 1.81%, and continued treatment was not associated with an increasing tendency of the incidence of first-onset ADRs.

In total, 4 patients reported serious ADRs (0.36%) during this surveillance (Table 3). The observed serious ADRs were malignant lung neoplasm, angina pectoris, palpitations, atrial fibrillation, cardiac failure, exertional dyspnoea, urinary retention and peripheral oedema in 0.09% each. All serious ADRs, except for urinary retention and angina pectoris, were resolved, and the outcome of the malignant lung neoplasm was unknown. The incidences of all ADRs and serious ADRs by PTs are described in Supplementary material 4.

ADR by age subgroups

No ADRs were observed in patients <45 years old or 55 to <65 years old. The incidence of ADRs was highest in patients 45 to <55 years old (5.00%); 3.87% in patients 65 to <75 years old, 4.46% in patients 75 to <85 years old and 3.45% in patients \geq 85 years old. Considering the group 75 to <85 years old (largest group) as the reference, the 95% CI of the risk ratios all contained 1, showing no significant differences among the age strata. Furthermore, there was no significant trend in the type (by SOC) or incidence of ADRs by age strata (Table 4).

Deaths

In total, 15 deaths were reported during the safety analysis period. AEs with fatal outcomes included acute cardiac failure and pneumonia in three patients each; chronic respiratory failure, COPD and cardio-respiratory arrest in two patients each; and skin cancer, back pain, sudden death, aortic dissection, concomitant disease aggravated, pneumothorax spontaneous, death, aspiration pneumonia, respiratory failure and vascular rupture in one patient each. None of the deaths were considered by the investigators to be related to treat-

Table 3. Incidence of Adverse and Serious Adverse Drug Reactions (Safety Analysis Population).

	Total number of patients (N=1,108)	
	Adverse drug reactions, n (%)	Serious adverse drug reactions, n (%)
Patients experiencing drug reactions	40 (3.61)	4 (0.36)
Neoplasms benign, malignant and unspecified	1 (0.09)	1 (0.09)
Nervous system disorders	2 (0.18)	-
Cardiac disorders	6 (0.54)	2 (0.18)
Respiratory, thoracic and mediastinal disorders	14 (1.26)	1 (0.09)
Gastrointestinal disorders	7 (0.63)	-
Skin and subcutaneous tissue disorders	2 (0.18)	-
Musculoskeletal and connective tissue disorders	3 (0.27)	-
Renal and urinary disorders	8 (0.72)	1 (0.09)
Reproductive system and breast disorders	1 (0.09)	-
General disorders and administration site conditions	1 (0.09)	1 (0.09)
Injury, poisoning and procedural complication	1 (0.09)	-

System organ class (SOC): shown in the order of international consensus. Multiple episodes of an event [preferred term (PT)] in the same patient are counted only once. MedDRA/J Version 22.0.

Table 4. Incidence of Adverse Drug Reactions by Age Category (Safety Analysis Population).

Characteristics	Age subgroups, years					
	<45	≥45 to <55	≥55 to <65	≥65 to <75	≥75 to <85	≥85
Number of patients	17	40	121	388	426	116
Risk ratio (95% CI)	-	1.12 (0.27 to 4.64)	-	0.87 (0.45 to 1.68)	Reference	0.77 (0.27 to 2.23)
Type of ADR by SOC	No. of applicable patients (%)					
Neoplasms benign, malignant and unspecified (including cysts and polyps)	-	-	-	-	1 (0.23)	-
Nervous system disorders	-	-	-	2 (0.52)	-	-
Cardiac disorders	-	1 (2.50)	-	1 (0.26)	3 (0.70)	1 (0.86)
Respiratory, thoracic and mediastinal disorders	-	2 (5.00)	-	5 (1.29)	6 (1.41)	1 (0.86)
Gastrointestinal disorders	-	-	-	2 (0.52)	5 (1.17)	-
Skin and subcutaneous tissue disorders	-	-	-	2 (0.52)	-	-
Musculoskeletal and connective tissue disorders	-	-	-	1 (0.26)	1 (0.23)	1 (0.86)
Renal and urinary disorders	-	-	-	3 (0.77)	4 (0.94)	1 (0.86)
Reproductive system and breast disorders	-	-	-	-	1 (0.23)	-
General disorders and administration site conditions	-	1 (2.50)	-	-	-	-
Injury, poisoning and procedural complications	-	-	-	-	1 (0.23)	-

Reference: reference for the risk ratios (age category with the largest sample size). System organ class (SOC): shown in the order of international consensus. Multiple episodes of an event (preferred term) in the same patient are counted only once. MedDRA/J Version 22.0.

ment with IND/GLY.

Priority variables

CCV adverse events and adverse reactions

Overall, the incidence of CCV AEs was 2.62% at Week 52 (Table 5). Commonly observed CCV AEs were palpitations (0.63%) and angina pectoris, cardiac failure and acute cardiac failure (0.27% each). Serious CCV AEs were observed in 1.26% of patients. The most common serious CCV AEs were acute cardiac failure (0.27%), atrial fibrillation, congestive cardiac failure and cardio-respiratory arrest (0.18% each).

Overall, CCV ADRs were reported by 6 patients (0.54%) in long-term treatment. These ADRs included palpitations

(0.36%), angina pectoris, arrhythmia, atrial fibrillation and cardiac failure (0.09% each). Serious CCV ADRs, which included angina pectoris, palpitations, atrial fibrillation and cardiac failure, occurred in four patients. All ADRs were resolving except for angina pectoris (not resolved).

CCV adverse events and adverse reactions by number of CCV disorder risk factors

There were no CCV AEs in patients without any CCV disorder risk factors. In patients with 1, 2 and ≥3 risk factors, the incidence of CCV AEs was 1.91%, 3.13% and 5.45%, respectively. The incidence of CCV AEs increased as the number of CCV disorder risk factors increased. Similarly, the incidence of CCV AEs per 1,000 patient-years increased as the number of CCV disorder risk factors in-

Table 5. Incidence of Cardiovascular/Cerebrovascular (CCV) Adverse Events (AEs) (Safety Analysis Population).

Type of AEs	Total number of patients (N=1,108)
Patients experiencing CCV AEs	29 (2.62)
Nervous system disorders	2 (0.18)
Cerebral artery embolism	1 (0.09)
Cerebral thrombosis	1 (0.09)
Cardiac disorders	26 (2.35)
Palpitations	7 (0.63)
Angina pectoris	3 (0.27)
Cardiac failure	3 (0.27)
Cardiac failure acute	3 (0.27)
Atrial fibrillation	2 (0.18)
Cardiac failure congestive	2 (0.18)
Cardio-respiratory arrest	2 (0.18)
Acute myocardial infarction	1 (0.09)
Arrhythmia	1 (0.09)
Bundle branch block left	1 (0.09)
Myocardial infarction	1 (0.09)
Myocardial ischaemia	1 (0.09)
Prinzmetal angina	1 (0.09)
Sinus tachycardia	1 (0.09)
Ventricular extrasystoles	1 (0.09)
General disorders and administration site conditions	1 (0.09)
Sudden death	1 (0.09)

Data presented as n (%). System organ class (SOC), preferred term (PT): MedDRA/J Version 22.0. Multiple episodes of an event (PT) in the same patient are counted only once. SOC: shown in the order of international consensus, PT: shown in descending order of incidence→PT codes.

Table 6. Incidence of CCV AEs and CCV ADRs by Number of CCV Disorder Risk Factors Present (Safety Analysis Population).

	AEs		ADRs	
	No. of patients with CCV AEs/no. of cases (%)	No. of patients with CCV AEs/PY (IR)	No. of patients with CCV ADRs/no. of cases (%)	No. of patients with CCV ADRs/PY (IR)
CCV history: yes	15/197 (7.61)	15/155 (97.00)	5/197 (2.54)	5/160 (31.26)
CCV risk factors: 0	0/46 (0.00)	0/39 (0.00)	0/46 (0.00)	0/39 (0.00)
CCV risk factors: 1	5/262 (1.91)	5/215 (23.24)	0/262 (0.00)	0/218 (0.00)
CCV risk factors: 2	7/224 (3.13)	7/191 (36.61)	0/224 (0.00)	0/194 (0.00)
CCV risk factors: ≥3	11/202 (5.45)	11/164 (67.19)	3/202 (1.49)	3/168 (17.84)

CCV risk factors include: (1) History of CCV disorder, (2) Hypertension, (3) Hyperlipidaemia, (4) Diabetes mellitus, (5) BMI:>30 kg/m², (6) Age ≥65 years, (7) Current smoker. AE: adverse event, ADR: adverse drug reaction, CCV: cardiovascular/cerebrovascular, IR: incident rate (per 1000 PY), PY: patient-year

creased (Table 6). CCV ADRs occurred only in patients with three or more CCV disorder risk factors (1.49%). A similar trend was seen in the incidence of CCV ADRs per 1,000 patient-years

β-adrenergic-related or anticholinergic adverse events

Overall, 22 (1.99%) patients reported β-adrenergic-related or anticholinergic AEs in the safety analysis population. The common AEs were dysuria and constipation (0.45% each) and increased blood pressure and urinary retention (0.27% each). Other AEs of this type were reported in 1 (0.09%) patient each and included anticholinergic syndrome, dizziness, pyrexia, muscle spasms, hypertension, increased sys-

tolic blood pressure and diabetes mellitus.

Serious β-adrenergic-related or anticholinergic AEs were reported by 2 patients (0.18%) and included urinary retention and pyrexia in 1 patient each. In total, β-adrenergic-related or anticholinergic ADRs were observed in 13 patients (1.17%). The common ADRs of this type were dysuria, constipation and urinary retention. Urinary retention was the only serious ADR of this type reported, and the outcome was unknown.

Cough

In the safety analysis population, 7 (0.63%) patients reported an AE of cough, whereas 5 (0.45%) patients reported

ADR of cough. No serious cough-related AEs or ADRs occurred during the long-term treatment period.

Efficacy outcomes

Global assessment (global impression of change)

The physician's global assessment (global impression of change) in the overall population at the last assessment was found to be "excellent" in 108 (9.75%) patients, "good" in 440 (39.71%), "moderate" in 274 (24.73%), "poor" in 170 (15.34%) and "worsening" in 17 (1.53%) patients. Considering "excellent", "good" and "moderate" as indicative of a response, the overall response rate at the last assessment was deemed to be 74.19% (822/1,108).

CAT scores for overall population and by COPD stages

At the start of IND/GLY, the mean (95% CI) CAT score was 15.2 (14.4-15.9) in the overall population. Treatment with IND/GLY resulted in improvement in COPD symptoms as evidenced by a decrease in the mean CAT score from the start of IND/GLY to Week 52 (Fig. 2a). The change in CAT score from baseline (start of IND/GLY therapy) exceeded the minimal clinically important difference (MCID) (≥ 2 -point reduction in CAT score) at each evaluated time point until Week 52. The mean (95% CI) change in absolute CAT score at the final assessment was -6.1 (-6.8 to -5.5).

By disease stage, the respective mean (95% CI) CAT scores at the start of IND/GLY therapy and Week 52 were 12.3 (10.9-13.8) and 7.0 (5.1-8.9) in the stage I (mild) group, 14.8 (13.7-15.9) and 8.6 (7.6-9.7) in the stage II (moderate) group, 18.1 (16.5-19.7) and 9.7 (8.0-11.5) in the stage III (severe) group and 22.3 (18.2-26.4) and 11.8 (7.3-16.2) in the stage IV (most severe) group. The CAT score decreased from start of IND/GLY to Week 52 in patients across all COPD stages (Fig. 2b). The change in the mean CAT score over time from the start of IND/GLY, by body weight, BMI, dyspnoea severity grade and elderly versus non-elderly population, is shown in Supplementary material 4.

The lung function of the overall population and by COPD stages

At the start of IND/GLY, the mean (95% CI) FEV₁ was 1.465 L (1.378 to 1.551), increasing over time from the start of therapy to Week 52, except for at Week 26. The mean (95% CI) change in FEV₁ over time from the start of IND/GLY was 0.098 L (0.002 to 0.194) at Week 52. Stratification by COPD stages showed that the lung function improved over time from the start of treatment in all stage COPD groups.

The mean (95% CI) change in FVC over time from the start of IND/GLY [2.616 L (2.500 to 2.731)] was 0.125 (-0.003 to 0.254) at Week 52. Stratification by COPD stages showed that the FVC improved over time from the start of IND/GLY to Week 52 in all stage COPD groups. The changes over time in FEV₁ and FVC for the overall population and by COPD stages are described in the Supplementary material 5.

Discussion

This post-marketing surveillance evaluated the long-term safety and efficacy of IND/GLY during the 52 weeks from the start of treatment in clinical use in Japanese patients who were diagnosed with COPD and prescribed IND/GLY for the first time. The results from this surveillance demonstrated that long-term treatment with IND/GLY was well tolerated.

Numerous clinical trials and observational studies have established the safety and efficacy of IND/GLY in patients with COPD (7, 8). In the current surveillance, the incidence of AEs and SAEs during the 52 weeks was 13.54% and 4.69%, respectively. The most frequently reported AEs in the current surveillance were COPD worsening, pneumonia, palpitations and cough. These findings are consistent with those reported in the global and Japanese population (13-18). In a subgroup analysis of Asian patients from the FLAME study, COPD worsening, nasopharyngitis, upper respiratory tract infection, pneumonia and cough were the most frequently reported AEs in patients treated with IND/GLY (19), comparable to the observations in the present surveillance. COPD was the most frequently reported SAE in the current surveillance, in line with reports from several clinical studies of IND/GLY (14, 15, 20).

Data on the effectiveness of IND/GLY in real-world clinical practice are limited. In a 12-week, pragmatic, open-label CRYSTAL study (21), the safety of IND/GLY was comparable to that of LABA or LAMA administered as monotherapy and LABA+inhaled corticosteroid, with no new safety signals observed. The outcomes of the CRYSTAL study were consistent with those observed in our study over a longer term. Overall, the occurrence of AEs and SAEs and safety profile with IND/GLY in this real-world surveillance in Japanese patients was in line with that observed in the global (14, 15, 18) and Japanese clinical studies (13, 16).

In the present surveillance, the incidence of ADRs and serious ADRs was 3.61% and 0.36%, respectively. The serious ADRs reported in this surveillance included palpitations, urinary retention, malignant lung neoplasm, angina pectoris, atrial fibrillation, cardiac failure, exertional dyspnoea and peripheral oedema, most of which were associated with the pharmacological effects of the individual components of IND/GLY or were due to events related to the underlying disease (COPD). Although, careful consideration should be given while comparing results from this surveillance with those from RCTs conducted under standardised conditions with fewer patients and strict selection criteria, the observational nature of this study enabled us to collect long-term safety and efficacy data from a larger pool of patients in a more realistic clinical setting.

The current surveillance also evaluated the incidence of CCV AEs, β -adrenergic-related or anticholinergic AEs and cough, designated as priority variables for the purpose of this surveillance. The observed incidence rate of CCV AEs

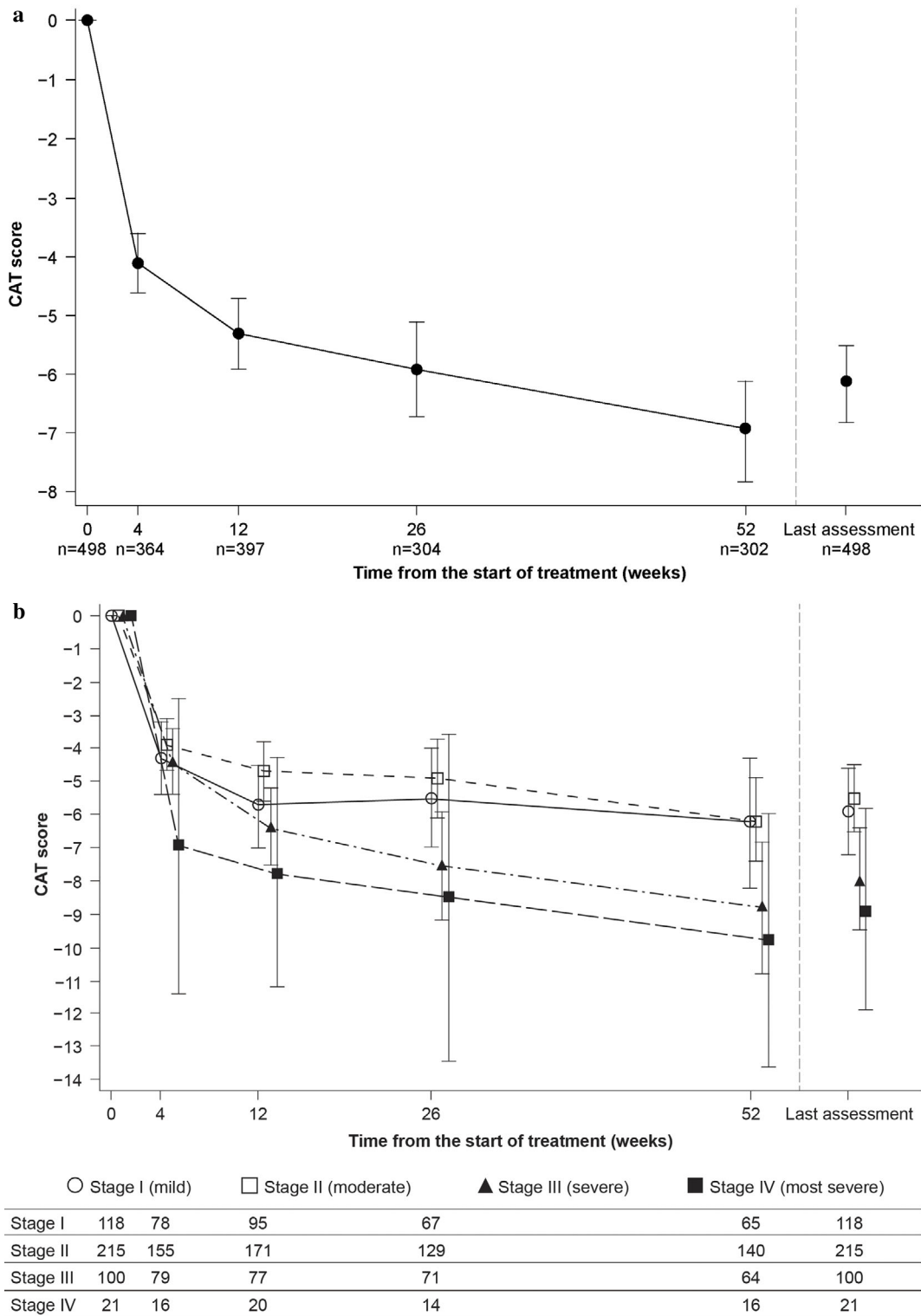


Figure 2. Changes from baseline in the CAT score (a) in the overall population and (b) by COPD stages (efficacy analysis population). Data are presented as the mean and 95% CI. CAT: COPD assessment test, CI: confidence interval, n: number of patients. COPD stages are based on the JRS Guidelines for the Management of COPD (version 4).

was 2.62% during the 52 weeks of treatment with IND/GLY. The most frequently observed CCV AEs in this surveillance were palpitations, angina pectoris, cardiac failure and acute cardiac failure. These findings are consistent with those reported previously in the ENLIGHTEN study, a 52-week,

randomised study in which the most commonly reported CCV AEs were congestive cardiac failure (1.3%) and supraventricular extrasystole (0.9%) (15).

In the current surveillance, 14 (1.26%) patients reported serious CCV AEs, the most frequent of which were acute

cardiac failure, atrial fibrillation, congestive cardiac failure and cardio-respiratory arrest. These findings were consistent with those observed in a pooled analysis (n=3,153) of the 6-month safety data extrapolated from 4 Phase III studies in which the CCV AEs were reported by 6 patients (0.6%). The serious CCV events that were reported in this pooled analysis included angina pectoris, atrial fibrillation and acute myocardial infarction (22). In our surveillance, the incidence of CVV AEs followed a linear trend with the number of CCV disorder risk factors. Patients with three or more CCV disorder risk factors had a higher incidence of CCV AEs. CCV ADRs were observed only in patients with three or more CCV disorder risk factors. The low level of CCV AEs and ADRs observed in this surveillance is consistent with a previous report from Italy, which assessed the safety risk of IND/GLY in COPD patients ≥ 80 years old, although the number of patients was much smaller (30 patients) than in the current surveillance (23).

In our surveillance, 1.99% of the patients reported β -adrenergic-related or anticholinergic AEs. Dysuria, constipation and urinary retention were the most commonly reported AEs of this type. Serious β -adrenergic-related or anticholinergic AEs were reported by two patients and included urinary retention and pyrexia in one patient each. Urinary retention has been reported to be the most common risk factor associated with anticholinergics. In patients with dysuria and concurrent prostatic hyperplasia, urinary retention may be more frequent; IND/GLY is thus contraindicated in such patients. However, urinary retention may also occur with IND/GLY in patients without dysuria. Cough was another safety concern identified during the approval stage and was designated as a priority variable in this observational study. Seven (0.63%) patients reported the AE of cough, while no serious cough-related events occurred during the long-term treatment. These results are consistent with those observed in the Japanese subgroup from a global clinical study (16) or in studies in which the indacaterol mono-component was evaluated (24). In a real-world study that evaluated the safety and effectiveness of indacaterol or other LABAs in mild-to-severe COPD patients, cough was the most commonly reported AE (4.2%) (24).

COPD is generally considered to be a disease of old age. In Japan, the average age of the patients diagnosed with COPD is around 70 years old, as reported by several cohort studies conducted in Japan (25, 26). The majority of patients included in our surveillance were elderly (≥ 65 years old), accounting for approximately 84% of the overall population. The safety profile of IND/GLY in these elderly patients was generally comparable to that of the overall population. The incidence of ADRs in patients ≥ 65 years old was higher than in patients < 65 years old (4.09% vs. 1.12%). The common ADRs in patients ≥ 65 years old were dysuria, cough, palpitations, constipation and urinary retention. The incidence of ADRs in older patients ≥ 75 years old was 4.24%, which was slightly higher than that of 3.00% in patients < 75 years old. The common ADRs observed in these patients in-

cluded urinary retention, palpitations, cough, laryngeal discomfort, oropharyngeal discomfort, constipation and dysuria.

Although the efficacy was not the main objective of this surveillance, it is important to evaluate the efficacy of IND/GLY in a real-world setting. In terms of the physician's global assessment (global impression of change), 74.19% of patients were found to be treatment responders, implying the appropriateness of IND/GLY therapy in these patients with COPD. In this post-marketing surveillance, we observed a sustained bronchodilator effect with IND/GLY as shown by the improvements in FEV₁ and FVC, which were maintained throughout the 52-week treatment period. Improvements in trough FEV₁, exceeding MCID of 100 mL, were observed after as few as 4 weeks (27). The improvements in the lung function observed in terms of the FEV₁ in this current surveillance are consistent with those observed in the IGNITE clinical programme (7, 28).

The mean CAT score decreased from Weeks 4 to 52 and remained consistently lower than that observed at the start of treatment. These findings are consistent with the previous results observed in clinical studies (29). The mean change in CAT score at Week 52 was -6.9, and the mean changes at all time points from the start of treatment exceeded the MCID of 2 points, demonstrating an improvement in COPD symptoms with IND/GLY. These improvements in CAT scores are consistent with those observed in a Canadian real-world study at Week 16, in which patients with COPD switched from tiotropium or salmeterol/fluticasone to IND/GLY (11). It should also be noted that the improvement in CAT score was observed in not only the overall population but also at all COPD stages, even in patients with stage I (mild), which is a population rarely included in the IGNITE programme or any other clinical trials enrolling patients with COPD.

As with all other observational studies, the results of this surveillance need to be interpreted carefully, as there was no comparison arm of patients who were not exposed to IND/GLY. The nature of the surveillance meant that the testing conditions were not stringent, so the pulmonary function test results need to be interpreted carefully. A potential limitation is that the timing of the respiratory function tests (time elapsed after bronchodilator inhalation) may have varied, since this was not a clinical trial. Therefore, it is not possible to determine the exact effect of IND/GLY on the respiratory function based on this surveillance. Despite these limitations, it should be noted that the safety and efficacy data of IND/GLY in clinical use were collected from a large pool of 1,108 patients in Japan, and therefore, the above-mentioned limitations and issues should not significantly interfere with the evaluation of the safety and efficacy of IND/GLY in a real-world clinical setting.

Conclusion

In this 52-week long-term, observational study, IND/GLY demonstrated an acceptable safety profile in Japanese pa-

tients with COPD. No new safety concerns were identified with use of IND/GLY in a clinical setting, nor any adverse drug reactions whose incidence increased during the long-term treatment. The long-term safety profile of IND/GLY in elderly patients and in terms of CCV, β -adrenergic-related or anticholinergic AEs and ADRs and cough showed no increase in incidence. Long-term clinical treatment with IND/GLY in COPD patients provided benefits in terms of the lung function and symptom improvements.

This post-marketing surveillance was in accordance with the Good Post-marketing Study Practice (GPSP) guidance. The protocol of this surveillance was agreed upon in consultation with the Japanese Pharmaceutical and Medical Devices Agency (PMDA), and as such, informed consent from the patients was not 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 scientific merit. All data provided are anonymized with respect to the privacy of the patients who participated in the trial, in line with applicable laws and regulations. The trial data availability is considered according to the criteria and process described on www.clinicalstudydatarequest.com

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

Chihiro Kato: Employment, Novartis Pharma. Hajime Yoshisue: Employment, Novartis Pharma. Noriko Nakamura: Employment, Novartis Pharma. Takayoshi Sasajima: Employment, Novartis Pharma.

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 Venkatesh Taadla and Vatsal Vitlani for providing medical writing/editorial support.

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