Reports on the Deliberation Results

September 11, 2012
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Seebri Inhalation Capsules 50 μg
[Non-proprietary name]	Glycopyrronium Bromide (JAN*)
[Applicant]	Novartis Pharma K.K.
[Date of application]	November 25, 2011

[Results of deliberation]
In the meeting held on September 6, 2012, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product; the re-examination period is 8 years; and the drug substance is classified as a powerful drug and the drug product is not classified as a poisonous drug or a powerful drug.

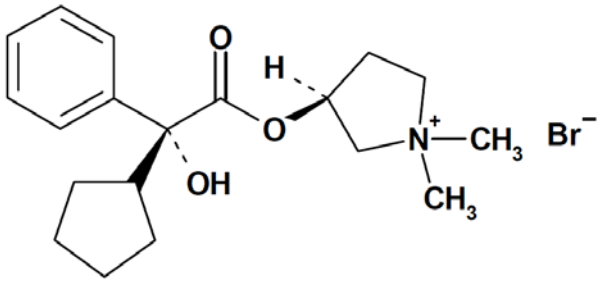
**Japanese Accepted Name (modified INN)*

Review Report

August 21, 2012
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name] Seebri Inhalation Capsules 50 μg
[Non-proprietary name] Glycopyrronium Bromide*
[Name of applicant] Novartis Pharma K.K.
[Date of application] November 25, 2011
[Dosage form/Strength] A hard capsule containing 63 μg of Glycopyrronium Bromide (50 μg as glycopyrronium)
[Application classification] Prescription drug (1) Drug with a new active ingredient
[Chemical structure]



and its enantiomers

Molecular formula: $C_{19}H_{28}BrNO_3$
Molecular weight: 398.33
Chemical name:
(3*RS*)-3-[(2*SR*)-(2-Cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide

[Items warranting special mention] None
[Reviewing office] Office of New Drug IV

* The Japanese name (JAN) has been changed according to the Notification No.0817-1 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated August 17, 2012.

Review Results

August 21, 2012

[Brand name] Seebri Inhalation Capsules 50 μg
[Non-proprietary name] Glycopyrronium Bromide*
[Name of applicant] Novartis Pharma K.K.
[Date of application] November 25, 2011
[Results of review]
Based on the submitted data, the efficacy of the drug product against chronic obstructive pulmonary disease (COPD) has been demonstrated and the safety of the product is acceptable in view of its observed benefits. Cardio- and cerebrovascular events and anticholinergic effect-related adverse events need to be further investigated via post-marketing surveillance.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indication and dosage and administration.

[Indication] Relief of symptoms of airway obstruction in patients with chronic obstructive pulmonary disease (chronic bronchitis and emphysema)
[Dosage and administration]
The usual adult dosage is one capsule (50 μg of glycopyrronium) administered once daily via an inhaler device.

* The Japanese name (JAN) has been changed according to the Notification No.0817-1 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated August 17, 2012.

Review Report (1)

July 13, 2012

I. Product Submitted for Registration

[Brand name] Seebri Inhalation Capsules 50 μg

[Non-proprietary name] Glycopyrronium Bromide

[Name of applicant] Novartis Pharma K.K.

[Date of application] November 25, 2011

[Dosage form/Strength] A hard capsule containing 63 μg of Glycopyrronium Bromide (50 μg as glycopyrronium)

[Proposed indication] Relief of symptoms of airway obstruction in patients with chronic obstructive pulmonary disease (chronic bronchitis and emphysema)

[Proposed dosage and administration]

Usually, for adults, one capsule (50 μg of glycopyrronium) should be administered once daily via an inhaler device.

II. Summary of the Submitted Data and the Outline of Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Glycopyrronium bromide (GB)[1], an active pharmaceutical ingredient of the product, is a long-acting muscarinic antagonist (LAMA), and the proposed product is an inhalant (capsule) for treatment of chronic obstructive pulmonary disease (COPD), developed by Arakis in the UK (current Sosei R&D) and Vectura in the UK with the intention of producing a sustained bronchodilatory effect with once-daily dosing.

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease characterized by airflow obstruction that is caused by prolonged exposure to a toxic substance and it is not fully reversible, and the major symptoms of COPD are chronic cough, expectoration, and exertional dyspnea. The management of COPD includes smoking cessation, drug therapy, pulmonary rehabilitation, oxygen therapy, ventilatory support, and surgical therapy, and according to severity and others, COPD will be comprehensively treated by a combination of these therapies. Bronchodilators play a central role in drug therapy for COPD and regular use of long-acting bronchodilators is recommended for patients with moderate to severe COPD. Within the class of long-acting inhaled bronchodilators, long-acting β_2 agonists (LABAs) (salmeterol xinafoate, indacaterol maleate, and formoterol fumarate hydrate), LAMAs (tiotropium bromide hydrate [Tio] and salmeterol xinafoate), and an inhaled corticosteroid (ICS) (a fluticasone propionate-containing

[1] Unless otherwise specified, the amount of GB is expressed as that of glycopyrronium in its free base form in this review report.

combination drug) have been approved in Japan for the indication of COPD treatment.

The clinical development of the drug product for treatment of COPD was started in 20[redacted] outside Japan. As of June 2012, the drug product is not approved in any country and under review in EU, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]. In foreign countries, injectable and oral formulations of GB are already marketed for the indication of peptic ulcers, preoperative treatment, hyperhidrosis and other symptoms. In Japan, an oral formulation of GB indicated for the treatment of gastroduodenal ulcer was also approved in 1974; however, the oral formulation was designated as a drug requiring reevaluation for quality in 1999 and after being discontinued in the market in the same year, its approval was withdrawn.

The clinical development of the drug product was started in [redacted] 20[redacted] in Japan and as the results from Japanese clinical studies and multi-regional studies including Japan have demonstrated the efficacy and safety of GB in Japanese patients with COPD, a marketing application has now been submitted.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white powder and has been determined for description, solubility, hygroscopicity, pH, melting point, dissociation constant, partition coefficient, optical rotation, crystalline polymorphism, differential scanning calorimetry (DSC), thermogravimetry (TG), and powder X-ray diffraction analysis.

The chemical structure of the drug substance has been examined by elementary analysis, ultraviolet spectroscopy (UV), infrared spectrophotometry (IR), nuclear magnetic resonance spectroscopy (^{1}H- and ^{13}C-NMR), mass spectrometry (MS), and X-ray crystallography. The drug substance is a racemic mixture of the 2S,3R and 2R,3S stereoisomers.

2.A.(1).2) Manufacturing process

The drug substance is synthesized using [redacted] and [redacted] as starting material.

Synthesis of [redacted] and synthesis of [redacted] are defined as critical process steps. In these process steps, in-process controls and action limits have been established.

2.A.(1).3) Control of drug substance

The proposed specifications for the drug substance include strength, description, identification (IR spectrum and X-ray powder diffraction method), purity (heavy metals, related substances [liquid chromatography,

HPLC], residual solvents [gas chromatography, GC]), loss on drying, residue on ignition, bacterial endotoxins, [redacted] (potentiometric titration), and assay (HPLC).

2.A.(1).4) Stability of drug substance

The stability studies of the drug substance were as shown in Table 1. Results obtained from the photostability testing indicated that the drug substance was not photosensitive.

Table 1. Stability studies of the drug substance

Name of the study	Reference batch	Temperature	Humidity	Storage conditions	Testing frequency
Long-term testing	Pilot Method A 3 batches	25°C	60%RH	A polyethylene bag (double-layer) in a metal drum	36 months
	Pilot Method B 3 batches				12 months
Accelerated testing	Pilot Methods A and B 3 batches	40°C	75%RH		6 months

Unlike Method A, Method B applied in production scale uses [redacted], including a compound B3, in the next reaction step without [redacted], but its manufacturing process is roughly the same as Method A.

From the results of the above stability studies, when the drug substance is packaged in a double-layer polyethylene bag, placed in a metal drum, and stored at room temperature, the retest period of 48 months has been proposed based on the “Guideline on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June 3, 2003; hereinafter referred to as ICH Q1E Guideline). The long-term stability testing will last for up to 60 months.

2.A.(2) Drug product

2.A.(2).1) Description, composition, and formulation development of the drug product

The drug product is a hard capsule filled with an inhalation powder containing 63 μg of drug substance (equivalent to 50 μg of glycopyrronium). The drug product contains lactose hydrate and magnesium stearate as excipients.

The product is to be administered via a single dose dry powder inhaler (Concept1). During inhalation, the drug substance particles attached to the surface of lactose hydrate, a carrier, is entrained into the turbulent airflow generated in the inhaler, leading to the detachment of the drug substance particles from the surface of the carrier, and the particles of the drug substance reach the bronchi. Concept1 is currently used for already approved Onbrez Inhalation Capsules 150 μg.

2.A.(2).2) Manufacturing process

The drug product is produced through the manufacturing process comprising Mixing, [redacted], [redacted], Sieving, Mixing, Encapsulation, and Packaging. Steps [redacted], [redacted], [redacted], and [redacted] are defined as critical process steps, for which process controls and action limits have been established. The drug product after [redacted] is regarded as [redacted] and process controls and action limits are also defined.

2.A.(2).3) Control of drug product

The proposed specifications for the drug product include strength, description (appearance), identification

(thin-layer chromatography [TLC]), purity (related substances [HPLC]), loss on drying, uniformity of dosage unit (content uniformity [HPLC]), bacterial endotoxins, fine particle dose (Next Generation Impactor), uniformity of delivered dose (HPLC), and assay (HPLC).

2.A.(2).4) Stability of drug product

The stability studies of the drug product were as shown in Table 2. Results obtained from the photostability testing indicated that the drug product was not photosensitive.

Table 2. Stability studies of the drug product

Name of the study	Reference batch	Temperature	Humidity	Storage conditions	Testing frequency
Long-term testing	Proposed commertial product Commerital production scale 3 batches	25°C	60%RH	Double-sided aluminum blister packaging	18 months
	Product for clinical studies Commerital production scale 2 batches				24 months
	Proposed commertial product that was submitted additionally Commerital production scale 3 batches				6 months
Intermediate testing	Proposed commertial product Commerital production scale 3 batches	30°C	75%RH		18 months
	Product for clinical studies Commerital production scale 2 batches				24 months
	Proposed commertial product that was submitted additionally Commerital production scale 3 batches				6 months
Accelerated testing	Proposed commertial product Commerital production scale 3 batches	40°C	75%RH		6 months
	Product for clinical studies Commerital production scale 2 batches				6 months
	Proposed commertial product that was submitted additionally Commerital production scale 3 batches				6 months

From the above, a shelf life of 18 months has been proposed for the drug product packed in double aluminum blister packaging (polyamide/aluminum/polyvinyl chloride film and polyethylene terephthalate/aluminum film) and stored at room temperature [for details, see "2.B. Outline of the review by PMDA"]. The long-term stability testing will last for up to 36 months.

2.B. Outline of the review by PMDA

As a result of the following review, PMDA concluded that the submitted data indicates that the quality of the drug substance and product is appropriately controlled.

2.B.(1) [redacted] of the drug product's [redacted]

Results from the stability studies using 3 batches of the proposed commertial product found an increase in [redacted], which were outside the specification limits, and decreases in fine particle dose and uniformity of delivered dose in 1 batch (X054BG). The applicant explained the cause as follows:

The following are the results of the investigation of the cause: (1) Microscopic observation indicated that the quality of [redacted]'s [redacted] in the relevant batch was not adequate; (2) The result of [redacted] showed that the

[redacted] of the relevant batch was low; (3) [redacted] was conducted by low [redacted] not by [redacted] at the time of batch production; and (4) Results of the stability studies (long-term testing, intermediate testing, and accelerated testing), where the [redacted] of the relevant batch was placed in [redacted], demonstrated that testing parameters complied with the specifications under all storage conditions and no changes were observed in the long-term and intermediate testing. Therefore, the cause of the test results outside the specification limits in the relevant batch seemed to be attributed to [redacted] of [redacted]. Furthermore, [redacted] [redacted] of [redacted] in [redacted] and inappropriate [redacted] of [redacted] appear to contribute to [redacted] of [redacted]'s [redacted], and the [redacted] of [redacted] was found to be improved by the following: (1) appropriate management of [redacted] and [redacted] at the time of [redacted] by [redacted] [redacted] of the drug product; (2) [redacted] of [redacted] for [redacted] and setting of [redacted] using [redacted] and [redacted]; and (3) introduction of [redacted] of [redacted]. With these improvements, the recurrence of [redacted] in [redacted] can be prevented.

PMDA concluded that the applicant's view that the test results outside the specification limits in 1 batch (X054BG) were caused by [redacted] of [redacted] and the applicant's actions taken to prevent the recurrence of [redacted] in [redacted] are justified.

2.B.(2) Shelf life for the drug product

The applicant explained the basis for establishing the shelf life of the drug product as 24 months as follows:

The results of [redacted], fine particle dose, and uniformity of delivered dose in 1 batch (X054BG) found for [redacted] do not represent to-be-marketed formulations, and these results obtained from the relevant batch were not used in determining the shelf life. The proposed shelf life of 24 months for the drug product seems appropriate for the following reasons:

(1) The results from the 18-month long-term testing and intermediate testing of the proposed commertial products, except those of [redacted], fine particle dose or uniformity of delivered dose in Batch X054BG, comply with the proposed specifications; (2) Based on the results from statistical analysis of stability studies using proposed commertial products, 18-month shelf life can be extrapolated to the proposed shelf life of 24 months according to ICH Q1E Guideline; (3) Stability is supported by the results from 24-month long-term testing and intermediate testing of 2 batches for clinical studies, the product for clinical studies differs from the proposed commertial product only in that capsules for the proposed product contain a dye (Yellow No.5), and drug products using both capsules show similar behavior for all testing parameters including fine particle dose and uniformity of delivered dose; and (4) Additional stability of 6 months was demonstrated in additional stability studies (long-term testing and intermediate testing) using 3 batches of the same drug product as the proposed commertial product (commertial production scale).

PMDA considers as follows:

With respect to [redacted], fine particle dose, and uniformity of delivered dose evaluated in the stability

studies of the proposed products, the results obtained from the 2 batches, excluding the 1 batch (X054BG) that yielded results outside the specifications, were used for evaluation. Since Batch X054BG has been found to be [redacted], the exclusion of the results obtained from Batch X054BG is acceptable. A dye contained in a capsule is the only difference between the proposed commertial product and the product for clinical studies, and there is no great difference between these products in values of all testing parameters including fine particle dose and uniformity of delivered dose, both of which are formulation attributes that are potentially affected by changes in dyes used in capsules. Thus, PMDA concluded that it is acceptable to use the results from stability studies of the proposed commertial product for evaluation of the drug product's stability, taking also into account of the results of stability studies of the product for clinical studies.

However, the "Stability Testing of New Drug Substances and Products" (PFSB/ELD Notification No. 0603001 dated June 3, 2003) specifies that if it can be assumed that "the same degredation relationship will continue to apply beyond the observed data," "limited extrapolation of the real time data beyond the observed range to extend the shelf life can be undertaken." Based on the fact that the uniformity of delivered dose and fine particle dose are specifications important in ensuring the quality of a drug product and that their time-course kinetics is unclear, PMDA considers that it is not appropriate to establish the shelf life of the drug product by predicting values for these parameters by statistical anaylsis, etc.

From the above, PMDA considered that the shelf life of 18 months is appropriate for the drug product based on the storage duration of the proposed commertial product and asked the applicant for reestablishment. The applicant responded that the shelf life of the drug product will be changed to 18 months.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

In primary pharmacodynamic studies, the affinity, selectivity, and functional activity of glycopyrronium for muscarinic receptors *in vitro* and the inhibition of bronchoconstriction *in vitro* and *in vivo* were investigated. In secondary pharmacology studies, the effects of GB's enantiomers and its metabolites' enantiomers on wide range of enzymes and receptors were examined. In safety pharmacology studies, the effect of GB on the central nervous system, respiratory system, and cardiovascular system was examined. No pharmacodynamic drug interaction studies have been performed.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) *In vitro* pharmacology studies

(a) *In vitro* activity and selectivity for muscarinic receptors (4.2.1.1-1 to -3)

Studies using GB

Using membrane fractions of Chinese hamster ovary (CHO) cells expressing human recombinant muscarinic M_1 to M_5 receptors, the glycopyrronium inhibitory activity (pKi) was determined for each receptor. Glycopyrronium inhibited the binding of [N-methyl-^{3}H]methylscopolamine to M_1 to M_5 receptors and the

pKi values (mean ± standard error [SE]) were 9.69 ± 0.04, 9.25 ± 0.02, 9.64 ± 0.03, 9.06 ± 0.01, and 8.91 ± 0.04, respectively. The pKi values for Tio binding to M_1 to M_5 receptors were 10.62 ± 0.04, 10.51 ± 0.03, 10.58 ± 0.03, 10.18 ± 0.07, and 9.76 ± 0.07, respectively, and glycopyrronium displayed slightly higher selectivity for the M_1 and M_3 receptors over the M_2 receptor as compared with Tio.

The selectivity of glycopyrronium towards each muscarinic receptor was determined in terms of binding kinetics. The dissociation rate constants (mean ± SE) of glycopyrronium for the M_1, M_2, and M_3 receptors were 0.05 ± 0.002, 0.646 ± 0.04, and 0.07 ± 0.004, respectively, and glycopyrronium showed faster dissociation from the M_2 receptor over the M_1 and M_3 receptors. The selectivity towards the M_2 and M_3 receptors was evaluated using the following calculation: dissociation rate constant for the M_2 receptor/dissociation rate constant for the M_3 receptor, and the values were about 9-fold for glycopyrronium, whereas 4-fold for Tio. From these findings, the applicant discussed that the selectivity towards the M_3 receptor appears to be higher in glycopyrronium than in Tio since glycopyrronium has a shorter M_2-receptor binding time compared to Tio at an equally efficacious dose.

The time of onset of action for GB was determined in terms of binding kinetics of glycopyrronium to M_3 receptor. The dissociation rate constant (k_{off}) of glycopyrronium at the M_3 receptor was 0.07 ± 0.004 compared with 0.015 ± 0.002 for Tio. The dissociation half lives from the M_3 receptor ($t_{1/2}$) calculated from these values were 9.9 minutes for glycopyrronium and 46.2 minutes for Tio, indicating the faster dissociation rate of glycopyrronium compared to Tio at the M_3 receptor. The applicant explained as follows:
In a rate equation for calculating the amount of a drug bound to a receptor ($Y = Y_{max}[1-e^{-kt}]$)[2], k_{off}, a key factor used for calculating the time required for a drug to reach the equilibrium, is higher in glycopyrronium than in Tio, suggesting that glycopyrronium will reach equilibrium binding for the M_3 receptor faster than Tio at an equally efficacious dose. When the time taken ($t_{1/2}$) for glycopyrronium and Tio to bind to 50% of the M_3 receptor population was calculated by the equation, $t_{1/2} = \ln 2/(k_{on}\cdot[\text{ligand}] + k_{off})$, it was 6.2 minutes for glycopyrronium and 23.9 minutes for Tio at their respective Kd concentrations, suggesting that glycopyrronium potentially demonstrates a faster onset of action than Tio.

Studies using glycopyrronium's enantiomers

Glycopyrronium is a racemic mixture of the [3R,2S] and [3S,2R] enantiomers. Using membrane fractions of CHO cells expressing human recombinant muscarinic M_1 to M_5 receptors, the inhibitory activity (pKi) of enantiomers was determined for each receptor. The inhibitory activity of QBA608 (3S,2R enantiomer) for the M_3 receptor was 100-fold higher than that of QBA609 (3R,2S enantiomer). The affinity of glycopyrronium's enantiomers towards the M_2 and M_3 receptors was determined in terms of binding kinetics. The dissociation rate constant of QBA608 at the M_3 receptor was 100-fold lower than that of QBA609, indicating a slower dissociation of QBA608 from the M_3 receptor compared to QBA609. According to the applicant's explanation, the above results have demonstrated that the majority of the biological activity

[2] Y, amount of a drug bound to a receptor; Y_{max}, amount of a drug bound to a receptor at the equilibrium; k, apparent reaction rate constant ($k = k_{on}\cdot[\text{ligand}] + k_{off}$); t, time since dosing

resides in the 3S,2R enantiomer of glycopyrronium, QBA608, in terms of receptor inhibitory activity and dissociation rate.

(b) Duration of action in isolated rat tracheas (4.2.1.1-4)

The duration of action of GB, Tio, and ipratropium was compared and evaluated by using isolated rat tracheas. GB, Tio, or ipratropium was added to isolated rat tracheas contracted with bethanechol (30 μM) and after bethanechol-induced contraction decreased by 30%, the nutrient solutions containing 30 μM of bethanechol was replaced every 15 minutes for drug cleaning. When the contraction following cleaning was determined every time the nutrient solutions were replaced, Tio (1, 3, and 30 nM) continuously inhibited bethanechol-induced bronchoconstriction for an observation period of 150 minutes, while the inhibition of bethanechol-induced bronchoconstriction was reduced in ipratropium (3, 10, and 30 nM) every nutrient solution replacement. GB (3, 10, and 30 nM) provided sustained inhibition of bethanechol-induced bronchoconstriction even after cleaning, and the duration of its action was shorter than Tio and longer than ipratropium.

3.(i).A.(1).2) *In vivo* pharmacology studies

(a) Duration of action in rats (4.2.1.1-5)

At 1, 6, or 24 hours after intratracheal administration of GB in anesthetized rats (3 to 9 rats in each group), 0.03, 0.1, 0.3, 1, 3, 10, 30, or 100 μg/kg of methacholine was administered intravenously at 5 minute intervals and the airway resistance was determined. Intratracheal administration of GB dose-dependently suppressed methacholine-induced bronchoconstriction at all time points studied (1, 6, and 24 hours post-dose), and ED50[3] (mean ± SE) at 24 hours post-dose was 1.20 ± 0.41 μg/kg. ED50 measured 24 hours after Tio treatment was 0.14 ± 0.01 μg/kg.

The effect of GB on salivation and cardiovascular parameters was also examined. The inhibition effect of GB on salivation, hypotension, and bradycardia induced by methacholine at 1, 6, and 24 hours post-dose was weaker than Tio.

(b) Duration of action in rabbits (4.2.1.1-6, -7)

After intravenous 10 μg/kg methacholine was administered repeatedly to anesthetized rabbits (3 rabbits in each group) until consistent bronchoconstriction was achieved, intratracheal GB was administered. Then, pulmonary inflation pressure was determined over time by repeatedly administering 10 μg/kg methacholine at 30 minute intervals, starting from 30 minutes after GB administration, until methacholine-induced bronchoconstriction resolved. Intratracheal administration of GB (20 μg) inhibited methacholine-induced bronchoconstriction and the effect continued during the observation period (for 6 hours post-dose). Similarly, ipratropium (20 μg) and Tio (3 μg) suppressed methacholine-induced bronchoconstriction for 6 hours post-dose.

[3] Calculated using the dose-response curve in the presence of 30 μg/kg methacholine.

The effect of GB on the cardiovascular system was also examined. GB (20 μg) had no effect on a methacholine-induced decrease in blood pressure and heart rate, while ipratropium (20 μg) and Tio (3 μg) attenuated the decrease mediated by methacholine.

(c) Onset of action and duration of action in rhesus monkeys (4.2.1.1-8)

Following 10-minute intratracheal administration of GB as an aerosol in anesthetized rhesus monkeys (3 to 8 monkeys in each group), the airway resistance was determined by administering methacholine over time (15, 105, 165, 225, and 285 minutes after the start of GB treatment). Intratracheal administration of GB (0.05, 0.15, 0.31, and 0.61 μg/kg), Tio (0.017, 0.05, and 0.14 μg/kg), or ipratropium (0.06, 0.13, 0.38, and 0.96 μg/kg) as an aerosol dose-dependently suppressed methacholine-induced bronchoconstriction that occurred 15 minutes after the start of treatment, and all of the drugs demonstrated a significant inhibition of bronchoconstriction compared to vehicle administration. A significant inhibition of bronchoconstriction was observed for 285 minutes after the start of administration of 0.61 μg/kg GB, 0.05 and 0.14 μg/kg Tio, and 0.96 μg/kg ipratropium. However, the duration of action by GB and ipratropium tended to be shorter than that by Tio.

The effect of GB on the cardiovascular system and respiratory system was also examined. No drugs had any significant effect on blood pressure and heart rate and GB and ipratropium had no effect on respiratory rate; an increase in respiratory rate was noted 10 minutes after the start of treatment at the maximum dose of Tio (0.14 μg/kg).

3.(i).A.(2) Secondary pharmacodynamics (4.2.1.2-1 to -3)

The effects of glycopyrronium's enantiomers (QBA608 and QBA609) on a wide range of enzymes and receptors were examined. At 10 μM no effect was observed in all enzymes studied for both enantiomers. Among receptors except for muscarinic M_3, M_4, and M_5 receptors, the ligand binding of Sigma σ_1 receptor was only inhibited by ≥ 50% (63% inhibition by each of the enantiomers at 10 μM). The extent of inhibition of the σ_1 receptor was approximately one ten-thousandth of glycopyrronium's binding to the M_3 receptor, indicating that binding to the σ_1 receptor will not occur at pharmacological doses of GB.

QAW665, an enantiomer of metabolite M9 (CJL603) which is a carboxylic acid derivative formed by hydrolysis of glycopyrronium, was assessed for its activity in a panel of 65 G-protein coupled receptors (GPCRs) including muscarinic receptors, transporters, ion channels, and enzymes. QAW665 showed no specific activity for any of these targets up to a concentration of 10 μM.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effect on the central nervous system and respiratory system

(a) Effect of inhaled GB on the central nervous system and respiratory system in rats[4] (4.2.1.3-1)

In a study in male rats (8 animals) administered a single inhaled dose of 0.168 mg/kg GB, slight and transient mydriasis was observed, but no other treatment-related effects were seen on functional observational battery (FOB), grip strength, hindlimb splay, or body temperature. In a study in male rats (5 animals) exposed to single inhalation of 0.168 mg/kg GB, no treatment-related effects were found on respiratory function (tidal volume, respiratory rate, and minute ventilation) or general signs.

3.(i).A.(3).2) Effect on the cardiovascular system

(a) Effect on hERG channels expressed on HEK293 cells (4.2.1.3-2, -3)

After HEK293 cells expressing hERG were treated with GB, the hERG current was measured by the whole-cell patch clamp method. The inhibition ratio of the hERG current was 0.6% for the vehicle, while those were 13.2% and 18.3% for 3.2 and 31.8 μg/mL of GB,[5] respectively.

In a study using 9.6, 31.8, and 95.5 μg/mL of GB,[6] the inhibition ratio of the hERG current was 0.3% for the vehicle, while it was 6.3%, 24.2%, and 30.6% for 9.6, 31.8, and 95.5 μg/mL of GB, respectively, indicating that the inhibition ratio was significantly higher in GB 31.8 and 95.5 μg/mL compared with the vehicle.

Since inhibition of the hERG current by ≥50% was not observed in both studies, IC50 could not be determined.

(b) Electrophysiology study using isolated rabbit hearts[7] (4.2.1.3-4)

The electrophysiological effect of GB on the heart was examined using isolated rabbit hearts. When the isolated hearts were treated with GB at concentrations of 0.3, 0.9, 3, 9, or 30 μM (0.1, 0.3, 1.0, 2.9, and 9.6 μg/mL) for 30 minutes, no electrophysiological effect was observed with no proarrhythmic effects indentified.

(c) Telemetry study of single intravenous GB in Beagle dogs (4.2.1.3-5)

The effect of single intravenous GB on the cardiovascular system was examined in male Beagle dogs in a telemetry study. This study comprised of observational and telemetry studies, and 0.01, 0.1, or 1.0 mg/kg GB (2 dogs in each group) was used in the observation study, and based on the results from the observation study, 0.01 or 0.1 mg/kg GB (3 to 4 dogs in each group) was used in the telemetry study. For changes in general signs, dry oral mucosa was observed in the treatment groups of ≥0.01 mg/kg, and mydriasis, tremor, dry nose, and decrease in food consumption or intake that seemed to be changes secondary to dry oral mucosa were

[4] Only results of GB alone were excerpted from studies of combination inhalants including GB.

[5] No giga ohm seal was formed at 95.5 μg/mL and the hERG current data were not obtained.

[6] Only results of GB alone were excerpted from studies of combination inhalants including GB.

[7] This study was conducted as a study not under the GLP.

seen in the treatment groups of ≥0.1 mg/kg. Slight weight loss was observed in the 1.0 mg/kg group. For the effect on the cardiovascular system, electrocardiogram (ECG) and telemetry recording revealed a dose-dependent increase in heart rate due to acute sinus rhythm associated with the pharmacological action of GB and associated secondary changes of short P width, PQ interval, QRS interval, QT interval, and QTc interval in the treatment groups of ≥0.01 mg/kg.

(d) Effect of inhaled GB on the cardiovascular system in Beagle dogs[8] (4.2.1.3-6)

In a study of male Beagle dogs (4 dogs) administered a single inhaled dose of 0.149 mg/kg GB, the effect of GB on the cardiovascular system was examined. During the study, no treatment-related death occurred. Following GB treatment, a transient increase in heart rate (about 82% increase during the exposure) was observed and the heart rate returned nearly to baseline 7 hours after treatment. Short PR interval, P width, and QT interval were observed with increased heart rate, and QTc was shortened by up to 30 msec for 2 hours after GB treatment compared with the baseline value. No abnormalities were found on systolic and diastolic blood pressure.

3.(i).B Outline of the review by PMDA

The duration of action of GB, despite differences among the test systems, is found to be shorter than Tio (clinical regimen, q.d.) and longer than ipratropium (clinical regimen, three to four times daily) in the *in vitro* study using isolated rat tracheas. PMDA asked the applicant to explain whether the proposed clinical dosage regimen of GB (50 μg q.d.) is supported also by nonclinical data, based on the predicted concentrations of glycopyrronium in human lung tissue, effective concentrations in nonclinical studies, elimination half-life for glycopyrronium in the lung, etc.

The applicant explained as follows:

(1) It is difficult to make an accurate measurement of glycopyrronium concentrations in the target sites in human lung tissue. However, when the concentrations of glycopyrronium in human lung tissue were predicted by compartmental analysis, the steady-state amount of glycopyrronium in the lung following repeated inhalation 50 μg q.d. was estimated to be about 100 μg, and according to the lung capacity of adult male subjects (1170 mL; Davis B and Morris T. *Pharmaceutical Research*. 1993;10:1093-5), the glycopyrronium concentration in human lung tissue was calculated to be about 85 ng/mL; (2) Results from studies conducted to evaluate the effect of glycopyrronium on bronchoconstriction induced by electrical stimulation in human isolated respiratory tracts (Haddad EB et al. *Br J Pharmacol.* 1999;127:413-420) and on carbachol-induced contraction in human isolated bronchial specimens (Villetti G et al. *Br J Pharmacol.* 2006;148:291-298) show that the effective concentarion of glycopyrronium is estimated to be in the range of 12.7 to 140.1 pg/mL in nonclinical studies; and (3) Following 4-week repeated inhalation of 0.1 mg/kg/day GB in rats, the elimination half-life for glycopyrronium in lung tissue ranged from 20 to 26 hours and glycopyrronium was eliminated slowly from the lung [see "3.(ii).A.(2).3) Glycopyrronium concentrations in

[8] Only results of GB alone were excerpted from studies of combination inhalants including GB.

lung tissue"]. The applicant considered that although it was difficult to directly compare glycopyrronium concentrations in human lung tissue with effective concentataions in nonclinical studies, repeated q.d. inhalation could maintain a sufficient concentration to exert its pharmacological action at the target site. Therefore, the clinical dosage regimen of GB has been justified by the data from clinical compartmental analyses in addition to those of nonclinical studies.

PMDA concluded that the submitted data have demonstrated the bronchodilatory effect of GB and the effect of GB on COPD can be explained. The justification for the clinical dosage regimen of GB (q.d.) will be determined taking account of results from clinical studies.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A *Summary of the submitted data*

As data on absorption, distribution, metabolism, excretion, and drug interactions, the results from studies of intratracheal, inhaled, intravenous, and oral GB in mice, rats, rabbits, and dogs were submitted. Pharmacokinetics was determined using GB and radiolabeled GB (^{14}C-labeled GB). The concentration of unchanged drug and metabolites in plasma was determined by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) (lower limit of quantification, 0.01 to 1 ng/mL), tissue radioactivity levels by quantitative whole body autoradiography (QWBA), and radioactivity levels of unchanged drug and metabolites in blood, plasma, urine, and feces by liquid scintillation counting (LSC).

Unless otherwise stated, pharmacokinetic parameters are represented as mean or mean ± standard deviation (SD).

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose studies (4.2.2.5-1 to -3, 4.2.3.4.1-1, 4.2.1.3-5, 4.2.2.2-1)

Pharmacokinetic parameters for plasma unchanged drug concentrations and radioactivity after single-dose administration of GB and ^{14}C-labeled GB in male mice, male rats, and male dogs were as shown in Table 3. The absorption rate and bioavailability of GB compared to intravenous administration were ≤11.4% and 0.625% following oral administration in mice, 22.4 ± 11.6% and 0.819% following oral administration in rats, and 96.3% and 96.0% following intratracheal administration in rats. The bioavailability of inhaled GB was 49.6% in rats. GB inhaled by rats was absorbed as rapidly as intratracheal administration.

Following single intravenous administration of 2 mg/kg GB in male rats (3 rats in each group), the plasma C_{max} of each enantiomer (QBA608 and QBA609) was 334 ± 70.9 and 271 ± 50.0 ng/mL, respectively, and the $AUC_{0\text{-}3h}$ was 136 ± 36.3 and 115 ± 31.5 ng·h/mL, respectively; the systemic exposure of the two enantiomers was nearly similar in rats. The C_{max} of QBA608 and QBA609 in plasma after single intravenous administration of 2 mg/kg QBA608 was 552 ± 104 and 31.5 to 50.0 ng/mL,[9] respectively, and the $AUC_{0\text{-}3h}$

[9] No QBA609 was detected in one rat and measurements were obtained only from two rats.

was 267 ± 61.5 and 64.6 to 68.1 ng·h/mL[10], respectively, while the plasma C_{max} of QBA608 and QBA609 after single intravenous administration of 2 mg/kg QBA609 was 59.9 ± 30.7 and 671 ± 134 ng/mL, respectively, and the $AUC_{0\text{-}3h}$ was 113 ± 87.2 and 327 ± 77.5 ng·h/mL, respectively. Therefore, the applicant discussed that administration of either of the two enantiomers resulted in chiral inversion *in vivo* in rats and an apparent equilibrium was reached.

Table 3. Pharmacokinetic parameters after single-dose administration of ^{14}C-labeled GB in mice, rats, and dogs

Animal species	Dose (mg/kg)	N	Route	Unchanged drug						Radioactivity			
				C_{max} (ng /mL)	T_{max} (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)	CLp (L/h/kg)	V_{ss} (L/kg)	C_{max} (ng Eq/mL)	T_{max} (h)	AUC_{last} (ng·Eq·h/mL)	$t_{1/2}$ (h)
Mice[a]	3.18	3	i.v.	615	0.083[f]	191	3.87	15.5	4.51	2153	0.083[f]	1592	77.0
	26.9	3	p.o.	2.41	0.5[f]	10.1	1.31	-	-	1455	8[f]	28086	10.2
Rats	0.07[b]	3	i.h.	2.93	0	6.70	na	-	-	-	-	-	-
	2.09[c, g]	3	i.t.	1328 ± 653	0.083[f]	459 ± 88	11.1 ± 0.824	-	-	1392 ± 452	0.083[f]	2589 ± 291	22.5 ± 4.09
	2.17[d, g]	4		0.326 ± 0.152	0.625[f]	1.08 ± 0.508	-	-	-	-	-	-	-
	4.01[c]	3	i.v.	2847 ± 1111	0.083[f]	927 ± 325	-	-	-	3949 ± 516	0.083[f]	5159 ± 1013	23.5 ± 1.99
	4.12[d]	3		1885 ± 1318	0.083[f]	787 ± 201	23.0 ± 11.6	5.43 ± 1.52	11.9 ± 7.44	3598 ± 1904	0.083[f]	5095 ± 385	41.7 ± 12.7
	33.5[c]	3	p.o.	106 ± 7	0.083[f]	63 ± 5	-	-	-	888 ± 236	8[f]	19042 ± 5159	-
	35.7[d]	3		145	0.083[f]	95	-	-	-	1185 ± 363	8[f]	20539 ± 10158	-
Dogs[e]	1.0	2	i.v.	-	-	330	4.4	3.2	5.4	-	-	-	-

Mean or mean ± SD; -, no data available; C_{max}, maximum peak concentration; T_{max}, time to reach maximum concentration; AUC, area under the curve; $t_{1/2}$, elimination half-life; CLp, plasma clearance; Vss, steady-state volume of distribution; i.h., inhalation; i.t., intratracheal; i.v., intravenous; p.o., oral; a, 4.2.2.5-1; b, 4.2.3.4.1-1; c, 4.2.2.5-3; d, 4.2.2.5-2; e, 4.2.1.3-5; f, median; g, the description of test substances and equipment used for administration differ between laboratory animals.

3.(ii).A.(1).2) Repeat-dose studies (toxicokinetics) (4.2.2.7-1, 4.2.3.2-2, -3, -4, -8, -9, 4.2.3.4.1-1, 4.2.3.5.2-1 to -3)

As repeat-dose studies of GB, toxicokinetics were examined in 4-, 26-, and 104-week inhalation studies in rats, a 12-day inhalation study in pregnant rats, a 13-day inhalation study in pregnant rabbits, and 4- and 39-week inhalation studies in dogs.

Repeated q.d. inhalation of 0.08, 0.49, or 3.39 mg/kg GB were given to rats (9 female and 9 male rats in each group) for 4 weeks. After the first GB inhalation, the plasma C_{max} of unchanged drug in female and male rats was 12.2 and 11.3 ng/mL in the 0.08 mg/kg group, 18.1 and 11.7 ng/mL in the 0.49 mg/kg group, and 70.8 and 57.7 ng/mL in the 3.39 mg/kg group, while the AUC_{8h} was 18.1 and 16.8 ng·h/mL in the 0.08 mg/kg group, 41.8 and 32.4 ng·h/mL in the 0.49 mg/kg group, 144 and 122 ng·h/mL in the 3.39 mg/kg group. On Day 28, the C_{max} in female and male rats was 13.3 and 30.6 ng/mL in the 0.08 mg/kg group, 20.2 and 12.0 ng/mL in the 0.49 mg/kg group, and 83.2 and 94.5 ng/mL in the 3.39 mg/kg group, while the AUC_{8h} was 24.1 and 34.4 ng·h/mL in the 0.08 mg/kg group, 42.0 and 36.3 ng·h/mL in the 0.49 mg/kg group, and 149 and 200 ng·h/mL in the 3.39 mg/kg group. No obvious gender differences were observed.

[10] No QBA609 was detected in one rat and measurements were obtained only from two rats.

Repeated q.d. inhalation of 0.09, 0.58, or 3.56 mg/kg GB were given to rats (9 female and 9 male rats in each group) for 26 weeks. At Week 4, the plasma C_{max} of unchanged drug in female and male rats was 2.4 and 2.1 ng/mL in the 0.09 mg/kg group, 18.5 and 7.1 ng/mL in the 0.58 mg/kg group, and 91.8 and 72.0 ng/mL in the 3.56 mg/kg group, while the $AUC_{0\text{-}24h}$ was 9.8 and 8.7 ng·h/mL in the 0.09 mg/kg group, 61.5 and 36.9 ng·h/mL in the 0.58 mg/kg group, and 230 and 198 ng·h/mL in the 3.56 mg/kg group. At Week 13, the C_{max} in female and male rats was 1.6 and 1.6 ng/mL in the 0.09 mg/kg group, 16.2 and 8.3 ng/mL in the 0.58 mg/kg group, and 44.8 and 52.4 ng/mL in the 3.56 mg/kg group, while the $AUC_{0\text{-}24h}$ was 5.6 and 9.9 ng·h/mL in the 0.09 mg/kg group, 48.4 and 34.5 ng·h/mL in the 0.58 mg/kg group, and 166 and 187 ng·h/mL in the 3.56 mg/kg group.

Repeated q.d. inhalation of 0.06, 0.17, or 0.45 mg/kg GB were given to rats (9 female and 9 male rats in each group) for 104 weeks. After the first GB inhalation, the plasma C_{max} of unchanged drug in female and male rats was 3.2 and 2.9 ng/mL in the 0.06 mg/kg group, 5.7 and 7.1 ng/mL in the 0.17 mg/kg group, and 9.4 and 19.5 ng/mL in the 0.45 mg/kg group, while the $AUC_{0\text{-}24h}$ was 6.9 and 6.7 ng·h/mL in the 0.06 mg/kg group, 15.3 and 16.3 ng·h/mL in the 0.17 mg/kg group, and 24.4 and 35.2 ng·h/mL in the 0.45 mg/kg group. At Week 52, the C_{max} in female and male rats was 1.9 and 2.3 ng/mL in the 0.06 mg/kg group, 6.3 and 5.0 ng/mL in the 0.17 mg/kg group, and 12.3 and 11.4 ng/mL in the 0.45 mg/kg group, while the $AUC_{0\text{-}24h}$ was 7.9 and 8.5 ng·h/mL in the 0.06 mg/kg group, 21.1 and 23.2 ng·h/mL in the 0.17 mg/kg group, and 38.3 and 34.6 ng·h/mL in the 0.45 mg/kg group.

Repeated q.d. inhalation of 0.09, 0.54, or 3.05 mg/kg GB were given to pregnant rats (9 rats in each group) for 12 days from gestation day 6 to 17. On gestation day 6, the serum C_{max} of unchanged drug in dams in each treatment group was 3.4, 6.0, and 216 ng/mL, respectively, and the $AUC_{0\text{-}24h}$ was 11.7, 21.9, and 367 ng·h/mL, respectively; on gestation day 17, the C_{max} was 2.4, 15.2, and 184 ng/mL, respectively, and the $AUC_{0\text{-}24h}$ was 7.9, 53.0, and 310 ng·h/mL, respectively.

Repeated q.d. inhalation of 0.08, 0.56, 1.92, or 3.60 mg/kg GB were given to pregnant rabbits (5 rabbits in each group) for 13 days from gestation day 7 to 19. The plasma C_{max} of unchanged drug in dams on gestation day 7 in each treatment group was 1.4, 4.9, 25.6, and 72.4 ng/mL, respectively, and the $AUC_{0\text{-}24h}$ was 9.3, 20.9, 74.6, and 164 ng·h/mL, respectively; the C_{max} on gestation day 19 was 6.8, 9.0, 37.2, and 129 ng/mL, respectively, and the $AUC_{0\text{-}24h}$ was 48.7, 89.2, 295, and 803 ng·h/mL, respectively.

Repeated q.d. inhalation of 0.02, 0.09, or 0.27 mg/kg GB were given to dogs (4 or 6 female and 4 or 6 male dogs in each group) for 39 weeks. After the first GB inhalation, the plasma C_{max} of unchanged drug in female and male dogs was 1.5 and 2.1 ng/mL in the 0.02 mg/kg group, 3.8 and 3.9 ng/mL in the 0.09 mg/kg group, and 18.1 and 16.9 ng/mL in the 0.27 mg/kg group, while the $AUC_{0\text{-}24h}$ was 4.0 and 6.6 ng·h/mL in the 0.02 mg/kg group, 10.4 and 9.0 ng·h/mL in the 0.09 mg/kg group, and 41.8 and 47.8 ng·h/mL in the 0.27 mg/kg group. At Week 13, the C_{max} in female and male dogs was 0.6 and 0.7 ng/mL in the 0.02 mg/kg group, 2.3

and 2.3 ng/mL in the 0.09 mg/kg group, and 9.3 and 9.1 ng/mL in the 0.27 mg/kg group, while the $AUC_{0\text{-}24h}$ was 1.8 and 2.1 ng·h/mL in the 0.02 mg/kg group, 9.1 and 8.8 ng·h/mL in the 0.09 mg/kg group, and 28.7 and 32.5 ng·h/mL in the 0.27 mg/kg group. At Week 39, the C_{max} in female and male dogs was 1.5 and 0.9 ng/mL in the 0.02 mg/kg group, 8.8 and 4.1 ng/mL in the 0.09 mg/kg group, and 8.2 and 42.1 ng/mL in the 0.27 mg/kg group, while the $AUC_{0\text{-}24h}$ was 4.6 and 4.6 ng·h/mL in the 0.02 mg/kg group, 33.6 and 21.3 ng·h/mL in the 0.09 mg/kg group, and 32.8 and 80.9 ng·h/mL in the 0.27 mg/kg group.

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Distribution in blood cells and plasma protein binding (4.2.2.3-1 to -3)

When mouse, rat, rabbit, dog, and human plasma or blood was added with ^{14}C-labeled GB at concentrations of 10 to 10000 ng/mL, the distribution in blood cells of glycopyrronium was 0%, 8.3%, 3.3%, 3.7%, and 0.3% to 1.6%, respectively, and the plasma protein binding was 23% to 25%, 27% to 30%, 30% to 45%, 25% to 29%, and 27% to 49%, respectively.

3.(ii).A.(2).2) Tissue distribution (4.2.2.5-1 to -3)

Following single intravenous administration of ^{14}C-labeled GB (3 mg/kg) in male mice (6 mice), total radiolabeled components were distributed throughout the body at 15 minutes post-dose, and high levels of radioactivity were observed in the liver, bile, thyroid, and kidney. At 168 hours post-dose, radioactivity was only detected in the eyes (choroid), Harderian glands, and liver. Following single oral administration of ^{14}C-labeled GB (25 mg/kg) in male mice (2 mice), radioactivity levels in the wall of the colon, stomach, wall of the small intestine, bile, liver, and penis were higher than those observed in blood at 24 hours post-dose, and radioactivity was only detected in the liver at 168 hours post-dose.

Following single intravenous administration of ^{14}C-labeled GB (4 mg/kg) in male albino rats (6 rats), total radiolabeled components were distributed throughout the body at 15 minutes post-dose, and high levels of radioactivity were observed in the liver and kidney. Radioactivity levels were high in the liver, brown fat cells, preputial glands, seminal vesicle (contour), adrenal cortex, kidney, thyroid, and stomach at 24 hours post-dose. At 168 hours post-dose, radioactivity above the lower limit of quantification was only detected in the liver, trigeminal nerve, kidney (corticomedullary junction and medulla), and pituitary gland. Following single intravenous administration of ^{14}C-labeled GB (4 mg/kg) in male pigmented rats (2 rats), higher levels of radioactivity were observed in melanin-containing tissues compared to albino rats at 24 hours post-dose, but they decreased at 168 hours post-dose. The applicant noted that the binding of GB to melanin-containing tissues is reversible.

Following single oral administration of ^{14}C-labeled GB (30 mg/kg) in male albino rats (6 rats), high levels of radioactivity were observed in the stomach, wall of the small intestine, esophagus, liver, kidney, and blood (LSC) at 15 minutes post-dose. Radioactivity above the lower limit of quantification was still detected in the liver, stomach, wall of the colon, wall of the small intestine, kidney (corticomedullary junction), and blood (LSC) at 24 hours post-dose; however, radioactivity was below the lower limit of quantification in all organs

after 72 hours post-dose.

Following single intratracheal administration of ^{14}C-labeled GB (1.7 mg/kg) in male albino rats (6 rats), total radiolabeled components were distributed throughout the body at 15 minutes post-dose, and high levels of radioactivity were observed especially in the tracheas, lung, liver, and kidney. Radioactivity was below the lower limit of quantification in tissues and blood, except the lung, liver, tracheas, and kidney, at 168 hours post-dose.

3.(ii).A.(2).3) Glycopyrronium concentrations in lung tissue (4.2.2.7-1)

Repeated q.d. inhalation of 0.1 mg/kg GB was given to rats (3 female and 3 male rats) for 4 weeks. After the first GB inhalation, the plasma C_{max} of unchanged drug in female and male rats was 0.508 and 0.519 ng/mL, and the C_{max} of unchanged drug in lung tissue was 898 and 984 ng/g, respectively. On Day 28, the plasma C_{max} of unchanged drug in female and male rats was 0.835 and 0.600 ng/mL, and the C_{max} of unchanged drug in lung tissue was 2520 and 2230 ng/g, respectively. The concentration of unchanged drug in lung tissue at 24 hours post-dose on Day 28 was 24% to 30% of the C_{max} following completion of the inhalation, while the concentration of unchanged drug in plasma at 11 hours post-dose on Day 28 was 20% to 30% of its C_{max} and it was below the lower limit of quantification at 24 hours post-dose, suggesting that glycopyrronium is eliminated more slowly from the lung than from the circulating blood. The $t_{1/2}$ for glycopyrronium in lung tissue was calculated to be 20 to 26 hours.

3.(ii).A.(2).4) Fetal distribution (4.2.3.5.2-3)

Repeated q.d. inhalation of 0.4, 1.3, or 3.5 mg/kg GB was given to pregnant rabbits (19 or 20 rabbits in each group) for 13 days from gestation day 7 to 19. On gestation day 19, the plasma C_{max} of unchanged drug in dams in each treatment group (3 or 5 rabbits) was 4.5, 19.9, and 45.3 ng/mL, and the $AUC_{0\text{-}24h}$ was 26.8, 59.3, and 118 ng·h/mL, respectively. The concentrations of glycopyrronium in fetuses measured 25 to 26 hours after the last inhalation were below the lower limit of quantification at all dose levels.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vitro* studies (4.2.2.4-1, -2, -5, -6)

When ^{14}C-labeled GB (5 μM) was added to liver microsomes obtained from mice, rats, rabbits, dogs, or humans and incubated, M1, M2, M3, M4, M5, M6, M7, M8, M9, or unchanged drug was detected. When ^{14}C-labeled GB (10 μM) was added to mouse, rat, rabbit, dog, or human hepatocytes and incubated, M1, M2, M3, M4, M5, M6, M6/M17, M7, M8, M9, M15, M32, M33, M34/M35, M36, or unchanged drug was detected. No unique human metabolites were identified in liver microsomes and hepatocytes. When ^{14}C-labeled GB (5 μM) was added to rat, dog, or human lung microsomes, rat or human small intestinal microsomes, and small intestine S9 fraction and incubated, no metabolites were detected.

When recombinant human cytochrome P-450 (CYP) and flavin-containing monooxygenase (FMO) expression systems were used to investigate the involvement of CYP and FMO enzymes in the metabolism

of GB, ^{14}C-labeled GB (100 μM) was slightly metabolized by CYP2D6, CYP1A2, CYP2B6, CYP2C9, CYP2C18, CYP2C19, and CYP3A4.

When mouse, rat, and human plasma were incubated with ^{14}C-labeled GB (2 μM) for 28 hours, the rates of M9 formation were 15.6%, 12.9%, and 30.8%, in mice, rats, and humans, respectively, and the M9 formation rate was 8.5% in control (phosphate buffer), suggesting that M9 is likely to be formed by non-enzymatic hydrolysis of GB.

3.(ii).A.(3).2) *In vivo* studies (4.2.2.5-1, -3)

Following single intravenous administration of ^{14}C-labeled GB (3 mg/kg) in male mice (3 mice), M8, M9, M20/M21, and unchanged drug were mainly detected in plasma and unchanged drug in urine and feces. Following single oral administration of ^{14}C-labeled GB (25 mg/kg), M9 was mainly detected in plasma, M2/M9/M28 in urine, and unchanged drug in feces.

Following single intravenous (4 mg/kg), oral (30 mg/kg), and intratracheal (1.7 mg/kg) administration of ^{14}C-labeled GB in male rats (3 rats), unchanged drug and M9 were mainly detected in plasma and the ratio of unchanged drug and M9 to total radioactivity AUC in each route of administration was 29.7% and 20.0%, 10.7% and 78.9%, and 26.6% and 26.2%, respectively. Unchanged drug was also mainly detected in urine and feces and the major metabolites detected were M2, M3, M5, M8, and M16 in urine as well as M42 in feces following single intravenous administration, M9 in feces following single oral administration, and M20 in feces following single intratracheal administration.

From the above investigation, it is inferred that the major metabolic pathways of GB are hydroxylation of cyclopentane and phenyl ring (M1, M3, M5, M6, M7, M10, M15, M23, M29, and M35), their dehydrogenation (M2, M8, M11, M12, M13, M16, M17, M19, M21, M28, and M45), and hydrolysis of ester bonds (M9) (see Figure 1 for possible metabolic pathways).

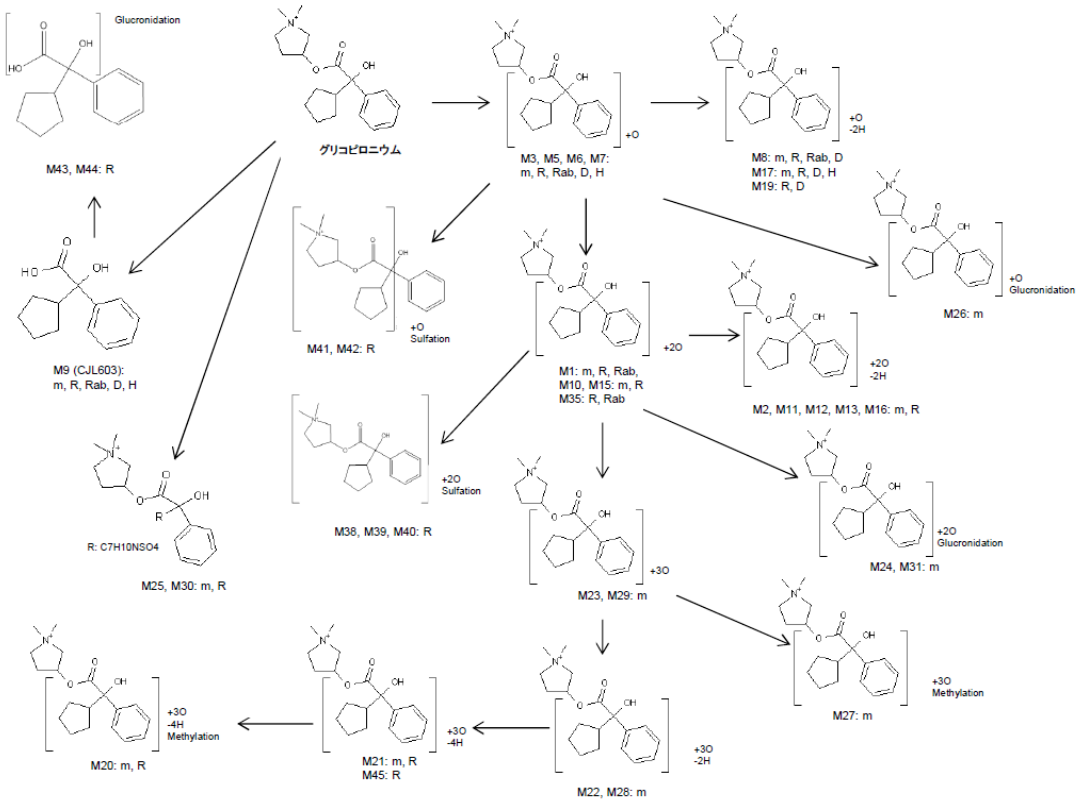


Figure 1. Putative major metabolic pathways of glycopyrronium

3.(ii).A. (4) Excretion

3.(ii).A. (4).1) Fecal, urinary, and biliary excretion (4.2.2.5-1 to -3)

Following single intravenous (3 mg/kg) or oral (25 mg/kg) administration of ^{14}C-labeled GB in male mice (3 mice), the fecal and urinary excretion rates (proportions of radioactivity to dose) for up to 168 hours post-dose were 29.0 ± 7.4% and 32.2 ± 15.1% following intravenous administration and 91.6 ± 2.72% and 3.67 ± 1.72% following oral administration, respectively.

Following single intravenous (4 mg/kg), oral (30 mg/kg), or intratracheal (1.7 mg/kg) administration of ^{14}C-labeled GB in male rats (3 rats), the fecal and urinary excretion rates for up to 168 hours post-dose were, 28.3 ± 3.85% and 65.7 ± 9.3% following intravenous administration, 95.8 ± 2.37% and 4.06 ± 0.31% following oral administration, and 56.0 ± 12.0% and 28.4 ± 15.7% following intratracheal administration, respectively. Following single intravenous (4 mg/kg) or oral (30 mg/kg) administration of ^{14}C-labeled GB in bile duct-cannulated rats (3 rats for each route), the biliary, fecal, and urinary excretion rates for up to 48 hours post-dose were, 7.27 ± 4.44%, 3.34 ± 3.31%, and 67.5 ± 10.6% following intravenous administration and 6.27 ± 5.17%, 41.4 ± 5.25%, and 13.7 ± 8.61% following oral administration, respectively.

Although the absorption rate of the lung when GB was administered intratrachealy in rats was 96.3% and the bioavailability was 96%, the majority of radioactivity following intratracheal ^{14}C-labeled GB administration was excreted in feces, dissimilar to when it was administered intravenously. The applicant discussed that this is attributed to a higher proportion of glycopyrronium distributed to the stomach after intratracheal administration.

3.(ii).A. (4).2) Excretion into milk (4.2.2.5-4)

Following single intravenous administration of ^{14}C-labeled GB (4 mg/kg) in lactating rats (4 rats), the C_{max} of total radioactivity in plasma and milk in dams was 3.57 and 5.75 μM, respectively, and the $AUC_{0\text{-}72h}$ was 12.7 and 102 μM·h, respectively. The C_{max} of unchanged drug in plasma and milk in dams was 0.990 and 2.00 μM, respectively, and the $AUC_{0\text{-}72h}$ was 3.54 and 40.0 μM·h, respectively. The ratio of exposure levels in milk/plasma was 8.03 for total radioactivity and 11.3 for unchanged drug, indicating that glycopyrronium and its metabolites were excreted in milk.

3.(ii).A. (5) Drug interactions

3.(ii).A. (5).1) Inhibition and induction (4.2.2.6-1 to -5)

The effect of GB (0.78 to 200 μM) to inhibit human CYP450 activity was assessed using human liver microsomes. The IC50 values were 100 ± 10 μM for CYP2D6 and 230 ± 40 μM for CYP3A4/5. GB showed no inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1.

GB (1 to 50 μM) was examined for its effect to induce activities of human CYP450 in human hepatocytes. GB did not induce metabolizing enzymes and transporters (human CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP3A5, UGT1A1, MDR1, and MRP2).

The effect of GB to inhibit transporter activity was assessed using cells expressing various transporters. The IC50 values were 47 ± 61 μM for human OCT1 and 17 ± 1.1 μM for human OCT2. No inhibition of BCRP, MRP2, and MDR1 was observed at glycopyrronium concentrations of ≤ 300 μM.

3.(ii).A. (5).2) Substrate recognition (4.2.2.6-6, -7)

The substrate recognition of glycopyrronium was investigated using cells expressing various transporters. Glycopyrronium was identified as a substrate for OCT1 and OCT2 with a K_m of 125 and 119 μM, respectively, suggesting that glycopyrronium is a substrate for MATE1, and not for MATE2K.

3.(ii).B Outline of the review by PMDA

Considering that high levels of radioactivity were observed in the lung until 24 hours post-dose in the distribution study of GB in rats after single intratracheal administration and that glycopyrronium was eliminated more slowly from the lung than from the circulating blood in the 4-week repeated inhalation study in rats, PMDA asked the applicant to explain the safety of glycopyrronium in the lung in detail.

The applicant explained that the clinical use of GB is less likely to cause problems in the lungs in terms of safety for the following reasons:

In the 13- and 26-week repeated inhalation toxicity studies in rats and 104-week repeated inhalation carcinogenicity study in rats, mild epithelial hypertrophy at the bronchioloalveolar junction was observed in the GB group, but this seemed to be a non-specific change frequently reported in inhalation toxicity studies

in rodents. The estimated lung deposition in the GB groups (0.06 to 0.45 mg/kg/day) in the carcinogenicity study in rats was 1 to 7.5 μg/g lung, which are 20- to 150-fold higher than the lung deposition in human subjects receiving an inhaled dose of GB 50 μg (0.05 μg/g lung) and therefore, high safety margins were obtained. Based on the pooled data from 2 phase III studies (Studies A2303 and A2304) (Core database), the incidence of adverse events categorized as "respiratory, thoracic and mediastinal disorders" (SOC) was 30.3%, 36.7%, and 38.1%, in the GB, Tio, and placebo group, respectively, in the Core 6-month population, while it was 45.1%, 42.7%, and 53.0%, respectively, in the Core 12-month population, indicating that the incidence in the GB group was lower than the placebo group and similar for the Tio group.

PMDA accepted the above response and considers as follows:
To date, no safety issues for glycopyrronium's local accumulation in the lung have been identified. However, this drug product is intended for long-term use and the evaluation through clinical studies is limited. Thus, the safety of long-term treatment with GB needs to be further evaluated via post-marketing surveillance.

3. (iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Toxicity studies of GB were conducted including repeat-dose toxicity, reproductive and developmental toxicity, genotoxicity, carcinogenicity, and local tolerance studies and other studies included a study on safety evaluation of impurities.

3.(iii).A.(1) Single-dose toxicity

No single-dose toxicity studies have been performed. Data on acute toxicity of GB are reported in the published literature (Franko BV et al. *Ann NY Acad Sci*. 1962;99:131-149; Franko BV et al. *Tox App Pharmacol*. 1970;17:361-365; and Saito G et al. *Oyo Yakuri*. 1973;7:627-653) following oral (p.o.), intraperitoneal (i.p.), subcutaneous (s.c.), or intravenous (i.v.) administration to mice, rats, rabbits, dogs, and cats. The 50% lethal dose was about 15 to 20 mg/kg (i.v.), about 100 to 120 mg/kg (i.p.), about 580 to 650 mg/kg (s.c.), and 550 to 970 mg/kg (p.o.) in mice, about 15mg/kg (i.v.), about 200 to 280 mg/kg (i.p.), about 830 to 960 mg/kg (s.c.), and about 1300 to 1800 mg/kg (p.o.) in rats, about 25 to 29 mg/kg (i.v.) and about 2400 mg (p.o.) in rabbits, about 15 to 30 mg/kg (i.v.) in dogs, and about 15 to 30 mg/kg (i.v.) in cats. Single-dose toxicity was investigated in a safety pharmacology study of intravenous GB in dogs [see "3.(i).A.(3) Safety pharmacology"] and a 1-week inhalation dose-finding study in dogs (4.2.3.2.-7; maximum dose, 1.04 mg/kg/day). These studies revealed changes in general signs including mydriasis, tachycardia, decrease in food consumption consistent with exaggerated pharmacological effects, but no GB-induced deaths.

3.(iii).A.(2) Repeat-dose toxicity

The main repeat-dose toxicity studies were inhalation toxicity studies conducted in rats (4, 13, and 26 weeks) and dogs (4 and 39 weeks). As major findings, those that seemed to be attributed to the anticholinergic effect of GB or secondary action of the effect (mydriasis, changes associated with reduced gland secretion, increase

in water consumption, decrease in food consumption and weight loss, increase in heart rate, etc.) were observed, and irritation of the nasal cavities and larynx and lens opacity (cataract) and epithelial hypertrophy at the bronchioloalveolar junction possibly resulting from muscarinic receptor inhibition were noted in rats. The extent of glycopyrronium exposure at the lowest observed adverse effect level (LOAEL) (0.07 mg/kg/day) in the 26-week inhalation study in rats or the no observed adverse effect level (NOAEL) in the 39-week inhalation study in dogs (0.02 mg/kg/day) is 22- to 38-fold and 10-fold higher, respectively, for AUC and 11- to 12-fold and 5- to 9-fold higher, respectively, for C_{max} compared with glycopyrronium exposure levels in human subjects receiving repeated doses of GB 50 μg (Study A2103). The estimated lung deposition[11] at the NOAEL in the 26-week (rats) or 39-week (dogs) inhalation studies was 24-fold and 9-fold higher, respectively in rats and dogs compared with that[12] in human subjects receiving an inhaled dose of GB 50 μg.

3.(iii).A.(2).1) 4-week inhalation toxicity study in rats (4.2.3.2-2)

Four-week inhalation of 0 (air), 0 (vehicle), 0.08, 0.49, or 3.39 mg/kg/day GB in Wistar rats was evaluated, and 2-week recovery was also evaluated in the high-dosage group. Mydriasis, increase in water consumption in female rats, acinar atrophy and hypertrophy in the mandibular glands, increase in porphyrin deposition accompanied by acinar hypertrophy in the Harderian glands, squamous metaplasia in the larynx, and acinar diffuse hypertrophy in the parotid gland were observed in the treatment groups of ≥0.08 mg/kg/day, weight loss in female rats, acinar diffuse atrophy in the lacrimal glands, hyaline inclusions in the propria mucosa of the olfactory/respiratory epithelium in the treatment groups of ≥0.49 mg/kg/day, and weight loss and increase in water consumption in male rats and decrease in body weight gain and decrease in food consumption in the 3.39 mg/kg/day group. All findings observed in this study, other than increase in water consumption, acinar hypertrophy in the parotid gland, squamous metaplasia in the larynx, and hyaline inclusions in the propria mucosa of the olfactory and respiratory epithelium, were recoverable. From the above results, findings that suggested to be due to the pharmacological effects of glycopyrronium or local tolerance were also found in the 0.08 mg/kg/day group. Therefore, the NOAEL was not determined in this study.

3.(iii).A.(2).2) 13-week inhalation toxicity study in rats (4.2.3.2-3)

An inhaled dose of 0 (air), 0 (vehicle), 0.09, 0.58, or 3.56 mg/kg/day GB was administered to Wistar rats for 13 weeks. This study was conducted as part of the 26-week inhalation toxicity study. Decreases in total albumin and albumin, increase in porphyrin deposition in the Harderian glands, eosinophilic globules in the olfactory epithelium in the nasal cavities, and squamous metaplasia of the epithelium at the base of the epiglottis in the larynx were observed in the treatment groups of ≥0.09 mg/kg/day, decrease in food consumption, decrease in body weight gain, decrease in serum calcium, and eosinophilic globules in the respiratory epithelium and hypertrophy/hyperplasia of goblet cells in the nasal cavities in the treatment

[11] Estimated deposition (μg/g lung) = total dosage at the NOAEL (μg) × (deposition coefficient/100)/lung weight (g). Values in the published literature (Snipes MB. Species comparison for pulmonary retention of inhaled particles. *Concepts in Inhalation Toxicology*. 1989;193-227; McClellan RO, Henderson RF (eds). Hemisphere Publishing Corporation, New York.) were used for the deposition coefficient for the lung and lung weight in animals tested.

[12] The estimated lung deposition (0.05 μg/g) was determined using 50 μg (an inhaled dose), 100% (lung deposition), and 1000 g (human lung weight).

groups of ≥0.58 mg/kg/day, and incomplete mydriasis following treatment with mydriasic drug, increases in total white blood cell count and neutrophil count accompanied by inflammation of the nasal cavities, basophilic acini in the Harderian glands, inflammation, exudates, and squamous metaplasia of the respiratory epithelium in the nasal cavities, and bronchiolar epithelial hypertrophy in the lungs in the 3.56 mg/kg/day group. There were neither dose-dependent changes in blood chemistry parameters nor hepatic and renal histopathological findings, indicating little toxicological significance. From the above results, findings that seemed to be due to the pharmacological effects of glycopyrronium or local tolerance were also found in the 0.09 mg/kg/day group. Therefore, the NOAEL was not determined in this study.

3.(iii).A.(2).3) 26-week inhalation toxicity study in rats (4.2.3.2-4)

Twenty-six-week inhalation of 0 (air), 0 (vehicle), 0.07, 0.54, or 3.98 mg/kg/day GB in Wistar rats was evaluated, and 4-week recovery was also evaluated in the 3.98 mg/kg/day group. Incomplete mydriasis following treatment with mydriatic drug, increase in porphyrin deposition in the Harderian glands, squamous metaplasia at the base of the epiglottis in the larynx, and eosinophilic globules in the respiratory/olfactory epithelium and hypertrophy/hyperplasia of goblet cells in the nasal cavities were observed in the treatment groups of ≥0.07 mg/kg/day, decrease in body weight gain, mydriasis before treatment with mydriatic drug, opacities in the anterior capsule of the lens, epithelial hypertrophy at the bronchioloalveolar junction in the lungs, and inflammation, exudates, squamous metaplasia of the respiratory epithelium and degeneration of the olfactory epithelium in the nasal cavities in the treatment groups of ≥0.54 mg/kg/day, and decrease in food consumption, increase in neutrophil count accompanied by inflammation of the nasal cavities, and prominent suture lines or opacities (cataract) in the anterior capsule of the lens in the 3.98 mg/kg/day group. All of these findings, other than those related to the larynx, nasal cavities, and lens, were recoverable. Immunostaining with Surfactant Protein B revealed that epithelial hypertrophy at the bronchioloalveolar junction in the lungs did not occur in Type II alveolar epithelial cells. The gene expression analysis of lung specimens in 13- and 26-week inhalation studies found no alteration in gene expression indicative of irritation, although there was an increase in expression of genes related to drug-metabolizing enzymes and the bronchial mucosa. The dose-dependent increase in mRNA expression of the mucus/Clara cells was detected similarily for specimens collected at weeks13 and 26, and fully recoverable after 4 weeks of recovery. From the above results, the NOAEL was not determined in this study.

3.(iii).A.(2).4) 4-week inhalation toxicity study in dogs (4.2.3.2-8)

Following 4-week inhalation of 0 (air), 0 (vehicle), or 0.03, 0.08, or 0.25 mg/kg/day of GB in Beagle dogs, 2-week recovery was also evaluated in the 0.25 mg/kg/day group. Decrease in food consumption, weight loss/suppression of body weight gain, corneal epithelial desquamation,[13] localized ulcer accompanied by epithelial/submucosal inflammation on the snout skin, immature prostate, and epididymides inclined to the initial spermatogenic stage were observed in the treatment groups of ≥0.03 mg/kg/day, pupils slowly responsive or unresponsive to light, tachycardia, shortened QT interval (corrections for heart rate have

[13] It was seen in the 0.03 and 0.25 mg/kg/day groups, not in the 0.08 mg/kg/day group.

indicated no apparent difference in QT intervals between the GB and control groups), high P-wave amplitudes, basophilic acini in the sublingual glands in the treatment groups of ≥0.08 mg/kg/day, and increased salivary gland weight, decreased prostate and testis weight, acinar hypertrophy in the sublingual glands, diffuse hypertrophy of mucinous acini in the submucosal glands in the mouth, nose, and pharynx, acinar hypertrophy in the lacrimal glands, corneal ulceration, crust formation on the snout, increased incidence of epithelial erosions accompanied by epithelial/submucosal inflammation and reactive epithelial hyperplasia as well as epithelial hyperkeratosis, and increased incidence of hepatocellular hypertrophy in the 0.25 mg/kg/day group. The histopathological changes in male reproductive organs found in all treatment groups and changes in weight of male reproductive organs seen in the 0.25 mg/kg/day did not occur in a 39-week inhalation study in dogs (4.2.3.2-9) and repeated inhalation studies in rats (4.2.3.2-2 to 4), and based on the fact that there was no effect on reproductive organ weight, sperm counts, and sperm motility in a fertility study (4.2.3.5.1-1), it is concluded that these histopathological changes and organ weight changes are not induced by GB treatment but caused by variations and deviations in sexual maturation of the animals tested. Since the findings observed in the 0.03 and 0.08 mg/kg/day groups with no structural changes or abnormal ophthalmological parameters identified, their incidence or extent of histopathological changes were similar for the GB and control groups, indicating that they are of low toxicological significance. All of these findings, except acinar hypertrophy in the sublingual glands and corneal ulceration, were recoverable. From the above results, the NOAEL was determined to be 0.08 mg/kg/day in this study.

3.(iii).A.(2).5) 39-week inhalation toxicity study in dogs (4.2.3.2-9)

Thirty-nine-week inhalation of 0 (air), 0 (vehicle), 0.02, 0.09, or 0.27 mg/kg/day GB in Beagle dogs was evaluated, and 4-week recovery was also evaluated in the 0.27 mg/kg/day group. Decreased lacrimal secretion and increased blood urea indicative of mild dehydration/decreased glomerular filtration rate at Week 13 were observed in the treatment groups of ≥0.02 mg/kg/day, decreases in body weight and body weight gain, mucinous secretion in the eyes, conjunctival hyperemia, corneal opacity, and focal corneal ulceration, hypertrophy of secretory cells in the lacrimal gland, red eyeballs, hypertrophy of secretory cells in the salivary gland, ectasia of the ducts and alveoli of the submucosal glands in the pharynx, increased incidence of inflammation of the ducts of the submucosal pharyngeal glands, and increase in mean heart rate in the treatment groups of ≥0.09 mg/kg/day, and decrease in food consumption, aqueous flare, diffuse corneal edema accompanied by corneal neovascularization, redness of the eyelids, and dry gums in the 0.27 mg/kg/day group. As for the findings observed in the 0.02 mg/kg/day group (decreased lacrimal secretion and increased blood urea) with no abnormal ophthalmological parameters identified, there were no lacrimal, corneal, or renal histopathological changes, indicating that they are of little toxicological significance. All of these findings were recoverable. From the above results, the NOAEL was determined to be 0.02 mg/kg/day in this study.

3.(iii).A.(3) Genotoxicity

GB was negative for genotoxicity in a bacterial reverse mutation assay (4.2.3.3.1-1), a chromosomal aberration assay using human peripheral blood lymphocytes (4.2.3.3.1-2), and an oral rat micronucleus assay

(4.2.3.3.2-1).

3.(iii).A.(4) Carcinogenicity

Carcinogenicity studies conducted are an oral carcinogenicity study in transgenic mice and an inhalation carcinogenicity study in rats. No neoplastic findings were identified in the study using transgenic mice, but epithelial hyperplasia in the forestomach was observed. There was no increase in the incidence of neoplastic findings in the rat carcinogenicity study.

3.(iii).A.(4).1) 26-week oral carcinogenicity study in transgenic mice (4.2.3.4.2-4)

Male rasH2 mice were administered 0 (vehicle), 10, 25, or 75 mg/kg/day GB and female rasH2 mice were administered 0 (vehicle), 10, 30, or 100 mg/kg/day GB by oral gavage for 26 weeks. In addition, wild-type (WT) mice were administered 0 (vehicle), 75 (male), or 100 (female) mg/kg/day GB by oral gavage for 26 weeks. Toxicokinetic studies indicated that GB was below the detection limit in the treatment groups other than GB 75 mg/kg/day (male) and GB 100 mg/kg/day (female) groups. In transgenic mice and WT mice, no treatment-related neoplastic findings were identified, but in the treatment groups of ≥10 mg/kg/day, increased incidence of epithelial hyperplasia in the forestomach including the limiting ridge (accompanied by increased incidence and severity of hyperkeratosis and mixed cell inflammation) was reported as a non-neoplastic finding. However, this non-neoplastic finding was determined to be caused by irritation resulting from oral gavage and the irritant effect of glycopyrronium with a high local concentration immediately after dosing.

3.(iii).A.(4).2) 104-week inhalation carcinogenicity study in rats (4.2.3.4.1-1)

Wistar rats were administered 0 (air, groups 1 and 2), 0 (vehicle), 0.06, 0.17, or 0.45 mg/kg/day GB by inhalation for 104 weeks. On comparison with the air control group 2 by Peto Trend test, a statistically significant increase in the incidence of endometrial stromal polyp was seen in the GB groups. However, pair-wise comparisons revealed no statistically significant difference in all groups. Endometrial stromal sarcoma was observed in the 0.06 mg/kg/day group. However, there was no statistically significant difference in the changes in the incidence of endometrial stromal polyp plus endometrial stromal sarcoma. In addition, examination of background data on the same strain of animals in the laboratory conducting carcinogenicity studies indicated that the naturally occurring incidence of endometrial stromal polyp varied from 6% to 22.0% (with a mean of 10.65%) and the incidences in the air control group 2 (2%) and vehicle control group (4%) were considerably lower than the naturally occurring incidence. Based on these results, none of the changes in the incidences of endometrial stromal polyp and the changes in the incidence of endometrial stromal polyp plus endometrial stromal sarcoma are considered related to treatment. Other non-neoplastic findings observed include increased incidence of opacities in the anterior capsule of the lens, eosinophilic globules in the olfactory epithelium, goblet cell hypertrophy/hyperplasia, and squamous metaplasia of the respiratory epithelium accompanied by inflammation in the nasal cavities, glandular, squamous metaplasia at the base of the epiglottis and posterior surface of the arytenoid cartilage in the larynx, increased incidence of foci or aggregations of alveolar macrophages in the lung, and epithelial hypertrophy

at the bronchioloalveolar junction.

3.(iii).A.(5) Reproductive and developmental toxicity

As subcutaneous studies of GB, a study of fertility and early embryonic development to implantation in rats and a rat study on pre- and postnatal development, including maternal function, were conducted. As inhalation studies, embryo-fetal development studies in rats and rabbits were conducted. None of the studies indicated treatment-related teratogenicity, and despite decreases in the number of corpora lutea and implantation sites with respect to female rat fertility parameters, no effects on parturition, embryo-fetal development, and pup development were noted. No placental transfer has been reported in rabbits (4.2.3.5.2.-3) but excretion into milk in rats (4.2.3.5-4) has been observed [see "3.(ii).A. (4) Excretion"].

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation in rats (4.2.3.5.1-1)

Wistar rats were administered 0 (vehicle), 0.15, 0.5, or 1.5 mg/kg/day GB; male rats received subcutaneous GB from 4 weeks prior to mating until the end of mating period and female rats from 2 weeks prior to mating until gestation day 6. In male rats, weight gain and decrease in food consumption were observed in the treatment groups of ≥0.5 mg/kg/day and erosion and crust formation around the injection site in the 1.5 mg/kg/day group; however, no treatment-related changes in male fertility parameters were seen. In female rats, increased incidence of estrous cycle abnormalities and low conception rate (excluding the 0.5 mg/kg/day group) were observed in all groups including the control group, and decrease in body weight gain and decreases in the number of corpora lutea and implantation sites in the 1.5 mg/kg/day group. With respect to the increased incidence of estrous cycle abnormalities, similar findings were also observed for the control group and as indicated in the repeated-dose toxicity studies, there was no effect on female reproductive system. In addition, low conception rate was also noted in the control group, with no dose-response identified. Therefore, both of the findings were considered not related to GB treatment. From the above results, the NOAELs in this study were determined to be 0.15 mg/kg/day for paternal general toxicity, 0.5 mg/kg/day for maternal general toxicity, and 1.5 mg/kg/day for paternal reproductive and embryonic development and 0.5 mg/kg/day for maternal reproductive and embryonic development.

3.(iii).A.(5).2) Embryo-fetal development studies

(a) Study in rats (4.2.3.5.2-1)

Pregnant Wistar rats were administered 0 (vehicle), 0.09, 0.54, or 3.05 mg/kg GB by inhalation from gestation days 6 to 17. Weight loss in dams from gestation day 6 to 9 and decrease in food consumption from gestation day 9 to 12 were observed in the 3.05 mg/kg/day group. There was no effect on fetuses. From the above results, the NOAELs in this study were determined to be 0.54 mg/kg/day for maternal general toxicity and 3.05 mg/kg/day for maternal reproductive and developmental toxicity and fetuses.

(b) Study in rabbits (4.2.3.5.2-3)

Pregnant NZW rabbits were administered 0 (vehicle), 0.4, 1.3, and 3.5 mg/kg/day GB by inhalation from gestation day 7 to 19. Changes in general signs were observed in 1 of 20 rabbits in the 0.4 and 1.3 mg/kg/day

groups (no-feces/reduced feces, emaciation, reduced activity, conceptus discharge, etc.). Of the 20 rabbits in the 3.5 mg/kg/day group, 1 rabbit was sacrificed due to worsening of clinical signs (listlessness, anorexia, dehydration-like symptoms, and mydriasis) seen on gestation day 25. Decrease in food consumption, decrease in body weight gain, and weight loss were observed in the treatment groups of ≥0.4 mg/kg/day, and the inhibition of salivation due to the pharmacological action of GB may contribute to the decrease in food consumption. The effects of these findings on dams were mild and transient in the 0.4 and 1.3 mg/kg/day groups and they were not classified as toxicity findings. For embryo-fetal effects, increased incidence of embryo resorptions and increased rate of post-implantation embryonic loss were noted in the treatment groups of ≥0.4 mg/kg/day, but these findings were not classified as treatment-related toxicity findings because they fell within the range of changes observed in background data in the laboratory. From the above results, the NOAELs in this study were determined to be 1.3 mg/kg/day for maternal general toxicity and 3.5 mg/kg/day for maternal reproductive and developmental toxicity and fetuses.

3.(iii).A.(5).3) Rat study on pre- and postnatal development including maternal function (4.2.3.5.3-1)

Pregnant Wistar rats were administered 0 (vehicle), 0.15, 0.5, or 1.5 mg/kg/day GB by subcutaneous route from gestation day 6 to Day 21, 22, or 23 post-partum. In dams, decrease in body weight gain was observed in the treatment groups of ≥0.15 mg/kg/day and decrease in food consumption in the 1.5 mg/kg/day group. In pups, low body weight was noted in the 1.5 mg/kg/day group. From the above results, the NOAELs in this study were determined to be 0.5 mg/kg/day for maternal general toxicity and F1 pups and 1.5 mg/kg/day for maternal reproductive and developmental toxicity.

3.(iii).A.(6) Local tolerance

3.(iii).A.(6).1) Murine local lymph node assay (4.2.3.6-1)

GB 50 μL at concentrations of 0.2, 2.4, or 24.0% (w/v) or 0.5% dinitrochlorobenzene 50 μL as positive control was applied q.d. to the dorsal auricle of male BALB/c mice for 3 days. Decrease in body weight gain was observed in the GB 2.4% and 24.0% groups. Reddening of the ear skin from the second day of application and an increase in lymph node weight occurred in the GB 24.0% group, and the NOAEL for lymph node weight was determined to be 2.4%. For the increased lymph node weight, no apparent changes in the number of cells in the lymph node were observed, indicating that this finding does not represent evidence of sensitization induced by GB but shows the local irritant effect of GB. From the above results, GB was not identified as a sensitizer.

3.(iii).A.(7) Other studies

To evaluate the safety of cyclopentylmandelic acid (CPMA) and 542-07, impurities of GB, a 4-week rat inhalation toxicity study and a genotoxicity study using GB containing these impurities were conducted. The results of these studies and published literature data on Impurity A, an impurity with mutagenicity, and intermediate 544-05, a hallucinogenic substance, indicate that all impurities have been demonstrated to be safe.

3.(iii).A.(7).1) 4-week rat inhalation toxicity study of impurities (4.2.3.7.6-1)

Wistar rats were administered 0.13 or 0.38 mg/kg/day GB containing CPMA (9.8%) and 542-07 (6.0%), and 0 (vehicle) or 0.56 mg/kg/day GB containing no impurities, by inhalation for 4 weeks. Decreases in body weight gain and food consumption, etc., were observed in all GB groups, and there were no differences in toxicological effects related to the presence or absence of impurities.

3.(iii).A.(7).2) Genotoxicity study of impurities (4.2.3.7.6-2, -3)

A bacterial reverse mutation assay and a chromosomal aberration assay using human peripheral blood lymphocytes were performed with GB containing CPMA (10.8%) and 542-07 (8.0%), and GB was negative for genotoxicity in both studies.

3.(iii).A.(7).3) Impurity A

Impurity A was positive for genotoxicity in a mutagenesis assay [redacted], but negative in carcinogenicity studies in rodents (mice and rats) [redacted]. Even assuming that the content of glycopyrronium in the drug substance was [redacted]%, equivalent to the lower specification limit, and all remaining [redacted]% ([redacted] μg/kg/day[14]) was Impurity A, the level fell within the threshold of toxicological concern (TTC) of 1.5 μg/day[15] (corresponding to a lifetime risk of cancer of 1 in 100,000). This level was about 170,000 times less than the dose reported to have no carcinogenic effect in the above-mentioned murine and rat carcinogenicity studies. Thus, it was concluded that the GB does not cause the risk of cancer in clinical use.

3.(iii).A.(7).4) 544-05

The intermediate 544-05 has hallucinogenic effects at oral doses of 2 to 4 mg [redacted] However, based on the specifications for individual related substances (≤ [redacted]%), the maximum dose of 544-05 will be [redacted] μg/day at the clinical GB dose of 50 μg/day and this dose level is [redacted] compared with 2 mg, the lowest dose inducing hallucination. Therefore, it was concluded that 544-05 is unlikely to induce hallucination in clinical use, even assuming differences in absorption between oral and inhalation regimens.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Effect on the eyes (lens and cornea)

With respect to findings in the lens observed in the 26-week rat inhalation toxicity study and ocular findings (such as conjunctival hyperemia, redness of the eyelids, red eyeballs, corneal opacity, and corneal ulceration) noted in the 4- and 39-week inhalation toxicity studies in dogs, PMDA asked the applicant to explain their mechanism and association with GB treatment as well as the ocular risk of GB in clinical settings.

[14] The body weight was assumed to be 60kg.

[15] EMEA Guideline (CPMP/SWP/5199/02)

The applicant responded that the ocular (lens) findings seen in rats were considered to be due to glycopyrronium exposure to the eyes during inhalation leading to high concentrations of glycopyrronium in ocular tissue.

Furthermore, the applicant explained as follows:

(1) Inhalation in rats, where test substance is sprayed into the nose, involves the potential to expose the substance to the entire face, including eyes. Meanwhile, in inhalation studies in dogs, face masks are used to cover the snout, resulting in an extremely low, direct exposure to test substance in eyes. In oral administration studies in mice, exposure to test substance is considered to take place only through systemic exposure. (2) In the 39-week inhalation toxicity study in dogs and 26-week oral carcinogenicity study in mice, no changes in lens were observed at the exposure levels ($AUC_{0\text{-}24h}$ 32.8 to 80.9 ng·h/mL in the 0.27 mg/kg/day group in dogs and $AUC_{0\text{-}24h}$ 15.3 to 75.6 ng·h/mL in the 75 to 100 mg/kg/day groups in mice) similar to the systemic exposure levels ($AUC_{0\text{-}24h}$ 55.0 to 68.1 ng·h/mL) in the 0.54 mg/kg/day group in the rat inhalation study, which showed a change in lens. (3) No changes in lens were observed in the 4- and 13-week rat inhalation toxicity studies conducted at the systemic exposure levels nearly similar to those in the 26-week rat inhalation toxicity study. Based on the above (1) to (3), a long-term direct exposure to glycopyrronium in eyes at a local concentration exceeding systemic exposure levels would be needed for development of the findings in the lens in rats. Therefore, changes in lens will not occur in clinical settings.

As for the ocular findings seen in dogs including redness of the eyelids, red eyeballs, corneal epithelial desquamation, corneal ulceration, corneal edema, or corneal opacity, the applicant explained as follows:(1) All of these findings were recoverable after a 2- or 4-week washout. (2) Since reduced tear production was confirmed by a Schirmer test in the 39-week inhalation toxicity study in dogs and hypertrophy of secretory cells in the lacrimal gland indicative of compensatory changes was seen in the GB group, these findings could be ascribed to secondary action due to reduced tear production associated with the pharmacological action of muscarinic antagonists following systemic exposure, and the resulting persistent dry eye led to corneal and conjunctival epithelial disorders, inducing inflammation in some animals tested. For the nature of mechanism, more severe ocular findings were made in the 39-week inhalation toxicity study compared with the 4-week inhalation study, but the comparison of the systemic exposure level at the NOAEL (0.02 mg/kg/day) in the 39-week inhalation study with the exposure level in human subjects receiving an inhaled clinical dose of GB 50 μg revealed a difference of ≥10-fold. Considering the above (1) and (2), the ocular risk of GB seems to be low in clinical use.

Furthermore, the applicant explained as follows:

To reduce the ocular risk associated with the pharmacological action of GB, GB is to be contraindicated in patients with angle-closure glaucoma in the package insert. To promote awareness, it will be cautioned that after patients are informed of the signs and symptoms of acute angle-closure glaucoma and if they fall under the description, GB should be immediately discontinued.

3.(iii).B.(2) Local tolerance

As for findings indicative of local irritant effect in the larynx and nasal cavities seen in the 4-, 13-, and 26-week rat inhalation toxicity studies and rat carcinogenicity study, PMDA asked the applicant to explain the risk of local irritant effects of GB in clinical settings, taking into account the fact that no recovery was observed in the 4- and 26-week inhalation studies.

The applicant explained as follows:

As for the findings in the nasal cavity, (1) rats breathe only through their noses and with the nature of the rat nasal cavity structure, inhaled substances tend to be trapped and concentrated in the nasal cavity and changes are easily made by a minor inhaled irritant compared to dogs and humans who can breathe through their noses and mouths, (2) the histological characteristics of the anterior nasal cavity differ between non-rodents and rodents, and the anterior nasal cavity comprising multiple layers of epithelia cells in monkeys and dogs is one of the reasons for their higher resistance to inhaled substance-induced disorders compared to rodents, and (3) while there are many reports on induction of pathological changes in the nasal cavity following inhalation in rodents, there have been no reports of changes in the nasal cavities accompanied by inhalation in dogs and monkeys (Renne RA et al. *Toxicologic Pathology*. 2007;35:163-169). Based on the above (1) to (3), considering that the clinical route of administration for GB is by inhalation, the potential to extrapolate the findings made in the nasal cavity of rats to humans is low and they are not changes of concern in clinical use. As for the findings in the larynx, although the laryngeal findings could be by mild irritation associated with persistent inhalation of large amounts of GB, (1) the larynx of rats is known to be highly sensitive to an inhalation regimen, which may be attributed to differences in the structure of the larynx and properties of epithelial cells (Gopinath et al. *Lancaster*. 1987; MTP Press Limited,25; Lewis DJ. *Toxicol. Lett*. 1981;9:189-194; Renne RA et al. *Toxicologic Pathology*. 2007;35:163-169), (2) pathological changes in the larynx accompanied by regeneration after degeneration of epithelial cells, hyperplasia, and squamous metaplasia were observed frequently in the inhalation toxicity studies conducted in rodents, and these changes are dependent on study period and dose rather than properties of individual compounds and also known to be caused by non-chemical factors (such as low humidity) other than factors attributable to the compounds (Lewis DJ. *Toxicologic Pathology*. 1991;19: 352-357), and (3) there have been no reports of these laryngeal changes indicating precancerous changes and they are clearly distinguished from other findings, and reversible, and does not exacerbate over time. Therefore, the findings made in the larynx will not pose a serious risk to use in humans (Osimitz T et al. *Toxicology and Applied Phrmacology*. 2007;225:229-237).

PMDA accepted the applicant's response regarding the effect on the eyes and local tolerance, considering that there is no specific problem with the toxicity of GB.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

As the evaluation data, the results of absolute bioavailability determination (5.3.1.1-1) were submitted.

Liquid chromatography-mass spectrometry (LC-MS/MS) method was used to determine the concentrations of glycopyrronium in plasma and urine and the concentration of a metabolite (CJL603, a carboxylic acid derivative) in plasma (lower limit of quantification, 3 to 4 pg/mL for glycopyrronium concentrations in plasma, 50 pg/mL for metabolite [CJL603] concentrations in plasma, 6 to 50 pg/mL for glycopyrronium concentrations in urine).

Unless otherwise stated, pharmacokinetic parameters are represented as mean or mean ± SD.

4.(i).A.(1) Evaluation of the absolute bioavailability of inhaled GB and ratio of lung absorption to gastrointestinal absorption in relation to plasma exposure levels of inhaled GB (5.3.1.1-1, Study A2108 [[redacted] 20[redacted] to [redacted] 20[redacted]])

In a randomized, crossover study in foreign healthy adult subjects (Part 1, 7 adult male subjects and 3 adult female subjects; Part 2, 16 adult males and 4 adult females), intravenous GB 120 μg or inhaled GB 200μg was administered as a single dose. The C_{max} of glycopyrronium in plasma following intravenous administration and inhalation was 9720 ± 2230 and 858 ± 391 pg/mL, the AUC_{last} was 2840 ± 450 and 1540 ± 259 pg·h/mL, respectively, and the AUC_{inf} was 2890 ± 453 and 2090 ± 462 pg·h/mL, respectively; the absolute bioavailability of inhaled GB (90% confidence interval [CI]) was 42.3 (38.3, 46.6)%.

The ratios of lung absorption and gastrointestinal absorption in relation to plasma exposure levels of inhaled GB were determined. Following single inhalation of GB 200 μg concomitantly administered with oral intake of activated charcoal 50 g, the C_{max} of glycopyrronium in plasma was 729 ± 297 pg/mL, the AUC_{last} was 1360 ± 309 pg·h/mL, and the AUC_{inf} was 2050 ± 566 pg·h/mL; the bioavailability of inhaled GB with activated charcoal relative to that without activated charcoal (90% CI) was 97.1 (89.7, 105)%. Following single oral administration of GB 400 μg concomitantly administered with and without 50 g of oral activated charcoal, the C_{max} of glycopyrronium in plasma with and without activated charcoal was 10.5 ± 5.62 and 78.8 ± 32.7 pg/mL, the AUC_{last} was 21.1 ± 20.3 and 432 ± 195 pg·h/mL, and the AUC_{inf} was 43.5 ± 19.8 and 456 ± 203 pg·h/mL, respectively. The bioavailability of inhaled GB with activated charcoal relative to that without activated charcoal calculated from the AUC_{last} was 1.87 ± 4.21%, demonstrating that concomitant charcoal blocked majority of the gastrointestinal absorption of orally administered GB. The above results indicated that when inhaled GB was administered with oral activated charcoal, almost all absorption of glycopyrronium took place through the lungs. Thus, the ratios of lung absorption and gastrointestinal absorption in relation to plasma exposure levels of inhaled GB (without activated charcoal) were calculated to be about 90% and about 10%.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

As the evaluation data, the results from a single-dose study in Japanese and foreign healthy adult subjects (5.3.3.1-1), examination of the effect on heart rates and QT intervals in foreign healthy adult subjects (5.3.1.1-1), evaluation of drug interactions with cimetidine in foreign healthy adult subjects (5.3.3.4-1), and evaluation in patients with impaired renal function (5.3.3.3-1) were submitted. As the reference data, the results from studies, including a multiple-dose study of foreign patients with COPD (5.3.3.2-1), were submitted.

Unless otherwise stated, pharmacokinetic parameters are represented as mean or mean ± SD.

4.(ii).A.(1) Evaluation in healthy adult subjects

4.(ii).A.(1).1) Single-dose study of Japanese and foreign healthy adult subjects (5.3.3.1-1, Study A2104 [to 20])

In a randomized, double-blind, 3-period, crossover study in Japanese and foreign healthy adult subjects (18 Japanese males and 19 foreign males), the pharmacokinetics of a single inhaled dose of GB 50, 100, or 200 μg were evaluated. The pharmacokinetic parameters were as shown in Table 4. The exposure of glycopyrronium in plasma was greater in Japanese subjects than in foreign subjects, and the geometric mean ratios of C_{max} and $AUC_{0\text{-}24h}$ were 1.76 to 1.84 and 1.23 to 1.34, respectively. The urinary excretion rates ($Ae_{0\text{-}48h}$) of enantiomers (QBA608 and QBA609) following single inhalation of GB 200 μg were 6.32 ± 1.46 and 6.17 ± 1.57%, respectively, in Japanese subjects and 4.18 ± 1.50 and 4.07 ± 1.62%, respectively, in foreign subjects, and there was no difference in $Ae_{0\text{-}48h}$ between the two enantiomers.

Table 4. Pharmacokinetic parameters after single inhalation of GB in Japanese and foreign healthy adult subjects

	Dose	C_{max} (pg/mL)	T_{max} (h)	$AUC_{0\text{-}24h}$ (pg·h/mL)	AUC_{last} (pg·h/mL)	$Ae_{0\text{-}48h}$ (%dose)
Japanese subjects	50 μg	181 ± 95.6	0.08 (0.08-0.08)	209 ± 106	257 ± 154	15.5 ± 5.23
	100 μg	328 ± 142	0.08 (0.02-0.15)	421 ± 147	578 ± 219	13.0 ± 4.28
	200 μg	801 ± 359	0.08 (0.08-0.17)	930 ± 287	1269 ± 357	13.2 ± 3.26
Foreign subjects	50 μg	94 ± 35.7	0.08 (0.08-0.25)	147 ± 77.5	164 ± 122	10.2 ± 4.34
	100 μg	192 ± 97.2	0.08 (0.08-0.25)	330 ± 115	416 ± 181	10.2 ± 3.55
	200 μg	401 ± 129	0.08 (0.08-0.25)	746 ± 175	968 ± 231	9.45 ± 3.23

Mean ± SD; T_{max} represents as a median (minimum-maximum); C_{max}, maximum plasma concentration; AUC, area under the plasma glycopyrronium concentration-time curve; $t_{1/2}$, elimination half-life; T_{max}, time to reach maximum plasma glycopyrronium concentration; Ae, urinary excretion in 17 to 19 subjects (each group); no summary statistics were calculated because $t_{1/2}$ (elimination half-life) data were only available from 3 patients.

4.(ii).A.(1).2) Evaluation of the pharmacokinetics of a metabolite (CJL603) in foreign healthy adult subjects (5.3.1.1-1, Study A2108 [20 to 20])

In a randomized, crossover study in foreign healthy adult subjects (Part 1, 7 adult male subjects and 3 adult female subjects; Part 2, 16 adult males and 4 adult females), the pharmacokinetics of a metabolite (CJL603) following single intravenous administration of GB 120 μg or single inhalation of GB 200 μg were evaluated. The C_{max} of CJL603 in plasma following single intravenous administration of GB 120 μg and single inhalation of GB 200 μg was 276 ± 73.0 and 137 ± 74.0 pg/mL, respectively, the T_{max} was 0.083 and 5.04 hours (median), respectively, the $AUC_{0\text{-}24h}$ was 78.6 ± 26.4 and 811 ± 568 pg·h/mL, respectively, the urinary

excretion ($Ae_{0\text{-}72h}$) was 0.330 ± 0.268 and 0.636 ± 0.293 μg, respectively, and the ratios of the metabolite to unchanged drug were 0.0418 ± 0.00960 and 0.286 ± 0.206 for C_{max}, 0.0403 ± 0.0131 and 1.23 ± 0.905 for $AUC_{0\text{-}24h}$, and 0.00620 ± 0.00462 and 0.0314 ± 0.0148 for $Ae_{0\text{-}72h}$ respectively.

4.(ii).A.(2) Evaluation in patients

4.(ii).A.(2).1) Multiple-dose study of foreign patients with COPD (Reference data, 5.3.3.2-1, Study A2103 [July to October 2007])

In a randomized, double-blind, placebo-controlled, parallel-group study in foreign patients with mild and moderate COPD (8 to 9 patients in each group), the pharmacokinetics of GB following repeated q.d. inhalation of 25, 50, 100, or 200 μg for 14 days were evaluated. After the administration on Days 1 and 14, the C_{max} of glycopyrronium in plasma was 41 ± 20.8 and 51 ± 17.4 pg/mL in the 25 μg/day group, 146 ± 109 and 166 ± 97.3 pg/mL in the 50 μg/day group, 360 ± 79.6 and 436 ± 135 pg/mL in the 100 μg/day group, and 565 ± 248 and 865 ± 545 pg/mL in the 200 μg/day group, respectively, and the $AUC_{0\text{-}24h}$ was 568 ± 146 and 778 ± 155 pg·h/mL in the 100 μg/day group, 1028 ± 320 and 1780 ± 653 pg·h/mL in the 200 μg/day group, respectively. The geometric means (90% CI) of cumulative ratios calculated from $AUC_{0\text{-}24h}$ were 1.44 (1.15, 1.79) and 1.69 (1.34, 2.13) in the 100 μg/day group and 200 μg/day group, respectively. The urinary excretion rates ($Ae_{0\text{-}24h}$) of enantiomers (QBA608 and QBA609) following repeated q.d. inhalation of GB 100 or 200 μg for 14 days were, respectively, 6.05 ± 1.95 and 6.31 ± 1.73% in the 100 μg/day group and 7.48 ± 3.24 and 7.67 ± 3.53% in the 200 μg/day group, and there was no difference in $Ae_{0\text{-}24h}$ between the two enantiomers.

4.(ii).A.(3) Population pharmacokinetic analysis (5.3.3.5-2, -3)

Using data on glycopyrronium concentrations in plasma (331 patients, 7771 measurement points) collected from clinical studies of patients with COPD (Studies A2103, A2303, and A2304), population pharmacokinetic analysis was performed with NONMEM software.

A 3-compartment model with first-order absorption was used as a basic model, with age for CL/F and Q3/F, body weight for CL/F, V2/F, Q3/F, Q4/F, V3/F, and V4/F[16], smoking status for Q3/F and V3/F, and race for V2/F as significant covariates.

Although not statistically significant, the AUC_{tau} estimate using the above nonlinear mixed-effects model was 30% higher in Japanese patients with COPD than in foreign patients with COPD. The AUC_{tau} was estimated to be 32% higher in COPD patients with a body weight of ≥60 kg and <70 kg compared with those with a body weight of ≥80 kg and <90 kg and Japanese and foreign COPD patients had a mean body weight of 61 kg and 80 kg, respectively, in this analysis. Thus, it is considered that this difference is attributed to a

[16] CL/F, apparent clearance from the central compartment; Q3/F, apparent clearance between the central compartment and peripheral compartment I; Q4/F, apparent clearance between the central compartment and peripheral compartment II; V2/F, apparent volume of distribution for the central compartment; V3/F, apparent volume of distribution for the peripheral compartment I ;V4/F, apparent volume of distribution for the peripheral compartment II

difference in body weight between Japanese and foreign patients.

When taking COPD patients with a body weight of ≥70 kg and <80 kg as reference, the estimated AUC_{tau} increased by 44% in those with a body weight of ≥40 kg and <50 kg and decreased by 15% in those with a body weight of ≥90 kg and <100 kg. When taking COPD patients aged ≥60 and <65 years as reference, it decreased by 25% in those aged ≥40 and <45 years and increased by 27% in those aged ≥75 and <80 years. From these findings, it was inferred that the smoking status had no effect on glycopyrronium exposure. The applicant explained that these differences are unlikely to be of clinical relevance and no dose adjustment is required according to body weight, age, and smoking status.

4.(ii).A.(4) Evaluation in special populations

4.(ii).A.(4).1) Evaluation of pharmacokinetics in patients with impaired renal function (5.3.3.3-1, Study A2105 [June to November 2010])

In an open-label, parallel-group study in foreign patients with mild (estimated glomerular filteration rate [eGFR], 50 to 80 mL/min/1.73 m^2), moderate (30 to 49 mL/min/1.73 m^2), and severe (<30 mL/min/1.73 m^2) renal impairment (8 patients in each group), foreign patients with end-stage renal disease (requiring dialysis) (6 patients), and foreign healthy adult subjects (matched with patients with impaired renal function on age, gender, and body weight) (>80 mL/min/1.73 m^2) (18 patients), the pharmacokinetics of GB following single inhalation of 100 μg were evaluated. The pharmacokinetic parameters by renal impairment were as shown in Table 5. Prolonged $t_{1/2}$ and increased AUC_{last} were noted in patients with renal impairment, and CLr decreased as the level of renal function impairment increased. The geometric mean ratios (patients with impaired renal function or those with end-stage renal disease/healthy adult subjects) of AUC_{last} (90% CI) were 1.42 (1.08, 1.87), in patients with mild renal impairment, 1.02 (0.78, 1.35) in those with moderate renal impairment, 2.21 (1.45, 3.36) in those with severe renal impairment, and 2.07 (1.35, 3.19) in those with end-stage renal disease. Based on a simulation of the relationship between eGFR and AUC exposure at steady state performed with a PPK model established using pooled pharmacokinetic data from this study and Study 2103 of COPD patients (5.3.3.5-1), an estimated AUC_{tau} following repeated inhalation of GB 50 μg in a group of virtual subjects with eGFR of 30 mL/min/1.73 m^2 (the lower limit of eGFR in patients with moderate renal impairment) was predicted to be 1.69-fold (90% CI, 1.58, 1.74) of healthy adult subjects (eGFR, 90 mL/min/1.73 m^2). Therefore, the applicant explained that the exposure of glycopyrronium is less likely to exceed the exposure level that has been demonstrated to be safe in patients with mild and moderate renal impairment and no dose adjustment is required. On the other hand, the applicant explained that glycopyrronium exposure is likely to exceed the exposure level that has been demonstrated to be safe in patients with severe renal impairment and careful consideration is needed for the use of GB in such patients. [For safety data by renal function collected from clinical studies, see “4.(iii).B.(2) Safety”]

Table 5. Pharmacokinetic parameters after single inhalation of GB 100 μg in patients with renal impairment, patients with end-stage renal disease, and healthy adult subjects

		Healthy adult subjects	Patients with mild renal impairment	Patients with moderate renal impairment	Patients with severe renal impairment	Patients with end-stage renal disease
	eGFR ($mL/min/1.73m^2$)	95.8 ± 13.11	59.1 ± 10.08	42.8 ± 5.87	20.8 ± 8.63	9.5 ± 7.45
In plasma	C_{max} (pg/mL)	356 ± 164	336 ± 158	277 ± 123	334 ± 106	303 ± 174
	AUC_{last} (pg·h/mL)	821 ± 288	1180 ± 428	847 ± 276	2080 ± 1410	1940 ± 1560
	AUC_{inf} (pg·h/mL)	1020 ± 400	1630 ± 485	1320 ± 320	2730 ± 1730	3740 ± 4970
	T_{max} (h)	0.083 (0.083-0.167)	0.083 (0.083-0.083)	0.083 (0.083-0.25)	0.083 (0.083-0.25)	0.125 (0.083-0.25)
	$t_{1/2}$ (h)	32.5 ± 23.4	50.9 ± 19.4	39.9 ± 27.6	46.0 ± 7.01	61.7 ± 38.0
	CL/F (L/h)	114 ± 46.2	66.8 ± 21.6	79.7 ± 20.3	49.5 ± 26.5	50.9 ± 23.1
In urine	$Ae_{0\text{-}96h}$ (μg)	20.0 ± 6.38	16.3 ± 4.39	9.89 ± 3.71	8.43 ± 4.28	-
	CLr (L/h)	23.0 ± 7.50	14.2 ± 4.52	10.4 ± 2.70	4.88 ± 2.63	-

Mean ± SD; T_{max} represents a median (minimum-maximum)
8 patients (patients with impaired renal function), 6 patients (patients with end-stage renal disease), and 18 patients (healthy adult subjects)

4.(ii).A.(5) Evaluation of drug interactions

4.(ii).A.(5).1) Drug interactions with cimetidine (5.3.3.4-1, Study A2109 [[redacted] to [redacted] 20[redacted]])

In an open-label, crossover study in foreign healthy adult subjects (20 male subjects), the pharmacokinetic interactions between GB and cimetidine, an inhibitor of organic cation transporters (OCT2 and MATE1), were evaluated. Following single inhalation of GB 100μg or repeated twice-daily (b.i.d.) oral administration of cimetidine 800 mg for 6 days plus a single inhaled dose of GB 100 μg on the fourth day, the C_{max} of glycopyrronium in plasma after administration of GB alone or in combination with cimetidine was 323 ± 149 and 312 ± 151 pg/mL, the T_{max} was 0.083 and 0.083 hours (median), the $AUC_{0\text{-}24h}$ was 434 ± 133 and 499 ± 109 pg·h/mL, the AUC_{inf} was 1000 ± 421 and 1390 ± 330 pg·h/mL, the $t_{1/2}$ was 45.3 ± 22.2 and 52.9 ± 19.9 hours, and the CL/F was 121 ± 67.6 and 75.4 ± 17.6 L/h, respectively. As for the geometric mean ratios of pharmacokinetic parameters (combination/alone) (90% CI), the C_{max} was 0.94 (0.82, 1.07), the AUC_{last} was 1.22 (1.12, 1.32), and the CLr was 0.77 (0.70, 0.85).

The applicant explained that the interaction potential of GB with other drugs is low based on the following reasons:

(1) *In vitro* studies suggested that tubular secretion by OCT2 and MATE1 contributed to the renal elimination of glycopyrronium, although the results from this study indicated that the inhibition of renal tubular secretion of glycopyrronium by concomitant drugs only resulted in a slight increase in glycopyrronium exposure levels; (2) *In vitro* studies revealed no inhibition or induction of metabolizing enzymes and transporters at the clinical dose of GB [see "3.(ii).A.(5) Drug interactions"]; and (3) A number of CYP isoforms are involved in the metabolism of glycopyrronium and considering that extrarenal elimination of glycopyrronium accounted

for about 40%[17] of the total clearance of systemically available glycopyrronium, the inhibition of glycopyrronium metabolism by concomitant drugs appeared to result only in a slight increase in glycopyrronium exposure. Therefore, the possibility is low for a drug-drug interaction to occur by concominant use of GB with other drugs.

4.(ii).A.(6) Pharmacodynamic study

4.(ii).A.(6).1) Effect on heart rates and QT intervals in foreign healthy adult subjects (5.3.1.1-1, Study A2108 [[redacted] 20[redacted] to [redacted] 20[redacted]])

In a randomized, crossover study in foreign healthy adult subjects (Part 1, 7 adult male subjects and 3 adult female subjects; Part 2, 16 adult males and 4 adult females), the heart rates and QT intervals following single intravenous administration of GB 120 μg or single inhalation of GB 200 μg were evaluated. The highest heart rate and mean heart rate for up to 24 hours post-dose decreased by 5.3 and 2.0 bpm, respectively, during the intravenous administration and increased by 1.7 bpm and decreased by 3.8 bpm, respectively, during the inhalation, as compared with intravenous administration of placebo; however, no clinically significant arrhythmia was reported for both routes of administration. From the above, the applicant explained that GB inhalation may result in a slight change in heart rates but it is not clinically significant.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Safety in patients with hepatic impairment

The applicant explained the pharmacokinetics in patients with impaired hepatic function as follows:

No clinical studies of patients with hepatic impairment have been conducted. Elimination routes other than renal excretion appear to account for about 40%[17] of the total clearance of systemically available glycopyrronium, and assuming that glycopyrronium is eliminated only by renal excretion due to hepatic impairment, the plasma exposure level of inhaled GB is calculated to be about 1.7-fold higher in patients with impaired hepatic function than in subjects with normal hepatic function. Since this increase is similar for an increase in exposure to glycopyrronium (1.69-fold) in patients with moderate renal impairment (eGFR, 30 mL/min/1.73 m^2) compared with subjects with normal renal function receiving inhaled GB, the exposure of glycopyrronium in patients with hepatic impairment is also less likely to exceed the exposure level that has been demonstrated to be safe in clinical studies. Therefore, no dose adjustment seems to be required for patients with hepatic impairment.

PMDA asked the applicant to compare safety information in subjects with hepatic impairment with that in other subject groups enrolled into clinical studies, and again explain the necessity of adjusting doses and promoting awareness among patients with impaired hepatic function.

The applicant explained as follows:

[17] Calculated from CL and CLr following intravenous administration of GB in foreign healthy adult subjects (42.5 and 26.0 L/h, respectively).

The pooled data from 2 phase III studies (Studies A2303 and A2304) (Core database) revealed that no clinically noteworthy baseline laboratory values related to hepatic function (total bilirubin, ≥ 34.2 μmol/L; ALP, γ-GTP, AST, and ALT, > 3 times the upper limit of the normal range) were reported in all subjects. To assess the safety of GB, subjects whose baseline laboratory values related to hepatic function (total bilirubin, ALP, γ-GTP, AST, and ALT) exceeded the upper limit of the normal range in at least one parameter were defined as having "impaired hepatic function" and other subjects who did not meet the above criteria were defined as having "no hepatic impairment." The number of adverse events per 100 person-years in the groups of subjects with impaired hepatic function and no hepatic impairment was 400.8 and 348.6 in the GB group, 363.1 and 390.5 in the Tio group, and 369.1 and 428.5 in the placebo group, respectively, and adverse events occurred frequently in the group of subjects with impaired hepatic function in the GB group. However, adverse events commonly reported in subjects with impaired hepatic function in the GB group (SOC) were "infections and infestations," "respiratory, thoracic and mediastinal disorders," "musculoskeletal and connective tissue disorders," and others, and these events are not related to those that may be caused by increased glycopyrronium exposure.

The applicant also explained as follows:
An adverse event of particular concern for GB that is caused by an increase in glycopyrronium exposure levels due to hepatic impairment is speculated to be an anticholinergic event. When "cardiac disorders," "gastrointestinal disorders," "eye disorders," and "renal and urinary disorders" in the SOC, including tachycardia, glaucoma and ocular hypertension, bladder obstruction and urinary retention, dry mouth, constipation and gastrointestinal hypomotility, all of which were considered typical anticholinergic adverse events, were evaluated, the number of adverse events per 100 person-years in the groups of subjects with impaired hepatic function and no hepatic impairment in the GB group was 14.5 and 9.7 for "cardiac disorders," 28.9 and 23.6 for "gastrointestinal disorders," 4.5 and 4.6 for "eye disorders," and 4.5 and 6.4 for "renal and urinary disorders", respectively. Although "cardiac disorders" and "gastrointestinal disorders" were reported frequently in the group of subjects with impaired hepatic function, the number of adverse events in the group of subjects with impaired hepatic function in the placebo and Tio group was 24.3 and 8.0, for "cardiac disorders" and 20.3 and 55.7, for "gastrointestinal disorders," respectively, indicating that no specific events occurred in the group of subjects with impaired hepatic function in the GB group. Therefore, the above results indicate that GB does not cause obvious safety concerns associated with increased exposure of glycopyrronium in patients with impaired hepatic function, and no dose adjustment is required, with no findings suggesting the necessity of promoting awareness.

PMDA concludes that based on the data available at this time, no dose adjustment is required for patients with hepatic impairment; however, PMDA also considers that due to the limited number of patients evaluated in clinical studies, careful continuous monitoring of patients with impaired hepatic function is required via post-marketing surveillance.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

As the evaluation data for efficacy and safety, the results from a phase II multi-regional study including Japanese patients with COPD (Study A2205 [5.3.5.1-4]), a phase III multi-regional study including Japanese patients with COPD (Study A2304 [5.3.5.1-2]), a phase III multi-regional study in foreign patients with COPD (Study A2303 [5.3.5.1-1]), and a Japanese long-term study in Japanese patients with COPD (Study A1302 [5.3.5.1-7]) were submitted. As the reference data, the results from studies, including a foreign phase II study in foreign patients with COPD (Study A2208 [5.3.5.1-6]) conducted according to FDA's directions, were submitted. [for the results of Study A2208, see "4.(iii).B.(1).2) Optimal dosage and administration"]

4.(iii).A.(1) Phase II multi-regional study (5.3.5.1-4, Study A2205 [July 2007 to December 2007])

A randomized, placebo-controlled, 4-period, incomplete block crossover study was conducted in Japan, Belgium, and France to evaluate the efficacy and safety of inhaled GB for 1 week in Japanese and foreign patients with COPD[18] (target sample size, 73 patients).

Patients were to receive double-blind inhaled GB 12.5, 25, 50, or 100 μg q.d. or placebo or open-label inhaled Tio 18 μg q.d. using a 4-period, 6-treatment crossover design. Each treatment was taken for 7 days with a 7 day washout between each period.

All 83 randomized patients received study drug and they were included in the safety analysis population and modified intention-to-treat (mITT) population; the mITT population was included in the efficacy analysis. Five patients discontinued the study (3 for adverse events and 2 for withdrawal of consent).

Of the 83 patients enrolled into the study, 25 were Japanese and all of them received study drug. Two patients discontinued the study (1 for an adverse event and 1 for withdrawal of consent).

The values of primary efficacy endpoint, trough forced expiratory volume in 1 second (FEV_1) (defined as the mean of the measurements taken at 23 hours and 15 minutes and 23 hours and 45 minutes post-dose)[19] on Day 7 of administration, was as shown in Table 6, and statistically significant differences were found between every dose group of GB and placebo ($P < 0.05$). Results of Japanese subpopulation were as shown in Table 7.

[18] Patients with moderate to severe COPD according to the GOLD Guidelines (2006) who satisfy the following criteria: (1) smoking history ≥ 10 pack-years; (2) post-bronchodilator FEV_1 ≥ 30% and < 80% of predicted normal values; (3) post-bronchodilator FEV_1/forced vital capacity (FVC) < 70%; and (4) ≥ 40 years of age.

[19] When FEV_1 was measured within 6 hours of treatment with rescue medication, the applicable measurement was handled as missing data. When either of the values measured at 23 hours and 15 minutes and 23 hours and 45 minutes post-dose in each treatment period was missing, the available value was used for trough FEV_1. When all of the values were missing, trough FEV_1 in the applicable treatment period was handled as missing data.

Table 6. Trough FEV_1 (L) on Day 7 (mITT population)

	Placebo	GB 12.5 μg	GB 25 μg	GB 50 μg	GB 100 μg	Tio 18 μg
N	49	55	51	53	53	55
Baseline in treatment period	1.267 ± 0.3576	1.225 ± 0.3955	1.274 ± 0.3560	1.271 ± 0.3684	1.213 ± 0.3923	1.263 ± 0.4142
Day 7	1.211 ± 0.3640	1.306 ± 0.4028	1.360 ± 0.3708	1.401 ± 0.3968	1.367 ± 0.3834	1.379 ± 0.4493
Least squaressquaress mean[a)]	1.243	1.317	1.333	1.374	1.385	1.370
Between-group difference (95% CI)[a)]		0.075 (0.023, 0.127)	0.090 (0.037, 0.143)	0.131 (0.078, 0.185)	0.142 (0.089, 0.195)	0.127 (0.085, 0.169)
P value[a, b)]	-	0.0020	0.0002	< 0.0001	< 0.0001	-

Mean ± SD

a) An analysis of variance (ANCOVA) model, where the results were adjusted on the basis of subjects, treatment period, treatment group, and baseline values at each treatment period

b) As for treatment contrasts (GB versus placebo), the multiplicity of tests was taken into account according to closed testing procedures based on the stepwise Dunnett method. The 95% CIs of between-group differences were calculated based on the single step Dunnett method.

Table 7. Trough FEV_1 (L) on Day 7 (Japanese subpopulation)

	Placebo	GB 12.5 μg	GB 25 μg	GB 50 μg	GB 100 μg	Tio 18 μg
N	15	18	13	16	16	15
Baseline in treatment period	1.211 ± 0.3761	1.018 ± 0.2306	1.093 ± 0.3821	1.054 ± 0.2449	1.065 ± 0.3456	1.063 ± 0.3924
Day 7	1.131 ± 0.3495	1.111 ± 0.2465	1.211 ± 0.3785	1.203 ± 0.2409	1.225 ± 0.2948	1.159 ± 0.4045
Least squaressquaress mean	1.078	1.160	1.190	1.212	1.200	1.205
Between-group difference (95% CI)		0.082 (0.016, 0.148)	0.113 (0.039, 0.186)	0.134 (0.063, 0.205)	0.123 (0.051, 0.194)	0.128 (0.073, 0.182)

Mean ± SD

An ANCOVA model, where the results were adjusted on the basis of subjects, treatment period, treatment group, and baseline values at each treatment period

The 95% CIs of between-group differences were calculated based on the single step Dunnett method.

Adverse events occurred in 20.0% (11 of 55 patients), 21.6% (11 of 51 patients), 20.8% (11 of 53 patients), 14.8% (8 of 54 patients), 12.7% (7 of 55 patients), and 13.0% (7 of 54 patients) of patients receiving GB 12.5 μg, GB 25 μg, GB 50 μg, GB 100 μg, placebo, and Tio, respectively. No deaths occurred. A serious adverse event was reported in 1 patient treated with GB 50 μg (gastric cancer), and its causal relationship to the study drug was denied. Pneumothorax experienced by 1 patient 14 days after the completion of the study was reported as a serious adverse event. Adverse events leading to treatment discontinuation occurred in 1 patient receiving GB 25 μg (chronic obstructive pulmonary disease), 1 receiving GB 50 μg (gastric cancer), and 1 receiving GB 100 μg (chronic obstructive pulmonary disease), and their causal relationship to the study drug was denied. Adverse events occurring in at least 2 patients treated with placebo, GB or Tio were headache (4 patients receiving GB 12.5 μg, 1 receiving GB 25 μg, 1 receiving GB 50 μg, 1 receiving GB 100 μg, and 2 receiving Tio), nasopharyngitis (2 patients receiving GB 12.5 μg, 2 receiving GB 25 μg, and 1 receiving placebo), cough (3 patients receiving GB 12.5 μg, 1 receiving GB 100 μg, and 2 receiving placebo), rhinitis (3 patients receiving GB 25 μg and 1 receiving placebo), and toothache (2 patients receiving GB 50 μg and 1 receiving Tio).

Adverse drug reactions occurred in 3.6% (2 of 55 patients), 2.0% (1 of 51 patients), 1.9% (1 of 53 patients), 0% (0 of 54 patients), 1.8% (1 of 55 patients), and 1.9% (1 of 54 patients) of patients receiving GB 12.5 μg, GB 25 μg, GB 50 μg, GB 100 μg, placebo, and Tio, respectively.

In the Japanese subpopulation, adverse events were reported in 27.8% (5 of 18 patients), 15.4% (2 of 13 patients), 25.0% (4 of 16 patients), 12.5% (2 of 16 patients), 11.8% (2 of 17 patients), and 13.3% (2 of 15

patients) of patients receiving GB 12.5 μg, GB 25 μg, GB 50 μg, GB 100 μg, placebo, and Tio, respectively. No deaths occurred. A serious adverse event was reported in 1 patient treated with GB 50 μg (gastric cancer), leading to treatment discontinuation, but its causal relationship to the study drug was denied. Pneumothorax experienced by 1 patient 14 days after the completion of the study was reported as a serious adverse event.

In the Japanese subpopulation, adverse drug reactions occurred in 11.1% (2 of 18 patients), 0% (0 of 13 patients), 0% (0 of 16 patients), 0% (0 of 16 patients), 5.9% (1 of 17 patients), and 6.7% (1 of 15 patients) of patients receiving GB 12.5 μg, GB 25 μg, GB 50 μg, GB 100 μg, placebo, and Tio, respectively.

Due to the fact that there were no significantly large differencein trough FEV_1 values for GB 50 μg and 100 μg dose groups, which both exceeded the predefined threshold for a minimal clinically important difference (MCID) (i.e., > 120 mL), that GB was well tolerated at all dose levels with a good overall safety profile, and that similar results were obtained for the Japanese subpopulation and overall population, the recommended dose of GB was determined to be 50 μg q.d., which was considered to be the minimal effective dose.

4.(iii).A.(2) Phase III multi-regional study (5.3.5.1-2, Study A2304 [October 2009 to December 2010])

A 26-week treatment, randomized, double-blind, placebo-controlled, parallel-group study was conducted in 13 countries including Japan to evaluate the efficacy and safety of inhaled GB in Japanese and foreign patients with COPD[20] (target sample size, 800 patients [535 in the GB group and 265 in the placebo group]).

Patients were to be randomized to receive inhaled GB 50 μg q.d. or placebo. The treatment period was 26 weeks.

Of all 822 allocated patients (552 in the GB group and 270 in the placebo group), 817 patients (550 in the GB group and 267 in the placebo group), were included in the safety analysis population. Excluded were 5 patients who received no study drug. Of the patients in the safety population, after excluding 23 participating in the study in one study center[21] where no data were considered reliable, 794 patients (534 in the GB group and 260 in the placebo group) were included in the full analysis set (FAS), and the FAS was used in the analysis of efficacy variables. Study discontinuations occurred in 18.5% (105 of 552 patients) of patients in the GB group and 21.5% (58 of 270 patients) of those in the placebo group; the main reasons for discontinuation included withdrawal of consent (6.9% [38 of 552 patients] in the GB group and 5.2% [14 of 270 patients] in the placebo group), adverse events (5.4% [30 of 552 patients] in the GB group and 5.9% [16 of 270 patients] in the placebo group), and administrative problems (3.8% [21 of 552 patients] in the GB group and 4.8% [13 of 270 patients] in the placebo group).

[20] Patients with moderate to severe COPD according to the GOLD Guidelines (2008) who satisfy the following criteria: (1) smoking history ≥ 10 pack-years; (2) post-bronchodilator FEV_1 ≥ 30% and < 80% of predicted normal values; (3) post-bronchodilator FEV_1/FVC < 70%; (4) ≥ 40 years of age; and (5) a total symptom score of 1 or more on at least 4 of the 7 days prior to study drug treatment.

[21] There was the potential for GCP noncompliance because inexplicable inconsistency in electrocardiogram recordings and unexpected uniformity in laboratory data were found in this study center; therefore, the applicant concluded that no data collected from the study center were reliable.

Of the 822 patients enrolled into the study, 96 (64 in the GB group and 32 in the placebo group) were Japanese and all of them received study drug. Study discontinuations occurred in 17.2% (11 of 64 patients) of patients in the GB group and 18.8% (6 of 32 patients) of those in the placebo group; the main reasons for discontinuation were adverse events (9.4% [6 of 64 patients] in the GB group and 9.4% [3 of 32 patients] in the placebo group) and withdrawal of consent (7.8% [5 of 64 patients] in the GB group and 9.4% [3 of 32 patients] in the placebo group).

The primary efficacy endpoint,[22] trough FEV_1 (defined as the mean of the measurements taken at 23 hours and 15 minutes and 23 hours and 45 minutes post-dose)[23] at Week 12, was as shown in Table 8, and statistically significant differences were found in pairwise comparison between the GB group and the placebo group, demonstrating the superiority of GB over placebo. Results of Japanese subpopulation were as shown in Table 9.

Table 8. Trough FEV_1 (L) at Week 12 (FAS, LOCF)

	Baseline	Week 12	Least squaressquaress mean[a)]	Between-group difference (95% CI)[a)]
Placebo group	1.261 ± 0.4567 (259)	1.270 ± 0.4779 (243)	1.301 (243)	
GB group	1.313 ± 0.4570 (534)	1.428 ± 0.4752 (514)	1.408 (512)	0.108 (0.0785, 0.1368) $P < 0.001$

Mean ± SD (N)
a) A mixed model, with treatment group, baseline smoking status (current/ex-smoker), baseline value, baseline ICS use, FEV_1 prior to use of short acting $beta_2$ agonists, and FEV_1 45 minutes after use of short acting $beta_2$ agonists as fixed effects and study center (nested within region) as a random effect.

Table 9. Trough FEV_1 (L) at Week 12 (Japanese subpopulation, LOCF)

	Baseline	Week 12	Least squaressquaress mean[a)]	Between-group difference (95% CI)[a)]
Placebo group	1.325 ± 0.4565 (32)	1.384 ± 0.5509 (30)	1.296 (30)	
GB group	1.253 ± 0.3965 (64)	1.365 ± 0.4751 (64)	1.404 (64)	0.108 (0.0158, 0.2011)

Mean ± SD (N)
a) A mixed model, with treatment group, baseline smoking status (current/ex-smoker), baseline value, baseline ICS use, FEV_1 prior to use of short acting $beta_2$ agonists, and FEV_1 45 minutes after use of short acting $beta_2$ agonists as fixed effects and study center (nested within region) as a random effect.

Adverse events occurred in 57.6% (317 of 550 patients) of patients in the GB group and 65.2% (174 of 267 patients) of those in the placebo group, and the major adverse events were as shown in Table 10. Deaths were reported in 2 patients in the GB group (lung neoplasm malignant in 1 patient and hepatic neoplasm malignant in 1 patient) and 3 patients in the placebo group (cardiac arrest in 1 patient, chronic obstructive pulmonary disease in 1 patient, and death in 1 patient), and their causal relationship to the study drug was denied. One patient died (suicide) during the 30-day follow-up period after discontinuation of study drug treatment due to

[22] The primary analysis was to conduct pairwise comparison between placebo group and the GB group. The primary endpoint (1) was "trough FEV_1," key secondary endpoints (2) were "total score of TDI" and "total score according to the SGRQ," and important secondary endpoints (3) were "time to first moderate or severe COPD exacerbation" and "daily rescue medication use (number of puffs)." A fixed sequence test procedure (if statistical significance is found for the first endpoint family of (1)to (3), the subsequent family will be tested in a sequential manner) was used for multiplicity adjustment, and the multiplicity of endpoints within the families (2) and (3) was handled using the Hochberg step up adjustment.

[23] When FEV_1 was measured within 6 hours of treatment with rescue medication or within 7 days of systemic corticosteroid use, the applicable measurement was handled as missing data. When either of the values measured at 23 hours and 15 minutes and 23 hours and 45 minutes post-dose was missing, the available value was used for trough FEV_1. When all of the values were missing, trough FEV_1 was handled as missing data. Missing trough FEV_1 values were imputed with their last observation on or after Day 15 (LOCF).

an adverse event (depression). Serious adverse events occurred in 7.5% (41 of 550 patients) of patients in the GB group and 9.0% (24 of 267 patients) of those in the placebo group, and a causal relationship to the study drug could not be denied in 3 patients in the GB group (chronic obstructive pulmonary disease/tracheobronchitis in 1 patient, atrial fibrillation in 1 patient, and respiratory failure in 1 patient). The most frequently reported adverse event was chronic obstructive pulmonary disease (1.6% [9 of 550 patients] in the GB group and 4.1% [11 of 267 patients] in the placebo group). Adverse events leading to treatment discontinuation were reported in 5.8% (32 of 550 patients) of patients in the GB group and 7.1% (19 of 267 patients) of those in the placebo group, and the most frequently reported adverse event was chronic obstructive pulmonary disease (1.8% [10 of 550 patients] in the GB group and 3.0% [8 of 267 patients] in the placebo group).

Adverse drug reactions occurred in 6.2% (34 of 550 patients) of patients in the GB group and 5.6% (15 of 267 patients) of those in the placebo group, and the most frequently reported adverse event was chronic obstructive pulmonary disease (1.5% [8 of 550 patients] in the GB group and 0.7% [2 of 267 patients] in the placebo group).

Table 10. Adverse events with an incidence of 2% or more in either of the treatment groups

	GB group (550 patients)	Placebo group (267 patients)
Diarrhoea	11 (2.0)	3 (1.1)
Pyrexia	17 (3.1)	13 (4.9)
Nasopharyngitis	28 (5.1)	21 (7.9)
Upper respiratory tract infection	23 (4.2)	20 (7.5)
Upper respiratory tract infection bacterial	17 (3.1)	12 (4.5)
Lower respiratory tract infection	8 (1.5)	7 (2.6)
Viral upper respiratory tract infection	4 (0.7)	8 (3.0)
Back pain	15 (2.7)	7 (2.6)
Headache	14 (2.5)	10 (3.7)
Chronic obstructive pulmonary disease	111 (20.2)	73 (27.3)
Cough	26 (4.7)	13 (4.9)
Dyspnoea	18 (3.3)	10 (3.7)
Hypertension	11 (2.0)	6 (2.2)

Number of patients (%)

In Japanese subpopulation, adverse events occurred in 56.3% (36 of 64 patients) of patients in the GB group and 78.1% (25 of 32 patients) of those in the placebo group, and the major adverse events were as shown in Table 11. Although no deaths occurred during the treatment period, one patient died (suicide) during the 30-day follow-up period after discontinuation of study drug treatment due to an adverse event (depression). Other serious adverse events occurred in 7.8% (5 of 64 patients) of patients in the GB group (pneumonia in 2 patients, cataract in 1 patient, colonic polyp in 1 patient, and chronic obstructive pulmonary disease in 1 patient) and 9.4% (3 of 32 patients) of those in the placebo group (diverticulum intestinal haemorrhagic in 1 patient, lung neoplasm malignant in 1 patient, and chronic obstructive pulmonary disease in 1 patient), and their causal relationship to the study drug was denied. Adverse events leading to treatment discontinuation were reported in 9.4% (6 of 64 patients) (chronic obstructive pulmonary disease in 3 patients, pneumonia in 1 patient, atrial fibrillation in 1 patient, and depression in 1 patient) of patients in the GB group and 9.4% (3 of 32 patients) of those in the placebo group (lung neoplasm malignant in 1 patient, diverticulum intestinal haemorrhagic in 1 patient, and hypertension in 1 patient).

In Japanese subpopulation, adverse drug reactions occurred in 6.3% (4 of 64 patients) of patients in the GB group (atrial fibrillation/hypertension in 1 patient, thirst in 1 patient, dermatitis contact in 1 patient, and rash in 1 patient) and 6.3% (2 of 32 patients) of those in the placebo group (non-cardiac chest pain/dysaesthesia in 1 patient and hypertension in 1 patient).

Table 11. Adverse events occurring in at least 2 patients in either of the treatment groups (Japanese subpopulation)

	GB group (64 patients)	Placebo group (32 patients)
Constipation	2 (3.1)	0
Diarrhoea	2 (3.1)	0
Enterocolitis	2 (3.1)	0
Nasopharyngitis	10 (15.6)	7 (21.9)
Bronchitis	5 (7.8)	2 (6.3)
Pneumonia	3 (4.7)	0
Upper respiratory tract infection	3 (4.7)	0
Upper respiratory tract infection bacterial	3 (4.7)	1 (3.1)
Cystitis	2 (3.1)	0
Back pain	2 (3.1)	1 (3.1)
Arthralgia	0	2 (6.3)
Headache	2 (3.1)	0
Insomnia	2 (3.1)	1 (3.1)
Chronic obstructive pulmonary disease	13 (20.3)	6 (18.8)
Haemoptysis	0	2 (6.3)
Rash	3 (4.7)	0
Hypertension	3 (4.7)	1 (3.1)

Number of patients (%)

4.(iii).A.(3) Foreign phase III study (5.3.5.1-1, Study A2303 [June 2009 to April 2011])

A 52-week treatment, randomized, parallel-group study with placebo or Tio as control was conducted to evaluate the efficacy and safety of inhaled GB in foreign patients with COPD[24] (target sample size, 1065 patients [535 in the GB group, 265 in the placebo group, and 265 in the Tio group]).

Patients were to be randomized to receive double-blind inhaled GB 50 μg q.d. or placebo or open-label inhaled Tio 18 μg q.d. The treatment period was 52 weeks.

Of all 1066 allocated patients (529 in the GB group, 269 in the placebo group, and 268 in the Tio group), after excluding 6 who received no study drug, 1060 patients (525 in the GB group, 268 in the placebo group, and 267 in the Tio group) were included in the safety analysis population and FAS, and the FAS was included in the efficacy analysis. Study discontinuations occurred in 22.3% (118 of 529 patients) of patients in the GB group, 28.3% (76 of 269 patients) of those in the placebo group, and 23.1% (62 of 268 patients) in the Tio group; the main reasons for discontinuation included withdrawal of consent (7.6% [40 of 529 patients] in the GB group, 8.6% [23 of 269 patients] in the placebo group, and 9.7% [26 of 268 patients] in the Tio group), adverse events (7.6% [40 of 529 patients] in the GB group, 10.8% [29 of 269 patients] in the placebo group, and 6.7% [18 of 268 patients] in the Tio group), and unsatisfactory therapeutic effect (3.8%

[24] Patients with moderate to severe COPD according to the GOLD Guidelines (2008) who satisfy the following criteria: (1) smoking history ≥ 10 pack-years; (2) post-bronchodilator FEV_1 ≥ 30% and < 80% of predicted normal values; (3) post-bronchodilator FEV_1/FVC < 70%; (4) ≥ 40 years of age; and (5) a total symptom score of 1 or more on at least 4 of the 7 days prior to study drug treatment.

[20 of 529 patients] in the GB group, 3.3% [9 of 269 patients] in the placebo group, and 2.2% [6 of 268 patients] in the Tio group).

The values of primary efficacy endpoint,[25] trough FEV_1 (defined as the mean of the measurements taken at 23 hours and 15 minutes and 23 hours and 45 minutes post-dose)[26] at Week 12, were as shown in Table 12, and statistically significant differences were found in the pairwise comparison between the GB group and the placebo group, demonstrating the superiority of GB over placebo.

Table 12. Trough FEV_1 (L) at Week 12 (FAS, LOCF)

	Baseline	Week 12	Least squares mean[a)]	Between-group difference (95% CI)[a)]	
				Treatment contrast (GB versus placebo)	Treatment contrast (GB versus Tio)
Placebo group	1.376 ± 0.4839 (267)	1.394 ± 0.5047 (246)	1.372 (245)		
GB group	1.340 ± 0.5019 (523)	1.460 ± 0.5158 (514)	1.469 (513)	0.097 (0.0646, 0.1302) $P < 0.001$	0.014 (−0.0185, 0.0464)
Tio group	1.324 ± 0.4986 (266)	1.426 ± 0.5039 (254)	1.455 (253)	0.083 (0.0456, 0.1214)	

Mean ± SD (N)

a) A mixed model, with treatment group, baseline smoking status (current/ex-smoker), baseline value, baseline ICS use, FEV_1 prior to use of short acting $beta_2$ agonists, and FEV_1 45 minutes after use of short acting $beta_2$ agonists as fixed effects and study center (nested within region) as a random effect.

Adverse events occurred in 76.6% (402 of 525 patients) of patients in the GB group, 76.5% (205 of 268 patients) of those in the placebo group, and 74.2% (198 of 267 patients) of those in the Tio group; the major adverse events were as shown in Table 13. Deaths were reported in 2 patients in the GB group (respiratory arrest in 1 patient and acute respiratory failure in 1 patient), 2 patients in the placebo group (cardiopulmonary failure in 1 patient and pneumonia in 1 patient), and 2 patients in the Tio group (respiratory failure in 1 patient and myocardial infarction in 1 patient); their causal relationship to the study drug was denied. One patient in the GB group died (pneumonia) within 30 days of discontinuation of study drug treatment, and one patient in the GB group died (lung cancer) at least 30 days after treatment discontinuation. Serious adverse events occurred in 12.4% (65 of 525 patients) of patients in the GB group, 16.0% (43 of 268 patients) of those in the placebo group, and 15.0% (40 of 267 patients) of those in the Tio group; a causal relationship to the study drug could not be denied in 6 patients in the GB group (transient ischaemic attack/mental disorder in 1 patient, acute coronary syndrome in 1 patient, transient ischaemic attack in 1 patient, atrial flutter in 1 patient, syncope in 1 patient, and angina pectoris in 1 patient) and 1 patient in the Tio group (chronic obstructive pulmonary disease/viral upper respiratory tract infection). The major adverse events included chronic obstructive pulmonary disease (3.6% [19 of 525 patients] in the GB group, 6.0% [16 of 268 patients] in the placebo group, and 4.9% [13 of 267 patients] in the Tio group) and pneumonia (1.3% [7 of 525

[25] The primary analysis was to conduct pairwise comparison between placebo group and the GB group. The primary endpoint (1) was "trough FEV1," key secondary endpoints (2) were "total score of TDI" and "total score according to the SGRQ," and important secondary endpoints (3) were "time to first moderate or severe COPD exacerbation" and "daily rescue medication use (number of puffs)." A fixed sequence test procedure (if statistical significance is found for the first endpoint family of (1)to (3), the subsequent family will be tested in a sequential manner) was used for multiplicity adjustment, and the multiplicity of endpoints within the families (2) and (3) was handled using the Hochberg step up adjustment.

[26] When FEV_1 was measured within 6 hours of treatment with rescue medication or within 7 days of systemic corticosteroid use, the applicable measurement was handled as missing data. When either of the values measured at 23 hours and 15 minutes and 23 hours and 45 minutes post-dose was missing, the available value was used for trough FEV_1. When all of the values were missing, trough FEV_1 was handled as missing data. Missing trough FEV_1 values were imputed with their last observation on or after Day 15 (LOCF).

patients] in the GB group, 2.6% [7 of 268 patients] in the placebo group, and 1.5% [4 of 267 patients] in the Tio group). Adverse events leading to treatment discontinuation occurred in 8.0% (42 of 525 patients) of patients in the GB group, 11.6% (32 of 268 patients) of those in the placebo group, and 7.5% (20 of 267 patients) of those in the Tio group; the major adverse events included chronic obstructive pulmonary disease (1.9% [10 of 525 patients] in the GB group, 4.9% [13 of 268 patients] in the placebo group, and 3.7% [10 of 267 patients] in the Tio group), pneumonia (1.0% [5 of 525 patients] in the GB group, 0.7% [2 of 268 patients] in the placebo group, and 0.7% [2 of 267 patients] in the Tio group), and dyspnea (0.2% [1 of 525 patients] in the GB group and 1.5% [4 of 268 patients] in the placebo group).

Adverse drug reactions occurred in 10.7% (56 of 525 patients) of patients in the GB group, 9.3% (25 of 268 patients) of those in the placebo group, and 8.2% (22 of 267 patients) of those in the Tio group; the major adverse events included dry mouth (2.5% [13 of 525 patients] in the GB group, 1.1% [3 of 268 patients] in the placebo group, and 1.5% [4 of 267 patients] in the Tio group), chronic obstructive pulmonary disease (1.0% [5 of 525 patients] in the GB group, 1.5% [4 of 268 patients] in the placebo group, and 1.1% [3 of 267 patients] in the Tio group), and cough (1.0% [5 of 525 patients] in the GB group and 0.4% [1 of 268 patients] in the placebo group).

Table 13. Adverse events with an incidence of 2% or more in any of the treatment groups

	GB group (525 patients)	Placebo group (268 patients)	Tio group (267 patients)
Dry mouth	16 (3.0)	5 (1.9)	4 (1.5)
Diarrhoea	10 (1.9)	6 (2.2)	5 (1.9)
Nausea	9 (1.7)	7 (2.6)	4 (1.5)
Gastrooesophageal reflux disease	4 (0.8)	6 (2.2)	3 (1.1)
Oedema peripheral	9 (1.7)	6 (2.2)	8(3.0)
Non-cardiac chest pain	5 (1.0)	2 (0.7)	7 (2.6)
Upper respiratory tract infection	57 (10.9)	33 (12.3)	30 (11.2)
Nasopharyngitis	47 (9.0)	15 (5.6)	21 (7.9)
Sinusitis	28 (5.3)	14 (5.2)	10 (3.7)
Upper respiratory tract infection bacterial	28 (5.3)	28 (10.4)	21 (7.9)
Lower respiratory tract infection	23 (4.4)	9 (3.4)	10 (3.7)
Bronchitis	22 (4.2)	10 (3.7)	12 (4.5)
Pneumonia	14 (2.7)	12 (4.5)	7 (2.6)
Urinary tract infection	14 (2.7)	8 (3.0)	16 (6.0)
Viral upper respiratory tract infection	9 (1.7)	13 (4.9)	11 (4.1)
Viral infection	1 (0.2)	7 (2.6)	4 (1.5)
Back pain	25 (4.8)	10 (3.7)	12 (4.5)
Arthralgia	10 (1.9)	7 (2.6)	7 (2.6)
Headache	25 (4.8)	14 (5.2)	12 (4.5)
Dizziness	9 (1.7)	7 (2.6)	5 (1.9)
Chronic obstructive pulmonary disease	191 (36.4)	116 (43.3)	90 (33.7)
Cough	21 (4.0)	13 (4.9)	12 (4.5)
Dyspnoea	14 (2.7)	13 (4.9)	6 (2.2)
Oropharyngeal pain	6 (1.1)	6 (2.2)	2 (0.7)
Rhinorrhoea	1 (0.2)	9 (3.4)	4 (1.5)
Hypertension	21 (4.0)	12 (4.5)	14 (5.2)
Angina pectoris	7 (1.3)	6 (2.2)	3 (1.1)

Number of patients (%)

4.(iii).A.(4) Long-term treatment study (5.3.5.1-7, Study A1302 [May 2010 to November 2011])

A 52-week, randomized, open-label, parallel-group study with Tio as an active comparator, was conducted to evaluate the efficacy and safety of inhaled GB in Japanese patients with COPD[27] (target sample size, 160 patients [120 in the GB group and 40 in the Tio group]).

Patients were to receive inhaled GB 50 μg q.d. or Tio 18 μg. The treatment period was 52 weeks.

All 163 allocated patients (123 in the GB group and 40 in the Tio group) received study drug and they were included in the safety analysis population and intention-to-treat (mITT) population; the ITT population was included in the efficacy analysis. Study discontinuations occurred in 15.4% (19 of 123 patients) of patients in the GB group and 17.5% (7 of 40 patients) in the Tio group. The main reasons for discontinuation were adverse events (8.9% [11 of 123 patients] in the GB group and 12.5% [5 of 40 patients] in the Tio group).

The values of efficacy endpoint, trough FEV_1 (defined as the mean of the measurements taken at 45 and 15 minutes pre-dose)[28] profile, was as shown in Table 14.

Table 14. Trough FEV_1 (L) profile (ITT population)

		Baseline	Week 12	Week 24	Week 52
GB group		1.304 ± 0.4808 (122)	1.410 ± 0.4593 (110)	1.394 ± 0.4529 (110)	1.371 ± 0.4625 (103)
	Change from baseline	-	0.101 ± 0.1455	0.094 ± 0.1614	0.068 ± 0.1829
Tio group		1.334 ± 0.4208 (40)	1.525 ± 0.4523 (37)	1.496 ± 0.4561 (37)	1.447 ± 0.5364 (33)
	Change from baseline	-	0.173 ± 0.1976	0.144 ± 0.1435	0.127 ± 0.2566

Mean ± SD (N)

Adverse events occurred in 82.9% (102 of 123 patients) of patients in the GB group and 82.5% (33 of 40 patients) of those in the Tio group, and the major adverse events were as shown in Table 15. No deaths were reported during the study. One patient in the GB group died (brain tumour) after discontinuation of study drug treatment, but its causal relationship to the study drug was denied. Other serious adverse events occurred in 13.0% (16 of 123 patients) of patients in the GB group and 15.0% (6 of 40 patients) of those in the Tio group. As for gastric cancer and loss of consciousness reported in the GB group, their causal relationship to the study drug could not be denied, but loss of consciousness resolved before the completion of the study. The serious adverse events occurring in at least 2 patients in either of the treatment groups were chronic obstructive pulmonary disease (2 patients in the GB group) and pneumonia (2 patients in the Tio group). Adverse events leading to treatment discontinuation occurred in 8.9% (11 of 123 patients) of patients in the GB group and 12.5% (5 of 40 patients) of those in the Tio group.

[27] Patients with moderate to severe COPD according to the GOLD Guidelines (2008) who satisfy the following criteria: (1) smoking history ≥ 10 pack-years; (2) post-bronchodilator FEV_1 ≥ 30% and < 80% of predicted normal values; (3) post-bronchodilator FEV_1/FVC < 70%; and (4) ≥ 40 years of age.

[28] The mean of the measurements taken at 45 minutes and 15 minutes pre-dose was defined as "pre-dose FEV_1" in the protocol , but as "trough FEV_1" in this review report. When FEV_1 was measured within 6 hours of treatment with rescue medication or within 7 days of systemic corticosteroid use, the applicable measurement were handled as missing data. When either of the values measured at 45 and 15 minutes pre-dose at each time point was missing, the available value was used for trough FEV_1. When all of the values were missing, trough FEV_1 was handled as missing data.

Adverse drug reactions occurred in 11.4% (14 of 123 patients) of patients in the GB group and 5.0% (2 of 40 patients) of those in the Tio group, and the adverse drug reactions occurring in at least 2 patients in either of the treatment groups were constipation (2 patients in the GB group), dry mouth (2 patients in the GB group and 1 patient in the Tio group), dysphonia (2 patients in the GB group), dysuria (2 patients in the GB group) and gamma-glutamyltransferase increased (2 patients in the GB group).

Table 15. Adverse events with an incidence of 2% or more in the GB group

	GB group (123 patients)	Tio group (40 patients)
Constipation	6 (4.9)	3 (7.5)
Gastrooesophageal reflux disease	5 (4.1)	0
Gastritis atrophic	3 (2.4)	1 (2.5)
Nasopharyngitis	38 (30.9)	13 (32.5)
Bronchitis	6 (4.9)	5 (12.5)
Pharyngitis	6 (4.9)	1 (2.5)
Upper respiratory tract infection	6 (4.9)	3 (7.5)
Upper respiratory tract infection bacterial	6 (4.9)	2 (5.0)
Gastroenteritis	3 (2.4)	1 (2.5)
Lower respiratory tract infection	3 (2.4)	2 (5.0)
Contusion	3 (2.4)	2 (5.0)
Gamma-glutamyltransferase increased	3 (2.4)	0
Diabetes mellitus	4 (3.3)	0
Back pain	6 (4.9)	1 (2.5)
Insomnia	3 (2.4)	1 (2.5)
Dysuria	3 (2.4)	0
Chronic obstructive pulmonary disease	30 (24.4)	13 (32.5)
Dysphonia	6 (4.9)	2 (5.0)
Sputum retention	4 (3.3)	0
Upper respiratory tract inflammation	4 (3.3)	1 (2.5)
Eczema	3 (2.4)	0
Hypertension	7 (5.7)	5 (12.5)

Number of patients (%)

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Efficacy and dosage and administration

4.(iii).B.(1).1) Justification of efficacy evaluation

The applicant explained that it was appropriate to participate in a multiregional confirmatory study (Study A2304) for the following reasons:

There was no great difference in extrinsic ethnic factors, such as disease concept, stage classification, and therapeutic strategies for COPD, between Japan and foreign countries and the results of Study 2104 evaluating the pharmacokinetics of GB in healthy adult subjects showed that the plasma exposure level of glycopyrronium was higher in Japanese subjects than in foreign subjects, while a similar dose-response relationship was observed for both Japanese subpopulation and overall population in a multiregional, dose-finding study (Study A2205) with no serious safety concerns identified.

With respect to patient demographics for Japanese subpopulation in Study A2304, PMDA asked the applicant to explain the potential influence of factors showing disparate trends compared with those for overall population on efficacy evaluations.

The applicant explained that the demographic factors for Japanese subpopulation had no effect on efficacy evaluations based on the following reasons:

The patient demographics for Japanese subpopulation were mainly characterized by a large number of elderly subjects aged 65 years or older (49.6% in overall population versus 76.0% in Japanese subpopulation), low body weight (72.2 kg in overall population versus 60.1 kg in Japanese subpopulation), low body mass index (BMI) (patients with BMI of $\leq$30.0 kg/m^2, 79.2% in overall population versus 96.9% in Japanese subpopulation), a small number of patients with severe or very severe COPD (39.2% in overall population versus 26.0% in Japanese subpopulation), a short duration of COPD (median) (4.54 years in overall population versus 1.96 years in Japanese subpopulation), a high amount of smoking (44.8 packs-years in overall population versus 53.2 packs-years in Japanese subpopulation), a small percentage of patients ICS usage at baseline (53.5% in overall population versus 19.8% in Japanese subpopulation), a small percentage of patients who used a short acting $beta_2$ agonist (SABA) as a prior therapy for COPD (32.4% in overall population versus 10.4% in Japanese subpopulation), a small percentage of patients who used an ICS/LABA (28.4% in overall population versus 8.3% in Japanese subpopulation), and a large percentage of patients who used a LAMA (29.9% in overall population versus 43.8% in Japanese subpopulation). Results of subgroup analysis of these demographic factors were as shown in Table 16. In all subgroups in overall population, a change from baseline in trough FEV_1 at Week 12 was greater consistently in the GB group than in the placebo group, and despite only limited interpretation of the results was possible due to the small sample size of subgroups, the Japanese subpopulation showed similar tendency as the overall population.

Table 16. Change from baseline in trough FEV_1 (L) at Week 12 (Study A2304, FAS)

Demographic factors		Treatment group	Overall population		Japanese subpopulation	
			N	Change	N	Change
Age	< 65 years	GB group	257	0.105 ± 0.2448	14	0.223 ± 0.2776
		Placebo group	125	−0.015 ± 0.2017	9	0.155 ± 0.3266
	≥ 65 years to < 75 years	GB group	188	0.104 ± 0.1815	37	0.081 ± 0.1741
		Placebo group	88	0.010 ± 0.1672	13	−0.017 ± 0.1524
	≥ 75 years	GB group	69	0.109 ± 0.1637	13	0.075 ± 0.1034
		Placebo group	30	0.003 ± 0.1365	8	0.018 ± 0.1210
Body weight	< 60 kg	GB group	139	0.102 ± 0.1831	33	0.083 ± 0.1133
		Placebo group	67	0.005 ± 0.1558	13	−0.007 ± 0.1500
	≥ 60 kg	GB group	375	0.106 ± 0.2236	31	0.141 ± 0.2570
		Placebo group	176	−0.006 ± 0.1919	17	0.083 ± 0.2587
BMI	< 22 kg/m^2	GB group	146	0.094 ± 0.1926	32	0.063 ± 0.1016
		Placebo group	68	0.015 ± 0.1458	15	0.019 ± 0.1680
	≥ 22 kg/m^2	GB group	368	0.109 ± 0.2209	32	0.159 ± 0.2528
		Placebo group	175	−0.011 ± 0.1947	15	0.069 ± 0.2653
Severity of COPD	Mild or moderate	GB group	319	0.107 ± 0.2197	42	0.099 ± 0.2171
		Placebo group	154	−0.010 ± 0.1997	27	0.041 ± 0.2303
	Severe or very severe	GB group	195	0.102 ± 0.2027	22	0.135 ± 0.1537
		Placebo group	89	0.009 ± 0.1481	3	0.073 ± 0.0937
Duration of COPD	≤ 5 years	GB group	292	0.099 ± 0.2157	53	0.122 ± 0.2117
		Placebo group	136	−0.001 ± 0.1863	21	0.040 ± 0.2483
	> 5 years	GB group	222	0.113 ± 0.2100	11	0.061 ± 0.0905
		Placebo group	107	−0.006 ± 0.1782	9	0.054 ± 0.1438
Pack-years	< 50 pack years	GB group	340	0.103 ± 0.2280	33	0.120 ± 0.2281
		Placebo group	155	0.001 ± 0.1905	13	0.083 ± 0.2862
	≥ 50 pack years	GB group	174	0.108 ± 0.1813	31	0.102 ± 0.1610
		Placebo group	88	-0.011 ± 0.1679	17	0.015 ± 0.1547
ICS use	Yes	GB group	241	0.104 ± 0.2202	47	0.122 ± 0.2033
		Placebo group	122	0.005 ± 0.1833	28	0.049 ± 0.2269
	No	GB group	273	0.106 ± 0.2072	17	0.081 ± 0.1812
		Placebo group	121	−0.012 ± 0.1818	2	−0.020 ± 0.0276
Prior therapy	SABA	GB group	175	0.099 ± 0.2342	6	−0.015 ± 0.1815
		Placebo group	76	0.001 ± 0.1784	4	0.044 ± 0.2500
	ICS/LABA	GB group	152	0.101 ± 0.2072	7	0.105 ± 0.0661
		Placebo group	63	−0.030 ± 0.1735	1	−0.040
	LAMA	GB group	152	0.096 ± 0.1865	24	0.102 ± 0.1498
		Placebo group	77	−0.003 ± 0.1614	17	0.007 ± 0.1552
	Others	GB group	161	0.102 ± 0.2271	28	0.079 ± 0.1724
		Placebo group	74	−0.009 ± 0.1762	11	0.008 ± 0.1813
	No	GB group	129	0.116 ± 0.1943	22	0.162 ± 0.2483
		Placebo group	70	0.016 ± 0.2061	10	0.122 ± 0.3195

Mean ± SD

Although the plasma exposure levels of glycopyrronium in Japanese subjects tended to be higher in Study A2104 compared with those in foreign subjects, this difference seemed to be attributed to a difference in body weight (see "4.(ii).A *Summary of the submitted data"*), and a similar dose-response relationship was observed for both Japanese subpopulation and overall population in Study A2205. Thus, PMDA concluded that the efficacy of GB can be evaluated in Japanese patients with COPD on the basis of the results from the multiregional study (Study A2304). The examination of patient background factors which were different between Japanese subpopulation and overall population in Study A2304 revealed that a change from baseline in trough FEV_1 was larger in the GB group than in the placebo group in the overall population and that a similar tendency was also seen in the Japanese subpopulation. Therefore, these observations do not suggest an intrinsic difference between Japanese subpopulation and overall population, and PMDA concluded that consistent efficacy is observed for both Japanese subpopulation and overall population, and the efficacy of GB in Japanese patients with COPD is demonstrated. Furthermore, PMDA also concluded that because consistent data outcomes were available from Study A2304 with regard to Japanese subpopulation and overall population, results from a foreign phase III study (Study A2303) conducted using a design similar to that of Study A2304 can possibly be used for reference.

4.(iii).B.(1).2) Optimal dosage and administration

According to FDA's directions, an additional clinical study was conducted to further evaluate the optimal dosage and administration of GB. PMDA asked the applicant to explain the background and appropriateness of the proposed dosage regiment of GB 50 μg q.d., based on the results of the additional study.

The applicant explained as follows:

When a randomized, double-blind, placebo-controlled, parallel-group study was conducted by Arakis for explatory investigation of the efficacy and safety of inhaled GB (the preparation and inhaler used were different from those used in the applicant's studies) (Kuna P et al. *Eur Respir J.* 2007;30[Suppl.51]:2135), changes in trough FEV_1 on Days 14 and 28 from that measured on Day 7 after GB inhalation were similar and therefore, each treatment period was set to 7 days in a dose-finding Study A2205. Following q.d. administration of GB 12.5, 25, 50, and 100 μg, a difference from placebo in trough FEV_1 on Day 7, the primary endpoint in Study 2205, was 0.075, 0.090, 0.131, and 0.142 L, respectively, and 50 μg q.d. was considered an optimal dose. However, FDA pointed out that GB [redacted]. In response to this comment, Novartis Pharma explained that an ineffective dose was 12.5 μg q.d., a minimum effective dose that had not proven to be sufficiently effective was 25 μg q.d., and an optimal dosage and administration was 50 μg q.d. exceeding the predefined threshold (a difference from placebo in trough FEV_1 > 0.120 L). However, FDA pointed out that [redacted]. Then, as an additional dose-finding study, a 28-week treatment, Study A2208 was conducted to examine the dosage and administration including b.i.d. dosing, and the following results were obtained.

Study A2208 was a randomized, double-blind, placebo-controlled, 2-period, incomplete block crossover study of 388 patients with moderate and severe COPD; patients were randomized to receive GB 12.5, 25, 50, and 100 μg q.d. or GB 12.5, 25, and 50 μg b.i.d. for 28 days. The primary efficacy endpoint, trough FEV_1 (mean of the measurements taken at 23 hours 15 minutes and 23 hours 45 minutes post-dose)[29] on Day 28, were as shown in Table 17, and the trough FEV_1 for a daily dose of GB 25, 50, and 100 μg was higher in a b.i.d. regimen than in a q.d. regimen. Following GB 12.5 μg q.d. and GB 25 μg q.d., the difference from placebo in trough FEV_1 was smaller than the minimal clinical relevant difference of 0.100 L (Donohue JF. *COPD.* 2005;2:111-124), but it exceeded 0.100 L at all other dose levels. Trough FEV_1 on Day 28 by treatment period was as shown in Table 18.

[29] When either of the values measured at 23 hours 15 minutes and 23 hours 45 minutes post-dose was missing, the available value was used for trough FEV_1. When all of the values were missing, trough FEV_1 at the applicable time point was handled as missing data.

Table 17. Trough FEV_1 (L) on Day 28 (Study A2208, FAS)

	GB 12.5 μg q.d.	GB 25 μg q.d.	GB 50 μg q.d.	GB 100 μg q.d.
N	81	88	88	90
Baseline in treatment period	1.282 ± 0.454	1.327 ± 0.471	1.286 ± 0.389	1.279 ± 0.512
Day 28	1.319 ± 0.505	1.368 ± 0.436	1.340 ± 0.400	1.410 ± 0.522
Change from baseline	0.037 ± 0.202	0.041 ± 0.223	0.054 ± 0.183	0.131 ± 0.176
Difference from placebo* (90% CI)*	0.051 (0.032, 0.081)	0.079 (0.054, 0.108)	0.109 (0.083, 0.135)	0.137 (0.111, 0.160)
	Placebo	GB 12.5 μg b.i.d.	GB 25 μg b.i.d.	GB 50 μg b.i.d.
N	82	90	87	81
Baseline in treatment period	1.337 ± 0.489	1.269 ± 0.456	1.264 ± 0.508	1.366 ± 0.463
Day 28	1.268 ± 0.483	1.354 ± 0.484	1.384 ± 0.472	1.493 ± 0.449
Change from baseline	−0.069 ± 0.207	0.085 ± 0.189	0.120 ± 0.216	0.127 ± 0.227
Difference from placebo* (90% CI)*	-	0.115 (0.082, 0.142)	0.141 (0.112, 0.163)	0.160 (0.135, 0.181)

Mean ± SD

*: Calculated by using model-averaged methods.[30] The explanatory variables include baseline FEV_1 at each treatment period, FEV_1 before and 45 minutes after ipratropium treatment 14 days before GB treatment at each treatment period, smoking status (current/ex-smoker), baseline ICS use, and treatment period as fixed effects. Random effects were determined to consider between-patient variability regarding effect, differences due to treatment period regarding effect, and differences due to treatment period regarding Emax.

Table 18. Trough FEV_1 (L) on Day 28 by treatment period (Study A2208, FAS)

	Treatment period	GB 12.5 μg q.d.	GB 25 μg q.d.	GB 50 μg q.d.	GB 100 μg q.d.
N	Period 1 Period 2	42 39	43 45	47 41	43 47
Baseline in treatment period	Period 1 Period 2	1.304 ± 0.478 1.258 ± 0.431	1.253 ± 0.497 1.398 ± 0.439	1.323 ± 0.398 1.244 ± 0.378	1.327 ± 0.576 1.235 ± 0.446
Day 28	Period 1 Period 2	1.330 ± 0.551 1.307 ± 0.456	1.315 ± 0.420 1.419 ± 0.449	1.358 ± 0.381 1.318 ± 0.425	1.471 ± 0.586 1.354 ± 0.453
Change from baseline	Period 1 Period 2	0.025 ± 0.218 0.049 ± 0.185	0.062 ± 0.258 0.020 ± 0.185	0.036 ± 0.162 0.075 ± 0.205	0.144 ± 0.185 0.119 ± 0.169
	Treatment period	Placebo	GB 12.5 μg b.i.d.	GB 25 μg b.i.d.	GB 50 μg b.i.d.
N	Period 1 Period 2	44 38	48 42	45 42	43 38
Baseline in treatment period	Period 1 Period 2	1.255 ± 0.412 1.431 ± 0.555	1.188 ± 0.436 1.363 ± 0.465	1.173 ± 0.400 1.362 ± 0.592	1.456 ± 0.453 1.264 ± 0.458
Day 28	Period 1 Period 2	1.218 ± 0.408 1.326 ± 0.558	1.301 ± 0.466 1.415 ± 0.503	1.329 ± 0.419 1.444 ± 0.522	1.608 ± 0.460 1.362 ± 0.403
Change from baseline	Period 1 Period 2	−0.037 ± 0.217 −0.106 ± 0.192	0.113 ± 0.171 0.052 ± 0.204	0.156 ± 0.197 0.082 ± 0.232	0.152 ± 0.266 0.098 ± 0.172

Mean ± SD

To evaluate the efficacy of q.d. and b.i.d. regimens as a daily dose of GB, diurnal changes in FEV_1 on Day 28 by daily dose were compared. As shown in Figure 2, the FEV_1 measured at a daily dose of GB 25 and 50 μg was higher in a q.d. regimen than in a b.i.d. regimen for up to 11 hours and 55 minutes post-dose, and it was higher in a b.i.d. regimen after 14 hours post-dose. Covariate-adjusted least squares means of diurnal changes in FEV_1 on Day 28 were as shown in Figure 3.

[30] Estimated by using a weighted-average for a difference from placebo estimated from 8 candidate models (a nonlinear mixed-effects model consisting of 4 different Emax types and 4 different sigmoid Emax types; the method of modeling post-treatment period effects differs among these models) based on time-course data on trough FEV_1 on Days 1, 7, 14, and 28. A bootstrap method was used to calculate the CIs.

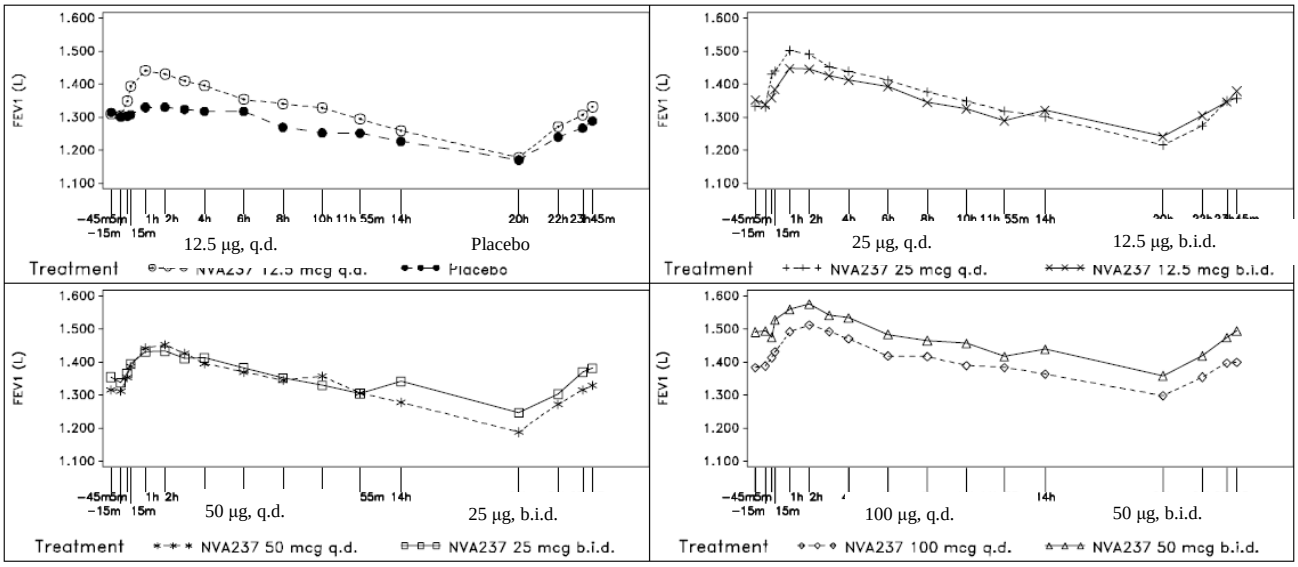


Figure 2. Diurnal changes in FEV_1 on Day 28 by daily dose (Study A2208, FAS)

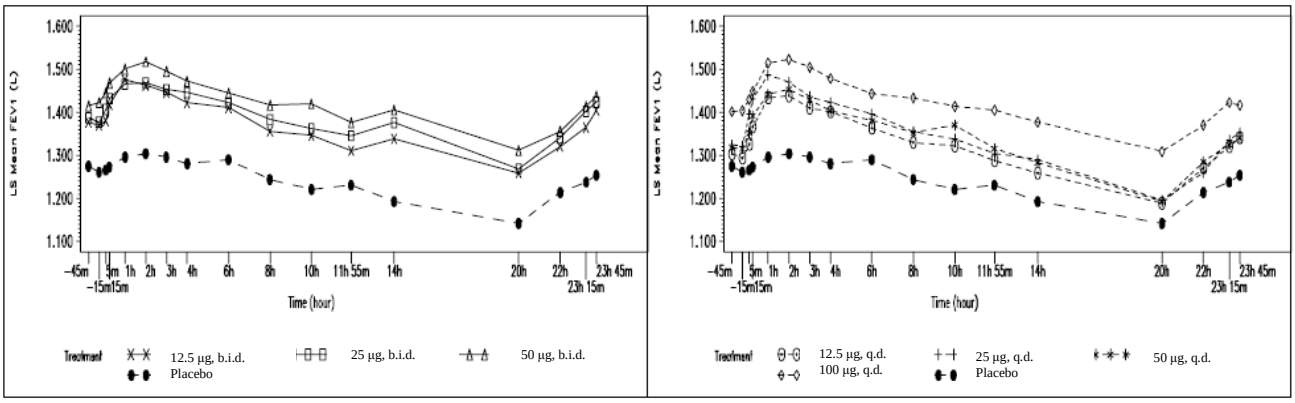


Figure 3. Covariate-adjusted least squares means of diurnal changes in FEV_1 on Day 28 (Study A2208, FAS)

Model-averaged differences from placebo in FEV_1 $AUC_{0\text{-}24h}$, FEV_1 $AUC_{0\text{-}12h}$, and FEV_1 $AUC_{12\text{-}24h}$ on Day 28 were as shown in Tables 19, 20, and 21. The FEV_1 $AUC_{0\text{-}24h}$ (L) measured at a daily dose of GB 25, 50, and 100 µg were similar for q.d. and b.i.d. regimens, while the FEV_1 $AUC_{0\text{-}12h}$ measured at a daily dose of 25, 50, and 100 µg tended to be higher in a q.d. regimen and the FEV_1 $AUC_{12\text{-}24h}$ tended to be higher in a b.i.d. regimen.

Table 19. Model-averaged differences from placebo in FEV_1 $AUC_{0\text{-}24h}$ (L) on Day 28 (Study A2208, FAS)

Treatment	Estimate (90% CI)	Treatment	Estimate (90% CI)
GB 12.5 μg q.d.	0.058 (0.039,0.079)		
GB 25 μg q.d.	0.089 (0.066, 0.113)	GB 12.5 μg b.i.d.	0.098 (0.071, 0.122)
GB 50 μg q.d.	0.123 (0.099, 0.145)	GB 25 μg b.i.d.	0.131 (0.106, 0.152)
GB 100 μg q.d.	0.152 (0.131, 0.171)	GB 50 μg b.i.d.	0.158 (0.138, 0.176)

Calculated by using model-averaged methods (see the footnote 30).

Table 20. Model-averaged differences from placebo in FEV_1 $AUC_{0\text{-}12h}$ (L) on Day 28 (Study A2208, FAS)

Treatment	Estimate (90% CI)	Treatment	Estimate (90% CI)
GB 12.5 μg q.d.	0.085 (0.061, 0.111)		
GB 25 μg q.d.	0.121 (0.094, 0.146)	GB 12.5 μg b.i.d.	0.104 (0.078, 0.130)
GB 50 μg q.d.	0.152 (0.128, 0.174)	GB 25 μg b.i.d.	0.139 (0.113, 0.162)
GB 100 μg q.d.	0.176 (0.155, 0.195)	GB 50 μg b.i.d.	0.166 (0.144, 0.186)

Calculated by using model-averaged methods (see the footnote 30).

Table 21. Model-averaged differences from placebo in FEV_1 $AUC_{12\text{-}24h}$ (L) on Day 28 (Study A2208, FAS)

Treatment	Estimate (90% CI)	Treatment	Estimate (90% CI)
GB 12.5 μg q.d.	0.051 (0.033, 0.080)		
GB 25 μg q.d.	0.079 (0.056, 0.108)	GB 12.5 μg b.i.d.	0.112 (0.080, 0.139)
GB 50 μg q.d.	0.111 (0.086, 0.137)	GB 25 μg b.i.d.	0.141 (0.112, 0.163)
GB 100 μg q.d.	0.141 (0.116, 0.163)	GB 50 μg b.i.d.	0.163 (0.138, 0.184)

Calculated by using model-averaged methods (see the footnote 30).

The examination of model-averaged FEV_1 $AUC_{0\text{-}4h}$ and FEV_1 $AUC_{0\text{-}8h}$ on Day 28 revealed that the differences between GB 50 μg q.d. and placebo were 0.165 and 0.156 L, respectively, and the differences between GB 25 μg b.i.d. and placebo were 0.153 and 0.145 L, respectively; the differences from placebo were larger in a 50 μg q.d. regimen compared with a 25 μg b.i.d. regimen for both parameters, indicating a tendency similar to that observed for FEV_1 $AUC_{0\text{-}12h}$.

In Study A2208, the b.i.d. dosing showed greater improvement in trough FEV_1 than the q.d. dosing for the same daily doses, although there was no clinically relevant difference in FEV_1 $AUC_{0\text{-}24h}$, an indicator of bronchodilatory effect over 24 hours post-dose, between the q.d. dosing and b.i.d. dosing for the same daily doses. The q.d. dosing showed greater improvement in FEV_1 $AUC_{0\text{-}12h}$, an indicator of daytime bronchodilatory effect, than the b.i.d. dosing; an improvement in respiratory function in the daytime compared to night is speculated to be more important to COPD patients, because they develop symptoms interfering with daily activities immediately after waking up (Partridge et al. *Thorax*. 2008;63[Suppl 7]:A74). The b.i.d. dosing did not offer any safety advantage over the q.d. dosing. In clinical practice, q.d. dosing appears to improve the patient's adherence to treatment regimens compared with b.i.d. dosing (Toy et al. *Respir Med.* 2011;105:435-441), and improved adherence is reported to significantly reduce the number of hospitalization associated with exacerbation of COPD (Vestbo et al. *Thorax.* 2009;64:939-943). Therefore, the q.d. dosing regimen is suggested to offer great benefits and the GB q.d. dosing seems to be more useful in clinical practice than the b.i.d. dosing.

As the q.d. dosing regimen, 50 μg is considered an optimal dose because it showed clinically relevant consistent improvement in trough FEV_1 and well-tolerated in both Study A2205 and Study A2208.

From the above findings, also taking in account of the results of Study A2208, 50 μg q.d. dosing is optimal dosage regimen and the justification of the optimal regimen has been confirmed by efficacy established in phase III studies (Studies A2303 and A2304).

Although the results of trough FEV_1 in Study A2208 suggested that 12.5 μg b.i.d. dosing or 25 μg b.i.d. dosing could possibly be the minimal effective dose of GB, PMDA considers that since the values of parameters such as FEV_1 $AUC_{0\text{-}24h}$ and FEV_1 $AUC_{0\text{-}12h}$ are lower in 12.5 μg b.i.d. dosing compared with other dosage regimens, and sufficient clinical efficacy may not be achieved with this dosing. On the other hand, when 25 μg b.i.d. and 50 μg q.d. dosing regimens were compared, differences from placebo in trough FEV_1 were 0.141 and 0.109 L, respectively, which was greater for 25 μg b.i.d. dosing. However, there was no great difference in diurnal changes in FEV_1 for up to 11 hours and 55 minutes post-dose between the 50 μg q.d. dosing and 25 μg b.i.d. dosing. As for trough FEV_1, the multiregional study (A2304) has indicated the superiority of GB 50 μg q.d. dosing over placebo and the efficacy of GB 50 μg q.d., as a drug used for long-term maintenance treatment of COPD, has been demonstrated. The 50 μg q.d. dosing regimen has posed no serious safety concerns [see "4.(iii).B.(2) Safety"] and it is understandable that q.d. dosing is convenient because GB treatment is assumed to be administeredfor a long period of time. Thus, it is considered acceptable to choose GB 50 μg q.d. as the recommended clinical dose, to Japanese patients with COPD.

The conclusion as to the justification of dosage and administration will be finalized, taking account of deliberations by the Expert Discussion.

4.(iii).B.(1).3) Clinical positioning

PMDA asked the applicant to discuss the fact that, although GB is a LAMA as well as an existing drug Tio and a difference from placebo in trough FEV_1 was similar for GB (0.097 L) and Tio (0.083 L) in Study A2303, the changes from baseline in trough FEV_1 in a Japanese long-term study (Study A1302) tended to be smaller in the GB group than in the Tio group. PMDA also asked the applicant to explain the positioning of GB versus Tio.

The applicant explained as follows:

Changes from baseline in trough FEV_1 (mean ± SD) at Weeks 12, 24, and 52 in Study A1302 were 0.101 ± 0.1455 L (110 patients), 0.094 ± 0.1614 L (110 patients), and 0.068 ± 0.1829 L (103 patients) in the GB group and 0.173 ± 0.1976 L (37 patients), 0.144 ± 0.1435 L (37 patients), and 0.127 ± 0.2566 L (33 patients) in the Tio group, respectively. Changes from baseline in trough FEV_1 (mean ± SD) at Weeks 12, 24, and 52 in Study A2303 were 0.114 ± 0.2406 L (514 patients), 0.119 ± 0.2425 L (452 patients), and 0.074 ± 0.2475 L (416 patients) in the GB group and 0.104 ± 0.2189 L (254 patients), 0.072 ± 0.2708 L (234 patients), and

0.056 ± 0.2590 L (211 patients) in the Tio group, respectively. In Study A1302, the changes from baseline in trough FEV_1 in the Tio group were larger than those reported in the results of Study A2303 and published literature (a package insert of Spiriva Inhalation Capsules 18 μg [8th version]; Moita J et al. *Pulm Pharmacol Ther*. 2008;21:146-151; and Johansson G et al. *Prim Care Respir J*. 2008;17:169-175) (0.074 to 0.12 L).

The applicant added the following explanations:

(1) While the proportions of subjects with severe COPD were similar for the treatment groups (35.6% in the GB group and 35.2% in the Tio group) in Study A2303, the GB group had a higher proportion of subjects with severe COPD (45.5% in the GB group and 30.0% in the Tio group) in Study A1302; and for Study 1302, the results of subgroup analysis by severity of COPD were as shown in Table 22, and the changes from baseline in trough FEV_1 in the GB group tended to be larger in the subgroup of subjects with severe or very severe COPD compared with that of those with mild or moderate COPD; and (2) the percentage of subjects who used LAMAs as prior therapy for COPD was higher in Study A1302 (63.4% in the GB group and 80.0% in the Tio group) than in Study A2303 (25.5% in the GB group and 34.5% in the Tio group), with a higher proportion of LAMA use in the Tio group in both studies, but the changes from baseline in trough FEV_1 in Study A1302 were equal to or greater than those in Study A2303 and the impact of different prior therapies on the data are considered to be small. Therefore, the differences in patient background factors, such as COPD severity, and prior therapies for COPD do not contribute to the tendency to induce lesser changes from baseline in trough FEV_1 in the GB group compared to the Tio group in Study A1302. The major factor affecting the tendency would be a small number of subjects in the Tio group (40 subjects) in Study A1302, and the fact that no central evaluation of spirometry data was conducted in Study A1302 would also have contributed to it.

Table 22. Change from baseline in trough FEV_1 (L) by COPD severity (Study A1302, ITT population)

	GB group			Tio group		
	Week 12	Week 24	Week 52	Week 12	Week 24	Week 52
Mild or moderate	0.069 ± 0.1384 (58)	0.064 ± 0.1733 (58)	0.038 ± 0.2017 (55)	0.158 ± 0.1883 (25)	0.154 ± 0.1545 (25)	0.160 ± 0.3008 (21)
Severe or very severe	0.136 ± 0.1465 (52)	0.128 ± 0.1410 (52)	0.102 ± 0.1538 (48)	0.206 ± 0.2208 (12)	0.123 ± 0.1209 (12)	0.070 ± 0.1467 (12)

Mean ± SD (N)

Then, the applicant explained as follows:

In Study A2303, differences from placebo in trough FEV_1 were 0.097 L in the GB group and 0.083 L in the Tio group, indicating that bronchodilatory effects were similar for the GB group and Tio group. FEV_1 measured immediately after treatment (5 to 30 minutes post-dose) was as shown in Table 23. On the first day of treatment, there were statistically significant differences in FEV_1 at 5 to 30 minutes post-dose between the GB group and the Tio group, and the FEV_1 measured immediately after treatment was also higher in the GB group than in the Tio group at Weeks 12 to 52, where the bronchodilatory effect reached a steady state. Therefore, GB exhibits an immediate bronchodilatory effect 5 minutes after dosing to reduce the burden on patients immediately after waking up, and is expected to improve treatment adherence compared with existing drugs.

Table 23. Differences in FEV_1 measured immediately after treatment between the GB group and Tio group (L) (Study A2303, FAS)

		Least squares mean (95% CI)	*P* value
Day 1	5 minutes post-dose	0.041 (0.0254, 0.0572)	< 0.001
	15 minutes post-dose	0.065 (0.0472, 0.0820)	< 0.001
	30 minutes post-dose	0.056 (0.0319, 0.0809)	< 0.001
Week 12	5 minutes post-dose	0.025 (−0.0082, 0.0581)	0.140
	15 minutes post-dose	0.026 (−0.0073, 0.0601)	0.125
	30 minutes post-dose	0.031 (−0.0023 ± 0.0644)	0.068
Week 26	5 minutes post-dose	0.050 (0.0138, 0.0862)	0.007
	15 minutes post-dose	0.046 (0.0086, 0.0834)	0.016
	30 minutes post-dose	0.062 (0.0254, 0.0992)	< 0.001
Week 52	5 minutes post-dose	0.016 (−0.0227, 0.0555)	0.410
	15 minutes post-dose	0.020 (−0.0205, 0.0596)	0.339
	30 minutes post-dose	0.020 (−0.0202, 0.0605)	0.328

A mixed model, with treatment group, baseline smoking status (current/ex-smoker), baseline value, baseline ICS use, FEV_1 prior to use of short acting $beta_2$ agonists, and FEV_1 45 minutes after use of short acting $beta_2$ agonists as fixed effects and study center (nested within region) as a random effect.

PMDA considers as follows:

In Japanese Study A1302, changes from baseline in trough FEV_1 in the GB group were smaller than those in the Tio group. Although the cause is not clear, the Tio group has a small number of patients and it cannot be clearly concluded that GB is inferior in efficacy to Tio in Japanese patients with COPD. In addition to that, foreign Study A2303 has demonstrated that GB and Tio have similar efficacy, and consistent results were obtained from Study A2304 in the overall and Japanese populations. Based on the above, it is inferred that potency is also similar for GB and Tio in Japanese and foreign subjects. Thus, no great difference in efficacy is considered to exist between GB and Tio in Japanese patients with COPD. The results of Study A2303 revealed greater improvement in the FEV_1 measured immediately after treatment in the GB group compared to the Tio group on the first day of treatment, but the usefulness of GB versus Tio has not been demonstrated in long-term treatment, in which a steady state for bronchodilatory effects seems to be reached, and in the light of the long-term use of GB for the maintenance of COPD, the positioning of GB also does not differ greatly from that of Tio.

4.(iii).B.(2) Safety

Based on the 6-month population database in the pooled data from two phase III studies (Studies A2303 and A2304) (Core database), the applicant explained adverse events by preferred term (PT): cardio- and cerebro-vascular events, and anticholinergic adverse events (glaucoma and ocular hypertension; bladder obstruction and urinary retention; anticholinergic syndrome; dry mouth; and constipation and gastrointestinal hypomotility) as follows:

In the Core 6-month population, adverse events occurred in 59.81% (643 of 1075 patients) in the GB group, 65.17% (174 of 267 patients) in the Tio group, and 66.73% (357 of 535 patients) in the placebo group. Adverse events with an incidence of 2% or more in any of the treatment groups were as shown in Table 24. The most frequently reported adverse event was chronic obstructive pulmonary disease in all groups, and in the GB group, that was followed by upper respiratory tract infection, nasopharyngitis, and cough.

Table 24. Adverse events with an incidence of 2% or more in any of the treatment groups (Core 6-month population)

	GB group (1075 patients)	Tio group (267 patients)	Placebo group (535 patients)
Chronic obstructive pulmonary disease	241 (22.42)	74 (27.72)	162 (30.28)
Upper respiratory tract infection	64 (5.95)	19 (7.12)	43 (8.04)
Nasopharyngitis	57 (5.30)	16 (5.99)	31 (5.79)
Cough	40 (3.72)	11 (4.12)	24 (4.49)
Upper respiratory tract infection bacterial	38 (3.53)	14 (5.24)	31 (5.79)
Headache	35 (3.26)	7 (2.62)	20 (3.74)
Back pain	32 (2.98)	8 (3.00)	15 (2.80)
Dyspnoea	29 (2.70)	3 (1.12)	23 (4.30)
Dry mouth	24 (2.23)	4 (1.50)	6 (1.12)
Sinusitis	24 (2.23)	5 (1.87)	13 (2.43)
Hypertension	23 (2.14)	11 (4.12)	13 (2.43)
Lower respiratory tract infection	23 (2.14)	9 (3.37)	14 (2.62)
Pyrexia	20 (1.86)	1 (0.37)	15 (2.80)
Bronchitis	19 (1.77)	9 (3.37)	11 (2.06)
Urinary tract infection	19 (1.77)	10 (3.75)	10 (1.87)
Pneumonia	11 (1.02)	5 (1.87)	11 (2.06)
Viral upper respiratory tract infection	11 (1.02)	8 (3.00)	15 (2.80)
Non-cardiac chest pain	7 (0.65)	6 (2.25)	4 (0.75)

Number of patients (%)

The incidence of adverse events related to cardio- and cerebro-vascular (CCV) events[31] was 4.09% (44 of 1075 patients) in the GB group, 4.49% (12 of 267 patients) in the Tio group, and 3.74% (20 of 535 patients) in the placebo group, and that of serious adverse events was 1.40% (15 of 1075 patients), 0.75% (2 of 267 patients), and 1.87% (10 of 535 patients). The incidence was similar among the three groups, but serious atrial fibrillation was reported only in 4 patients in the GB group. When reassessment of the atrial fibrillation and atrial flutter was performed by an independent cardiologist in a blinded manner after the completion of the study, the number of subjects who had no history of atrial fibrillation or atrial flutter with a new clinically significant ECG finding of atrial fibrillation or atrial flutter was similar for the three groups; however, clinically significant atrial fibrillation or atrial flutter recurred more frequently among GB-treated subjects with a history of atrial fibrillation/atrial flutter than in subjects on Tio or placebo (Table 25).

Table 25. Percentages of subjects with a diagnosis of atrial fibrillation or atrial flutter by medical history (Core 6-month population)

History of atrial fibrillation or atrial flutter	Clinical significance	GB group (1075 subjects)	Tio group (267 subjects)	Placebo group (535 subjects)
No history	Insignificant	4/1044 (0.4)	2/259 (0.8)	0/521 (0.0)
	Significant	3/1044 (0.3)	2/259 (0.8)	1/521 (0.2)
	Total	7/1044 (0.7)	4/259 (1.5)	1/521 (0.2)
With history	Insignificant	14/31 (45.2)	5/8 (62.5)	10/14 (71.4)
	Significant	5/31 (16.1)	0/8 (0.0)	0/14 (0.0)
	Total	19/31 (61.3)	5/8 (62.5)	10/14 (71.4)

Number of subjects (%)

Adverse events related to a major adverse cardiovascular event (MACE)[32] occurred in 0.37% (4 of 1075 patients) in the GB group, 0.75% (2 of 267 patients) in the Tio group, and 0.37% (2 of 535 patients) in the placebo group, and the incidence was similar among the three groups.

[31] Standardized MedDRA query (SMQ) narrow scopes for “myocardial infarction,” “other ischaemic heart diseases,” “cardiac failure” and “cerebrovascular disorder” and an SMQ broad scope for “arrhythmia (including bradyarrhythmia and tachyarrhythmia).”

[32] Events related to cardiovascular death, in addition to an MACE defined by FDA.

Tachycardia-related adverse events[33] occurred in the 0.93% (10 of 1075 patients) in the GB group, 2.25% (6 of 267 patients) in the Tio group, and 0.75% (4 of 535 patients) in the placebo group, and the incidence was higher in the Tio group than in the GB group and placebo group.

The incidence of adverse events related to QTc interval prolongation[34] was 0.09% (1 of 1075 patients) in the GB group, 0.75% (2 of 267 patients) in the Tio group, and 0.37% (2 of 535 patients) in the placebo group, and the incidence was similar among the three groups.

Adverse events related to glaucoma and ocular hypertension[35] occurred only in 0.19% (2 of 1075 patients) of patients in the GB group.

The incidence of adverse events related to bladder obstruction and urinary retention[36] was 1.12% (12 of 1075 patients) in the GB group, 1.12% (3 of 267 patients) in the Tio group, and 0.75% (4 of 535 patients) in the placebo group, and the incidence was similar among the three groups.

The incidence of adverse events related to anticholinergic syndrome[37] was 6.23% (67 of 1075 patients) in the GB group, 4.49% (12 of 267 patients) in the Tio group, and 5.79% (31 of 535 patients) in the placebo group; the incidence was similar for the GB group and placebo group, while that was higher compared with the Tio group.

The incidence of adverse events related to dry mouth[38] was 2.42% (26 of 1075 patients) in the GB group, 1.50% (4 of 267 patients) in the Tio group, and 1.12% (6 of 535 patients) in the placebo group, and the incidence was similar for the GB group and Tio group, while that was higher compared with the placebo group.

The incidence of adverse events related to constipation and gastrointestinal hypomotility[39] was 1.21% (13 of 1075 patients) in the GB group, 0.75% (2 of 267 patients) in the Tio group, and 2.43% (13 of 535 patients) in the placebo group, and the incidence was lower in the GB group and Tio group than in the placebo group.

4.(iii).B.(2).1) CCV event

PMDA asked for the applicant's view on the risk of serious CCV events and deaths caused by GB.

The applicant explained that GB has a low risk of serious CCV events and deaths and shows no difference from placebo for the following reasons:

[33] An SMQ narrow scope for "tachyarrhythmia (including supraventricular tachyarrhythmia and ventricular tachyarrhythmia)."
[34] An SMQ broad scope for "Torsade de pointes/electrocardiogram QT prolonged."
[35] An SMQ narrow scope for "glaucoma."
[36] HLT "Bladder and urethral symptoms"
[37] An SMQ broad scope for "anticholinergic syndrome."
[38] HLT "Oral dryness and saliva altered"
[39] HLT "Gastrointestinal atonic and hypomotility disorders NEC"

The incidence of adverse events related to MACEs in Core 6- and 12-month populations was as shown in Table 26, and there was no difference between the GB group and placebo group for both populations. The odds ratio (GB group/placebo group) (95% CI) was 0.96 (0.17, 5.54) in the Core 6-month population and 0.51 (0.03, 8.18) in the Core 12-month population. The number of adverse events related to MACEs per 100 person-years in the Major database (pooled data from Studies A2303, A2304, A2205, A2207, A2208, and A2310) was slightly lower in the GB group and placebo group than in the Tio group (Table 27).

Table 26. Incidence of adverse events related to MACEs and odds ratio (Core 6- and 12-month populations)

	Core 6-month population			Core 12-month population		
	GB group (1075 patients)	Tio group (267 patients)	Placebo group (535 patients)	GB group (525 patients)	Tio group (267 patients)	Placebo group (268 patients)
Number of patients with adverse events (%)	4 (0.37)	2 (0.75)	2 (0.37)	1 (0.19)	3 (1.12)	1 (0.37)
Odds ratio (versus the placebo group) (95% CI)*	0.96 (0.17, 5.54) *P* = 0.9883	2.02 (0.18, 22.36) *P* = 0.5608		0.51 (0.03, 8.18) *P* = 0.6278	3.03 (0.31, 29.36) *P* = 0.3141	

*: Mantel-Haenszel test stratified by study

Table 27. Number of adverse events related to MACEs adjusted for total duration of exposure (Major database)

	GB group (1353 patients)	Tio group (267 patients)	Placebo group (816 patients)
Number of patients with adverse events	6	3	2
Number of adverse events	6	3	2
Total duration of exposure (person-years)	711.7	230.8	347.4
Number of adverse events per 100 person-years	0.8	1.3	0.6
Cerebrovascular accident	0.3	0.4	0.0
Myocardial infarction	0.3	0.4	0.3
Acute myocardial infarction	0.1	0.0	0.3
Sudden death	0.1	0.0	0.0
Haemorrhagic stroke	0.0	0.4	0.0

The applicant also explained that GB does not increase the risk of CCV adverse events even in patients at risk of CCV events for the following reasons:

Incidences of CCV adverse events by the number of risk factors[40] in Core 6- and 12-month populations were as shown in Table 28. The incidence of CCV adverse events was similar for the GB group and placebo group in patients with a history of CCV events. Although the incidence of CCV adverse events tended to increase as the number of CCV risk factors rose, the incidence was similar for the GB group and placebo group in the subgroup of CCV risk factors ≥ 3, and the GB group showed no tendency to a higher incidence of serious CCV adverse events compared with the placebo group.

[40] CCV risk factors were (1) CCV history, (2) hypertension, (3) hyperlipidemia, (4) diabetes mellitus, (5) BMI of > 30 kg/m^2, (6) 65 years or older, and (7) smoking.

Table 28. CCV adverse events by number of risk factors (Core 6- and 12-month populations)

	Core 6-month population			Core 12-month population		
	GB group (1075 patients)	Tio group (267 patients)	Placebo group (535 patients)	GB group (525 patients)	Tio group (267 patients)	Placebo group (268 patients)
CCV history	18/201 (8.96)	4/68 (5.88)	10/117 (8.55)	16/106 (15.09)	5/68 (7.35)	12/69 (17.39)
No CCV risk factors	0/93	0/12	1/40 (2.50)	0/26	0/12	0/10
One CCV risk factor	2/262 (0.76)	2/64 (3.13)	1/122 (0.82)	4/119 (3.36)	4/64 (6.25)	1/58 (1.72)
Two CCV risk factors	14/299 (4.68)	6/72 (8.33)	2/144 (1.39)	11/148 (7.43)	8/72 (11.11)	5/68 (7.35)
Three or more CCV risk factors	28/421 (6.65)	4/119 (3.36)	16/229 (6.99)	25/232 (10.78)	7/119 (5.88)	16/132 (12.12)

Number of patients (%)

PMDA also asked the applicant to discuss the fact that clinically significant atrial fibrillation or atrial flutter reccurred frequently in the GB group.

The applicant explained as follows:

On the subjects who were reassessed as having atrial fibrillation or atrial flutter of clinical significance, the percentage of having or not having history of atrial fibrillation or atrial flutter were as shown in Table 29. The number of subjects with a history of atrial fibrillation or atrial flutter in the whole Core population was 31 in the GB group, 8 in the Tio group, and 14 in the placebo group. Despite a limited interpretation of the results obtained from a small number of subjects in all groups, the GB group had a higher proportion of subjects with a history of atrial fibrillation or atrial flutter compared with the Tio and placebo groups. Recurrence of clinically significant atrial fibrillation occurred in 5 subjects with a history of atrial fibrillation or atrial flutter in the GB group, and all of them had past history of hypertension or tachycardia. Of the 5 subjects, 2 appeared to have had a high risk of recurrence particularly on the basis of the medical history and circumstances at the time of occurrence (history of mitral valve repair and tricuspid valve repair and recurrence after excessive alcohol consumption).

Table 29. Percentages of subjects with a diagnosis of clinically significant atrial fibrillation or atrial flutter by medical history (Core 6- and 12-month populations)

History of atrial fibrillation or atrial flutter	Database	GB group (1075 subjects)	Tio group (267 subjects)	Placebo group (535 subjects)
No history	6 months	2/1044 (0.19)	2/259 (0.77)	0/521
	12 months	2/510 (0.39)	2/259 (0.77)	1/261 (0.38)
	Total	3/1044 (0.29)	2/259 (0.77)	1/521 (0.19)
With history	6 months	3/31 (9.68)	0/8	0/14
	12 months	3/15 (20.00)	0/8	0/7
	Total	5/31 (16.13)	0/8	0/14

Number of patients (%)

Taking account of the above, the applicant explained that treatment with GB does not cause atrial fibrillation or atrial flutter based on the following reasons:

Patients with a history of atrial arrhythmia had been expected to have high recurrence rates and a small number of patients experienced a new onset of atrial fibrillation or atrial flutter after GB treatment. The incidence ratio of atrial fibrillation or atrial flutter in Core populations was as shown in Table 30, and the incidence was similar for the GB group, placebo group, and Tio group. An oral formulation of GB marketed overseas (indicated for the treatment of peptic ulcers and others; the glycopyrronium exposure at a dose approved in foreign countries is 16-fold higher than that observed following inhalation of GB 50 μg) has not been reported to increase the risk of atrial fibrillation or atrial flutter. The comparison of plasma

glycopyrronium concentrations among patients with and without atrial fibrillation or atrial flutter revealed no association to plasma glycopyrronium concentration.

Table 30. Incidence ratio for atrial fibrillation or atrial flutter (Core populations)

	Incidence (event/person-year)		Incidence ratio (95% CI)	*P* value
GB group	0.037 (26/696.52)	GB/placebo	1.00 (0.491, 2.024)	0.994
Placebo group	0.033 (11/332.41)	Tio/placebo	1.16 (0.462, 2.933)	0.746
Tio group	0.039 (9/230.83)	GB/Tio	0.86 (0.374, 1.959)	0.714

PMDA considers as follows:

In clinical studies, although recurrence of clinically significant atrial fibrillation or atrial flutter was reported only in the GB group, the number of patients was small, and there was no increased risk of atrial fibrillation or atrial flutter following GB treatment in the group of subjects with no history of atrial fibrillation or atrial flutter. In addition, an oral formulation of GB, which exhibits higher systemic exposure compared to an inhalant, also carries no risk of atrial fibrillation or atrial flutter. From these findings, there will be no clear association between GB and occurrence of atrial fibrillation or atrial flutter and the submitted clinical data is not of a great concern for the risk of CCV adverse events caused by GB. On the other hand, inhalation of anticholinergic drugs is reported to increase the risk of deaths due to cardiovascular events as a result of meta-analysis of existing drugs (Singh S et al. *JAMA.* 2008;300:1439-1450; and Singh S et al. *BMJ.* 2011;342.d3215[online]), and the data available at this time indicate that there is no great difference in a tendency for GB and Tio to develop CCV events. Therefore, it is necessary to collect sufficient information on GB, including domestic and international post-marketing safety information, and continuously examine the tendency of developing CCV events with care. Moreover, as with the package insert of Tio, it is appropriate to include “patients with cardiac failure, atrial fibrillation, or extrasystole or those with a history of any of these symptoms” in the section of “Careful Administration,” and “atrial fibrillation” in the section of “Clinically significant adverse reactions” to promote awareness of cardiovascular risks.

4.(iii).B.(2).2) Effects of age, body weight, and renal clearance

The applicant explained the effect of age on the safety of GB as follows:

Incidences of adverse events by age group (< 65 years, 65 to < 75 years, ≥ 75 years; < 65 years and ≥ 65 years for CCV adverse events) calculated based on the data from the Core 6-month population were as shown in Table 31. In the GB group, age groups were not associated with differences in incidence for all adverse events, and although the incidence of serious adverse events tended to be higher in the subgroup of older patients, it was lower compared with the placebo group. The incidence of CCV adverse events was higher in the subgroup of patients aged 65 years or older in the GB group. There was no tendency to a higher incidence of adverse events related to anticholinergic syndrome in the subgroup of older patients.

Table 31. Incidences of adverse events by age (Core 6-month population)

	Age category (years)	GB group (1075 patients)	Tio group (267 patients)	Placebo group (535 patients)
Adverse events	< 65	329/555 (59.28)	99/144 (68.75)	185/273 (67.77)
	65 to < 75	236/388 (60.82)	58/97 (59.79)	121/195 (62.05)
	≥ 75	78/132 (59.09)	17/26 (65.38)	51/67 (76.12)
Serious adverse events	< 65	35/555 (6.31)	12/144 (8.33)	28/273 (10.26)
	65 to < 75	29/388 (7.47)	7/97 (7.22)	15/195 (7.69)
	≥ 75	11/132 (8.33)	6/26 (23.08)	10/67 (14.93)
CCV adverse events	< 65	15/555 (2.70)	7/144 (4.86)	10/273 (3.66)
	≥ 65	29/520 (5.58)	5/123 (4.07)	10/262 (3.82)
Adverse events related to anticholinergic syndrome	< 65	40/555 (7.21)	4/144 (2.78)	16/273 (5.86)
	65 to < 75	17/388 (4.38)	6/97 (6.19)	12/195 (6.15)
	≥ 75	10/132 (7.58)	2/26 (7.69)	3/67 (4.48)

Number of patients (%)

PMDA asked the applicant to explain the potential influence of body weight and renal clearance, both of which are suggested to affect the systemic exposure of glycopyrronium, on the safety of GB.

The applicant explained as follows:

Incidences of adverse events by body weight (< 50 kg, 50 to < 75 kg, ≥ 75 kg) calculated based on the data from the Core 6-month population were as shown in Table 32. None of serious adverse events, CCV adverse events, and adverse events related to anticholinergic syndrome occurred frequently in the subgroup of patients with a body weight of <50 kg. All adverse events occurred frequently in the subgroup of patients with a body weight of <50 kg in the GB group, but similar results were also obtained for the placebo group. In the Core 6- and 12-month populations, the incidence of adverse events such as bronchitis, lower respiratory tract infection, and constipation was high in the subgroup of patients with a body weight of <50 kg in the GB group. However, the results from Study A1302, a Japanese long-term study of Japanese subjects, demonstrated that the incidence of these events did not tend to be high in the subgroup of patients with a body weight of <50 kg in the GB group. Therefore, the safety of GB in low-weight patients (< 50 kg) does not show difference in the trends observed with other body weight categories.

Table 32. Incidences of adverse events by body weight (Core 6-month population)

	Body weight category (kg)	GB group (1075 patients)	Tio group (267 patients)	Placebo group (535 patients)
Adverse events	< 50	54/84 (64.29)	4/5 (80.00)	32/40 (80.00)
	50 to < 75	279/468 (59.62)	85/123 (69.11)	156/253 (61.66)
	≥ 75	310/523 (59.27)	85/139 (61.15)	169/242 (69.83)
Serious adverse events	< 50	9/84 (10.71)	0/5 (0.00)	9/40 (22.50)
	50 to < 75	20/468 (4.27)	13/123 (10.57)	22/253 (8.70)
	≥ 75	46/523 (8.80)	12/139 (8.63)	22/242 (9.09)
CCV adverse events	< 50	3/84 (3.57)	0/5 (0.00)	1/40 (2.50)
	50 to < 75	16/468 (3.42)	5/123 (4.07)	9/253 (3.56)
	≥ 75	25/523 (4.78)	7/139 (5.04)	10/242 (4.13)
Adverse events related to anticholinergic syndrome	< 50	6/84 (7.14)	1/5 (20.00)	6/40 (15.00)
	50 to < 75	36/468 (7.69)	4/123 (3.25)	12/253 (4.74)
	≥ 75	25/523 (4.78)	7/139 (5.04)	13/242 (5.37)

Number of patients (%)

The applicant also explained as follows:

Incidences of adverse events by renal impairment (eGFR of ≥ 60 mL/min/1.73 m^2, mild renal impairment; eGFR of < 60 mL/min/1.73 m^2, moderate or severe renal impairment) calculated based on the data from the Core 6-month population were as shown in Table 33. The incidence of adverse events and serious adverse events was higher in the subgroup of patients with moderate or severe renal impairment than in that of those

with mild renal impairment, although a similar tendency was noted for the Tio group and placebo group. Diarrhoea (1.14% [11 of 968 patients] in patients with mild renal impairment versus 4.67% [5 of 107 patients] in those with moderate or severe renal impairment) and arthralgia (0.62% [6 of 968 patients] versus 3.74% [4 of 107 patients], respectively), both of which were reported more frequently in the subgroup of patients with moderate or severe renal impairment in the GB group, were not unique to GB treatment. With respect to adverse events related to anticholinergic syndrome, the incidence of dry mouth was higher in the subgroup of patients with moderate or severe renal impairment in the GB group (1.96% [19 of 968 patients] in patients with mild renal impairment versus 4.67% [5 of 107 patients] in those with moderate or severe renal impairment) compared with the placebo group (1.05% [5 of 477 patients] versus 1.72% [1 of 58 patients]). However, in consideration of a small number of patients included in the subgroup for moderate or severe renal impairment, the difference is slight and renal clearance seems to have a small impact on the safety of GB. Similarly, renal clearance also had a limited effect on the safety of GB in the Core 12-month population and in Study A1302.

Table 33. Incidences of adverse events by renal function (Core 6-month population)

	eGFR ≥ 60 mL/min/1.73 m^2			eGFR < 60 mL/min/1.73 m^2		
	GB group (968 patients)	Tio group (246 patients)	Placebo group (477 patients)	GB group (107 patients)	Tio group (21 patients)	Placebo group (58 patients)
Adverse events	563 (58.16)	158 (64.23)	309 (64.78)	80 (74.77)	16 (76.19)	48 (82.76)
Serious adverse events	64 (6.61)	20 (8.13)	46 (9.64)	11 (10.28)	5 (23.81)	7 (12.07)
CCV adverse events	39 (4.03)	12 (4.88)	17 (3.56)	5 (4.67)	0	3 (5.17)
Adverse events related to anticholinergic syndrome	56 (5.79)	12 (4.88)	26 (5.45)	11 (10.28)	0	5 (8.62)

Number of patients (%)

PMDA considers that the safety of GB in elderly subjects (particularly, low-weight patients and those with reduced renal clearance) needs to be further investigated via post-marketing surveillance for the following reasons:

GB will be used primarily by the elderly and a relatively large number of elderly patients are speculated to have a low body weight. Physiological functions such as renal clearance generally decline with age as well, and the possibility of renal impairment affecting the systemic exposure of glycopyrronium cannot be ruled out.

4.(iii).B.(3) Post-marketing surveillance, etc.

The applicant plans to conduct post-marketing surveillance to investigate the safety and efficacy of long-term GB use under usage conditions after marketing.

Based on the discussion in "4.(iii).B.(2) Safety," PMDA considers that post-marketing surveillance needs to be conducted to evaluate the safety of GB in an elderly population that was not evaluated with large sample size in clinical studies. Adverse events such as CCV events and anticholinergic adverse events, in association with demographic factors (including age, body weight, and renal clearance) should be evaluated as well.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspection and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted data.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-2, 5.3.5.1-3, and 5.3.5.1-4). As a result, non-compliance with procedures for study drug management (supply of a wrong study drug and its administration to a subject), protocol deviations (enrollment of subjects who met the exclusion criteria, etc.), and inconsistencies between the source document and the CRF (an adverse event and a concomitant drug were undocumented) were found at some study sites. In addition, part of the above protocol deviations and inconsistencies between the source document and the CRF were not properly monitored by the sponsor. Despite the above issues to be resolved, PMDA concluded that the clinical studies were conducted on the whole in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted data.

IV. Overall Evaluation

Based on the submitted data, the efficacy of GB against COPD has been demonstrated and the safety of GB is acceptable in view of its observed benefits. GB serves as a new treatment option for COPD and be of clinical significance. As for safety, patients need to be carefully monitored for cardio- and cerebro-vascular events and anticholinergic adverse events, and the safety of GB needs to be further investigated under usage conditions via post-marketing surveillance.

PMDA considers that the product may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

August 20, 2012

I. Product Submitted for Registration

[Brand name] Seebri Inhalation Capsules 50 μg
[Non-proprietary name] Glycopyrronium Bromide[41]
[Name of applicant] Novartis Pharma K.K.
[Date of application] November 25, 2011

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc by the Pharmaceuticals and Medical Devices Agency" (PMDA Administration Rule No. 8/2008 dated December 25, 2008).

(1) Dosage and administration

As a result of the phase II multi-regional study including Japanese subjects (Study A2205), 50 μg q.d. dosing is selected for the dosage and administration of GB, and the phase III multi-regional study including Japanese subjects (Study A2304) has demonstrated the superiority of GB 50 μg q.d. over placebo with respect to trough FEV_1. On the other hand, according to FDA's directions, the additional dose-ranging clinical study including b.i.d. dosing (Study A2208) has been conducted to further evaluate the optimal dosage and administration of GB. However, with the consideration of the results of additional study, PMDA concludes that 50 μg q.d. dosing is acceptable for the dosage and administration of GB in Japanese patients with COPD. This conclusion of PMDA was supported by the expert advisors.

(2) Post-marketing surveillance, etc.

PMDA asked the applicant to organize a post-marketing surveillance plan to appropriately collect information about the occurrence of cardio- and cerebro-vascular adverse events and anticholinergic adverse events, including glaucoma and urinary retention.

The applicant explained that they will conduct a long-term specified drug use-results survey, with a follow-up period of 1 year, and examine cardio- and cerebro-vascular adverse events and anticholinergic adverse events as items for priority investigation, and that they will analyze the safety data obtained by 10-year age group to evaluate the safety of GB in elderly patients. Furthermore, the applicant explained that

[41] The Japanese name (JAN) has been changed according to the Notification No.0817-1 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated August 17, 2012.

they will compare data collected in Japan via post-marketing surveillance with results from a post-marketing safety study[42] scheduled to be conducted in [redacted] for evaluation of GB's [redacted].

PMDA considers that the surveillance should be conducted immediately and newly available information should be provided properly to clinical practice.

III. Overall Evaluation

As a result of its review, PMDA concludes that the product may be approved for the indication and the dosage and administration as shown below. The re-examination period is 8 years, the drug product is not classified as a poisonous drug or a powerful drug, and it is not classified as a biological product or a specified biological product.

[Indication] Relief of symptoms of airway obstruction in patients with chronic obstructive pulmonary disease (chronic bronchitis and emphysema)

[Dosage and administration]

The usual adult dosage is one capsule (50 μg of glycopyrronium) administered once daily via an inhaler device.

[42] A [redacted] study conducted by extracting [redacted] GB and [redacted] from [redacted] and comparing and assessing [redacted].