Report on the Deliberation Results

June 3, 2019

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Breztri Aerosphere 56 Inhalations, Breztri Aerosphere 120 Inhalations
Non-proprietary Name	Budesonide/Glycopyrronium Bromide/Formoterol Fumarate Hydrate (JAN*)
Applicant	AstraZeneca K.K.
Date of Application	September 4, 2018

Results of Deliberation

In its meeting held on May 30, 2019, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented 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, and the re-examination period is 6 years. The drug product is not classified as a poisonous drug or a powerful drug.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

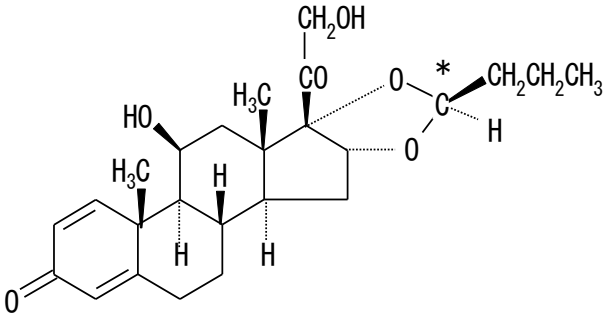
May 14, 2019
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Breztri Aerosphere 56 Inhalations, Breztri Aerosphere 120 Inhalations
Non-proprietary Name	Budesonide/Glycopyrronium Bromide/Formoterol Fumarate Hydrate
Applicant	AstraZeneca K.K.
Date of Application	September 4, 2018
Dosage Form/Strength	Inhalation aerosols containing 160 μg of Budesonide, 9.0 μg of Glycopyrronium Bromide (7.2 μg of Glycopyrronium), and 5.0 μg of Formoterol Fumarate Hydrate (4.8 μg of Formoterol Fumarate) per actuation
Application Classification	Prescription drug, (1) Drugs with a new active ingredient / (2) New combination drugs

Chemical Structure

Budesonide



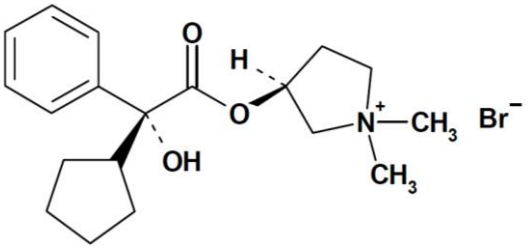
and epimer at C*

Molecular formula: $C_{25}H_{34}O_6$

Molecular weight: 430.53

Chemical name: (+)-[(*RS*)-16α, 17α-butylidenedioxy-11β, 21-dihydroxy-1, 4-pregnadiene-3, 20-dione]

Glycopyrronium Bromide



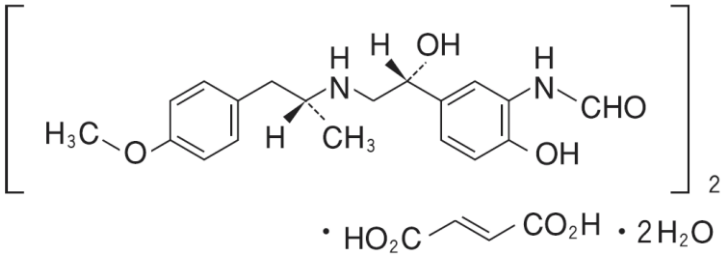
and enantiomer

Molecular formula: $C_{19}H_{28}BrNO_3$

Molecular weight: 398.33

Chemical name: (*3RS*)-3-[(*2SR*)-(2-Cyclopentyl-2-hydroxy-2-phenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide

Formoterol Fumarate Hydrate



and enantiomer

Molecular formula: $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$

Molecular weight: 840.91

Chemical name: *N*-(2-Hydroxy-5-{(1*RS*)-1-hydroxy-2-[(1*RS*)-2-(4-methoxyphenyl)-1-methylethylamino]ethyl}phenyl) formamid hemifumarate monohydrate

Reviewing Office Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of chronic obstructive pulmonary disease (COPD), and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. The occurrence of cardiovascular events in its clinical use, etc. should be further investigated through post-marketing surveillance.

Indication	Relief of symptoms of chronic obstructive pulmonary disease (chronic bronchitis, emphysema) (requiring a combination therapy with an inhaled corticosteroid, an inhaled long-acting muscarinic antagonist, and an inhaled long-acting beta2 agonist)
Dosage and Administration	The usual adult dosage is 2 inhalations (320 μg of Budesonide, 14.4 μg of Glycopyrronium, and 9.6 μg of Formoterol Fumarate) twice daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

April 10, 2019

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Products Submitted for Approval

(a)

Brand Name	Bevespi Aerosphere 28 Inhalations, Bevespi Aerosphere 120 Inhalations
Non-proprietary Name	Glycopyrronium Bromide/Formoterol Fumarate Hydrate
Applicant	AstraZeneca K.K.
Date of Application	September 7, 2018
Dosage Form/Strength	Inhalation aerosols containing 9.0 μg of Glycopyrronium Bromide (7.2 μg of Glycopyrronium) and 5.0 μg of Formoterol Fumarate Hydrate (4.8 μg of Formoterol Fumarate) per actuation
Proposed Indication	Relief of symptoms of chronic obstructive pulmonary disease (chronic bronchitis, emphysema) secondary to airway obstructive disorder (requiring a combination therapy with an inhaled long-acting muscarinic antagonist and an inhaled long-acting beta2 agonist)
Proposed Dosage and Administration	The usual adult dosage is 2 inhalations (14.4 μg of Glycopyrronium and 9.6 μg of Formoterol Fumarate) twice daily.

(b)

Brand Name	Trivespi Aerosphere 56 Inhalations, Trivespi Aerosphere 120 Inhalations
Non-proprietary Name	Budesonide/Glycopyrronium Bromide/Formoterol Fumarate Hydrate
Applicant	AstraZeneca K.K.
Date of Application	September 4, 2018
Dosage Form/Strength	Inhalation aerosols containing 160 μg of Budesonide, 9.0 μg of Glycopyrronium Bromide (7.2 μg of Glycopyrronium), and 5.0 μg of Formoterol Fumarate Hydrate (4.8 μg of Formoterol Fumarate) per actuation
Proposed Indication	Relief of symptoms of chronic obstructive pulmonary disease (chronic bronchitis, emphysema) (requiring a combination therapy with an inhaled corticosteroid, an inhaled long-acting muscarinic antagonist, and an inhaled long-acting beta2 agonist)
Proposed Dosage and Administration	The usual adult dosage is 2 inhalations (320 μg of Budesonide, 14.4 μg of Glycopyrronium, and 9.6 μg of Formoterol Fumarate) twice daily.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Bevespi Aerosphere (GP/FF) 28 or 120 Inhalations and Trivespi Aerosphere (BD/GP/FF) 56 or 120 Inhalations are pressurized inhalation aerosols developed by Pearl Therapeutics, a US-based company. The active ingredients of GP/FF are Glycopyrronium Bromide (glycopyrronium bromide), a long-acting muscarinic antagonist (LAMA), and Formoterol Fumarate Hydrate (formoterol fumarate dihydrate), a long-acting beta2 agonist (LABA). BD/GP/FF contains Budesonide (budesonide), an inhaled corticosteroid (ICS), GP, and FF as active ingredients. Table 1 shows 7 products with these active ingredients approved for marketing in Japan.

Table 1. Approval status of inhalations containing active ingredients of GP/FF or BD/GP/FF inhalations in Japan

Brand name	Active ingredient(s)	Dosage form	Indication	Approved in
Pulmicort 100μg Turbuhaler 112 Doses and other strengths/doses[a)]	BD	Metered-dose dry powder inhaler	Bronchial asthma	June 1999
Pulmicort Respules 0.25mg and other strengths[a)]	BD	Inhalation suspension	Bronchial asthma	July 2006
Symbicort Turbuhaler 30 Doses and other doses[a)]	BD, FF	Metered-dose dry powder inhaler	Bronchial asthma Chronic obstructive pulmonary disease (COPD)	October 2009 August 2012
Oxis 9μg Turbuhaler 28 Doses and other doses[a)]	FF	Metered-dose dry powder inhaler	COPD	June 2012
Seebri Inhalation Capsules 50μg	GP	Metered-dose dry powder inhaler	COPD	September 2012
Flutiform 50 Aerosol 56 Puffs and other strengths/puffs	FF, FP	Inhalation aerosol	Bronchial asthma	September 2013
Ultibro Inhalation Capsules	GP, IND	Metered-dose dry powder inhaler	COPD	September 2013

FP, fluticasone propionate; IND, indacaterol maleate
a) The applicant, AstraZeneca, is the marketing authorization holder of the approved drug.

Chronic obstructive pulmonary disease (COPD) is a group of lung diseases caused by long-term exposure to primarily tobacco smoke and other factors, and is characterized by progressive airflow obstruction, and clinically, by symptoms including dyspnea on exertion and chronic cough and sputum production (JRS 2018). Bronchodilators are central to the pharmacotherapy of patients with stable COPD, and short-acting beta2 agonists, LABAs, and LAMAs are used in a step-wise manner according to the severity of the patient's condition. If monotherapy fails to produce satisfactory results, or more severe symptoms develop, 2 or more bronchodilators may be used in combination (JRS 2018, and GOLD 2019). In Japan, for prevention of exacerbation, the addition of an ICS was recommended for the treatment of patients with repeated exacerbations of COPD who had received bronchodilators (JRS 2013); however, according to the latest guidelines in Japan revised in April 2018, ICS should be concomitantly used when it is suspected that the patient's condition is complicated by asthma (JRS 2018). In previous editions of the international guidelines, addition of ICS was recommended for patients with recurrent exacerbation during LAMA or LABA monotherapy or LAMA and LABA (GOLD 2018) combination therapy. However, the revised 2019 guidelines state that; the addition of ICS should be considered for, among patients with COPD whose treatment focus should be the prevention of worsening, rather than improvement, of dyspnea, those who are on LAMA or LABA alone and experiencing recurrent exacerbation with a blood eosinophil count of ≥300 mm^3 or a blood eosinophil count of ≥100 mm^3, or those who are on LAMA/LABA combination and have a blood eosinophil count of ≥100 mm^3 (GOLD 2019).

Inhaled combination therapies with different mechanisms of action, such as LAMA/LABA and ICS/LAMA/LABA, are widely used in the clinical setting. The administration of combined 2 or 3 agents via a single inhaler will improve both medication adherence and convenience for patients. In Japan, the following inhaled combination drugs have been approved for COPD-related indications: GP/indacaterol maleate, umeclidinium bromide/vilanterol trifenatate, and tiotropium bromide hydrate/olodaterol hydrochloride as LAMA/LABA inhaled combination drugs, and fluticasone furoate/umeclidinium bromide/vilanterol trifenatate as an ICS/LAMA/LABA inhaled combination drug. GP/FF and BD/GP/FF have been developed as new LAMA/LABA, and ICS/LAMA/LABA combination drugs, respectively.

Clinical development of GP/FF metered-dose inhaler (MDI) for the treatment of COPD started in November 2008 outside Japan. GP/FF MDI was approved in April 2016 in the US, in December 2018 in Europe, and in a total of 36 countries and regions as of April 2019. Clinical development of BD/GP/FF MDI for COPD started in November 2008 outside Japan. As of April 2019, the drug is under review in the US and Europe.

In Japan, clinical development of GP/FF MDI and BD/GP/FF MDI for COPD started in January 2015, and this time, marketing approval was filed respectively for GP/FF MDI and BD/GP/FF MDI based on the results of global studies including those conducted in Japan. While applications for marketing approval were filed individually for GP/FF MDI and BD/GP/FF MDI, given that the same data relating to quality (drug substances), non-clinical studies (pharmacology, pharmacokinetics, and toxicity), and clinical studies (pharmacology, efficacy and safety) have been used, it was decided that evaluation results are to be described together. Furthermore, the brand name for BD/GP/FF MDI will be changed from the proposed name “Trivespi Aerosphere 56 Inhalations; Trivespi Aerosphere 120 Inhalations” to “Breztri Aerosphere 56 Inhalations; Breztri Aerosphere 120 Inhalations” to prevent medical accidents.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Drug substances GP and FF are used in GP/FF MDI, while drug substances BD, GP, and FF are used in BD/GP/FF MDI.

Of the drug substances, FF is listed in the Japanese Pharmacopoeia, and the drug substance registered in the master file (MF) by [redacted] (MF Registration No.[redacted]) is used.

2.1 Drug substance (GP)

The drug substance GP is manufactured from [redacted]GP registered in the MF by [redacted] (MF Registration No.[redacted]).

2.1.1 Characterization

Drug substance GP is a white powder. Its description, solubility, hygroscopicity, melting point, dissociation constant, partition coefficient, and crystalline polymorphism were investigated.

The chemical structure of drug substance GP was elucidated by infrared spectrophotometry (IR), nuclear magnetic resonance spectrometry (NMR) (^{1}H-, and ^{13}C-NMR), mass spectrometry (MS), and elemental analysis. Drug substance GP is a racemic mixture of 2 stereoisomers (*2S, 3R*), and (*2R, 3S*).

2.1.2 Manufacturing process

Attachment 1 shows the manufacturing process from the starting materials to [redacted]GP. The drug substance GP is manufactured by [redacted]. Steps [redacted] and [redacted] were specified as critical steps.

2.1.3 Control of drug substance

The proposed specifications for drug substance GP consist of content, description, identification (IR), purity ([redacted] [redacted], [redacted] [redacted], and [redacted] [redacted]), loss on drying, residue on ignition, particle size distribution, microbial limit, and assay (HPLC).

In the review process, content, purity ([redacted] [redacted], [redacted] [redacted], and [redacted] [redacted]), loss on drying, residue on ignition, and assay (HPLC) were specified.

2.1.4 Stability of drug substance

Table 2 shows the main stability studies of drug substance GP. The results of photostability testing demonstrated that drug substance GP was photostable.

Table 2. Stability studies of drug substance GP

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	3 production batches	25°C	60%RH	High-density polyethylene container (airtight stopper) + desiccant + aluminum bag	48 months
Accelerated	3 production batches	40°C	75%RH		6 months

Based on the results of the above studies, a retest period of [redacted] months was proposed for drug substance GP when stored at room temperature in a high-density polyethylene container placed in an aluminum bag with desiccant.

2.2 Drug substance (BD)

Drug substance BD, which is included in the Japanese Pharmaceutical Codex, is identical to drug substance BD contained in approved products such as “Pulmicort 100μg Turbuhaler 112 Doses,” etc. However, the manufacturing process, in particular, the starting materials and the process parameters of the fine grinding step, is currently under reconsideration. In the review process of the application, the proposed starting materials were changed from [redacted], and it was decided that the MF registered by [redacted] under MF Registration No. [redacted] would be referred to for manufacturing from the newly specified starting materials to [redacted]. Manufacturing from the starting materials to [redacted] is shown in Attachment 2.[1)]

[1)] Because drug substance BD is not used in GP/FF MDI, Attachment 2 is not attached to the Review Report for Product (a).

2.3 Drug product (GP/FF MDI)

2.3.1 Description and composition of drug product and formulation development

Drug product GP/FF is an inhaled aerosol, and the delivered dose per actuation contains drug substance GP 9.0 μg (glycopyrronium 7.2 μg), and drug substance FF 5.0 μg (formoterol fumarate 4.8 μg). Drug product GP/FF contains porous particles and 1,1,1,2-tetrafluoroethane (HFA-134a) as excipients. The active ingredients and the porous particles are suspended in HFA-134a propellant, and a pressurized [redacted]-mL aluminum canister is filled with the suspension. A metering valve capable of delivering [redacted] μL per actuation is crimped onto the canister, which has a dose indicator on top. The canister/dose indicator is fitted into a polypropylene actuator and a cap.

2.3.2 Manufacturing process

Drug product GP/FF MDI is manufactured through a process comprising the following steps: [redacted], [redacted], [redacted], [redacted] and [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and packaging. Step [redacted] was specified as a critical step, and process controls and process control values were specified in Steps [redacted] and [redacted].

2.3.3 Control of drug product

The proposed specifications for drug product GP/FF MDI consist of description, identification (HPLC [GP and FF]), delivered dose uniformity (HPLC [GP and FF]), [redacted], water content, aerodynamic particle size (next generation pharmaceutical impactor [GP and FF]), and [redacted].

2.3.4 Stability of drug product

Table 3 shows the main stability studies of drug product GP/FF MDI.

Table 3. Stability studies of GP/FF MDI

Study	Formulation	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	28 inhalations	3 pilot batches	25°C	60%RH	Desiccant + aluminum bag	24 months
	120 inhalations	3 pilot batches				24 months
Mid-term	120 inhalations	3 pilot batches	30°C	65%RH		12 months
Accelerated	28 inhalations	3 pilot batches	40°C	75%RH		6 months
	120 inhalations	3 pilot batches				

The stability of unpackaged products was investigated assuming normal usage conditions. Samples stored under the long-term storage conditions (formulation for 28 inhalations, [redacted] or [redacted] months; formulation for 120 inhalations, [redacted], [redacted], [redacted], or [redacted] months) were removed from the aluminum bag, and stored at 25°C and 75%RH (formulation for 28 inhalations, for 3 weeks; formulation for 120 inhalations, for 3 months) to evaluate stability. The results indicated no significant changes in physicochemical or pharmaceutical properties.

Based on the above, a shelf life of 24 months has been proposed for drug product GP/FF MDI when stored at room temperature in an aluminum bag with desiccant. The long-term stability study will be continued for up to [redacted] months.

2.4 Drug product (BD/GP/FF MDI)

2.4.1 Description and composition of drug product and formulation development

Drug product BD/GP/FF MDI is an inhaled aerosol, and the delivered dose per actuation contains drug substance BD 160 µg, drug substance GP 9.0 µg (glycopyrronium 7.2 µg), and drug substance FF 5.0 µg (formoterol fumarate 4.8 µg). Drug product BD/GP/FF MDI contains porous particles and 1,1,1,2-tetrafluoroethane (HFA-134a) as excipients. The active ingredients and the porous particles are suspended in HFA-134a propellant, and a pressurized [redacted]-mL aluminum canister is filled with the suspension. A metering valve capable of delivering [redacted] µL per actuation is crimped onto the canister, which has a dose indicator on top. The canister/dose indicator is fitted into a polypropylene actuator and a cap.

2.4.2 Manufacturing process

Drug product BD/GP/FF MDI is manufactured through a process comprising the following steps: [redacted], [redacted], [redacted], [redacted] and [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and packaging. Step [redacted] was specified as a critical step, and process controls and process control values were specified in Steps [redacted] and [redacted], and functional testing.

2.4.3 Control of drug product

The proposed specifications for drug product BD/GP/FF MDI consist of description, identification (HPLC [BD, GP, and FF]), delivered dose uniformity (HPLC [BD, GP, and FF]), [redacted], water content, aerodynamic particle size (next generation pharmaceutical impactor [BD, GP, and FF]), and [redacted].

2.4.4 Stability of drug product

Table 4 shows the main stability studies of drug product BD/GP/FF MDI. A bracketing design was used in the stability studies using the formulation for 120 inhalations and the formulation for 28 inhalations. The latter formulation was manufactured in the development phase (the formulation for 28 inhalations has an identical pharmaceutical formulation and an identical closure system to those of the formulations for 56 inhalations and for 120 inhalations, but different filling amount). Testing of the formulation for 56 inhalations was omitted.

Table 4. Stability studies of BD/GP/FF MDI

Study	Formulation	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	28 inhalations	3 pilot batches	25°C	60%RH	Desiccant + aluminum bag	24 months
	120 inhalations	3 production batches				
Mid-term	28 inhalations	3 pilot batches	30°C	75%RH		12 months
	120 inhalations	3 production batches				
Accelerated	28 inhalations	3 pilot batches	40°C	75%RH		6 months
	120 inhalations	3 production batches				

The stability of unpackaged products was investigated assuming normal usage conditions. Samples stored under the long-term storage conditions (formulation for 28 inhalations, [redacted] or [redacted] months; formulation for 120 inhalations, [redacted] or [redacted] months) were removed from the aluminum bag, and stored at 25°C and 75%RH to evaluate stability. The results demonstrated that the formulations for 28 inhalations and for 120 inhalations are stable for 3 weeks, and 3 months, respectively.

Based on the above, a shelf life of 24 months was proposed for drug product BD/GP/FF MDI when stored at room temperature in an aluminum bag with desiccant. The long-term stability study will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substances and the drug products is adequately controlled.

2.R.1 Novel excipient

A novel excipient, 1,2-distearoyl-s*n*-glycero-3-phosphocholine (DSPC), which has never been used for formulations administered by any route, is used as a component of porous particles in GP/FF MDI and BD/GP/FF MDI.

During the review process, the novel excipient has been changed from porous particles to DSPC.

2.R.1.1 Specifications and stability

The applicant's explanation about porous particles:

DSPC and calcium chloride form a porous structure in [redacted], which allow drug crystals to be associated with DSPC and calcium chloride, thereby maintaining the suspension stability of GP/FF MDI and BD/GP/FF MDI.

PMDA concluded that [redacted] of DSPC and calcium chloride, as well as their quality should be assured so that the physicochemical characteristics and functional properties of porous particles could be obtained. PMDA therefore designated DSPC as a novel excipient in order to have it managed as a standard ingredient listed in the appendix, while specifying DSPC and calcium chloride, which consist of porous particles, as excipients. PMDA concluded that there are no other problems with the specifications and stability of DSPC.

2.R.1.2 Safety

Local administration site and systemic toxicity of DSPC was evaluated as the component of the solvent in 6-month repeated-dose inhalation toxicity studies in rats and dogs, and carcinogenicity studies by inhalation in rats and mice for GP [see Sections 5.2 and 5.4]. The following studies were performed to evaluate genotoxicity: the Ames test using DSPC, chromosomal aberration study using cultured cells, and micronucleus study in rodents by intraperitoneal administration. The following studies were performed to evaluate reproductive and developmental toxicity: the study of fertility and early embryonic development to implantation in rats by intraperitoneal administration, embryo-fetal development studies in rats and rabbits, and study of pre- and postnatal development including maternal function in rats [see Sections 5.3 and 5.5].

In the repeated-dose inhalation toxicity study in rats, and carcinogenicity studies by inhalation in rats and mice, an increased incidence of hyaline degeneration of the nasal respiratory/olfactory epithelium, squamous metaplasia of the nasopharyngeal epithelium occurred compared with air controls; however, given that GP/FF MDI and BD/GP/FF MDI are administered by oral inhalation, it was concluded that they are unlikely to cause

concerns about safety in humans. The results of genotoxicity studies were negative, and no toxicity findings were observed in reproductive and developmental toxicity studies.

PMDA's view:

It is possible to use DSPC as an excipient for oral inhalation based on the results from non-clinical studies of GP/FF MDI and BD/GP/FF MDI. However, it is known that, the deposition of inhaled material onto respiratory tissue depends on the particle size, density, and morphology of the material (*Toxicology,* 3rd edition. 2018;229-32. Asakura Publishing Co., Ltd.), and given that the safety evaluation in this study is performed using porous particles with [redacted] and [redacted] within specific ranges, it is appropriate to allow the use of DSPC for inhalation only if its particle size, density, and morphology are equivalent to those of DSPC contained in GP/FF MDI and BD/GP/FF MDI.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

"Non-clinical pharmacology data" of BD, FF, and BD/FF MDI have already been evaluated when applications for inhalations including "Pulmicort 100μg Turbuhaler 112 Doses" and other strengths/doses and "Symbicort Turbuhaler 30 Doses" and other doses were approved. In the present application, as data on primary pharmacodynamics for GP, the results from studies on binding affinity for the subtypes of the muscarinic receptor, and effects on methacholine-induced entry of extracellular calcium into cells, and methacholine-induced bronchoconstriction in isolated guinea pig trachea were submitted. No secondary pharmacology studies or pharmacodynamic drug interaction studies were conducted. Although safety pharmacology studies were not conducted, effects on the central nervous system were evaluated in the repeated-dose inhalation toxicity studies in rats and dogs, and effects on the cardiovascular and respiratory systems in the repeated-dose toxicity studies in dogs using BD, FF, GP, GP/FF MDI, and BD/GP/FF MDI. Unless otherwise specified, pharmacological parameters are expressed in mean values.

3.1 Primary pharmacodynamics

3.1.1 Binding affinity of GP for the subtypes of the muscarinic receptor (CTD 4.2.1.1.1 to 7)

The binding affinity of GP for each muscarinic receptor was evaluated using cell membrane preparations prepared from Chinese hamster ovary cells expressing human muscarinic receptors M_1 to M_5 or guinea pig muscarinic receptor M_3. Table 5 shows the pIC_{50} of GP or atropine against [^{3}H] N-methylscopolamine (concentration for each test: human M_1, human M_4, and guinea pig M_3, 0.1 nmol/L; human M_2 and M_3, 0.2 nmol/L; human M_5, 0.25 nmol/L).

Table 5. Inhibitory activity of GP on muscarinic receptors (pIC_{50})

Compound	Human					Guinea pig
	Receptor M_1	Receptor M_2	Receptor M_3	Receptor M_4	Receptor M_5	Receptor M_3
GP	9.9 (2)	9.3 (3)	9.5 (8)	9.8 (3)	9.7 (3)	9.3 (4)
Atropine	9.1 (2)	9.0 (3)	8.7 (8)	9.0 (3)	8.9 (3)	8.9 (4)

Mean (Number of tests)

Binding to the cell membrane of [^{35}S] GTPγS (0.5 nmol/L) induced by methacholine (1 μmol/L) was evaluated using the cell membrane preparations expressing human muscarinic receptor M_2. The results demonstrated that

GP and atropine inhibited methacholine-induced GTPγS binding with the pIC_{50} being 8.6 for GP, and 8.0 for atropine.

3.1.2 Effects of GP on methacholine-induced entry of extracellular calcium into cells (CTD 4.2.1.1.8)

Methacholine-induced (0.1 nmol/L to 30 μmol/L) entry of extracellular calcium into cells was evaluated using cell membrane preparations expressing human muscarinic receptor M_3 [see Section 3.1.1]. The results demonstrated that GP and atropine inhibited the entry of extracellular calcium into cells with the pA_2 being 10.3 for GP, and 9.2 for atropine.

3.1.3 Effects of GP on methacholine-induced bronchoconstriction in isolated guinea pig trachea (CTD 4.2.1.1.9)

Methacholine-induced (3 nmol/L to 1 mmol/L) bronchoconstriction in the presence (3 nmol/L) or absence of GP was evaluated using isolated guinea pig trachea. The results indicated that GP inhibited methacholine-induced bronchoconstriction with the pA_2 being 10.2.

3.2 Safety pharmacology

No safety pharmacology studies have been conducted. Effects on the central nervous system were evaluated in the repeated-dose inhalation toxicity studies in rats and dogs, and effects on the cardiovascular and respiratory systems in the repeated-dose toxicity studies in dogs using MDI formulations with BD, FF, GP, GP/FF, and BD/GP/FF. The results indicated impact on the heart in the animal groups receiving FF by inhalation [see Section 5.2].

3.R Outline of the review conducted by PMDA

The applicant's explanation about the pharmacological significance of using GP in combination with FF or BD/FF MDI:

A combination of LABA/LAMA, FF and GP, which are bronchoconstrictors with different mechanisms of action, is likely to provide additive effects on lung functions compared with individual agents given alone (*Pulm Pharmacol Ther.* 2010;23:257-67). Given that non-clinical studies have reported that GP and indacaterol, a LABA, acted synergistically to produce bronchoconstriction (*Respir Res.* 2016;17:1-15); and that FF and aclidinium bromide, a LAMA, acted synergistically to cause human airway smooth muscle relaxation (*Eur J Pharmacol.* 2014;745:135-43), a LABA/LAMA combination is useful and beneficial in effecting airway smooth muscle relaxation for the treatment in patients with COPD.

PMDA's view:

The submitted pharmacological data and the applicant's explanation indicate the pharmacological significance of using FF or BD/FF MDI in combination with GP. Furthermore, given the results of toxicity studies, GP/FF MDI and BD/GP/FF MDI are unlikely to have effects on the central nervous, cardiovascular, or respiratory system.

Central nervous system

- No findings suggestive of effects on the central nervous system were observed in the rat and dog repeated-dose inhalation toxicity studies conducted with BD MDI, FF MDI, and GP MDI [see Section 5.2].
- No abnormal findings suggestive of new effects on the central nervous system were observed when compared with the toxicity findings of individual active ingredients given alone in the rat and dog repeated-dose inhalation toxicity studies conducted with GP/FF MDI and BD/GP/FF MDI [see Section 5.2].

Cardiovascular and respiratory systems

- No findings suggestive of effects on the respiratory or cardiovascular system were observed in the dog repeated-dose inhalation toxicity study conducted with GP MDI [see Section 5.2].
- In the dog repeated-dose inhalation toxicity study conducted with FF MDI or GP/FF MDI, increases in tidal volume and heart rate, and cardiac papillary muscle fibrosis were observed [see Section 5.2]. However, these findings are considered to be related to the pharmacological action of FF in dogs, which are highly sensitive to β receptor stimulation; therefore, it is unlikely to cause concerns about safety in humans.
- Based on the results from the dog repeated-dose inhalation toxicity study conducted with GP/FF MDI and BD/GP/FF MDI, BD and GP are unlikely to have effects on abnormal cardiac findings caused by FF [see Section 5.2].

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

"Non-clinical pharmacokinetic data" of BD and FF have already been evaluated when applications for "Pulmicort 100μg Turbuhaler 112 Doses" and other strengths/doses and "Symbicort Turbuhaler 30 Doses" and other doses were approved. In the present application, as data relating to absorption, distribution, metabolism, excretion, and drug-drug interaction of GP, data from the inhalation, oral, and intravenous administration studies in rats and dogs, data from the combination GP/FF inhalation studies in dogs, and data from the combination BD/GP/FF inhalation studies in rats and dogs were submitted. For the evaluation of GP pharmacokinetics, GP and ^{14}C-labelled GP were used, and the plasma GP concentration was determined by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) (lower limit of quantitation, 10.0 pg/mL), or ultra-high performance liquid chromatography-tandem mass spectrometry (UHPLC-MS/MS) (lower limit of quantitation, 10.0 pg/mL or 50.0 pg/mL). The plasma BD concentration was determined by HPLC-MS/MS (lower limit of quantitation, 50.0 pg/mL) or UHPLC-MS/MS (lower limit of quantitation, 5000 pg/mL). The plasma FF concentration was determined by UHPLC-MS/MS (lower limit of quantitation, 10.0 pg/mL or 50.0 pg/mL). Unless otherwise specified, dosage is expressed as glycopyrronium bromide for GP, formoterol fumarate for FF, and budesonide for BD, and pharmacokinetic parameters are mean values.

4.1 Absorption

4.1.1 Repeated-dose studies (toxicokinetics)

4.1.1.1 Administration of GP alone (CTD 4.2.3.2.4,[Product (a)] 4.2.3.2.6,[Product (b)] 4.2.3.2.5,[Product (a)] 4.2.3.2.7,[Product (b)] 4.2.3.2.10,[Product (a)] 4.2.3.2.18[Product (b)])

In the rat 14-day, dog 14-day, and dog 6-month repeated-dose toxicity studies [see Section 5.2], toxicokinetics following repeated-dose inhalation of GP was evaluated. The pharmacokinetic parameters of GP in plasma are presented in Table 6.

Table 6. Pharmacokinetic parameters of GP in plasma following repeated-dose inhalation of GP

Species	Administration period	Dose (µg/kg/day)		Time point (Day)	C_{max} (pg/mL)		AUC_{last} (pg·h/mL)		t_{max} (h)		$t_{1/2}$ (h)	
		Male	Female		Male	Female	Male	Female	Male	Female	Male	Female
Rat	14 days[a)]	46	49	1	330	540	-	-	0.5	0.5	-	-
				14	410	680	-	-	24	3	-	-
		254	276	1	1460	2660	-	-	3	3	-	-
				14	7290	3640	-	-	0.5	0.5	-	-
		514	555	1	6310	6240	-	-	0.5	0.5	-	-
				14	5390	3890	-	-	0.5	0.5	-	-
Dog	14 days[b)]	16	17	1	106	105	91.8	147	0.1	0.1	1.0	1.6
				14	86.5	62.0	215	235	0.2	0.1	6.1	13.5
		29	31	1	283	272	298	401	0.1	0.1	2.1	2.4
				14	70.3	227	86.8	833	0.2	1.1	2.1	21.1
		77	83	1	387	1050	623	1710	0.1	0.1	2.6	1.9
				14	340	593	1670	3360	0.4	0.1	12.4	20.7
	6 months[c)]	18	19	1	1090	1320	2050	1610	0.1	0.1	8.7	7.3
				180	743	1410	1990	2480	0.1	0.3	11.3	10.7
		59	57	1	3760	2940	6060	6490	0.1	0.1	9.4	10.9
				180	6540	3780	10,100	8840	0.1	0.2	8.6	7.5
		77	73	1	3110	1820	6170	3930	0.1	0.1	8.4	6.9
				180	22,100	10,600	30,700	21,500	0.2	0.1	6.1	12.5

Mean value
a) n = 1, b) n = 3 to 4, c) n = 4

4.1.1.2 GP/FF combination administration (CTD 4.2.3.2.6,[Product (a)] 4.2.3.2.11,[Product (b)] 4.2.3.2.7,[Product (a)] 4.2.3.2.12,[Product (b)] 4.2.3.2.8,[Product (a)] 4.2.3.2.15[Product (b)])

In the rat 14-day, dog 14-day, and dog 3-month repeated-dose toxicity studies [see Section 5.2], toxicokinetics following repeated-dose inhalation of GP/FF MDI was evaluated. The pharmacokinetic parameters of GP and FF in plasma are presented in Table 7.

Table 7. Pharmacokinetic parameters of GP and FF in plasma following repeated-dose inhalation of GP/FF MDI

Species	Administration period	GP/FF MDI dose (µg/kg/day)		Time point (Day)	GP				FF			
					C_{max} (pg/mL)		AUC_{last} (pg·h/mL)		C_{max} (pg/mL)		AUC_{last} (pg·h/mL)	
		Male	Female		Male	Female	Male	Female	Male	Female	Male	Female
Rat	14 days[a)]	72/14	77/15	1	660	1390	-	-	503	531	-	-
				14	2030	1440	-	-	445	375	-	-
		226/42	241/45	1	4390	5160	-	-	3850	3320	-	-
				14	3560	5140	-	-	1630	2430	-	-
		368/69	394/73	1	4530	3770	-	-	2060	2700	-	-
				14	7690	7100	-	-	2440	4510	-	-
Dog	14 days[b)]	17/3	17/3	1	788	533	1400	940	191	95.0	768	496
				14	1120	634	3380	1720	215	144	1430	782
		51/9	52/9	1	1500	4690	4340	6440	374	746	1600	2120
				14	4030	5850	9030	8660	646	708	2210	2480
		74/13	75/13	1	5990	3890	5810	5850	915	677	2310	2410
				14	11,600	11,100	17,000	13,400	1040	1140	3630	4160
	3 months[c)]	17/4	18/5	1	289	373	589	673	116	137	443	527
				90	1910	1080	3780	2340	434	253	1650	1020
		43/10	44/11	1	1020	2680	2530	3710	433	800	1300	2160
				90	4020	11,000	12,200	9430	765	1130	3440	2670
		59/14	62/15	1	399	3440	1440	4690	257	553	1300	2060
				90	3670	8330	10,300	20,200	747	2000	4610	4490

Mean value
a) n = 1, b) n = 4, c) n = 4

4.1.1.2 BD/GP/FF combination administration (CTD 4.2.3.2.13,[Product (b)] 4.2.3.2.9,[Product (b)] 4.2.3.2.16[Product (b)])

In the rat 14-day, dog 14-day, and dog 3-month repeated-dose toxicity studies [see Section 5.2], toxicokinetics following repeated-dose inhalation of BD/GP/FF MDI was evaluated. The pharmacokinetic parameters of BD, GP, and FF in plasma are presented in Table 8.

Table 8. Pharmacokinetic parameters of BD, GP, and FF in plasma following repeated-dose inhalation of BD/GP/FF MDI

Species	Adminis-tration period	BD/GP/FF MDI dose (µg/kg/day)		Time point (Day)	BD				GP				FF			
					C_{max} (pg/mL)		AUC_{last} (pg·h/mL)		C_{max} (pg/mL)		AUC_{last} (pg·h/mL)		C_{max} (pg/mL)		AUC_{last} (pg·h/mL)	
		Male	Female		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Rat	14 days[a)]	1820/96/56	1950/103/60	1	19,900	49,700	-	-	269	729	-	-	371	646	-	-
				14	19,000	128,000	-	-	295	625	-	-	870	486	-	-
		3680/197/114	3940/211/122	1	191,000	155,000	-	-	780	1170	-	-	902	1400	-	-
				14	114,000	98,900	-	-	1560	4830	-	-	2630	3040	-	-
		7660/407/236	8160/434/251	1	113,000	208,000	-	-	904	2460	-	-	2300	2600	-	-
				14	128,000	814,000	-	-	5260	3310	-	-	3960	3700	-	-
Dog	14 days[b)]	131/7/4	132/7/4	1	8990	12,200	12,000	11,900	224	257	309	562	205	278	628	747
				14	10,700	17,600	16,700	18,700	513	385	979	839	290	329	838	753
		257/13/8	263/14/9	1	13,300	20,700	13,300	22,800	360	305	634	1060	311	495	999	992
				14	29,400	46,400	39,600	48,200	1330	937	2180	3250	648	774	1730	4780
		424/22/14	431/22/14	1	51,900	46,400	48,300	53,300	957	1020	2260	2680	1090	946	2670	2860
				14	55,100	61,600	81,800	93,800	1970	4970	2910	7880	985	1750	3150	4140
	3 months[c)]	3/0.2/0.1	3/0.2/0.1	1	497	436	297	233	-	-	-	-	-	-	-	-
				90	822	446	426	285	-	-	-	-	-	-	-	-
		17/1/0.6	18/1/0.6	1	1640	2270	1190	1400	29.4	40.1	19.0	24.7	23.4	20.4	13.5	27.3
				90	1900	4990	1960	3120	33.6	51.4	38.8	29.1	29.8	44.0	34.7	50.6
		58/3/2	61/4/2	1	7080	8670	5260	6120	66.8	90.4	119	87.3	78.7	107	164	169
				90	22,900	18,600	13,800	13,100	324	380	634	688	346	219	370	324

Mean value
a) n = 1, b) n = 3 to 4, c) n = 1 to 4

4.2 Distribution

4.2.1 Plasma protein binding (CTD 5.3.2.1.1)

Following addition of GP 2 to 500 nmol/L[2)] to mouse, rat, rabbit,[3)] dog, or human plasma, the unbound fraction of GP to plasma proteins was 60.6% to 64.9% in mouse plasma, 68.9% to 78.5% in rat plasma, 77.7% to 82.2% in rabbit plasma, 61.5% to 66.0% in dog plasma, and 45.8% to 56.8% in human plasma, suggesting roughly consistent results independent of concentration.

4.2.2 Tissue distribution (CTD 4.2.2.3.1)

Radioactivity levels in tissues were evaluated following the administration of ^{14}C-labelled GP intravenously at 4 mg/kg, or orally at 30 mg/kg to male and female albino rats and male pigmented rats (n = 1/time point).[4)] In the majority of tissues, the radioactivity levels peaked 15 minutes after intravenous administration and 1 hour after oral administration. High radioactivity was detected by 24 hours post-dose in the liver, kidney, and small intestine in intravenous administration, and in the stomach, small intestine, liver, esophagus, kidney, and cecum after oral administration. The radioactivity levels in the tissues decreased over time, and fell below the lower limit of quantitation at 168 hours after intravenous administration, and 72 hours after oral administration in the majority of tissues except for the liver and a few other tissues. The radioactivity levels in the eyeball were higher in pigmented rats than in albino rats after either intravenous or oral administration.

No radioactivity was detected in the uvea and pigmented skin of orally administered pigmented rats. In intravenously administered pigmented rats, the radioactivity levels peaked 15 minutes after administration, and radioactivity was detectable up to 168 hours in the uvea and 72 hours in the pigmented skin. These results suggest that GP has an affinity for melanin. However, given that radioactivity was detected in the uvea and pigmented skin only in rats receiving an intravenous dose and that radioactivity decreased over time, the melanin binding of GP is considered reversible.

4.3 Metabolism

4.3.1 *In vitro* metabolism (CTD 5.3.2.2.1, 5.3.2.2.2)

When ^{14}C-labelled GP was added to and incubated with lung microsomes of humans, rats, or dogs, or hepatocytes of humans, rats, dogs, mice, or rabbits, GP was not metabolized in the microsomes of any of the animal species. In the hepatocytes, 4 hours after incubation, unchanged GP represented 94.3% in humans, 94.6% in dogs, 6.1% in rats, 49.8% in mice, and 9.7% in rabbits, and major metabolites of GP were mono-hydroxylated metabolites (M1, M2, and M3), di-hydroxylated metabolites (M4 and M6), and a mono-hydroxylated metabolite with unsaturation (M13).

Using the human cytochrome P450 (CYP) expression system, CYP isoforms involved in GP metabolism (i.e., CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5)

[2)] Binding of GP at a concentration of 0.2 nmol/L was evaluated by equilibrium dialysis; however, the results were below the lower limit of quantitation (<0.1 nmol/L) at all 3 measuring time points, and therefore it was not evaluated in rabbit plasma by ultrafiltration.
[3)] In rabbit plasma, GP was not stable, and the recovery rate was relatively low using the equilibrium dialysis method; therefore, results by ultrafiltration are presented.
[4)] Radioactivity levels were measured at 24 and 168 hours in male and female albino rats, and at 0.25, 1, 4, 24, 72, and 168 hours in male pigmented rats.

were investigated. The results showed that GP was metabolized primarily by CYP2D6, and that CYP2A6, CYP2C9, CYP2E1, CYP3A4, and CYP3A5 were also involved in GP metabolism to a limited extent.

4.3.2 *In vivo* metabolism (CTD 4.2.2.4.1)

^{14}C-labelled GP was administered to rats (n = 6/sex) intravenously at 4 mg/kg, or orally at 30 mg/kg. Radioactivity detected in plasma was primarily unchanged GP in intravenously administered rats, and carboxylated GP (M15) formed by hydrolysis in orally administered rats. Urinary radioactivity detected up until 24 hours after administration was unchanged GP in intravenously administered rats, and glucuronic acid conjugates of M15 (M21 and M22) in orally administered rats.

Based on the above findings, the estimated metabolic pathway of GP is shown in Figure 1.

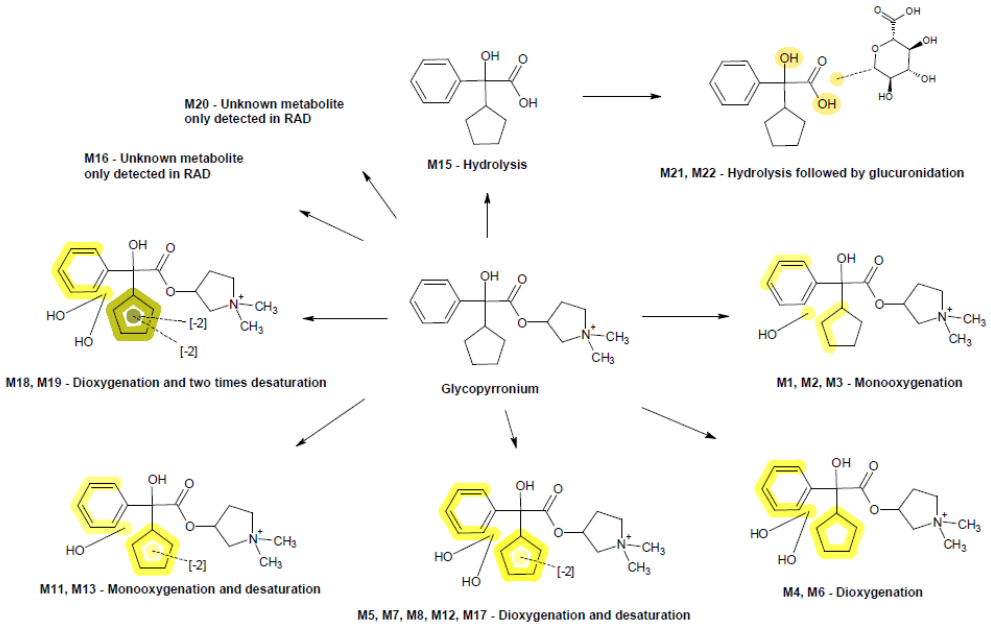

Figure 1. Estimated metabolic pathway of GP (estimated based on rat plasma and urinary metabolites)

4.4 Excretion

4.4.1 Urinary excretion (CTD 4.2.2.3.1)

^{14}C-labelled GP was administered to rats (n = 2/sex) intravenously at 4 mg/kg, or orally at 30 mg/kg. The excretion of radioactivity in urine (expressed as a percentage of the dose administered) up to 48 hours post-dose was 60% in intravenously administered rats, and 7.5% for orally administered rats.

4.4.2 Excretion in milk (CTD 4.2.3.5.3.1)

Plasma GP concentrations in maternal and neonatal rats were evaluated following subcutaneous administration of GP at 0.1, 1, or 10 mg/kg to maternal rats on day 4 of lactation. Plasma GP concentrations reached a maximum 30 minutes after administration in maternal rats (11.3, 158, and 1610 ng/mL, respectively), and 30 minutes to 1 hour after administration in neonatal rats (2.5, 12.1, and 96.0 ng/mL, respectively). The low levels of GP exposure in neonatal rats were considered attributable to exposure to GP via breast milk of maternal rats.

4.5 Pharmacokinetic drug interactions

4.5.1 Enzyme inhibition and induction (CTD 5.3.2.2.3, 5.3.2.2.4, 5.3.2.2.5, 5.3.2.2.6, 5.3.2.3.1, 5.3.2.3.2, 5.3.2.3.3, 5.3.2.3.4, and 5.3.2.3.5)

Using human liver microsomes, the inhibitory effects of GP (0.1-30 μmol/L) on CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) were evaluated. The results indicated no inhibition of any of the CYP isoforms by GP. Time-dependent inhibition of CYP isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) by GP (0.1 or 1 μmol/L) was evaluated. The results indicated no inhibition of any of the CYP isoforms by GP.

Using human hepatocytes, the inductive effects of GP (0.206-50 μmol/L) on the enzyme activity and mRNA expression levels of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) were evaluated. The results indicated no inductive effects of GP on any of the CYP isoforms.

4.5.2 Inhibitory effects of transporters (CTD 5.3.2.3.1, 5.3.2.3.3, 5.3.2.3.4, and 5.3.2.3.5)

Using human embryonic kidney (HEK) 293 cells expressing organic anion transporting polypeptide (OATP) 1B1, OATP1B3, and organic cation transporter (OCT) 1, inhibitory effects of GP (0.3-100 μmol/L) on the transport of substrates mediated by transporters were evaluated. The results indicated no inhibitory effects of GP on OATP1B3. The IC_{50} values of GP for OATP1B1 and OCT1 were ≥100 μmol/L, sufficiently higher than the maximum hepatic inlet concentration of the drug in plasma, $[I]_{inlet,max}$ (3 nmol/L), suggesting that GP is unlikely to inhibit OATP1B1 and OCT1 in clinical use.

Using HEK-293 cells expressing OCT2, organic anion transporter (OAT) 1, OAT3, multidrug and toxin extrusion protein (MATE) 1, and MATE2-K, inhibitory effects of GP (0.3-100 μmol/L) on the transport of substrates mediated by transporters were evaluated. The results indicated no inhibitory effects of GP on OAT1 or OAT3. While GP at 100 μmol/L inhibited substrate transport mediated by OCT2, MATE1, and MATE2-K by 56.3%, 59.9%, and 33.5%, respectively, the dose level evaluated is sufficiently higher than the unbound C_{max} of GP (0.15 nmol/L) following administration of BD/GP/FF MDI at the clinical dose level. Therefore, GP is unlikely to inhibit OCT2, MATE1, and MATE2-K in clinical use.

Using Madin-Darby canine kidney (MDCK) II cells or Caco-2 cells, inhibitory effects of GP (1-300 μmol/L) on the transport of substrates mediated by P-glycoprotein (P-gp), or breast cancer resistance protein (BCRP) were evaluated. The results indicated no inhibitory effects of GP on P-gp or BCRP.

4.5.3 Identification of transporters mediating transport of GP (CTD 5.3.2.3.1, 5.3.2.3.2)

Using HEK-293 cells expressing OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2-K, transport of GP at 0.1 to 100 μmol/L mediated by transporters was evaluated. The results suggested that GP is not a substrate of OAT1 or OAT3. In cells expressing OCT1, OCT2, MATE1, and MATE2-K, the intracellular uptake rate of GP was ≥2.0-fold compared with cells not expressing the transporters, indicating that GP is a substrate of OCT1, OCT2, MATE1, and MATE2-K.

Using MDCK cells expressing P-gp or BCRP, transport of GP at 0.1 to 100 μmol/L mediated by P-gp or BCRP was evaluated. The results indicated that GP is not a substrate of P-gp or BCRP.

Using human hepatocytes, uptake of GP by OATP1B1/1B3 into hepatocytes was evaluated. Uptake of GP into human hepatocytes decreased by 26% in the presence of rifamycin SV, an OATP1B1/1B3 inhibitor, suggesting that GP is a weak substrate of OATP1B1/1B3.

4.R Outline of the review conducted by PMDA

Based on the submitted data from non-clinical pharmacokinetic studies, PMDA concluded that the *in vivo* behavior of GP can be ascertained to a certain extent.

5. Toxicity and Outline of the Review Conducted by PMDA

Data from single-dose and repeated-dose toxicity studies on BD and FF were submitted. Genotoxicity, carcinogenicity, and reproductive and developmental toxicity studies had already been evaluated at the time of approval of applications for "Pulmicort 100μg Turbuhaler 112 Doses" and other strengths/doses and "Symbicort Turbuhaler 30 Doses" and other doses, and therefore, no new data were submitted for the present application. Data from single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity studies on GP were submitted. Data from single-dose and repeated-dose toxicity studies on simultaneous inhalation of BD/FF, BD/GP, GP/FF, or BD/GP/FF were also submitted.

As a vehicle for inhalation, 1,1,1,2-tetrafluoroethane (HFA-134a) containing 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC) and calcium chloride was used. Unless otherwise specified, dosage is expressed as glycopyrronium bromide for GP, formoterol fumarate for FF, and budesonide for BD.

5.1 Single-dose toxicity

Single-dose inhalation toxicity studies were performed using MDI formulations with BD, FF, GP, BD/FF, BD/GP, GP/FF, and BD/GP/FF (Table 9). No deaths or acute symptoms occurred with BD. In dog studies, acute symptoms of increased respiration and heart rate occurred with FF, which was attributed to changes related to β-receptor stimulation. No deaths or acute symptoms occurred with GP, BD/FF, or BD/GP. No deaths occurred with GP/FF; however, acute symptoms of increased respiration and heart rate occurred in dogs. No deaths occurred with BD/GP/FF; however, an acute symptom of increased heart rate occurred in dogs.

Table 9. Summary of the results from single-dose toxicity studies

Test substance	Species	Adminis-tration route	Dosage[a)] (μg/kg)	Major finding	Approximate lethal dose (μg/kg)	CTD
BD	M/F rat (SD)	Inhalation	M: 1950/0/0; 2186/0/0; 3328/0/0 F: 2083/0/0; 2412/0/0; 3586/0/0	None	>3460[b)]	4.2.3.1.1[g)]
	M/F dog (beagle dog)	Inhalation	M: 361/0/0 F: 364/0/0	None	>363[b)]	4.2.3.1.2[g)]

Test substance	Species	Adminis-tration route	Dosage[a] (µg/kg)	Major finding	Approximate lethal dose (µg/kg)	CTD
FF	M/F rat (SD)	Inhalation	M: 0/0/20; 0/0/16[c]; 0/0/25; 0/0/50 F: 0/0/22; 0/0/17[c]; 0/0/27; 0/0/53	≥25 (M)/27 (F): vascular congestion, the lung color changed to white or red	>52[b]	4.2.3.1.1[f] 4.2.3.1.3[g]
	M/F dog (beagle dog)	Inhalation	M: 0/0/5; 0/0/9; 0/0/14 F: 0/0/5; 0/0/14	≥14: increased body temperature, increased respiratory rate, and increased heart rate (M/F)	>14	4.2.3.1.2[f] 4.2.3.1.4[g]
GP	M/F rat (SD)	Inhalation	0/480/0; 0/1010/0	None	>1010[b]	4.2.3.1.3[f] 4.2.3.1.5[g]
	M/F dog (beagle dog)	Inhalation	M: 0/155/0 F: 0/161/0	None	>160[b]	4.2.3.1.4[f] 4.2.3.1.6[g]
BD/FF	M/F rat (SD)	Inhalation	M: 1817/0/65; 1889/0/145; 4082/0/124 F: 1949/0/70; 2034/0/157; 4405/0/134	None	BD/FF: >4240/129[b]	4.2.3.1.1[g]
	M/F dog (beagle dog)	Inhalation	M: 389/0/11.3 F: 392/0/11.4	389/11.3 (M), 392/11.4 (F): increased heart rate	BD/FF: >391/11[b]	4.2.3.1.2[g]
BD/GP	M/F dog (beagle dog)	Inhalation	M: 454/22.2/0 F: 456/22.3/0	None	BD/GP: >455/22[b]	4.2.3.1.2[g]
GP/FF	M/F rat (SD)	Inhalation	M: 0/120/24; 0/195/39; 0/327/66 F: 0/132/26; 0/214/42; 0/354/72	327/66 (M), 354/72 (F): lung color changed to red 327/66 (M): labored breathing	GP/FF: >341/69[b]	4.2.3.1.5[f] 4.2.3.1.7[g]
	M/F dog (beagle dog)	Inhalation	M: 0/14/3; 0/78/15 F: 0/14/3; 0/79/15; 0/129/17[d]	78/15 (M), 79/15 (F): erythema, increased respiratory rate, and increased heart rate	GP/FF: >79/15[b]	4.2.3.1.6[f] 4.2.3.1.8[g]
BD/GP/ FF	M/F rat (SD)	Inhalation	M: 2643/283/162 1944/362/192 F: 2817/302/172; 2083/388/206	2643/2817/283/302/162/172[e]: dyspnea (M/F) 2817/302/172: tachypnea, lung linear recess (F)	BD/GP/FF: >2010/375/199[b]	4.2.3.1.1[g]
	M/F dog (beagle dog)	Inhalation	M: 218/14/8; 472/26/14 F: 222/14/8; 476/26/14	≥218/222/14/14/8/8[e]: increased heart rate (M/F)	BD/GP/FF: >474/26/14[b]	4.2.3.1.2[g]

M, male; F, female
a) BD/GP/FF
b) Mean of male and female data
c) Intermediate dose level per animal
d) Re-tested. The data were not used for the decision on approximate lethal dose levels.
e) BD (M)/BD (F)/GP (M)/GP (F)/FF (M)/FF (F)
f) Product (a)
g) Product (b)

5.2 Repeated-dose toxicity

Repeated-dose inhalation toxicity studies were performed using MDI formulations with BD, FF, GP, BD/FF, BD/GP, GP/FF, and BD/GP/FF.

Repeated-dose toxicity studies with BD were performed in rats (14 days) and dogs (3 months) (Table 10). In neither study was it possible to determine the no-observed-adverse-effect level (NOAEL). In rats or dogs, major systemic toxicity findings included decreased lymphocytes in blood or lymphatic tissue, suppression of bone marrow proliferation (only in rats), adrenal atrophy, anomalies in lipid metabolism and hepatic function, gastric mucosal degeneration (including erosion)/ulcer (only in rats), and bacterial infection-related changes.

Hepatocellular changes in the hepatic portal vein, which are changes related to drug-metabolizing enzyme induction, occurred in rats and dogs.

Table 10. Summary of the results from repeated-dose toxicity studies with BD

Species	Administration route	Administration period	Dosage (M/F µg/kg/day)	Major finding	NOAEL (µg/kg/day)	CTD
M/F rat (SD)	Inhalation	14 days (once daily)	0/0[a)] 0/0[b)] 691/734 2200/2340 4420/4680	≥691/734: low lymphocyte count, low white blood cell count,* high blood albumin,* high glucose,* high blood triglycerides, low weights of the adrenal glands/spleen/thymus, adrenal zona fasciculata/zona reticularis atrophy, accumulation of alveolar macrophages, glandular stomach mucosal epithelial degeneration (including erosion)/ulcer, decreased lymphocytes in thymic cortex (M/F) ≥691: high hematocrit, high hemoglobin, high red blood cell count, low reticulocyte percentage, high albumin/globulin (A/G) ratio (M) ≥734: low basophil count, low eosinophil count, high neutrophil count, high alanine aminotransferase (ALT)/aspartate aminotransferase (AST)/bilirubin in blood, low inorganic phosphorus in blood, hepatocellular lipidosis, decreased lymphocytes in tracheobronchial lymph nodes, decreased lymphocytes in periarteriolar lymphoid sheaths and lymph follicles in the spleen (F) ≥2200/2340: high monocyte count (M/F) ≥2200: high neutrophil count, high blood bilirubin/total protein, low weights of the lung/testis (M) ≥2340: hepatocellular changes (hepatic portal vein area) (F) 4420/4680: low platelet count, decreased sternal bone marrow cell count, decreased lymphocytes in mesenteric lymph nodes (M/F) 4420: low eosinophil count, high blood ALT/cholesterol, low inorganic phosphorus in blood, hepatocellular cytoplasmic change in the hepatic portal vein area, hepatocellular lipidosis, decreased lymphocytes in tracheobronchial lymph nodes, decreased lymphocytes in periarteriolar lymphoid sheaths and lymph follicles in the spleen (M) 4680: high total protein in blood (F) Reversibility: yes	<691 (M) <734 (F)	4.2.3.2.1[c)]
M/F dog (beagle dog)	Inhalation	14 days (once daily)	0/0[a)] 0/0[b)] 138/144 280/291 354/366	≥138/144: high γ-glutamyltransferase (GGT), high triglycerides, low adrenal gland weight, high liver weight, low lung weight, low thymus weight, adrenal zona fasciculata/zona reticularis atrophy, hepatocellular changes (hepatic portal vein area), decreased lymphocytes in thymic cortex (M/F) ≥138: high blood albumin (M) ≥144: low ovary weight (F) ≥280/291: high total protein in blood (M/F) ≥280: decreased lymphocytes in tracheobronchial lymph nodes (M) ≥291: high neutrophil count, low blood chloride, low blood creatinine, high blood globulin, low blood glucose (F) 354: high blood alkaline phosphatase (ALP), low blood chloride, low creatinine (M) 366: high platelet count, high mean cell volume, decreased lymphocytes in tracheobronchial lymph nodes (F) Reversibility: yes	<138 (M) <144 (F)	4.2.3.2.2[c)]

Species	Administration route	Administration period	Dosage (M/F µg/kg/day)	Major finding	NOAEL (µg/kg/day)	CTD
M/F dog (beagle dog)	Inhalation	3 months (once daily)	0/0[a)] 0/0[b)] 3/3 31/32 103/106	≥3/3: low adrenal gland weight, high liver weight, low thymus weight, hepatocellular changes (hepatic portal vein area) (M/F) ≥3: decreased lymphocytes in thymic cortex (M) ≥31/32: adrenal zona fasciculata/zona reticularis atrophy (M/F) ≥32: high blood triglycerides, decreased lymphocytes in thymic cortex (F) 103: high blood triglycerides (M)	<3 (M) <3 (F)	4.2.3.2.14[c)]

M, male; F, female
a) Air control
b) Vehicle
c) Product (b)
*Excluding 2340 group (F)

Repeated-dose toxicity studies with FF were performed in rats (14 days) and dogs (14 days and 3 months) (Table 11). The NOAEL of FF in dogs (3 months) was determined to be 10.18 µg/kg/day for males and 10.46 µg/kg/day for females. The AUC_{last} at the NOAEL of FF was 2480 pg·h/mL for males, and 3510 pg·h/mL for females. This was approximately 23-fold for males, and approximately 32-fold for females, as compared with estimated $AUC_{0\text{-}24h}$ (110 pg·h/mL) of FF following the administration of BD/GP/FF 640/36/20 µg to patients with COPD; and approximately 16-fold for males, and approximately 23-fold for females as compared with estimated $AUC_{0\text{-}24h}$ (152 pg·h/mL) of FF following the administration of GP/FF 36/19.2 µg to patients with COPD. Major systemic toxicity or abnormal findings were as follows: fibrosis of the myocardium, hyperplasia/fibrosis of alveolar epithelium, increased heart rate, and hepatocellular vacuolization or cytoplasm swelling in dogs. Abnormal findings in the liver were considered as changes associated with drug-metabolizing enzyme induction, and the increase in heart rate is a change caused by β-receptor stimulation of FF, and therefore these findings were not determined to be signs of toxicity.

Table 11. Summary of the results from repeated-dose toxicity studies with FF

Species	Adminis-tration route	Adminis-tration period	Dosage (µg/kg)	Major finding	NOAEL (µg/kg/day)	CTD
M/F rat (SD)	Inhalation	14 days (once daily)	0/0[a)] 0/0[b)] 35/38 88/94 153/163	None	153 (M) 163 (F)	4.2.3.2.1[d)] 4.2.3.2.3[e)]
M/F dog (beagle dog)	Inhalation	14 days (once daily)	0/0[a)] 0/0[b)] 9/9 13/13 27/21	≥9.02/9.38: hepatocellular vacuolization in the liver, increased heart rate (M/F) ≥12.89/13.26: fibrosis of the myocardium in the heart (M/F) 9.38: spindle-shaped cells[c)] in the myocardium (papillary muscle) (F) Reversibility: yes	9.02 (M) 9.38 (F)	4.2.3.2.2[d)] 4.2.3.2.4[e)]
M/F dog (beagle dog)	Inhalation	3 months (once daily)	0/0[a)] 0/0[b)] 4/5 10/10 14/14	≥4.36/4.53: increased heart rate (M/F) ≥10.46: high body weight (F) 14.05: cytoplasm swelling in the liver, hyperplasia/fibrosis of alveolar epithelium (M) 10.46: cytoplasm swelling in the liver (F)	10.18 (M) 10.46 (F)	4.2.3.2.8[d)] 4.2.3.2.15[e)]

M, male; F, female
a) Air control
b) Vehicle
c) This was considered to be an anomaly specific to the individual animal (half-life extension of FF in blood), and the data were not used for determination of NOAEL
d) Product (a)
e) Product (b)

Repeated-dose toxicity studies with GP were performed in rats (14 days and 6 months), and in dogs (14 days and 6 months) (Table 12). The NOAEL of GP in dogs (6 months) was determined to be 77 µg/kg/day for males, and 73 µg/kg/days for females. The AUC_{last} at the NOAEL of GP was 30,650 pg·h/mL for males, and 21,483 pg·h/mL for females. This was approximately 207-fold for males, and approximately 145-fold for females as compared with estimated $AUC_{0\text{-}24h}$ (148 pg·h/mL) for GP following the administration of BD/GP/FF 640/36/20 µg to patients with COPD; and approximately 165-fold for males, and approximately 116-fold for females as compared with estimated $AUC_{0\text{-}24h}$ (186 pg·h/mL) for GP following the administration of GP/FF 36/19.2 µg to patients with COPD. Major abnormal findings were hyaline degeneration of the nasal respiratory/olfactory epithelium, and squamous metaplasia of the laryngeal epithelium in rats. Squamous metaplasia is a change unique to rats, which are highly sensitive to disorders affecting the respiratory mucosa (*Toxicol Pathol.* 1991;19:352-7, *Fundam Appl Toxicol.* 1997;38:143-7), while hyaline degeneration of the nasal respiratory/olfactory epithelium is an adaptive response to inhalation of xenobiotic materials by rodents (*Toxicol Sci.* 1998;45:58-65, *Toxicol Pathol.* 2006;34:252-69, *Ind Health.* 2000;38:309-18). Because the drug is inhaled through the mouth in humans, it was concluded that these findings are unlikely to cause concerns about safety in humans. There were changes in blood cell parameters in rats, and low heart weight in dogs; however, these findings were not accompanied by histopathological changes or other findings, and therefore their toxicological significance was considered to be low.

Table 12. Summary of the results from repeated-dose toxicity studies with GP

Species	Adminis-tration route	Adminis-tration period	Dosage (M/F µg/kg/day)	Major finding	NOAEL (µg/kg/day)	CTD
M/F rat (SD)	Inhalation	14 days (once daily)	0/0[a)] 0/0[b)] 46/49 254/279 514/555	≥254: low reticulocyte percentage (M) 514: high red blood cell count, high hemoglobin, high hematocrit, high mean cell hemoglobin concentration (M) 555: low neutrophil count (F)	514 (M) 555 (F)	4.2.3.2.4[c)] 4.2.3.2.6[d)]
M/F rat (SD)	Inhalation	6 months (once daily)	0/0[a)] 0/0[b)] 65/70 264/286 523/572	≥264/286: hyaline degeneration of the nasal respiratory/olfactory epithelium, squamous metaplasia of the laryngeal epithelium (M/F) Recovery period: none	523 (M) 572 (F)	4.2.3.2.9[c)] 4.2.3.2.17[d)]
M/F dog (beagle dog)	Inhalation	14 days (once daily)	0/0[a)] 0/0[b)] 16/17 29/31 77/83	None	77 (M) 83 (F)	4.2.3.2.5[c)] 4.2.3.2.7[d)]
M/F dog (beagle dog)	Inhalation	6 months (once daily)	0/0[a)] 0/0[b)] 18/19 59/57 77/73	77: low heart weight (M) Recovery period: none	77 (M) 73 (F)	4.2.3.2.10[c)] 4.2.3.2.18[d)]

M, male; F, female
a) Air control
b) Vehicle
c) Product (a)
d) Product (b)

Repeated-dose toxicity studies with BD/FF MDI were performed in rats (14 days), and in dogs (14 days and 3 months) (Table 13). Major systemic toxicity findings included decreased lymphocytes in blood or lymphatic tissue, adrenal atrophy, anomalies in lipid metabolism and hepatic function, gastric mucosal degeneration (including erosion)/ulcer and suppression of bone marrow proliferation (only in rats), and bacterial infection-related changes in rats or dogs, which are considered to be the effect of BD administration. Hepatocellular changes in the hepatic portal vein, which are changes related to drug-metabolizing enzyme induction, occurred in rats and dogs. Toxicity findings related to administration sites were squamous metaplasia of the laryngeal epithelium and accumulation of alveolar macrophages in rats. Squamous metaplasia is considered as a change unique to rats, which are highly sensitive to disorders affecting the respiratory mucosa (*Toxicol Pathol.* 1991;19:352-7, *Fundam Appl Toxicol.* 1997;38:143-7), while accumulation of alveolar macrophages is considered to be a physiological, adaptive response to foreign materials (*J Appl Toxicol.* 2014;34:319-31), and therefore these findings are unlikely to cause concerns about safety in humans.

Table 13. Summary of the results from repeated-dose toxicity studies with BD/FF MDI

Species	Administration route	Administration period	Dosage[a] (µg/kg)	Major finding	NOAEL (µg/kg/day)	CTD
M/F rat (SD)	Inhalation	14 days (once daily)	0/0/0/0[b] 0/0/0/0[c] 450/480/13/14 1500/1580/44/46 3060/3260/90/95	3260/95: death[d] (F, 2/15) ≥450/480/13/14: low body weight gain, low weights of the adrenal glands/spleen/thymus, adrenal zona fasciculata/zona reticularis atrophy, decreased lymphocytes in thymic cortex (M/F) ≥480/14: skin lesions (e.g., hair loss), hepatocellular lipidosis, decreased lymphocytes in periarteriolar lymphoid sheaths and lymph follicles in the spleen (F) ≥1500/1800/44/46: glandular stomach mucosal epithelial degeneration (including erosion)/ulcer (M/F) ≥1500/44: skin lesions (e.g., hair loss), hepatocellular changes (hepatic portal vein area), hepatocellular lipidosis, decreased lymphocytes in periarteriolar lymphoid sheaths and lymph follicles in the spleen (M) ≥1580/46: accumulation of alveolar macrophages (F) 3060/3260/90/95: decreased bone marrow cell count in the femur and sternum, squamous metaplasia of the laryngeal epithelium, decreased lymphocytes in mandibular, tracheobronchial, and mesenteric lymph nodes (M/F) 3060/90: accumulation of alveolar macrophages (F) Reversibility: yes	<450/13 (M) <480/14 (F)	4.2.3.2.8[e]
M/F dog (beagle dog)	Inhalation	14 days (once daily)	0/0/0/0[b] 0/0/0/0[c] 88/89/3/3 174/176/6/6 304/308/10/10	≥88/89/3/3: watery/soft feces, high total protein in blood,* high liver weight, low adrenal gland/thymus weights, adrenal zona fasciculata/zona reticularis atrophy, hepatocellular changes (hepatic portal vein area), decreased lymphocytes in tracheobronchial lymph nodes and thymic cortex (M/F) ≥88/3: low lung weight (M) ≥89/3: low eosinophil count (F) ≥174/176/6/6: high monocyte count/neutrophil count** (M/F) ≥176/6: high blood globulin (F) 304/10: high ALP/globulin/triglycerides in blood (M) Reversibility: yes	<88/3 (M) <89/3 (F)	4.2.3.2.9[e]
M/F dog (beagle dog)	Inhalation	3 months (once daily)	0/0/0/0[b] 0/0/0/0[c] 3/3/0.1/0.1 13/14/0.5/0.5 68/71/2/2	≥3/3/0.1/0.1: low adrenal gland weight, decreased lymphocytes in thymic cortex (M/F) ≥3/0.1: low body weight gain (M) ≥3/0.1: low thymus weight, hepatocellular changes (hepatic portal vein area) (F) ≥13/14/0.5/0.5: adrenal zona fasciculata/zona reticularis atrophy (M/F) ≥13/0.5: high blood albumin, hepatocellular changes (hepatic portal vein area) (M) ≥14/0.5: low body weight gain, high blood triglycerides (F) 68/71/2/2: high blood ALP, high liver weight (M/F) 71/2: high blood albumin (F)	<3/0.1 (M) <3/0.1 (F)	4.2.3.2.16[e]

M, male; F, female
a) BD (male)/BD (female)/FF (male)/FF (female)
b) Air control
c) Vehicle
d) This was determined to be attributable to bacterial infection associated with immunosuppression
e) Product (b)
*Excluding 174/6 group (M); ** excluding 304/10 group (M)

Repeated-dose toxicity studies with BD/GP MDI were performed in rats (14 days), and in dogs (14 days and 3 months) (Table 14). It was not possible to determine the NOAEL. Major systemic toxicity findings included decreased lymphocytes in blood or lymphatic tissue, adrenal atrophy, anomalies in lipid metabolism and

hepatic function, gastric mucosal degeneration (including erosion)/ulcer and suppression of bone marrow proliferation (only in rats), and bacterial infection-related changes in rats or dogs, which are considered to be the effect of BD administration. Hepatocellular changes in the hepatic portal vein, which are changes related to drug-metabolizing enzyme induction, occurred in rats and dogs. Toxicity findings related to administration sites were squamous metaplasia of the laryngeal epithelium and accumulation of alveolar macrophages in rats.

Table 14. Summary of the results from repeated-dose toxicity studies with BD/GP MDI

Species	Administration route	Administration period	Dosage[a)] (µg/kg)	Major finding	NOAEL (µg/kg/day)	CTD
M/F rat (SD)	Inhalation	14 days (once daily)	0/0/0/0[b)] 0/0/0/0[c)] 621/660/33/36 2110/2260/144/122 4350/4650/235/251	2260/122: death[d)] (F, 1/15) 4350/4650/235/251: death[d)] (M, 1/15; F, 3/15) ≥621/660/33/36: skin lesions (hair loss, scratching), low body weight/low body weight gain, high monocyte count/neutrophil count, high total protein in blood, high blood triglycerides, low weights of the adrenal glands/spleen/thymus, adrenal zona fasciculata/zona reticularis atrophy, hepatocellular changes (hepatic portal vein area), hepatocellular lipidosis, accumulation of alveolar macrophages,*** decreased lymphocytes in periarteriolar lymphoid sheaths and lymph follicles in the spleen and in thymic cortex (M/F) ≥621/33: high hematocrit, high hemoglobin, high red blood cell count,* high blood albumin, high albumin/globlin (A/G) ratio, decreased lymphocytes in tracheobronchial lymph nodes (M) ≥660/36: low lymphocyte count, low platelet count, high blood ALT/AST,** high blood urea nitrogen, high blood glucose,*** low uterus weight, glandular stomach mucosal epithelial degeneration (including erosion)/ulcer (F) ≥2110/2260/144/122: low lymphocyte count, squamous metaplasia of the laryngeal epithelium (M/F) ≥2110/144: glandular stomach mucosal epithelial degeneration (including erosion)/ulcer (M) ≥2260/122: low eosinophil count, low inorganic phosphorus in blood, high liver weight, decreased lymphocytes in tracheobronchial lymph nodes (F) 4350/4650/235/251: decreased sternal bone marrow cell count, decreased lymphocytes in mesenteric lymph nodes (M/F) 4350/235: low reticulocyte count, high blood ALT/AST/BUN, low inorganic phosphorus in blood (M) 4650/251: high blood bilirubin (F) Reversibility: yes	<621/33 (M) <660/36 (F)	4.2.3.2.10[e)]
M/F dog (beagle dog)	Inhalation	14 days (once daily)	0/0/0/0[b)] 0/0/0/0[c)] 166/172/9/10 382/396/21/22 524/544/29/30	≥160/172/9/10: high platelet count, high urea nitrogen/creatinine ratio/total protein, low adrenal gland/thymus weights, high liver weight, adrenal zona fasciculata/zona reticularis atrophy, hepatocellular changes (hepatic portal vein area), decreased lymphocytes in tracheobronchial lymph nodes and thymic cortex (M/F) ≥166/9: high blood albumin (M) ≥172/10: low blood creatinine (F) ≥382/396/21/22: high monocyte count/neutrophil count, high GGT (M/F) ≥382/22: low blood creatinine (M) 524/544/29/30: low blood chloride (M/F) 524/29: high blood A/G ratio (M) Reversibility: yes	<166/9 (M) <172/10 (F)	4.2.3.2.2[e)]

Species	Administration route	Administration period	Dosage[a)] (µg/kg)	Major finding	NOAEL (µg/kg/day)	CTD
M/F dog (beagle dog)	Inhalation	3 months (once daily)	0/0/0/0[b)] 0/0/0/0[c)] 4/4/0.2/0.2 31/31/2/2 97/100/5/6	≥4/4/0.2/0.2: low adrenal gland weight, low thymus weight, hepatocellular changes (hepatic portal vein area),[#] decreased lymphocytes in thymic cortex (M/F) ≥4/0.2: high blood triglycerides (F) ≥31/31/2/2: adrenal zona fasciculata/zona reticularis atrophy (M/F) ≥31/2: high liver weight (F) 97/5: high blood triglycerides, high liver weight (M)	<4/0.2 (M) <4/0.2 (F)	4.2.3.2.14[e)]

M, male; F, female
a) BD (male)/BD (female)/GP (male)/GP (female)
b) Air control
c) Vehicle
d) Infection-related changes associated with immunosuppression were observed (neutrophilic/histiocytic inflammation and bacterial infections in systemic organs)
e) Product (b)
* Excluding 2110/144 group (M); ** excluding 2260/122 (F); *** excluding 4650/251 (F)
[#] Excluding 4/0.2 group (F)

Repeated-dose toxicity studies with GP/FF MDI were performed in rats (14 days), and in dogs (14 days and 3 months) (Table 15). The NOAEL of GP/FF in dogs (3 months) was determined to be 43/10 µg/kg/day for males, and 44/11 µg/kg/day for females. The AUC_{last} at the NOAEL of GP/FF was 12,200/3440 pg·h/mL for males, and 9430/2670 pg·h/mL for females. This was approximately 82-fold/31-fold for males, and approximately 64-fold/24-fold for females, as compared with estimated $AUC_{0\text{-}24h}$ (148/110 pg·h/mL) for GP/FF following administration of BD/GP/FF 640/36/20 µg to patients with COPD; and approximately 66-fold/22-fold for males, and approximately 61-fold/17-fold for females, as compared with estimated $AUC_{0\text{-}24h}$ (186/154 pg·h/mL) for GP/FF following administration of GP/FF 36/19.2 µg to patients with COPD. Major toxicity findings included fibrosis of papillary muscles, swelling/hyperplasia of alveolar epithelium, and fibrosis of alveolar interstitium in dogs, which are considered to be the effect of FF administration. Swelling of hepatocytes was considered to be a change related to drug-metabolizing enzyme induction, and increases in heart rate and tidal volume, and the like were considered to be changes related to β-receptor stimulation, and therefore these findings were not determined to be signs of toxicity.

Table 15. Summary of the results from repeated-dose toxicity studies with GP/FF MDI

Species	Administration route	Administration period	Dosage[a] (µg/kg)	Major finding	NOAEL (µg/kg/day)	CTD
M/F rat (SD)	Inhalation	14 days (once daily)	0/0/0/0[b] 0/0/0/0[c] 72/77/14/15 226/241/42/45 368/394/69/73	Testing period: none Recovery period: none	368/69 (M) 394/73 (F)	4.2.3.2.6[d] 4.2.3.2.11[e]
M/F dog (beagle dog)	Inhalation	14 days (once daily)	0/0/0/0[b] 0/0/0/0[c] 17/17/3/3 51/52/9/9, 74/75/13/13	≥17/17/3/3: skin erythema, cytoplasm swelling in the liver, high heart rate, high cardiac output per minute (M/F) ≥17/3: high tidal volume (M) ≥51/9: fibrosis of papillary muscles (M) 75/13: fibrosis of papillary muscles (F) Reversibility: yes	17/3 (M) 17/3 (F)	4.2.3.2.7[d] 4.2.3.2.12[e]
M/F dog (beagle dog)	Inhalation	3 months (once daily)	0/0/0/0[b] 0/0/0/0[c] 17/18/4/5 43/44/10/11 59/62/14/15	≥17/18/4/5: swelling of hepatocytes,* high heart rate (high) ≥44/11: high tidal volume (F) 59/14: accumulation of alveolar macrophages, high cardiac output per minute (M) 62/15: swelling/hyperplasia of alveolar epithelium, fibrosis of alveolar interstitium (F)	43/10 (M) 44/11 (F)	4.2.3.2.8[d] 4.2.3.2.15[e]

M, male; F, female
a) GP (male)/GP (female)/FF (male)/FF (female)
b) Air control
c) Vehicle
d) Product (a)
e) Product (b)
* Excluding 43/10 group (M)

Repeated-dose toxicity studies with BD/GP/FF MDI were performed in rats (14 days), and in dogs (14 days and 3 months) (Table 16). It was not possible to determine the NOAEL. Changes including decreased lymphocytes in blood or lymphatic tissue, adrenal atrophy, anomalies in lipid metabolism and hepatic function, gastric mucosal degeneration (including erosion)/ulcer and suppression of bone marrow proliferation (only in rats), and bacterial infection-related changes in rats or dogs are considered to be the effect of BD administration. Hepatocellular changes in the hepatic portal vein, which are related to drug-metabolizing enzyme induction, occurred in rats and dogs. Toxicity findings related to administration sites were squamous metaplasia of the laryngeal epithelium and accumulation of alveolar macrophages in rats.

Table 16. Summary of the results from repeated-dose toxicity studies with BD/GP/FF MDI

Species	Administration route	Administration period	Dosage[a] (µg/kg)	Major finding	NOAEL (µg/kg/day)	CTD
M/F rat (SD)	Inhalation	14 days (once daily)	0/0/0/0/0/0[b] 0/0/0/0/0/0[c] 1820/1950/96/103/56/63 3680/3940/197/211/114/112 7660/8160/407/434/236/251	1820/96/56: death[d] (M, 1/15) 3940/211/112 death[d] (F, 2/15) 8160/434/251: death[d] (F, 4/15) ≥1820/1950/96/103/56/63: low body weight gain, skin lesions (hair loss, scratching, and laceration), low eosinophil count/lymphocyte count/monocyte count/neutrophil count, high total bilirubin in blood,* high triglycerides, high adrenal gland weight, low spleen/thymus weight, adrenal zona fasciculata/zona reticularis atrophy, decreased lymphocytes in tracheobronchial lymph nodes and thymic cortex, glandular stomach mucosal epithelial degeneration (including erosion)/ulcer (M/F)	<1820/96/56 (M) <1950/103/63 (F)	4.2.3.2.13[e]

Species	Administration route	Administration period	Dosage[a)] (µg/kg)	Major finding	NOAEL (µg/kg/day)	CTD
				≥1820/96/56: squamous metaplasia of the laryngeal epithelium, accumulation of alveolar macrophages* (M) ≥1950/103/63: high blood AST/ALT, hepatocellular lipidosis, decreased lymphocytes in periarteriolar lymphoid sheaths and lymph follicles in the spleen (F) ≥3680/197/114: high blood AST, hepatocellular cytoplasmic change in the hepatic portal vein area, hepatocellular lipidosis, accumulation of alveolar macrophages, decreased lymphocytes in periarteriolar lymphoid sheaths and lymph follicles in the spleen (M) 7660/8160/407/434/236/251: decreased bone marrow cell count in the femur and sternum, decreased lymphocytes in mandibular and mesenteric lymph nodes (M/F) 7660/407/236: low blood ALP, high blood AST (M) Reversibility: yes		
M/F dog (beagle dog)	Inhalation	14 days (once daily)	0/0/0/0/0/0[b)] 0/0/0/0/0/0[c)], 131/132/7/7/4/4 257/263/13/14/8/9 424/431/22/22/14/14	≥131/132/7/7/4/4: watery/soft feces, high white blood cell count, high blood ALP/GGT/total protein,[#] low adrenal gland weight, low lung weight, low heart weight,[##] high liver weight, low thymus weight, adrenal zona fasciculata/zona reticularis atrophy, hepatocellular changes (hepatic portal vein area), decreased lymphocytes in tracheobronchial,[###] decreased lymphocytes in thymic cortex (M/F) ≥131/7/4: high blood globulin, high monocyte count (M) ≥132/7/4: low eosinophil count, high monocyte count[####] (F) ≥257/263/13/14/8/9: high neutrophil count (M/F) ≥257/13/8: low blood cholesterol (M) 424//22/14: low basophil count, low lymphocyte count (M) Reversibility: yes	<131/7/4 (M) <132/7/4 (F)	4.2.3.2.9[e)]
M/F dog (beagle dog)	Inhalation	3 months (once daily)	0/0/0/0/0/0[b)] 0/0/0/0/0/0[c)] 3/3/0.2/0.2/0.1/0.1 17/18/1/1/0.6/0.6 58/61/3/4/2/2	≥3/3/0.2/0.2/0.1/0.1: high blood albumin,[$] low adrenal gland weight, hepatocellular changes (hepatic portal vein area), decreased lymphocytes in thymic cortex (M/F) ≥3/0.2/0.1: low body weight gain, low thymus weight (F) ≥17/18/1/1/0.6/0.6: adrenal zona fasciculata/zona reticularis atrophy (M/F) ≥17/1/0.6: high blood triglycerides (M) 58/61/3/4/2/2: high blood ALP (M/F) 61/4/2: high blood triglycerides (F)	<3/0.2/0.1 (M) <3/0.2/0.1 (F)	4.2.3.2.16[e)]

M, male; F, female
a) BD (male)/BD (female)/GP (male)/GP (female)/FF (male)/FF (female)
b) Air control
c) Vehicle
d) Infection-related changes associated with immunosuppression were observed (neutrophilic/histiocytic inflammation and bacterial infections in systemic organs)
e) Product (b)
* Excluding 8160/434/251 group (F)
[#] Excluding 263/14/9 group (F); [##] excluding 257/13/8 group (M); [###] excluding 132/7/4 (F); [####] excluding 424/22/14 group (M)
[$] excluding 3/0.2/0.1 (M)

5.3 Genotoxicity (GP)

Genotoxicity studies of GP consisted of an *in vitro* bacterial reverse mutation assay (Ames assay), an *in vitro* micronucleus assay with mouse lymphoma TK cells (mammalian cell micronucleus assay), and an *in vivo* micronucleus induction assay in rat bone marrow (rodent micronucleus assay) (Table 17). The results indicated that GP is not genotoxic.

Table 17. Summary of genotoxicity study results

Test		Species	Metabolic activation (treatment)	Concentration or dosage	Test result	CTD
In vitro	Ames assay	*Salmonella typhimurium:* TA98, TA100, TA1535, and TA1537	S9−/+	0,[a] 100, 333, 1000, 3333, 5000 µg/plate	Negative	4.2.3.3.1.1
		E. coli: WP2*uvr*A				
	Mammalian cell micronucleus assay	Mouse lymphoma TK6 cells	S9− (27 hours)	0,[a] 100, 200, 398 µg/mL	Negative	4.2.3.3.1.2
			S9+ (4 hours)			
In vivo	Rodent micronucleus assay	Male rat (SD) Bone marrow		0,[b] 500, 1000, 2000 mg/kg (oral, single-dose)	Negative	4.2.3.3.2.1

a) Vehicle: sterilized water
b) Vehicle: deionized water

5.4 Carcinogenicity (GP)

Inhalation carcinogenicity studies of GP in mice and rats (104 weeks) were performed (Table 18). The results did not show any findings suggesting that GP is carcinogenic. Major non-neoplastic lesions were observed in the GP groups: increased incidences of hyaline degeneration in nasal cavity epithelium and eosinophilic material in the nasal cavity of mice; and increased incidences of neutrophil infiltration in the nasal cavity, hyaline degeneration in nasal cavity epithelium, and squamous metaplasia in rats. Increased incidences of hyaline degeneration in nasal cavity epithelium and hyperplasia of the glandular stomach were observed in the mouse vehicle group compared with air controls. Hyperplasia of the glandular stomach is a naturally occurring lesion found in long-term treated mice (*Toxicol Pathol.* 2016;29:1S-124S, *A Color Atlas.* Saunders/Elsevier pp.45-72), and the increased incidence is likely to be due to exposure of the stomach to the vehicle via its precipitation in the oropharynx. Because the amount of oral intake in clinical use is estimated to be very low, it was concluded that it is unlikely to cause concerns about safety in humans.

Table 18. Summary of carcinogenicity study results

Species	Administration route	Administration period	Major lesions	Sex	Dosage (M/F, µg/kg/day)					Non-carcinogenic dose (µg/kg/day)	CTD
					0/0[a)]	0/0[b)]	347/335	705/700	1460/1420		
				n	MF 60	MF 60	MF 60	MF 60	MF 60		
M/F mouse (B6C3F1)	Inhalation	104 weeks (once daily)	Neoplastic lesion							1460 (M) 1420 (F)	4.2.3.4.1.1
			Harderian glands/ adenocarcinoma	M	0	3	1	2	5		
				F	1	1	1	0	2		
			Systemic histiocytic sarcoma	M	2	0	2	3	0		
				F	3	1	3	0	1		
			Thyroid gland/ follicular adenoma	M	8	19	11	14	9		
				F	12	27	17	14	12		
			Duodenum/adenoma	M	1	0	0	1	2		
				F	0	0	3	0	0		
			Lung/bronchiolar adenoma	M	8	9	9	5	2		
				F	3	2	8	1	8		
			Lung/bronchiolar adenocarcinoma	M	4	9	9	4	5		
				F	3	2	1	2	3		
			Mammary gland/ adenocarcinoma	M	–	–	–	–	–		
				F	0	0	0	0	2		
			Skin/fibrosarcoma	M	1	0	0	0	0		
				F	1	1	5	2	1		
			Non-neoplastic lesion							–	
			≥347/335: low body weight gain, increased incidences of hyaline degeneration in the olfactory nasal epithelium/acute inflammation in the nasal cavity*/hyperplasia of the glandular stomach (M/F), increased incidence of eosinophilic material in the nasal cavity (M) ≥700: increased incidence of eosinophilic material in the nasal cavity (F) Vehicle: increased incidence of hyaline degeneration in the nasal respiratory epithelium (M/F)								

Species	Administration route	Administration period	Major lesions	Sex	Dosage (M/F, µg/kg/day)					Non-carcinogenic dose (µg/kg/day)	CTD
					0/0[a)]	0/0[b)]	152/166	303/331	620/684		
				n	MF 70	MF 70	MF 70	MF 70	MF 70		
M/F rat (SD)	Inhalation	104 weeks (once daily)	Neoplastic lesion							620 (M) 684 (F)	4.2.3.4.1.2
			Adrenal gland/adenoma/adenocarcinoma	M	0	0	1	0	0		
				F	0	2	3	0	0		
			Adrenal gland/ pheochromocytoma (benign/malignant)	M	8	9	5	7	8		
				F	1	0	1	1	1		
			Mammary gland/adenoma/ adenocarcinoma	M	0	0	0	0	0		
				F	11	17	20	8	8		
			Mammary gland/fibroadenoma	M	0	0	0	0	0		
				F	11	14	20	17	14		
			Thyroid gland/C-cell adenoma/cancer	M	2	3	1	3	1		
				F	5	2	2	6	4		
			Non-neoplastic lesion							–	
			≥152/166: increased incidence of neutrophil infiltration in the nasal cavity, increased incidences of hyaline degeneration in the olfactory nasal epithelium** and squamous laryngeal metaplasia in the nose** (M/F) ≥151: low body weight (M) 684: low body weight (F) Vehicle group***: increased incidences of neutrophil infiltration in the nasal cavity and squamous laryngeal metaplasia in the nose (M/F), hyaline degeneration in the olfactory nasal epithelium (F)								

M, male; F, female
"–" indicates not evaluated
a) Air control
b) Vehicle
*Excluding 700 and 1420 groups (F); ** excluding 166 group (F); *** comparison with air controls

5.5 Reproductive and developmental toxicity (GP)

Reproductive and developmental toxicity studies of GP consisted of a study on fertility and early embryonic development to implantation in male and female rats, embryo-fetal development studies in rats and rabbits, and a study of pre- and postnatal development including maternal function in rats (Table 19). Major toxicity

findings included low fetal weight in the rat embryo-fetal development study, and low body weight of newborn rats in the study on rat pre- and postnatal development including maternal function. Decreased fetal survival found in the rabbit embryo-fetal development study was attributable to a small number of ova accidentally occurring in the animals used in the GP group but not to the effect of GP administration.

Table 19. Summary of reproductive and developmental toxicity study results

Test	Species	Administration route	Administration period	Dosage (mg/kg/day)	Major finding	NOAEL (mg/kg/day)	CTD
Fertility and early embryonic development to implantation	M/F rat (SD)	Sub-cutaneous	M, from 4 weeks prior to mating through mating period until necropsy (once daily) F, from 2 weeks prior to mating through gestational day 6 (once daily)	0,[a] 0.1, 1, and 10	Parent animals, ≥0.1: low body weight (M) ≥1: low body weight (F) Fertility: none	Parent animals (general toxicity): <1 Parent animals (fertility): 10	4.2.3.5.1.1
Embryo-fetal development	F rat (SD)	Sub-cutaneous	From gestational day 6 to 17 (once daily) Cesarean section, at gestational day 21	0,[a] 0.1, 1, and 10	Dams, 10: low food intake/body weight/body weight gain Embryo/fetus, low fetal weight	Dams (general toxicity): 1 Embryo-fetal development: 1	4.2.3.5.2.2
	F rabbit (New Zealand White)	Sub-cutaneous	From gestational day 6 to 18 (once daily) Cesarean section, at gestational day 29	0,[a] 0.1, 1, and 10	Dams, ≥1: low fecal amount/food intake/body weight/body weight gain Fetus, ≥0.1: low fetal survival 10: low body weight	Dams (general toxicity): 0.1 Embryo-fetal development: 1	4.2.3.5.2.4
Pre- and post-natal development including maternal function	F rat (SD)	Sub-cutaneous	Dams, from gestational day 6 to postnatal day 21 (once daily)	0,[a] 0.1, 1, and 10	Dams, ≥1: labored respiration, low food intake/body weight/body weight gain F1 generation rats, 10: low body weight	Parent animals (general toxicity): 0.1 Dams (fertility): 10 F1 generation rat development: 1 F1 generation rat fertility: 10	4.2.3.5.3.1

M, male; F, female

a) Physiological saline

5.R Outline of the review conducted by PMDA

5.R.1 GP/FF

The applicant's explanation about systemic toxicity following simultaneous administration of GP and FF in MDI formulations:

A β-receptor stimulation-related change, a pharmacological action of FF, was observed. However, it is unlikely that simultaneous administration of GP and FF will increase the toxicity of individual active ingredients or cause new toxicity as compared with the repeated-dose toxicity studies in which GP or FF was administered as a monocomponent.

PMDA accepted the applicant's explanation.

5.R.2 BD/GP/FF

The applicant's explanation about systemic toxicity following simultaneous administration of BD, GP, and FF in MDI formulations:

A glucocorticoid action-related change, a pharmacological action of BD, was observed. However, it is unlikely that simultaneous administration of BD, GP, and FF combination therapy will increase toxicity of individual active ingredients or cause new toxicity as compared with the repeated-dose toxicity studies in which BD, GP, or FF was administered as a monocomponent.

PMDA accepted the applicant's explanation.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Results from foreign phase I studies in healthy adults (Studies PT003010, PT010001, and PT010002) and other studies were submitted.

Concentrations of GP, FF, and BD in plasma were determined by LC-MS/MS (lower limit of quantitation, 1.00, 1.00, and 3.00 pg/mL, respectively). Unless otherwise specified, dosage is expressed in terms of the delivered dose, as glycopyrronium for GP, formoterol fumarate for FF, and budesonide for BD, and measured values and pharmacokinetic parameters are expressed as mean ± standard deviation.

6.1.1 Relative bioavailability study of GP/FF (CTD 5.3.3.1.2,[Product (a)] Reference CTD 5.3.3.1.4,[Product (b)] Study PT003010 [July 2014 to September 2014])

A randomized, double-blind, 4-treatment, 4-period cross-over study (foreign study) in healthy Japanese adults was conducted to evaluate pharmacokinetic parameters following single-dose administration of 2 inhalations each of GP/FF 14.4/4.8 μg or 7.2/4.8 μg, or GP 14.4 μg or 7.2 μg. The pharmacokinetic parameters are presented in Table 20. As for $AUC_{0\text{-}12h}$ and C_{max} of GP, the least squares mean ratio of GP/FF 28.8/9.6 μg to GP 28.8 μg with its 90% confidence interval (CI) for $AUC_{0\text{-}12h}$ was 0.91 [0.77, 1.08], and that for C_{max} was 1.00 [0.80, 1.25]. The least squares mean ratio of GP/FF 14.4/9.6 μg to GP 14.4 μg with its 90% CI was 0.88 [0.74, 1.05] for $AUC_{0\text{-}12h}$ and 1.23 [0.97, 1.55] for C_{max}, indicating that the ratios are roughly similar.

Table 20. Pharmacokinetic parameters of GP and FF in plasma following single-dose administration of GP/FF or GP (healthy adults)

Measured	Formulation	GP/FF dose (μg)	n	AUC_{0-12h} (pg·h/mL)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)
GP	GP/FF	28.8/9.6	24	45.4 ± 19.4	15.2 ± 7.7	0.1 [0.0, 4.0]	9.5 ± 12.0[a)]
		14.4/9.6	22	21.8 ± 9.0	9.09 ± 6.50	0.1 [0.0, 0.1]	4.1 ± 1.4[a)]
	GP	28.8	24	50.6 ± 22.5	16.9 ± 12.9	0.1 [0.0, 2.0]	24.9 ± 30.3[b)]
		14.4	23	24.7 ± 10.8	7.26 ± 4.26	0.1 [0.0, 4.1]	19.1 ± 51.8[c)]
FF	GP/FF	28.8/9.6	24	44.2 ± 15.3	10.7 ± 3.5	0.1 [0.1, 1.0]	5.5 ± 2.4[d)]
		14.4/9.6	23	42.5 ± 12.0	12.0 ± 7.1	0.1 [0.1, 2.0]	5.3 ± 2.3[e)]

Mean ± standard deviation; t_{max} is the median [range]
a) n = 14, b) n = 10, c) n = 13, d) n = 21, e) n = 20

6.1.2 Relative bioavailability study of BD/GP/FF (Reference CTD 5.3.3.1.4,[Product (a)] 5.3.3.1.1:[Product (b)] Study PT010001 [November 2013 to December 2013], Reference CTD 5.3.3.1.2:[Product (b)] Study PT010002 [June 2014 to September 2014])

A randomized, double-blind, 6-treatment, 4-period cross-over study (foreign study) in healthy adults was conducted to evaluate pharmacokinetic parameters following single-dose administration of 2 inhalations each of BD/GP/FF 40/7.2/4.8 μg, BD/GP/FF 80/7.2/4.8 μg, BD/GP/FF 160/7.2/4.8 μg, GP/FF 7.2/4.8 μg, or BD/FF MDI 80/4.5 μg or 160/4.5 μg, an approved formulation outside Japan. The pharmacokinetic parameters are presented in Table 21.

Table 21. Pharmacokinetic parameters of BD, GP, and FF in plasma following single-dose administration of BD/GP/FF, GP/FF, or BD/FF MDI (healthy adults)

Measured	Formulation	BD/GP/FF dose (μg)	n	AUC_{0-12h} (pg·h/mL)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)
BD	BD/GP/FF	320/14.4/9.6	79	1800 ± 678	574 ± 343	0.4 [0.0, 4.0]	2.9 ± 0.5[a)]
		160/14.4/9.6	26	958 ± 358	283 ± 138	0.3 [0.1, 4.0]	2.9 ± 0.6
		80/14.4/9.6	27	474 ± 184	145 ± 82	0.4 [0.0, 2.0]	3.0 ± 0.5
	BD/FF MDI	320/0/9	77	1560 ± 623	603 ± 453	0.3 [0.0, 4.0]	3.0 ± 0.6[b)]
		160/0/9	28	905 ± 348	307 ± 164	0.3 [0.0, 2.0]	3.0 ± 0.4[c)]
GP	BD/GP/FF	320/14.4/9.6	73	33.9 ± 25.1[d)]	14.1 ± 12.8	0.1 [0.0, 2.1]	3.2 ± 1.8[d)]
		160/14.4/9.6	23	26.7 ± 15.6[e)]	13.4 ± 10.2	0.1 [0.0, 1.0]	3.1 ± 1.7[e)]
		80/14.4/9.6	24	31.4 ± 27.3[f)]	14.3 ± 15.4	0.1 [0.0, 0.6]	3.1 ± 1.8[f)]
	GP/FF	0/14.4/9.6	67	31.8 ± 17.5[g)]	13.3 ± 13.4	0.1 [0.0, 4.0]	3.2 ± 1.7[g)]
FF	BD/GP/FF	320/14.4/9.6	79	61.1 ± 18.8[h)]	12.0 ± 5.5	0.3 [0.0, 4.0]	4.9 ± 1.7[i)]
		160/14.4/9.6	26	57.9 ± 15.6[j)]	11.0 ± 5.1	0.6 [0.0, 2.0]	5.8 ± 2.2[k)]
		80/14.4/9.6	27	62.6 ± 20.2[l)]	11.8 ± 5.8	0.6 [0.0, 4.0]	4.9 ± 2.3[f)]
	GP/FF	0/14.4/9.6	77	58.2 ± 21.9[m)]	11.0 ± 7.1	0.6 [0.1, 8.0]	5.1 ± 2.0[n)]
	BD/FF MDI	320/0/9	77	51.4 ± 17.1[o)]	10.4 ± 5.8	0.1 [0.0, 8.0]	5.2 ± 1.6[p)]
		160/0/9	28	47.2 ± 19.2[l)]	9.4 ± 5.4	0.5 [0.0, 4.0]	5.6 ± 1.6[q)]

Mean ± standard deviation; t_{max} is the median [range]
a) n = 75, b) n = 71, c) n = 27, d) n = 35, e) n = 14, f) n = 15, g) n = 37, h) n = 76, i) n = 48, j) n = 25, k) n = 13, l) n = 24, m) n = 72, n) n = 51, o) n = 66, p) n = 39, q) n = 16

A randomized, double-blind, 3-treatment, 3-period cross-over study (foreign study) in healthy adults was conducted to evaluate pharmacokinetic parameters following single-dose administration of 2 inhalations each of BD/GP/FF 160/7.2/4.8 μg, BD/FF 160/4.8 μg, or BD/FF dry powder inhaler (DPI) 160/4.5 μg, an approved formulation. The pharmacokinetic parameters are presented in Table 22. As for AUC_{0-12h} and C_{max}, the least squares mean ratio of BD/GP/FF 320/14.4/9.6 μg to BD/FF DPI with its 90% CI was 1.25 [1.07, 1.47] for AUC_{0-12h} of BD, 1.02 [0.81, 1.30] for C_{max} of BD, 1.65 [1.41, 1.93] for AUC_{0-12h} of FF, and 1.25 [1.02, 1.54] for C_{max} of FF, indicating that the ratios are higher at BD/GP/FF 320/14.4/9.6 μg compared with BD/FF DPI.

Table 22. Pharmacokinetic parameters of BD, GP, and FF in plasma following single-dose administration of BD/GP/FF, BD/FF, or BD/FF DPI (healthy adults)

Measured	Formulation	BD/GP/FF dose (μg)	n	AUC_{0-12h} (pg·h/mL)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)
BD	BD/GP/FF	320/14.4/9.6	64	1760 ± 754	529 ± 348	0.3 [0.1, 4.0]	3.1 ± 0.4
	BD/FF	320/0/9.6	65	1830 ± 739	505 ± 265	0.7 [0.0, 4.0]	3.1 ± 0.6
	BD/FF DPI	320/0/9	65	1520 ± 826	595 ± 512	0.3 [0.0, 2.0]	3.0 ± 0.5[a)]
GP	BD/GP/FF	320/14.4/9.6	53	21.6 ± 8.6	9.73 ± 7.62	0.1 [0.0, 10.0]	3.9 ± 2.5[b)]
FF	BD/GP/FF	320/14.4/9.6	60	42.9 ± 18.2	9.36 ± 4.98	0.7 [0.1, 12.0]	5.1 ± 2.2[c)]
	BD/FF	320/0/9.6	62	42.3 ± 14.9	8.34 ± 3.61	0.7 [0.1, 8.0]	5.2 ± 2.5[d)]
	BD/FF DPI	320/0/9	58	26.7 ± 14.3	8.39 ± 5.42	0.1 [0.0, 2.0]	5.2 ±1.8[e)]

Mean ± standard deviation; t_{max} is the median [range]
a) n = 64, b) n = 29, c) n = 40, d) n = 47, e) n = 28

6.2 Clinical pharmacology

The data submitted were results from studies including a foreign phase I study in healthy adults (Study PT010003), a foreign phase I study in patients with COPD (Study PT010018), a foreign phase III study (Study PT003006), a global phase III study (Study PT010006), and population pharmacokinetic analyses.

6.2.1 Studies in healthy adults

6.2.1.1 Foreign phase I study (CTD 5.3.3.1.3[Product (b)], Study PT010003 [September 2014 to October 2014])

A randomized, double-blind, placebo-controlled, 3-treatment, 2-period cross-over study in healthy Japanese adults was conducted to evaluate pharmacokinetic parameters following administration of a single dose or repeated doses, twice daily for 7 days, at 2 inhalations each of BD/GP/FF 80/7.2/4.8 µg or 160/7.2/4.8 µg. The pharmacokinetic parameters are presented in Table 23.

Table 23. Pharmacokinetic parameters of BD, GP, and FF in plasma following single-dose or repeated-dose administration of BD/GP/FF (healthy adults)

Measured	BD/GP/FF dose (µg)	Measuring time point (Day)	n	AUC_{0-12h} (pg·h/mL)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)
BD	160/14.4/9.6	1	16	1080 ± 293	314 ± 92	0.3 [0.1, 2.0]	3.9 ± 0.9
		8	16	1540 ± 441	380 ± 107	0.3 [0.0, 1.0]	NC
	320/14.4/9.6	1	15	2260 ± 746	671 ± 205	0.3 [0.0, 1.0]	4.6 ± 0.6
		8	15	3280 ± 780	854 ± 189	0.3 [0.1, 1.0]	NC
GP	160/14.4/9.6	1	16	23.1 ± 10.3[a)]	8.76 ± 6.82	0.1 [0.0, 1.0]	6.7 ± 6.7[b)]
		8	16	82.0 ± 28.5	19.8 ± 8.3	0.1 [0.0, 0.3]	NC
	320/14.4/9.6	1	11	30.5 ± 7.6[c)]	12.3 ± 6.4	0.1 [0.0, 0.1]	13.1 ± 17.4[d)]
		8	11	90.8 ± 28.3	24.6 ± 11.4	0.1 [0.0, 0.3]	NC
FF	160/14.4/9.6	1	16	64.1 ± 16.1	11.5 ± 3.3	1.0 [0.1, 4.0]	7.4 ± 3.0[e)]
		8	16	92.7 ± 25.0	24.3 ± 8.6	0.1 [0.1, 0.3]	NC
	320/14.4/9.6	1	15	58.0 ± 14.9	13.7 ± 3.8	0.1 [0.1, 0.7]	4.9 ± 2.1[a)]
		8	15	102 ± 28	27.5 ± 7.8	0.1 [0.1, 0.7]	NC

Mean ± standard deviation; t_{max} is the median [range]
NC, not calculated
a) n = 9, b) n = 8, c) n = 10, d) n = 6, e) n = 11

6.2.2 Studies in patients with COPD

6.2.2.1 Foreign phase I study (Reference CTD 5.3.3.2.1,[Product (b)] Study PT010018 [August 2017 to December 2017])

An open-label, uncontrolled study in patients with COPD was conducted to evaluate pharmacokinetic parameters following administration of a single dose or repeated doses, twice daily for 7 days, at 2 inhalations each of BD/GP/FF 160/7.2/4.8 µg. The pharmacokinetic parameters are presented in Table 24.

Table 24. Pharmacokinetic parameters of BD, GP, and FF in plasma following single-dose or repeated-dose administration of BD/GP/FF 320/14.4/9.6 µg (patients with COPD)

Measured	Measuring time point (Day)	n	AUC_{0-12h} (pg·h/mL)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)
BD	1	29	2600 ± 904	796 ± 350	0.3 [0.1, 1.0]	6.3 ± 1.6[a)]
	8	27	3380 ± 1510	766 ± 365	0.7 [0.1, 2.0]	NC
GP	1	27	46.5 ± 20.1[b)]	21.2 ± 12.5	0.0 [0.0, 4.0]	13.8 ± 17.2[c)]
	8	25	81.9 ± 33.3[d)]	21.7 ± 13.2	0.1 [0.0, 1.0]	NC
FF	1	29	33.9 ± 10.1[e)]	6.9 ± 2.6	0.3 [0.1, 10.0]	6.3 ± 2.7[f)]
	8	27	49.3 ± 13.5[e)]	7.9 ± 2.6	0.7 [0.0, 12.0]	NC

Mean ± standard deviation; t_{max} is the median [range]
NC, not calculated
a) n = 24, b) n = 22, c) n = 12, d) n = 23, e) n = 25, f) n = 16

6.2.2.2 Foreign phase III study (CTD 5.3.5.1.12,[Product (a)] Reference CTD 5.3.5.1.13:[Product (b)] Study PT003006 [June 2013 to February 2015])

A foreign phase III study was conducted in patients with COPD[5)] to evaluate pharmacokinetic parameters following administration of repeated doses, twice daily, at 2 inhalations each of GP/FF 7.2/4.8 µg, GP 7.2 µg, or FF 4.8 µg. The pharmacokinetic parameters are presented in Table 25.

Table 25. Pharmacokinetic parameters of GP and FF in plasma following repeated-dose administration of GP/FF, GP or FF (patients with COPD)

Measured	Formulation	GP/FF dose (µg)	Measuring time point	n	AUC_{0-12h} (pg·h/mL)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)
GP	GP/FF	14.4/9.6	Day 1	73	42.0 ± 21.8[a)]	20.0 ± 14.7	0.1 [0.0, 8.0]	2.8 ± 1.5[b)]
			Week 12	60	93.4 ± 58.3[a)]	28.7 ± 20.4	0.1 [0.0, 4.5]	4.6 ± 1.2[c)]
	GP	14.4/0	Day 1	58	47.3 ± 28.0[d)]	19.6 ± 14.7	0.1 [0.0, 1.1]	3.1 ± 1.1[e)]
			Week 12	52	89.3 ± 43.9[f)]	23.5 ± 16.6	0.1 [0.0, 12.0]	5.2[g)]
FF	GP/FF	14.4/9.6	Day 1	74	49.2 ± 20.1[h)]	9.85 ± 4.97	0.4 [0.0, 4.0]	4.3 ± 1.0[i)]
			Week 12	60	77.4 ± 32.5[j)]	13.2 ± 6.2	0.4 [0.0, 8.0]	4.2 ± 0.7[k)]
	FF	0/9.6	Day 1	62	44.3 ± 14.3[a)]	8.33 ± 3.94	1.0 [0.0, 12.0]	4.3 ± 0.8[l)]
			Week 12	52	75.7 ± 44.4[m)]	12.3 ± 6.1	1.0 [0.1, 8.0][n)]	4.6 ± 0.6[b)]

Mean ± standard deviation; t_{max} is the median [range]
a) n = 48, b) n = 10, c) n = 2, d) n = 36, e) n = 7, f) n = 39, g) n = 1, h) n = 60, i) n = 18, j) n = 49, k) n = 9, l) n = 16, m) n = 40, n) n = 51

6.2.2.3 Global phase III study (CTD 5.3.5.1.16, Study PT010006 [August 2015 to January 2018])

A global phase III study was conducted in patients with COPD [see Section 7.2.2] to evaluate pharmacokinetic parameters following administration of repeated doses, twice daily for 24 weeks, at 2 inhalations each of BD/GP/FF 160/7.2/4.8 µg, GP/FF 7.2/4.8 µg, BD/FF 160/4.8 µg, or BD/FF DPI 160/4.5 µg. The pharmacokinetic parameters are presented in Table 26.

Table 26. Pharmacokinetic parameters of BD, GP, and FF in plasma following repeated-dose administration of BD/GP/FF, GP/FF, BD/FF, or BD/FF DPI (patients with COPD)

Measured	Formulation	BD/GP/FF dose (µg)	n	AUC_{0-12h} (pg·h/mL)	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)
BD	BD/GP/FF	320/14.4/9.6	75	2,970 ± 1430[a)]	760 ± 394	0.4 [0.0, 12.1][b)]	4.6 ± 1.7[c)]
	BD/FF	320/0/9.6	39	2,890 ± 1290[d)]	744 ± 354	1.0 [0.0, 4.2]	4.7 ± 1.7[e)]
	BD/FF DPI	320/0/9	27	2,520 ± 1130[f)]	716 ± 371	0.3 [0.0, 1.0]	4.6 ± 1.3[g)]
GP	BD/GP/FF	320/14.4/9.6	74	88.3 ± 56.9[h)]	22.9 ± 15.7	0.1 [0.0, 12.1]	8.0 ± 3.0[i)]
	GP/FF	0/14.4/9.6	61	102 ± 77.1[j)]	28.0 ± 31.3	0.1 [0.0, 12.0][k)]	7.4 ± 2.7[l)]
FF	BD/GP/FF	320/14.4/9.6	74	64.5 ± 46.0[h)]	10.1 ± 6.8	1.0 [0.0, 12.1]	5.8 ± 2.3[i)]
	GP/FF	0/14.4/9.6	61	63.8 ± 35.4[m)]	13.9 ± 13.9	0.9 [0.0, 12.1][n)]	7.5 ± 5.8[o)]
	BD/FF	320/0/9.6	39	51.1 ± 18.9[p)]	8.50 ± 4.29	1.0 [0.1, 10.0][i)]	7.7 ± 5.2[q)]

Mean ± standard deviation; t_{max} is the median [range]
a) n = 65, b) n = 73, c) n = 51, d) n = 35, e) n = 29, f) n = 24, g) n = 21, h) n = 53, i) n = 38, j) n = 54, k) n = 60, l) n = 41, m) n = 49, n) n = 59, o) n = 36, p) n = 27, q) n = 18

6.2.3 Population pharmacokinetic analyses

6.2.3.1 GP/FF population pharmacokinetic analysis (Reference CTD 5.3.3.5.1[Product (a)])

Population pharmacokinetic analyses were performed using a non-linear mixed-effect model on plasma GP concentration data (311 subjects, 6025 measuring time points) and plasma FF concentration data (437 subjects, 7783 measuring time points) obtained from studies in patients with COPD, namely, foreign phase I/II studies (Studies PT0010801 and PT0050801), foreign phase II studies (Studies PT0031002, PT005003, and PT009001), and foreign phase III studies (Studies PT003006 and PT003013) ([redacted]).

[5)] A randomized, double-blind, placebo-, GP-, and FF-controlled, parallel-group study to evaluate the efficacy and safety of GP/FF

In the final models of GP and FF, pharmacokinetics was described by a 2-compartment model with first-order absorption. The following covariates were chosen for GP: baseline body weight and eGFR for CL/F and Q/F, baseline body weight for the apparent volume of distribution in the central compartment, smoking status for *K*a, and smoking status, spacer use, and drug-drug interaction for F_{rel}. The following covariates were chosen for FF: body weight and smoking status for CL/F, baseline body weight for the apparent volume of distribution in the central compartment, and smoking status and severity of COPD for *K*a.

CL/F [relative standard error], and Vc/F [relative standard error] estimated from the final models are as follows: 143 L/h [4.85%] and 712 L [6.49%], respectively, for GP; and 97.9 L/h [2.93%] and 971 L [3.23%], respectively, for FF.

6.2.3.2 BD/GP/FF population pharmacokinetic analysis (Reference CTD 5.3.3.5.1[Product (b)])

Population pharmacokinetic analyses were performed using a non-linear mixed-effect model on plasma BD concentration data (220 subjects, 3930 measuring time points), plasma GP concentration data (481 subjects, 7612 measuring time points), and plasma FF concentration data (652 subjects, 10,277 measuring time points) obtained from studies in patients with COPD, namely, a foreign phase I study (Study PT010018), foreign phase I/II studies (Studies PT0010801 and PT0050801), foreign phase II studies (Studies PT0031002, PT005003, and PT009001), foreign phase III studies (Studies PT003006 and PT003013), and a global phase III study (Study PT010006) ([redacted]).

In the final model of BD, pharmacokinetics was described by a 3-compartment model with first-order absorption, while in the final models of GP and FF, pharmacokinetics was described by a 2-compartment model with first-order absorption. The following covariates were chosen for BD: body weight for apparent inter-compartmental clearance [Qp1/F and Qp2/F], and age for CL/F. The following covariates were chosen for GP: eGFR for CL/F, body weight for the apparent volume of distribution in the central and peripheral compartments [Vc/F and Vp/F] and Q/F, smoking status for *K*a, and smoking status, spacer use, and inter-trial variability for F_{rel}. The following covariates were chosen for FF: body weight and smoking status for CL/F, body weight for Vc/F, smoking status and severity of COPD for *K*a, and formulation difference and inter-trial variability for F_{rel}.

CL/F [relative standard error] and Vc/F [relative standard error] estimated from the final models are as follows: 122 L/h [0.753%] and 357 L [1.08%], respectively, for BD; 166 L/h [0.944%] and 1120 L [0.829%], respectively, for GP; and 124 L/h [0.891%] and 1240 L [0.721%], respectively, for FF.

6.2.4 Pharmacodynamic studies

6.2.4.1 Effects on QT/QTc interval (CTD 5.3.4.1.1,[Product (a)] Reference CTD 5.3.4.1.1:[Product (b)] Study PT003009 [[redacted]])

A randomized, double-blind, placebo-controlled, 5-treatment, 4-period cross-over study (foreign study) in healthy adults was conducted to evaluate the effects of GP on QTc interval. Following administration of a single dose inhalation of GP 57.6 μg, GP/FF 7.2/4.8 μg, GP/FF 57.6/19.2 μg, or placebo, at 2 inhalations, or a

single oral dose of moxifloxacin 400 mg (positive control), change from baseline in QTc interval (QTcI) was investigated. The largest mean difference from placebo (corrected mean [90% CI]) was 0.8 [−1.3, 3.0] milliseconds at GP 115.2 μg, 3.1 [1.4, 4.7] milliseconds at GP/FF 14.4/9.6 μg, and 7.6 [6.0, 9.2] milliseconds at GP/FF 115.2/38.4 μg, indicating that the upper limit of 90% CI was <10 milliseconds in all groups. In contrast, the largest mean difference between the moxifloxacin and placebo groups [90% CI] was 9.3 [7.7, 10.9] milliseconds, indicating that the lower limit of 90% CI was ≥5 milliseconds. Table 27 shows pharmacokinetic parameters of GP and FF in plasma.

Table 27. Pharmacokinetic parameters of GP and FF in plasma following a single-dose administration of GP/FF or GP (healthy adults)

Formulation	Dose (μg)	GP		FF	
		C_{max} (pg/mL)	$AUC_{0\text{-}12h}$ (pg·h/mL)	C_{max} (pg/mL)	$AUC_{0\text{-}12h}$ (pg·h/mL)
GP/FF	14.4/9.6 115.2/38.4	15.8 ± 11.6[a)] 105 ± 156	29.9 ± 23.4[a)] 179 ± 102	11.6 ± 6.7 39.4 ± 21.8	40.7 ± 17.6 148 ± 59
GP	115.2	97.4 ±102.8	220 ± 122	—	—

Mean ± standard deviation (n = 66)
a) n = 55

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic difference

6.R.1.1 GP/FF

The applicant's explanation about ethnic difference in pharmacokinetics of GP and FF following administration of GP/FF MDI:

Based on the data including the results from a foreign phase I study in healthy Japanese adults (Study PT003010) and a foreign phase I study in healthy non-Japanese adults (Study PT010001), there were no clear differences between Japanese and non-Japanese subjects in the pharmacokinetic parameters of either GP or FF following administration of GP/FF MDI (Table 20 and Table 21).

6.R.1.2 BD/GP/FF

The applicant's explanation about ethnic difference in pharmacokinetics of BD, GP, and FF following administration of BD/GP/FF MDI:

Taking into consideration the following points on the data including the results from a foreign phase I study in healthy Japanese adults (Study PT010003) and foreign phase I studies in healthy non-Japanese adults (Studies PT010001 and PT010002), there were no clear differences between Japanese and non-Japanese subjects in the pharmacokinetic parameters of BD, GP, or FF following administration of BD/GP/FF MDI.

- While exposure to BD was higher in Japanese subjects than in non-Japanese subjects following administration of BD/GP/FF MDI (Table 21 through Table 23), the distribution range of Japanese subjects was roughly within the distribution range of non-Japanese subjects both for C_{max} and $AUC_{0\text{-}12h}$ (the range of C_{max} for BD following single-dose administration of BD/GP/FF 320/14.4/9.6 μg: [291, 984] pg/mL in Study PT010003, and [48.4, 1690] pg/mL in Studies PT010001 and PT010002; the range of $AUC_{0\text{-}12h}$ for BD following single-dose administration of BD/GP/FF 320/14.4/9.6 μg: [1371, 4436] pg·h/mL in Study PT010003, and [281, 4209] pg·h/mL in Studies PT010001 and PT010002).

- There were no clear differences between Japanese and non-Japanese subjects in the pharmacokinetic parameters of GP or FF following administration of BD/GP/FF MDI (Table 21 through Table 23).

Based on the above, PMDA accepted the applicant's explanation about studies in Sections 6.R.1.1 and 6.R.1.2, and considered that there are no particular problems from a pharmacokinetic viewpoint in using the results of the global studies which included Japanese patients with COPD as evidence for the efficacy and safety of GP/FF MDI and BD/GP/FF MDI. However, BD exposure following administration of BD/GP/FF tended to be higher in Japanese subjects than non-Japanese subjects, and FF exposure following administration of the FF-containing formulation using an inhaler identical to that used for GP/FF MDI or BD/GP/FF MDI tended to be higher compared with the administration of approved formulations (Table 22). Taking into consideration the above and other aspects, GP/FF and BD/GP/FF regimens for Japanese patients with COPD should be carefully determined based on the results of clinical studies.

6.R.2 Effects of kidney function

6.R.2.1 GP/FF

The applicant's explanation about the effects of renal function on GP or FF exposure following administration of GP/FF MDI:

Under the assumption that patients with COPD had an eGFR lower than that of the target patients of population pharmacokinetic analyses, GP exposure was estimated using a population pharmacokinetic analysis model. The estimation suggested that in patients with mild, moderate, and severe renal impairment (assuming 60, 30, and 15 mL/min/1.73m^2 as eGFR), the steady state $AUC_{0\text{-}12h}$ would be increased by approximately 20%, 70%, and 130%, respectively. Renal function did not affect FF exposure. Based on the above results, the applicant will inform healthcare professionals of the increase in GP exposure associated with deteriorated renal function via the package insert.

6.R.2.2 BD/GP/FF

The applicant's explanation about the effects of renal function on BD, GP, or FF exposure following administration of BD/GP/FF MDI:

Under the assumption that a patient with COPD had an eGFR of 45.0 mL/min, GP exposure was estimated using a population pharmacokinetic analysis model. The estimation suggested that the parameters would be increased as follows: C_{min} by 95%, C_{max} by 28%, and $AUC_{0\text{-}12h}$ by 68%. Renal function did not affect BD or FF exposure. Based on the above results, the applicant will inform healthcare professionals of the increase in GP exposure associated with deteriorated renal function via the package insert.

PMDA accepted the applicant's explanation in the discussions in Sections 6.R.2.1 and 6.R.2.2.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the pivotal efficacy and safety evaluation data from 7 studies listed in Table 28. Unless otherwise specified, dosage is expressed in terms of the delivered dose, as glycopyrronium for GP, formoterol fumarate for FF, and budesonide for BD.

Table 28. List of clinical studies on main efficacy and safety

Region	Study	Phase	Target patients	Number of subjects	Summary of regimen	Main endpoints
Japan	PT001004	II	Patients with COPD	66	Twice-daily inhalation administration of GP 7.2 µg, 14.4 µg, 28.8 µg, or placebo	Efficacy Safety
Foreign	PT005003	II	Patients with COPD	50	Single inhaled administration of FF 7.2 µg, 9.6 µg, 19.2 µg, FF DPI 10 µg, 20 µg, or placebo	Efficacy Safety PK
Foreign	PT003005	II	Patients with COPD	159	Inhaled administration of GP/FF 0.96/9.6 µg, 1.9/9.6 µg, 3.7/9.6 µg, 7.2/9.6 µg, 14.4/9.6 µg, FF 9.6 µg, or GP 14.4 µg, twice daily, or tiotropium bromide 18 µg once daily	Efficacy Safety
Foreign	PT009001[a)]	II	Patients with COPD	180	Twice-daily inhalation administration of BD/FF 80/9.6 µg, 160/9.6 µg, 320/9.6 µg, BD 320 µg, or FF 9.6 µg	Efficacy Safety PK
Global	PT003014[b)]	III	Patients with COPD	(1) 555 (2) 483 (3) 480 (4) 238	Twice-daily inhalation administration of (1) GP/FF 14.4/9.6 µg (2) FF 9.6 µg (3) GP 14.4 µg (4) placebo	Efficacy Safety
Global	PT010006	III	Patients with COPD	(1) 640 (2) 627 (3) 316 (4) 319	Twice-daily inhalation administration of (1) BD/GP/FF 320/14.4/9.6 µg (2) GP/FF 14.4/9.6 µg (3) BD/FF 320/9.6 µg (4) BD/FF DPI 320/9 µg	Efficacy Safety PK
Japan	PT010007	III	Japanese patients with COPD who were enrolled in Study PT010006	347	Twice-daily inhalation administration of (1) BD/GP/FF 320/14.4/9.6 µg (2) GP/FF 14.4/9.6 µg (3) BD/FF 320/9.6 µg (4) BD/FF DPI 320/9 µg	Efficacy Safety

a) Reference data in the clinical package for Product (a)
b) Reference data in the clinical package for Product (b)

7.1 Phase II studies

7.1.1 GP Japanese phase II study (CTD 5.3.5.1.4, Study PT001004 [January 2015 to September 2015])

A randomized, double-blind, placebo-controlled, 4-treatment, 4-period cross-over study was conducted in patients with COPD[6)] (target sample size, 60 subjects) to assess the efficacy and safety of GP.

Subjects received 2 inhalations each of GP 3.6 µg, 7.2 µg, 14.4 µg, or placebo, twice daily (GP 7.2 µg-treatment period, GP 14.4 µg-treatment period, GP 28.8 µg-treatment period, and placebo period, respectively). There was a 5- to 21-day washout period between each 7-day treatment period.

A total of 66 subjects were randomized to GP 7.2 µg, 14.4 µg, 28.8 µg, or placebo in Treatment period 1. At the end of Treatment period 4, the number of subjects who received the study drug for each treatment was 62 subjects (GP 7.2 µg), 63 subjects (GP 14.4 µg), 61 subjects (GP 28.8 µg), and 65 subjects (placebo). All 66 subjects were included in the intention-to-treat (ITT) population and safety analysis population. Among these, subjects whose respiratory function data following study drug administration from ≥2 treatment periods were collected were included in the modified ITT (mITT) population and efficacy analysis population: 62 subjects (GP 7.2 µg), 61 subjects (GP 14.4 µg), 61 subjects (GP 28.8 µg), and 62 subjects (placebo). Treatment

[6)] Patients with COPD with smoking history ≥10 pack-years, pre- and post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratios <0.70, post-bronchodilator FEV_1 ≥30% and <80% of the predicted value.

discontinuation occurred in 7.6% of subjects (5 of 66 subjects), with the main reason being "patient's request" (2 subjects).

The primary endpoint, change from baseline in morning trough FEV_1 on Day 8, is shown in Table 29.

Table 29. Change from baseline in morning trough FEV_1 (mL) on Day 8 (mITT population)

Treatment period	GP 7.2 µg	GP 14.4 µg	GP 28.8 µg	Placebo
Baseline[a)]	1569 ± 552 (62)	1582 ± 547 (61)	1582 ± 547 (61)	1582 ± 547 (61)
Day 8	1648 ± 548 (62)	1679 ± 527 (61)	1682 ± 524 (61)	1549 ± 555 (61)
Change from baseline	79 ± 130 (62)	97 ± 121 (61)	101 ±151 (61)	−32 ± 126 (61)
Difference vs placebo treatment[b)]	108	129	131	
[95% CI]	[72, 144]	[93, 165]	[95, 168]	

Mean ± standard deviation (number of subjects)
a) Mean pre-initial dose value at each dose level (mean of the 60 and 30 minutes pre-dose values)
b) A linear mixed-effect model with treatment, baseline, and treatment period as the fixed effects, and subject as the random effect

Adverse events occurred in 11.3% of subjects (7 of 62 subjects) in the GP 7.2-µg treatment period, 9.5% of subjects (6 of 63 subjects) in the GP 14.4-µg treatment period, 8.2% of subjects (5 of 61 subjects) in the GP 28.8-µg treatment period, and 9.2% of subjects (6 of 65 subjects) in the placebo period. Major adverse events were nasopharyngitis (1 subject during the GP 7.2-µg treatment period, 2 subjects during the GP 14.4-µg treatment period, and 1 subject during the placebo period), and rash (2 subjects during the GP 28.8-µg treatment period).

No deaths occurred. An adverse event in 1 subject in the placebo group (pneumonia/chronic obstructive pulmonary disease) was classified as a serious adverse event, which led to treatment discontinuation.

Adverse reactions occurred in 1.6% of subjects (1 of 62 subjects) in the GP 7.2-µg treatment period, 1.6% of subjects (1 of 63 subjects) in the GP 14.4-µg treatment period, and 1.5% of subjects (1 of 65 subjects) in the placebo group.

7.1.2 FF foreign phase II study (CTD 5.3.5.1.6, Study PT005003 [May 2011 to July 2011])

In patients with COPD[7)] (target sample size, 48 subjects), a randomized, double-blind,[8)] placebo-controlled, 6-treatment, 6-period cross-over study was conducted in the US to assess the efficacy and safety of FF.

A single dose of 2 inhalations each of FF 3.6 µg, FF 4.8 µg, FF 9.6 µg, or placebo, or 1 inhalation or 2 inhalations FF DPI 10 µg, approved formulation outside Japan, were administered in each treatment period (FF 7.2-µg treatment period, FF 9.6-µg treatment period, FF 19.2-µg treatment period, placebo period, FF DPI 10-µg treatment period, and FF DPI 20-µg treatment period). There was a 3- to 10 day-washout period between treatment periods.

[7)] Patients with COPD with smoking history ≥10 pack-years, pre- and post-bronchodilator FEV_1/FVC ratios <0.70, a post-bronchodilator FEV_1 ≥30% and <80% of the predicted value, and airway reversibility (an increase in FEV_1 by >12% and >150 mL following 4 inhalations of salbutamol; or an increase in FEV_1 by ≥200 mL following 2 inhalations of salbutamol).
[8)] Subjects in the FF DPI group received the study drug under an open-label condition.

A total of 50 subjects were randomized to the treatment period of FF 7.2 µg, FF 9.6 µg, FF 19.2 µg, placebo, FF DPI 10 µg, or FF DPI 20 µg in Treatment period 1. At the end of Treatment period 6, the number of subjects who received the study drug for each treatment was 47 subjects (FF 7.2 µg), 47 subjects (FF 9.6 µg), 46 subjects (FF 19.2 µg), 48 subjects (placebo), 46 subjects (FF DPI 10 µg), and 48 subjects (FF DPI 20 µg). All 50 subjects were included in the ITT population and safety analysis population. Among these, subjects who had sufficient data in ≥3 treatment periods with respiratory data over 12 hours were included in the mITT and efficacy analysis population: 47 subjects (FF 7.2 µg), 46 subjects (FF 9.6 µg), 45 subjects (FF 19.2 µg), 43 subjects (placebo), 45 subjects (FF DPI 10 µg), and 46 subjects (FF DPI 20 µg). Treatment discontinuation occurred in 10.0% (5 of 50 subjects), with the main reasons being "patient's request" and "violation of discontinuation criteria" (2 subjects each).

Table 30 shows post-dose normalized $FEV_1AUC_{0\text{-}12}$ [see Section 10 for the definition], the primary efficacy endpoint, demonstrating a statistically significant difference between each dose level of FF MDI or FF DPI and the placebo.

Table 30. Normalized $FEV_1AUC_{0\text{-}12}$ following single dose administration (mL) (mITT population)

Treatment period	FF 7.2 µg	FF 9.6 µg	FF 19.2 µg	FF DPI 10 µg	FF DPI 20 µg	Placebo
Baseline FEV_1[a)]	1213 ± 436 (47)	1222 ± 462 (46)	1223 ± 465 (45)	1220 ± 484 (45)	1229 ± 484 (46)	1226 ± 491 (43)
Normalized $FEV_1AUC_{0\text{-}12}$	1437 ± 452 (46)	1440 ± 465 (45)	1482 ± 487 (44)	1469 ± 497 (44)	1523 ± 478 (46)	1279 ± 481 (41)
Normalized $FEV_1AUC_{0\text{-}12}$[b)]	1445	1450	1492	1489	1541	1281
[95% CI]	[1382, 1508]	[1387, 1513]	[1430, 1555]	[1426, 1552]	[1478, 1603]	[1218, 1344]
Difference from placebo[b)]	164	169	211	208	260	
[95% CI]	[130, 198]	[135, 203]	[177, 245]	[174, 242]	[226, 293]	
p-value[b),c)]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	

Mean ± standard deviation (number of subjects)

a) Mean of FEV_1 values 60 and 30 minutes prior to administration

b) A linear mixed effect model with treatment, baseline FEV_1, treatment period, and treatment sequence as the fixed effects, and subject as the random effect

c) Two-sided 5% significance level. Multiplicity was adjusted using a hierarchical testing

Adverse events occurred in 6.4% of subjects in the FF 7.2-µg treatment period (3 of 47 subjects; hypertension/osteoarthritis [1], corneal abrasion [1], pyrexia [1]), 4.3% of subjects in the FF 9.6-µg treatment period (2 of 47 subjects; tooth avulsion [1], urinary tract obstruction [1]), 6.5% of subjects in the FF 19.2-µg treatment period (3 of 46 subjects; tremor [1], intervertebral disc degeneration [1], Type 2 diabetes mellitus [1]), 8.7% of subjects in the FF DPI 10-µg treatment period (4 of 46 subjects; tremor [2], blood bilirubin increased [1], blood potassium decreased [1]), 10.4% of subjects in the FF DPI 20-µg treatment period (5 of 48 subjects; nasopharyngitis [1], nasopharyngitis/hepatic enzyme increased [1], upper respiratory tract infection [1], myalgia [1], pain in extremity [1]), and 4.2% of subjects in the placebo period (2 of 48 subjects; dyspnoea [1], diarrhoea [1]).

No deaths or serious adverse events occurred. An adverse event led to treatment discontinuation in 1 subject in the FF DPI 20-µg treatment period.

Adverse reactions occurred in 4.3% of subjects (2 of 46 subjects) in the FF DPI 10-µg treatment period.

7.1.3 GP/FF foreign phase II study (CTD 5.3.5.1.11,[Product (a)] 5.3.5.1.12:[Product (b)] Study PT003005 [May 2012 to September 2012])

In patients with COPD (target sample size, 160 subjects),[9)] a randomized, double-blind,[10)] GP- and FF-controlled, 8-treatment, 4-period cross-over study was conducted in the US to assess the efficacy and safety of GP/FF MDI.

Subjects received GP/FF 0.48/4.8 µg, GP/FF 0.96/4.8 µg, GP/FF 1.8/4.8 µg, GP/FF 3.6/4.8 µg, GP/FF 7.2/4.8 µg, GP 7.2 µg, or FF 4.8 µg, administered as 2 inhalations twice daily, or tiotropium bromide DPI (approved formulation) 18 µg, administered as 1 inhalation once daily (GP/FF 0.96/9.6-µg treatment period, GP/FF 1.9/9.6-µg treatment period, GP/FF 3.7/9.6-µg treatment period, GP/FF 7.2/9.6-µg treatment period, GP/FF 14.4/9.6-µg treatment period, GP 14.4-µg treatment period, FF 9.6-µg treatment period, and tiotropium treatment period, respectively). There was a 7- to 21-day washout period between each 7-day period.

In this study, each subject was assigned to undergo 4 treatment periods. Subjects were randomized to 4 of the 8 treatments. A total of 159 subjects were randomized.[11)] At the end of Treatment period 4, the number of subjects who received the study drug for each treatment was 68 subjects (GP/FF 0.96/9.6 µg), 71 subjects (GP/FF 1.9/9.6 µg), 67 subjects (GP/FF 3.7/9.6 µg), 70 subjects (GP/FF 7.2/9.6 µg), 71 subjects (GP/FF 14.4/9.6 µg), 66 subjects (GP 14.4 µg), 73 subjects (FF 9.6 µg), and 71 subjects (tiotropium). Subjects who had baseline data and efficacy data after study drug administration were included in the ITT population and safety analysis population. Among these, subjects who had pre-dose efficacy data on Days 1 and 7 and 2-hour post-dose efficacy data on Day 7 in ≥2 treatment periods were included in the mITT and efficacy analysis populations: 65 subjects (GP/FF 0.96/9.6 µg), 61 subjects (GP/FF 1.9/9.6 µg), 61 subjects (GP/FF 3.7/9.6 µg), 56 subjects (GP/FF 7.2/9.6 µg), 63 subjects (GP/FF 14.4/9.6 µg), 60 subjects (GP 14.4 µg), 62 subjects (FF 9.6 µg), and 63 subjects (tiotropium). Treatment discontinuation occurred in 24.5% of subjects (39 of 159 subjects), with the main reasons being "adverse events" (14 subjects), "violation of discontinuation criteria" (9 subjects), and "patient's request" (7 subjects).

Table 31 shows normalized $FEV_1AUC_{0\text{-}12}$ on Day 7 [see Section 10 for the definition], the primary efficacy endpoint.

[9)] Patients with COPD with smoking history ≥10 pack-years, pre- and post-bronchodilator FEV_1/FVC ratios <0.70, a post-bronchodilator FEV_1 ≥750 mL, and ≥30% and <80% of the predicted value.
[10)] Subjects in the tiotropium treatment period received the study drug under an open-label condition.
[11)] Subjects with pre-bronchodilator FEV_1 <80% of the predicted value were randomized.

Table 31. Normalized FEV_1AUC_{0-12} on Day 7 (mL) (mITT population)

Treatment period	GP/FF 0.96/9.6 µg	GP/FF 1.9/9.6 µg	GP/FF 3.7/9.6 µg	GP/FF 7.2/9.6 µg	GP/FF 14.4/9.6 µg	GP 14.4 µg	FF 9.6 µg	Tiotropium
Baseline FEV_1[a)]	1245 ± 514 (65)	1369 ± 572 (61)	1274 ± 463 (61)	1359 ± 477 (56)	1300 ± 482 (63)	1299 ± 583 (60)	1368 ± 587 (62)	1260 ± 534 (63)
Normalized FEV_1AUC_{0-12} on Day 7	1466 ± 566 (60)	1646 ± 555 (57)	1511 ± 458 (57)	1606 ± 477 (52)	1583 ± 526 (59)	1461 ± 580 (57)	1536 ± 588 (57)	1441 ± 533 (60)
Normalized FEV_1AUC_{0-12}[b)] on Day 7 [95% CI]	1508 [1472, 1545]	1538 [1502, 1575]	1539 [1502, 1575]	1547 [1509, 1585]	1591 [1554, 1628]	1452 [1415, 1489]	1467 [1430, 1505]	1489 [1453, 1525]
Difference from GP 14.4 µg[b)] [95% CI]	57 [15, 99]	87 [44, 130]	87 [44, 130]	95 [51, 139]	139 [97, 182]			
Difference from FF 9.6 µg[b)] [95% CI]	41 [−1, 83]	71 [29, 114]	71 [29, 114]	79 [35, 124]	124 [81, 166]			

Mean ± standard deviation (number of subjects)

a) Mean pre-initial dose value at each dose level (mean of FEV_1 values 60 and 30 minutes prior to administration)

b) A linear mixed-effect model with treatment, baseline FEV_1, reversibility, treatment sequence, and treatment period as the fixed effects, and subject as the random effect

Adverse events occurred in 14.7% of subjects (10 of 68 subjects) in the GP/FF 0.96/9.6-µg treatment period, 28.2% of subjects (20 of 71 subjects) in the GP/FF 1.9/9.6-µg treatment period, 28.4% of subjects (19 of 67 subjects) in the GP/FF 3.7/9.6-µg treatment period, 27.1% of subjects (19 of 70 subjects) in the GP/FF 7.2/9.6-µg treatment period, 23.9% of subjects (17 of 71 subjects) in the GP/FF 14.4/9.6-µg treatment period, 36.4% of subjects (24 of 66 subjects) in the GP 14.4-µg treatment period, 28.8% of subjects (21 of 73 subjects) in the FF 9.6-µg treatment period, and 26.8% of subjects (19 of 71 subjects) in the tiotropium treatment period. Major adverse events are presented in Table 32.

Deaths occurred in 1 subject in the GP/FF 0.96/9.6-µg treatment period (cardio-respiratory arrest), and 1 subject in the FF 9.6-µg treatment period (sudden death). A causal relationship to the study drug was ruled out for both deaths. Serious adverse events occurred in 2 subjects in the GP/FF 0.96/9.6-µg treatment period (cardio-respiratory arrest, tachycardia), 1 subject in the GP/FF 1.9/9.6-µg treatment period (spinal compression fracture), 1 subject in the GP/FF 14.4/9.6-µg treatment period (transient ischaemic attack), 1 subject in the GP 14.4-µg treatment period (pneumothorax), and 1 subject in the FF 9.6-µg treatment period (sudden death). Adverse events led to treatment discontinuation in 2 subjects in the GP/FF 0.96/9.6-µg treatment period, 1 subject in the GP/FF 1.9/9.6-µg treatment period, 2 subjects in the GP/FF 7.2/9.6-µg treatment period, 3 subjects in the GP/FF 14.4/9.6-µg treatment period, 1 subject in the GP 14.4-µg treatment period, 2 subjects in the FF 9.6-µg treatment period, and 2 subjects in the tiotropium treatment period.

Adverse reactions occurred in 7.4% of subjects (5 of 68 subjects) in the GP/FF 0.96/9.6-µg treatment period, 14.1% of subjects (10 of 71 subjects) in the GP/FF 1.9/9.6-µg treatment period, 10.4% of subjects (7 of 67 subjects) in the GP/FF 3.7/9.6-µg treatment period, 18.6% of subjects (13 of 70 subjects) in the GP/FF 7.2/9.6-µg treatment period, 11.3% of subjects (8 of 71 subjects) in the GP/FF 14.4/9.6-µg treatment period, 16.7% of subjects (11 of 66 subjects) in the GP 14.4-µg treatment period, 9.6% of subjects (7 of 73 subjects) in the FF 9.6-µg treatment period, and 9.9% of subjects (7 of 71 subjects) in the tiotropium treatment period.

Table 32. Adverse events with an incidence of ≥2.0% in any treatment period (safety analysis population)

Adverse event	GP/FF 0.96/9.6 µg (n = 68)	GP/FF 1.9/9.6 µg (n = 71)	GP/FF 3.7/9.6 µg (n = 67)	GP/FF 7.2/9.6 µg (n = 70)	GP/FF 14.4/9.6 µg (n = 71)	GP 14.4 µg (n = 66)	FF 9.6 µg (n = 73)	Tiotropium (n = 71)
Dry mouth	1 (1.5)	5 (7.0)	3 (4.5)	3 (4.3)	2 (2.8)	8 (12.1)	6 (8.2)	6 (8.5)
Tremor	1 (1.5)	4 (5.6)	2 (3.0)	5 (7.1)	0	0	2 (2.7)	0
Headache	1 (1.5)	0	1 (1.5)	0	0	1 (1.5)	2 (2.7)	0
Atrial fibrillation	1 (1.5)	0	0	0	0	0	0	2 (2.8)
Nasopharyngitis	0	2 (2.8)	1 (1.5)	1 (1.4)	1 (1.4)	0	0	1 (1.4)
Fall	0	2 (2.8)	0	1 (1.4)	0	0	0	0
Contusion	0	1 (1.4)	0	2 (2.9)	0	0	1 (1.4)	0
Musculoskeletal pain	0	1 (1.4)	0	2 (2.9)	0	0	0	0
Hyperkalaemia	0	1 (1.4)	0	1 (1.4)	0	2 (3.0)	0	2 (2.8)
Upper respiratory tract infection	0	0	2 (3.0)	1 (1.4)	2 (2.8)	0	0	0
Nasal congestion	0	0	1 (1.5)	1 (1.4)	0	2 (3.0)	0	0
Cough	0	0	1 (1.5)	0	2 (2.8)	0	2 (2.7)	1 (1.4)
Chronic obstructive pulmonary disease	0	0	0	1 (1.4)	3 (4.2)	0	1 (1.4)	1 (1.4)
Vomiting	0	0	0	1 (1.4)	1 (1.4)	3 (4.5)	0	1 (1.4)
Pneumonia	0	0	0	0	0	0	0	2 (2.8)

Number of subjects (%)

7.1.4 BD/FF foreign phase II study (CTD 5.3.5.1.7,[Product (a)] 5.3.5.1.8:[Product (b)] Study PT009001 [August 2014 to March 2015])

A randomized, double-blind, BD- and FF-controlled, 5-treatment, 4-period cross-over study in patients with COPD[12)] (target sample size, 160 subjects) was conducted in the US to assess the efficacy and safety of BD/FF MDI.

Subjects received BD/FF 40/4.8 µg, BD/FF 80/4.8 µg, BD/FF 160/4.8 µg, BD 160 µg, or FF 4.8 µg, administered as 2 inhalations twice daily (BD/FF 80/9.6-µg treatment period, BD/FF 160/9.6-µg treatment period, BD/FF 320/9.6-µg treatment period, BD 320-µg treatment period, and FF 9.6-µg treatment period, respectively). There was a 14- to 21-day washout period between each 29-day treatment period.

In this study, each subject was assigned to undergo 4 treatment periods. Subjects were randomized to either one of 12 sequences of treatments in which 4 of the 5 treatments were arranged in a certain order. A total of 180 subjects were randomized.[13),14)] The number of subjects who received the study drug for each treatment was 103 subjects (BD/FF 80/9.6 µg), 106 subjects (BD/FF 160/9.6 µg), 155 subjects (BD/FF 320/9.6 µg), 108 subjects (BD 320 µg), and 157 subjects (FF 9.6 µg). All randomized subjects were included in the ITT and safety analysis populations. Among these, subjects who had efficacy data following study drug administration in ≥2 treatment periods were included in the mITT and efficacy analysis populations: 98 subjects (BD/FF 80/9.6 µg), 100 subjects (BD/FF 160/9.6 µg), 152 subjects (BD/FF 320/9.6 µg), 104 subjects (BD 320 µg), and 148 subjects (FF 9.6 µg). Treatment discontinuation occurred in 26.1% of subjects (47 of 180 subjects) with the main reasons being "violation of discontinuation criteria" (24 subjects) and "patient's request" (14 subjects).

12) Patients with COPD with smoking history ≥10 pack-years, a FEV_1/FVC ratio <0.70, a post-bronchodilator FEV_1 ≥30% and <80% of the predicted value.
13) Patients with a pre-bronchodilator FEV_1/FVC ratio <0.70, and the mean of FEV_1 values 60 and 30 minutes prior to study drug administration <80% of the predicted value were randomized.
14) Enrollment into the pharmacokinetic study was selected as the stratification factor.

Table 33 shows normalized FEV_1AUC_{0-12} on Day 29 [see Section 10 for the definition], the primary efficacy endpoint, demonstrating a statistically significant difference between each dose level of BD/FF MDI and BD 320 µg.

Table 33. Normalized FEV_1AUC_{0-12} on Day 29 (mL) (mITT population)

Treatment period	BD/FF 80/9.6 µg	BD/FF 160/9.6 µg	BD/FF 320/9.6 µg	BD 320 µg	FF 9.6 µg
Baseline FEV_1[a)]	1247 ± 433 (98)	1236 ± 499 (100)	1238 ± 466 (152)	1225 ± 454 (104)	1225 ± 458 (148)
Normalized FEV_1 AUC_{0-12} on Day 29	209 ± 249 (96)	202 ± 241 (98)	240 ± 232 (148)	19 ± 170 (99)	188 ± 217 (142)
Normalized FEV_1 AUC_{0-12}[b)] on Day 29 [95% CI]	205 [165, 244]	197 [158, 236]	231 [197, 266]	11 [−28, 50]	176 [141, 210]
Difference from BD 320 µg[b)] [95% CI] p-value[b),c)]	194 [150, 237] <0.0001	186 [143, 230] <0.0001	221 [182, 259] <0.0001		
Difference from FF 9.6 µg[b)] [95% CI]	29 [−10, 68]	21 [−18, 60]	56 [22, 90]		

Mean ± standard deviation (number of subjects)
a) Mean pre-initial dose value at each dose level (mean of FEV_1 values 60 and 30 minutes prior to administration)
b) A linear mixed-effect model with treatment, baseline FEV_1, reversibility, and treatment period as the fixed effects, and subject as the random effect
c) Two-sided 5% significance level. Multiplicity in testing was adjusted by the sequential testing procedure, step-down from higher dose

Adverse events occurred in 29.1% of subjects (30 of 103 subjects) in the BD/FF 80/9.6-µg treatment period, 28.3% of subjects (30 of 106 subjects) in the BD/FF 160/9.6-µg treatment period, 31.0% of subjects (48 of 155 subjects) in the BD/FF 320/9.6-µg treatment period, 27.8% of subjects (30 of 108 subjects) in the BD 320-µg treatment period, and 26.1% of subjects (41 of 157 subjects) in the FF 9.6-µg treatment period. Major adverse events are presented in Table 34.

No deaths occurred. Serious adverse events occurred in 3 subjects in the BD/FF 80/9.6-µg treatment period (cerebrovascular accident [1], acute myocardial infarction [1], angina pectoris/chronic obstructive pulmonary disease [1]), 2 subjects in the BD/FF 160/9.6-µg treatment period (back pain, small intestinal obstruction), 4 subjects in the BD/FF 320/9.6-µg treatment period (chronic obstructive pulmonary disease [1], laryngeal oedema [1], coronary artery disease [1], gastroenteritis [1]), 4 subjects in the BD 320-µg treatment period (osteoarthritis [1], clostridium difficile colitis/chronic obstructive pulmonary disease [1], chronic obstructive pulmonary disease [1], prostate cancer [1]), and 2 subjects in the FF 9.6-µg treatment period (appendicitis, anxiety). Adverse events led to treatment discontinuation in 3 subjects in the BD/FF 80/9.6-µg treatment period, 1 subject in the BD/FF 320/9.6-µg treatment period, and 2 subjects in the BD 320-µg treatment period.

Adverse reactions occurred in 3.9% of subjects (4 of 103 subjects) in the BD/FF 80/9.6-µg treatment period, 2.8% of subjects (3 of 106 subjects) in the BD/FF 160/9.6-µg treatment period, 3.2% of subjects (5 of 155 subjects) in the BD/FF 320/9.6-µg treatment period, 5.6% of subjects (6 of 108 subjects) in the BD 320-µg treatment period, and 1.9% of subjects (3 of 157 subjects) in the FF 9.6-µg treatment period.

Table 34. Adverse events with an incidence of ≥2.0% in any treatment period (safety analysis population)

Adverse event	BD/FF 80/9.6 µg (n = 103)	BD/FF 160/9.6 µg (n = 106)	BD/FF 320/9.6 µg (n = 155)	BD 320 µg (n = 108)	FF 9.6 µg (n = 157)
Nasopharyngitis	2 (1.9)	1 (0.9)	5 (3.2)	2 (1.9)	5 (3.2)
Hypertension	1 (1.0)	1 (0.9)	2 (1.3)	3 (2.8)	2 (1.3)
Upper respiratory tract infection	1 (1.0)	0	4 (2.6)	0	0
Cough	1 (1.0)	0	1 (0.6)	3 (2.8)	1 (0.6)

Number of subjects (%)

7.2 Phase III studies

7.2.1 GP/FF global phase III study (CTD 5.3.5.1.14,[Product (a)] 5.3.5.1.15:[Product (b)] Study PT003014 [April 2015 to August 2017])

A randomized, double-blind, placebo-, GP-, and FF-controlled, parallel-group study in patients with COPD[15] (target sample size, 1614 subjects; 514 subjects [GP/FF], 440 subjects [GP], 440 subjects [FF], and 220 subjects [placebo]) was conducted in 11 countries including Japan, the US, and China, to assess the efficacy and safety of GP/FF MDI.

Subjects received GP/FF 7.2/4.8 µg, GP 7.2 µg, FF 4.8 µg, or placebo, administered as 2 inhalations twice daily for 24 weeks.

All 1756 randomized[16] subjects (555 subjects [GP/FF], 480 subjects [GP], 483 subjects [FF], and 238 subjects [placebo]) received the study drug. Of these, 14 subjects treated at study sites that provided unreliable source data (3 subjects [GP/FF], 6 subjects [GP], 2 subjects [FF], and 3 subjects [placebo]), and 1 subject enrolled in 2 study sites (GP/FF and FF groups) were excluded, and the remaining 1740 subjects (551 subjects [GP/FF], 474 subjects [GP], 480 subjects [FF], and 235 subjects [placebo]) were included in the ITT and safety analysis populations, and also the efficacy analysis population. Treatment discontinuation occurred in 10.9% of subjects (60 of 551 subjects) in the GP/FF group, 13.3% of subjects (63 of 474 subjects) in the GP group, 13.5% of subjects (65 of 480 subjects) in the FF group, and 16.2% of subjects (38 of 235 subjects) in the placebo group. Main reasons for discontinuation included "patient's request" (18 subjects [GP/FF], 23 subjects [GP], 17 subjects [FF], and 14 subjects [placebo]), "violation of discontinuation criteria" (17 subjects [GP/FF], 14 subjects [GP], 13 subjects [FF], and 8 subjects [placebo]), and "adverse events" (15 subjects [GP/FF], 15 subjects [GP], 14 subjects [FF], and 3 subjects [placebo]).

In the ITT population, the Japanese subpopulation consisted of 150 subjects (49 subjects [GP/FF], 42 subjects [GP], 44 subjects [FF], and 15 subjects [placebo]). In the Japanese subpopulation, treatment discontinuation occurred in 8.2% of subjects (4 of 49 subjects) in the GP/FF group, 14.3% of subjects (6 of 42 subjects) in the GP group, 6.8% of subjects (3 of 44 subjects) in the FF group, and 26.7% of subjects (4 of 15 subjects) in the placebo group, with the main reasons being "adverse events" (2 subjects [GP/FF], 1 subject [GP], 1 subject [FF], and 1 subject [placebo]) and "violation of discontinuation criteria" (2 subjects [GP/FF], 3 subjects [GP]).

[15] Patients with COPD with smoking history ≥10 pack-years, pre- and post-bronchodilator FEV_1/FVC ratios <0.70, pre- and post-bronchodilator FEV_1 <80% of the predicted value, and if <30% of the predicted value, ≥750 mL.

[16] Airway reversibility following salbutamol administration, and severity of COPD (moderate, severe, or very severe) were selected as stratification factors.

The primary efficacy endpoint[17] was the change from baseline in morning trough FEV_1 measured over Weeks 12 to 24, as shown in Table 35, which demonstrates a statistically significant difference between the GP/FF, GP, or FF group and the placebo group, as well as a statistically significant difference between the GP/FF group and the GP or FF group. Results for the Japanese subpopulation are shown in Table 36.

Table 35. Change from baseline in morning trough FEV_1 (mL) measured over Weeks 12 to 24 (ITT population)

Treatment group	GP/FF	GP	FF	Placebo
Baseline[a]	1278 ± 452 (550)	1316 ± 477 (474)	1279 ± 437 (480)	1302 ± 485 (235)
Week 12-24[b]	1413 ± 481 (517)	1403 ± 488 (437)	1345 ± 456 (436)	1312 ± 484 (205)
Change from baseline	131 ± 186 (517)	75 ± 176 (437)	55 ± 173 (436)	−17 ± 220 (205)
Difference from placebo[c] [95% CI] p-value[c),d)]	153 [125, 181] <0.0001	99 [70, 128] <0.0001	80 [50, 109] <0.0001	
Difference from GP[c] [95% CI] p-value [c),d)]	54 [31, 76] <0.0001			
Difference from FF[c] [95% CI] p-value [c),d)]	73 [51, 96] <0.0001			

Mean ± standard deviation (number of subjects)

a) Mean of values 60 and 30 minutes prior to initial administration
b) Mean of values at Weeks 12, 16, 20, and 24
c) A repeated measures linear model with treatment, baseline, reversibility, visit, and the treatment-by-visit interaction as covariates, assuming an unstructured variance covariance matrix
d) Two-sided 5% significance level. Adjustment was made for multiplicity according to a scheme in which GP/FF is demonstrated to be effective only if the difference is statistically significant in all the following combinations: GP/FF vs placebo, GP vs placebo, FF vs placebo, GP/FF vs GP, and GP/FF vs FF.

Table 36. Change from baseline in morning trough FEV_1 (mL) measured over Weeks 12 to 24 (ITT population, Japanese subgroup)

Treatment group	GP/FF	GP	FF	Placebo
Baseline[a]	1349 ± 462 (49)	1349 ± 520 (42)	1357 ± 384 (44)	1357 ± 384 (15)
Weeks 12-24[b]	1501 ± 481 (45)	1469 ± 506 (39)	1438 ± 427 (42)	1377 ± 388 (11)
Change from baseline	133 ± 150 (45)	65 ± 141 (39)	69 ± 139 (42)	−136 ± 156 (11)
Difference from placebo[c] [95% CI]	275 [180, 370]	206 [110, 302]	215 [120, 310]	
Difference from GP[c] [95% CI]	69 [8, 131]			
Difference from FF[c] [95% CI]	60 [−1, 121]			

Mean ± standard deviation (number of subjects)

a) Mean of values 60 and 30 minutes prior to initial administration
b) Mean of values at Weeks 12, 16, 20, and 24
c) A repeated measures linear model with treatment, baseline, reversibility, visit, and the treatment-by-visit interaction as covariates, assuming an unstructured variance covariance matrix.

Adverse events occurred in 55.5% of subjects (306 of 551 subjects) in the GP/FF group, 52.7% of subjects (250 of 474 subjects) in the GP group, 53.3% of subjects (256 of 480 subjects) in the FF group, and 55.7% of subjects (131 of 235 subjects) in the placebo group. Table 37 shows major events.

Deaths occurred in 1 subject in the GP/FF group (lung cancer metastatic), 1 subject in the GP group (haemorrhagic stroke), 1 subject in the FF group (lung cancer metastatic), and 1 subject in the placebo group (lung cancer metastatic). A causal relationship to the study drug was ruled out for all 4 deaths. Serious adverse events occurred in 9.6% of subjects (53 of 551 subjects) in the GP/FF group, 7.2% of subjects (34 of 474 subjects) in the GP group, 8.3% of subjects (40 of 480 subjects) in the FF group, 8.1% of subjects (19 of 235 subjects) in the placebo group. Major serious adverse events included chronic obstructive pulmonary disease (16 subjects [GP/FF], 12 subjects [GP], 13 subjects [FF], and 7 subjects [placebo]) and pneumonia (7 subjects

[17] In the US and China, the primary endpoint was change from baseline in morning trough FEV_1 (mL) at 24 weeks after administration. Difference from placebo [95% CI] was 165 [132, 198] in the GP/FF group, 105 [71, 140] in the GP group, and 92 [58, 126] in the FF group. In Europe, South Korea, and Taiwan, the primary endpoint was change from baseline in morning trough FEV_1 (mL) over 24 weeks, and difference from placebo [95% CI] was 155 [129, 180] in the GP/FF group, 99 [73, 125] in the GP group, and 83 [57, 109] in the FF group.

[GP/FF], 3 subjects [GP], 2 subjects [FF], and 3 subjects [placebo]). Adverse events led to treatment discontinuation in 4.9% of subjects (27 of 551 subjects) in the GP/FF group, 5.3% of subjects (25 of 474 subjects) in the GP group, 5.0% of subjects (24 of 480 subjects) in the FF group, and 4.3% of subjects (10 of 235 subjects) in the placebo group.

Adverse reactions occurred in 10.0% of subjects (55 of 551 subjects) in the GP/FF group, 10.8% of subjects (51 of 474 subjects) in the GP group, 9.6% of subjects (46 of 480 subjects) in the FF group, and 9.8% of subjects (23 of 235 subjects) in the placebo group.

Table 37. Adverse events with an incidence of ≥2.0% in any group (safety analysis population)

Adverse event	GP/FF (n = 551)	GP (n = 474)	FF (n = 480)	Placebo (n = 235)
Viral upper respiratory tract infection	50 (9.1)	44 (9.3)	46 (9.6)	16 (6.8)
Upper respiratory tract infection	37 (6.7)	33 (7.0)	29 (6.0)	20 (8.5)
Chronic obstructive pulmonary disease	16 (2.9)	12 (2.5)	13 (2.7)	7 (3.0)
Hypertension	16 (2.9)	6 (1.3)	3 (0.6)	8 (3.4)
Headache	15 (2.7)	11 (2.3)	10 (2.1)	3 (1.3)
Back pain	15 (2.7)	7 (1.5)	5 (1.0)	1 (0.4)
Cough	13 (2.4)	10 (2.1)	8 (1.7)	2 (0.9)
Dyspnoea	11 (2.0)	6 (1.3)	7 (1.5)	7 (3.0)
Pharyngitis	11 (2.0)	3 (0.6)	4 (0.8)	0
Pneumonia	9 (1.6)	5 (1.1)	5 (1.0)	6 (2.6)
Dizziness	8 (1.5)	12 (2.5)	4 (0.8)	1 (0.4)
Bronchitis	4 (0.7)	8 (1.7)	6 (1.3)	5 (2.1)

Number of subjects (%)

In the Japanese subpopulation, adverse events occurred in 55.1% of subjects (27 of 49 subjects) in the GP/FF group, 71.4% of subjects (30 of 42 subjects) in the GP group, 54.5% of subjects (24 of 44 subjects) in the FF group, and 40.0% of subjects (6 of 15 subjects) in the placebo group. Table 38 shows major events.

No deaths occurred. Serious adverse events occurred in 12.2% of subjects (6 of 49 of subjects) in the GP/FF group, 9.5% of subjects (4 of 42 subjects) in the GP group, 6.8% of subjects (3 of 44 subjects) in the FF group, and 6.7% of subjects (1 of 15 subjects) in the placebo group. Major serious adverse events were chronic obstructive pulmonary disease (2 subjects [GP/FF], 3 subjects [GP]), pneumonia (2 subjects [GP], 1 subject [FF], 1 subject [placebo]). Adverse events led to treatment discontinuation in 8.2% of subjects (4 of 49 subjects) in the GP/FF group, 9.5% of subjects (4 of 42 subjects) in the GP group, 2.3% of subjects (1 of 44 subjects) in the FF group, and 6.7% of subjects (1 of 15 subjects) in the placebo group.

Adverse reactions occurred in 2.0% of subjects (1 of 49 subjects) in the GP/FF group, 2.4% of subjects (1 of 42 subjects) in the GP group, and 4.5% of subjects (2 of 44 subjects) in the FF group.

Table 38. Adverse events that occurred in ≥3 subjects in any group (safety analysis population, Japanese subgroup)

Adverse event	GP/FF (n = 49)	GP (n = 42)	FF (n = 44)	Placebo (n = 15)
Viral upper respiratory tract infection	6 (12.2)	12 (28.6)	8 (18.2)	2 (13.3)
Chronic obstructive pulmonary disease]	2 (4.1)	3 (7.1)	0	0
Influenza	1 (2.0)	4 (9.5)	1 (2.3)	0
Bronchitis	1 (2.0)	4 (9.5)	3 (6.8)	2 (13.3)
Pneumonia	0	3 (7.1)	1 (2.3)	2 (13.3)

Number of subjects (%)

7.2.2 BD/GP/FF global phase III study (CTD 5.3.5.1.16, Study PT010006 [August 2015 to January 2018])

In patients with COPD (target sample size, 1800 subjects),[18] a randomized, double-blind, GP/FF MDI-, BD/FF MDI-, and BD/FF DPI (approved formulation)-controlled, parallel-group[19] study was conducted in Japan, the US, China, and Canada, to assess the efficacy and safety of BD/GP/FF MDI.

Subjects received BD/GP/FF 160/7.2/4.8 µg, GP/FF 7.2/4.8 µg, BD/FF 160/4.8 µg, or BD/FF DPI 160/4.5 µg, administered as 2 inhalations twice daily for 24 weeks.

A total of 1902 subjects were randomized[20] in a 2:2:1:1 ratio to BD/GP/FF, GP/FF, BD/FF, or BD/FF DPI group (640 subjects [BD/GP/FF], 627 subjects [GP/FF], 316 subjects [BD/FF], and 319 subjects [BD/FF DPI]). Of these, 3 subjects who did not receive the study drug and 3 subjects who participated in >1 clinical study were excluded, and the remaining 1896 subjects (639 subjects [BD/GP/FF], 625 subjects [GP/FF], 314 subjects [BD/FF], and 318 subjects [BD/FF DPI]) were included in the ITT and safety analysis populations, and also the mITT and efficacy analysis populations. The per-protocol set (PPS) consisted of 1788 subjects who were randomized and had no serious protocol deviations (608 subjects [BD/GP/FF], 587 subjects [GP/FF], 298 subjects [BD/FF], and 295 subjects [BD/FF DPI]). Treatment discontinuation occurred in 11.4% of subjects (73 of 639 subjects) in the BD/GP/FF group, 16.2% of subjects (101 of 625 subjects) in the GP/FF group, 15.3% of subjects (48 of 314 subjects) in the BD/FF group, 12.6% of subjects (40 of 318 subjects) in the BD/FF DPI group, with the main reasons being "patient's request" (14 subjects [BD/GP/FF], 37 subjects [GP/FF], 19 subjects [BD/FF], and 15 subjects [BD/FF DPI]) and "adverse events" (28 subjects [BD/GP/FF], 30 subjects [GP/FF], 11 subjects [BD/FF], and 11 subjects [BD/FF DPI]).

In the ITT population, the Japanese subpopulation consisted of 416 subjects (139 subjects [BD/GP/FF], 138 subjects [GP/FF], 70 subjects [BD/FF], and 69 subjects [BD/FF DPI]). In the Japanese subpopulation, treatment discontinuation occurred in 6.5% of subjects (9 of 139 subjects) in the BD/GP/FF group, 14.5% of subjects (20 of 138 subjects) in the GP/FF group, 8.6% of subjects (6 of 70 subjects) in the BD/FF group, and 5.8% of subjects (4 of 69 subjects) in the BD/FF DPI group, with the main reasons being "adverse events" (6 subjects [BD/GP/FF], 6 subjects [GP/FF], 2 subjects [BD/FF], and 2 subjects [BD/FF DPI]) and "patient's request" (1 subject [BD/GP/FF], 6 subjects [GP/FF], 2 subjects [BD/FF], and 1 subject [BD/FF DPI]).

The primary efficacy endpoint[21] was the change from baseline in morning trough FEV_1 measured over Weeks 12 to 24, as shown in Table 39, which demonstrates a statistically significant difference between the BD/GP/FF

[18] Patients with COPD who had been taking ≥2 kinds of inhaled formulations as maintenance therapy for stable COPD for ≥6 weeks, with smoking history ≥10 pack-years, pre- and post-bronchodilator FEV_1/FVC ratios <0.70, a post-bronchodilator FEV_1 ≥25% and <80% of the predicted value, and a COPD assessment test (CAT) score ≥10.

[19] Subjects in the BD/FF DPI group received the study drug under an open-label condition.

[20] Airway reversibility, country, and severity (moderate, or severe to very severe) were selected as stratification factors.

[21] In Europe and Canada, the primary endpoint was normalized $FEV_1AUC_{0\text{-}4}$ (mL) over 24 weeks, and change from baseline in morning trough FEV_1 (mL) over 24 weeks. The between-group difference [95% CI] in normalized $FEV_1AUC_{0\text{-}4}$ (mL) was 104 [77, 131] for BD/GP/FF vs BD/FF, and 91 [64, 117] for BD/GP/FF vs BD/FF DPI; in contrast, the between-group difference [95% CI] in change from baseline in morning trough FEV_1 (mL) was 22 [4, 39] for BD/GP/FF vs GP/FF, and −10 [−36, 16] for BD/FF vs BD/FF DPI. In the US, the primary endpoint was normalized $FEV_1AUC_{0\text{-}4}$ (mL) at 24 weeks after administration, and change from baseline in morning trough FEV_1 (mL) at 24 weeks after administration, and difference in normalized $FEV_1AUC_{0\text{-}4}$ (mL) between BD/GP/FF and BD/FF [95% CI] was 116 [80, 152], while difference in morning trough FEV_1 (mL) between BD/GP/FF and GP/FF [95% CI] was 13 [−9, 36].

group and the GP/FF or BD/FF group. Furthermore, the lower limit of the 95% CI for the difference between the BD/FF and BD/FF DPI groups was >−50 mL, the prescribed non-inferiority margin, which demonstrated the non-inferiority of the BD/FF group to the BD/FF DPI group. Table 40 shows the results of the Japanese subpopulation.

Table 39. Change from baseline in morning trough FEV_1 (mL) measured over Weeks 12 to 24 (mITT population)

Treatment group	BD/GP/FF	GP/FF	BD/FF	BD/FF DPI[e)]
Baseline[a)]	1183 ± 451 (638)	1167 ± 434 (625)	1174 ± 428 (314)	1195 ± 454 (318)
Weeks 12-24[b)]	1319 ± 474 (593)	1285 ± 455 (561)	1226 ± 444 (278)	1259 ± 456 (289)
Change from baseline	135 ± 175 (592)	113 ± 175 (561)	57 ± 174 (278)	72 ± 150 (289)
Difference from BD/GP/FF[c)] [95% CI] p-value[c),d)]		20 [1, 39] 0.0424	77 [53, 100] <0.0001	
Difference from BD/FF[c)] [95% CI]				−11[e)] [−39, 17][f)]

Mean ± standard deviation (number of subjects)
a) Mean of values 60 and 30 minutes prior to initial administration
b) Mean of values at Weeks 12, 16, 20, and 24
c) A repeated measures linear model with treatment, visit, the treatment-by-visit interaction, ICS use at screening, baseline, baseline eosinophil count, and post-bronchodilator FEV_1 improvement as covariates, assuming an unstructured variance covariance matrix
d) Two-sided 5% significance level. Multiplicity in testing was adjusted by the sequential testing procedure (test BD/GP/FF vs BD/FF; then BD/GP/FF vs GP/FF; then BD/FF vs BD/FF DPI)
e) The results for the BD/FF DPI group, and comparison of the BD/FF vs BD/FF DPI groups were based on the PPS
f) A non-inferiority margin of −50 mL was selected.

Table 40. Change from baseline in morning trough FEV_1 (mL) measured over Weeks 12 to 24 (Japanese subpopulation)

Treatment group	BD/GP/FF	GP/FF	BD/FF	BD/FF DPI[d)]
Baseline[a)]	1188 ± 419 (139)	1228 ± 434 (138)	1230 ± 419 (70)	1289 ± 434 (69)
Weeks 12-24[b)]	1318 ± 427 (134)	1326 ± 459 (126)	1313 ± 434 (65)	1398 ± 437 (65)
Change from baseline	131 ± 149 (134)	92 ± 143 (126)	61 ± 150 (65)	85 ± 144 (65)
Difference from BD/GP/FF[c)] [95% CI]		37 [3, 72]	67 [25, 109]	
Difference from BD/FF[c)] [95% CI]				−31[d)] [−80, 17]

Mean ± standard deviation (number of subjects)
a) Mean of values 60 and 30 minutes prior to initial administration
b) Mean of values at Weeks 12, 16, 20, and 24
c) A repeated measures linear model with treatment, visit, the treatment-by-visit interaction, ICS use at screening, baseline, baseline eosinophil count, and post-bronchodilator FEV_1 improvement as covariates, assuming an unstructured variance covariance matrix
d) The results for the BD/FF DPI group, and comparison of the BD/FF vs BD/FF DPI groups were based on the PPS.

Adverse events occurred in 60.7% of subjects (388 of 639 subjects) in the BD/GP/FF group, 61.4% of subjects (384 of 625 subjects) in the GP/FF group, 55.7% of subjects (175 of 314 subjects) in the BD/FF group, and 57.5% of subjects (183 of 318 subjects) in the BD/FF DPI group. Table 41 shows major events.

Deaths occurred in 6 subjects in the BD/GP/FF group (cerebral infarction [1], acute myeloid leukaemia [1], acute myocardial infarction [1], respiratory fume inhalation disorder [1], sepsis [1], small cell lung cancer metastatic [1]), 3 subjects in the GP/FF group (pneumonia [1], cardio-respiratory arrest [1], death [1]), 2 subjects in the BD/FF group (brain cancer metastatic/central nervous system lesion [1], squamous cell carcinoma of lung [1]), and 1 subject in the BD/FF DPI group (metastases to spine). Among these events, a causal relationship to the study drug could not be ruled out for the events of pneumonia and death in the GP/FF group. Serious adverse events occurred in 8.6% of subjects (55 of 639 subjects) in the BD/GP/FF group, 10.9% of subjects (68 of 625 subjects) in the GP/FF group, 6.7% of subjects (21 of 314 subjects) in the BD/FF group,

and 9.1% of subjects (29 of 318 subjects) in the BD/FF DPI group. Major serious adverse events included chronic obstructive pulmonary disease (17 subjects [BD/GP/FF], 32 subjects [GP/FF], 8 subjects [BD/FF], and 13 subjects [BD/FF DPI]), pneumonia (8 subjects [BD/GP/FF], 6 subjects [GP/FF], and 1 subject [BD/FF]), and acute respiratory failure (4 subjects [BD/GP/FF], 1 subject [GP/FF], and 1 subject [BD/FF DPI]). Adverse events led to treatment discontinuation in 4.7% of subjects (30 of 639 subjects) in the BD/GP/FF group, 4.8% of subjects (30 of 625 subjects) in the GP/FF group, 3.5% of subjects (11 of 314 subjects) in the BD/FF group, and 3.5% of subjects (11 of 318 subjects) in the BD/FF DPI group.

Adverse reactions occurred in 17.5% of subjects (112 of 639 subjects) in the BD/GP/FF group, 14.6% of subjects (91 of 625 subjects) in the GP/FF group, 15.3% of subjects (48 of 314 subjects) in the BD/FF group, and 12.6% of subjects (40 of 318 subjects) in the BD/FF DPI group.

Table 41. Adverse events with an incidence of ≥2.0% in any group (safety analysis population)

Adverse event	BD/GP/FF (n = 639)	GP/FF (n = 625)	BD/FF (n = 314)	BD/FF DPI (n = 318)
Upper respiratory tract infection	65 (10.2)	38 (6.1)	18 (5.7)	22 (6.9)
Nasopharyngitis	49 (7.7)	41 (6.6)	26 (8.3)	30 (9.4)
Muscle spasms	21 (3.3)	8 (1.3)	17 (5.4)	6 (1.9)
Bronchitis	20 (3.1)	15 (2.4)	12 (3.8)	9 (2.8)
Dysphonia	20 (3.1)	5 (0.8)	15 (4.8)	6 (1.9)
Chronic obstructive pulmonary disease	17 (2.7)	32 (5.1)	8 (2.5)	13 (4.1)
Hypertension	13 (2.0)	10 (1.6)	8 (2.5)	4 (1.3)
Dyspnoea	9 (1.4)	9 (1.4)	8 (2.5)	8 (2.5)
Back pain	8 (1.3)	12 (1.9)	4 (1.3)	8 (2.5)
Nausea	7 (1.1)	3 (0.5)	4 (1.3)	7 (2.2)

Number of subjects (%)

In the Japanese subpopulation, adverse events occurred in 66.9% of subjects (93 of 139 subjects) in the BD/GP/FF group, 66.7% of subjects (92 of 138 subjects) in the GP/FF group, 72.9% of subjects (51 of 70 subjects) in the BD/FF group, and 59.4% of subjects (41 of 69 subjects) in the BD/FF DPI group. Table 42 shows major events.

Deaths occurred in 1 subject in the GP/FF group (cardio-respiratory arrest) and 1 subject in the BD/FF group (squamous cell carcinoma of lung), and a causal relationship to the study drug was ruled out for both events. Serious adverse events occurred in 7.9% of subjects (11 of 139 subjects) in the BD/GP/FF group, 10.1% of subjects (14 of 138 subjects) in the GP/FF group, 10.0% of subjects (7 of 70 subjects) in the BD/FF group, and 8.7% of subjects (6 of 69 subjects) in the BD/FF DPI group. Major serious adverse events included chronic obstructive pulmonary disease (4 subjects [BD/GP/FF], 5 subjects [GP/FF], 2 subjects [BD/FF], and 1 subject [BD/FF DPI]) and pneumonia (4 subjects [BD/GP/FF]). Adverse events led to treatment discontinuation in 4.3% of subjects (6 of 139 subjects) in the BD/GP/FF group, 4.3% of subjects (6 of 138 subjects) in the GP/FF group, 2.9% of subjects (2 of 70 subjects) in the BD/FF group, and 2.9% of subjects (2 of 69 subjects) in the BD/FF DPI group.

Adverse reactions occurred in 20.9% of subjects (29 of 139 subjects) in the BD/GP/FF group, 8.0% of subjects (11 of 138 subjects) in the GP/FF group, 17.1% of subjects (12 of 70 subjects) in the BD/FF group, and 5.8% of subjects (4 of 69 subjects) in the BD/FF DPI group.

Table 42. Adverse events with an incidence of ≥2.0% in any group (Japanese subpopulation)

Adverse event	BD/GP/FF (n = 139)	GP/FF (n = 138)	BD/FF (n = 70)	BD/FF DPI (n = 69)
Nasopharyngitis	29 (20.9)	23 (16.7)	14 (20.0)	16 (23.2)
Muscle spasms	12 (8.6)	2 (1.4)	5 (7.1)	2 (2.9)
Dysphonia	9 (6.5)	1 (0.7)	8 (11.4)	3 (4.3)
Upper respiratory tract infection	7 (5.0)	5 (3.6)	1 (1.4)	1 (1.4)
Bronchitis	6 (4.3)	6 (4.3)	7 (10.0)	3 (4.3)
Pneumonia	6 (4.3)	1 (0.7)	1 (1.4)	0
Upper respiratory tract inflammation	4 (2.9)	6 (4.3)	3 (4.3)	0
Chronic obstructive pulmonary disease	4 (2.9)	5 (3.6)	2 (2.9)	1 (1.4)
Constipation	4 (2.9)	3 (2.2)	2 (2.9)	0
Oropharyngeal pain	4 (2.9)	1 (0.7)	0	1 (1.4)
Rhinitis	4 (2.9)	1 (0.7)	0	1 (1.4)
Contusion	3 (2.2)	1 (0.7)	0	1 (1.4)
Vertigo	3 (2.2)	1 (0.7)	0	0
Oral candidiasis	3 (2.2)	0	2 (2.9)	2 (2.9)
Oesophageal candidiasis	3 (2.2)	0	0	0
Pharyngitis	2 (1.4)	3 (2.2)	2 (2.9)	2 (2.9)
Gamma-glutamyltransferase increased	2 (1.4)	0	2 (2.9)	0
Influenza	1 (0.7)	4 (2.9)	1 (1.4)	4 (5.8)
Back pain	1 (0.7)	3 (2.2)	1 (1.4)	1 (1.4)
Cataract	1 (0.7)	3 (2.2)	1 (1.4)	0
Eczema	1 (0.7)	2 (1.4)	2 (2.9)	3 (4.3)
Large intestine polyp	1 (0.7)	0	2 (2.9)	0
Non-cardiac chest pain	0	0	2 (2.9)	0
Myalgia	0	0	1 (1.4)	2 (2.9)

Number of subjects (%)

7.2.3 Japanese extension study (CTD 5.3.5.1.20,[Product (a)] 5.3.5.1.17:[Product (b)] Study PT010007 [August 2016 to June 2018])

An extension study was conducted in Japanese patients with COPD who were enrolled in Study PT010006 (target sample size, 324 subjects; 108 subjects [BD/GP/FF], 108 subjects [GP/FF], 54 subjects [BD/FF], and 54 subjects [BD/FF DPI]), with GP/FF MDI, BD/FF MDI, and BD/FF DPI as controls to assess the safety and efficacy of BD/GP/FF MDI and GP/FF MDI in long-term treatment.

Subjects continued to receive the study drug to which they were randomized in Study PT010006, namely, BD/GP/FF 160/7.2/4.8 µg, GP/FF 7.2/4.8 µg, BD/FF 160/4.8 µg, or BD/FF DPI 160/4.5 µg, administered as 2 inhalations twice daily for 28 weeks (a total of 52 weeks including the period of Study PT010006).

All 416 subjects (139 subjects [BD/GP/FF], 138 subjects [GP/FF], 70 subjects [BD/FF], and 69 subjects [BD/FF DPI]) from the Japanese subpopulation (subjects who were enrolled in study sites in Japan) in the mITT population of Study PT010006 were included in the Japanese mITT population and Japanese safety analysis population, regardless of participation in Study PT010007. Of these, 39 subjects discontinued treatment in Study PT010006, and 30 subjects did not move into Study PT010007. The remaining 347 subjects were included in the safety analysis population of Study PT010007 (116 subjects [BD/GP/FF], 111 subjects

[GP/FF], 58 subjects [BD/FF], and 62 subjects [BD/FF DPI]). In the overall period,[22)] treatment discontinuation occurred in 19.4% of subjects (27 of 139 subjects) in the BD/GP/FF group, 26.1% of subjects (36 of 138 subjects) in the GP/FF group, 20.0% of subjects (14 of 70 subjects) in the BD/FF group, and 21.7% of subjects (15 of 69 subjects) in the BD/FF DPI group, with the main reasons being "adverse events" (10 subjects [BD/GP/FF], 12 subjects [GP/FF], 4 subjects [BD/FF], and 6 subjects [BD/FF DPI]), and "patient's request" (15 subjects [BD/GP/FF], 13 subjects [GP/FF], 8 subjects [BD/FF], and 7 subjects [BD/FF DPI]).

In the overall period,[22)] adverse events occurred in 82.7% of subjects (115 of 139 subjects) in the BD/GP/FF group, 82.6% of subjects (114 of 138 subjects) in the GP/FF group, 82.9% of subjects (58 of 70 subjects) in the BD/FF group, and 82.6% of subjects (57 of 69 subjects) in the BD/FF DPI group. Table 43 shows major events.

Deaths occurred in 3 subjects in the BD/GP/FF group (road traffic accident [1], arrhythmia [1], disseminated intravascular coagulation/pneumonia [1]), 1 subject in the GP/FF group (cardio-respiratory arrest), 1 subject in the BD/FF group (squamous cell carcinoma of lung), and 1 subject in the BD/FF DPI group (lung adenocarcinoma). A causal relationship to the study drug was ruled out for all these events. Serious adverse events occurred in 15.1% of subjects (21 of 139 subjects) in the BD/GP/FF group, 21.7% of subjects (30 of 138 subjects) in the GP/FF group, 15.7% of subjects (11 of 70 subjects) in the BD/FF group, and 20.3% of subjects (14 of 69 subjects) in the BD/FF DPI group. Major serious adverse events included chronic obstructive pulmonary disease (7 subjects [BD/GP/FF], 11 subjects [GP/FF], 2 subjects [BD/FF], and 2 subjects [BD/FF DPI]), pneumonia (8 subjects [BD/GP/FF], 3 subjects [GP/FF], 1 subject [BD/FF], and 2 subjects [BD/FF DPI]). Adverse events led to treatment discontinuation in 7.2% of subjects (10 of 139 subjects) in the BD/GP/FF group, 8.7% of subjects (12 of 138 subjects) in the GP/FF group, 5.7% of subjects (4 of 70 subjects) in the BD/FF group, and 8.7% of subjects (6 of 69 subjects) in the BD/FF DPI group.

Adverse reactions occurred in 24.5% of subjects (34 of 139 subjects) in the BD/GP/FF group, 11.6% of subjects (16 of 138 subjects) in the GP/FF group, 22.9% of subjects (16 of 70 subjects) in the BD/FF group, and 13.0% of subjects (9 of 69 subjects) in the BD/FF DPI group.

[22)] A total of 52 weeks including the period of Study PT010006.

Table 43. Adverse events with an incidence of ≥2.0% in any group (Japanese safety analysis population)

Adverse event	BD/GP/FF (n = 139)	GP/FF (n = 138)	BD/FF (n = 70)	BD/FF DPI (n = 69)
Nasopharyngitis	45 (32.4)	43 (31.2)	22 (31.4)	24 (34.8)
Muscle spasms	16 (11.5)	6 (4.3)	6 (8.6)	3 (4.3)
Bronchitis	15 (10.8)	11 (8.0)	8 (11.4)	7 (10.1)
Pneumonia	14 (10.1)	5 (3.6)	4 (5.7)	4 (5.8)
Upper respiratory tract infection	10 (7.2)	8 (5.8)	1 (1.4)	2 (2.9)
Dysphonia	10 (7.2)	1 (0.7)	9 (12.9)	3 (4.3)
Chronic obstructive pulmonary disease	7 (5.0)	11 (8.0)	2 (2.9)	2 (2.9)
Constipation	6 (4.3)	5 (3.6)	4 (5.7)	2 (2.9)
Upper respiratory tract inflammation	5 (3.6)	7 (5.1)	5 (7.1)	0
Influenza	5 (3.6)	7 (5.1)	3 (4.3)	6 (8.7)
Oropharyngeal pain	5 (3.6)	1 (0.7)	1 (1.4)	1 (1.4)
Contusion	5 (3.6)	1 (0.7)	0	1 (1.4)
Oral candidiasis	5 (3.6)	0	3 (4.3)	3 (4.3)
Rhinitis	4 (2.9)	1 (0.7)	0	1 (1.4)
Pyrexia	3 (2.2)	6 (4.3)	0	0
Pharyngitis	3 (2.2)	5 (3.6)	3 (4.3)	2 (2.9)
Diarrhoea	3 (2.2)	2 (1.4)	1 (1.4)	1 (1.4)
Insomnia	3 (2.2)	2 (1.4)	0	1 (1.4)
Pneumonia bacterial	3 (2.2)	1 (0.7)	0	1 (1.4)
Chronic gastritis	3 (2.2)	1 (0.7)	0	0
Vertigo	3 (2.2)	1 (0.7)	0	0
Oesophageal candidiasis	3 (2.2)	0	1 (1.4)	1 (1.4)
Hypertension	3 (2.2)	0	1 (1.4)	1 (1.4)
Back pain	2 (1.4)	4 (2.9)	2 (2.9)	1 (1.4)
Cataract	2 (1.4)	4 (2.9)	1 (1.4)	0
Headache	2 (1.4)	3 (2.2)	1 (1.4)	0
Seasonal allergy	2 (1.4)	3 (2.2)	1 (1.4)	0
Nausea	2 (1.4)	1 (0.7)	2 (2.9)	0
Gamma-glutamyltransferase increased	2 (1.4)	1 (0.7)	2 (2.9)	0
Herpes zoster	2 (1.4)	0	2 (2.9)	1 (1.4)
Tinea pedis	1 (0.7)	4 (2.9)	1 (1.4)	0
Eczema	1 (0.7)	3 (2.2)	4 (5.7)	4 (5.8)
Gastroenteritis	1 (0.7)	3 (2.2)	1 (1.4)	0
Diabetes mellitus	1 (0.7)	3 (2.2)	1 (1.4)	0
Gastritis	1 (0.7)	3 (2.2)	0	1 (1.4)
Urinary tract infection	1 (0.7)	3 (2.2)	0	0
Large intestine polyp	1 (0.7)	0	2 (2.9)	2 (2.9)
Dental caries	0	4 (2.9)	1 (1.4)	0
Rib fracture	0	1 (0.7)	2 (2.9)	0
Myalgia	0	1 (0.7)	1 (1.4)	2 (2.9)
Seborrhoeic dermatitis	0	1 (0.7)	0	2 (2.9)
Oropharyngeal candidiasis	0	0	2 (2.9)	0
Dehydration	0	0	2 (2.9)	0
Non-cardiac chest pain	0	0	2 (2.9)	0
Dyslipidaemia	0	0	1 (1.4)	2 (2.9)
Dry eye	0	0	0	2 (2.9)
Acute myocardial infarction	0	0	0	2 (2.9)

Number of subjects (%)

The change from baseline in morning trough FEV_1 (mean ± standard deviation) in the overall period,[22)] the primary efficacy endpoint, was 126 ± 139 mL (137 subjects) in the BD/GP/FF group, 93 ± 136 mL (134 subjects) in the GP/FF group, 57 ± 143 mL (68 subjects) in the BD/FF group, and 85 ± 140 mL (68 subjects) in the BD/FF DPI group.

7.R Outline of the review conducted by PMDA

7.R.1 Dosage regimens in phase III studies

The applicant's explanation about the rationale for the GP/FF and BD/GP/FF regimens in phase III studies in patients with COPD:

A combined dose level of FF 9.6 μg (2 inhalations of 4.8 μg) was selected based on the results of clinical studies including the following:

- In the foreign phase I/II study (Study PT0050801), which assessed the dose response of FF monocomponent (2.4-9.6 μg single-dose administration) in patients with COPD, the normalized $FEV_1AUC_{0\text{-}12}$ [95% CI] following single-dose administration, the primary endpoint, was 31.2 [−13.6, 76.0] mL for the FF 2.4-μg treatment period, 53.2 [7.5, 98.8] mL for the FF 4.8-μg treatment period, 125.7 [78.5, 172.8] mL for the FF 9.6-μg treatment period, and −50.3 [−97.4, −3.1] mL for the placebo period, indicating that the highest level was observed following FF 9.6 μg administration.
- In the foreign phase II study (Study PT005003), which assessed the dose response of FF monocomponent (7.2-19.2 μg single-dose administration) in patients with COPD, the normalized $FEV_1AUC_{0\text{-}12}$ following single-dose administration, the primary endpoint, showed a statistically significant difference in the treatment periods of FF 7.2 μg, 9.6 μg, and 19.2 μg compared with that of placebo. There were no differences in terms of safety between the dose levels [see Section 7.1.2].
- The dose levels of FF in other FF-containing inhaled formulations approved in Japan indicated for the treatment of COPD, "Symbicort Turbuhaler 30 Doses" and other doses, and "Oxis 9μg Turbuhaler 28 Doses" and other doses, are FF 9 μg twice daily.

A combined dose level of 14.4 μg (2 inhalations of 7.2 μg) was selected for GP based on the results of clinical studies including the following:

- In the Japanese phase II study (Study PT001004), which assessed the dose response of GP monocomponent (7.2-28.8 μg twice daily) in patients with COPD, change from baseline in morning trough FEV_1 on Day 8, the primary endpoint, was greater in the GP 14.4-μg treatment period than in the GP 7.2-μg treatment period, and did not differ significantly between the GP 14.4-μg and GP 28.8-μg treatment periods. There were no significant differences in terms of safety between the dose levels [see Section 7.1.1].
- In the foreign phase II study (Study PT003005), which assessed the dose response of GP/FF (0.96-14.4/9.6 μg twice daily) in patients with COPD, the normalized $FEV_1AUC_{0\text{-}12}$ on Day 7, the primary endpoint, was higher in the GP/FF 14.4/9.6-μg treatment period than in other treatment periods. There were no significant differences in terms of safety between GP/FF combination and monocomponent treatments [see Section 7.1.3].

A combined dose level of 320 μg (2 inhalations of 160 μg) was selected for BD based on the results of clinical studies including the following:

- In the foreign phase II study (Study PT008001), which assessed the dose response of BD monocomponent (40-320 μg twice daily) in patients with asthma (in whom a dose-response relationship between ICS and

respiratory function tends to occur), change (mean ± standard deviation) from baseline in morning trough FEV_1 on Day 29, the primary endpoint, was −34 ± 172 mL for the BD 40-µg treatment period, −27 ± 179 mL for the BD 80-µg treatment period, 0 ± 146 mL for the BD 160-µg treatment period, −2 ± 132 mL for the BD 320-µg treatment period, and −116 ± 250 mL for the placebo period. Dose-dependent increases in change from baseline were observed in the BD 40 to 160 µg treatment periods, while the change was similar between BD 160 µg and 320 µg. There were no significant differences in terms of safety between the dose levels.

- In the foreign phase II study (Study PT009001), which assessed the dose response of BD/FF (80-320 µg/9.6 µg) in patients with COPD, the normalized FEV_1AUC_{0-12} on Day 29, the primary endpoint, was higher in the BD/FF 320/9.6-µg treatment period than in other treatment periods. There were no significant differences in terms of safety between BD/FF combination and monocomponent treatments [see Section 7.1.4].

Based on the above results, GP/FF 14.4/9.6 µg (2 inhalations of GP/FF 7.2/4.8 µg) twice daily, and BD/GP/FF 320/14.4/9.6 µg (2 inhalations of BD/GP/FF 160/7.2/4.8 µg) twice daily were selected as the regimens for phase III studies.

PMDA accepted the applicant's explanation.

7.R.2 Efficacy

7.R.2.1 GP/FF

The applicant's explanation about the efficacy of GP/FF:

The following findings including results from the global phase III study (Study PT003014) and foreign phase III studies (Studies PT003006 and PT003007) demonstrate the efficacy of GP/FF 14.4/9.6 µg, GP 14.4 µg, and FF 9.6 µg, and an additive effect of FF 9.6 µg to GP 14.4 µg, and that of GP 14.4 µg to FF 9.6 µg in patients with COPD.

- The primary endpoint of Study PT003014 was change from baseline in morning trough FEV_1 over Weeks 12 to 24. As shown in Table 35, there were statistically significant differences between GP/FF, GP, and FF vs placebo, and the results demonstrated the superiority of GP/FF 14.4/9.6 µg, GP 14.4 µg, and FF 9.6 µg over placebo. Furthermore, comparison of GP/FF with GP and FF monocomponents indicated statistical significance, demonstrating superiority of GP/FF 14.4/9.6 µg over GP 14.4 µg and FF 9.6 µg [see Section 7.2.1].
- In Studies PT003006 and PT003007, the change from baseline in morning trough FEV_1 over Weeks 12 to 24, the primary endpoint, was similar to that of Study PT003014 (Table 44).

Table 44. Change from baseline in morning trough FEV_1 (mL) measured over Weeks 12 to 24 (ITT population)

Treatment group	GP/FF	GP	FF	Placebo
Study PT003006				
Baseline[a)]	1273 ± 507 (526)	1247 ± 491 (451)	1277 ± 516 (448)	1276 ± 489 (219)
Weeks 12-24	1400 ± 524 (474)	1338 ± 500 (388)	1363 ± 518 (395)	1313 ± 455 (175)
Change from baseline	145 ± 165 (474)	89 ± 189 (388)	90 ± 173 (395)	−9 ± 206 (175)
Difference from placebo[b)] [95% CI]	153 [123, 182]	95 [65, 125]	93 [63, 123]	
Difference from GP[b)] [95% CI]	58 [35, 81]			
Difference from FF[b)] [95% CI]	60 [37, 83]			
Study PT003007				
Baseline[a)]	1287 ± 507 (510)	1265 ± 491 (439)	1318 ± 522 (437)	1247 ± 483 (223)
Weeks 12-24	1425 ± 537 (470)	1371 ± 496 (394)	1403 ± 544 (384)	1251 ± 462 (189)
Change from baseline	137 ± 184 (470)	84 ± 169 (394)	74 ± 197 (384)	0 ± 163 (189)
Difference from placebo[b)] [95% CI]	129 [99, 158]	76 [46, 106]	68 [38, 98]	
Difference from GP[b)] [95% CI]	53 [29, 76]			
Difference from FF[b)] [95% CI]	61 [37, 84]			

Mean ± standard deviation (number of subjects)

a) Mean of values 60 and 30 minutes prior to initial administration

b) A repeated measures linear model with treatment, baseline, reversibility, smoking history (former or current smoker), ICS use, visit, and the treatment-by-visit interaction as covariates.

- In analyses of pooled data from Studies PT003014, PT003006, and PT003007,[23)] the results for the analysis of time to first moderate or severe COPD exacerbation [see Section 10 for the definition] are presented in Table 45 and Figure 2. The hazard ratio for time to first moderate or severe COPD exacerbation tended to be lower in the GP/FF, GP, and FF groups compared with placebo. The hazard ratio also tended to be lower in the GP/FF group compared with the GP and FF groups.

Table 45. Incidence of moderate or severe COPD exacerbation (pooled data from Studies PT003014, PT003006, and PT003007, ITT population)

Treatment group	GP/FF (n = 1585)	GP (n = 1362)	FF (n = 1360)	Placebo (n = 676)
Number of subjects with exacerbation (%)	281 (17.7)	275 (20.2)	260 (19.1)	146 (21.6)
Hazard ratio compared with placebo [95% CI]	0.72 [0.59, 0.88]	0.88 [0.72, 1.07]	0.84 [0.69, 1.03]	
Hazard ratio compared with GP [95% CI]	0.82 [0.69, 0.96]			
Hazard ratio compared with FF [95% CI]	0.85 [0.72, 1.01]			

[23)] Due to insufficient number of cases in each of the phase III studies to demonstrate difference in the therapeutic effect for COPD exacerbation, the pooled data from the 3 studies (Studies PT003014/PT003006/PT003007) were used for prescribed analyses of COPD exacerbation.

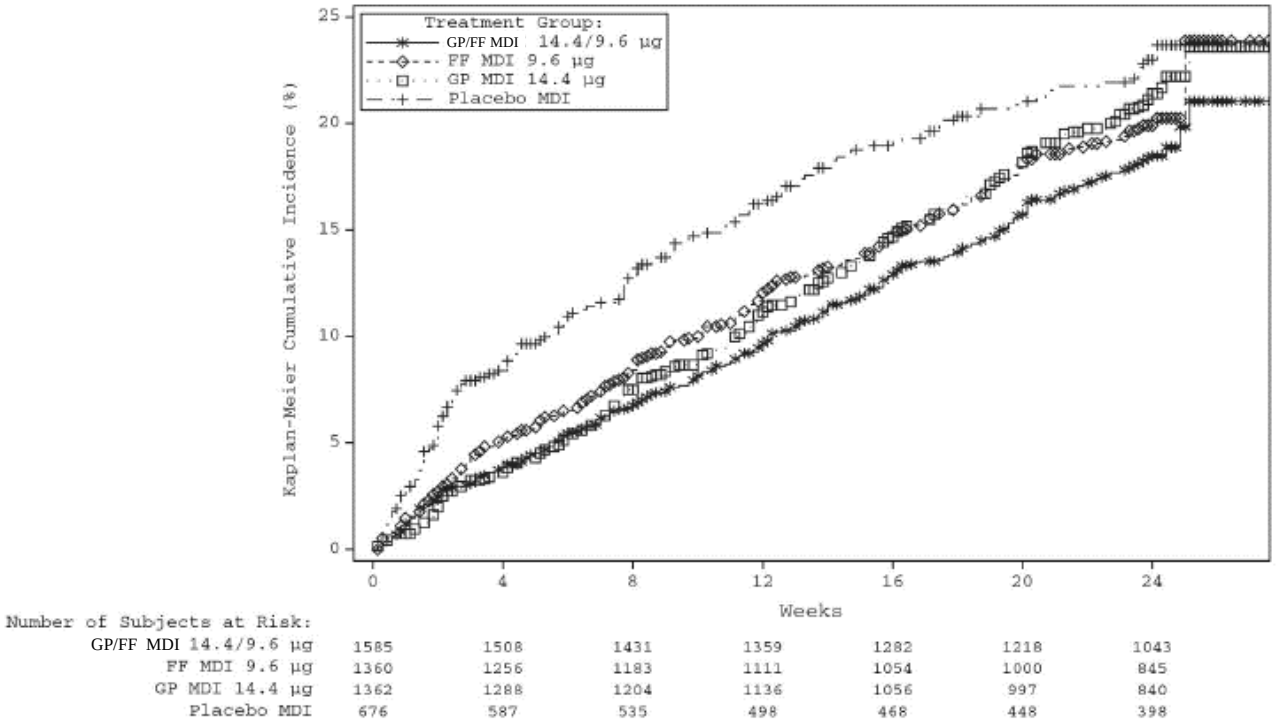

Figure 2. Kaplan-Meier curves with first moderate or severe COPD exacerbation as an event (pooled data from Studies PT003014, PT003006, and PT003007, ITT population)

- Table 46 shows the incidence rate of moderate or severe COPD exacerbations[24)] up to Week 24 in pooled data from Studies PT003014, PT003006, and PT003007. The exacerbation incidence rate tended to be lower in the GP/FF, GP, and FF groups compared with placebo. The exacerbation incidence rate also tended to be lower in the GP/FF group compared with the GP and FF groups.

[24)] In Studies PT003006, PT003007 and PT003014, patients who developed severe COPD exacerbations, or ≥3 moderate COPD exacerbations had to discontinue treatment.

Table 46. The incidence rate of moderate or severe COPD exacerbations up to Week 24 (pooled data from Studies PT003014, PT003006, and PT003007, ITT population)

Treatment group	GP/FF (n = 1585)	GP (n = 1362)	FF (n = 1360)	Placebo (n = 676)
Total observation period[a] (person-years)	666.37	558.54	557.62	260.06
Number of subjects with exacerbations	281	275	260	146
Number of exacerbations[b] (events)	343	317	311	175
Exacerbation incidence rate[c] (exacerbations/person-years)	0.51	0.57	0.56	0.67
Exacerbation incidence rate[d] (exacerbations/person-years) [95% CI]	0.48 [0.43, 0.55]	0.55 [0.48, 0.63]	0.54 [0.47, 0.62]	0.66 [0.55, 0.79]
Percentage to placebo[d] [95% CI]	0.74 [0.59, 0.92]	0.84 [0.68, 1.05]	0.83 [0.66, 1.03]	
Percentage to GP[d] [95% CI]	0.88 [0.73, 1.05]			
Percentage to FF[d] [95% CI]	0.89 [0.75, 1.07]			

a) Duration of an exacerbation or in the 7 days following an exacerbation was not included in the calculation of exposure
b) COPD exacerbations were regarded as separate events provided there were ≥7 days between stop and start dates
c) Total number of exacerbations/total years of exposure across all patients who received the treatment. Duration of an exacerbation or in the 7 days following an exacerbation was not included in the calculation of exposure
d) A negative binomial regression model with percent predicted FEV_1, COPD assessment test (CAT) score, COPD exacerbation history, smoking history (former or current smoker), eosinophil count, ICS use, and study (PT003006/PT003007/PT003014) as covariates, and time of exposure as an offset variable.

The applicant's explanation about the efficacy of GP/FF MDI in long-term treatment:

Study PT003008 was a foreign extension study in patients with COPD who had participated in Study PT003006 or PT003007 to assess the long-term safety and efficacy of GP/FF MDI. The primary efficacy endpoint, adjusted mean change from baseline in morning trough FEV_1 [95% CI], was 121 [108, 135] mL in the GP/FF group, 64 [49, 79] mL in the GP group, 61 [46, 76] mL in the FF group, and 99 [77, 120] mL in the tiotropium group at Week 24; 103 [82, 124] mL in the GP/FF group, 45 [21, 69] mL in the GP group, 29 [5, 53] mL in the FF group, and 96 [67, 125] mL in the tiotropium group at Week 52, indicating that improved respiratory function observed at 24 weeks following GP/FF administration was generally maintained up to Week 52.

The applicant's further explanation about efficacy in Japanese patients with COPD:

- In Study PT003014, the results of change from baseline in morning trough FEV_1 over Weeks 12 to 24 in the Japanese subpopulation (Table 36) show that differences from placebo tended to be greater in the GP/FF, GP, and FF groups compared with the entire study population (Table 35) [see Section 7.2.1]. However, the change from baseline in all active treatment groups of the Japanese subpopulation did not clearly differ from that in the entire study population, and thus the greater difference from placebo described above was attributed to a greater decrease in FEV_1 in the placebo group of the Japanese subpopulation. Results of comparisons between the GP/FF group and the monocomponents, the GP and FF groups in the Japanese subpopulation tended to be similar to those in the entire study population (Table 35 and Table 36).
- As for the long-term treatment efficacy of GP/FF MDI in Japanese patients with COPD, the adjusted mean change from baseline in morning trough FEV_1 [95% CI], the primary efficacy endpoint of Study PT010007 (a Japanese extension study), was 76 [47, 105] mL at Week 24, and 53 [19, 86] mL at Week 52 in the GP/FF group, indicating that improved respiratory function observed at 24 weeks following GP/FF administration was generally maintained up to Week 52.

It is considered that the above results demonstrate the efficacy of GP/FF MDI in Japanese patients with COPD.

PMDA's view:
Analyses of the primary endpoint of Study PT003014, change from baseline in morning trough FEV_1 over Weeks 12 to 24, demonstrated a statistically significant difference from placebo in each of the GP/FF, GP, and FF groups, and between the GP/FF group and the monocomponents, the GP and FF groups. Results of the secondary endpoints indicated a trend toward increased efficacy in the GP/FF, GP, and FF groups compared with placebo, and increased efficacy in the GP/FF group compared with the monocomponents, the GP and FF groups. These results demonstrate the efficacy of GP/FF 14.4/9.6 μg, GP 14.4 μg, and FF 9.6 μg, and an additive effect of FF 9.6 μg to GP 14.4 μg, and that of GP 14.4 μg to FF 9.6 μg in patients with COPD. Given that the results in the Japanese subpopulation are similar to those in the entire study population, GP/FF MDI can be expected to be effective in Japanese patients with COPD.

7.R.2.2 BD/GP/FF

The applicant's explanation about the efficacy of BD/GP/FF MDI:
Data including the results from Study PT010006 (a global phase III study) demonstrated an additive effect of GP 14.4 μg to BD/FF 320/9.6 μg, and that of BD 320 μg to GP/FF 14.4/9.6 μg.

- In Study PT010006, the analysis of change from baseline in morning trough FEV_1 over Weeks 12 to 24, the primary endpoint, indicated statistically significant differences in the comparison of BD/GP/FF with BD/FF or GP/FF, demonstrating the superiority of BD/GP/FF 320/14.4/9.6 μg over BD/FF 320/9.6 μg or GP/FF 14.4/9.6 μg.
- The efficacy of BD/FF 320/9.6 μg, one of the controls used in Study PT010006, in the treatment of COPD was assessed in terms of non-inferiority to a BD/FF DPI ("Symbicort Turbuhaler 30 Doses" and other doses), which has already been approved for treatment of COPD in Japan. The analysis of change from baseline in morning trough FEV_1 over Weeks 12 to 24, the primary endpoint, indicated that the lower limit of the 95% CI for the difference between BD/FF and BD/FF DPI was greater than the prescribed non-inferiority margin, demonstrating the non-inferiority of BD/FF 320/9.6 μg to BD/FF DPI [see Section 7.2.2]. The efficacy of GP/FF 14.4/9.6 μg, another control used in Study PT010006, in the treatment of COPD was assessed based on the results from Study PT003014 and other data [see Section 7 R.2.1].
- As for the additive effect of BD to GP/FF, the difference between the GP/FF and BD/GP/FF groups was 20 mL, which was smaller than the between-group difference of 35 mL estimated in the planning stage. This may be partly attributable to the fact that steroids improve respiratory function in an indirect manner via inhibition of airway inflammation, which works gradually and mildly compared with bronchodilators. However, the additive effect of BD to FF in the clinical studies on a BD/FF combination drug approved in Japan and other countries in patients with COPD (Studies D5899C00001, D5899C00002, D589CC00003, D589UC00001, and D7820C00001; the treatment period was 6 months in all the studies) was generally between 20 and 40 mL, which indicates that the additive effect of BD to GP/FF in BD/GP/FF MDI was similar to that of BD to FF in the approved BD/FF combination drug, suggesting that BD/GP/FF MDI has clinical significance.

- The results of time to first moderate or severe COPD exacerbation [see Section 10 for the definition] in Study PT010006 are presented in Table 47 and Figure 3. The hazard ratio for time to first moderate or severe COPD exacerbation tended to be lower in the BD/GP/FF group compared with the GP/FF, BD/FF, and BD/FF DPI groups.

Table 47. Incidence of moderate or severe COPD exacerbations (Study PT010006, mITT population)

Treatment group	BD/GP/FF (n = 639)	GP/FF (n = 625)	BD/FF (n = 314)	BD/FF DPI (n = 318)
Number of subjects with exacerbation (%)	108 (16.9)	157 (25.1)	65 (20.7)	61 (19.2)
Hazard ratio of BD/GP/FF compared with the 2-component combination drugs [95% CI]		0.59 [0.46, 0.76]	0.75 [0.55, 1.02]	0.85 [0.62, 1.17]

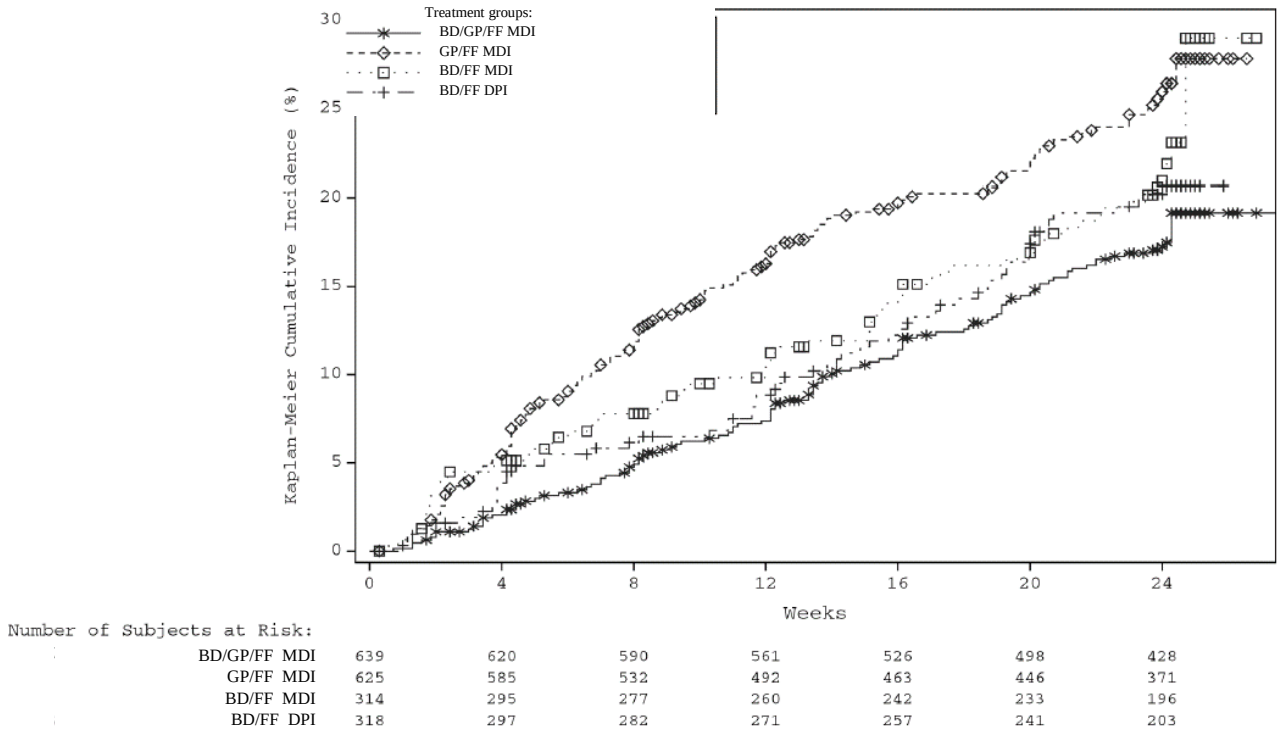

Figure 3. Kaplan-Meier curves with first moderate or severe COPD exacerbation as an event (Study PT010006, mITT population)

- Table 48 shows the incidence rates of moderate or severe COPD exacerbations up to Week 24 in Study PT010006. The Exacerbation incidence rate tended to be lower in the BD/GP/FF group compared with that in the GP/FF, BD/FF, and BD/FF DPI groups.

Table 48. The incidence rate of moderate or severe COPD exacerbations up to Week 24 (Study PT010006, mITT population)

Treatment group	BD/GP/FF (n = 639)	GP/FF (n = 625)	BD/FF (n = 314)	BD/FF DPI (n = 318)
Total observation period[a] (person-years)	272.16	256.08	129.45	133.57
Number of subjects with exacerbations	108	157	65	61
Number of exacerbations[b] (events)	132	228	74	77
Exacerbation incidence rate[c] (exacerbations/person-years)	0.49	0.89	0.57	0.58
Exacerbation incidence rate[d] (exacerbations/person-years) [95% CI]	0.46 [0.37, 0.57]	0.95 [0.79, 1.14]	0.56 [0.42, 0.74]	0.55 [0.41, 0.73]
Percentage of BD/GP/FF to each of the 2-component combination drugs [d] [95% CI]		0.48 [0.37, 0.64]	0.82 [0.58 1.17]	0.83 [0.59 1.18]

a) Duration of an exacerbation or in the 7 days following an exacerbation was not included in the calculation of exposure
b) COPD exacerbations were regarded as separate events provided there were ≥7 days between stop and start dates
c) Total number of exacerbations/total years of exposure across all patients who received the treatment. Duration of an exacerbation or in the 7 days following an exacerbation was not included in the calculation of exposure
d) A negative binomial regression model with percent predicted post-bronchodilator FEV_1, eosinophil count, history of COPD exacerbations (0, 1, or ≥2), country, and ICS use as covariates, and duration of observation as an offset variable.

The applicant's further explanation about efficacy in Japanese patients with COPD:

- The results of change from baseline in morning trough FEV_1 over Weeks 12 to 24 in the Japanese subpopulation of Study PT010006 tended to be similar to those in the entire study population [see Section 7.2.2].
- As for the long-term treatment efficacy of BD/GP/FF, the adjusted mean change from baseline in morning trough FEV_1 [95% CI], the primary efficacy endpoint of Study PT010007 (Japanese extension study), was 114 [86, 142] mL at Week 24, and 82 [49, 115] mL at Week 52 in the BD/GP/FF group, indicating that improved respiratory function observed at 24 weeks following BD/GP/FF administration was generally maintained up to Week 52.

It is considered that the above results demonstrate the efficacy of BD/GP/FF MDI in Japanese patients with COPD.

PMDA's view:

Analyses of the primary endpoint of Study PT010006, change from baseline in morning trough FEV_1 over Weeks 12 to 24, indicated statistically significant differences in the comparison of BD/GP/FF with BD/FF or GP/FF. Analyses of the secondary endpoints also indicated higher efficacy in the BD/GP/FF group compared with that in the GP/FF and BD/FF groups, demonstrating an additive effect of BD 320 µg to GP/FF 14.4/9.6 µg, and that of GP 14.4 µg to BD/FF 320/9.6 µg. Furthermore, the difference between the BD/GP/FF and GP/FF groups observed in the analysis of change from baseline in morning trough FEV_1 over Weeks 12 to 24 was similar to the additive effect of BD in the clinical studies of the approved BD/FF combination drug, suggesting that BD/GP/FF MDI is expected to be clinically useful to a certain degree. In the evaluation of efficacy with COPD exacerbations as an indicator (e.g., time to first moderate or severe COPD exacerbation, and the incidence rate of moderate or severe COPD exacerbations), the efficacy of BD/GP/FF tended to be higher than that of GP/FF, a result which supports the additive effect of BD 320 µg to GP/FF 14.4/9.6 µg. Results in the Japanese subpopulation tended to be similar to those in the entire study population, suggesting that BD/GP/FF MDI is expected to be effective in Japanese patients with COPD.

The above conclusion by PMDA will be finalized based on comments from the Expert Discussion.

7.R.3 Safety

7.R.3.1 GP/FF

The applicant's explanation about the safety of GP/FF MDI based on safety data from the following studies: pooled safety data from Study PT003014 (a global phase III study in patients with COPD) and Studies PT003006 and PT003007 (foreign phase III studies in patients with COPD); Study PT003008 (a foreign extension study in patients with COPD who participated in Study PT003006 or PT003007); data on the Japanese subpopulation of Study PT003014; and Study PT010007 (Japanese extension study):

Adverse events in the pooled data from Studies PT003014, PT003006, and PT003007, and in Study PT003008 are summarized in Table 49. The incidence of adverse events was similar across the treatment groups. Adverse events in the Japanese subpopulation of Study PT003014 and in Study PT010007 are summarized in Table 50. The incidence of adverse events was similar to that in the entire study population.

Table 49. Summary of adverse events (pooled data from Studies PT003014/PT003006/PT003007; Study PT003008, safety analysis population)

Study	Pooled data from PT003014/PT003006/PT003007 (up to Week 24)					PT003008 (Weeks 24-52)			
Treatment group	GP/FF (n = 1588)	GP (n = 1364)	FF (n = 1370)	Placebo (n = 678)	Tiotropium (n = 451)	GP/FF (n = 290)	GP (n = 219)	FF (n = 213)	Tiotropium (n = 171)
Total exposure period (person-years)	680.31	570.29	571.46	267.18	195.44	146.27	110.64	107.17	85.87
All adverse events	923 (58.1) 340.6	750 (55.0) 341.2	762 (55.6) 326.5	386 (56.9) 344.7	283 (62.7) 385.8	163 (56.2) 348.0	112 (51.1) 273.0	98 (46.0) 236.1	98 (57.3) 259.7
Serious adverse events	133 (8.4) 25.1	107 (7.8) 27.2	106 (7.7) 22.6	50 (7.4) 24.3	36 (8.0) 21.5	36 (12.4) 34.9	17 (7.8) 19.9	15 (7.0) 14.0	13 (7.6) 16.3
Deaths	6 (0.4) 1.0	2 (0.1) 0.4	2 (0.1) 2.6	2 (0.3) 0.8	4 (0.9) 2.1	0	0	1 (0.5) 0.9	1 (0.6) 1.2
Adverse events leading to treatment discontinuation	91 (5.7) 18.4	80 (5.9) 23.3	71 (5.2) 21.0	43 (6.3) 21.0	22 (4.9) 11.8	17 (5.9) 17.8	9 (4.1) 9.0	6 (2.8) 9.3	6 (3.5) 7.0
Adverse reactions	172 (10.8) 40.6	150 (11.0) 44.9	144 (10.5) 39.9	69 (10.2) 43.0	46 (10.2) 42.0	19 (6.6) 17.8	15 (6.8) 23.5	9 (4.2) 8.4	15 (8.8) 25.6

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years

Table 50. Summary of adverse events (Japanese subpopulation in Study PT003014, and Study PT010007, safety analysis population)

Study	Japanese subpopulation in PT003014 (up to Week 24)				PT010007 (Weeks 24-52)	
Treatment group	GP/FF (n = 49)	GP (n = 42)	FF (n = 44)	Placebo (n = 15)	GP/FF (n = 111)	BD/FF DPI (n = 62)
Total exposure period (person-years)	21.13	18.45	19.63	5.24	57.04	31.04
All adverse events	27 (55.1) 246.1	30 (71.4) 379.5	24 (54.5) 234.4	6 (40.0) 228.9	77 (69.4) 336.6	42 (67.7) 248.1
Serious adverse events	6 (12.2) 42.6	4 (9.5) 27.1	3 (6.8) 15.3	1 (6.7) 19.1	19 (17.1) 43.8	8 (12.9) 35.4
Deaths	0	0	0	0	0	1 (1.6) 3.2
Adverse events leading to treatment discontinuation	4 (8.2) 28.4	4 (9.5) 21.7	1 (2.3) 10.2	1 (6.7) 19.1	6 (5.4) 10.5	4 (6.5) 12.9
Adverse reactions	1 (2.0) 4.7	1 (2.4) 5.4	2 (4.5) 10.2	0	5 (4.5) 8.8	6 (9.7) 19.3

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years

7.R.3.1.1 Cardiovascular events

The applicant's explanation about the incidence of cardiovascular events that may be caused by LABA or LAMA treatment:

Table 51 shows the incidence of cardiovascular events in pooled data from Studies PT003014, PT003006, and PT003007, and results from Study PT003008. The incidence of cardiac failure tended to be higher in the GP/FF and FF groups compared with placebo. The incidence of cardiac failure in the GP/FF group tended to be higher at Weeks 24 to 52, compared with the incidence up to Week 24; however, a causal relationship to the study drug was ruled out for all the events of cardiac failure that occurred at Week 24 or later. Of the notable cardiovascular events by preferred term (PT), atrial fibrillation occurred most frequently (in pooled data from Studies PT003014/PT003006/PT003007, 0.6% [9 of 1588 subjects] in the GP/FF group, 0.7% [9 of 1364 subjects] in the GP group, 0.5% [7 of 1370 subjects] in the FF group, 0.3% [2 of 678 subjects] in the placebo group, and 0.4% [2 of 451 subjects] in the tiotropium group; in Study PT003008, 0 subjects in the GP/FF group and 0.6% [1 of 171 subjects] in the tiotropium group), indicating that the incidence of atrial fibrillation tended to be higher in the GP/FF group compared with placebo.

Table 52 shows the incidence of cardiovascular events in the Japanese subpopulation of Study PT003014 and in Study PT010007, indicating no clear difference compared with the incidence in the entire study population.

Table 51. Incidence of cardiovascular events (pooled data from Studies PT003014/PT003006/PT003007; Study PT003008, safety analysis population)

Study	Pooled data from PT003014/PT003006/PT003007 (up to Week 24)					PT003008 (Weeks 24-52)			
Treatment group	GP/FF (n = 1588)	GP (n = 1364)	FF (n = 1370)	Placebo (n = 678)	Tiotropium (n = 451)	GP/FF (n = 290)	GP (n = 219)	FF (n = 213)	Tiotropium (n = 171)
Total exposure period (person-years)	680.31	570.29	571.46	267.18	195.44	146.27	110.64	107.17	85.87
Arrhythmia	30 (1.9) 4.6	20 (1.5) 4.4	23 (1.7) 4.4	9 (1.3) 3.4	3 (0.7) 2.1	5 (1.7) 3.4	3 (1.4) 3.6	2 (0.9) 2.8	2 (1.2) 2.3
Torsade de pointes/QT prolonged	3 (0.2) 0.4	2 (0.1) 0.4	3 (0.2) 0.5	2 (0.3) 0.8	0	0	0	0	0
Cardiac failure	8 (0.5) 1.2	3 (0.2) 0.5	7 (0.5) 1.2	1 (0.1) 0.4	1 (0.2) 1.5	3 (1.0) 3.4	1 (0.5) 0.9	0	1 (0.6) 1.2
Ischaemic heart disease	14 (0.9) 2.5	11 (0.8) 2.8	12 (0.9) 2.8	7 (1.0) 3.4	3 (0.7) 3.1	2 (0.7) 1.4	0	0	2 (1.2) 2.3
Central nervous system vascular disorders	4 (0.3) 0.7	5 (0.4) 0.9	4 (0.3) 0.7	2 (0.3) 0.8	1 (0.2) 0.5	2 (0.7) 1.4	0	0	1 (0.6) 1.2

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years

Table 52. Incidence of cardiovascular events (Japanese subpopulation in Study PT003014, and Study PT010007, safety analysis population)

Study	Japanese subpopulation in PT003014 (up to Week 24)				PT010007 (Weeks 24-52)	
Treatment group	GP/FF (n = 49)	GP (n = 42)	FF (n = 44)	Placebo (n = 15)	GP/FF (n = 111)	BD/FF DPI (n = 62)
Total exposure period (person-years)	21.13	18.45	19.63	5.24	57.04	31.04
Arrhythmia	0	0	0	0	0	1 (1.6) 3.2
Torsade de pointes/QT prolonged	0	0	0	0	0	0
Cardiac failure	0	0	0	0	0	0
Ischaemic heart disease	1 (2.0) 4.7	0	0	0	1 (0.9) 1.8	1 (1.6) 3.2
Central nervous system vascular disorders	0	0	0	0	1 (0.9) 1.8	1 (1.6) 3.2

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years

PMDA's view:

When using GP/FF MDI in the treatment of patients with COPD, close attention should be paid to the possible occurrence of cardiovascular events, based on the following findings in clinical studies: the incidence of atrial

fibrillation and other cardiovascular events tended to be higher in the GP/FF group compared with placebo; incidence of serious atrial fibrillation also tended to be higher in the GP/FF group compared with placebo (pooled data from Studies PT003014/PT003006/PT003007, 0.3% [5 of 1588 subjects] in the GP/FF group, 0.1% [2 of 1364 subjects] in the GP group, 0.1% [1 of 1370 subjects] in the FF group, and 0 subjects in the placebo group); and elderly people, who are likely to be at high risk for cardiovascular disease, account for a significant proportion of patients with COPD. As with other similar drugs, it is therefore appropriate to provide a cautionary statement regarding the risk of cardiovascular events including atrial fibrillation, and to continue close monitoring for these events.

7.R.3.1.2 LAMA-related adverse events

The applicant's explanation about the incidence of expected adverse events as class effects of LAMA, other than cardiovascular events:

Table 53 shows the incidence of LAMA-related adverse events in the pooled data from Studies PT003014, PT003006, and PT003007, and results from Study PT003008. With the exception of palpitations, the incidence of all events tended to be higher in the GP/FF and GP groups compared with placebo, and the incidence was similar to that of tiotropium, which has been approved in Japan.

Table 54 shows the incidence of LAMA-related adverse events in the Japanese subpopulation of Study PT003014 and in Study PT010007. While the incidence of anticholinergic syndrome in the GP/FF group tended to be higher at Weeks 24 to 52 compared with the entire study population, all the events of anticholinergic syndrome in the Japanese subpopulation were non-serious.

Table 53. Incidence of LAMA-related adverse events (pooled data from Studies PT003014/PT003006/PT003007; Study PT003008, safety analysis population)

Study	Pooled data from PT003014/PT003006/PT003007 (up to Week 24)					PT003008 (Weeks 24-52)			
Treatment group	GP/FF (n = 1588)	GP (n = 1364)	FF (n = 1370)	Placebo (n = 678)	Tiotropium (n = 451)	GP/FF (n = 290)	GP (n = 219)	FF (n = 213)	Tiotropium (n = 171)
Total exposure period (person-years)	680.31	570.29	571.46	267.18	195.44	146.27	110.64	107.17	85.87
Agitation/anxiety	14 (0.9) 2.2	20 (1.5) 3.5	12 (0.9) 2.1	4 (0.6) 1.5	6 (1.3) 3.1	3 (1.0) 2.1	0	1 (0.5) 0.9	1 (0.6) 1.2
Anticholinergic syndrome	70 (4.4) 12.1	55 (4.0) 11.8	45 (3.3) 8.4	18 (2.7) 8.2	24 (5.3) 14.3	11 (3.8) 8.9	3 (1.4) 2.7	1 (0.5) 0.9	5 (2.9) 5.8
Glaucoma	3 (0.2) 0.4	3 (0.2) 0.5	2 (0.1) 0.4	0	2 (0.4) 1.0	0	0	0	1 (0.6) 1.2
Visual disorder	7 (0.4) 1.0	6 (0.4) 1.2	4 (0.3) 0.7	2 (0.3) 0.8	2 (0.4) 1.0	2 (0.7) 2.1	0	1 (0.5) 0.9	1 (0.6) 1.2
Palpitations	4 (0.3) 0.6	3 (0.2) 0.5	1 (0.1) 0.2	2 (0.3) 0.8	1 (0.2) 0.5	0	1 (0.5) 0.9	0	1 (0.6) 1.2
Bowel obstruction	1 (0.1) 0.2	2 (0.1) 0.4	4 (0.3) 0.7	0	2 (0.4) 1.0	1 (0.3) 0.7	1 (0.5) 0.9	0	0
Urinary retention	10 (0.6) 1.6	5 (0.4) 1.1	6 (0.4) 1.1	2 (0.3) 0.8	4 (0.9) 2.1	1 (0.3) 0.7	2 (0.9) 1.8	1 (0.5) 0.9	0

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years

Table 54. Incidence of LAMA-related adverse events (Japanese subpopulation in Study PT003014, and Study PT010007, safety analysis population)

Study	Japanese subpopulation in PT003014 (up to Week 24)				PT010007 (Weeks 24-52)	
Treatment group	GP/FF (n = 49)	GP (n = 42)	FF (n = 44)	Placebo (n = 15)	GP/FF (n = 111)	BD/FF DPI (n = 62)
Total exposure period (person-years)	21.13	18.45	19.63	5.24	57.04	31.04
Agitation/anxiety	0	0	0	0	0	0
Anticholinergic syndrome	3 (6.1) 14.2	1 (2.4) 5.4	0	0	9 (8.1) 21.0	2 (3.2) 9.7
Glaucoma	0	0	0	0	0	0
Visual disorder	0	0	0	0	0	0
Palpitations	0	0	0	0	0	0
Bowel obstruction	0	0	0	0	0	0
Urinary retention	0	0	0	0	0	0

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years

PMDA's view:

Although adverse events expected as class effects of LAMA have been reported in clinical studies, observed risk is not higher than that for the approved LAMA monocomponent. It is therefore appropriate to implement safety measures similar to those implemented for similar drugs, and to continue monitoring closely.

7.R.3.1.3 LABA-related adverse events

The applicant's explanation about the incidence of expected adverse events as class effects of LABA, other than cardiovascular events:

Table 55 shows the incidence of LABA-related adverse events in the pooled data from Studies PT003014, PT003006, and PT003007, and results from Study PT003008. The incidence of tremor and headache tended to be higher in the GP/FF and FF groups compared with placebo, while most of the events were mild or moderate.

Table 56 shows the incidence of LABA-related adverse events in the Japanese subpopulation of Study PT003014 and in Study PT010007. While the incidence of headache in the GP/FF group at Weeks 24 to 52 tended to be higher compared with the entire study population, all the events of headache in the Japanese subpopulation were non-serious, and a causal relationship to the study drug was ruled out for these events.

Table 55. Incidence of LABA-related adverse events (pooled data from Studies PT003014/PT003006/PT003007; Study PT003008, safety analysis population)

Study	Pooled data from PT003014/PT003006/PT003007 (up to Week 24)					PT003008 (Weeks 24-52)			
Treatment group	GP/FF (n = 1588)	GP (n = 1364)	FF (n = 1370)	Placebo (n = 678)	Tiotropium (n = 451)	GP/FF (n = 290)	GP (n = 219)	FF (n = 213)	Tiotropium (n = 171)
Total exposure period (person-years)	680.31	570.29	571.46	267.18	195.44	146.27	110.64	107.17	85.87
Hyperglycaemia/onset of diabetes mellitus	28 (1.8) 4.4	25 (1.8) 4.4	19 (1.4) 3.5	12 (1.8) 4.5	4 (0.9) 2.1	9 (3.1) 6.2	5 (2.3) 4.5	1 (0.5) 0.9	2 (1.2) 2.3
Agitation/anxiety	14 (0.9) 2.2	20 (1.5) 3.5	12 (0.9) 2.1	4 (0.6) 1.5	6 (1.3) 3.1	3 (1.0) 2.1	0	1 (0.5) 0.9	1 (0.6) 1.2
Effect on sleep	11 (0.7) 1.6	14 (1.0) 2.5	12 (0.9) 2.1	3 (0.4) 1.1	5 (1.1) 2.6	1 (0.3) 0.7	2 (0.9) 1.8	4 (1.9) 3.7	1 (0.6) 1.2
Tremor (excl congenital)	10 (0.6) 1.9	3 (0.2) 0.5	8 (0.6) 1.4	0	1 (0.2) 0.5	2 (0.7) 1.4	0	0	0
Hypertension	36 (2.3) 5.7	29 (2.1) 5.3	29 (2.1) 5.1	27 (4.0) 10.9	12 (2.7) 7.2	6 (2.1) 4.8	4 (1.8) 5.4	2 (0.9) 1.9	2 (1.2) 2.3
Palpitations	4 (0.3) 0.6	3 (0.2) 0.5	1 (0.1) 0.2	2 (0.3) 0.8	1 (0.2) 0.5	0	1 (0.5) 0.9	0	1 (0.6) 1.2
Asthma/bronchospasm	1 (0.1) 0.2	0	3 (0.2) 0.5	0	0	0	0	0	0
Hypokalaemia	6 (0.4) 0.9	12 (0.9) 2.1	7 (0.5) 1.2	3 (0.4) 1.1	1 (0.2) 0.5	3 (1.0) 2.1	3 (1.4) 2.7	0	0
Headache	30 (1.9) 4.6	31 (2.3) 5.4	35 (2.6) 6.5	7 (1.0) 3.0	6 (1.3) 3.1	2 (0.7) 1.4	2 (0.9) 1.8	1 (0.5) 0.9	3 (1.8) 3.5

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years

Table 56. Incidence of LABA-related adverse events (Japanese subpopulation in Study PT003014, and Study PT010007, safety analysis population)

Study	Japanese subpopulation in PT003014 (up to Week 24)				PT010007 (Weeks 24-52)	
Treatment group	GP/FF (n = 49)	GP (n = 42)	FF (n = 44)	Placebo (n = 15)	GP/FF (n = 111)	BD/FF DPI (n = 62)
Total exposure period (person-years)	21.13	18.45	19.63	5.24	57.04	31.04
Hyperglycaemia/onset of diabetes mellitus	1 (2.0) 4.7	0	0	0	4 (3.6) 7.0	1 (1.6) 3.2
Agitation/anxiety	0	0	0	0	0	0
Effect on sleep	0	1 (2.4) 5.4	1 (2.3) 5.1	0	2 (1.8) 3.5	0
Tremor (excl congenital)	0	0	0	0	0	0
Hypertension	0	0	0	0	0	0
Palpitations	0	0	0	0	0	0
Asthma/bronchospasm	0	0	0	0	0	0
Hypokalaemia	0	0	0	0	0	0
Headache	0	0	0	0	3 (2.7) 5.3	0

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years

In the pooled data from Studies PT003014, PT003006, and PT003007, the number of subjects whose grading of low serum potassium changed from Grade 0 at baseline to Grade 3 during the study period based on the Common Terminology Criteria for Adverse Events (CTCAE) was 3 of 1556 subjects in the GP/FF group, 0 of 1331 subjects in the GP group, 1 of 1344 subjects in the FF group, and 0 of 651 subjects in the placebo group.

PMDA's view:

The incidence of hypokalaemia in the GP/FF and FF groups was not higher than that of placebo in the clinical studies; however, in the pooled data from Studies PT003014, PT003006, and PT003007, worsening of low

serum potassium from CTCAE Grade 0 at baseline to Grade 3 during the study period only occurred in subjects in the GP/FF and FF groups, and cases of a serious decrease in serum potassium levels have been reported in the voluntary reporting for an inhaled formulation containing FF after marketing launch in Japan. Based on the above findings, as with similar drugs, a cautionary statement on potential serious decreases in serum potassium level should be provided when using GP/FF MDI for patients with COPD. At present, no particular concerns have been raised regarding other class effects of LABA; therefore, it is appropriate to implement safety measures similar to those implemented for similar drugs, and to continue monitoring closely.

7.R.3.1.4 Safety in elderly patients

The applicant's explanation about the safety of GP/FF MDI in elderly patients, which make up a significant portion of patients with COPD:

Table 57 shows the incidence of notable adverse events by age category in the pooled data from Studies PT003014, PT003006, and PT003007. The incidence of arrhythmia tended to increase with increasing age, while the occurrence is consistent across the treatment groups of the same age group. Based on the results, there are no additional safety concerns to be considered when administering GP/FF MDI to elderly patients.

Table 57. Incidence of notable adverse events by age group (pooled data from Studies PT003014/PT003006/PT003007, safety analysis population)

Notable adverse event	Age group	GP/FF (n = 1588)	GP (n = 1364)	FF (n = 1370)	Placebo (n = 678)	Tiotropium (n = 451)
Arrhythmia	≤64	16/837 (1.9)	4/732 (0.5)	11/729 (1.5)	3/354 (0.8)	1/247 (0.4)
	≥65 and ≤74	13/630 (2.1)	12/502 (2.4)	7/543 (1.3)	5/261 (1.9)	0/162 (0)
	≥75	1/121 (0.8)	4/130 (3.1)	5/98 (5.1)	1/63 (1.6)	2/42 (4.8)
Torsade de pointes/QT prolonged	≤64	2/837 (0.2)	0/732 (0)	2/729 (0.3)	1/354 (0.3)	0/247 (0)
	≥65 and ≤74	1/630 (0.2)	2/502 (0.4)	1/543 (0.2)	1/261 (0.4)	0/162 (0)
	≥75	0/121 (0)	0/130 (0)	0/98 (0)	0/63 (0)	0/42 (0)
Cardiac failure	≤64	2/837 (0.2)	1/732 (0.1)	1/729 (0.1)	1/354 (0.3)	0/247 (0)
	≥65 and ≤74	6/630 (1.0)	1/502 (0.2)	3/543 (0.6)	0/261 (0)	0/162 (0)
	≥75	0/121 (0)	1/130 (0.8)	3/98 (3.1)	0/63 (0)	1/42 (2.4)
Ischaemic heart disease	≤64	7/837 (0.8)	6/732 (0.8)	4/729 (0.5)	3/354 (0.8)	2/247 (0.8)
	≥65 and ≤74	4/630 (0.6)	4/502 (0.8)	5/543 (0.9)	3/261 (1.1)	0/162 (0)
	≥75	3/121 (2.5)	1/130 (0.8)	3/98 (3.1)	1/63 (1.6)	1/42 (2.4)
Central nervous system vascular disorders	≤64	1/837 (0.1)	4/732 (0.5)	2/729 (0.3)	1/354 (0.3)	0/247 (0)
	≥65 and ≤74	3/630 (0.5)	0/502 (0)	1/543 (0.2)	0/261 (0)	0/162 (0)
	≥75	0/121 (0)	1/130 (0.8)	1/98 (1.0)	1/63 (1.6)	1/42 (2.4)
Agitation/anxiety	≤64	9/837 (1.1)	9/732 (1.2)	8/729 (1.1)	4/354 (1.1)	4/247 (1.6)
	≥65 and ≤74	5/630 (0.8)	9/502 (1.8)	4/543 (0.7)	0/261 (0)	1/162 (0.6)
	≥75	0/121 (0)	2/130 (1.5)	0/98 (0)	0/63 (0)	1/42 (2.4)
Anticholinergic syndrome	≤64	36/837 (4.3)	21/732 (2.9)	22/729 (3.0)	10/354 (2.8)	8/247 (3.2)
	≥65 and ≤74	28/630 (4.4)	25/502 (5.0)	18/543 (3.3)	6/261 (2.3)	14/162 (8.6)
	≥75	6/121 (5.0)	9/130 (6.9)	5/98 (5.1)	2/63 (3.2)	2/42 (4.8)
Glaucoma	≤64	1/837 (0.1)	1/732 (0.1)	0/729 (0)	0/354 (0)	0/247 (0)
	≥65 and ≤74	2/630 (0.3)	1/502 (0.2)	2/543 (0.4)	0/261 (0)	1/162 (0.6)
	≥75	0/121 (0)	1/130 (0.8)	0/98 (0)	0/63 (0)	1/42 (2.4)
Visual disorder	≤64	4/837 (0.5)	2/732 (0.3)	1/729 (0.1)	2/354 (0.6)	2/247 (0.8)
	≥65 and ≤74	3/630 (0.5)	3/502 (0.6)	3/543 (0.6)	0/261 (0)	0/162 (0)
	≥75	0/121 (0)	1/130 (0.8)	0/98 (0)	0/63 (0)	0/42 (0)
Palpitations	≤64	4/837 (0.5)	1/732 (0.1)	1/729 (0.1)	2/354 (0.6)	0/247 (0)
	≥65 and ≤74	0/630 (0)	2/502 (0.4)	0/543 (0)	0/261 (0)	1/162 (0.6)
	≥75	0/121 (0)	0/130 (0)	0/98 (0)	0/63 (0)	0/42 (0)
Bowel obstruction	≤64	0/837 (0)	0/732 (0)	4/729 (0.5)	0/354 (0)	1/247 (0.4)
	≥65 and ≤74	1/630 (0.2)	2/502 (0.4)	0/543 (0)	0/261 (0)	1/162 (0.6)
	≥75	0/121 (0)	0/130 (0)	0/98 (0)	0/63 (0)	0/42 (0)
Urinary retention	≤64	2/837 (0.2)	3/732 (0.4)	2/729 (0.3)	1/354 (0.3)	2/247 (0.8)
	≥65 and ≤74	8/630 (1.3)	1/502 (0.2)	4/543 (0.7)	1/261 (0.4)	1/162 (0.6)
	≥75	0/121 (0)	1/130 (0.8)	0/98 (0)	0/63 (0)	1/42 (2.4)
Hyperglycaemia/onset of diabetes mellitus	≤64	17/837 (2.0)	14/732 (1.9)	11/729 (1.5)	7/354 (2.0)	4/247 (1.6)
	≥65 and ≤74	11/630 (1.7)	9/502 (1.8)	5/543 (0.9)	5/261 (1.9)	0/162 (0)
	≥75	0/121 (0)	2/130 (1.5)	3/98 (3.1)	0/63 (0)	0/42 (0)
Effect on sleep	≤64	9/837 (1.1)	8/732 (1.1)	8/729 (1.1)	2/354 (0.6)	4/247 (1.6)
	≥65 and ≤74	1/630 (0.2)	4/502 (0.8)	2/543 (0.4)	1/261 (0.4)	1/162 (0.6)
	≥75	1/121 (0.8)	2/130 (1.5)	2/98 (2.0)	0/63 (0)	0/42 (0)
Tremor (excl congenital)	≤64	4/837 (0.5)	1/732 (0.1)	4/729 (0.5)	0/354 (0)	1/247 (0.4)
	≥65 and ≤74	5/630 (0.8)	2/502 (0.4)	3/543 (0.6)	0/261 (0)	0/162 (0)
	≥75	1/121 (0.8)	0/130 (0)	1/98 (1.0)	0/63 (0)	0/42 (0)
Hypertension	≤64	21/837 (2.5)	19/732 (2.6)	13/729 (1.8)	18/354 (5.1)	4/247 (1.6)
	≥65 and ≤74	13/630 (2.1)	9/502 (1.8)	11/543 (2.0)	6/261 (2.3)	6/162 (3.7)
	≥75	2/121 (1.7)	1/130 (0.8)	5/98 (5.1)	3/63 (4.8)	2/42 (4.8)
Asthma/bronchospasm	≤64	0/837 (0)	0/732 (0)	2/729 (0.3)	0/354 (0)	0/247 (0)
	≥65 and ≤74	1/630 (0.2)	0/502 (0)	1/543 (0.2)	0/261 (0)	0/162 (0)
	≥75	0/121 (0)	0/130 (0)	0/98 (0)	0/63 (0)	0/42 (0)
Hypokalaemia	≤64	5/837 (0.6)	6/732 (0.8)	3/729 (0.4)	1/354 (0.3)	1/247 (0.4)
	≥65 and ≤74	1/630 (0.2)	2/502 (0.4)	2/543 (0.4)	2/261 (0.8)	0/162 (0)
	≥75	0/121 (0)	4/130 (3.1)	2/98 (2.0)	0/63 (0)	0/42 (0)
Headache	≤64	22/837 (2.6)	19/732 (2.6)	16/729 (2.2)	5/354 (1.4)	4/247 (1.6)
	≥65 and ≤74	7/630 (1.1)	7/502 (1.4)	18/543 (3.3)	1/261 (0.4)	2/162 (1.2)
	≥75	1/121 (0.8)	5/130 (3.8)	1/98 (1.0)	1/63 (1.6)	0/42 (0)

Number of subjects (%)

PMDA's view:

While clinical studies have raised no particular safety concerns about the use of GP/FF MDI in elderly patients, given that elderly patients represent a significant proportion of patients with COPD in Japan, and decline in physiological function in elderly patients may affect GP/FF systemic exposure, it is appropriate to continue to monitor events for which elderly patients are considered to be at high risk.

The above conclusion by PMDA in Sections 7.R.3.1.1 through 7.R.3.1.4 will be finalized based on comments from the Expert Discussion.

7.R.3.2 BD/GP/FF

The applicant's explanation about the safety of BD/GP/FF MDI based on safety data from the following studies: Study PT010006 (a global phase III study in patients with COPD); pooled safety data from Study PT010008 (a foreign extension study in patients with COPD who participated in Study PT010006) and Study PT010007 (a Japanese extension study); data on the Japanese subpopulation in Study PT010006; and Study PT010007.

Adverse events in Study PT010006 and the pooled data from Studies PT010008 and PT010007 are summarized in Table 58. The incidence of adverse events was similar across the treatment groups. Adverse events in the Japanese subpopulation of Study PT010006 and in Study PT010007 are summarized in Table 59. The incidence of adverse events was generally similar to that in the entire study population. The incidence of deaths in the BD/GP/FF group tended to be higher at Weeks 24 to 52 compared with the entire study population; however, a causal relationship to the study drug was ruled out for all deaths in Study PT010007 [see Section 7.2.3].

Table 58. Summary of adverse events (Study PT010006, and pooled data from Studies PT010008/PT010007, safety analysis population)

Study	PT010006 (up to Week 24)				Pooled data from PT010008/PT010007 (Weeks 24-52)			
Treatment group	BD/GP/FF (n = 639)	GP/FF (n = 625)	BD/FF (n = 314)	BD/FF DPI (n = 318)	BD/GP/FF (n = 276)	GP/FF (n = 259)	BD/FF (n = 128)	BD/FF DPI (n = 62)
Total exposure period (person-years)	277.25	264.46	132.23	136.55	140.85	131.46	66.63	31.04
All adverse events	388 (60.7) 339.0	384 (61.4) 339.6	175 (55.7) 301.7	183 (57.5) 353.0	166 (60.1) 279.0	163 (62.9) 299.7	69 (53.9) 216.1	42 (67.7) 248.1
Serious adverse events	55 (8.6) 26.3	68 (10.9) 37.4	21 (6.7) 20.4	29 (9.1) 30.0	30 (10.9) 29.8	30 (11.6) 32.0	7 (5.5) 16.5	8 (12.9) 35.4
Deaths	6 (0.9) 2.2	3 (0.5) 1.1	2 (0.6) 2.3	1 (0.3) 0.7	3 (1.1) 2.8	1 (0.4) 0.8	0	1 (1.6) 3.2
Adverse events leading to treatment discontinuation	30 (4.7) 13.0	30 (4.8) 14.0	11 (3.5) 11.3	11 (3.5) 11.7	9 (3.3) 7.8	13 (5.0) 12.2	4 (3.1) 9.0	4 (6.5) 12.9
Adverse reactions	112 (17.5) 62.4	91 (14.6) 52.6	48 (15.3) 56.0	40 (12.6) 57.9	20 (7.2) 18.5	18 (6.9) 15.2	14 (10.9) 28.5	6 (9.7) 19.3

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years

Table 59. Summary of adverse events (Japanese subpopulation in Study PT010006, and Study PT010007, safety analysis population)

Study	Japanese subpopulation in PT010006 (up to Week 24)				PT010007 (Weeks 24-52)			
Treatment group	BD/GP/FF (n = 139)	GP/FF (n = 138)	BD/FF (n = 70)	BD/FF DPI (n = 69)	BD/GP/FF (n = 116)	GP/FF (n = 111)	BD/FF (n = 58)	BD/FF DPI (n = 62)
Total exposure period (person-years)	61.96	59.38	30.51	30.67	61.17	57.04	30.92	31.04
All adverse events	93 (66.9) 343.8	92 (66.7) 288.0	51 (72.9) 370.4	41 (59.4) 273.9	78 (67.2) 287.7	77 (69.4) 336.6	33 (56.9) 255.5	42 (67.7) 248.1
Serious adverse events	11 (7.9) 22.6	14 (10.1) 35.4	7 (10.0) 23.0	6 (8.7) 22.8	12 (10.3) 31.1	19 (17.1) 43.8	4 (6.9) 19.4	8 (12.9) 35.4
Deaths	0	1 (0.7) 1.7	1 (1.4) 3.3	0	3 (2.6) 6.5	0	0	1 (1.6) 3.2
Adverse events leading to treatment discontinuation	6 (4.3) 14.5	6 (4.3) 10.1	2 (2.9) 6.6	2 (2.9) 6.5	4 (3.4) 9.8	6 (5.4) 10.5	2 (3.4) 12.9	4 (6.5) 12.9
Adverse reactions	29 (20.9) 59.7	11 (8.0) 20.2	12 (17.1) 62.3	4 (5.8) 13.0	11 (9.5) 21.3	5 (4.5) 8.8	7 (12.1) 25.9	6 (9.7) 19.3

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years

7.R.3.2.1 ICS-related adverse events

The applicant's explanation about the incidence of expected adverse events as class effects related to ICS:

Table 60 shows the incidence of ICS-related adverse events in Study PT010006 and the pooled data from Studies PT010008 and PT010007. The incidence of candidiasis, dysphonia, aphonia, or other events tended to be higher in the BD/GP/FF group than in the GP/FF group, which does not contain ICS. However, the incidence was clearly higher than that of BD/FF DPI, an approved drug in Japan, in terms of the risk associated with treatment.

Table 61 shows the incidence of ICS-related adverse events in the Japanese subpopulation of Study PT010006 and in Study PT010007. The incidence of the events was generally similar to that in the entire study population. In the Japanese subpopulation, the incidence of infectious pneumonia was higher in the BD/GP/FF group than in the GP/FF group.

Table 60. Incidence of ICS-related adverse events (Study PT010006, and pooled data from Studies PT010008/PT010007, safety analysis population)

Study	PT010006 (up to Week 24)				Pooled data from PT010008/PT010007 (Weeks 24-52)			
Treatment group	BD/GP/FF (n = 639)	GP/FF (n = 625)	BD/FF (n = 314)	BD/FF DPI (n = 318)	BD/GP/FF (n = 276)	GP/FF (n = 259)	BD/FF (n = 128)	BD/FF DPI (n = 62)
Total exposure period (person-years)	277.25	264.46	132.23	136.55	140.85	131.46	66.63	31.04
Candidiasis[a)]	13 (2.0) 5.8	5 (0.8) 1.9	5 (1.6) 3.8	5 (1.6) 3.7	7 (2.5) 6.4	0	5 (3.9) 7.5	3 (4.8) 9.7
Lower respiratory tract infection other than pneumonia	21 (3.3) 8.3	15 (2.4) 6.4	13 (4.1) 11.3	10 (3.1) 7.3	14 (5.1) 12.1	14 (5.4) 16.0	1 (0.8) 1.5	5 (8.1) 16.1
Infectious pneumonia	16 (2.5) 5.8	12 (1.9) 5.3	8 (2.5) 6.1	6 (1.9) 4.4	11 (4.0) 7.8	9 (3.5) 6.9	5 (3.9) 7.5	5 (8.1) 19.3
Adrenal suppression[b)]	0	0	0	0	0	0	0	0
Effect on mental status[c)]	3 (0.5) 1.1	2 (0.3) 0.8	2 (0.6) 1.5	2 (0.6) 1.5	0	1 (0.4) 0.8	1 (0.8) 1.5	1 (1.6) 3.2
Cataract	5 (0.8) 2.2	4 (0.6) 1.5	3 (1.0) 3.8	0	10 (3.6) 8.5	1 (0.4) 0.8	3 (2.3) 6.0	0
Dysphonia or aphonia	20 (3.1) 7.2	5 (0.8) 2.3	15 (4.8) 11.3	6 (1.9) 4.4	3 (1.1) 2.1	0	2 (1.6) 3.0	0
Throat irritation	1 (0.2) 0.4	3 (0.5) 1.1	0	1 (0.3) 0.7	0	0	0	0
Dysgeusia/ageusia	2 (0.3) 0.7	0	1 (0.3) 0.8	1 (0.3) 0.7	0	0	0	0
Fracture	3 (0.5) 1.4	10 (1.6) 3.8	3 (1.0) 3.0	4 (1.3) 2.9	3 (1.1) 2.1	1 (0.4) 0.8	2 (1.6) 6.0	0
Osteoporosis/osteopenia	2 (0.3) 0.7	1 (0.2) 0.4	1 (0.3) 0.8	3 (0.9) 2.2	1 (0.4) 0.7	4 (1.5) 3.0	4 (3.1) 6.0	0

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years
a) Oral candidiasis, oesophageal candidiasis, and oropharyngeal candidiasis
b) Adrenal cortical hypofunctions (high level term; HLT), cortisol decreased, and cortisol free urine decreased
c) Depressed mood, depression, depressive symptom, dysphoria, euphoric mood, and psychotic disorder

Table 61. Incidence of ICS-related adverse events (Japanese subpopulation in Study PT010006, and Study PT010007, safety analysis population)

Study	Japanese subpopulation in PT010006 (up to Week 24)				PT010007 (Weeks 24-52)			
Treatment group	BD/GP/FF (n = 139)	GP/FF (n = 138)	BD/FF (n = 70)	BD/FF DPI (n = 69)	BD/GP/FF (n = 116)	GP/FF (n = 111)	BD/FF (n = 58)	BD/FF DPI (n = 62)
Total exposure period (person-years)	61.96	59.38	30.51	30.67	61.17	57.04	30.92	31.04
Candidiasis[a)]	6 (4.3) 12.9	0	2 (2.9) 6.6	2 (2.9) 6.5	5 (4.3) 11.4	0	4 (6.9) 12.9	3 (4.8) 9.7
Lower respiratory tract infection other than pneumonia	6 (4.3) 11.3	6 (4.3) 11.8	7 (10.0) 29.5	3 (4.3) 9.8	11 (9.5) 22.9	8 (7.2) 24.5	1 (1.7) 3.2	5 (8.1) 16.1
Infectious pneumonia	8 (5.8) 12.9	1 (0.7) 1.7	2 (2.9) 6.6	0	10 (8.6) 16.4	6 (5.4) 10.5	5 (8.6) 16.2	5 (8.1) 19.3
Adrenal suppression[b)]	0	0	0	0	0	0	0	0
Effect on mental status[c)]	0	0	1 (1.4) 3.3	0	0	0	0	1 (1.6) 3.2
Cataract	1 (0.7) 1.6	3 (2.2) 5.1	1 (1.4) 3.3	0	1 (0.9) 1.6	1 (0.9) 1.8	0	0
Dysphonia or aphonia	9 (6.5) 14.5	1 (0.7) 1.7	8 (11.4) 26.2	3 (4.3) 9.8	1 (0.9) 1.6	0	1 (1.7) 3.2	0
Throat irritation	0	0	0	0	0	0	0	0
Dysgeusia/ageusia	1 (0.7) 1.6	0	0	0	0	0	0	0
Fracture	0	2 (1.4) 3.4	0	1 (1.4) 3.3	2 (1.7) 3.3	1 (0.9) 1.8	2 (3.4) 12.9	0
Osteoporosis/osteopenia	0	1 (0.7) 1.7	0	0	0	0	1 (1.7) 3.2	0

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years
a) Oral candidiasis, oesophageal candidiasis, and oropharyngeal candidiasis
b) Adrenal cortical hypofunctions (HLT), cortisol decreased, and cortisol free urine decreased
c) Depressed mood, depression, depressive symptom, dysphoria, euphoric mood, and psychotic disorder

To evaluate the function of the hypothalamic-pituitary-adrenal (HPA) axis, the time course of serum cortisol levels was measured in Study PT010006. The ratio from baseline of serum cortisol weighted mean (0-24 hours) (mean ± standard deviation) was 0.93 ± 0.46 in the BD/GP/FF group, 1.00 ± 0.35 in the GP/FF group, 0.76 ± 0.20 in the BD/FF group, and 0.98 ± 0.30 in the BD/FF DPI group. The results did not necessarily indicate that the rate of reduction in serum cortisol level in the BD/GP/FF group was clearly lower than that in other treatment groups.

Bone mineral density (BMD) at the lumbar vertebra was measured in Study PT010008. The between-group difference in the percent change from baseline in BMD at the lumbar vertebra at Week 52 [95% CI] was −0.5% [−1.4%, 0.5%] for BD/GP/FF vs GP/FF, 0.5% [−0.7%, 1.7%] for GP/FF vs BD/FF, indicating no significant difference between the treatment groups.

PMDA's view:
Although adverse events expected as class effects of ICS have been reported in clinical studies, observed risk is not clearly higher than that for the approved BD/FF combination drug. It is therefore appropriate to implement safety measures similar to those implemented for similar drugs. In the Japanese subpopulation, however, the incidence of infectious pneumonia tended to be higher in the BD/GP/FF group than in the GP/FF group, and therefore these adverse events should be continuously monitored.

7.R.3.2.2 LAMA- or LABA-related adverse events

The applicant's explanation about the incidence of expected adverse events as class effects of LAMA or LABA:
Table 62 shows the incidence of LAMA- or LABA-related adverse events in Study PT010006 and the pooled data from Studies PT010008 and PT010007. The results did not necessarily indicate that the incidence was clearly higher than that of GP/FF MDI or BD/FF DPI, an approved drug in Japan, in terms of the risk associated with treatment. Table 63 shows the incidence of LAMA- or LABA-related adverse events in the Japanese subpopulation of Study PT010006 and in Study PT010007. The results did not indicate that the incidence of each adverse event was clearly higher than that in the entire study population.

Table 62. Incidence of LAMA- or LABA-related adverse events (Study PT010006, and pooled data from Studies PT010008/PT010007, safety analysis population)

Study	PT010006 (up to Week 24)				Pooled data from PT010008/PT010007 (Weeks 24-52)			
Treatment group	BD/GP/FF (n = 639)	GP/FF (n = 625)	BD/FF (n = 314)	BD/FF DPI (n = 318)	BD/GP/FF (n = 276)	GP/FF (n = 259)	BD/FF (n = 128)	BD/FF DPI (n = 62)
Total exposure period (person-years)	277.25	264.46	132.23	136.55	140.85	131.46	66.63	31.04
Arrhythmia	11 (1.7) 4.0	9 (1.4) 3.8	5 (1.6) 3.8	2 (0.6) 1.5	5 (1.8) 3.6	1 (0.4) 0.8	2 (1.6) 3.0	1 (1.6) 3.2
Torsade de pointes/QT prolonged	1 (0.2) 0.4	0	0	0	0	1 (0.4) 0.8	0	0
Cardiac failure	2 (0.3) 0.7	4 (0.6) 1.5	0	0	2 (0.7) 1.4	0	0	0
Ischaemic heart disease	7 (1.1) 2.9	10 (1.6) 6.4	5 (1.6) 3.8	4 (1.3) 2.9	4 (1.4) 2.8	4 (1.5) 3.8	0	1 (1.6) 3.2
Central nervous system vascular disorders	4 (0.6) 2.5	4 (0.6) 1.5	1 (0.3) 0.8	1 0.3) 0.7	0	2 (0.8) 1.5	0	1 (1.6) 3.2
Agitation/anxiety	1 (0.2) 0.4	2 (0.3) 0.8	1 (0.3) 0.8	2 (0.6) 1.5	1 (0.4) 0.7	1 (0.4) 0.8	0	0
Anticholinergic syndrome	11 (1.7) 4.0	18 (2.9) 7.6	3 (1.0) 2.3	9 (2.8) 7.3	11 (4.0) 8.5	14 (5.4) 12.9	2 (1.6) 6.0	2 (3.2) 9.7
Glaucoma	1 (0.2) 0.4	0	2 (0.6) 1.5	0	3 (1.1) 2.1	4 (1.5) 3.0	2 (1.6) 3.0	0
Visual disorder	0	0	0	2 (0.6) 1.5	0	2 (0.8) 1.5	1 (0.8) 1.5	0
Palpitations	0	2 (0.3) 0.8	1 (0.3) 0.8	1 (0.3) 1.5	0	0	1 (0.8) 1.5	0
Bowel obstruction	0	3 (0.5) 1.1	0	0	1 (0.4) 0.7	0	0	0
Urinary retention	2 (0.3) 0.7	2 (0.3) 0.8	1 (0.3) 0.8	1 (0.3) 0.7	1 (0.4) 0.7	1 (0.4) 0.8	0	0
Hyperglycaemia/onset of diabetes mellitus	13 (2.0) 4.7	15 (2.4) 6.1	4 (1.3) 3.0	3 (0.9) 2.9	2 (0.7) 1.4	8 (3.1) 6.1	2 (1.6) 3.0	1 (1.6) 3.2
Effect on sleep	4 (0.6) 1.4	5 (0.8) 1.9	0	3 (0.9) 2.2	4 (1.4) 2.8	3 (1.2) 2.3	0	0
Tremor (excl congenital)	5 (0.8) 1.8	1 (0.2) 0.4	1 (0.3) 0.8	1 (0.3) 0.7	1 (0.4) 0.7	0	0	0
Hypertension	15 (2.3) 5.4	10 (1.6) 3.8	9 (2.9) 6.8	5 (1.6) 3.7	4 (1.4) 2.8	3 (1.2) 2.3	2 (1.6) 3.0	0
Asthma/bronchospasm	0	2 (0.3) 0.8	0	1 (0.3) 0.7	0	0	1 (0.8) 1.5	0
Hypokalaemia	7 (1.1) 2.9	8 (1.3) 3.4	5 (1.6) 4.5	4 (1.3) 3.7	0	1 (0.4) 0.8	0	0
Headache	5 (0.8) 1.8	6 (1.0) 2.3	3 (1.0) 2.3	4 (1.3) 2.9	2 (0.7) 1.4	4 (1.5) 3.0	1 (0.8) 1.5	0

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years

Table 63. Incidence of LAMA- or LABA-related adverse events (Japanese subpopulation in Study PT010006, and Study PT010007, safety analysis population)

Study	Japanese subpopulation in PT010006 (up to Week 24)				PT010007 (Weeks 24-52)			
Treatment group	BD/GP/FF (n = 139)	GP/FF (n = 138)	BD/FF (n = 70)	BD/FF DPI (n = 69)	BD/GP/FF (n = 116)	GP/FF (n = 111)	BD/FF (n = 58)	BD/FF DPI (n = 62)
Total exposure period (person-years)	61.96	59.38	30.51	30.67	61.17	57.04	30.92	31.04
Arrhythmia	0	1 (0.7) 1.7	1 (1.4) 3.3	0	3 (2.6) 4.9	0	0	1 (1.6) 3.2
Torsade de pointes/QT prolonged	0	0	0	0	0	0	0	0
Cardiac failure	0	0	0	0	1 (0.9) 1.6	0	0	0
Ischaemic heart disease	0	3 (2.2) 5.1	0	2 (2.9) 6.5	1 (0.9) 1.6	1 (0.9) 1.8	0	1 (1.6) 3.2
Central nervous system vascular disorders	0	0	0	0	0	1 (0.9) 1.8	0	1 (1.6) 3.2
Agitation/anxiety	0	0	0	0	0	0	0	0
Anticholinergic syndrome	3 (2.2) 4.8	2 (1.4) 3.4	0	1 (1.4) 3.3	5 (4.3) 8.2	9 (8.1) 21.0	1 (1.7) 3.2	2 (3.2) 9.7
Glaucoma	1 (0.7) 1.6	0	0	0	0	0	0	0
Visual disorder	0	0	0	0	0	0	0	0
Palpitations	0	0	0	0	0	0	0	0
Bowel obstruction	0	0	0	0	1 (0.9) 1.6	0	0	0
Urinary retention	0	1 (0.7) 1.7	1 (1.4) 3.3	1 (1.4) 3.3	0	0	0	0
Hyperglycaemia/onset of diabetes mellitus	3 (2.2) 4.8	1 (0.7) 1.7	0	0	1 (0.9) 1.6	4 (3.6) 7.0	1 (1.7) 3.2	1 (1.6) 3.2
Effect on sleep	0	0	0	1 (1.4) 3.3	3 (2.6) 4.9	2 (1.8) 3.5	0	0
Tremor (excl congenital)	0	0	1 (1.4) 3.3	0	1 (0.9) 1.6	0	0	0
Hypertension	3 (2.2) 4.8	0	1 (1.4) 3.3	1 (1.4) 3.3	1 (0.9) 1.6	0	0	0
Asthma/bronchospasm	0	2 (1.4) 3.4	0	0	0	0	1 (1.7) 3.2	0
Hypokalaemia	0	0	0	1 (1.4) 3.3	0	0	0	0
Headache	1 (0.7) 1.6	0	1 (1.4) 3.3	0	2 (1.7) 3.3	3 (2.7) 5.3	0	0

Top, number of subjects (%); bottom, exposure-period adjusted incidence per 100 person-years

PMDA's view:

Although adverse events expected as class effects of LAMA or LABA have been reported in the clinical studies, observed risk is not clearly higher than that for GP/FF MDI or the approved BD/FF combination drug. It is therefore appropriate to implement safety measures similar to those implemented for GP/FF MDI [see Sections 7.R.3.1.1 through 7.R.3.1.3].

7.R.3.2.3 Safety in elderly patients

The applicant's explanation about the safety of BD/GP/FF MDI in elderly patients, which make up a significant portion of patients with COPD:

Table 64 shows the incidence of notable adverse events by age category in Study PT010006, which indicates generally similar trends across the treatment group within the same age category. Based on the results, there are no additional safety concerns to be considered when administering BD/GP/FF MDI to elderly patients.

Table 64. Incidence of notable adverse events by age group (Study PT010006, safety analysis population)

Notable adverse event	Age group	BD/GP/FF (n = 639)	GP/FF (n = 625)	BD/FF (n = 314)	BD/FF DPI (n = 318)
Candidiasis[a)]	≤64	4 (1.4)	3 (1.1)	1 (0.7)	2 (1.5)
	≥65 and ≤74	7 (2.6)	2 (0.7)	4 (2.9)	3 (2.2)
	≥75	2 (2.6)	0	0	0
Lower respiratory tract infection other than pneumonia	≤64	9 (3.0)	5 (1.8)	6 (4.1)	6 (4.5)
	≥65 and ≤74	9 (3.4)	7 (2.5)	4 (2.9)	3 (2.2)
	≥75	3 (3.8)	3 (4.2)	3 (9.4)	1 (2.1)
Infectious pneumonia	≤64	5 (1.7)	6 (2.2)	4 (2.7)	2 (1.5)
	≥65 and ≤74	8 (3.0)	5 (1.8)	3 (2.2)	3 (2.2)
	≥75	3 (3.8)	1 (1.4)	1 (3.1)	1 (2.1)
Adrenal suppression[b)]	≤64	0	0	0	0
	≥65 and ≤74	0	0	0	0
	≥75	0	0	0	0
Effect on mental status[c)]	≤64	2 (0.7)	2 (0.7)	1 (0.7)	1 (0.8)
	≥65 and ≤74	1 (0.4)	0	0	1 (0.7)
	≥75	0	0	1 (3.1)	0
Cataract	≤64	3 (1.0)	0	1 (0.7)	0
	≥65 and ≤74	2 (0.8)	2 (0.7)	2 (1.5)	0
	≥75	0	2 (2.8)	0	0
Dysphonia or aphonia	≤64	6 (2.0)	3 (1.1)	4 (2.7)	4 (3.0)
	≥65 and ≤74	8 (3.0)	2 (0.7)	9 (6.6)	1 (0.7)
	≥75	6 (7.7)	0	2 (6.3)	1 (2.1)
Throat irritation	≤64	1 (0.3)	1 (0.4)	0	0
	≥65 and ≤74	0	1 (0.4)	0	1 (0.7)
	≥75	0	1 (1.4)	0	0
Dysgeusia/ageusia	≤64	1 (0.3)	0	0	1 (0.8)
	≥65 and ≤74	1 (0.4)	0	1 (0.7)	0
	≥75	0	0	0	0
Fracture	≤64	2 (0.7)	4 (1.5)	3 (2.1)	3 (2.3)
	≥65 and ≤74	0	5 (1.8)	0	1 (0.7)
	≥75	1 (1.3)	1 (1.4)	0	0
Osteoporosis/osteopenia	≤64	1 (0.3)	0	0	1 (0.8)
	≥65 and ≤74	1 (0.4)	1 (0.4)	1 (0.7)	1 (0.7)
	≥75	0	0	0	1 (2.1)
Arrhythmia	≤64	3 (1.0)	2 (0.7)	0	1 (0.8)
	≥65 and ≤74	7 (2.6)	6 (2.1)	5 (3.7)	1 (0.7)
	≥75	1 (1.3)	1 (1.4)	0	0
Torsade de pointes/QT prolonged	≤64	0	0	0	0
	≥65 and ≤74	0	0	0	0
	≥75	1 (1.3)	0	0	0
Cardiac failure	≤64	1 (0.3)	2 (0.7)	0	0
	≥65 and ≤74	1 (0.4)	2 (0.7)	0	0
	≥75	0	0	0	0
Ischaemic heart disease	≤64	3 (1.0)	4 (1.5)	3 (2.1)	2 (1.5)
	≥65 and ≤74	4 (1.5)	3 (1.1)	2 (1.5)	2 (1.4)
	≥75	0	3 (4.2)	0	0
Central nervous system vascular disorders	≤64	1 (0.3)	1 (0.4)	0	0
	≥65 and ≤74	3 (1.1)	2 (0.7)	1 (0.7)	0
	≥75	0	1 (1.4)	0	1 (2.1)
Agitation/anxiety	≤64	1 (0.3)	0	0	2 (1.5)
	≥65 and ≤74	0	2 (0.7)	1 (0.7)	0
	≥75	0	0	0	0
Anticholinergic syndrome	≤64	5 (1.7)	4 (1.5)	1 (0.7)	4 (3.0)
	≥65 and ≤74	5 (1.9)	12 (4.3)	2 (1.5)	4 (2.9)
	≥75	1 (1.3)	2 (2.8)	0	1 (2.1)
Glaucoma	≤64	1 (0.3)	0	1 (0.7)	0
	≥65 and ≤74	0	0	1 (0.7)	0
	≥75	0	0	0	0
Visual disorder	≤64	0	0	0	2 (1.5)
	≥65 and ≤74	0	0	0	0
	≥75	0	0	0	0

Notable adverse event	Age group	BD/GP/FF (n = 639)	GP/FF (n = 625)	BD/FF (n = 314)	BD/FF DPI (n = 318)
Palpitations	≤64	0	1 (0.4)	0	1 (0.8)
	≥65 and ≤74	0	1 (0.4)	1 (0.7)	0
	≥75	0	0	0	0
Bowel obstruction	≤64	0	2 (0.7)	0	0
	≥65 and ≤74	0	0	0	0
	≥75	0	1 (1.4)	0	0
Urinary retention	≤64	0	1 (0.4)	0	0
	≥65 and ≤74	1 (0.4)	1 (0.4)	0	1 (0.7)
	≥75	1 (1.3)	0	1 (3.1)	0
Hyperglycaemia/onset of diabetes mellitus	≤64	7 (2.4)	7 (2.6)	3 (2.1)	1 (0.8)
	≥65 and ≤74	4 (1.5)	7 (2.5)	1 (0.7)	1 (0.7)
	≥75	2 (2.6)	1 (1.4)	0	1 (2.1)
Effect on sleep	≤64	1 (0.3)	2 (0.7)	0	1 (0.8)
	≥65 and ≤74	2 (0.8)	3 (1.1)	0	2 (1.4)
	≥75	1 (1.3)	0	0	0
Tremor (excl congenital)	≤64	2 (0.7)	1 (0.4)	0	0
	≥65 and ≤74	2 (0.8)	0	1 (0.7)	1 (0.7)
	≥75	1 (1.3)	0	0	0
Hypertension	≤64	5 (1.7)	4 (1.5)	5 (3.4)	3 (2.3)
	≥65 and ≤74	9 (3.4)	4 (1.4)	4 (2.9)	2 (1.4)
	≥75	1 (1.3)	2 (2.8)	0	0
Asthma/bronchospasm	≤64	0	0	0	1 (0.8)
	≥65 and ≤74	0	1 (0.4)	0	0
	≥75	0	1 (1.4)	0	0
Hypokalaemia	≤64	1 (0.3)	2 (0.7)	2 (1.4)	2 (1.5)
	≥65 and ≤74	5 (1.9)	4 (1.4)	3 (2.2)	1 (0.7)
	≥75	1 (1.3)	2 (2.8)	0	1 (2.1)
Headache	≤64	3 (1.0)	1 (0.4)	1 (0.7)	3 (2.3)
	≥65 and ≤74	2 (0.8)	5 (1.8)	1 (0.7)	0
	≥75	0	0	1 (3.1)	1 (2.1)

Number of subjects (%)
a) Oral candidiasis, oesophageal candidiasis, and oropharyngeal candidiasis
b) Adrenal cortical hypofunctions (HLT), cortisol decreased, and cortisol free urine decreased
c) Depressed mood, depression, depressive symptom, dysphoria, euphoric mood, and psychotic disorder

PMDA's view:

The results of the clinical studies indicated no safety concerns unique to the use of BD/GP/FF MDI in elderly patients. It is appropriate to closely monitor the risks that are considered to be high in elderly patients.

The above conclusion by PMDA in Sections 7.R.3.2.1 through 7.R.3.2.3 will be finalized based on comments from the Expert Discussion.

7.R.4 Clinical positioning

7.R.4.1 GP/FF

PMDA's view:

GP/FF MDI may be needed for primary treatment depending on the condition of the patient. According to clinical practice guidelines in and outside Japan, however, the treatment should be intensified in a stepwise fashion as a rule, with the severity of disease taken into account. For COPD patients with severe airflow obstruction and repeated exacerbations, a LAMA/LABA combination is recommended (JRS 2018, GOLD 2019). In addition, given that the risk of serious cardiovascular adverse events in patients who have been on long-term LAMA/LABA treatment is not fully understood, it is not appropriate to administer GP/FF MDI to all patients with COPD across the board. As with the existing LAMA/LABA combination drugs, GP/FF MDI should be recognized as a formulation to be prescribed only for patients who need to receive a LAMA/LABA drug concomitantly.

7.R.4.2 BD/GP/FF

PMDA's explanation about the clinical positioning of BD/GP/FF MDI based on the results from Study PT010006 (global phase III study), and guidelines in and outside Japan:

- Study PT010006 enrolled patients with COPD who had been taking ≥2 kinds of inhaled formulations as maintenance therapy for stable COPD on a regular basis for ≥6 weeks, with moderate or severer airflow obstruction and a CAT score of ≥10. Patients were enrolled regardless of history of asthma, although patients with COPD having concomitant asthma were excluded. In the study, respiratory function, inhibition of COPD exacerbation, and health-related QOL tended to improve in the BD/GP/FF group as compared with the GP/FF and BD/FF groups [see Section 7.2.2].
- According to the latest guidelines in Japan, for maintenance treatment in stable COPD according to severity, if bronchodilator (LAMA or LABA) monotherapy is not sufficient to have a therapeutic effect, 2 or more bronchodilators should be used in combination. When a patient is suspected of having asthma, ICS should be used in combination (JRS 2018). Patients with asthma and COPD overlap (ACO) are estimated to account for 15% to 20% of all patients with COPD. In addition to information on the history of asthma and rhinitis allergic, the following data are also considered to be useful in the diagnosis of ACO (JRS 2018): fraction of exhaled nitric oxide (FeNO), blood IgE, blood and sputum eosinophil counts, and airway hyperreactivity. While patients with ACO were excluded from Study PT010006, a subgroup analysis was performed using baseline blood eosinophil counts and airway reversibility[25)] data collected at screening. In the subgroup with low blood eosinophil counts and no airway reversibility, a group which is likely to have few asthma-like characteristics, there was no evidence of an additive effect of BD to GP/FF in the analysis of change from baseline in morning trough FEV_1 over Weeks 12 to 24, the primary endpoint of Study PT010006 (Table 65); however, there was evidence for an additive effect of BD to GP/FF in the same subgroup in terms of inhibition of COPD exacerbations (Table 66). Based on the results, BD/GP/FF MDI is expected to be effective not only in patients with ACO, but also in patients with COPD for improving respiratory function or inhibiting COPD exacerbation.

[25)] Improvement in post-bronchodilator FEV_1 by ≥12% and ≥200 mL was defined as reversible.

Table 65. Change from baseline in morning trough FEV_1 (mL) over Weeks 12 to 24 by blood eosinophil count/airway reversibility category (Study PT010006, mITT population)

Blood eosinophil count class Presence of airway reversibility		BD/GP/FF	GP/FF	BD/FF	BD/FF DPI
Blood eosinophil ≥300/μL and airway reversibility: yes	Number of subjects	38	37	15	12
	Change from baseline[a)] [95% CI]	234 [149, 318]	57 [−30, 145]	205 [82, 329]	88 [−52, 228]
	Difference from BD/GP/FF[a)] [95% CI]		176 [65, 288]	28 [−117, 173]	145 [−13, 304]
Blood eosinophil ≥300/μL and airway reversibility: no	Number of subjects	30	37	21	21
	Change from baseline[a)] [95% CI]	100 [34, 165]	38 [−20, 96]	4 [−74, 83]	77 [2, 152]
	Difference from BD/GP/FF[a)] [95% CI]		62 [−23, 146]	95 [−4, 194]	23 [−76, 122]
Blood eosinophil <300/μL and airway reversibility: yes	Number of subjects	239	208	104	115
	Change from baseline[a)] [95% CI]	182 [160, 204]	162 [140, 185]	92 [61, 124]	113 [83, 143]
	Difference from BD/GP/FF[a)] [95% CI]		20 [−10, 50]	90 [52, 127]	69 [33, 105]
Blood eosinophil <300/μL and airway reversibility: no	Number of subjects	285	277	138	140
	Change from baseline[a)] [95% CI]	97 [80, 115]	102 [84, 120]	28 [3, 53]	46 [21, 72]
	Difference from BD/GP/FF[a)] [95% CI]		−5 [−29, 20]	69 [39, 99]	51 [20, 81]

a) A repeated measures mixed model with treatment, baseline, post-bronchodilator FEV_1 improvement, baseline eosinophil count, visit, the treatment-by-visit interaction, ICS use at screening as covariates.

Table 66. The incidence rate of moderate or severe COPD exacerbation up to Week 24 by blood eosinophil count/airway reversibility category (Study PT010006, mITT population)

Blood eosinophil count class Presence of airway reversibility		BD/GP/FF	GP/FF	BD/FF	BD/FF DPI
Blood eosinophil ≥300/μL and airway reversibility: yes	Number of subjects	38	43	17	14
	Exacerbation incidence rate (exacerbations/person-years)[a)]	0.47	2.35	0.41	0.35
	Percentage of BD/GP/FF to each of the 2-component combination drugs[b)] [95% CI]		0.15 [0.05, 0.44]	1.10 [0.20, 5.99]	1.44 [0.21, 9.77]
Blood eosinophil ≥300/μL and airway reversibility: no	Number of subjects	34	42	23	24
	Exacerbation incidence rate (exacerbations/person-years)[a)]	0.57	0.96	0.31	0.70
	Percentage of BD/GP/FF to each of the 2-component combination drugs[b)] [95% CI]		0.34 [0.07, 1.82]	2.62 [0.33, 21.00]	1.19 [0.18, 7.74]
Blood eosinophil <300/μL and airway reversibility: yes	Number of subjects	248	223	113	126
	Exacerbation incidence rate (exacerbations/person-years)[a)]	0.48	0.61	0.57	0.34
	Percentage of BD/GP/FF to each of the 2-component combination drugs[c)] [95% CI]		0.66 [0.42, 1.03]	0.73 [0.42, 1.27]	1.27 [0.69, 2.35]
Blood eosinophil <300/μL and airway reversibility: no	Number of subjects	319	315	161	153
	Exacerbation incidence rate (exacerbations/person-years)[a)]	0.48	0.92	0.63	0.77
	Percentage of BD/GP/FF to each of the 2-component combination drugs[c)] [95% CI]		0.53 [0.37, 0.76]	0.81 [0.51, 1.29]	0.67 [0.43, 1.04]

a) Duration of an exacerbation or in the 7 days following an exacerbation was not included in the calculation of exposure
b) A negative binomial regression model with duration of observation as an offset variable, including no other covariates
c) A negative binomial regression model with percent predicted post-bronchodilator FEV_1, eosinophil count, history of COPD exacerbations (0, 1, or ≥2), country, and ICS use as covariates, and duration of observation as an offset variable.

Based on the above results, BD/GP/FF MDI is expected to improve respiratory function and suppress the exacerbation of COPD of not only patients with ACO but also symptomatic COPD patients in general with declined respiratory function requiring the combination therapy with ICS, LAMA, and LABA.

PMDA's view:
The applicant explained that BD/GP/FF MDI is expected to be effective in symptomatic COPD patients whose respiratory function has declined, and who require treatment with ICS, LAMA, and LABA in combination, regardless of coexistence with asthma. While this explanation is understandable based on the target populations and results of Study PT010006, it is also important that the use of BD/GP/FF MDI should be carefully determined depending on the condition of the patient, taking into consideration the following points:
Study PT010006 enrolled patients with COPD who had been taking ≥2 kinds of inhaled formulations as maintenance therapy for stable COPD on a regular basis for ≥6 weeks; therefore, the additive effect of BD to GP/FF, or that of GP to BD/FF in patients who had been on monotherapy such as LAMA as a pre-treatment is not known; and special attention is required for cardiovascular events, serious low serum potassium levels, and other adverse events when administering BD/GP/FF MDI [see Section 7.R.3].

The above conclusion by PMDA will be finalized based on comments from the Expert Discussion.

7.R.5 Indications

7.R.5.1 GP/FF

Based on the submitted data, and discussions in Sections 7.R.2.1, 7.R.3.1, and 7.R.4.1, PMDA concluded that the indication for GP/FF MDI is defined as follows, without modifying the proposed indication, "Relief of symptoms secondary to airway obstructive disorder in patients with chronic obstructive pulmonary disease (chronic bronchitis, emphysema) (who require a combination therapy with an inhaled long-acting muscarinic antagonist and an inhaled long-acting beta2 agonist)."

7.R.5.2 BD/GP/FF

Based on the submitted data, and discussions in Sections 7.R.2.2, 7.R.3, and 7.R.4.2, PMDA concluded that the indication for BD/GP/FF MDI can be defined as follows, without modifying the proposed indication, "Relief of symptoms of chronic obstructive pulmonary disease (chronic bronchitis, emphysema) (who require a combination therapy with an inhaled corticosteroid, an inhaled long-acting muscarinic antagonist, and an inhaled long-acting beta2 agonist)."

The above conclusion by PMDA will be finalized based on comments from the Expert Discussion.

7.R.6 Dosage and administration

7.R.6.1 GP/FF

Based on the submitted data, and discussions in Sections 7.R.1, 7.R.2.1, and 7.R.3.1, PMDA concluded that the dosage regimen of GP/FF MDI for COPD is be defined as GP/FF 7.2/4.8 μg, administered as 2 inhalations twice daily, as proposed by the applicant.

7.R.6.2 BD/GP/FF

Based on the submitted data, and discussions in Sections 7.R.1, 7.R.2.2, and 7.R.3, PMDA concluded that the dosage regimen of BD/GP/FF MDI for COPD is defined as BD/GP/FF 160/7.2/4.8 μg, administered as 2 inhalations twice daily, as proposed by the applicant.

7.R.7 Post-marketing safety measures

7.R.7.1 GP/FF

PMDA's view:

Information on cardiovascular events, serious low serum potassium levels, and asthma-associated deaths, hospitalization, and intubation needs to be gathered according to an appropriate risk management plan. The details of the information gathering procedure will be further discussed.

7.R.7.2 BD/GP/FF

PMDA's view:

Information on cardiovascular events, serious low serum potassium levels, pneumonia, the systemic effect of adrenocorticosteroid (e.g., adrenocortical suppression, bone disorders, eye disorders), and asthma-associated deaths, hospitalization, and intubation needs to be gathered according to an appropriate risk management plan. The details of the information gathering procedure will be further discussed.

Furthermore, according to the latest Japanese guidelines, patients with ACO could become a major patient population in which BD/GP/FF MDI will be used (JRS 2018) [see Section 7.R.4.2]. Based on the dosage of approved BD-containing drugs for asthma (Table 67), when administering BD/GP/FF MDI to patients with ACO, the dose of BD may not be sufficient for some patients and consequently asthma symptoms may not be well controlled. It is therefore important to exercise caution to ensure that asthma control can be sufficiently achieved.

Table 67. Dosage regimens of BD-containing formulations for asthma (adults)

Brand name	Dosage regimen
Pulmicort 100μg Turbuhaler 112 Doses and other strengths/doses	The usual adult dosage is budesonide 100 to 400 μg twice daily. The dose may be modified according to the patient's symptoms; however, the maximum daily dose should not exceed 800 μg.
Pulmicort Respules 0.25mg and other strengths	The usual adult dosage is budesonide 0.5 mg twice daily, or 1 mg once daily, administered by inhalation using a nebulizer. The dose may be modified according to the patient's symptoms; however, the maximum daily dose should not exceed 2 mg.
Symbicort Turbuhaler 30 Doses and other doses	The usual adult dosage for maintenance therapy is 160 μg of budesonide and 4.5 μg of formoterol fumarate dihydrate, administered as 1 inhalation twice daily. The dose may be modified according to the patient's symptoms; however, the maximum daily dose for maintenance therapy should not exceed 4 inhalations twice daily (a total of 8 inhalations, 1280 μg of budesonide and 36 μg of formoterol fumarate dihydrate). Patients on maintenance therapy who receive 1 inhalation or 2 inhalations twice daily, may additionally take the drug on an as-needed basis to relieve asthma attacks. When taking the drug in addition to maintenance therapy, 1 inhalation should be taken at the time of attack. If the attack persists for several minutes, another 1 inhalation can be taken. This should be repeated as needed; however, the total inhalations should not exceed 6 inhalations per each attack. Normally, the maximum daily dose, the sum of inhalations for maintenance therapy and on an as-needed basis, is up to 8 inhalations; however, temporarily, the total daily dose may be increased to 12 inhalations (1920 μg of budesonide, and 54 μg of formoterol fumarate dihydrate).

The above conclusion by PMDA will be finalized based on comments from the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (Trivespi Aerosphere: CTD 5.3.5.1.16, and CTD 5.3.5.1.17; Bevespi Aerosphere: CTD 5.3.5.1.14, CTD 5.3.5.1.16, and CTD 5.3.5.1.20) were subjected to an on-site GCP inspection in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The results of the inspection demonstrated that overall, the study was conducted in accordance with GCP. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. However, the following issue was found regarding some of the study sites and the study sponsor (in-country clinical caretaker), albeit with no major impact on the overall study evaluation, and the issue was notified to the study site directors and the study sponsor (in-country clinical caretaker) as findings requiring corrective action.

Findings requiring corrective action

Study sites

- Protocol deviation (non-compliance with the provision on prohibited concomitant drugs)
- Inconsistency between the source document and case reports (adverse events were not recorded)

Study sponsor (in-country clinical caretaker)

- Delay in annual safety reporting to the investigators and study site directors
- Failure to provide complete information about serious, unpredictable adverse reactions to the investigators or study site directors in a timely manner
- Failure to identify the inconsistency between the source document and case reports through monitoring

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that GP/FF MDI and BD/GP/FF MDI have efficacy in the treatment of COPD, and that both products have acceptable safety in view of their benefits. As a LAMA/LABA combination inhaler and ICS/LAMA/LABA combination inhaler, GP/FF MDI and BD/GP/FF MDI are clinically meaningful because they offer new treatment options for patients with COPD. The safety of GP/FF MDI and BD/GP/FF MDI in Japanese patients with COPD in clinical use should be further evaluated in post-marketing surveillance.

PMDA has concluded that GP/FF MDI and BD/GP/FF MDI may be approved if GP/FF MDI and BD/GP/FF MDI are not considered to have any particular problems based on comments from the Expert Discussion.

10. Other

Definitions of endpoints in the clinical studies are as shown below.

Item	Definition
Studies PT005003, PT003005, and PT009001	
Normalized $FEV_1AUC_{0\text{-}12}$	The area under curve of FEV_1 measured over time was calculated using the trapezoidal rule, divided by the observation time to normalize for time
Studies PT003014, PT003006, and PT003007	
COPD exacerbation	Unusual worsening of symptoms of dyspnoea, cough, or sputum (increased sputum volume or sputum purulent [color]) persisting for ≥3 consecutive days
Moderate COPD exacerbation	COPD exacerbation that requires systemic corticosteroid therapy or antibiotic therapy, but does not result in hospitalization or death
Severe COPD exacerbation	COPD exacerbation resulting in hospitalization or death
Study PT010006	
COPD exacerbation	Unusual worsening of ≥1 major symptoms (dyspnoea, increase in sputum volume, sputum purulent [color]), and ≥1 other major or other symptoms (cough, wheezing, pharyngeal pain, cold [nasal discharge, nasal congestion], pyrexia from no other causes) persisting for ≥2 consecutively days
Moderate COPD exacerbation	COPD exacerbation requiring systemic corticosteroid therapy, or antibiotic therapy for ≥3 days
Severe COPD exacerbation	COPD exacerbation resulting in hospitalization or death

Review Report (2)

May 14, 2019

Products Submitted for Approval

(a)

Brand Name	Bevespi Aerosphere 28 Inhalations; Bevespi Aerosphere 120 Inhalations
Non-proprietary Name	Glycopyrronium Bromide/Formoterol Fumarate Hydrate
Applicant	AstraZeneca K.K.
Date of Application	September 7, 2018

(b)

Brand Name	Breztri Aerosphere 56 Inhalations; Breztri Aerosphere 120 Inhalations
Non-proprietary Name	Budesonide/Glycopyrronium Bromide/Formoterol Fumarate Hydrate
Applicant	AstraZeneca K.K.
Date of Application	September 4, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy, clinical positioning, and indication

1.1.1 GP/FF

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the efficacy, clinical positioning, and indication of GP/FF MDI presented in Review Report (1).

1.1.2 BD/GP/FF

At the Expert Discussion, the expert advisors basically supported PMDA's conclusion on the efficacy, clinical positioning, and indication of BD/GP/FF MDI presented in Review Report (1), while raising the following comments:

- The latest Japanese guidelines (JRS 2018) advises that ICS be used only for patients with suspected complications of asthma, while also noting that ICS may be effective in the treatment of COPD patients with a high peripheral eosinophil count who are even free from concomitant asthma. In Study PT010006 on BD/GP/FF MDI, the results of change from baseline in morning trough FEV_1 over Weeks 12 to 24, the

primary endpoint, suggested an additive effect of BD to GP/FF in the subgroups with baseline blood eosinophil count of ≥300/μL (Table 68), as compared with the subgroups with that of <300/μL. The results will be helpful in determining the target population of BD/GP/FF MDI.

- In light of the description of the ICS target population in the latest Japanese guidelines (JRS 2018), and given that therapies with ICS generally increase a risk of pneumonia, BD/GP/FF MDI should be used only for patients needing to be treated with concomitant ICS, LAMA, and LABA, and the use of BD/GP/FF MDI should be carefully determined depending on the condition of each patient. The proper use of BD/GP/FF MDI should be strictly adhered to so that the product will not be used carelessly.

Table 68. Change from baseline in morning trough FEV_1 (mL) over Weeks 12 to 24 by blood eosinophil count category (Study PT010006, mITT population)

Baseline blood eosinophil count		BD/GP/FF	GP/FF	BD/FF	BD/FF DPI
≥300/μL	Number of subjects	68	74	36	33
	Change from baseline[a)] [95% CI]	171 [118, 224]	48 [−3, 99]	103 [32, 173]	89 [17, 161]
	Difference from BD/GP/FF[a)] [95% CI]		123 [53, 193]	68 [−18, 154]	82 [−6, 170]
<300/μL	Number of subjects	524	458	242	255
	Change from baseline[a)] [95% CI]	134 [120, 148]	129 [115, 144]	56 [36, 75]	75 [56, 94]
	Difference from BD/GP/FF[a)] [95% CI]		5 [−15, 24]	78 [55, 102]	59 [36, 82]

a) A repeated measures mixed model with treatment, baseline, post-bronchodilator FEV_1 improvement, baseline eosinophil count, visit, the treatment-by-visit interaction, ICS use at screening as covariates.

Based on the discussions at the Expert Discussion, PMDA requested the applicant to provide healthcare professionals with written information presented below, in addition to cautionary advice on cardiovascular events, serious low serum potassium levels, etc., so as to select appropriate patients for the treatment with BD/GP/FF MDI. The applicant agreed.

- Subgroup analysis results of Study PT010006 on efficacy based on blood eosinophil count and airway reversibility
- The fact that Study PT010006 was conducted in patients using ≥2 kinds of inhalations regularly as maintenance therapy for stable COPD
- The facts that patients with COPD on ICS are suggested to be generally at high risk of pneumonia and the Japanese subpopulation of Study PT010006 revealed a tendency toward higher incidence of pneumonia in the BD/GP/FF group than in the GP/FF and BD/FF DPI groups

1.2 Safety and risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion on the safety of GP/FF MDI and BD/GP/FF MDI, as well as post-marketing safety measures described in Review Report (1).

In view of the discussion in Section "7.R.7 Post-marketing safety measures" in Review Report (1) and comments from the Expert Discussion, PMDA has concluded that the risk management plan (draft) for GP/FF MDI and BD/GP/FF MDI should include the safety and efficacy specifications presented in Table 69 (GP/FF MDI) and Table 71 (BD/GP/FF MDI), and that the applicant should conduct additional pharmacovigilance activities, survey/studies on efficacy, and risk minimization activities presented in Table 70 (GP/FF MDI) and

Table 72 (BD/GP/FF MDI). PMDA requested the applicant to conduct post-marketing surveillance that is designed to allow for the investigations of these items.

Table 69. Safety and efficacy specifications in the risk management plan (draft) for GP/FF MDI

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Cardiovascular events • Serious low serum potassium levels	• Asthma-associated deaths, hospitalization, and intubation	• None
Efficacy specification		
• None		

Table 70. Summary of additional pharmacovigilance activities, survey/studies on efficacy, and risk minimization activities included under the risk management plan (draft) for GP/FF MDI

Additional pharmacovigilance activities	Survey/studies on efficacy	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing database survey in patients with COPD (cardiovascular events)	• None	• Provision of information available from early post-marketing phase vigilance

Table 71. Safety and efficacy specifications in the risk management plan (draft) for BD/GP/FF MDI

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Cardiovascular events • Serious low serum potassium levels	• Pneumonia • Systemic actions of adrenocorticosteroid (e.g., adrenocortical suppression, bone disorders, eye disorders) • Asthma-associated deaths, hospitalization, and intubation	• None
Efficacy specification		
• None		

Table 72. Summary of additional pharmacovigilance activities, survey/studies on efficacy, and risk minimization activities included under the risk management plan (draft) for BD/GP/FF MDI

Additional pharmacovigilance activities	Survey/studies on efficacy	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing database survey in patients with COPD (cardiovascular events)	• None	• Provision of information available from early post-marketing phase vigilance

The applicant explained that it will evaluate the risk of cardiovascular events in patients with COPD by comparing GP/FF MDI vs non-GP/FF LAMA/LABA, and BD/GP/FF MDI vs non-BD/GP/FF ICS/LAMA/LABA based on data from the post-marketing database survey.

PMDA accepted the applicant's plan for the activities. Obtained information should be provided to healthcare professionals in an appropriate and prompt manner. The method of information gathering via post-marketing database survey, etc. should be further discussed in detail, and the survey should be conducted based on a proper plan.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the products may be approved for the indication and dosage and administration shown below, with the following condition. Each product, GP/FF MDI and BD/GP/FF MDI, is a drug with a new active ingredient, and a new combination drug. “Seebri Inhalation Capsules 50μg” (approved in September 2012) and “Ultibro Inhalation Capsules” (approved in September 2013) containing GP as new active ingredient have already been used in Japan for patients with COPD. Thus the re-examination period is 6 years for both GP/FF and BD/GP/FF MDIs. The products are not classified as biological products or specified biological products. The products are not classified as poisonous or powerful drugs.

Bevespi Aerosphere 28 Inhalations, Bevespi Aerosphere 120 Inhalations

Indication

Relief of symptoms of chronic obstructive pulmonary disease (chronic bronchitis, emphysema) secondary to airway obstructive disorder (requiring a combination therapy with an inhaled long-acting muscarinic antagonist and an inhaled long-acting beta2 agonist)

Dosage and Administration

The usual adult dosage is 2 inhalations (containing 14.4 μg of glycopyrronium and 9.6 μg of formoterol fumarate) twice daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Breztri Aerosphere 56 Inhalations, Breztri Aerosphere 120 Inhalations

Indication

Relief of symptoms of chronic obstructive pulmonary disease (chronic bronchitis, emphysema) (requiring a combination therapy with an inhaled corticosteroid, an inhaled long-acting muscarinic antagonist, and an inhaled long-acting beta2 agonist)

Dosage and Administration

The usual adult dosage is 2 inhalations (containing 320 μg of budesonide, 14.4 μg of glycopyrronium, and 9.6 μg of formoterol fumarate) twice daily.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ACO	Asthma and COPD overlap
A/G ratio	Albumin/globulin ratio
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC_{last}	Area under the concentration-time curve from time zero to the time of the last positive concentration
AUC_{0-t}	Area under the concentration-time curve from time zero to 't' (where t = the final time of detection)
BA	Bioavailability
BCRP	Breast cancer resistance protein
BD	Budesonide
BD/FF	Inhalation aerosol containing budesonide and formoterol fumarate dihydrate
BD/GP/FF	Trivespi Aerosphere (Breztri Aerosphere)
BMI	Body mass index
CL	Total clearance
CL/F	Apparent total clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
COPD	Chronic obstructive pulmonary disease
CYP	Cytochrome P450
DPI	Dry powder inhaler
eGFR	Estimated glomerular filtration rate
FEV_1	Forced expiratory volume in one second
FF	Formoterol fumarate dihydrate
F_{rel}	Relative bioavailability
FVC	Forced vital capacity
GGT	γ-glutamyltransferase
GOLD 2018	Global Initiative for Chronic Obstructive Lung Disease (2018 Report)
GOLD 2019	Global Initiative for Chronic Obstructive Lung Disease (2019 Report)
GP	Glycopyrronium bromide
GP/FF	Bevespi Aerosphere
HEK-293	Human embryonic kidney 293 cell
HPLC	High performance liquid chromatography
HPLC-MS/MS	High performance liquid chromatography-tandem mass spectrometry
IC_{50}	Half maximal inhibitory concentration
$[I]_{inlet,max}$	Maximum portal vein plasma concentration
IR	Infrared absorption spectrum
JRS 2013	Guidelines for the Diagnosis and Treatment of COPD (Chronic Obstructive Pulmonary Disease), 4th edition, 2013. Edited by the Japanese Respiratory Society.
JRS 2018	Guidelines for the Diagnosis and Treatment of COPD (Chronic Obstructive Pulmonary Disease), 5th edition, 2018. Edited by the Japanese Respiratory Society.
Ka	Absorption rate constant
LABA	Long-acting beta2 agonist
LAMA	Long-acting muscarinic antagonist
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
MATE	Multidrug and toxin extrusion protein
MDCKII	Madin-Darby canine kidney II cells
MDI	Metered-dose inhalers

MDR1	Multi drug resistance associated protein
MF	Master file
MPP+	1-methyl-4-phenylpyridinium
MS	Mass spectrum
NADPH	Nicotinamide adenine dinucleotide phosphate
NMR	Nuclear magnetic resonance spectrum
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
pA_2	A negative logarithm of the drug concentration causing a 2-fold shift to the right of an agonist concentration-response curve
P-gp	P-glycoprotein
pIC_{50}	Negative logarithm of the IC_{50}
PMDA	Pharmaceuticals and Medical Devices Agency
Q/F	Apparent inter-compartmental clearance
RH	Relative humidity
t_{max}	Time to reach maximum concentration
$t_{1/2}$	Elimination half-life
UHPLC-MS/MS	Ultra high performance liquid chromatography-tandem mass spectrometry
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution