# Pharmacokinetics of indacaterol, glycopyrronium and mometasone furoate as a fixed-dose combination in Japanese and Caucasian healthy subjects

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# Introduction

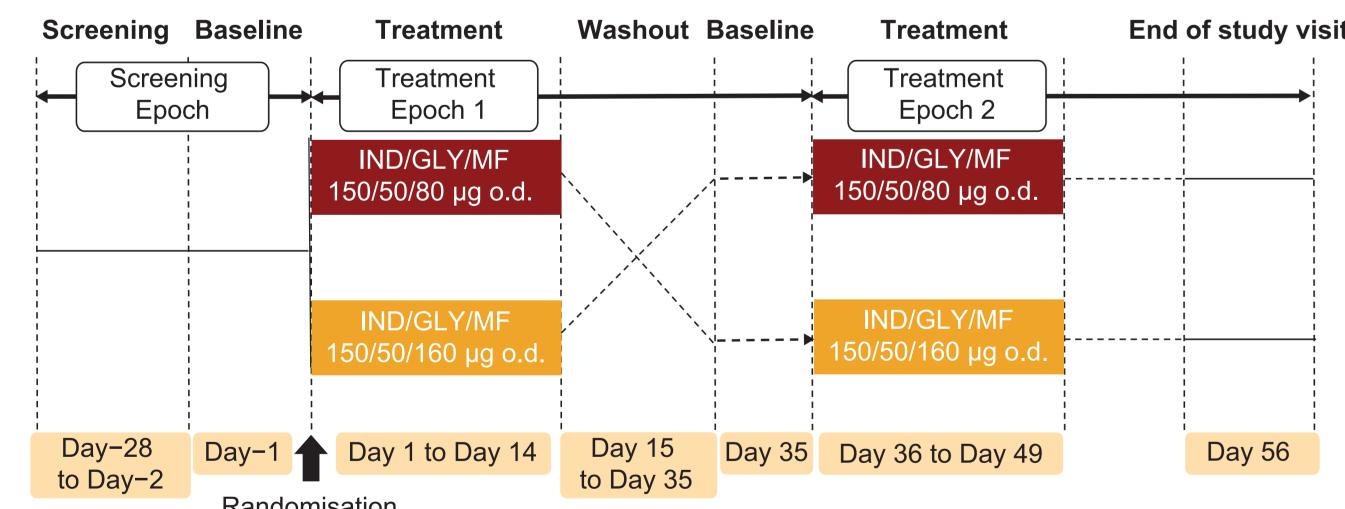
- Asthma is a chronic inflammatory disease of the airways characterised by respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough together with variable expiratory airflow limitation<sup>1</sup>
- Global Initiative for Asthma 2019, recommends the addition of a long-acting muscarinic antagonist (LAMA) for patients with asthma who remain uncontrolled despite treatment with a combination of a medium- or high-dose inhaled corticosteroid (ICS) with a long-acting  $\beta_2$ -agonist (LABA)<sup>1</sup>
- IND/GLY/MF is a combination of indacaterol acetate (IND, a LABA), glycopyrronium bromide (GLY, a LAMA), and mometasone furoate (MF, an ICS). It is being developed as once-daily (o.d.) maintenance treatment for asthma, to be delivered via the Breezhaler® inhalation device
- Ethnicity is a factor that may account for the differences observed in pharmacokinetics (PK) and pharmacodynamics of a drug, thereby resulting in variations in the treatment response<sup>2,3</sup>
- Here, we present the results from Phase I study, in which the steady-state PK of IND, GLY and MF between Japanese and Caucasian healthy male subjects was compared after multiple o.d. inhalations of IND/GLY/MF combinations delivered via the Breezhaler® device

# Methods

# Study design

- This was a non-confirmatory, single-centred, randomised, open-label, multiple-dose, two-treatment epochs crossover study in Japanese and Caucasian healthy male subjects
- The study consisted of a screening visit, two treatment epochs (each with a baseline and treatment period), a 21-day washout period and an end-of-study visit (Figure 1)
- Patients were randomised in pairs (Caucasian/Japanese) to one of the two treatment sequences in the ratio of 1:1

## Figure 1. Study design



IND/GLY/MF is a combination of indacaterol acetate 150 μg, glycopyrronium bromide 50 μg and mometasone furoate 80 μg (medium-dose ICS) or 160 μg (high-dose ICS) delivered o.d. via the Breezhaler® GLY, glycopyrronium bromide; IND, indacaterol acetate; MF, mometasone furoate; o.d., once daily.

# **Patients**

# Key inclusion criteria

- Healthy male subjects aged 20 to 45 years, weighing at least 50 kg and having a body mass index in the range of 18-30 kg/m<sup>2</sup>
- Both, Japanese and Caucasian subjects included were of first generation ethnic origin

# Key exclusion criteria

- Use of other investigational drugs at screening, or within 5 half-lives of enrolment, or within 4 months, whichever is longer
- Laboratory abnormalities and history of clinically significant ECG abnormalities, family history or known presence of long QT syndrome
- Inability to use the Breezhaler® device at screening

# **Objectives**

### Primary objective

• To compare the steady state plasma PK parameters (C<sub>max</sub> [maximum plasma concentration] and AUC<sub>0-24h</sub> [area under the plasma concentration-time curve from 0 to 24 hours]) for IND, GLY and MF between Japanese and Caucasian healthy male subjects after multiple once-daily inhalation of IND/GLY/MF 150/50/80 µg (medium-dose ICS), and similarly of IND/GLY/MF 150/50/160 µg (high-dose ICS) on Day 14

# Secondary objective

- To compare the PK (C<sub>max</sub> and AUC<sub>0-24h</sub>) for IND, GLY and MF between Japanese and Caucasian subjects after a single oral inhalation of IND/GLY/MF 150/50/80 µg, and similarly of IND/GLY/MF 150/50/160 µg, delivered via the Breezhaler® on Day 1
- To assess the safety and tolerability of IND/GLY/MF 150/50/80 µg and IND/GLY/MF 150/50/160 µg

# Statistical analysis

- The safety analysis set included all subjects who received any study drug
- The PK analysis set included all subjects with at least one valid PK concentration measurement, who received any study drug
- Day 14 log-transformed primary PK parameters (AUC<sub>0-24h</sub> and C<sub>max</sub>) for IND, GLY and MF were analysed by day using a linear mixed effects model
- All matched pairs with evaluable PK parameters for at least one subject were included for the analysis

# Results

# **Patients**

- In total, 33 subjects (16 Japanese and 17 Caucasian) were randomised to one of the two treatment sequences
- Median age of Japanese subjects was 31 years and median age of Caucasian subjects was 27 years
- The mean body weight and body mass index was higher in Caucasian subjects than in Japanese subjects. A summary of the subjects' demographics is presented in **Table 1**

# Table 1. Baseline demographics (safety analysis set)

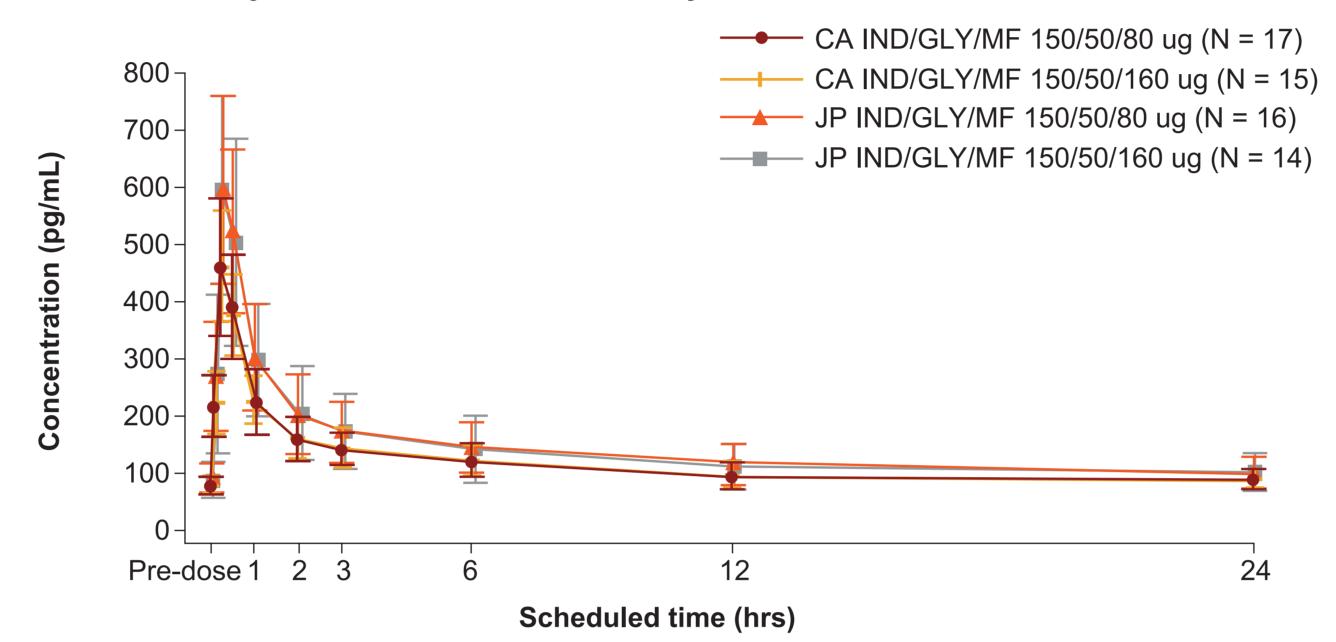
	Japanese (N = 16)	Caucasian (N = 17)
Age in years, median (range)	31.0 (20 to 40)	27.0 (21 to 43)
Weight (kg)	68.25 ± 6.10	75.01 ± 7.99
Height (cm)	173.3 ± 4.14	178.7 ± 4.48
Body mass index (kg/m²)	22.69 ± 2.07	23.44 ± 2.32
Data presented as mean ± SD unless otherwise specified		

# **Pharmacokinetics**

### AUC<sub>0-24h</sub> for IND in Japanese and Caucasian subjects on Day 14 following treatment with IND/GLY/MF

- For IND, the mean plasma AUC<sub>0-24h</sub> on Day 14 was slightly higher in Japanese than Caucasian subjects for both IND/GLY/MF medium- and high-dose ICS (Table 2)
- Overlapping mean plasma concentration-time profiles of IND were observed between treatment groups (IND/GLY/MF medium- and high-dose ICS) in both Japanese and Caucasian subjects (Figure 2)
- The mean plasma trough concentrations on Day 12 and Day 14 were similar, suggesting steady state was achieved by Day 12

# Figure 2. Plasma concentration-time profiles of IND were comparable in Japanese and Caucasian subjects with IND/GLY/MF on Day 14

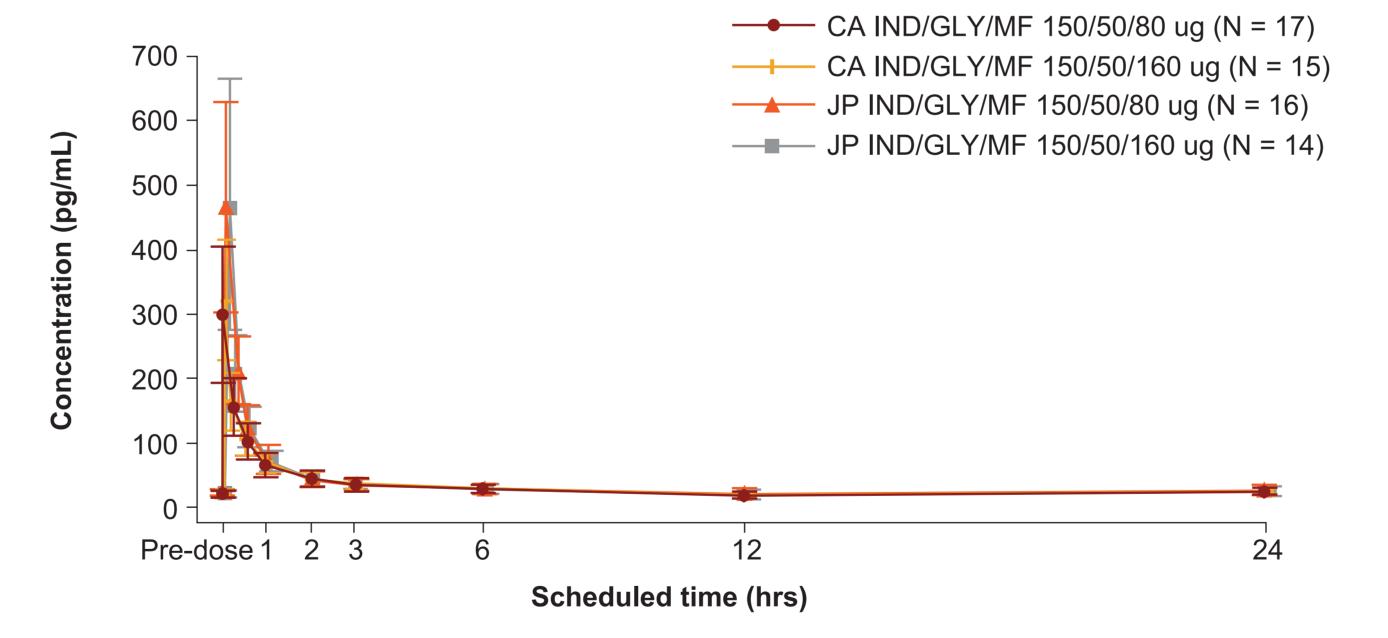


#### Data presented as mean ± SD IND/GLY/MF is a combination of indacaterol acetate 150 μg, glycopyrronium bromide 50 μg and mometasone furoate 80 μg (medium-dose ICS) or 160 µg (high-dose ICS) delivered o.d. via the Breezhaler® CA, Caucasians; GLY, glycopyrronium bromide; IND, indacaterol acetate; JP, Japanese; MF mometasone furoate; o.d., once daily

## AUC<sub>0-24h</sub> for GLY in Japanese and Caucasian subjects on Day 14 following treatment with IND/GLY/MF

- For GLY, the mean plasma AUC<sub>0-24h</sub> on Day 14 was comparable in Japanese and Caucasian subjects (Table 2)
- GLY also showed overlapping mean plasma concentration-time profiles between the treatment groups (IND/GLY/MF medium- and high-dose ICS) in both Japanese and Caucasian subjects (Figure 3); steady state was attained by Day 12

# Figure 3. Plasma concentration-time profiles of GLY were comparable in Japanese and Caucasian subjects with IND/GLY/MF on Day 14



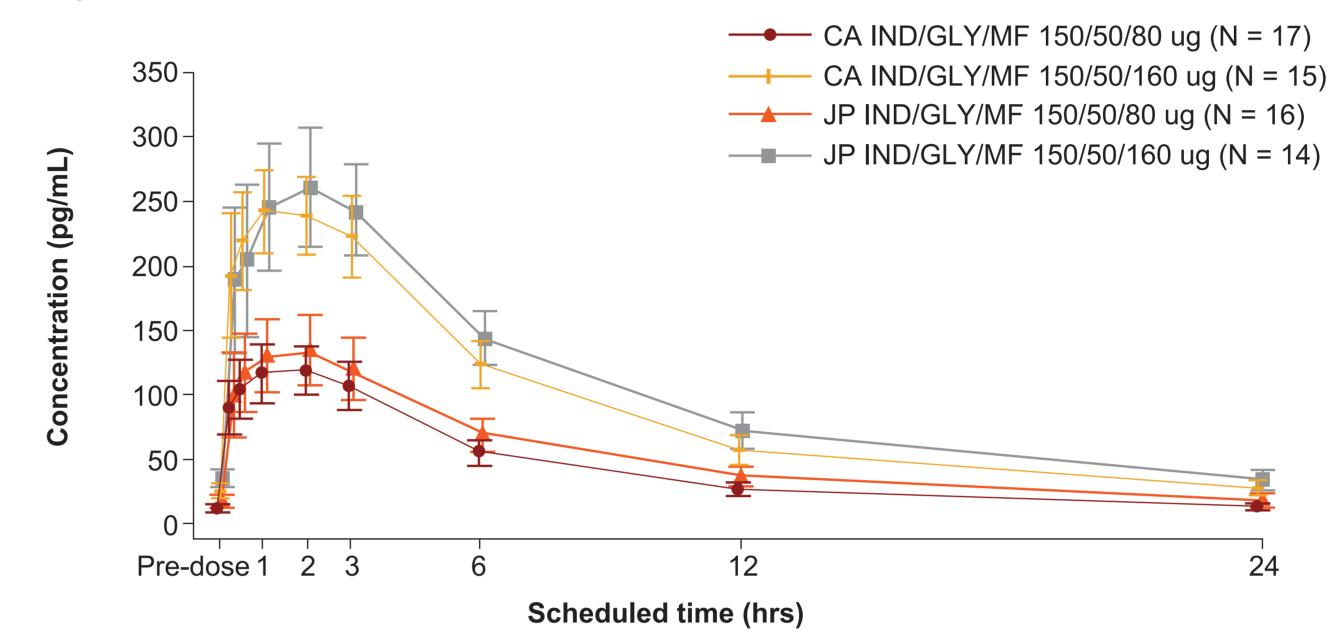
# Data presented as mean ± SD

IND/GLY/MF is a combination of indacaterol acetate 150 μg, glycopyrronium bromide 50 μg and mometasone furoate 80 μg (medium-dose ICS) or 160 µg (high-dose ICS) delivered via o.d. the Breezhaler® CA, Caucasians; GLY, glycopyrronium bromide; IND, indacaterol acetate; JP, Japanese; MF mometasone furoate; o.d., once daily

# AUC<sub>0-24h</sub> for MF in Japanese and Caucasian subjects on Day 14 following treatment with IND/GLY/MF

- For MF, the mean AUC<sub>0-24h</sub> on Day 14 was slightly higher in Japanese than Caucasian subjects (Table 2)
- Exposure of MF increased proportionally with dose between the treatment groups (IND/GLY/MF medium- and high-dose ICS) for both Japanese and Caucasians on Day 14 (Figure 4)
- The mean trough concentrations were similar on Day 7 and Day 14, suggesting steady state was achieved by Day 7

# Figure 4. Dose dependent plasma concentration-time profiles were observed for MF in Japanese and Caucasian subjects with IND/GLY/MF (150/50/80 μg and 150/50/160 μg) on **Day 14**



#### Data presented as mean ± SD IND/GLY/MF is a combination of indacaterol acetate 150 μg, glycopyrronium bromide 50 μg and mometasone furoate 80 μg (medium-dose ICS) or 160 µg (high-dose ICS) delivered o.d. via the Breezhaler® CA, Caucasians; GLY, glycopyrronium bromide; IND, indacaterol acetate; JP, Japanese; MF mometasone furoate; o.d., once dail

# C<sub>max</sub> for IND, GLY and MF in Japanese and Caucasians on Day 14 following treatment with IND/GLY/MF

- For IND and GLY, the mean C<sub>max</sub> was slightly higher in Japanese than Caucasian subjects for both IND/GLY/MF medium- and high-dose ICS on Day 14 (Table 2)
- The mean C<sub>max</sub> for MF was comparable in both ethnicities for medium- and high-dose IND/GLY/MF on Day 14 (Table 2)

# Table 2. Summary statistics of plasma PK parameters of IND/GLY/MF after multiple doses on Day 14 (PK analysis set)

	Japanese		Caucasian		
PK parameters (unit)	IND/GLY/MF 150/50/80 μg N = 15/16	IND/GLY/MF 150/50/160 μg N = 13/14	IND/GLY/MF 150/50/80 μg N = 16	IND/GLY/MF 150/50/160 μg N = 15	
IND					
C <sub>max</sub> (pg/mL)	595 (27.2)	593 (27.9)	460 (25.8)	461 (21.1)	
AUC <sub>0-24h</sub> (h*pg/mL)	3360 (30.3)	3330 (37.1)	2750 (23.0)	2800 (20.3)	
T <sub>max</sub> (h)	0.250 (0.250 to 0.250)	0.250 (0.250 to 0.250)	0.250 (0.250 to 0.250)	0.250 (0.250 to 0.250)	
GLY					
C <sub>max</sub> (pg/mL)	467 (35.1)	464 (42.7)	300 (34.7)	322 (28.9)	
AUC <sub>0-24h</sub> (h*pg/mL)	772 (21.0)	751 (17.5)	734 (25.3)	734 (20.7)	
T <sub>max</sub> (h)	0.083 (0.083 to 0.083)	0.083 (0.083 to 0.083)	0.083 (0.083 to 0.083)	0.083 (0.083 to0.083)	
MF					
C <sub>max</sub> (pg/mL)	141 (18.8)	268 (18.9)	123 (17.9)	252 (14.8)	
$AUC_{0-24h}$ (h*pg/mL)	1270 (15.8)	2540 (14.0)	1040 (16.2)	2220 (12.6)	
T <sub>max</sub> (h)	2.00 (0.250 to 3.00)	2.00 (0.250 to 3.00)	1.00 (0.250 to 3.00)	1.00 (0.250 to 2.00)	

Data are presented as arithmetic mean (CV%) for AUC<sub>0-24h</sub> and  $C_{max}$ ; for  $T_{max}$  data are presented as median (min-max) IND/GLY/MF is a combination of indacaterol acetate 150 μg, glycopyrronium bromide 50 μg and mometasone furoate 80 μg (medium-dose ICS) or 160 µg (high-dose ICS) delivered o.d. via the Breezhaler® AUC<sub>0-24h</sub>, area under the concentration-time curve from 0 to 24 hours; C<sub>max</sub>, maximum concentration; CV; coefficient of variation; GLY, glycopyrronium bromide; GMR, geometric mean ratio; IND, indacaterol acetate; MF, mometasone furoate;

# Comparison of AUC<sub>0-24h</sub> and C<sub>max</sub> for IND, GLY and MF in Japanese versus Caucasian subjects on Day 14 (Geometric mean ratios)

o.d., once daily; PK, pharmacokinetics; T<sub>max</sub>; time to reach maximum concentration

- The geometric mean ratios (GMRs) for AUC<sub>0-24h</sub> and C<sub>max</sub> for IND, GLY and MF for IND/GLY/MF medium- and high-dose ICS on Day 14 are presented in Table 3
- Similar trends in GMR were observed for all mono-components at high dose ICS and medium-dose ICS on Day 1

# Table 3. Adjusted GMRs (Japanese vs. Caucasians) for AUC<sub>0-24h</sub> and C<sub>max</sub> on Day 14 for IND, GLY and MF (PK analysis set)

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Treatment	PK parameter -	Adjusted GMR (90% CI) (Japanese/ Caucasian)		
		IND	GLY	MF
IND/GLY/MF 150/50/80 µg	C <sub>max</sub> (pg/mL)	1.30 (1.13 to 1.49)	1.54 (1.27 to 1.87)	1.15 (1.04 to 1.26
	AUC <sub>0-24h</sub> (h*pg/mL)	1.21 (1.05 to 1.40)	1.06 (0.93 to 1.21)	1.23 (1.12 to 1.34
IND/GLY/MF 150/50/160 µg	C <sub>max</sub> (pg/mL)	1.31 (1.13 to 1.51)	1.38 (1.13 to 1.69)	1.07 (0.97 to 1.18
	AUC <sub>0-24h</sub> (h*pg/mL)	1.17 (1.01 to 1.35)	1.05 (0.92 to 1.20)	1.15 (1.05 to 1.27
Data are presented	as GMR (90% CI)			

IND/GLY/MF is a combination of indacaterol acetate 150 μg, glycopyrronium bromide 50 μg and mometasone furoate 80 μg (medium-dose ICS) or 160 µg (high-dose ICS) delivered via the Breezhaler®

 $AUC_{0-24h}$ , area under the concentration-time curve from 0 to 24 hours;  $C_{max}$ , maximum concentration; CI, confidence interval; GLY, glycopyrronium bromide; GMR, geometric mean ratio; IND, indacaterol acetate; MF, mometasone furoate; o.d., once daily; PK, pharmacokinetics

# Safety

- Overall, 10 subjects (30.3%) had ≥1 adverse event (AE); incidence of AEs in Japanese subjects was 18.8% compared with 41.2% in Caucasian subjects
- No serious AEs or deaths were reported. None of the AEs were considered to be related to the study drug. Headache, constipation and nasopharyngitis were the most frequent AEs. Safety results are summarised in **Table 4**

### Table 4. Overall incidence of AEs (safety set)

	Japanese		Caucasian			
	IND/GLY/MF 150/50/80 μg N = 16	IND/GLY/MF 150/50/160 μg N = 14	Total N = 16	IND/GLY/MF 150/50/80 μg N = 17	IND/GLY/MF 150/50/160 μg N = 15	Tota N = 1
Subjects with AEs	2 (12.5)	2 (14.3)	3 (18.8)	6 (35.3)	3 (20.0)	7 (41.
Severe AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.
Serious AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.
AEs leading to discontinuation of treatment	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	1 (3.0

IND/GLY/MF is a combination of indacaterol acetate 150 µg, glycopyrronium bromide 50 µg and mometasone furoate 80 µg (medium-dose ICS) or 160 µg (high-dose ICS) delivered o.d. via the Breezhaler®

AE, adverse event; GLY, glycopyrronium bromide; IND, indacaterol acetate; MF, mometasone furoate; o.d., once daily

# Conclusions

- Pharmacokinetics of indacaterol acetate, glycopyrronium bromide and mometasone furoate (high and medium dose) when delivered as combination were comparable between Japanese and Caucasian subjects
- IND/GLY/MF medium- and high-dose ICS combinations were well-tolerated in both Japanese and Caucasian subjects and no new safety signals were detected
- These results confirm that no dose adjustment for IND/GLY/MF is required in Japanese population

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