Report on the Deliberation Results

August 13, 2015
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Spiolto Respimat 28 puffs, Spiolto Respimat 60 puffs
[Non-proprietary name]	Tiotropium Bromide Hydrate/Olodaterol Hydrochloride (JAN*)
[Applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	October 17, 2014

[Results of deliberation]
In the meeting held on August 3, 2015, 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 re-examination period for the product is 8 years. One of the drug substances (olodaterol hydrochloride) is classified as a powerful drug, while the drug product is classified as neither poisonous nor powerful. The product is also classified as neither a biological product nor a specified biological product.

[Conditions for approval]
The applicant is required to develop and appropriately implement a risk management plan.

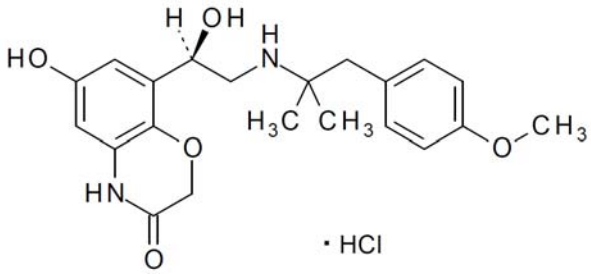
**Japanese Accepted Name (modified INN)*

Review Report

July 23, 2015
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Spiolto Respimat 28 puffs, Spiolto Respimat 60 puffs
[Non-proprietary name]	Tiotropium Bromide Hydrate/Olodaterol Hydrochloride
[Applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	October 17, 2014
[Dosage form/Strength]	Inhalation Solution: Each puff contains 3.124 μg of tiotropium bromide hydrate (equivalent to 2.5 μg of tiotropium) and 2.736 μg of olodaterol hydrochloride (equivalent to 2.5 μg of olodaterol).
[Application classification]	Prescription drug: (1) Drug with a new active ingredient, (2) New combination prescription drug
[Chemical structure]	Olodaterol hydrochloride



Molecular formula: $C_{21}H_{26}N_2O_5 \cdot HCl$

Molecular weight: 422.90

Chemical name: 6-Hydroxy-8-((1*R*)-1-hydroxy-2-{[2-(4-methoxyphenyl)-1,1-dimethylethyl]amino}ethyl)-2*H*-1,4-benzoxazin-3(4*H*)-one monohydrochloride

[Items warranting special mention] None

[Reviewing office] Office of New Drug IV

Review Results

July 23, 2015

[Brand name]	Spiolto Respimat 28 puffs, Spiolto Respimat 60 puffs
[Non-proprietary name]	Tiotropium Bromide Hydrate/Olodaterol Hydrochloride
[Applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	October 17, 2014

[Results of review]

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of chronic obstructive pulmonary disease (COPD) has been demonstrated and its safety is acceptable in view of its observed benefits. The safety of the product in long-term use and in elderly patients and the occurrence of adverse cardiovascular events, etc. should be further investigated through post-marketing surveillance.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions.

[Indication]

Relief of symptoms of airflow obstruction in patients with chronic obstructive pulmonary disease (chronic bronchitis and emphysema) who require combination therapy with a long-acting inhaled anticholinergicagent and a long-acting inhaled β2-agonist.

[Dosage and administration]

The usual adult dosage is 2 inhalations once daily (5 μg of tiotropium and 5 μg of olodaterol).

[Conditions for approval]

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

Review Report (1)

June 18, 2015

I. Product Submitted for Registration

[Brand name]	Spiolto Respimat 28 puffs, Spiolto Respimat 60 puffs
[Non-proprietary name]	Tiotropium Bromide Hydrate/Olodaterol Hydrochloride
[Applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	October 17, 2014
[Dosage form/Strength]	Inhalation Solution: Each puff contains 3.124 μg of tiotropium bromide hydrate (equivalent to 2.5 μg of tiotropium) and 2.736 μg of olodaterol hydrochloride (equivalent to 2.5 μg of olodaterol).
[Proposed indication]	Relief of symptoms of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD, i.e., chronic bronchitis and emphysema)
[Proposed dosage and administration]	The usual adult dosage is 2 inhalations once daily (5 μg of tiotropium and 5 μg of olodaterol).

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

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery and usage conditions in non-Japanese countries etc.

Spiolto Respimat 28 puffs and Spiolto Respimat 60 puffs (hereinafter correctively referred to as "Spiolto Respimat") are both composed of a solution for inhalation containing 2 active ingredients, tiotropium bromide hydrate (Tio) and olodaterol hydrochloride (Olo), and a dedicated inhaler (Respimat). Tio is a long-acting muscarinic antagonist (LAMA), while Olo is a long-acting β_2-agonist (LABA). Spiolto Respimat has been developed by Boehringer Ingelheim GmbH in Germany for the treatment of chronic obstructive pulmonary disease (COPD).

In Japan, Tio is available for the treatment of COPD in 2 formulations: Spiriva 18 μg inhalation capsules (Spiriva) and Spiriva 2.5 μg Respimat 60 puffs (Spiriva Respimat). Spiriva capsules contain inhalation powder administered through the HandiHaler inhalation device. Spiriva was approved in October 2004. Spiriva Respimat is inhalation solution administered through the Respimat inhaler. Spiriva Respimat was approved in January 2010. Although Olo is yet to be approved in Japan as of May 2015, it has been approved in more than 40 countries including the United States, for the treatment of COPD as an inhalation solution formulation delivered with the Respimat inhaler.

COPD is an inflammatory lung disease caused by long-term exposure to toxic substances typically found in cigarette smoke. COPD is characterized by progressive airflow obstruction, and its clinical signs include exertional shortness of breath, chronic coughing, and sputum. The mainstay of drug therapy for patients with stable COPD is bronchodilators, and short-acting β_2-agonists (SABAs), LABAs, and LAMAs are used in a stepwise manner according to the severity of the patient's condition. The Guidelines for the Diagnosis and Treatment of COPD (4th ed. the Japanese Respiratory Society; 2013) ("the JRS guidelines") and the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease ("the GOLD guidelines 2011"), recommend the regular use of LABAs or LAMAs for treatment of patients with moderate to severe COPD and the combined use of at least 2 bronchodilators in patients who have an inadequate response to a LABA or LAMA monotherapy or in those with particularly severe symptoms.

LAMAs and LABAs act by different mechanisms. In clinical practice, the combined use of a LAMA and a LABA is common. A fixed dose combination of a LAMA and a LABA allows both agents to be administered through a single inhaler. Its once-daily formulation is expected to contribute to improvement of treatment adherence and patient convenience. In Japan, glycopyrronium bromide/indacaterol maleate and umeclidinium bromide/vilanterol triphenylacetate have been approved as inhaled formulations of LAMA/LABA combination for treatment of COPD. Spiolto Respimat has been developed as a new fixed dose LAMA/LABA combination that would be an additional therapeutic option for COPD.

Spiolto Respimat was approved for the treatment of COPD in the United States and Europe in May 2015.

In Japan, clinical studies of Spiolto Respimat in patients with COPD began in January 2008. The applicant has filed a new drug application based on the results of multiregional clinical studies involving Japanese patients.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance tiotropium bromide hydrate is also contained in Spiriva 2.5 μg Respimat 60 puffs. Therefore, no new data for tiotropium bromide hydrate, one of the 2 drug substances, were submitted in this application. The drug substance section describes the other drug substance olodaterol hydrochloride.

Olodaterol hydrochloride is a white powder. Its description, melting point, hygroscopicity, optical rotation, dissociation constant, partition coefficient, crystalline polymorphism, and solubility were determined. Differential scanning calorimetry (DSC), thermogravimetry (TG), and X-ray powder

diffraction were performed. [redacted]

The chemical structure of olodaterol hydrochloride has been determined by hydrogen nuclear magnetic resonance spectrometry (^{1}H-NMR and ^{13}C-NMR), electrospray ionization collision-induced dissociation (ESI-CID), infrared spectroscopy (IR), UV-Vis absorption spectroscopy, elemental analysis, and structural analysis by single crystal X-ray diffraction. The drug substance has 1 asymmetric carbon atom, and the *R*-enantiomer is synthesized.

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

[redacted]

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

[redacted]

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

Table 1 shows the stability of the drug substance. Photostability studies indicated that the drug substance is photostable.

Table 1. Stability studies of the drug substance

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long term	3 production batches	25°C	60%RH	A double-layered polyethylene bag in a fiber drum	48 months
Accelerated	3 production batches	40°C	75%RH		12 months

Based on the above, a retest period of [redacted] months has been proposed for the drug substance when stored at room temperature in a double-layered polyethylene bag in a fiber drum. The long-term testing will be continued for up to [redacted] months.

2.A.(2) Drug product

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

The drug product consists of a cartridge filled with inhalation solution and a metered-dose inhaler (Respimat). Each puff contains 3.12 μg of tiotropium bromide hydrate (equivalent to 2.5 μg of tiotropium) and 2.74 μg of olodaterol hydrochloride (equivalent to 2.5 μg of olodaterol). Before the first use, the cartridge is inserted into the inhaler. [redacted] Excipients contained in the drug product are benzalkonium chloride solution, disodium edetate hydrate, 1 mol/L hydrochloric acid, and purified water. [redacted]

A single actuation of the Respimat inhaler allows a metered volume of the inhalation solution to be released through the 2 fine openings of the nozzles. Two jets of the solution released from the nozzles collide with each other, thereby forming an aerosol cloud to be inhaled by the patient. The Respimat device is also used with an approved product, Spiriva 2.5 μg Respimat 60 puffs.

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

The manufacturing process of the drug product consists of solution preparation, filling, and packaging. Solution preparation and filling have been defined as the critical steps, and in-process controls and process control values have been determined for these steps.

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

[redacted]

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

Table 2 shows a summary of the stability studies of the drug product.

Table 2. Stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long term	3 production batches	25°C	60%RH	[redacted]	36 months
Accelerated	3 production batches	40°C	75%RH		6 months

[redacted]

2.B Outline of the review by PMDA

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

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

The pharmacology study results of tiotropium bromide hydrate (Tio) was evaluated in the regulatory review of the application for Spiriva 18 μg inhalation capsules (see the Review Report of "Spiriva 18 μg inhalation capsules" dated August 3, 2004 [in Japanese only]). The results from the following primary pharmacodynamic studies were submitted for the present application: *in vitro* studies on the affinity, functional activity, and selectivity of olodaterol hydrochloride (Olo) for the β_2-adrenoceptor; and *in vivo* studies on the inhibitory effects of Olo and Tio + Olo on airway contraction. The results of other studies submitted included the secondary pharmacodynamic studies on the effects of Olo on different adrenoceptors and transporters, and safety pharmacology studies on the effects of Olo on the central nervous, cardiovascular, and respiratory systems and the effects of Tio + Olo on the cardiovascular system.

The doses and concentrations of Tio, Olo, and formoterol administered are expressed as their free bases, unless otherwise specified.

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

3.(i).A.(1).1) Binding of Olo to receptors and receptor stimulation by Olo (4.2.1.1 to 4.2.1.11)

Binding affinity (pK_i) of Olo, formoterol, and isoprenaline for β-adrenoceptors was studied using membrane preparations of Chinese hamster ovary (CHO) cells expressing the human β_1-, β_2-, or β_3-adrenoceptors. The results showed that Olo has high affinity for the β_2-adrenoceptor. The mean pK_i values at β_1-, β_2-, and β_3-adrenoceptors were 7.33, 9.14, and 5.26, respectively, for Olo; 6.07, 8.29, and 5.58, respectively, for formoterol; and 6.49, 6.54, and 5.57, respectively, for isoprenaline. The effect of β-adrenoceptor stimulation by Olo, formoterol, and isoprenaline was investigated based on the production of intracellular adenosine 3',5'-cyclic monophosphate (cAMP) by adenylyl cyclase. The negative logarithm values of 50% effective concentration (pEC_{50}) (mean) of stimulation of β_1-, β_2-, and β_3-adrenoceptors were 7.55, 9.93, and 6.57, respectively, for Olo; 7.83, 9.73, and 7.60, respectively, for formoterol; and 9.27, 8.58, and 7.86, respectively, for isoprenaline.

3.(i).A.(1).2) Binding of Olo metabolites to receptors and receptor stimulation by Olo metabolites (4.2.1.1 to 4.2.1.9, and 4.2.1.10)

Binding affinity (pK_i) of Olo metabolites CD 992, SOM 1522, CD 11249, and CD 10915 (0.001 pmol/L to 100 μmol/L for each metabolite) and CD 12656 (1 pmol/L to 100 μmol/L) for the human β_1- and β_2-adrenoceptors, and β-adrenoceptor stimulation by these Olo metabolites, were studied in CHO cells expressing the human β_1- or β_2-adrenoceptors (membrane preparations or cells) [see "3.(ii) Summary of

pharmacokinetic studies"]. The mean pK_i values of the metabolites CD 992, SOM 1522, CD 11249, CD 10915, and CD 12656 for the β_2-adrenoceptor were 7.16, 9.37, 6.36, 5.91, and 7.8, respectively; and the pEC_{50} values of the β_2-adrenoceptor were 6.91, 9.03, 6.55, 6.29, and 7.9, respectively. In contrast, the mean pK_i values of the metabolites CD 992, SOM 1522, CD 11249, CD 10915, and CD 12656 for β_1-adrenoceptor were <5, 7.65, <5, <5, and 5.9, respectively; and the pEC_{50} values of β_1-adrenoceptor were <5, 7.34, <5, <5, and 6.6, respectively.

The applicant's explanation:
The results suggested that SOM 1522, a metabolite of Olo, had pharmacological activity against the β_2-adrenoceptor as with unchanged Olo. On the other hand, in Study 1222.3,[1] in which a single dose of Olo 40 μg was administered by inhalation to patients with chronic obstructive pulmonary disease (COPD), SOM 1522 was not detected in the plasma from the majority of subjects. Therefore, SOM 1522 is unlikely to exhibit the pharmacological action in humans.

3.(i).A.(1).3) *In vivo* studies of efficacy and duration of inhibitory effect against bronchoconstriction

(a) Effects of Olo against acetylcholine-induced bronchoconstriction in guinea pigs (4.2.1.1-1, 4.2.1.1-3, and 4.2.1.1-6)

The effect of Olo on acetylcholine (ACh)-induced bronchoconstriction was evaluated in anesthetized male and female guinea pigs (n = 6/group). After repeated intravenous administration of 8 to 12 μg/kg of ACh at 10-minute intervals to the anesthetized animals to induce bronchoconstriction, a single dose of 0.91, 2.73, or 9.14 μg/kg of Olo was administered by inhalation. The air flow rate was measured for 60 minutes. Olo was shown to reduce ACh-induced bronchoconstriction in a dose-dependent manner. The percentage inhibition of bronchoconstriction 10 minutes post-dose in the 0.91, 2.73, and 9.14 μg/kg groups was 83%, 100%, and 100%, respectively, and the bronchoprotective effect was maintained for up to 60 minutes post-dose in all dose groups.

The effect of the test substances on Ach-induced bronchoconstriction was evaluated in male and female guinea pigs (n = 2/group). After repeated intravenous administration of 8 to 12 μg/kg of ACh at 10-minute intervals to the anesthetized animals to induce bronchoconstriction, a single dose of 0.91 or 2.73 μg/kg of Olo, or 0.09, 0.26, or 0.86 μg/kg of formoterol was administered by inhalation. The air flow rate was measured for 300 minutes. In the Olo 0.91 and 2.73 μg/kg groups, the percentage inhibition of ACh-induced bronchoconstriction was 81% and 100%, respectively, 10 minutes post-dose, and 73% and 100%, respectively, 300 minutes post-dose. In the formoterol 0.09, 0.26, and 0.86 μg/kg groups, the percentage inhibition of ACh-induced bronchoconstriction was 13%, 77%, and 100%, respectively, 10 minutes post-dose, and 0%, 0%, and 25%, respectively, 300 minutes post-dose.

[1] The study consisted of the main part, conducted under double-blind conditions, in which a single dose of 2,5,10, or 20 μg of Olo or placebo was administered by inhalation to patients with COPD (n = 36) using a cross-over design; and the extension part, conducted under open-label conditions, in which a single dose of 40 μg of Olo was administered by inhalation (5.3.5.1-1).

(b) Effects of the Olo metabolite on ACh-induced bronchoconstriction in guinea pigs (4.2.1.1-8)

The effect of CD 992, a major metabolite observed in humans, on ACh-induced bronchoconstriction was evaluated in male and female guinea pigs (n = 2/group). After repeated intravenous administration of 8 to 12 μg/kg of ACh at 10-minute intervals to the anesthetized animals to induce bronchoconstriction, a single dose of CD 992 (3, 10, or 30 μg/kg as the acetate salt) was administered by inhalation. The air flow rate was measured for 300 minutes. No inhibition of bronchoconstriction was observed in the 3 μg/kg group. However, in the 10 μg/kg group, the maximum inhibition was observed between 50 and 60 minutes post-dose, with the percentage inhibition of 29%. In the 30 μg/kg group, the inhibition peaked between 100 and 300 minutes post-dose, with the percentage inhibition of 46%.

(c) Effects of Olo on ACh-induced bronchoconstriction in dogs (4.2.1.1-2 and 4.2.1.1-4)

The effect of the test substances on ACh-induced bronchoconstriction was evaluated in male and female dogs (n = 4 to 6/group). After repeated intravenous administration of 10 μg/kg of ACh to the anesthetized animals to induce bronchoconstriction, a single dose of 1.3, 2.7, 5.5, or 11.0 μg of Olo, or 2.6, 5.2, or 10.4 μg of formoterol was administered by inhalation. The air flow rate was measured for 180 minutes. In the Olo 1.3, 2.7, 5.5, and 11.0 μg groups, the maximum inhibition of bronchoconstriction was achieved 10 or 30 minutes post-dose with the maximum percentage inhibition of 36%, 54%, 62%, and 53%, respectively, at the measuring time points. The percentage inhibition 180 minutes post-dose was 3%, 14%, 31%, and 20%, respectively. In the formoterol 2.6, 5.2, and 10.4 μg groups, the maximum inhibition of bronchoconstriction was achieved 5 or 10 minutes post-dose, with the maximum percentage inhibition of 52%, 72%, and 53%, respectively, at the measuring time points. The percentage inhibition 180 minutes post-dose was 16%, 23%, and 19%, respectively.

The effect of the test substances on ACh-induced bronchoconstriction was evaluated in male and female dogs (n = 2 to 6/group). After repeated intravenous administration of 10 μg/kg of ACh to the anesthetized animals to induce bronchoconstriction, a single dose of 2.7 or 5.5 μg of Olo, or 5.2 μg of formoterol was administered by inhalation. The air flow rate was measured for 24 hours. The percentage inhibition of bronchoconstriction in the groups of Olo 2.7 μg, Olo 5.5 μg, and formoterol 5.2 μg was 34%, 62%, and 52%, respectively, at 30 minutes post-dose; 16%, 37%, and 18%, respectively at 6 hours post-dose; and 3%, 19%, and 1%, respectively, at 24 hours post-dose.

(d) Effects of the combination of Tio and Olo on ACh-induced bronchoconstriction in dogs (4.2.1.1-12 and 4.2.1.1-13)

The effect of the test substances on ACh-induced bronchoconstriction was evaluated in male and female dogs (n = 4/group). After repeated intravenous administration of 10 μg/kg of ACh to the anesthetized animals to induce bronchoconstriction, 0.8 μg of Tio and/or 2.7 μg of Olo were administered alone or in combination by inhalation. The air flow rate was measured for 180 minutes. The percentage inhibition of bronchoconstriction in the groups of Tio alone, Olo alone, and Tio + Olo was 17%, 60%, and 73%, respectively, at 10 minutes post-dose; 56%, 42%, and 72%, respectively, at 60 minutes post-dose; 51%,

23%, and 74%, respectively, at 120 minutes post-dose; and 40%, 11%, and 75%, respectively, 180 minutes post-dose.

The effect of the test substances on ACh-induced bronchoconstriction was evaluated in male and female dogs (n = 3 to 4/group). After 0.8 μg of Tio and/or 2.7 or 5.5 μg of Olo were administered alone or in combination by inhalation to the anesthetized animals, 10 μg/kg of ACh was intravenously administered twice at 15-minute intervals prior to each measuring time point to induce bronchoconstriction, and the air flow rate was measured. The percentage inhibition of bronchoconstriction in the groups of Tio 0.8 μg + Olo 0 μg, Tio 0 μg + Olo 2.7 μg, Tio 0.8 μg + Olo 2.7 μg, Tio 0 μg + Olo 5.5 μg, and Tio 0.8 μg + Olo 5.5 μg was as follows: 41%, 38%, 64%, 65%, and 79%, respectively, at 30 minutes post-dose; 35%, 6%, 46%, 33%, and 82%, respectively, at 6 hours post-dose; 15%, 2%, 43%, 19%, and 59%, respectively, at 12 hours post-dose; and 8%, 3%, 32%, 19%, and 33%, respectively, at 24 hours post-dose.

(e) Effects of the combination of Tio and Olo on ACh-induced bronchoconstriction in guinea pigs (4.2.1.1.14)

The effect of the test substances on ACh-induced bronchoconstriction was evaluated in male and female guinea pigs (n = 5 to 11/group). The anesthetized animals received 0.08 μg/kg of Tio, and/or 0.27 or 0.91 μg/kg of Olo by inhalation, followed 24 hours later by intravenous administration of 2 to 20 μg/kg of ACh before measurement of the air flow rate. Assuming that bronchoconstriction induced by Ach 20 μg/kg is 100%, the percentage of bronchoconstriction 24 hours post-dose in the untreated group and groups of animals receiving Tio 0.08 μg/kg + Olo 0 μg/kg, Tio 0 μg/kg + Olo 0.27 μg/kg, Tio 0 μg/kg + Olo 0.91 μg/kg, Tio 0.08 μg/kg + Olo 0.27 μg/kg, and Tio 0.08 μg/kg + Olo 0.91 μg/kg was 43%, 49%, 34%, 11%, 9%, and 9%, respectively.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1) Effects on adrenoceptors (4.2.1.2-1 and 4.2.1.2-2)

The effects of 1 μmol/L of Olo added to 75 types of adrenoceptor subtypes and transporters were investigated *in vitro*. Olo inhibited ligand binding to the α_1-, β_1-, and β_2-adrenoceptors and the serotonin 5-HT_{2A} receptor by 87%, 96%, 97%, and 59%, respectively.

The effects of Olo on the α_1-adrenoceptor and serotonin 5-HT_{2A} receptor were further investigated. The effect of Olo on phenylephrine- or serotonin-induced bronchoconstriction was studied in rabbit thoracic aortic ring specimens, and the IC_{50} values of Olo against the α_1-adrenoceptor and serotonin 5-HT_{2A} receptor were about 1 μmol/L and ≥10 μmol/L, respectively.

The applicant's explanation:

The IC_{50} values of Olo against the α_1-adrenoceptor and 5-HT_{2A} receptor were about ≥80,000 times the C_{max} of Olo (12.6 pmol/L) determined in a study[2] in which the fixed dose combination (FDC) of Tio +

[2] Study 1237.24. This study is also mentioned in the following sections.

Olo 5/5 μg was administered to Japanese patients with COPD once daily for 3 weeks. Therefore, Olo's inhibition of receptors is unlikely to pose systemic safety problems in clinical practice.

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

3.(i).A.(3).1) Effects of Olo on the central nervous system (4.2.1.3-3)

The effect of Olo on general symptoms, behavior, body temperature, and locomotor activity in male rats (n = 4/group) given a single dose of 17.1, 63.4, or 483 μg/kg of Olo by inhalation was studied by the modified Irwin's test. No behavioral or physiological changes were observed in any groups following administration of Olo.

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

(a) Effects on the action potential of hERG channel and the papillary muscle of guinea pigs (4.2.1.3-1)

The effect of 0.1 to 30 μmol/L of Olo on hERG current was studied by the whole-cell patch-clamp technique in human embryonic kidney cells (HEK293 cells) expressing hERG potassium channel. No effect on hERG current was observed at any concentration.

The effect of 0.1 to 10 μmol/L of Olo on action potential waveform was studied using guinea pig papillary muscle. Olo decreased the action potential duration at 90% repolarization at concentrations of ≥1 μmol/L in a concentration-dependent manner, while increasing myocardial contractility at concentrations of ≥0.3 μmol/L in a concentration-dependent manner. The effect of Olo was observed at concentrations equivalent to approximately 79,000-fold and 24,000-fold the C_{max} (12.6 pmol/L) of Olo determined in the study in which the fixed dose combination of Tio + Olo 5/5 μg was administered by inhalation to Japanese patients with COPD once daily for 3 weeks.

(b) *In vivo* studies

Study on Olo administered alone (4.2.1.3-4)

The effect of Olo on the cardiovascular system of dogs (n = 2/sex) after the inhalation of a single dose of 0.91, 2.7, or 9.1 μg/kg was studied. As compared with baseline values, the following changes were noted in the 2.7 and 9.1 μg/kg groups: increased heart rate (70 and 78 bpm), decreased mean arterial pressure (−21 and −24 mmHg), and shortening of QT interval (−27 and −26 ms). The $C_{0.083h}$ of Olo in the 2.7 μg/kg group was 181 pmol/L, approximately 14-fold the C_{max} of Olo (12.6 pmol/L) determined in the study in which the fixed dose combination of Tio + Olo 5/5 μg was administered by inhalation to Japanese patients with COPD once daily for 3 weeks.

Study on coadministration of Tio and Olo (4.2.1.3-7)

A single dose of Tio 3.2 μg/kg + Olo 3.1 μg/kg, Tio 8.9 μg/kg + Olo 8.5 μg/kg, or Tio 26.6 μg/kg + Olo 26.2 μg/kg was administered to dogs (n = 2/sex) by inhalation to study the effect on the cardiovascular system. As compared with the vehicle group, heart rates increased between 90 and 120 minutes post-dose in the Tio 3.2 μg/kg + Olo 3.1 μg/kg group, between 300 and 600 minutes post-dose in the Tio 8.9

μg/kg + Olo 8.5 μg/kg group, and between 6 and 1440 minutes post-dose in the Tio 26.6 μg/kg + Olo 26.2 μg/kg group. In the Tio 8.9 μg/kg + Olo 8.5 μg/kg group and the Tio 26.6 μg/kg + Olo 26.2 μg/kg group, increased heart rate was accompanied by decreased mean arterial pressure, but decreased body temperature or significantly abnormal ECG waveform was not observed. In the Tio 3.2 μg/kg + Olo 3.1 μg/kg group, $C_{0.167h}$ of Tio was 209 pmol/L and that of Olo was 42.5 pmol/L, which are approximately 5-fold and 3-fold the C_{max} values of Tio (44.5 pmol/L) and Olo (12.6 pmol/L), respectively, determined in the study in which the fixed dose combination of Tio + Olo 5/5 μg was administered by inhalation to Japanese patients with COPD once daily for 3 weeks.

3.(i).A.(3).3) Effects on the respiratory system (4.2.1.3-2)

The effect on the respiratory function of male rats (n = 8/group) given a single dose of 17.2, 64.3, or 485 μg/kg of Olo by inhalation was studied by plethysmography. No effect on respiratory rate, tidal volume, or minute volume was observed in any groups.

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

The applicant's explanation on the pharmacological significance of the coadministration of Tio and Olo:

Tio has high affinity for the muscarinic ACh receptor subtypes (M1, M2, and M3), particularly for the M3 receptor. Tio relieves tension on the vagus nerve in the airway, and inhibits bronchoconstriction and mucus secretion. On the other hand, the high affinity and selectivity of Olo for β_2-adrenoceptors are expected to promote the activation of β_2-adrenoceptors, which leads to an increase in the production of intracellular cAMP, thereby relaxing airway smooth muscle cells. The expression of muscarinic ACh receptors is prominent on the central airway, while β_2-adrenoceptors are abundantly expressed on the peripheral airways. Therefore, the combination of a LAMA and a LABA, each acting by a different mechanism is expected to contribute to dilatation of the whole bronchial tree (Dale PR et al. *Curr. Opin. Pharmacol.* 16: 31-42, 2014).

PMDA concluded from the submitted pharmacological study data and the applicant's response that the combination of Tio and Olo has pharmacological significance.

3.(ii) Summary of pharmacokinetic studies

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

The pharmacokinetics of Tio was evaluated in the regulatory review of the application for Spiriva 18 μg inhalation capsules (see the Review Report of "Spiriva 18 μg inhalation capsules" dated August 3, 2004 [in Japanese only]). The data on the absorption, distribution, metabolism, excretion, drug-drug interactions of Olo submitted for the present application included study results in mice, rats, rabbits, and dogs using different routes of administration (inhalation, intratracheal, oral, and intravenous) and toxicokinetics data from the toxicology studies on Tio and Olo coadministered by inhalation. The pharmacokinetics of Olo was investigated using Olo and ^{14}C-labeled Olo. Plasma concentrations of olodaterol were measured by high-performance liquid chromatography-tandem mass spectrometry

(HPLC-MS/MS) (lower limits of quantitation, 25.0 pmol/L for mouse and rat; 20.0 pmol/L for rabbits and dogs). Radioactivity levels were measured by liquid scintillation counting (LSC), and tissue radioactivity levels were measured by whole autoradiography. The pharmacokinetics of Tio was investigated using Tio and ^{14}C-labeled Tio. Plasma concentrations of tiotropium were measured by HPLC-MS/MS (lower limits of quantitation, 25.0 pmol/L for rats and dogs). Radioactivity levels were measured by LSC.

The amounts and concentrations of the agents administered are expressed as their free bases, and pharmacokinetic parameters are presented as mean or mean ± standard deviation, unless otherwise specified.

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

3.(ii).A.(1).1) Single-dose studies

(a) Olo administered alone (4.2.2.2-1, 4.2.2.2-3, 4.2.2.2-5, 4.2.2.2-6, 4.2.2.5-1, 4.2.2.5-2, 4.2.2.5-3, and 4.2.3.2-2)

Tables 3 and 4 show the pharmacokinetic parameters of olodaterol in plasma and blood radioactivity levels following single-dose administration of Olo (unlabeled Olo and ^{14}C-labeled Olo) to mice, rats, rabbits and dogs.

Table 3. Pharmacokinetic parameters of olodaterol in plasma following single-dose administration of Olo (unlabeled Olo or ^{14}C-labeled Olo)

Animal species	Dose (μg/kg)	Number of animals	Route of administration	C_{max} (pmol/L)	t_{max} a) (h)	$AUC_{0-\infty}$ (pmol·h/L)	$t_{1/2}$ (h)	Data reference number
Mouse	200	Male (10)	i.h.	21,800	0.583	66,700	5.69	4.2.3.2-2
	155	Male (24)	i.v.	354,000	0.0333	103,000	13.2	4.2.2.2-3
	155	Male (30)	p.o.	616	1.0	4100	1.84	4.2.2.2-3
Rat	200	Male (5), Female (5)	i.h.	16,400	0.583	53,500	6.6	4.2.2.2-5
	155	Male (4), Female (4)	i.t.	48,400	0.333	93,200	5.44	4.2.2.2-1
	155	Male (4), Female (5)	i.v.	539,000	0.033	159,000	5.81	4.2.2.2-1
	155	Male (4), Female (4)	p.o.	429	1.25	2770	4.41	4.2.2.2-1
Rabbit	301	Female (3)	i.v.	1,920,000	0.0333	664,000	14.5	4.2.2.5-3
	301	Female (2)	p.o.	70.3	0.750	163.5	—	4.2.2.5-3
Dog	60	Male (4), Female (4)	i.h.	2225	0.333	9465	9.43	4.2.2.2-6
	30	Male (2), Female (2)	i.v.	185,000	0.0333	51,600	17.5	4.2.2.5-2
	100	Male (1), Female (2)	p.o.	2280	2.0	23,000	17.6	4.2.2.5-2

Mean values; —, no data. C_{max}, maximum concentration; t_{max}, time to maximum plasma concentration; AUC, area under the plasma concentration-time curve; $t_{1/2}$, elimination half-life. i.h., inhalation administration; i.v., intravenous administration; p.o., oral administration; i.t., intratracheal administration. a) median values.

Table 4. Pharmacokinetic parameters of blood radioactivity following single-dose administration of ^{14}C-labeled Olo

Animal species	Dose (μg/kg)	Number of animals	Route of administration	C_{max} (pmol/L)	t_{max} a) (h)	$AUC_{0-\infty}$ (pmol·h/L)	$t_{1/2}$ (h)	Data reference number
Rat	311	Male (4)	i.t.	186,000	0.333	2,210,000	91.9	4.2.2.5-1
	155	Male (5)	i.v.	628,000	0.0333	1,570,000	39.1	4.2.2.5-1
	155	Male (5)	p.o.	6130	1.0	116,000	58.6	4.2.2.5-1
Rabbit	301	Female (3)	i.v.	3,340,000	0.0333	3,850,000	27.5	4.2.2.5-3
	301	Female (2)	p.o.	26,050	1.0	295,000	53.9	4.2.2.5-3
Dog	30	Male (2), Female (2)	i.v.	253,000	0.0333	933,000	62.2	4.2.2.5-2
	100	Male (1), Female (2)	p.o.	6660	8.0	825,000	91.8	4.2.2.5-2

Mean values. C_{max}, maximum concentration; t_{max}, time to maximum plasma concentration; AUC, area under the plasma concentration-time curve; $t_{1/2}$, elimination half-life. i.t., intratracheal administration; i.v., intravenous administration; p.o., oral administration. a) median values.

(b) Tio + Olo coadministration (4.2.2.6-1 and 4.2.2.6-2)

Table 5 shows the pharmacokinetic parameters of tiotropium and olodaterol in plasma following a single inhaled dose of Tio + Olo in rats and dogs. No apparent interactions were observed following the coadministration of Tio and Olo.

Table 5. Pharmacokinetic parameters of tiotropium and olodaterol in plasma following a single inhaled dose of Tio + Olo in rats and dogs

Animal species	Tio/Olo dose (μg/kg)	Number of animals	Tiotropium		Olodaterol	
			C_{max} (pmol/L)	$AUC_{0-\infty}$ (pmol·h/L)	C_{max} (pmol/L)	$AUC_{0-\infty}$ (pmol·h/L)
Rat	75/0	Male (4), Female (4)	6650	16,900		
	75/75		6760	12,500	4380	16,200
	0/75				5930	24,600
Dog	15/0	Male (3), Female (3)	1750	1370		
	15/15	Male (3), Female (3)	1660	1350	251	2190
	0/15	Male (3), Female (2)			348	1980

Mean values. C_{max}, maximum concentration; AUC, area under the plasma concentration-time curve.

3.(ii).A.(1).2) Repeated-dose studies (toxicokinetics)

(a) Olo administered alone (4.2.3.2-1, 4.2.3.2-5, 4.2.3.2-13, 4.2.3.2-14, 4.2.3.4.1-1, and 4.2.3.4.1-2)

Toxicokinetics following repeated inhalation of Olo was investigated in 13-week studies in mice, rats, and dogs, a 52-week study in dogs, and 104-week carcinogenicity studies in mice and rats. Table 6 shows the pharmacokinetic parameters of olodaterol in plasma following repeated inhalation of Olo. The values increased in a dose-dependent manner. No significant accumulation was observed following repeated inhalation, and no significant sex differences were observed.

Table 6. Pharmacokinetic parameters of olodaterol in plasma following repeated inhalation of Olo

	Treatment duration	Dose (μg/kg)	Number of animals	Time point	Male		Female	
					C_{max} (pmol/L)	AUC_{0-24} (pmol·h/L)	C_{max} (pmol/L)	AUC_{0-24} (pmol·h/L)
Mouse	13 weeks	50	2/sex/time point	Day 1	45,300	69,900	45,800	54,300
				Day 87	5110	12,100	4320	15,400
		200		Day 1	84,600	187,000	62,200	177,000
				Day 87	15,500	35,000	17,600	49,700
		800		Day 1	185,000	590,000	168,000	496,000
				Day 87	92,200	150,000	91,200	125,000
		3200		Day 1	628,000	1,250,000	704,000	1,410,000
				Day 87	254,000	413,000	284,000	699,000
	104 weeks	25	4/sex/time points	Day 359	2410	5750	3020	5680
		75		Day 359	4610	15,400	6650	14,300
		250		Day 359	19,300	61,200	28,400	42,800
Rat	13 weeks	50	4/sex/time point	Day 1	2240	7220	1540	6720
				Day 91	1970	7820	3130	9470
		200		Day 1	23,800	58,100	18,000	33,700
				Day 91	16,400	34,800	19,200	40,000
		800		Day 1	90,600	201,000	85,200	161,000
				Day 91	87,700	191,000	98,800	188,000
		2400		Day 1	331,000	712,000	315,000	535,000
				Day 91	249,000	533,000	310,000	495,000
	104 weeks	25	2 to 5/sex/time point	Day 1	1190	4630	895	4760
				Day 360	1710	4620	1020	4550
				Day 726	465	2890	564	2410
		75		Day 1	5920	14,800	6110	15,800
				Day 360	4440	16,300	4830	15,000
				Day 726	2150	8720	2830	8510
		250		Day 1	30,300	62,100	30,900	62,700
				Day 360	20,800	55,100	32,400	65,700
				Day 726	8810	31,000	15,100	26,600
Dog	13 weeks	5	4/sex/time point	Day 1	170	822	104	844
				Day 86	195	616	67.9	689
		15	4/sex/time point	Day 1	546	2320	648	2410
				Day 86	143	1540	258	2080
		150	6/sex/time point	Day 1	6570	30,300	5090	24,900
				Day 86	2780	18,500	3060	18,600
	52 weeks	15	4/sex/time point	Day 1	197	1160	359	1930
				Day 358	381	2160	423	3560
		60	4/sex/time point	Day 1	1960	7750	2550	8500
				Day 358	1620	7970	1490	9910
		300	6/sex/time point	Day 1	13,100	50,200	15,100	59,900
				Day 358	8990	46,000	11,500	50,200

Mean values. C_{max}, maximum concentration; AUC, area under the plasma concentration-time curve.

(b) Tio + Olo coadministration (4.2.3.2-7, 4.2.3.2-16, and 4.2.3.2-18)

Toxicokinetics following repeated inhalation of Tio and Olo was investigated in 4-week studies in rats and dogs, and a 13-week repeated study in dogs. Table 7 shows the pharmacokinetic parameters of tiotropium and olodaterol in plasma following repeated inhalation of Olo. The values increased in a dose-dependent manner; no significant accumulation was observed following repeated administration, or no significant differences were observed as compared to the results of Tio or Olo alone.

Table 7. Pharmacokinetic parameters of tiotropium and olodaterol in plasma following repeated inhalation of Tio + Olo

	Tio/Olo dose (μg/kg)	Number of animals	Time point	Tiotropium				Olodaterol			
				Male		Female		Male		Female	
				C_{max} (pmol/L)	AUC_{0-t} (pmol·h/L)	C_{max} (pmol/L)	AUC_{0-t} (pmol·h/L)	C_{max} (pmol/L)	AUC_{0-t} (pmol·h/L)	C_{max} (pmol/L)	AUC_{0-t} (pmol·h/L)
Rat	75/75	1 each of males and females	Day 1	19,900	16,500	10,300	10,600	15,900	18,800	8670	16,800
			Day 28	12,700	29,700	21,800	17,400	14,800	44,600	20,800	34,900
	500/500		Day 1	413,000	267,000	221,000	164,000	192,000	229,000	132,000	185,000
			Day 28	78,500	76,300	115,000	115,000	69,800	138,000	83,200	173,000
	2000/2000		Day 1	1,400,000	1,050,000	1,250,000	805,000	727,000	1,100,000	703,000	869,000
			Day 28	217,000	204,000	374,000	271,000	155,000	280,000	225,000	321,000
Dog	5/5	3 to 5 each of males and females	Day 1	274	491	528	746	89.7	503	251	1080
			Day 28	1070	2040	1300	2780	190	2560	503	3800
	15/15		Day 1	1630	2220	2630	2390	385	2570	575	3740
			Day 28	2580	5590	3880	6730	747	5690	1310	7670
	150/150		Day 1	12,000	15,900	24,100	32,000	3370	21,200	7730	33,200
			Day 28	47,300	44,300	54,100	69,100	10,600	48,800	16,100	52,100
	15/15	4 to 6 each of males and females	Day 1	1570	1830	1370	1860	371	1960	341	1870
			Day 86	1500	2040	2910	4290	231	1850	409	2910
	60/60		Day 1	6570	9120	7550	9500	1610	7340	1920	6890
			Day 86	6140	9310	7970	9920	1550	8140	1540	7370
	300/300		Day 1	34,800	54,300	49,300	61,700	15,800	47,000	14,500	46,600
			Day 86	45,800	51,000	78,300	69,200	9540	43,400	15,500	51,000

Mean values. C_{max}, maximum concentration; AUC, area under the plasma concentration-time curve.

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

3.(ii).A.(2).1) Tissue distribution (4.2.2.3-1 and 4.2.2.3-4)

A single dose of ^{14}C-labeled Olo (773 μg/kg) was intratracheally administered to male albino rats (n = 1/measuring time point). At 5 minutes post-dose, radioactivity was distributed throughout the body and higher radioactivity levels were detected particularly in the pancreas, kidney, pituitary gland, adrenal glands, salivary glands, and liver. Radioactivity levels peaked by 2 hours post-dose in most of these organs. On the other hand, radioactivity levels peaked 24 hours post-dose in the pancreas, choroid plexus, and accessory genital glands, and 72 hours post-dose in the testicle. Following single intravenous administration of ^{14}C-labeled Olo at 773 μg/kg to male pigmented rats (n = 1/measuring time point), radioactivity levels were high particularly in the kidney, pancreas, choroid plexus, salivary glands, and pituitary gland. Radioactivity levels peaked by 2 hours post-dose in most of these organs. On the other hand, radioactivity levels peaked 24 hours post-dose in the accessory genital glands and testicle, and 72 hours post-dose in adrenal glands.

Following repeated intratracheal administration of ^{14}C-labeled Olo at 309 μg/kg to male albino rats (n = 3 or 6/measuring time point) for 14 days, radioactivity levels reached a steady state 96 hours post-dose in most of the organs, and were high particularly in the lungs, pancreas, digestive organs, and pituitary gland. The accumulation of radioactivity was observed in the testicle, liver, brain, heart, lungs, and thyroid gland after repeated-dose administration, with the accumulation factors (ratio of the radioactivity level at 15 days post-dose to that at 1 day post-dose) being 10.5, 3.1, 3.1, 3.1, 2.9, and 2.6, respectively.

3.(ii).A.(2).2) Plasma protein binding and distribution to blood cells (4.2.2.3-2, 5.3.2.1-1, 5.3.2.1-2, and 5.3.2.1-3)

When ^{14}C-labeled Olo (1 to 100 nmol/L) or ^{3}H-labeled Olo (0.01 to 1 nmol/L) was added to the mouse, rat, rabbit, dog, and human plasma, the plasma protein binding rates were 65.1% to 78.1%, 47.4% to 56.1%, 58.6% to 59.5%, 55.5% to 65.2%, and 56.1% to 68.9%, respectively, indicating that plasma protein binding was almost constant over the concentration range. When 0.01 nmol/L of ^{3}H-labeled Olo was added to plasma of healthy human adults, patients with renal impairment, and patients with liver dysfunction, the plasma protein binding rates were 59.8% to 60.1%, 63.7%, and 56.6% to 62.8%, respectively.

^{14}C-labeled Olo (10 nmol/L) was added to rat, dog, and human blood. The blood-to-plasma radioactivity concentration ratios for male and female animal or human subjects were 5.73 and 4.65, respectively, in rats, 2.97 and 3.04, respectively, in dogs, and 2.48 and 2.97, respectively, in humans. The results suggested that Olo can be distributed to the blood cells in all the species studied.

3.(ii).A.(2).3) Transfer to fetus (4.2.2.3-5)

A single dose of ^{14}C-labeled Olo (884 μg/kg) was administered intratracheally to rat on gestation day 12 or 17 (n = 1/measuring time point). The radioactivity levels in maternal heart blood, placenta, and fetal heart blood peaked by 8 hours post-dose and were 106, 334, and 87.6 nmol/kg, respectively. High radioactivity levels in fetal tissues were detected in the liver (178 nmol/kg) and lungs (122 nmol/kg), suggesting that unchanged Olo and its metabolites can transfer across the placenta to fetus.

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

3.(ii).A.(3).1) *In vitro* studies (5.3.2.2-2, 5.3.2.2-6, and 5.3.2.2-12)

^{14}C-labeled Olo (50 μmol/L) was added to human liver microsomes for incubation. Olo metabolites, SOM 1522, U4, and U6, and unchanged Olo were detected, and the percentage of these compounds to the total radioactivity was 5.5%, 0.3%, 1.0%, and 93.2%, respectively. Cytochrome P450 (CYP) isoforms involved in the metabolism of Olo (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP4A11) were investigated using CYP inhibitors, human CYP expression system, and anti-CYP antibodies. The results suggested that Olo was metabolized primarily by CYP2C8 and CYP2C9, into SOM 1522.

^{14}C-labeled Olo (10 or 50 μmol/L) was added to rat or human hepatocytes for incubation. CD 992 and M565(2) (glucuronide conjugates of Olo), SOM 1522 (a metabolite formed by demethylation), CD 11249 and CD 10915 (glucuronide conjugates of SOM 1522), CD 12656 (a sulfate conjugate of SOM 1522), and unchanged Olo were detected. The percentages of these compounds to the total radioactivity in rat hepatocytes and human hepatocytes were 12.1% and 10.1%, respectively, for CD 992, 1.0% and infinitesimal, respectively, for M565(2), 1.1% and 5.8%, respectively, for SOM 1522, 15.1% and 2.8%, respectively, for CD 11249, 0.5% and 12.3%, respectively, for CD 10915, infinitesimal and 5.4%, respectively, for CD 12656, and 64.7% and 61.4%, respectively, for unchanged Olo.

When 100 μmol/L of Olo was added to human liver microsomes, kidney microsomes, intestinal microsomes, or lung microsomes for incubation, high glucuronidation rates were observed in the liver and kidney microsomes. Human UDP-glucuronosyltransferase (UGT) isoforms involved in the metabolism of Olo (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, and UGT2B17) were investigated using UGT expression system. The results suggested that Olo was metabolized to CD 992 through glucuronidation mainly by UGT2B7, UGT1A1, UGT1A7, and UGT1A9.

When 0.5 to 200 μmol/L[3] of SOM 1522 was added to human liver or intestinal cytosol, or human liver, lung, or kidney S9000 fractions for incubation, a high sulfate conjugation rate was observed in intestinal cytosol. Human sulfotransferase (SULT) isoforms involved in the metabolism of SOM 1522 (SULT1A1, SULT1A3, and SULT1B1) were investigated using SULT expression system. The results suggested that SOM 1522 was metabolized to CD 12656 through sulfate conjugation mainly by SULT1A1 and SULT1A3.

3.(ii).A.(3).2) *In vivo* studies (4.2.2.4-1 to 4.2.2.4-4, and 5.3.2.2-9)

A single dose of 1000 μg/kg of ^{14}C-labeled Olo was administered intravenously or intratracheally to mice (n = 4 to 6/sex/group). CD 992, the glucuronide conjugate of Olo, was the dominant compound in plasma 1 hour and 4 hours post-dose. Unchanged Olo and CD 992 were detected in urine, and unchanged Olo and SOM 1522 were detected in feces up to 48 hours post-dose for both routes of administration.

A single dose of ^{14}C-labeled Olo (155 μg/kg) was administered intravenously or intratracheally to rats (n = 5 or 8/sex/group). Unhanged Olo was the dominant compound in plasma 20 minutes and 3 hours post-dose. Unchanged Olo was mainly detected in urine, and unchanged Olo and SOM 1522 were mainly detected in feces up to 48 hours post-dose for both routes of administration.

A single dose of ^{14}C-labeled Olo (301 μg/kg) was administered intravenously to female rabbits (n = 1 or 3). CD 992 was the dominant compound in plasma 1 hour and 6 hours post-dose. Up to 72 hours post-dose, CD 992 and unchanged Olo were detected in urine; and up to 120 hours post-dose, unchanged Olo and SOM 1522 were detected in feces.

A single dose of ^{14}C-labeled Olo (30 μg/kg) was administered to dogs (n = 2/sex). Unchanged Olo was the dominant compound in plasma 20 minutes post-dose. Unchanged Olo was mainly detected in urine up to 48 hours post-dose, and in feces up to 96 hours post-dose.

A single dose of ^{14}C-labeled Olo (20 μg) was administered intravenously to men (n = 5). Unchanged Olo, CD 992, and CD 10915 were mainly detected in plasma at 3.17 hours, 4 hours and 6 hours post-

[3] In the investigation of SULT, SOM 1522 (0.5 to 100 μmol/L) was added.

dose. Unchanged Olo and CD 992 were mainly detected in urine up to 72 hours post-dose, while SOM 1522 and unchanged Olo were mainly detected in feces up to 216 hours post-dose.

Figure 1 shows the metabolic pathways of Olo, which are predicted based on the above findings.

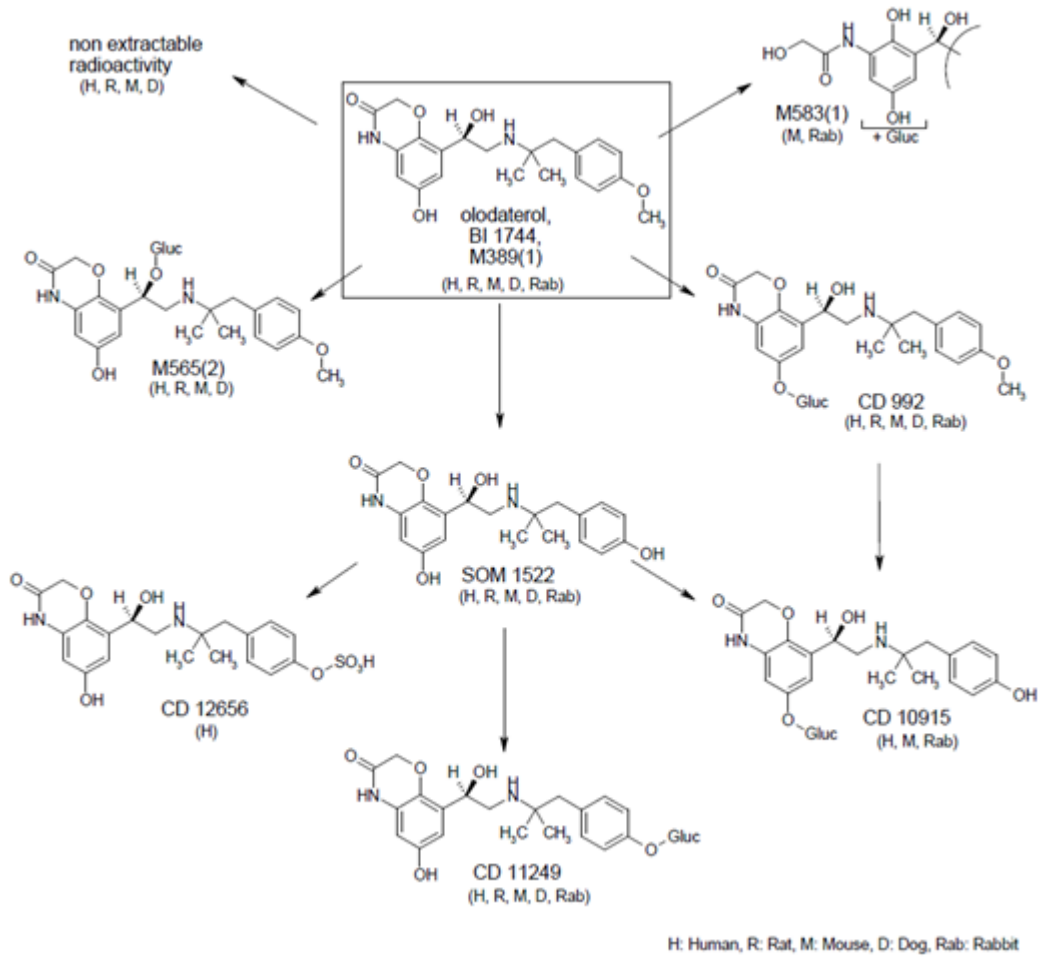


Figure 1. Putative metabolic pathways of Olo in humans and animal species

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

3.(ii).A.(4).1) Excretion in urine and feces (4.2.2.4-3, 4.2.2.5-1 to 3, and 4.2.2.5-5)

A single dose of ^{14}C-labeled Olo (1000 µg/kg) was administered intravenously or intratracheally to mice (n = 4/sex/group). The urinary and fecal radioactivity excretion rates (radioactivity excreted in urine or feces / the administered radioactivity) up to 96 hours post-dose were 25.8% and 68.4%, respectively, in the intravenous administration group, and 13.6% and 70.0%, respectively, in the intratracheal administration group.

A single dose of ^{14}C-labeled Olo (77.7 µg/kg) was administered intravenously or intratracheally to male rats (n = 5/group). The urinary and fecal radioactivity excretion rates were 23.6% and 69.1%, respectively, up to 168 hours post-dose in the intravenous administration group, and 15.3% and 79.2%, respectively, up to 120 hours post-dose in the intratracheal administration group. A single dose of ^{14}C-

labeled Olo (38.8 or 77.7 μg/kg) was administered to male rats (n = 5/group). The biliary radioactivity excretion rates up to 6 hours post-dose were 39.5% and 25.6% in the intravenous and intratracheal administration groups, respectively.

A single dose of ^{14}C-labeled Olo (301 μg/kg) was administered intravenously to female rabbits (n = 2 or 3). The urinary and fecal radioactivity excretion rates up to 168 hours post-dose were 54.8% and 42.1%, respectively, and the biliary radioactivity excretion rate up to 6 hours post-dose was 16.1%.

A single dose of ^{14}C-labeled Olo (30 μg/kg) was administered intravenously to dogs (n = 2/sex). The urinary and fecal radioactivity excretion rates up to 168 hours post-dose were 16.7% and 66.3%, respectively, and the biliary radioactivity excretion rate up to 4 hours post-dose was 27.0%.

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

A single dose of ^{14}C-labeled Olo (155 μg/kg) was administered intravenously to lactating rats on lactation day 12 (n = 5). The radioactivity in plasma and breast milk of the maternal animals peaked (26.5 and 169 nmol/L, respectively) 1 hour and 6 hours post-dose, respectively, indicating that unchanged Olo and its metabolites can transfer to breast milk. The $AUC_{0\text{-inf}}$ of breast milk radioactivity (2700 to 3890 nmol·h/kg) was approximately 7-fold the $AUC_{0\text{-inf}}$ of plasma radioactivity (402 to 556 nmol·h/kg).

3.(ii).A.(5) Pharmacokinetic drug interactions

3.(ii).A.(5).1) Enzyme inhibitory action and enzyme induction (5.3.2.2-1, 5.3.2.2-10, and 5.3.2.2-11)

The inhibitory effect of Olo (0.1 to 100 μmol/L) on the CYP isoforms (CYP1A1/1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP4A11) was investigated using human liver microsomes. The IC_{50} of Olo against CYP2D6 was 4.25 μmol/L, and IC_{50} values against the other CYP isoforms studied were ≥100 μmol/L. The inhibitory effect of CD 992 (0.1 to 100 μmol/L) on the CYP isoforms (CYP1A1/1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) was investigated using human liver microsomes. While 100 μmol/L of CD 992 slightly inhibited CYP2D6 in an irreversible manner, no inhibitory effect was observed on the other CYP isoforms.

The inductive effect of Olo (0.5 to 1000 pmol/L) on the enzyme activities and mRNA expression levels of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4) was investigated using human hepatocytes. No inductive effect was observed on any of the CYP isoforms.

Following the administration of 5 μg of Olo once daily for 4 weeks to non-Japanese patients with COPD, the C_{max} of olodaterol and CD 992 in plasma at steady state was 11.6 and 10.6 pmol/L, respectively. Based on the above results, the applicant considered that CYP2D6 is unlikely to be inhibited by Olo in clinical use.

3.(ii).A.(5).2) Transporters (5.3.2.3-1, and 5.3.2.3-3 to 5)

Transport of ^{14}C-labeled Olo by P-glycoprotein (P-gp) was investigated using a human colon cancer cell line (Caco-2 cells). The apparent permeability coefficient ratio[4] of ^{14}C-labeled Olo 10 μmol/L was 43.5, and the apparent permeability coefficient ratio of ^{14}C-labeled Olo in the presence of a P-gp inhibitor, cyclosporin or verapamil, was approximately 1. The results suggested that Olo is a substrate for P-gp. Further, inhibitory effect of ^{14}C-labeled Olo (10 to 600 μmol/L) on the transport of digoxin was investigated using Caco-2 cells. The apparent permeability coefficient ratio in the presence of Olo 600 μmol/L was 1.17, and the apparent IC_{50} in both directions was 365 μmol/L. Therefore, the results suggested a weak P-gp inhibitory effect of Olo.

Transport of ^{14}C-labeled Olo by human breast cancer resistance protein (BCRP) was investigated using the Madin-Darby canine kidney-II (MDCK-II) cell line expressing human BCRP. No change in the apparent permeability ratio of ^{14}C-labeled Olo was observed in the presence of Ko143, a BCRP inhibitor; suggesting that Olo was not a substrate for BCRP. Inhibitory effect of Olo (0.1 to 100 μmol/L) on BCRP-mediated uptake of ^{3}H-labeled estrone-3-sulfate was investigated using MDCK-II cell lines expressing BCRP. The results showed that BCRP-mediated uptake of ^{3}H-labeled estrone-3-sulfate was inhibited by Olo in a concentration-dependent manner. The IC_{50} of Olo was estimated to be 10 to 100 μmol/L, suggesting an inhibitory effect of Olo on BCRP.

Transport of ^{14}C-labeled Olo by transporters was investigated using human embryonic kidney 293 cells (HEK 293 cells) expressing human organic anion transporting polypeptide (OATP) 2, OATP8, OATP-B, organic anion transporters (OAT) 1, OAT3, organic cation transporter (OCT) 1, OCT2, or OCT3. No Uptake of ^{14}C-labeled Olo was not observed in OATP2-, OATP8-, OATP-B-, OCT2-, or OCT3-expressing cells, but was observed in OAT1-, OAT3-, and OCT1-expressing cells. Further, uptake of ^{14}C-labeled Olo in the OAT1-, OAT3-, and OCT1-expressing cells was inhibited by probenecid, an OAT inhibitor, or by corticosterone, an OCT inhibitor. Therefore, it was suggested that Olo was the substrate for OAT1, OAT3, and OCT1. Inhibitory effect of Olo (0.01 to 100 μmol/L on the uptake of substrates mediated by the above-mentioned transporters[5] was investigated. OCT1-mediated uptake of substrates was inhibited in an Olo concentration-dependent manner, and the IC_{50} was 14.1 μmol/L. Further, Olo did not inhibit the uptake of substrates mediated by transporters other than OCT1.

Following the administration of Olo 5 μg once daily for 4 weeks to patients with COPD, the C_{max} of plasma olodaterol at steady state was 11.6 pmol/L. Given this result, the applicant considered that Olo is unlikely to cause clinically significant drug-drug interaction when used in combination with a compound that is a substrate for transporters which were found to have some effect in these studies.

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[4] The ratio of the apparent permeability in the basolateral to apical direction ($P_{app}B\rightarrow A$) to the apparent permeability in the apical to basolateral direction ($P_{app}A\rightarrow B$). ($P_{app}B\rightarrow A$ / $P_{app}A\rightarrow B$).

[5] Substrates of each transporter: ^{3}H-labeled paraaminohippuric acid (OAT1), ^{3}H-labeled estrone-3-sulfate (OAT3), ^{3}H-labeled 1-methyl-4-phenylpyridinium (OCT1)

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

In the distribution study of Olo, the accumulation factor following repeated-dose administration (the ratio of the radioactivity level at 15 days post-dose to that at 1 day post-dose) was higher in the testicle than in other organs, and radioactivity was eliminated more slowly from the testicle than from other organs. Therefore, PMDA asked the applicant whether there were any findings or adverse events that may be related to the accumulation of Olo in the testicle in toxicity studies and clinical studies.

The applicant's explanation:

In the 26-week inhalation toxicity study in rats (4.2.3.2-6), the absolute weight of testicle slightly decreased in the 3400 μg/kg group, without histopathological changes. In the 2-week oral toxicity study in rats (4.2.3.2-10), one of the toxicity studies by other routes of administration, a degenerative change in the testicle (vacuolarization of Sertoli cells) was observed only in the Olo 50 mg/kg group. However, the exposure to Olo (C_{max}, 1050 nmol/L; $AUC_{0\text{-}24}$, 5150 nmol·h/L) in the animal showing the change was about ≥19,000-fold the exposure to Olo (C_{max}, 17.9 pmol/L; AUC, 287 pmol·h/L) in Japanese patients with COPD treated with Olo 5 μg by inhalation for 4 weeks. In 4 non-Japanese phase III studies of Olo monotherapy (Studies 1222.11, 1222.12, 1222.13, and 1222.14), the incidence of adverse events that are classified as the System Organ Class of reproductive system and breast disorders was 2.4% (21 of 876 subjects) in the Olo 5 μg group, 1.0% (9 of 883 subjects) in the Olo 10 μg group, and 1.0% (9 of 885 subjects) in the placebo group, suggesting no significant differences among the treatment groups. Based on these findings, the clinical use of Olo is unlikely to cause any adverse events related to accumulated Olo in the testicle.

PMDA accepted the applicant's response. PMDA considers that there have been no evidence suggestive of safety issues caused by Olo accumulated in the testicle so far.

3.(iii) Summary of toxicology studies

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

The toxicity of Tio was evaluated in the regulatory review of the application for Spiriva 18 μg inhalation capsules (see the Review Report of "Spiriva 18 μg inhalation capsules" dated August 3, 2004 [in Japanese only]). The results from the following toxicity studies for Olo were submitted for the present application: single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other toxicity studies (toxicity studies using juvenile animals), and repeated-dose toxicity studies of combined Tio and Olo.

Inhaled doses are expressed as lung dose.[6] The doses and concentrations of Tio and Olo are expressed as their free bases.

[6] Lung dose = test substance concentration (μg/L) × respiratory minute volume (L/min) × spraying time (min) / body weight (kg)

3.(iii).A.(1) Single-dose toxicity (4.2.3.1-1 to 12)

Inhalation, intravenous, and oral toxicity studies in mice and rats were conducted to evaluate single-dose toxicity of Olo in rodents. Toxicity in non-rodents was evaluated based on the data from the early treatment phase of repeat-dose toxicity studies in dogs. Inhalation toxicity studies were conducted in mice and rats to evaluate single-dose toxicity of Tio + Olo.

3.(iii).A.(1).1) Olo administered alone

(a) Inhalation toxicity (4.2.3.1-1, 4.2.3.1-7, and 4.2.3.2-14)

Following the administration of a single inhaled dose of Olo to male and female NMRI mice at51.7 and 47.7 mg/kg, respectively, no deaths occurred. The approximate lethal doses were therefore determined to be >51.7 mg/kg for male mice and >47.7 mg/kg for female mice. Following the administration of a single inhaled dose of Olo to male and female Wistar rats at 26.6 and 22.8 mg/kg, respectively, no deaths occurred. Accordingly, the approximate lethal doses were determined to be >26.6 mg/kg for male rats and >22.8 mg/kg for male rats. Following the administration of inhaled doses of Olo (15, 60, or 330 μg/kg/day) to male and female beagle dogs for 4 weeks, no deaths occurred. The approximate lethal dose was determined to be >330 μg/kg/day for the dogs. Changes in the animals treated with Olo were as follows: decreased locomotor activity, ataxic gait, tremor, eyes closed, abdominal breathing, and piloerection in mice and rats; increased cardiac contractile force, increased heart rate, and dryness of oral mucosa in dogs.

(b) Intravenous toxicity (4.2.3.1-5 and 4.2.3.1-11)

Following the intravenous administration of Olo to male and female NMRI mice at a single dose of 10, 20, or 40 mg/kg, deaths occurred in the 40 mg/kg group. The approximate lethal dose was determined to be more than >20 mg/kg and <40 mg/kg for the mice. Following the intravenous administration of Olo to male and female Wistar rats at a single dose of 10, 20, 40, or 80 mg/kg, a death occurred in the 80 mg/kg group. The approximate lethal dose was determined to be >40 mg/kg and <80 mg/kg for the rats. Changes in the mice and rats treated with Olo included decreased locomotor activity, prone position, tachypnea, and piloerection.

(c) Oral toxicity (4.2.3.1-6 and 4.2.3.1-12)

Following the oral administration of Olo to male and female NMRI mice at of a single dose of 100, 316, 1000, or 2000 mg/kg, deaths occurred in the 2000 mg/kg group. The approximate lethal dose was determined to be >1000 mg/kg and <2000 mg/kg for the mice. Following the oral administration of Olo to male and female Wistar rats at a single dose of 100, 316, or 1000 mg/kg, deaths occurred in the 1000 mg/kg group. The approximate lethal dose was determined to be >316 mg/kg and <1,000 mg/kg. Changes in mice and rats treated with Olo included tachypnea and decreased locomotor activity.

3.(iii).A.(1).2) Tio + Olo coadministration (4.2.3.1-2 to 4.2.3.1-4, and 4.2.3.1-8 to 4.2.3.1-10)

Following the administration of Tio + Olo to male and female NMRI mice at a single inhaled dose of 34.8 + 36.6, 41.9 + 22.3, 2.5 + 16.4, 4.5 + 29.2, or 10.3 + 66.0 mg/kg, deaths occurred in all dose groups except for the 2.5 + 16.4 mg/kg group.

Following the administration of Tio + Olo to male and female Wistar rats at a single dose of 17.9 + 18.8, 21.2 + 11.3, or 5.2 + 33.2 mg/kg, no deaths occurred. Changes in the rats and mice treated with Tio + Olo included the following: mydriasis, mydriatic rigidity, eyes closed, decreased locomotor activity, ataxia, dyspnoea, abdominal breathing, and unkempt fur in mice; mydriasis, mydriatic rigidity, decreased locomotor activity, dyspnoea, abdominal breathing, pallor or reddening of the skin, mucosal dryness, red scab formation in the nostril, and unkempt fur in rats.

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

Inhalation toxicity studies were conducted in mice (13 weeks), rats (up to 26 weeks), or dogs (up to 52 weeks) to evaluate the repeat-dose toxicity of Olo. Inhalation toxicity studies were conducted in rats (4 weeks), and dogs (up to 13 weeks) to evaluate the repeat-dose toxicity of Tio and Olo.

In animals receiving Olo alone, irritative changes in the nasal cavity, the larynx, and the tracheal bifurcation (in mice, rats, and dogs) were noted as local toxicity. Systemic toxicity findings included the following: increased weight, hypertrophy and degeneration of skeletal muscle (in rats and dogs); cardiovascular changes including cardiac hypertrophy, increased heart rate, and myocardial fibrosis (in rats and dogs); accumulation of alveolar macrophages in the lung (in rats); prostatic atrophy (in dogs); changes in the female reproductive system including expansion of the uterus, corpus luteum cyst, and corpus luteum hemorrhage (in rats). The combination of Tio and Olo did not cause clinically significant problems including an increase in the known toxicity and new toxicological findings in association with either of the compounds.

The exposure to Olo at the no-observed-adverse-effect-level (NOAEL) of Olo (200 μg/kg/day) determined in the 26-week inhalation toxicity study in rats and that at the NOAEL of Olo determined in the 52-week inhalation toxicity study in dogs (15 μg/kg/day) were compared with the Olo exposure ($C_{max,}$ 17.9 pmol/L; AUC, 287 pmol·h/L) in Japanese patients with COPD who received Olo 5 μg once daily for 4 weeks. The C_{max} values in rats and dogs were 712-fold and 22-fold, respectively, human exposure and the AUC values in rats and dogs were131-fold and 10-fold, respectively, human exposure.

3.(iii).A.(2).1) Olo administered alone

(a) Thirteen-week inhalation toxicity study in mice (4.2.3.2-1)

Male and female CD-1 mice received inhaled doses of Olo at 0 (air or vehicle, an aqueous solution containing 0.01% benzalkonium chloride, 0.01% sodium ethylenediaminetetraacetic acid, and 0.003% citric acid [BAC/Na-EDTA/citric acid aqueous solution]), 63, 211, 900, or 3258 μg/kg/day via the muzzle for 13 weeks. Changes observed in the ≥63 μg/kg/day groups were excessive salivation,

increased body weight, increased food consumption, increased blood potassium levels, decreased blood triglycerides, increases in lung and spleen weights in both males and females, and increases in heart and uterus weights in females. Changes observed in the ≥211 μg/kg/day groups were squamous metaplasia in the larynx in males and increased ovary weight in females. Changes in the ≥900 μg/kg/day groups were increased skeletal muscle mass in both males and females and squamous metaplasia in the larynx in females. Changes in the 3258 μg/kg/day group were myometrial thickening, increased corpus luteum number, and increased cystic endometrial glands in females. Both in the vehicle and Olo groups, hyperplasia of the transitional epithelium in the larynx was observed. The changes seen in the 63 μg/kg/day group were not accompanied by histopathological changes and thus were not considered to be toxicological findings. The NOAEL for the study was therefore determined to be 63 μg/kg/day.

(b) Four-week inhalation toxicity study in rats (4.2.3.2-4)

Male and female Wistar rats received Olo at an inhaled dose of 0 (vehicle, BAC/Na-EDTA/citric acid aqueous solution), 78, 260, or 1360 μg/kg/day via the muzzle for 4 weeks. Changes observed in the ≥78 μg/kg/day groups were increased food consumption, increased body weight, increased tidal volume, elevated aspartate aminotransferase in blood (AST), elevated alanine aminotransferase in blood (ALT), decreased blood glucose, increased heart weight, and accumulation of alveolar macrophages in the lung in both males and females, and decreased thymus weight in males. Both in the vehicle and Olo groups, squamous metaplasia and necrosis in the U-shaped cartilage of the larynx, and increased number of goblet cells in the nasal mucosa were observed. In the 1360 μg/kg/day group, increases in the severity and frequency of necrosis in the U-shaped cartilage of the larynx were observed. Except necrosis in the U-shaped cartilage of the larynx, all the changes were reversible after the 4-week recovery period. The NOAEL for this study was determined to be 260 μg/kg/day based on the increases in the severity and frequency of necrosis in the U-shaped cartilage of the larynx, which was observed in the 1360 μg/kg/day group.

(c) Thirteen-week inhalation toxicity study in rats (4.2.3.2-5)

Male and female Wistar rats received Olo at an inhaled dose of 0 (air or vehicle, BAC/Na-EDTA/citric acid aqueous solution), 62, 239, 971, or 2833 μg/kg/day via the muzzle for 13 weeks. Changes observed in the ≥62 μg/kg/day groups were excessive salivation, increased total white blood cell count, high blood calcium levels, high blood potassium levels, low blood glucose levels, low urine potassium levels, squamous metaplasia in the larynx, and necrosis of the U-shaped cartilage in the larynx in both males and females, high blood creatinine levels, increased urine output, and decreased kidney weight in males, and high blood AST levels, increased heart weight, and increased spleen weight in females. Changes observed in the ≥239 μg/kg/day groups were high blood AST levels and decreased epididymis weight in males. Changes in the ≥971 μg/kg/day groups were low levels of blood triglyceride in both males and females, and increased food consumption, increased body weight, and increased urine output in females. Both in the vehicle and Olo groups, squamous metaplasia and necrosis in the U-shaped cartilage of the larynx were observed. In the ≥971 μg/kg/day groups, the severity and frequency of these changes increased. Except necrosis in the U-shaped cartilage of the larynx, all the changes were reversible after

the 4-week recovery period. The NOAEL for this study was determined to be 239 μg/kg/day based on the increases in the severity and frequency of necrosis in the U-shaped cartilage of the larynx, which was observed in the ≥971 μg/kg/day groups.

(d) Twenty-six week inhalation toxicity study in rats (4.2.3.2-6)

Male and female Wistar rats received Olo at an inhaled dose of 0 (vehicle, BAC/Na-EDTA/citric acid aqueous solution), 49, 200, or 3400 μg/kg/day via the muzzle for 26 weeks. Changes observed in the ≥49 μg/kg/day groups were increased food consumption, increased body weight, exophthalmos, high levels of blood ALT, AST, and alkaline phosphatase (ALP), skeletal muscle hypertrophy, decreased white adipose tissue, increased heart weight, atrophy of the corneal epithelium, and accumulation of alveolar macrophages in both males and females, and necrosis in the U-shaped cartilage of the larynx in females. In the ≥200 μg/kg/day groups, squamous hyperplasia, metaplasia, and epithelial atrophy in the larynx, and decreased glycogen levels stored in the hepatic lobules were observed in both males and females, and necrosis in the U-shaped cartilage of the larynx in males. In the 3400 μg/kg/day group, scattered skeletal muscle fiber necrosis, epithelial hyperplasia and metaplasia in the nasal cavity, inflammation, and squamous metaplasia in the tracheal bifurcation were observed in both males and females, and expansion of the uterus, ovary discoloration, corpus luteum cyst, and corpus luteum hemorrhage in females. Except necrosis in the U-shaped cartilage of the larynx, all the changes were reversible after the 4-week recovery period. The changes in the 49 μg/kg/day and 200 μg/kg/day groups were considered attributable to anabolism, a pharmacological action, of Olo, or of secondary changes such as adaptive responses, and are therefore not toxicological findings. Accordingly, the NOAEL for this study was determined to be 200 μg/kg/day based on the scattered skeletal muscle fiber necrosis.

(e) Four-week inhalation dose toxicity study in dogs (4.2.3.2-12)

Male and female beagle dogs received Olo at an inhaled dose of 0 (vehicle, BAC/Na-EDTA/citric acid aqueous solution), 2.2, 13.7, or 127 μg/kg/day for 4 weeks. Changes observed in both males and females in the ≥2.2 μg/kg/day groups were increased body weight, increased heart rate, and high blood potassium level. Changed observed in the ≥13.7 μg/kg/day groups included increased cardiac contractile force, shortening of the PR interval and QT interval, and high blood phosphorus levels in both males and females, and increased glycogen in perilobular hepatocytes in females. All the changes were reversible after the 4-week recovery period. These changes were attributable to the pharmacological action of Olo. However, the NOAEL for the study was determined to be 13.7 μg/kg/day, based on the observation of highly significant increases in heart rate accompanied by shortening of the QT interval in both males and females in the 127 μg/kg/day group.

(f) Thirteen-week inhalation toxicity study in dogs (4.2.3.2-13)

Male and female beagle dogs received Olo at an inhaled dose of 0 (air or vehicle, BAC/Na-EDTA/citric acid aqueous solution), 4.9, 15, or 160 μg/kg/day for 13 weeks. Changes observed in the ≥4.9 μg/kg/day groups were increased body weight, high blood creatinine, creatinine kinase (CK), and urea levels in both male and females, and decreased heart weight and lung weight in males In the ≥15 μg/kg/day

groups, increased glycogen in perilobular hepatocytes was observed in both males and females. In the 160 μg/kg/day group, increased heart rate, increased cardiac contractile force, and decreased glycogen in centrilobular hepatocytes were observed in both males and females, and high blood AST and ALT levels in females. All the changes were reversible after the 4-week recovery period and none of them were accompanied by histophathological findings. The changes therefore were attributable to pharmacological action of Olo. Inflammation in the tracheal bifurcation, respiratory epithelium atrophy, squamous metaplasia, etc. were observed both in the control and Olo groups. The NOAEL for the study was determined to be 160 μg/kg/day.

(g) Fifty-two week inhalation toxicity study in dogs (4.2.3.2-14)

Male and female beagle dogs received Olo at an inhaled dose of 0 (vehicle, BAC/Na-EDTA/citric acid aqueous solution), 15, 60, or 330 μg/kg/day for 52 weeks. In the ≥15 μg/kg/day groups, increased body weight, increased cardiac contractile force, increased heart rate, dryness of oral mucosa, high or relatively high blood creatinine level, and relatively high blood CK level were observed in both males and females. In the ≥60 μg/kg/day groups, elevated cardiac troponin blood levels (cTnI), fibrosis of papillary muscle of the left ventricle, decreased glycogen in centrilobular hepatocytes, and increased glycogen in perilobular hepatocytes were observed in both males and females, decreased prostate gland weight and prostatic atrophy in males, and increased food consumption, ventricular extrasystoles, and ventricular tachycardia in females; in the 330 μg/kg/day group, high blood CK-MB level in males, elevated systolic and diastolic pressure, and whitening of papillary muscle of the left ventricle in females. Other than myocardial fibrosis and prostatic atrophy, all the changes were reversible after the 4-week recovery period. Based on the presence or absence of organic lesions, the NOAEL for the study was determined to be 15 μg/kg/day.

3.(iii).A.(2).2) Tio + Olo coadministration

(a) Four-week Tio + Olo inhalation toxicity studies in rats (4.2.3.2-7 and 4.2.3.2-8)

Male and female Wistar rats received Tio + Olo at an inhaled dose of 0 + 0 (vehicle, an aqueous solution containing 0.01% benzalkonium chloride, 0.01% sodium ethylenediaminetetraacetic acid, and 1 mol/L hydrochloric acid [pH 2.9]; [BAC/Na-EDTA/hydrochloric acid aqueous solution], 85.2 + 78.6, 577 + 555, or 2266 + 2174 μg/kg/day via the muzzle for 4 weeks. A total of 3 animals died, and the causes of the deaths were lung abscess and pleurisy (1 male in the 2266 + 2174 μg/kg/day group), and asphyxia from food (1 male each in the 577 + 555 μg/kg/day and 2266 + 2174 μg/kg/day groups), none of which were considered likely to be related to the combined use of Tio and Olo. In surviving animals, the following changes were noted: in the ≥ 85.2 + 78.6 μg/kg/day groups, decreased food consumption, decreased body weight gain, mydriasis, increased total white blood cell count, prolonged prothrombin time, increased urine output accompanied by low urine sodium, chloride, and potassium levels, decreased specific gravity urine, increased lung weight, dark red discoloration of the lung, accumulation of foamy materials in the airway, and lung congestion in both males and females, and low blood glucose and triglyceride levels in females; in the ≥ 577 + 555 μg/kg/day groups, decreased activated partial thromboplastin time, squamous metaplasia of the ventral nasal meatus of the nasal cavity in both males

and females, and squamous metaplasia in the epithelium of the arytenoid cartilage in the larynx in females; in the 2266 + 2174 μg/kg/day group, epithelial atrophy of the dorsal nasal meatus of the nasal cavity, and squamous metaplasia in the epithelium of the arytenoid cartilage in the larynx in males. Necrosis and squamous metaplasia in the U-shaped cartilage of the larynx, and squamous metaplasia of the epithelium covering the base of epiglottis were observed both in the vehicle group and in the Tio + Olo groups.

(b) Four-week Tio + Olo inhalation toxicity study in dogs (4.2.3.2-16)

Male and female beagle dogs received Tio + Olo at an inhaled dose of 0 + 0 (vehicle, BAC/Na-EDTA/hydrochloric acid aqueous solution), 6.07 + 5.71, 16.8 + 16.1, or 157 + 152 μg/kg/day for 4 weeks. In the 6.07 + 5.71, 16.8 + 16.1, and 157 + 152 μg/kg/day groups, oral mucosa and nasal dryness, laryngitis, decreased hematocrit levels and reticulocyte count, decreased blood albumin, decreased urine output, increased urine sodium and potassium, increased glycogen in perilobular hepatocytes were observed in both males and females. In the 16.8 + 16.1 and 157 + 152 μg/kg/day groups, decreased food consumption, decreased body weight gain, mydriasis, increased heart rate, decreased ALP, increased blood phosphorus levels, increased blood potassium levels, and decreased thymus gland weight were observed in both males and females, and increased blood urea level in females, and in the 157 + 152 μg/kg/day group, keratoconjunctivitis with hyperaemia and exudation and rhinitis were observed in males and females.

(c) Thirteen-week Tio + Olo inhalation dose toxicity study in dogs (4.2.3.2-18)

Male and female beagle dogs received Tio + Olo at an inhaled dose of 0 + 0 (vehicle, BAC/Na-EDTA/hydrochloric acid aqueous solution), 14 + 16, 57 + 62, 290 + 310, 310 + 0, or 0 + 290 μg/kg/day for 13 weeks. In the Tio alone group, a trend toward reducing weight gain, increased cardiac contractile force, increased heart rate, dryness of oral mucosa and nasal region, mydriasis, eyeball dryness, eyelid swelling, and conjunctival hyperemia were observed in both males and females. In the Olo alone group, a trend toward increasing weight gain, increased cardiac contractile force, increased heart rate, decreased PR and QT intervals, increased cTnI and CK-MB levels, increased blood CK and blood creatinine levels, decreased blood glucose levels, fibrotic foci in the papillary muscle of the left ventricle, increased glycogen in perilobular hepatocytes were observed in both males and females. Similar changes were observed also in the Tio + Olo groups, and the combination of Tio and Olo did not lead to increased toxicity of the individual compounds.

3.(iii).A.(3) Genotoxicity (4.2.3.3.1 to 4.2.3.3.2)

The genotoxicity of Olo was evaluated in the bacterial reverse mutation assay, mouse lymphoma TK assay, rat bone marrow micronucleus assay by intravenous administration, and rat bone marrow micronucleus assay by repeated inhalation of Olo alone or Tio + Olo combination. There were no positive results of these assays except for the rat bone marrow micronucleus assay by intravenous administration.

In the rat bone marrow micronucleus assay by intravenous administration, an increase in the frequency of micronucleated polychromatic erythrocytes was observed in the Olo 10 mg/kg and Olo 40 mg/kg groups. The applicant concluded that the finding was not suggestive of a genotoxic effect of Olo, and that there would be no genotoxic concerns in the clinical use of Olo for the following reasons:

- In the mechanistic investigation of erythropoiesis (4.2.3.3.2-2), 40 mg/kg of Olo increased blood erythropoietin levels 6 and 24 hours post-dose, promoted the increase and maturation of erythroid progenitor cells, and increased peripheral reticulocytes and extramedullary hemopoiesis in the spleen 24 and 48 hours post-dose. These results suggest that high-dose Olo caused a marked increase in heart rate and decreased blood pressure which induced hypoxia, thereby promoting the production of erythropoietin and leading to erythropoiesis in the femoral bone marrow. This may have resulted in increased spontaneous micronucleus formation.
- The AUC of Olo was 8.77 μmol·h/L in rats used in the study which revealed the increase in the frequency of micronucleated polychromatic erythrocytes. The AUC value was 30,000-fold the AUC of Olo (287 pmol·h/L) determined in Japanese patients with COPD receiving Olo at an inhaled dose of 5 μg/day for 4 weeks.

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

Carcinogenicity studies of Olo was conducted in mice and rats by inhalation. Proliferative changes and neoplastic lesions in the female reproductive organs were observed in mice and rats; however, these changes are expected to occur following the administration of β_2-adrenoceptor agonists and were not considered to be relevant for humans.

3.(iii).A.(4).1) Carcinogenicity study in mice (4.2.3.4.1-1)

Male and female CD-1 mice received Olo at an inhaled dose of 0 (air or vehicle, BAC/Na-EDTA/citric acid aqueous solution), 26.1, 76.9, or 255 μg/kg/day via the muzzle for 104 weeks. The study for females in the 76.9 μg/kg/day group was discontinued at Week 103 because the mortality reached 75%. Although the mortality of females in the 76.9 μg/kg/day group was higher than that in the vehicle control group, mortality in the 26.1 and 255 μg/kg/day groups was comparable to that in the vehicle group, showing no dose-response relationship. For this reason, the applicant considered that the deaths were unlikely to be attributable to Olo. Neoplastic lesions related to Olo include: uterine leiomyosarcoma (2 of 60 animals in the vehicle group, 5 of 60 animals in the 26.1 μg/kg/day group, 10 of 60 animals in the 76.9 μg/kg/day group, and 4 of 60 animals in the 255 μg/kg/day group), and uterine leiomyoma (9 of 60 animals in the vehicle group, 18 of 60 animals in the 26.1 μg/kg/day group, 19 of 60 animals in the 76.9 μg/kg/day group, and 22 of 60 animals in the 255 μg/kg/day group). Non-neoplastic lesions in the vehicle group and the Olo groups were necrosis in the U-shaped cartilage and squamous metaplasia in the larynx in both males and females. Those in the ≥26.1 μg/kg/day groups were increased skeletal muscle mass, myocardial fibrosis and vacuolation in both males and females, left atrial thrombus in males, and decreased incidence of age-related atrophic vaginitis in females. Those in the ≥76.9 μg/kg/day groups were myocardial hypertrophy in males, and focal hyperplasia in the sex cord or

stromal ovary in females. Those in the 255 μg/kg/day group were increased incidence of squamous metaplasia in the larynx in both males and females, epicardial fibrosis in males and focal hyperplasia of the corpus lutea in females.

3.(iii).A.(4).2) Carcinogenicity study in rats (4.2.3.4.1-2)

Male and female Wistar rats received Olo at an inhaled dose of 0 (air or vehicle, BAC/Na-EDTA/citric acid aqueous solution), 25.8, 75.9, or 270 μg/kg/day via the muzzle for 104 weeks. Neoplastic lesions related to Olo include mesovarial leiomyoma (0 of 55 animals in the vehicle group, 1 of 55 animals in the 25.8 μg/kg/day group, 0 of 55 animals in the 75.9 μg/kg/day group, and 4 of 55 animals in the 270 μg/kg/day group). Non-neoplastic lesions in the vehicle group and all of the Olo groups include squamous metaplasia in the larynx in both males and females. Ovarian cyst was noted in females in the ≥25.8 μg/kg/day groups, and mesovarial smooth muscle hyperplasia in females in the ≥75.9 μg/kg/day groups.

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

A study for fertility and early embryonic development in rats, studies for embryo-fetal development in rats and rabbits, a study for the effects on pre- and postnatal development including maternal function in rats were conducted to evaluate the reproductive and developmental toxicity of Olo. Fetal effects related to Olo include skeletal, eye, and cardiovascular developmental abnormalities in rabbits. The exposures to Olo in rats and rabbits at the NOAELs for reproductive and developmental toxicity were 1280-fold and 634-fold the human exposure to Olo (AUC, 287 pmol·h/L), which was obtained from Japanese patients with COPD receiving Olo at an inhaled dose of 5 μg for 4 weeks. Transfer across the placenta and transfer to breast milk of Olo have been reported [see "3.(ii) Summary of pharmacokinetic studies"].

3.(iii).A.(5).1) Study for fertility and early embryonic development (4.2.3.5.1-1)

Male and female SD rats received Olo at an inhaled dose of 0 (vehicle, BAC/Na-EDTA/citric acid aqueous solution), 58, 193, or 3068 μg/kg/day. Male animals were treated from 4 weeks prior to mating to the end of mating period, and female animals from 2 weeks prior to mating to gestation day 7. One of 24 males died and 1 of 24 females was sacrificed moribund in the 3068 μg/kg/day group. Effects of Olo on paternal animals include: increased food consumption, increased weight gain, reddening of skin, excessive salivation, decreased testicle weight and epididymis weight in the ≥58 μg/kg/day groups; and decreased locomotor activity in the 3068 μg/kg/day group. The following effects on maternal animals were observed: increased food consumption and increased weight gain in the ≥58 μg/kg/day groups; reddening of skin and excessive salivation in the ≥193 μg/kg/day groups; and decreased locomotor activity in the 3068 μg/kg/day group. No effects on mating, fertility, or pregnancy were observed. The effects on the testicle observed in paternal animals were not considered to be of toxicological significance because related findings were not identified by the histopathological examination. The NOAEL for general toxicity in parental animals was determined to be 58 μg/kg/day based on the effects

on general condition in both males and females. The NOAEL for fertility and early embryonic development was determined to be 3068 μg/kg/day.

3.(iii).A.(5).2) Rat embryo-fetal development study (4.2.3.5.2-1)

Pregnant SD rats received Olo at an inhaled dose of 0 (vehicle, BAC/Na-EDTA/citric acid aqueous solution), 64, 222, or 1054 μg/kg/day from gestation day 6 to gestation day 17. Effects on maternal animals included increased food consumption and increased body weight gain in the ≥64 μg/kg/day groups. Effects on fetuses included increased body weight in the ≥64 μg/kg/day groups and incomplete ossification of the sternebra in the ≥222 μg/kg/day groups. The latter was considered not suggestive of effects on postnatal development for the reasons listed below. The NOAELs for general toxicity in both maternal animals and fetuses were determined to be 1054 μg/kg/day.

- The incidence of incomplete ossification of the sternebra in the vehicle group was higher than historical controls, suggesting the change seen in the animals used in the study was highly attributable to genetic predisposition.
- There were no observed effects on fetal weight suggestive of delayed development.
- In the study on effects of Olo on pre- and postnatal development, neonatal rats that received higher doses of Olo did not show any changes suggesting abnormal skeletal growth or development.

3.(iii).A.(5).3) Rabbit embryo-fetal development study (4.2.3.5.2-3)

Pregnant NZW rabbits received Olo at an inhaled dose of 0 (vehicle, BAC/Na-EDTA/citric acid aqueous solution), 289, 974, or 2489 μg/kg/day from gestation day 6 to gestation day 19. One of 24 animals in the 974 μg/kg/day group was sacrificed moribund due to a sign of abortion. An observed effect on maternal animals was accelerated body weight gain in the ≥289 μg/kg/day groups. In fetuses, teratogenic changes were observed in the 2489 μg/kg/day group. These changes include unossifying areas and patchy ossification on the cranial bones/ribs/long bones, thickened ribs, distorted rib cage, short or bent scapula/humerus/radius/ulna/femur/tibia/fibula, limb flexure, partially open eye lids, cleft palate, acrania, absent eyes, cervicothoracic spine and rib abnormalities, split sternum, gastroschisis, retina fold abnormalities, cardiovascular abnormalities (dilated ascending aorta/aortic arch, narrow pulmonary trunk, pulmonary artery originating directly from the aortic arch, enlarged left ventricle/small right ventricle, small right atrium), and dorsoventral distortion of the sternum. Therefore, the NOAELs for the general toxicity of maternal animals and for fetuses were determined to be 2489 μg/kg/day, and 974 μg/kg/day, respectively.

3.(iii).A.(5).4) Rat study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3-1)

Pregnant SD rats received Olo at an inhaled dose of 0 (vehicle, BAC/Na-EDTA/citric acid aqueous solution), 59, 297, or 3665 μg/kg/day from gestation days 6 to 20, and from postpartum days 2 to 21. Observed effects on maternal animals were accelerated body weight gain and excessive salivation in the ≥59 μg/kg/day groups; accelerated or decreased locomotor activity, and partially open eye lids in the

3665 μg/kg/day group. In fetuses in the ≥59 μg/kg/day groups, a decrease in the number of days required for eyelid opening was observed. However, given the small degree of change, it was considered to be of no toxicological significance. The NOAELs for both the general toxicity of maternal animals and fetuses were determined to be 3665 μg/kg/day.

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

A skin irritation study, eye irritation study, and local tolerance studies by intravenous, paravenous, intra-arterial, or intramuscular administration were conducted to evaluate the local tolerance of Olo. Olo is considered to be mildly to moderately irritating when applied to the eyes and mildly irritating when intravenously administered.

3.(iii).A.(6).1) Skin irritation study in rabbits (4.2.3.6-1)

Female NZW rabbits received 500 mg of Olo (mixed with deionized water into a paste, which was then applied onto the skin) transcutaneously for 4 hours. No skin reaction or systemic toxicity was observed up to 4 hours post-dose; therefore, Olo is considered to be a non-irritant and non-corrosive substance.

3.(iii).A.(6).2) Eye irritation study in rabbits (4.2.3.6-2)

A single dose of 2 or 10 mg of Olo was administered into the conjunctival sac of female NZW rabbits. Observed changes were conjunctival congestion and eyelid swelling in the 2 mg group; and lacrimation, conjunctival congestion, eyelid swelling, and diffused crimson color in the 10 mg group. The findings observed in the 2 and 10 mg groups resolved by 48 hours and 72 hours post-dose, respectively. Based on the above results, Olo is considered to be mildly to moderately irritating.

3.(iii).A.(6).3) Single-dose intravenous and intramuscular tolerance study in rabbits (4.2.3.6-3)

A single dose (0.5 mL) of 0 (physiological saline), 0.004, or 0.010 mg/mL of Olo was administered to female NZW rabbits intravenously into the lateral auricular vein or intramuscularly. Mild changes including perivascular hemorrhage, necrosis, granulocyte infiltration, edema, thrombus formation inside the blood vessel, and necrosis of the blood vessel wall were observed 24 hours and 96 hours post-dose in the 0.010 mg/mL intravenous administration group. No Olo-related changes were observed in the intramuscular administration groups.

3.(iii).A.(6).4) Single-dose intra-arterial tolerance study in rabbits (4.2.3.6-4)

A single dose (0.5 mL) of 0 (physiological saline), 0.004, or 0.010 mg/mL of Olo was administered to female NZW rabbits intra-arterially into the auricular central artery. While no local reactions to Olo were observed 24 hours and 96 hours post-dose, animals in the 0.010 mg/mL group appeared distressed at the time of administration.

3.(iii).A.(6).5) Single-dose paravenous tolerance study in rats (4.2.3.6-5)

A single dose (0.2 mL) of 0 (physiological saline), 0.004, or 0.010 mg/mL of Olo was administered around the right jugular vein of female Wistar rats. No Olo-related changes were observed 24 hours or 96 hours post-dose.

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

3.(iii).A.(7).1) Toxicity study in juvenile animals (4.2.3.7.7-2)

Inhaled doses of 0 (air or vehicle, BAC/Na-EDTA/citric acid aqueous solution), 120, 324, or 1046 μg/kg/day of Olo were administered to male and female juvenile beagle dogs (15 to 19 days of age) for 13 weeks. One of 5 males and 1 of 5 females in the 324 μg/kg/day group died. The cause of death was aspiration purulent bronchopneumonia for the male dog but was unknown for the female dog while sedation, decreased body temperature, pallor, and abdominal distension were noted in the female animal. The death of the female dog was considered to be unrelated to Olo, because neither deaths nor general symptoms similar to those of the dead female dog were observed in other groups including the 1046 μg/kg/day group. The following changes were noted among surviving animals: accelerated increase in body weight gain (in males) in the 120 μg/kg/day group; increased glycogen in perilobular hepatocytes, and increased hepatocyte density (in both males and females) in the ≥120 μg/kg/day groups; accelerated increase in body weight gain (in females), decreased mean cell hemoglobin (in both males and females) in the ≥324 μg/kg/day groups; decrease in body weight gain (in both males and females), decreased testicle weight and thymus gland weight (in males) in the 1046 μg/kg/day group. All these findings were reversible after the 4-week washout period. Findings observed in the 120 μg/kg/day group were adaptive changes that are common with β_2-adrenoceptor agonists; therefore, they were not determined to be toxicological findings. The NOAEL for the study was determined to be 324 μg/kg/day.

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

Neoplastic lesions in female reproductive organs observed in the carcinogenicity study

Given that uterine leiomyoma and uterine leiomyosarcoma were observed in most treatment groups of the inhalation carcinogenicity study of Olo in mice, PMDA asked the applicant to explain the potential risk of tumorigenesis in humans in relation to these findings.

The applicant's response:

In the inhalation carcinogenicity study of Olo in mice, uterine leiomyoma and uterine leiomyosarcoma were observed in all treatment groups including those receiving the lowest dose of 26.1 μg/kg. The exposure to Olo in mice treated at 26.1 μg/kg was compared with the exposure in Japanese patients with COPD receiving once-daily inhalation of 5 μg of Olo for 4 weeks (lung dose calculated on the basis of body surface area,[7] 3.7 μg/m^2; AUC, 287 pmol·h/L). The lung dose in mice was 21-fold that in humans and the AUC in mice was 20-fold that in humans. Uterine leiomyoma and uterine smooth muscle hyperplasia were observed in mice receiving medroxalol, a β_1- and β_2-agonist, for at least 12 months (Jack D et al. *Toxicology*. 27:315-320,1983), and the induction of uterine leiomyoma is known to be

[7] The calculation was based on assumed body weight of 50 kg.

suppressed by propranolol, a nonselective β-blocker (Gibson JP et al. *Toxicol Pathol*. 15:468-473,1987). The pathogenesis of leiomyoma has been reported to be associated with stimulation of β_2-receptors (Greaves P. *Histopathology of preclinical toxicity studies: Interpretation and relevance in drug safety evaluation, 4th ed.*,689-690,2012). Uterine sensitivity to β_2-agonists differs among mouse strains, and is considered to be high in CD-1 mice (Gibson JP et al. *Toxicol Pathol*. 15:468-473,1987), which were used in the carcinogenicity studies of Olo. The findings of the carcinogenicity study of Olo do not suggest that the carcinogenic risk of Olo is any higher than that of other β_2-agonists. Furthermore, uterine tissue relaxation induced by β_2-receptor stimulation, which differs among species, is known to be greater in mice than in rats (Gibson JP et al. *Toxicol Pathol*. 15:468-473,1987) and is negligible in humans (Lossius K et al. *Acta Pharmacol. Toxicol*. 39:198-208,1976; Berg-Johnsen P et al. *Acta Pharmacol. Toxicol*. 39:209-213,1976). Accordingly, the findings in question are unlikely to be relevant for humans.

In the clinical studies, no leiomyoma occurred in the female reproductive organs as a class effect of β_2-agonists. In the long-term administration studies of Olo, there were no reports of adverse events possibly related to the impairment of the reproductive organs, mammary gland, or endocrine system. Accordingly, the uterine neoplastic lesions in mice are considered to have resulted from the stimulating effect of Olo on β_2-receptors and are not relevant for humans The risk of promoting carcinogenesis or tumor growth in humans is therefore of no major concern.

PMDA accepted the applicant's explanation and concluded that there are no particular concerns associated with the combination of Tio and Olo, based on the toxicity profile of Olo similar to those of other approved β_2 agonists and because of neither potentiation nor generation of toxicity caused by the combination of Tio and Olo.

4. Clinical data

4.(i) Summary of biopharmaceutical studies and clinical pharmacology studies

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

The following studies were submitted as the evaluation data: single-dose and repeated-dose studies of Olo in healthy adults (5.3.3.1-7, Study 1222.21; 5.3.3.1-4, Study 1222.7; 5.3.3.1-1, Study 1222.1; 5.3.3.1-2, Study 1222.2), Olo mass balance study (5.3.3.1-5, Study 1222.9), repeated-dose inhalation studies of Olo in patients with COPD (5.3.5.1-4, Study 1222.22; 5.3.5.1-3, Study 1222.5), inhaled administration studies of the fixed-dose combination of Tio + Olo in patients with COPD (5.3.3.2-1, Study 1237.24; 5.3.5.1-15, Study 1237.20), studies in special populations (5.3.3.3-1, Study 1222.20; 5.3.3.3-2, Study 1222.35), drug-drug interaction studies (5.3.3.4-1, Study 1222.47; 5.3.3.4-2, Study 1222.48), and pharmacodynamic study (5.3.4.1-1, Study 1222.8).

Olodaterol and its metabolite (SOM 1522) concentrations and tiotropium concentrations in plasma and urine were determined using a high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) method (lower limit of quantification, 2.0 pg/mL for olodaterol in plasma, 10.0 pg/mL for olodaterol in urine, 10.0 pg/mL for SOM 1522 in plasma, 100 pg/mL for SOM 1522 in urine, 1.0

pg/mL for tiotropium in plasma, and 10.0 pg/mL for tiotropium in urine). The concentrations of CD 992, a glucuronide conjugate of olodaterol, were calculated from the difference in the measurement values for olodaterol before and after β-glucuronidase pretreatment.

The doses and concentrations of the agents are expressed as their free bases, and measured values and pharmacokinetic parameters are presented as mean or mean ± standard deviation, unless otherwise specified.

4.(i).A.(1) Studies in healthy adult subjects

4.(i).A.(1).1) Olo monotherapy

(a) Japanese multiple-dose inhalation study of Olo (5.3.3.1-7, Study 1222.21 [January 2008 to May 2008])

A double-blind, randomized, placebo-controlled, dose-escalation study was conducted in healthy adults (n = 12/group [9 subjects in the Olo group and 3 subjects in the placebo group]). The pharmacokinetic parameters of unchanged Olo and CD 992 in plasma following once-daily inhalation of 5, 10, or 20 μg of Olo for 14 days are shown in Table 8. The C_{max} and AUC of the unchanged Olo increased in a dose-proportional manner.

Table 8. Pharmacokinetic parameters of unchanged Olo and its metabolite following 14-day inhalation of Olo in Japanese healthy adults

Dose	Measuring time point	Number of subjects	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{0-24} (pg·h/mL)	AUC_{0-tz} (pg·h/mL)
Unchanged Olo							
5 μg	After first dose	7	2.89 ± 0.67	0.167 (0.167–0.367)	—	—	1.27 ± 0.87
	At steady state	9	3.43 ± 0.82	0.500 (0.167–0.500)	—	—	7.85 ± 8.25
10 μg	After first dose	9	5.65 ± 1.69	0.167 (0.167–0.500)	—	—	15.4 ± 12.4
	At steady state	9	7.48 ± 3.06	0.333 (0.167–0.333)	—	90.2 ± 15.7 [a)]	72.9 ± 37.4
20 μg	After first dose	9	11.4 ± 4.04	0.333 (0.167–0.333)	20.0 ± 8.80 [c)]	—	50.6 ± 29.4
	At steady state	9	13.8 ± 5.98	0.333 (0.167–0.500)	36.9 ± 9.63 [b)]	138 ± 37.7 [b)]	128 ± 47.6
CD 992							
5 μg	After first dose	6	0.80 ± 0.65	0.417 (0.333–1.00)	—	—	0.24 ± 0.25
	At steady state	9	1.55 ± 0.45	1.00 (0.333–2.00)	—	—	2.79 ± 2.21
10 μg	After first dose	9	2.35 ± 1.21	2.00 (0.333–4.00)	—	—	8.48 ± 7.58
	At steady state	9	3.19 ± 1.64	4.00 (0.333–12.0)	—	—	37.0 ± 26.4
20 μg	After first dose	9	6.29 ± 2.54	4.00 (2.00–6.00)	—	—	45.2 ± 25.9
	At steady state	9	10.0 ± 4.06	2.00 (1.00–4.00)	—	104 ± 57.8 [b)]	101 ± 54.8

Mean ± SD, except t_{max} indicating the median value (minimum–maximum); C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration; AUC, area under the plasma concentration-time curve. —, not calculated; [a)] 7 subjects; [b)] 8 subjects; [c)] 6 subjects

(b) Foreign single-dose intravenous administration study of Olo (5.3.3.1-4, Study 1222.7 [October 2006 to February 2007])

A single-blind, placebo-controlled, randomized, dose-escalation study was conducted in healthy adults (n = 8/group [6 subjects in the Olo group and 2 subjects in the placebo group]). The pharmacokinetic parameters of unchanged Olo and CD 992 in plasma following a single-dose intravenous infusion of 0.5

to 25 μg of Olo are shown in Table 9. The C_{max} and AUC of the unchanged Olo increased in a dose-proportional manner. The plasma concentrations of CD 992 were lower than those of the unchanged Olo, and SOM 1522 was not detected in plasma.

Tale 9. Pharmacokinetic parameters of unchanged Olo and its metabolite following a single-dose intravenous infusion of Olo in healthy non-Japanese adults

Dose (duration of infusion)	Number of subjects	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}tz}$ (pg·h/mL)	$AUC_{0\text{-}\infty}$ (pg·h/mL)
Unchanged Olo						
0.5 μg (30 min)	6	5.29 ± 0.41	0.359 (0.233-0.483)	—	—	—
2.5 μg (30 min)	6	24.7 ± 1.97	0.483 (0.250-0.483)	—	11.6 ± 1.14	—
5 μg (30 min)	6	48.0 ± 3.35 [a)]	0.483 (0.483-0.500) [a)]	—	25.3 ± 1.60 [a)]	—
10 μg (30 min)	6	89.0 ± 14.6	0.483 (0.483-0.483)	—	51.3 ± 9.15	—
15 μg (30 min)	6	135 ± 20.6	0.483 (0.483-0.500)	16.4 ± 3.66 [a)]	101 ± 19.3	160 ± 30.2 [a)]
15 μg (3 hours)	6	32.2 ± 4.19	2.98 (2.98-3.10)	7.63 ± 2.22 [a)]	111 ± 10.7	136 ± 19.1 [a)]
20 μg (3 hours)	6	44.0 ± 3.56	2.98 (0.500-3.05)	13.4 ± 5.87	157 ± 25.3	217 ± 46.1
25 μg (3 hours)	6	52.0 ± 7.96 [a)]	2.98 (2.98-2.98) [a)]	15.0 ± 5.93 [a)]	202 ± 45.3 [a)]	282 ± 54.9 [a)]
CD 992 [b)]						
25 μg (3 hours)	6	33.3 ± 4.79 [a)]	3.05 (2.98-3.17) [a)]	—	147 ± 12.2 [a)]	—

Mean ± SD except t_{max} indicating the median value (minimum–maximum); C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration; AUC, area under the plasma concentration-time curve; —, not calculated; [a)] 5 subjects; [b)] only the 25 μg group was measured.

(c) Foreign single-dose inhalation study of Olo (5.3.3.1-1, Study 1222.1 [February 2005 to July 2005])

A double-blind, placebo-controlled, randomized, dose-escalation study was conducted in healthy adults (n = 8/group [6 subjects in the Olo group and 2 subjects in the placebo group]). The pharmacokinetic parameters of unchanged Olo following a single-dose inhalation of 0.5 to 70 μg of Olo are shown in Table 10.[8] The C_{max} and AUC of the unchanged Olo increased in a dose-proportional manner. Only unchanged Olo was detected in plasma.

Table 10. Pharmacokinetic parameters of unchanged Olo following a single-dose inhalation of Olo in healthy non-Japanese adults

Dose	Number of subjects	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}tz}$ (pg·h/mL)	$AUC_{0\text{-}\infty}$ (pg·h/mL)
10 μg	6	3.71 ± 0.84	0.333 (0.167-0.500)	—	4.03 ± 2.66	—
15 μg	6	5.40 ± 2.54	0.367 (0.200-0.533)	—	14.8 ± 15.5	—
20 μg	6	6.38 ± 3.97	0.350 (0.183-0.850)	—	15.5 ± 17.3	—
30 μg	6	19.7 ± 9.44	0.275 (0.167-0.500)	24.5 ± 26.0	80.7 ± 39.5	158 ± 111
40 μg	6	18.3 ± 13.2	0.367 (0.117-0.517)	18.5 ± 9.28	119 ± 99.1	178 ± 125
50 μg	6	27.0 ± 6.92	0.292 (0.200-0.550)	51.1 ± 50.0	205 ± 101	451 ± 339
60 μg	6	34.5 ± 17.1	0.292 (0.217-0.550)	42.3 ± 16.3	241 ± 96.1	431 ± 204
70 μg	5	36.6 ± 21.0	0.233 (0.217-0.383)	25.4 ± 13.9	266 ± 186	386 ± 242

Mean ± SD except t_{max} indicating the median value (minimum–maximum); C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration; AUC, area under the plasma concentration-time curve; —, not calculated

(d) Foreign multiple-dose inhalation study of Olo (5.3.3.1-2, Study 1222.2 [January 2006 to September 2006])

A double-blind, placebo-controlled, randomized, dose escalation study was conducted in healthy adults (n = 12/group [9 subjects in the Olo group and 3 subjects in the placebo group]). The pharmacokinetic parameters[9] of unchanged Olo and its metabolite in plasma following once-daily inhalation of 2.5, 10,

[8] The calculation of the pharmacokinetic parameters for unchanged Olo in plasma following administration of 0.5 to 5 μg of Olo was not possible.

[9] The calculation of the pharmacokinetic parameters for unchanged Olo and glucuronide conjugate in plasma at 2.5 μg of Olo, and for glucuronide conjugate in plasma at 10 μg of Olo was not possible.

or 30 μg of Olo for 14 days are shown in Table 11. The plasma concentrations of unchanged Olo reached steady state by Day 10, and the C_{max} and AUC increased in a dose-proportional manner. The glucuronide conjugate of Olo was detected in plasma as early as 2 hours post-dose, and attained steady state 10 to 13 days after administration. In plasma, SOM 1522 was not detected.

Table 11. Pharmacokinetic parameters of unchanged Olo and its metabolite following 14-day inhalation of Olo in healthy non-Japanese adults

Dose	Measuring time point	Number of subjects	C_{max} (pg/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{0-24} (pg·h/mL)	AUC_{0-tz} (pg·h/mL)
Unchanged Olo							
10 μg	After first dose	9	4.24 ± 1.10 [a)]	0.333 (0.150–0.333) [a)]	1.91 ± 0.66 [a)]	—	5.50 ± 4.11 [a)]
	At steady state	9	6.08 ± 3.55 [b)]	0.342 (0.333–1.00) [b)]	45.7 ± 59.2 [b)]	82.7 ± 22.7 [c)]	47.3 ± 40.6 [b)]
30 μg	After first dose	9	9.76 ± 5.15	0.167 (0.083–0.500)	9.02 ± 8.32	—	39.5 ± 37.3
	At steady state	9	11.6 ± 4.79	0.333 (0.167–0.667)	47.8 ± 17.8	132 ± 42.1	132 ± 42.1
Glucuronide conjugate							
30 μg	After first dose	9	8.69 ± 2.27	2.00 (2.00–4.00)	9.19 ± 5.27	—	68.6 ± 26.9
	At steady state	9	11.0 ± 3.65	2.00 (1.00–4.02)	—	95.5 ± 32.6	—

Mean ± SD except t_{max} indicating the median value (minimum–maximum); C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration; AUC, area under the plasma concentration-time curve; —, not calculated. [a)] 7 subjects; [b)] 8 subjects; [c)] 4 subjects.

(e) Study of mass balance of Olo in humans (5.3.3.1-5, Study 1222.9 [February 2008 to April 2008])

Mass balance of Olo was investigated in an open-label study in healthy adults (n = 6/group). Following a single dose of ^{14}C-labeled Olo by 3-hour intravenous infusion at 20 μg or oral administration of ^{14}C-labeled Olo at 40 μg, the pharmacokinetic parameters of unchanged Olo in plasma were as follows: C_{max}, 123 and 7.63 pmol/L, respectively; AUC_{0-tz}, 763 and 17.1 pmol·h/L, respectively; and t_{max}, (median) 2.98 and 1.00 hours, respectively. The $t_{1/2}$ of unchanged Olo in plasma in the intravenous treatment group was 23.9 hours. Excretion of Olo in urine (fe_{0-tz}) was 19.0% of the dose at 38 hours after intravenous infusion.

The pharmacokinetic parameters of glucuronide conjugates of Olo in plasma in the intravenous and oral treatment groups were as follows: C_{max}, 33.1 and 50.3 pmol/L, respectively; AUC_{0-tz}, 184 and 275 pmol·h/L, respectively; t_{max} (median), 3.07 and 2.00 hours, respectively; and $t_{1/2}$, 16.9 and 2.63 hours, respectively. The ratios (glucuronide conjugates of Olo / unchanged Olo) of C_{max} and AUC were 0.262 and 0.206, respectively, in the intravenous treatment group; and 6.48 and 18.3, respectively, in the oral treatment group.

The recovery of radioactivity in urine and feces was 42.5% and 53.0%, respectively, of the administered dose in the intravenous treatment group, and 8.9% and 84.4%, respectively, of the administered dose in the oral treatment group. The following 6 metabolites were detected in urine and feces: CD 992 and M565(2) (both of which are glucuronide conjugates of Olo), SOM 1522 (a desmethyl of Olo), CD 11249 and CD 10915 (both of which are glucuronide conjugates of SOM 1522), and CD 12656 (a sulfate conjugate of SOM 1522).

4.(i).A.(2) Studies in patients with COPD

4.(i).A.(2).1) Olo monotherapy

(a) Japanese multiple-dose inhalation study of Olo (5.3.5.1-4, Study 1222.22 [January 2009 to March 2010])

A double-blind, placebo-controlled, randomized, parallel-group study was conducted in patients with COPD (n = 79 to 86/group) to evaluate the pharmacokinetic parameters of unchanged Olo in plasma following once-daily inhalation of Olo 2, 5, or 10 μg for 4 weeks. The pharmacokinetic parameters of unchanged Olo in plasma in the 5 and 10 μg groups were as follows: the C_{max}, 6.91 and 15.0 pg/mL (n = 67 and 78), respectively; t_{max} (median), 0.333 and 0.300 hours (n = 67 and 78), respectively; $AUC_{0\text{-}tz}$, 12.7 and 28.7 pg·h/mL (n = 67 and 78), respectively; and $AUC_{0\text{-}24}$, 111 and 173 pg·h/mL (n = 27 and 62), respectively. The calculation of the pharmacokinetic parameters of unchanged Olo in plasma in the 2 μg group was not possible.

(b) Foreign multiple-dose inhalation study of Olo (5.3.5.1-3, Study 1222.5 [March 2007 to January 2008])

A double-blind, placebo-controlled, randomized, parallel-group study was conducted in patients with COPD (n = 79 to 86/group) to evaluate the pharmacokinetic parameters of unchanged Olo in plasma following once-daily inhalation of Olo 2, 5, 10, or 20 μg for 4 weeks. The pharmacokinetic parameters of unchanged Olo in plasma in the 5, 10, and 20 μg groups were as follows: the C_{max}, 4.47, 8.54, and 19.4 pg/mL (n = 46, 72, and 72), respectively; t_{max} (median), 0.192, 0.200, and 0.200 hours (n = 46, 72, and 72), respectively; $AUC_{0\text{-}tz}$, 7.99, 27.0, and 52.3 pg·h/mL (n = 39, 69, and 72), respectively. The calculation of the pharmacokinetic parameters of unchanged Olo in plasma in the 2 μg group was not possible.

4.(i).A.(2).2) Tio + Olo fixed-dose combination therapy

(a) Japanese multiple-dose inhalation study (5.3.3.2-1, Study 1237.24 [October 2012 to March 2013])

An open-label study was conducted in patients with COPD (n = 16/group) to evaluate the pharmacokinetic parameters of tiotropium and olodaterol in plasma following once-daily inhalation of Tio + Olo fixed-dose combination (Tio + Olo FDC) 2.5/5 μg or 5/5 μg for 3 weeks. The pharmacokinetic parameters of tiotropium in plasma in the 2 dose groups were as follows: C_{max}, 7.15 and 21.8 pg/mL (n = 14 and 13), respectively; t_{max} (median), 0.1 and 0.1 hours (n = 14 and 13), respectively; and $AUC_{0\text{-}tz}$, 11.7 and 25.4 pg·h/mL (n = 13 and 12), respectively. The pharmacokinetic parameters of olodaterol in plasma in the 2 dose groups were as follows: C_{max}, 3.63 and 4.85 pg/mL (n = 15 and 13), respectively; t_{max} (median), 0.217 and 0.183 hours (n = 15 and 13), respectively; and $AUC_{0\text{-}tz}$, 8.72 and 10.4 pg·h/mL (n = 14 and 12), respectively.

(b) Foreign multiple-dose inhalation study (5.3.5.1-15, Study 1237.20 [March 2012 to August 2013])

A randomized, double-blind, 4-period, cross-over study was conducted in patients with COPD (n = 136 to 139/group) using an incomplete block design. The pharmacokinetic parameters of tiotropium and olodaterol in plasma were investigated following 3-week once-daily inhalation of Tio + Olo FDC (2.5/5 μg or 5/5 μg), Tio (2.5 or 5 μg), or Olo (5 μg). The results are as shown in Table 12. Comparisons were made between the Tio + Olo FDC groups and the Tio or Olo alone group. The adjusted geometric mean ratios (GMRs) [90% confidence intervals (CIs)] (Tio + Olo FDC 2.5/5 μg versus Tio 2.5 μg) of C_{max} and $AUC_{0\text{-}tz}$ were 0.98 [0.74, 1.28] and 0.99 [0.56, 1.73], respectively; the adjusted GMRs [90% CIs] (Tio + Olo FDC 5/5 μg versus Tio 5 μg) of C_{max} and $AUC_{0\text{-}tz}$ were 1.17 [0.91, 1.51] and 1.09 [0.71, 1.65], respectively; the adjusted GMRs [90% CIs] (Tio + Olo FDC 2.5/5 μg versus Olo 5 μg) of C_{max} and $AUC_{0\text{-}tz}$ were 1.12 [0.89, 1.41] and 0.98 [0.76, 1.26], respectively; and the adjusted GMRs [90% CIs] (Tio + Olo FDC 5/5 μg versus Olo 5 μg) of C_{max} and $AUC_{0\text{-}tz}$ were 1.32 [1.06, 1.65] and 1.17 [0.94, 1.47], respectively.

Table 12. Pharmacokinetic parameters following multiple inhalation of Tio + Olo FDC, Tio or Olo in patients with COPD

		Tio+Olo FDC 2.5/5 μg (36 subjects)	Tio+Olo FDC 5/5 μg (35 subjects)	Tio 2.5 μg (35 subjects)	Tio 5 μg (35 subjects)	Olo 5 μg (35 subjects)
Tiotropium	C_{max} (pg/mL)	6.15	15.3	6.07	12.5	
	t_{max} (hours)	0.083	0.083	0.117	0.083	
	$AUC_{0\text{-}tz}$ (pg·h/mL)	14.9	47.8	13.6	45.0	
	AUCτ (pg·h/mL)	—	72.9 [a)]	—	66.1 [b)]	
Olodaterol	C_{max} (pg/mL)	3.66	4.22			3.12
	t_{max} (hours)	0.167	0.167			0.167
	$AUC_{0\text{-}tz}$ (pg·h/mL)	34.3	40.6			32.8
	AUCτ (pg·h/mL)	36.8 [c)]	40.6			32.8

Mean values except t_{max} indicating the median value; C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration; AUC, area under the plasma concentration-time curve; —, not calculated. [a)] 19 subjects; [b)] 20 subjects; [c)] 33 subjects.

4.(i).A.(3) Studies in special populations

4.(i).A.(3).1) Pharmacokinetics in patients with hepatic impairment (5.3.3.3-1, Study 1222.20 [July 2009 to December 2009])

An open-label study was conducted in non-Japanese subjects, consisting of 8 subjects with mild hepatic impairment (Child Pugh score of 5 to 6), 8 subjects with moderate hepatic impairment (Child Pugh score of 7 to 9), and 16 healthy adults matched for age, sex, and body weight to the patients with hepatic impairment. The pharmacokinetics of plasma olodaterol following a single inhaled dose of Olo was evaluated in the study. Following a single inhaled dose of 30 μg of Olo in healthy adults, C_{max} (dose-adjusted C_{max}) was 12.4 pg/mL (0.412 pg/mL/μg) (n = 15), t_{max} (median) was 0.217 hours (n = 15), $t_{1/2}$ was 9.47 hours (n = 14), $AUC_{0\text{-}4}$ (dose-adjusted $AUC_{0\text{-}4}$) was 26.2 pg·h/mL (0.874 pg·h/mL/μg) (n = 15), and $AUC_{0\text{-}\infty}$ (dose adjusted $AUC_{0\text{-}\infty}$) was 86.1 pg·h/mL (2.87 pg·h/mL/μg) (n = 14). Following a single inhaled dose of 20 μg of Olo in patients with mild or moderate hepatic impairment, C_{max} (dose-adjusted C_{max}) was 9.75 and 8.28 pg/mL (0.488 and 0.414 pg/mL/μg) (n = 8 and 7), respectively; t_{max} (median) was 0.200 and 0.367 hours (n = 8 and 7), respectively; $t_{1/2}$[10] was 5.38 hours (n = 8), $AUC_{0\text{-}4}$

[10] The values were not calculated for patients with moderate hepatic impairment.

(dose-adjusted AUC_{0-4}) was 17.0 and 18.1 pg·h/mL (0.849 and 0.906 pg·h/mL/μg) (n = 8 and 6), respectively; $AUC_{0-\infty}$ (dose adjusted $AUC_{0-\infty}$)[11] was 39.1 pg·h/mL (1.95 pg·h/mL/μg) (n = 8). The dose-adjusted GMR [90% CI] of patients with mild hepatic impairment to healthy adults was 1.12 [0.84, 1.51] for C_{max} and 0.97 [0.75, 1.25] for AUC_{0-4}, and the dose-adjusted GMR [90% CI] of patients with moderate hepatic impairment to healthy adults was 0.99 [0.73, 1.35] for C_{max} and 1.05 [0.79, 1.40] for AUC_{0-4}, suggesting that there was no increase in exposure in patients with hepatic impairment.

4.(i).A.(3).2) Pharmacokinetics in patients with renal impairment (5.3.3.3-2, Study1222.35 [August 2009 to December 2009])

An open-label study was conducted in non-Japanese subjects, consisting of 8 subjects with severe renal impairment (creatinine clearance <30 mL/min) and 14 healthy adults (creatinine clearance >80 mL/min) matched for age, sex, and body weight to the subjects with hepatic impairment, to evaluate pharmacokinetics following a single dose of 30 μg of Olo The pharmacokinetic parameters of plasma olodaterol in healthy adults and patients with severe renal impairment were as follows: C_{max}, 8.94 and 14.1 pg/mL (n = 13 and 7), respectively; t_{max} (median), 0.233 and 0.383 hours (n = 13 and 7), respectively; $t_{1/2}$,19.3 and 15.2 hours (n = 13 and 7), respectively; AUC_{0-4}, 18.4 and 26.8 pg·h/mL (n = 13 and 7), respectively; $AUC_{0-\infty}$, 98.8 and 106 pg·h/mL (n = 13 and 7), respectively. The GMR [90% CI] of patients with severe renal impairment to healthy adults was 1.37 [0.84, 2.22] for C_{max}, and 1.35 [0.94, 1.95] for AUC_{0-4}.

4.(i).A.(4) Drug-drug interactions

4.(i).A.(4).1) Effects of ketoconazole on Olo (5.3.3.4-1, Study 1222.47 [May 2010 to August 2010])

A foreign open-label study was conducted in healthy adults (n = 32) to investigate pharmacokinetic drug-drug interactions between Olo and ketoconazole, a P-gp inhibitor. In Treatment Period 1, subjects received Olo at an inhaled dose of 10 μg once daily for 8 days. In Treatment Period 2, subjects received Olo at an inhaled dose of 10 μg once daily for 14 days, plus oral ketoconazole at 400 mg once daily for 14 days 1 hour before inhalation of Olo.

The pharmacokinetic parameters of olodaterol in plasma for Olo alone and Olo + ketoconazole were as follows: C_{max}, 3.41 and 5.47 pg/mL (n = 26 and 31), respectively; t_{max} (median),0.250 and 0.333 hours (n = 26 and 31), respectively; AUC_{0-1}, 2.85 and 4.49 pg·h/mL (n = 24 and 31), respectively; and AUC_{0-tz}, 10.4 and 34.4 pg·h/mL (n = 26 and 31), respectively. The GMR [90% CI] of Olo + ketoconazole to Olo alone was 1.66 [1.54, 1.80] for C_{max}, and 1.68 [1.56, 1.82] for AUC_{0-1}(an analysis of variance [ANOVA] was performed using log-transformed data of C_{max} and AUC_{0-1}, with treatment group as a fixed effect, and subject as a random effect). A P-gp inhibitor ketoconazole is also known to inhibit CYP2C8 and CYP2C9, UGT1A1, UGT1A9, and UGT2B7. This suggests that the combination of Olo with a P-gp, CYP, or UGT inhibitor results in an increase in exposure to olodaterol.

[11] The values were not calculated for patients with moderate hepatic impairment.

4.(i).A.(4).2) Effects of fluconazole on Olo (5.3.3.4-2, Study 1222.48 [May 2010 to July 2010])

A foreign open-label study was conducted in healthy adults (n = 35) to investigate pharmacokinetic drug-drug interactions between Olo and fluconazole, a CYP2C9 inhibitor. In Treatment Period 1, subjects received Olo at an inhaled dose of 10 μg once daily for 8 days. In Treatment Period 2, subjects were treated with Olo at inhaled dose of 10 μg once daily for 14 days, plus once-daily oral fluconazole at 800 mg on Day 1 and at 400 mg on Days 2 to 14, 1 hour before inhalation of Olo.

The pharmacokinetic parameters of olodaterol in plasma for Olo alone and Olo + fluconazole were as follows: C_{max}, 5.70 and 6.00 pg/mL (n = 30 and 32), respectively; t_{max} (median), 0.250 and 0.250 hours (n = 30 and 32), respectively; $AUC_{0\text{-}6}$, 20.9 and 22.9 pg·h/mL (n = 24 and 28), respectively; and $AUC_{0\text{-}tz}$, 39.3 and 53.8 pg·h/mL (n = 31 and 32), respectively. The geometric mean ratio [90% CI] of Olo + fluconazole to Olo was 1.09 [1.02, 1.17] for C_{max}, and 1.13 [1.06, 1.21] for $AUC_{0\text{-}6}$ (an ANOVA was performed using log-transformed data of C_{max} and $AUC_{0\text{-}6}$, with treatment group as a fixed effect, and subject as a random effect).

4.(i).A.(5) Pharmacodynamic studies

4.(i).A.(5).1) Foreign thorough QT study of Olo in healthy adults (5.3.4.1-1, Study 1222.8 [June 2007 to October 2007])

A foreign double-blind, randomized, placebo-controlled, 6-way crossover study including an open-label positive control (moxifloxacin) was conducted in healthy adults (n = 24) to investigate the effects of Olo on QT/QTc interval. The treatment periods were separated by a washout period of ≥13 days. Subjects received a single inhaled dose of Olo (10, 20, 30, or 50 μg) or placebo, or a single oral dose of 400 mg of moxifloxacin as an open-label positive control.

The largest differences in QTc interval (QTcI)[12] changes from baseline (adjusted mean values [two-sided 90% CIs]) between the Olo 10, 20, 30, or 50 μg groups and the placebo group were 2.1 [−1.4, 5.5], 6.3 [2.3, 10.2], 7.7 [3.7, 11.8], and 8.6 [4.7, 12.6] msec, respectively (based on mixed-effect models with repeated measures, with the treatment sequence, treatment period, treatment group, treatment group-time interaction, treatment period-time interaction, and treatment period baseline value as fixed effects, subjects nested within sequence as a random effect, and time as a repeating effect). The upper limits of the two-sided 90% CI was greater than 10 msec at dose levels of ≥20 μg of Olo, and dose-dependent QTcI prolongation was observed at >10 msec. The largest difference in QTcI changes from baseline between the moxifloxacin and placebo groups (adjusted mean values [two-sided 90% CIs]) was 15.0 [11.7, 18.3] (2 hours post-dose). C_{max} of plasma olodaterol following a single inhaled dose of 10, 20, 30, or 50 μg of Olo was 3.56, 5.90, 11.0, and 18.6 pg/mL (n = 17, 24, 22, and 24), respectively. $AUC_{0\text{-}tz}$ at 10 μg was not calculated, and $AUC_{0\text{-}tz}$ at 20, 30, and 50 μg of Olo was 17.7, 35.5, and 60.8 pg·h/mL (n = 23, 22, and 24), respectively.

[12] A QT interval corrected for each subject's heart rate.

The applicant explained that a through QT (TQT) study was unnecessary for Tio + Olo FDC for the following reasons: in a foreign TQT study of Tio (Study 205.302),[13] no QT prolongation was observed following the administration of 18 or 54 μg of Tio; and Study 1237.20, in which drug-drug interactions between Tio and Olo were investigated, suggested that drug-drug interactions between Tio and Olo are unlikely to occur.

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

4.(i).B.(1) Ethnic differences in pharmacokinetics of Olo

The applicant's explanation on ethnic differences in the pharmacokinetics of Olo:

The C_{max} and AUC_{0-1} of Olo (dose-adjusted geometric mean of values obtained in all treatment groups) were 0.661 pg/mL/μg and 0.554 pg·h/mL/μg, respectively, in healthy Japanese adults receiving Olo at inhaled doses of 5 to 20 μg once daily for 14 days, and 0.448 pg/mL/μg and 0.367 pg·h/mL/μg, respectively, in healthy non-Japanese adults receiving Olo at inhaled doses of 2.5 to 30 μg once daily for 14 days. The exposure to Olo was thus shown to be about 50% higher in healthy Japanese adults than in healthy non-Japanese adults. The C_{max} and AUC_{0-1} of Olo (dose-adjusted geometric mean of values obtained in all treatment groups) were 1.30 pg/mL/μg and 1.07 pg·h/mL/μg, respectively, in Japanese patients with COPD receiving Olo at inhaled doses of 5 or 10 μg once daily for 4 weeks, and 0.745 pg/mL/μg and 0.587 pg·h/mL/μg, respectively, in non-Japanese patients with COPD receiving Olo at inhaled doses of 2 to 20 μg once daily for 4 weeks. As seen in healthy adults, the exposure to Olo was shown to be approximately 70% to 80% higher in Japanese patients with COPD than in non-Japanese patients with COPD. An investigation of the characteristics of subjects enrolled in the clinical studies revealed a difference in body weight between Japanese and non-Japanese subjects. Therefore Olo exposure in Japanese and non-Japanese subjects was analyzed after adjustment for dose and body weight. The Japanese/non-Japanese ratios of geometric mean C_{max} and AUC_{0-1} were 1.09 and 1.12, respectively, in healthy adults, and 1.27 and 1.34, respectively, in patients with COPD. The ethnic differences in the pharmacokinetics of Olo was thus basically accountable by the difference in body weight for healthy adults, but the results also suggested that other factors other than body weight may have contributed to the ethnic differences observed in patients with COPD. However, given that the ≤10 μg groups in phase II studies (Japanese Study 1222.22 and foreign Study 1222.5) showed no ethnic differences in pharmacodynamic parameters such as blood potassium levels, heart rate, QT interval, and blood pressure, the ethnic differences in the pharmacokinetics of Olo are considered to be of no clinical significance.

PMDA's view:

Although contributory factors to the ethnic differences in the pharmacokinetics of Olo in patients with COPD other than body weight are unknown, the applicant explained that the observed ethnic differences

[13] A double-blind, randomized, placebo-controlled, 3-way crossover study including an open label positive control, moxifloxacin (5.3.4.1-2), conducted in healthy adults (n = 56). In the study, subjects received once-daily inhaled doses of Tio (18 or 54 μg) or placebo with the HandiHaler device (HH) for 12 days (Tio HH 18 μg is equivalent to Tio 5μg with Respimat), or a single oral dose of 400 mg of moxifloxacin as an open-label positive control.

are of no clinical significance. The applicant's explanation is acceptable in this regard. This issue would not affect the use of foreign clinical data from the pharmacokinetic point of view.

4.(i).B.(2) Effects of hepatic and renal impairment

The pharmacokinetic study in patients with severe renal impairment (Study 1222.35) showed increased exposure to Olo. Because Tio is a renally excreted agent, PMDA asked the applicant to assess the effect of renal impairment on the pharmacokinetics of Tio + Olo FDC, based on the safety data from the clinical studies and other relevant information.

The applicant's explanation:

In Study 1222.35, adverse events occurred in 13.6% (3 of 22 subjects) of healthy adults, but were all mild or moderate in severity and the outcome was "recovered." No adverse events occurred in patients with severe renal impairment. A pooled analysis of foreign phase III studies of Olo alone (Studies 1222.11, 1222.12, 1222.13, and 1222.14) yielded the following incidences of adverse events by severity of renal impairment: 71.7% (1013 of 1413 subjects) in patients with normal renal function, 70.2% (937 of 1334 subjects) in those with mild renal impairment, 72.8% (235 of 323 subjects) in those with moderate renal impairment, and 71.4% (15 of 21 subjects) in those with severe renal impairment. The severity of renal impairment had no impact on the incidence of adverse events. A pooled analysis of multiregional phase III studies of Tio + Olo FDC (Studies 1237.5 and 1237.6) yielded the following incidences of adverse events by severity of renal impairment: 72.4% (1543 of 2131 subjects) in patients with normal renal function, 74.4% (1644 of 2210 subjects) in those with mild renal impairment, 80.0% (569 of 711 subjects) in those with moderate renal impairment, and 91.7% (11 of 12 subjects) in those with severe renal impairment. Although the incidence of adverse events tended to be higher in patients with moderate to severe renal impairment than in those with normal renal function or mild renal impairment, the incidences of adverse events were similar between groups receiving Tio + Olo FDC and groups receiving Tio or Olo alone. Although the small number of patients with severe renal impairment enrolled in the studies precluded rigorous comparisons, the safety profile of Tio + Olo FDC in patients with renal impairment was not differ significantly regardless of the severity of renal impairment. Therefore, dose adjustment of Tio + Olo FDC is not necessary in patients with renal impairment.

PMDA asked the applicant to discuss reasons why plasma olodaterol concentrations did not increase in patients with hepatic impairment in Study 1222.20 conducted in patients with hepatic impairment, based on the metabolic and excretion pathways of Olo.

The applicant's explanation:

As the result of a comparison of the dose-adjusted $AUC_{0-\infty}$ of Olo in healthy adults between single-dose inhalation of 30 to 70 μg (Study 1222.1) and single-dose intravenous infusion of 20 μg (Study 1222.9), the absolute bioavailability of inhaled Olo was estimated to be approximately 30%. The urinary excretion rate of unchanged Olo was 5% to 7% in healthy adults receiving inhaled Olo at 2.5 to 30 μg

once daily for 14 days (Study 1222.2). These findings indicate that Olo is primarily metabolized in the liver.

Patients with hepatic impairment are generally likely to have increased exposure to hepatically metabolized drugs due to decreased hepatic clearance resulting from reduced hepatic blood flow, increased protein binding, reduced activity of metabolic enzymes in the liver, etc. However, the hepatic clearance of olodaterol, with its hepatic extraction ratio of 0.25 to 0.44,[14] is unlikely to be affected by hepatic blood flow. Study 1222.20, conducted in patients with hepatic impairment, did not show changes in the protein binding of olodaterol in proportion to the severity of hepatic impairment. The metabolic activities of CYP2C9 and UGT, enzymes that is involved in metabolism of olodaterol, are reported to be unaffected by hepatic impairment (Villeneuve JP et al. *Curr Drug Metab.* 5:273-282,2004, George J et al. *Hepatology.* 21:120-128, 1995, Pacifici GM et al. *Br J Clin Pharmacol.* 30:427-435,1990). These findings indicate the possibility that hepatic clearance of olodaterol is not characteristically affected by hepatic impairment, and this would explain why the pharmacokinetics of Olo was unaffected by hepatic impairment in Study 1222.20. Based on the mentioned characteristics and the results of Study 1222.20, the applicant considers that no dose adjustment is required for use of Olo in patients with hepatic impairment.

PMDA's view:
The applicant's explanation that no dose adjustment is required for use of Olo in patients with mild to moderate hepatic or renal impairment is acceptable. Nevertheless, given the limited number of subjects with hepatic or renal impairment who received Tio + Olo FDC in the clinical studies, the safety assessment of Tio + Olo FDC in patients with hepatic or renal impairment should be continued through post-marketing surveillance, etc.

4.(i).B.(3) Drug interactions

In a drug-drug interaction study of Olo and ketoconazole (Study 1222.47), the increase in exposure to Olo was about 1.7-fold In a foreign phase II study in patients with COPD (Study 1222.5), plasma potassium concentrations did not decrease in groups receiving Olo at ≤10 μg, and the incidences of adverse events were similar among the treatment groups. Based on these findings, the applicant explained that precautionary advice about drug interactions with P-gp, CYP, or UGT inhibitors would not be necessary.

PMDA, while accepting the applicant's explanation, considers that the safety of Tio + Olo FDC in combination with a P-gp, CYP, or UGT inhibitor in clinical practice should be further investigated through post-marketing surveillance, given limited safety data on drug-drug interactions from the clinical studies.

[14] Calculated based on: hepatic clearance / (hepatic blood flow × blood to plasma concentration ratio).

4.(ii) Summary of clinical efficacy and safety

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

Submitted efficacy and safety evaluation data for Olo include the results from a Japanese phase II study in patients with COPD (5.3.5.1-4, Study 1222.22) designed as a bridging study, a foreign phase II study in patients with COPD (5.3.5.1-3, Study 1222.5) for which the Japanese bridging study was conducted, a foreign late phase II study in patients with COPD to evaluate efficacy and safety of Olo alone (5.3.5.4-4, Study 1222.26), and foreign phase III studies (5.3.5.1-5, Study 1222.11; 5.3.5.1-6, Study 1222.12; 5.3.5.1-7, Study 1222.13; 5.3.5.1-8, Study 1222.14). Submitted efficacy and safety evaluation data for Tio + Olo FDC include the results from multiregional phase III studies conducted in patients with COPD in several countries including Japan to evaluate the efficacy and safety of Tio + Olo FDC (5.3.5.1-12, Study 1237.5; 5.3.5.1-13, Study 1237.6) and Japanese long-term treatment study in patients with COPD (5.3.5.1-14, Study 1237.22).

The doses of agents used are expressed as their free bases, unless otherwise specified.

4.(ii).A.(1) Olo monotherapy

4.(ii).A.(1).1) Japanese phase II study (5.3.5.1-4, Study 1222.22 [January 2009 to March 2010]) (Japanese bridging study)

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in patients with COPD[15] (target sample size, 320 [80 subjects/group]) to evaluate the efficacy and safety of Olo.

Patients received Olo at an inhaled dose of 2, 5, or 10 μg, or placebo once daily for 4 weeks.

The full analysis set (FAS) consisted of all randomized 328 subjects (84 in the Olo 2 μg group, 79 in the Olo 5 μg group, 86 in the Olo 10 μg group, and 79 subjects in the placebo group). The FAS was used for the safety and efficacy analyses. The study drug was discontinued in 2.4% (2 of 84) of subjects in the Olo 2 μg group, 3.8% (3 of 79) of subjects in the Olo 5 μg group, 5.8% (5 of 86) of subjects in the Olo 10 μg group, and 6.3% (5 of 79) of subjects in the placebo group.

Table 13 shows changes from baseline in the trough value of forced expiratory volume in 1 second (FEV_1)[16] after 4 weeks of treatment, which is the primary efficacy endpoint. The differences from placebo were statistically significant in all Olo treatment groups.

[15] Patients who had a diagnosis of COPD with relatively stable symptoms and who met the following criteria: (1) post-bronchodilator forced expiratory volume in 1 second (FEV_1) of ≥30% of predicted value (based on the prediction equation reported by the Clinical Pulmonary Functions Committee of the Japanese Respiratory Society) and <80% of predicted value (GOLD II to III) at screening visit; (2) post-bronchodilator FEV_1/forced vital capacity (FVC) <70% at screening visit; (3) aged ≥40 years; and (4) a current or former smoker with a smoking history of >10 pack-years ([number of cigarettes smoked/day/20] × number of years of smoking).

[16] The baseline was defined as the mean of FEV_1 values measured 1 hour before, and 10 minutes before the first inhalation of the study drug; and trough FEV_1 was defined as the mean of FEV_1 values measured 1 hour before, and 10 minutes before the inhalation of the study drug on the next day.

Table 13. Changes from baseline in trough FEV_1 (L) after 4 weeks of treatment (FAS, WOCF)

	Olo 2 μg	Olo 5 μg	Olo 10 μg	Placebo
Baseline	1.215 ± 0.509 (84)	1.171 ± 0.420 (79)	1.178 ± 0.431 (86)	1.177 ± 0.378 (79)
After 4 weeks of treatment	1.275 ± 0.504 (84)	1.273 ± 0.444 (79)	1.281 ± 0.436 (86)	1.147 ± 0.361 (79)
Change	0.059 ± 0.145 (84)	0.102 ± 0.121 (79)	0.103 ± 0.146 (86)	−0.030 ± 0.117 (79)
Difference from placebo [95% CI][a], p-value[a), b)]	0.091 [0.051, 0.131] p<0.0001	0.132 [0.091, 0.172] p<0.0001	0.132 [0.092, 0.172] p<0.0001	

Mean ± standard deviation (number of subjects)
[a)] Based on the linear mixed effect model, with treatment group and baseline as fixed effects, and center as a random effect.
[b)] The p-values were adjusted for multiplicity by a step-down multiple comparison procedure in the specified hierarchical order, from highest to lower dose.

The incidence of adverse events was 33.3% (28 of 84 subjects) in the Olo 2 μg group, 31.6% (25 of 79 subjects) in the Olo 5 μg group, 41.9% (36 of 86 subjects) in the Olo 10 μg group, and 35.4% (28 of 79 subjects) in the placebo group. Table 14 shows the adverse events with an incidence of ≥2% in any group. No deaths occurred.

Serious adverse events occurred in 3 of 84 subjects in the Olo 2 μg group (3.6%; angina pectoris, cataract, and COPD in 1 subject each), 1 of 79 subjects in the Olo 5 μg group (1.3%; COPD), 3 of 86 subjects in the Olo 10 μg group (3.5%; herpes zoster, hand fracture, and Meniere's disease in 1 subject each), and 2 of 79 subjects in the placebo group (2.5%; pneumothorax and influenza/COPD in 1 subject each). A causal relationship to the study drug was ruled out for all the serious adverse events.

Adverse events leading to the discontinuation of treatment occurred in 1 of 84 subjects (1.2%) in the Olo 2 μg group, 1 of 79 subjects (1.3%) in the Olo 5 μg group, 3 of 86 subjects (3.5%) in the Olo 10 μg group, and 4 of 79 subjects (5.1%) in the placebo group.

Adverse events for which a causal relationship to the study drug could not be ruled out (adverse reactions) occurred in 2 of 84 subjects (2.4%) in the Olo 2 μg group, 5 of 79 subjects (6.3%) in the Olo 5 μg group, 6 of 86 subjects (7.0%) in the Olo 10 μg group, and 3 of 79 subjects (3.8%) in the placebo group.

Table 14. Adverse events with an incidence of ≥2% in any group (safety analysis population)

Event	Olo 2 μg (84 subjects)	Olo 5 μg (79 subjects)	Olo 10 μg (86 subjects)	Placebo (79 subjects)
Nasopharyngitis	9 (10.7)	3 (3.8)	5 (5.8)	3 (3.8)
COPD	3 (3.6)	3 (3.8)	1 (1.2)	3 (3.8)
Pneumonia	1 (1.2)	2 (2.5)	0	0
Diarrhoea	1 (1.2)	2 (2.5)	1 (1.2)	0
Dysphonia	0	2 (2.5)	0	1 (1.3)
Syncope	0	2 (2.5)	0	0
Nausea	0	1 (1.3)	2 (2.3)	1 (1.3)
Eosinophilia	2 (2.4)	0	0	0
Dizziness	0	0	2 (2.3)	1 (1.3)
Cataract	2 (2.4)	0	0	0
Myalgia	0	0	0	4 (5.1)

Number of subjects (%)

4.(ii).A.(1).2) Foreign phase II study (5.3.5.1-3, Study 1222.5 [March 2007 to January 2008]) (the study for which the Japanese bridging study was conducted)

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in patients with COPD[17] (target sample size, 400 [80 subjects/group]) to evaluate the efficacy and safety of Olo.

In this study, patients received an inhaled dose of 2, 5, 10, or 20 μg of Olo, or placebo once daily for 4 weeks.

The FAS consisted of all randomized 405 subjects (81 in the Olo 2 μg group, 80 in the Olo 5 μg group, 86 in the Olo 10 μg group, 79 in the Olo 20 μg group, and 79 subjects in the placebo group). The FAS was used for the safety and efficacy analyses. The study drug was discontinued in 1.2% (1 of 81) of subjects in the Olo 2 group, 8.8% (7 of 80) of subjects in the Olo 5 group, 1.2% (1 of 86) of subjects in the Olo 10 group, 3.8% (3 of 79) of subjects in the Olo 20 group, and 6.3% (5 of 79) of subjects in the placebo group.

Table 15 shows changes from baseline in the trough value[18] of FEV_1 after 4 weeks of treatment, which is the primary efficacy endpoint. The differences from placebo were statistically significant in all Olo treatment groups.

Table 15. Changes from baseline in trough FEV_1 (L) after 4 weeks of treatment (FAS, WOCF)

	Olo 2 μg	Olo 5 μg	Olo 10 μg	Olo 20 μg	Placebo
Baseline	1.228 ± 0.459 (81)	1.294 ± 0.484 (80)	1.281 ± 0.511 (86)	1.236 ± 0.503 (79)	1.225 ± 0.437 (79)
After 4 weeks of treatment	1.263 ± 0.460 (81)	1.366 ± 0.513 (80)	1.381 ± 0.569 (86)	1.343 ± 0.527 (79)	1.200 ± 0.445 (79)
Change	0.035 ± 0.158 (81)	0.072 ± 0.188 (80)	0.100 ± 0.229 (86)	0.107 ± 0.161 (79)	−0.025 ± 0.139 (79)
Difference from placebo [95% CI][a], p-value[a), b)]	0.061 [0.008, 0.113] p=0.0233	0.097 [0.044, 0.149] p=0.0003	0.123 [0.072, 0.175] p<0.0001	0.132 [0.080, 0.185] p<0.0001	

Mean ± standard deviation (number of subjects)
a) Based on the linear mixed effect model, with treatment group and baseline as fixed effects, and center as a random effect.
b) The p-values were adjusted for multiplicity by a step-down multiple comparison procedure in the specified hierarchical order, from highest to lowest dose.

The incidence of adverse events was 37.0% (30 of 81 subjects) in the Olo 2 μg group, 41.3% (33 of 80 subjects) in the Olo 5 μg group, 30.2% (26 of 86 subjects) in the Olo 10 μg group, 38.0% (30 of 79 subjects) in the Olo 20μg group, and 36.7% (29 of 79 subjects) in the placebo group. Table 16 shows the adverse events with an incidence of ≥2% in any group. No deaths occurred.

Serious adverse events occurred in 2 of 81 subjects in the Olo 2 μg group (2.5%; lung neoplasm malignant, and road traffic accident/pleural effusion in 1 subject each), 2 of 80 subjects in the Olo 5 μg

[17] Patients who had a diagnosis of COPD with relatively stable symptoms and who met the following criteria: (1) post-bronchodilator FEV_1 of ≥30% of predicted value and <80% of predicted value (GOLD II to III) at screening visit; (2) post-bronchodilator FEV_1/FVC <70% at screening visit; (3) aged ≥40 years; and (4) is a current or former smoker with a smoking history of >10 pack-years.

[18] The baseline was defined as the mean of FEV_1 values measured 1 hour before, and 10 minutes before the first inhalation of the study drug; and trough FEV_1 was defined as the mean of FEV_1 values measured 1 hour before, and 10 minutes before the inhalation of the study drug on the next day.

group (2.5%; Diverticulitis and fall/hip fracture in 1 subject each), 2 of 86 subjects in the Olo 10 μg group (2.3%; bronchitis/COPD and humerus fracture in 1 subject each), 2 of 79 subjects in the Olo 20 μg group (2.5%; COPD/upper respiratory tract infection and upper gastrointestinal haemorrhage in 1 subject each). A causal relationship to the study drug was ruled out for all the serious adverse events.

Adverse events leading to the discontinuation of treatment in 1 of 81 subjects (1.2%) in the Olo 2 μg group, 5 of 80 subjects (6.3%) in the Olo 5 μg group, 2 of 79 subjects (2.5%) in the Olo 20 μg group, and 1 of 79 subjects (1.3%) in the placebo group.

Adverse reactions occurred in 4 of 81 subjects (4.9%) in the Olo 2 μg group, 3 of 80 subjects (3.8%) in the Olo 5 μg group, 2 of 86 subjects (2.3%) in the Olo 10 μg group, 1 of 79 subjects (1.3%) in the Olo 20 μg group, 5 of 79 subjects (6.3%) in the placebo group.

Table 16. Adverse events with an incidence of ≥2% in any group (safety analysis population)

Event	Olo 2 μg (81 subjects)	Olo 5 μg (80 subjects)	Olo 10 μg (86 subjects)	Olo 20 μg (79 subjects)	Placebo (79 subjects)
Nasopharyngitis	2 (2.5)	6 (7.5)	4 (4.7)	2 (2.5)	1 (1.3)
Cough	4 (4.9)	6 (7.5)	2 (2.3)	2 (2.5)	2 (2.5)
Bronchitis	1 (1.2)	3 (3.8)	2 (2.3)	0	0
COPD	3 (3.7)	2 (2.5)	4 (4.7)	2 (2.5)	2 (2.5)
Upper respiratory tract infection	0	2 (2.5)	1 (1.2)	4 (5.1)	1 (1.3)
Dyspnoea	3 (3.7)	2 (2.5)	0	3 (3.8)	6 (7.6)
Fall	0	2 (2.5)	1 (1.2)	0	0
Urinary tract infection	1 (1.2)	2 (2.5)	0	0	0
Headache	3 (3.7)	1 (1.3)	3 (3.5)	1 (1.3)	4 (5.1)
Dizziness	2 (2.5)	1 (1.3)	2 (2.3)	0	1 (1.3)
Electrocardiogram QT prolonged	1 (1.2)	1 (1.3)	0	2 (2.5)	0
Productive cough	1 (1.2)	1 (1.3)	2 (2.3)	0	0
Pharyngolaryngeal pain	0	1 (1.3)	1 (1.2)	2 (2.5)	1 (1.3)
Diarrhoea	2 (2.5)	1 (1.3)	1 (1.2)	0	1 (1.3)
Muscle spasms	1 (1.2)	1 (1.3)	0	2 (2.5)	0
Arthralgia	2 (2.5)	1 (1.3)	0	0	0
Dry mouth	2 (2.5)	0	1 (1.2)	0	0
Pain in extremity	2 (2.5)	0	1 (1.2)	0	0
Respiratory tract congestion	2 (2.5)	0	0	1 (1.3)	0
Vomiting	2 (2.5)	0	0	0	0
Bursitis	2 (2.5)	0	0	0	1 (1.3)

Number of subjects (%)

4.(ii).A.(1).3) Foreign phase III study (5.3.5.1-5, Study 1222.11 [November 2008 to September 2010])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in patients with COPD[19] (target sample size, 600 [200 subjects/group]) to evaluate the efficacy and safety of Olo.

In this study, subjects received an inhaled dose of 5 or 10 μg of Olo, or placebo once daily for 48 weeks.

Of 625 subjects randomized and stratified by use or non-use of Tio at enrollment, 624 subjects who received the study drug were included in the safety analysis population (208 subjects in the Olo 5 μg

[19] Patients who had a diagnosis of COPD with relatively stable symptoms and who met the following criteria: (1) post-bronchodilator FEV_1 of <80% of predicted value at screening visit; (2) post-bronchodilator FEV_1/FVC <70% at screening visit; (3) aged ≥40 years; and (4) a current or former smoker with a smoking history of >10 pack-years.

group, 207 subjects in the Olo 5 10 μg group, and 209 subjects in the placebo group). Of the 624 subjects, 4 subjects[20] were excluded from the analysis, and the remaining 620 subjects (206 subjects each in the Olo 5 and 10 μg groups and 208 subjects in the group) were included in the FAS and the efficacy analysis population. The study drug was discontinued in 16.8% (35 of 208) of subjects in the Olo 5μg group, 16.9% (35 of 207) of subjects in the Olo 10 μg group, and 23.9% (50 of 209) of subjects in the placebo group.

Table 17 shows the changes from baseline in the $FEV_1AUC_{0\text{-}3}$[21] and trough FEV_1 values[22] after 12 weeks of treatment, which are co-primary efficacy endpoints. For both endpoints, the differences from placebo were statistically significant in both Olo 5 and 10 μg groups, demonstrating the superiority of Olo 5 and 10 μg over placebo.

Table 17. Changes from baseline in the $FEV_1AUC_{0\text{-}3}$ and trough FEV_1 values (L) after 12 weeks of treatment (FAS, WOCF)

	Olo 5 μg	Olo 10 μg	Placebo
$FEV_1AUC_{0\text{-}3}$			
Baseline	1.123 ± 0.459 (206)	1.156 ± 0.471 (206)	1.138 ± 0.468 (208)
After 12 weeks of treatment	1.287 ± 0.491 (192)	1.344 ± 0.513 (192)	1.147 ± 0.473 (188)
Change	0.167 ± 0.185 (192)	0.171 ± 0.199 (192)	−0.002 ± 0.169 (188)
Difference from placebo [95% CI],[a] p-value[a), b)]	0.164 [0.120, 0.209] p<0.0001	0.155 [0.111, 0.199] p<0.0001	
Trough FEV_1			
Baseline	1.123 ± 0.459 (206)	1.156 ± 0.471 (206)	1.138 ± 0.468 (208)
After 12 weeks of treatment	1.170 ± 0.478 (191)	1.229 ± 0.490 (192)	1.110 ± 0.456 (188)
Change	0.051 ± 0.169 (191)	0.057 ± 0.180 (192)	−0.039 ± 0.156 (188)
Difference from placebo [95% CI],[a] p-value[a), b)]	0.084 [0.040, 0.129] p=0.0002	0.080 [0.037, 0.124] p=0.0003	

Mean ± standard deviation (number of subjects)

a) The analysis was based on a mixed effect model with repeated measures (MMRM), with a spatial power covariance structure for within patient variation. This model included treatment group, co-administration of Tio, treatment day, treatment group-by-treatment day interaction, treatment group-by-Tio co-administration interaction, Tio co-administration-by-treatment day interaction, interaction among treatment group, Tio co-administration, and treatment day, baseline, baseline-by-treatment day interaction as fixed-effects; and subject as a random effect.

b) The p-values were adjusted for multiplicity by a step-down multiple comparison procedure in the prespecified order of comparisons in $FEV_1AUC_{0\text{-}3}$ and trough FEV_1 values after 12 weeks of treatment, first between the Olo 10 μg and placebo groups and second between the Olo 5 μg and placebo groups.

The incidence of adverse events was 72.6% (151 of 208 subjects) in the Olo 5 μg group, 70.5% (146 of 207 subjects) in the Olo 10 μg group, and 74.2% (155 of 209 subjects) in the placebo group. Table 18 shows the adverse events with an incidence of ≥2% in any group.

A total of 5 deaths occurred in the Olo 5 μg group (lung infection, acute respiratory failure, respiratory failure, pneumonia, [23] and multi-organ failure/diabetes mellitus/hypoproteinaemia/cardiac failure/COPD/respiratory failure[23] in 1 subject each), 2 in the Olo 10 μg group (small cell lung cancer and small intestinal obstruction[23] in 1 subject each), and 3 in the placebo group (aortic aneurysm, multi-

[20] Subjects who received the study drug but had no baseline or post-dose data for primary endpoint.

[21] Values of the area under the FEV_1-time curve from 0 to 3 hours after administration calculated by the trapezoidal rule and adjusted to area per unit time.

[22] Baseline was the mean of FEV_1 values measured 1 hour before and 10 minutes before the first inhalation of the study drug; and trough FEV_1 was the mean of FEV_1 values measured 1 hour before and 10 minutes before the inhalation of the study drug on the next day.

[23] The adverse event was observed after the end of the study drug treatment period, or after the completion of the study.

organ failure,[23] and unknown[23] in 1 subject each). A causal relationship to the study drug was ruled out for all cases of death.

Serious adverse events occurred in 39 of 208 subjects (18.8%) in the Olo 5 μg group, 43 of 207 subjects (20.8%) in the Olo 10 μg group, and 34 of 209 subjects (16.3%) in the placebo group. One of the common serious adverse events was COPD, which occurred in 10 of 208 subjects (4.8%) in the Olo 5 μg group, 18 of 207 subjects (8.7%) in the Olo 10 μg group, 14 of 209 subjects (6.7%) in the placebo group. A causal relationship to the study drug could not be ruled out for atrial fibrillation in 1 subject in the Olo 10 μg group.[24] The subject died due to small cell lung cancer, for which a causal relationship to the study drug was ruled out.

Adverse events leading to the discontinuation of treatment occurred in 15 of 208 subjects (7.2%) in the Olo 5 μg group, 16 of 207 subjects (7.7%) in the Olo 10 μg group, and 20 of 209 subjects (9.6%) in the placebo group.

Adverse reactions occurred in 16 of 208 subjects (7.7%) in the Olo 5 μg group, 10 of 207 subjects (4.8%) in the Olo 10 μg group, and 19 of 209 subjects (9.1%) in the placebo group.

Table 18. Adverse events with an incidence of ≥2% in any group (safety analysis population)

Event	Olo 5 μg (208 subjects)	Olo 10 μg (207 subjects)	Placebo (209 subjects)
COPD	50 (24.0)	67 (32.4)	71 (34.0)
Upper respiratory tract infection	21 (10.1)	13 (6.3)	15 (7.2)
Nasopharyngitis	21 (10.1)	13 (6.3)	13 (6.2)
Cough	14 (6.7)	7 (3.4)	8 (3.8)
Bronchitis	11 (5.3)	6 (2.9)	8 (3.8)
Dyspnoea	10 (4.8)	4 (1.9)	11 (5.3)
Urinary tract infection	9 (4.3)	5 (2.4)	4 (1.9)
Diarrhoea	9 (4.3)	4 (1.9)	7 (3.3)
Dizziness	7 (3.4)	4 (1.9)	4 (1.9)
Arthralgia	7 (3.4)	1 (0.5)	2 (1.0)
Pharyngitis	6 (2.9)	1 (0.5)	0
Sputum increased	6 (2.9)	5 (2.4)	3 (1.4)
Benign prostatic hyperplasia	6 (2.9)	2 (1.0)	2 (1.0)
Nasal congestion	5 (2.4)	0	0
Nausea	5 (2.4)	7 (3.4)	4 (1.9)
Lower respiratory tract infection	5 (2.4)	0	3 (1.4)
Fall	5 (2.4)	2 (1.0)	2 (1.0)
Back pain	4 (1.9)	7 (3.4)	4 (1.9)
Pneumonia	3 (1.4)	3 (1.4)	6 (2.9)
Hypertension	3 (1.4)	8 (3.9)	12 (5.7)
Constipation	3 (1.4)	6 (2.9)	7 (3.3)
Oedema peripheral	3 (1.4)	5 (2.4)	0
Chest pain	2 (1.0)	3 (1.4)	6 (2.9)
Sinusitis	1 (0.5)	7 (3.4)	8 (3.8)
Insomnia	1 (0.5)	6 (2.9)	6 (2.9)
Ecchymosis	1 (0.5)	5 (2.4)	3 (1.4)
Cataract	0	2 (1.0)	6 (2.9)

Number of subjects (%)

[24] Four months later, atrial fibrillation developed. The subject had underlying lipid metabolism disorder and peripheral vascular disease, and the sponsor concluded that atrial fibrillation was attributable to the underlying conditions.

4.(ii).A.(1).4) Foreign phase III study (5.3.5.1-6, Study 1222.12 [February 2009 to September 2010])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in patients with COPD[19] (target sample size, 600 [200 subjects/group]) to evaluate the efficacy and safety of Olo.

This study was conducted using a design identical to that of Study 1222.11, a foreign phase III study conducted in patients with COPD.

Of 644 subjects who were randomized, 642 subjects who received the study drug were included in the safety analysis population (209 in the Olo 5 μg group, 217 in the Olo 10 μg group, and 216 subjects in the placebo group). Of the 642 subjects, 5 subjects[20] were excluded from the analysis, and the remaining 637 subjects (207 in the Olo 5 μg group, 215 in the Olo 10 μg group, and 215 subjects in the placebo group) were included in the FAS and the efficacy analysis population. The study drug was discontinued in 11.5% (24 of 209) of subjects in the Olo 5 μg group, 16.6% (36 of 217) of subjects in the Olo 10 μg group, and 19.0% (41 of 216) of subjects in the placebo group.

Table 19 shows the changes from baseline in the FEV_1AUC_{0-3} and trough FEV_1 values after 12 weeks of treatment, which are co-primary efficacy endpoints. The differences from placebo were statistically significant in both Olo 5 and 10 μg groups for FEV_1AUC_{0-3}, but were not significant for trough FEV_1 values.

Table 19. Changes from baseline in the FEV_1AUC_{0-3} and trough FEV_1 values (L) after 12 weeks of treatment (FAS, WOCF)

	Olo 5 μg	Olo 10 μg	Placebo
FEV_1AUC_{0-3}			
Baseline	1.163 ± 0.465 (207)	1.134 ± 0.505 (215)	1.157 ± 0.526 (215)
After 12 weeks of treatment	1.328 ± 0.516 (196)	1.293 ± 0.545 (201)	1.173 ± 0.525 (197)
Change	0.158 ± 0.204 (196)	0.151 ± 0.170 (201)	0.008 ± 0.197 (197)
Difference from placebo [95% CI],[a)] p-value[a), b)]	0.134 [0.090, 0.177] p<0.0001	0.130 [0.087, 0.172] p<0.0001	
Trough FEV_1			
Baseline	1.163 ± 0.465 (207)	1.134 ± 0.505 (215)	1.157 ± 0.526 (215)
After 12 weeks of treatment	1.213 ± 0.493 (196)	1.185 ± 0.530 (200)	1.157 ± 0.515 (194)
Change	0.043 ± 0.180 (196)	0.045 ± 0.155 (200)	−0.002 ± 0.200 (194)
Difference from placebo [95% CI],[a)] p-value[a), b)]	0.033 [−0.013, 0.080]	0.045 [−0.001, 0.090] p=0.0563	

Mean ± standard deviation (number of subjects)
[a)] See note a) of Table 17 for the models
[b)] See note b) of Table 17 for multiplicity

The incidence of adverse events was 67.9% (142 of 209 subjects) in the Olo 5 μg group, 75.1% (163 of 217 subjects) in the Olo 10 μg group, and 67.6% (146 of 216 subjects) in the placebo group. Table 20 shows the adverse events with an incidence of ≥2% in any group.

One death occurred in the Olo 5 μg group (death[25]), 6 in the Olo 10 μg group (respiratory failure, pneumonia legionella, small cell lung cancer, sudden cardiac death, respiratory failure, [25] and renal impairment[25] in 1 subject each), 3 in the placebo group (pneumonia, pneumonitis/ obstructive airways

[25] The adverse event was observed after the end of the study drug treatment period, or after the completion of the study.

disorder/alveolar aeration excessive,[25] death[25] in 1 subject each). A causal relationship to the study drug was ruled out for all deaths.

Serious adverse events occurred in 32 of 209 subjects (15.3%) in the Olo 5 μg group, 37 of 217 subjects (17.1%) in the Olo 10 μg group, and 32 of 216 subjects (14.8%) in the placebo group. Common serious adverse events include COPD, which occurred in 7 of 209 subjects (3.3%) in the Olo 5 μg group, 12 of 217 subjects (5.5%) in the Olo 10 μg group, and 12 of 216 subjects (5.6%) in the placebo group; and pneumonia, which occurred in 3 of 209 subjects (1.4%) in the Olo 5 μg group, 5 of 217 subjects (2.3%) in the Olo 10 μg group, and 4 of 216 subjects (1.9%) in the placebo group. A causal relationship to the study drug could not be ruled out for the events experienced by 2 subjects in the Olo 5 μg group (ventricular tachycardia and chest pain in 1 subject each), 1 subject in the Olo 10 μg group (respiratory failure), and 2 subjects in the placebo group (staphylococcal sepsis and atrial fibrillation in 1 subject each).

Adverse events leading to the discontinuation of treatment occurred in 9 of 209 subjects (4.3%) in the Olo 5 μg group, 19 of 217 subjects (8.8%) in the Olo 10 μg group, 19 of 216 subjects (8.8%) in the placebo group.

Adverse reactions occurred in 18 of 209 subjects (8.6%) in the Olo 5 μg group, 16 of 217 subjects (7.4%) in the Olo 10 μg group, 18 of 216 subjects (8.3%) in the placebo group.

Table 20. Adverse events with an incidence of ≥2% in any group (safety analysis population)

Event	Olo 5 μg (209 subjects)	Olo 10 μg (217 subjects)	Placebo (216 subjects)
COPD	46 (22.0)	59 (27.2)	55 (25.5)
Upper respiratory tract infection	20 (9.6)	22 (10.1)	17 (7.9)
Nasopharyngitis	19 (9.1)	25 (11.5)	18 (8.3)
Cough	10 (4.8)	3 (1.4)	4 (1.9)
Back pain	8 (3.8)	8 (3.7)	3 (1.4)
Hypertension	8 (3.8)	5 (2.3)	7 (3.2)
Bronchitis	7 (3.3)	7 (3.2)	6 (2.8)
Headache	7 (3.3)	4 (1.8)	11 (5.1)
Ventricular extrasystoles	6 (2.9)	7 (3.2)	2 (0.9)
Dizziness	6 (2.9)	6 (2.8)	6 (2.8)
Dyspnoea	5 (2.4)	4 (1.8)	4 (1.9)
Pneumonia	4 (1.9)	9 (4.1)	5 (2.3)
Diarrhoea	4 (1.9)	6 (2.8)	4 (1.9)
Oropharyngeal pain	4 (1.9)	5 (2.3)	3 (1.4)
Sinusitis	3 (1.4)	6 (2.8)	7 (3.2)
Urinary tract infection	3 (1.4)	5 (2.3)	0
Sinus congestion	2 (1.0)	5 (2.3)	4 (1.9)
Nausea	2 (1.0)	5 (2.3)	3 (1.4)
Nasal congestion	1 (0.5)	0	5 (2.3)
Constipation	0	5 (2.3)	3 (1.4)
Respiratory failure	0	5 (2.3)	2 (0.9)

Number of subjects (%)

4.(ii).A.(1).5) Foreign phase III study (5.3.5.1-7, Study 1222.13 [February 2009 to December 2010])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in patients with COPD[26] (target sample size, 860 [215 subjects/group]) to evaluate the efficacy and safety of Olo.

Subjects received 5 or 10 μg of Olo once daily, or 12 μg of formoterol fumarate dihydrate[27] twice daily by inhalation[28] for 48 weeks. A double dummy technique was used.

Of 906 subjects who were randomized and stratified by use or non-use of Tio at enrollment, 904 received the study drug and were included in the safety analysis population (227 in the Olo 5 μg group, 225 in the Olo 10 μg group, 227 in the formoterol group, and 225 in the placebo group). Of the 904 subjects, 19 subjects[29] were excluded from the analysis, and the remaining 885 subjects (222 in the Olo 5 μg group, 223 in the Olo 10 μg group, 223 in the formoterol group, and 217 in the placebo group) were included in the FAS and the efficacy analysis population. The study drug was discontinued in 15.9% (36 of 227) of subjects in the Olo 5 μg group, 17.3% (39 of 225) of subjects in the Olo 10 μg group, 18.9% (43 of 227) of subjects in the formoterol group, and 25.3% (57 of 225) of subjects in the placebo group.

Table 21 shows changes from baseline in the $FEV_1AUC_{0\text{-}3}$[30] and trough FEV_1 values[31] after 24 weeks of treatment, which were co-primary efficacy endpoints. For both endpoints, the differences from placebo were statistically significant in both Olo 5 and 10 μg groups, demonstrating the superiority of Olo 5 and 10 μg over placebo.

[26] Patients who had a diagnosis of COPD with relatively stable symptoms and who met the following criteria: (1) post-bronchodilator FEV_1 of <80% of predicted value at screening visit; (2) post-bronchodilator FEV_1/FVC <70% at screening visit; (3) aged ≥40 years; and (4) a current or former smoker with a smoking history of >10 pack-years.

[27] Foradil Aerolizer, contains 12 μg of formoterol fumarate dihydrate, delivered by a metered dose inhaler.

[28] Olo were administered with Respimat and formoterol with Aerolizer.

[29] Subjects with poor adherence to medication, or with missing baseline or co-primary endpoint measurement data.

[30] Values of the area under the FEV_1-time curve from 0 to 3 hours after administration calculated according to the trapezoidal rule and adjusted to area per unit.

[31] The baseline was the mean of FEV_1 values measured 1 hour before and 10 minutes before the first inhalation of the study drug, trough FEV_1 was the FEV_1 value measured 10 minutes before the inhalation of the study drug on the next day.

Table 21. Changes from baseline in the FEV_1AUC_{0-3} and trough FEV_1 values (L) after 24 weeks of treatment (FAS, WOCF)

	Olo 5 μg	Olo 10 μg	Formoterol fumarate dihydrate	Placebo
FEV_1AUC_{0-3}				
Baseline	1.240 ± 0.486 (222)	1.174 ± 0.513 (223)	1.223 ± 0.462 (223)	1.178 ± 0.474 (217)
After 24 weeks of treatment	1.403 ± 0.542 (204)	1.331 ± 0.544 (199)	1.410 ± 0.505 (196)	1.195 ± 0.466 (177)
Change	0.144 ± 0.237 (204)	0.157 ± 0.208 (199)	0.170 ± 0.232 (196)	−0.000 ± 0.243 (177)
Difference from placebo [95% CI],[a] p-value[a), b)]	0.151 [0.110, 0.193] p<0.0001	0.165 [0.124, 0.206] p<0.0001	0.177 [0.136, 0.218] p<0.0001	
Trough FEV_1				
Baseline	1.240 ± 0.486 (222)	1.174 ± 0.513 (223)	1.223 ± 0.462 (223)	1.178 ± 0.474 (217)
After 24 weeks of treatment	1.281 ± 0.519 (200)	1.211 ± 0.520 (198)	1.246 ± 0.475 (194)	1.148 ± 0.452 (174)
Change	0.024 ± 0.207 (200)	0.034 ± 0.197 (198)	0.004 ± 0.206 (194)	−0.044 ± 0.234 (174)
Difference from placebo [95% CI],[a] p-value[a), b)]	0.078 [0.037, 0.118] p=0.0002	0.085 [0.044, 0.125] p<0.0001	0.054 [0.014, 0.095] p=0.0088	

Mean ± standard deviation (number of subjects)

a) The analysis was based on a mixed effect model with repeated measures (MMRM), with a spatial power covariance structure for within subject variation. The model included treatment group, co-administration of Tio, treatment day, treatment group-by-treatment day interaction, baseline, baseline-by-treatment day interaction as fixed effects; and subject as a random effect.

b) The p-values were adjusted for multiplicity by a step-down multiple comparison procedure, in the specified order of comparisons of FEV_1AUC_{0-3} and trough FEV_1 values after 24 weeks of administration, first between the Olo 10 μg and placebo groups, and second between the Olo 5 μg and placebo groups.

The incidence of adverse events was 70.5% (160 of 227 subjects) in the Olo 5 μg group, 72.9% (164 of 225 subjects) in the Olo 10 μg group, 65.6% (149 of 227 subjects) in the formoterol group, and 68.0% (153 of 225 subjects) in the placebo group. Table 22 shows the adverse events with an incidence of ≥2% in any group.

A total of 5 deaths occurred in the Olo 5 μg group (lung neoplasm malignant, acute respiratory failure/COPD, COPD, cardio-respiratory arrest,[32] and COPD[32] in 1 subject each), 6 in the Olo 10 μg group (pneumonia in 2 subjects; pneumonia/acute respiratory failure, lung adenocarcinoma, oesophageal squamous cell carcinoma/tracheo-oesophageal fistula, and completed suicide in 1 subject each), 6 in the formoterol group (lung adenocarcinoma, cardiac failure, aortic aneurysm rupture, sudden death, respiratory failure,[32] and cardiac death[32] in 1 subject each), and 8 in the placebo group (myocardial infarction, cardio-respiratory arrest, sudden death, acute respiratory failure/COPD, death, acute myocardial infarction,[32] acute respiratory failure/COPD/haemoptysis,[32] and death[32] in 1 subject each). A causal relationship to the study drug was ruled for all deaths except for 1 subject in the placebo group (myocardial infarction).

Serious adverse events occurred in 33 of 227 subjects (14.5%) in the Olo 5 μg group, 26 of 225 subjects (11.6%) in the Olo 10 μg group, 33 of 227 subjects (14.5%) in the formoterol group, 31 of 225 subjects (13.8%) in the placebo group. Common serious adverse events included COPD and pneumonia. COPD occurred in 10 of 227 subjects (4.4%) in the Olo 5 μg group, 13 of 225 subjects (5.8%) in the Olo 10 μg group, 9 of 227 subjects (4.0%) in the formoterol group, and 9 of 225 subjects (4.0%) in the placebo group. Pneumonia occurred in 5 of 227 subjects (2.2%) in the Olo 5 μg group, 7 of 225 subjects (3.1%) in the Olo 10 μg group, 3 of 227 subjects (1.3%) in the formoterol group, and 3 of 225 subjects (1.3%) in the placebo group. A causal relationship to the study drug could not be ruled out for the events

[32] The adverse event was observed after the end of the study drug treatment period, or after the completion of the study.

experienced by 4 subjects in the Olo 5 μg group (COPD in 3 subjects and pneumonia in 1 subject), 2 subjects in the formoterol group (atrial fibrillation, and electrocardiogram QT prolonged/electrocardiogram T wave inversion/chest pain in 1 subject each), and 1 subject in the placebo group (myocardial infarction).

Adverse events leading to the discontinuation of treatment occurred in 15 of 227 subjects (6.6%) in the Olo 5 μg group, 15 of 225 subjects (6.7%) in the Olo 10 μg group, 19 of 227 subjects (8.4%) in the formoterol group, and 16 of 225 subjects (7.1%) in the placebo group.

Adverse reactions occurred in 16 of 227 subjects (7.0%) in the Olo 5 μg group, 12 of 225 subjects (5.3%) in the Olo 10 μg group, 25 of 227 subjects (11.0%) in the formoterol group, and 17 of 225 subjects (7.6%) in the placebo group.

Table 22. Adverse events with an incidence of ≥2% in any group (safety analysis population)

Event	Olo 5 μg (227 subjects)	Olo 10 μg (225 subjects)	Formoterol (227 subjects)	Placebo (225 subjects)
COPD	77 (33.9)	75 (33.3)	62 (27.3)	60 (26.7)
Nasopharyngitis	22 (9.7)	25 (11.1)	23 (10.1)	15 (6.7)
Upper respiratory tract infection	17 (7.5)	12 (5.3)	11 (4.8)	15 (6.7)
Bronchitis	10 (4.4)	8 (3.6)	5 (2.2)	9 (4.0)
Dyspnoea	9 (4.0)	13 (5.8)	6 (2.6)	11 (4.9)
Back pain	9 (4.0)	6 (2.7)	9 (4.0)	8 (3.6)
Pneumonia	8 (3.5)	10 (4.4)	5 (2.2)	6 (2.7)
Influenza	8 (3.5)	3 (1.3)	5 (2.2)	7 (3.1)
Urinary tract infection	8 (3.5)	3 (1.3)	0	1 (0.4)
Cough	7 (3.1)	13 (5.8)	13 (5.7)	7 (3.1)
Hypertension	6 (2.6)	6 (2.7)	2 (0.9)	5 (2.2)
Arthralgia	6 (2.6)	5 (2.2)	2 (0.9)	2 (0.9)
Headache	5 (2.2)	11 (4.9)	6 (2.6)	8 (3.6)
Gastroenteritis	5 (2.2)	2 (0.9)	8 (3.5)	7 (3.1)
Myalgia	5 (2.2)	1 (0.4)	3 (1.3)	3 (1.3)
Pyrexia	4 (1.8)	5 (2.2)	3 (1.3)	5 (2.2)
Muscle spasms	4 (1.8)	3 (1.3)	6 (2.6)	2 (0.9)
Dizziness	3 (1.3)	7 (3.1)	3 (1.3)	6 (2.7)
Diarrhoea	3 (1.3)	3 (1.3)	7 (3.1)	6 (2.7)
Chest pain	2 (0.9)	7 (3.1)	6 (2.6)	3 (1.3)
Dyspepsia	0	3 (1.3)	5 (2.2)	2 (0.9)
Gastritis	0	1 (0.4)	2 (0.9)	5 (2.2)

Number of subjects (%)

4.(ii).A.(1).6) Foreign phase III study (5.3.5.1-8, Study 1222.14 [January 2009 to December 2010])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in patients with COPD[26] (target sample size, 860 [215 subjects/group]) to evaluate the efficacy and safety of Olo.

This study was conducted using a design that was identical to that of Study 1222.13, a foreign phase III study in patients with COPD.

Of 937 subjects who were randomized, 934 subjects who received the study drug were included in the safety analysis population (232 in the Olo 5 μg group, 234 in the Olo 10 μg group, 233 in the formoterol group, and 235 in the placebo group). A total of 6 subjects[29] were excluded, and the remaining 928 subjects (230 in the Olo 5 μg group, 233 in the Olo 10 μg group, 232 in the formoterol group, and 233

in the placebo group) were included in the FAS and the efficacy analysis population. Subjects who discontinued the study were 16.0% (37 of 232 subjects) in the Olo 5 μg group, 15.4% (36 of 234 subjects) in the Olo 10 μg group, 17.2% (40 of 233 subjects) in the formoterol group, and 21.7% (51 of 235 subjects) in the placebo group.

Table 23 shows changes from baseline in the FEV_1AUC_{0-3} and trough FEV_1 values after 24 weeks of treatment, which are co-primary efficacy endpoints. For both endpoints, the differences from placebo were statistically significant in the Olo 5 and 10 μg groups, demonstrating the superiority of Olo 5 and 10 μg over placebo.

Table 23. Changes from baseline in the FEV_1AUC_{0-3} and trough FEV_1 values (L) after 24 weeks of treatment (FAS, WOCF)

	Olo 5 μg	Olo 10 μg	Formoterol	Placebo
FEV_1AUC_{0-3}				
Baseline	1.225 ± 0.457 (230)	1.221 ± 0.446 (233)	1.167 ± 0.453 (232)	1.232 ± 0.485 (233)
After 24 weeks of treatment	1.350 ± 0.499 (210)	1.374 ± 0.478 (212)	1.328 ± 0.501 (209)	1.231 ± 0.462 (198)
Change	0.124 ± 0.245 (210)	0.146 ± 0.207 (212)	0.148 ± 0.226 (209)	−0.013 ± 0.201 (198)
Difference from placebo [95% CI],[a)] p-value[a), b)]	0.129 [0.091, 0.167] p<0.0001	0.154 [0.116, 1.191] p<0.0001	0.150 [0.112, 0.188] p<0.0001	
Trough FEV_1				
Baseline	1.225 ± 0.457 (230)	1.221 ± 0.446 (233)	1.167 ± 0.453 (232)	1.232 ± 0.485 (233)
After 24 weeks of treatment	1.228 ± 0.492 (209)	1.253 ± 0.459 (211)	1.175 ± 0.468 (208)	1.191 ± 0.458 (198)
Change	0.004 ± 0.241 (209)	0.022 ± 0.202 (211)	−0.001 ± 0.210 (208)	−0.052 ± 0.211 (198)
Difference from placebo [95% CI],[a)] p-value[a), b)]	0.053 [0.015, 0.090] p=0.0055	0.069 [0.032, 0.106] p=0.0003	0.042 [0.005, 0.080] p=0.0270	

Mean ± standard deviation (number of subjects)
[a)] See note [a)] of Table 21 for the model
[b)] See note [b)] of Table 21 for multiplicity

The incidence of adverse events was 72.8% (169 of 232 subjects) in the Olo 5 μg group, 72.2% (169 of 234 subjects) in the Olo 10 μg group, 72.5% (169 of 233 subjects) in the formoterol group, and 73.6% (173 of 235 subjects) in the placebo group. Table 24 shows the adverse events with an incidence of ≥2% in any group.

A total of 9 deaths occurred in the Olo 5 μg group (cardio-respiratory arrest, COPD, atrial fibrillation/cardiac failure/dyspnoea/oedema peripheral, sudden cardiac death, respiratory failure, liver neoplasm malignant, COPD/malnutrition, pneumonia/sepsis/cardio-respiratory arrest/multi-organ failure,[33] and acute myocardial infarction[33] in 1 subject each), 7 in the Olo 10 μg group (cardiac failure congestive, metastases to lung, lung neoplasm malignant, laryngeal cancer, COPD, death, and pancreatic carcinoma,[33] in 1 subject each), 7 in the formoterol group (cardiac arrest/dyspnoea, COPD, death, anaphylactic shock/arthropod sting, pneumonia/sepsis/multi-organ failure, arrhythmia/myocardial infarction, and pneumonia aspiration[33] in 1 subject each), and 9 in the placebo group (COPD in 2 subjects; cardiac failure acute, COPD/respiratory failure, death, cerebrovascular accident, road traffic accident,[33] septic shock,[33] and myocardial infarction[33] in 1 subject each). A causal relationship to the study drug was ruled out for all deaths.

[33] The adverse event was observed after the end of the study drug treatment period, or after the completion of the study.

Serious adverse events occurred in 34 of 232 subjects (14.7%) in the Olo 5 μg group, 41 (17.5%) of 234 subjects in the Olo 10 μg group, 36 of 233 subjects (15.5%) in the formoterol group, and 48 of 235 subjects (20.4%) in the placebo group. Common serious adverse events included COPD and pneumonia. COPD occurred in 14 of 232 subjects (6.0%) in the Olo 5 μg group, 17 of 234 subjects (7.3%) in the Olo 10 μg group, 18 of 233 subjects (7.7%) in the formoterol group, and 18 of 235 subjects (7.7%) in the placebo group. Pneumonia occurred in 2 of 232 subjects (0.9%) in the Olo 5 μg group, 7 of 234 subjects (3.0%) in the Olo 10 μg group, 4 of 233 subjects (1.7%) in the formoterol group, and 2 of 235 subjects (0.9%) in the placebo group. A causal relationship to the study drug could not be ruled out for the events experienced by 2 subjects in the Olo 10 μg group (acute myocardial infarction and dizziness[34] in 1 subject each), 5 subjects in the formoterol group (COPD in 3 subjects, exacerbation of COPD due to infection, and ventricular extrasystoles in 1 subject each), 4 subjects in the placebo group (atrial fibrillation, myocardial infarction/acute coronary syndrome/angina unstable,[33] pulmonary tuberculosis,[33] and pneumothorax, 1 subject each).

Adverse events leading to the discontinuation of treatment occurred in 15 of 232 subjects (6.5%) in the Olo 5 μg group, 16 of 234 subjects (6.8%) in the Olo 10 μg group, 17 of 233 subjects (7.3%) in the formoterol group, and 19 of 235 subjects (8.1%) in the placebo group.

Adverse reactions occurred in 12 of 232 subjects (5.2%) in the Olo 5 μg group, 14 of 234 subjects (6.0%) in the Olo 10 μg group, 26 of 233 subjects (11.2%) in the formoterol group, and 25 of 235 subjects (10.6%) in the placebo group.

Table 24. Adverse events with an incidence of ≥2% in any group (safety analysis population)

Event	Olo 5 μg (232 subjects)	Olo 10 μg (234 subjects)	Formoterol (233 subjects)	Placebo (235 subjects)
COPD	54 (23.3)	65 (27.8)	69 (29.6)	69 (29.4)
Nasopharyngitis	37 (15.9)	28 (12.0)	23 (9.9)	22 (9.4)
Upper respiratory tract infection	14 (6.0)	15 (6.4)	21 (9.0)	19 (8.1)
Bronchitis	13 (5.6)	10 (4.3)	8 (3.4)	9 (3.8)
Dyspnoea	11 (4.7)	4 (1.7)	19 (8.2)	11 (4.7)
Headache	10 (4.3)	11 (4.7)	9 (3.9)	10 (4.3)
Back pain	10 (4.3)	7 (3.0)	9 (3.9)	9 (3.8)
Diarrhoea	9 (3.9)	9 (3.8)	4 (1.7)	5 (2.1)
Pyrexia	6 (2.6)	13 (5.6)	9 (3.9)	8 (3.4)
Pneumonia	6 (2.6)	12 (5.1)	9 (3.9)	7 (3.0)
Cough	6 (2.6)	12 (5.1)	14 (6.0)	16 (6.8)
Hypertension	6 (2.6)	7 (3.0)	6 (2.6)	6 (2.6)
Oropharyngeal pain	6 (2.6)	6 (2.6)	3 (1.3)	5 (2.1)
Respiratory tract infection	6 (2.6)	5 (2.1)	4 (1.7)	2 (0.9)
Abdominal pain	6 (2.6)	1 (0.4)	3 (1.3)	3 (1.3)
Chest pain	5 (2.2)	3 (1.3)	7 (3.0)	5 (2.1)
Dyspepsia	5 (2.2)	3 (1.3)	3 (1.3)	3 (1.3)
Myalgia	4 (1.7)	8 (3.4)	2 (0.9)	1 (0.4)
Influenza	3 (1.3)	5 (2.1)	6 (2.6)	4 (1.7)
Pain in extremity	3 (1.3)	3 (1.3)	5 (2.1)	4 (1.7)
Urinary tract infection	2 (0.9)	3 (1.3)	5 (2.1)	4 (1.7)
Ventricular extrasystoles	2 (0.9)	0	5 (2.1)	2 (0.9)
Musculoskeletal pain	1 (0.4)	6 (2.6)	3 (1.3)	3 (1.3)
Constipation	1 (0.4)	5 (2.1)	2 (0.9)	2 (0.9)

Number of subjects (%)

[34] The adverse event was observed between 12 days after the administration of the last dose and the completion of the study.

4.(ii).A.(2) Tio + Olo fixed dose combination study

4.(ii).A.(2).1) Multiregional phase III study (5.3.5.1-12, Study 1237.5 [September 2011 to September 2013])

A randomized, double-blind, active-controlled, parallel-group study was conducted in patients with COPD[35] (target sample size, 2500 [500 subjects/group]) in 25 countries including Japan, the US, China, and Germany, to evaluate the efficacy and safety of Tio + Olo FDC.

Subjects received inhaled doses of Tio + Olo FDC (2.5/5 μg or 5/5 μg), or Tio (2.5 μg or 5 μg), or Olo (5 μg) once daily for 52 weeks.

All 2624 randomized subjects were included in the safety analysis population (522 subjects [Tio + Olo 2.5/5 μg], 522 subjects [Tio + Olo 5/5 μg], 525 subjects [Tio 2.5 μg], 527 subjects [Tio 5 μg], and 528 subjects [Olo 5 μg]). After 2 subjects[36] were excluded, the remaining 2622 subjects (522 subjects [Tio + Olo 2.5/5 μg], 522 subjects [Tio + Olo 5/5 μg], 524 subjects [Tio 2.5 μg], 526 subjects [Tio 5 μg], and 528 subjects [Olo 5 μg]) were included in the FAS and the efficacy analysis population. Subjects who discontinued the study were 11.5% (60 of 522 subjects) in the Tio + Olo 2.5/5 μg group, 10.7% (56 of 522 subjects) in the Tio + Olo 5/5 μg group, 14.7% (77 of 525 subjects) in the Tio 2.5 μg group, 13.7% (72 of 527 subjects) in the Tio 5 μg group, and 18.4% (97 of 528 subjects) in the Olo 5 μg group.

In the FAS, the Japanese subpopulation consisted of 204 subjects (35 subjects [Tio + Olo 2.5/5 μg], 45 subjects [Tio + Olo 5/5 μg], 33 subjects [Tio 2.5 μg], 38 subjects [Tio 5 μg], and 53 subjects [Olo 5 μg]). subjects who discontinued the study in the Japanese subpopulation were 11.4% (4 of 35 subjects) in the Tio + Olo 2.5/5 μg group, 13.3% (6 of 45 subjects) in the Tio + Olo 5/5 μg group, 15.2% (5 of 33 subjects) in the Tio 2.5 μg group, 7.9% (3 of 38 subjects) in the Tio 5 μg group, 17.0% (9 of 53 subjects) in the Olo 5 μg group.

Changes from baseline in the $FEV_1AUC_{0\text{-}3}$[37] and trough FEV_1 values[38] after 24 weeks of treatment were the co-primary efficacy endpoints of the study. The St George's Respiratory Questionnaire (SGRQ) total score[39] after 24 weeks of treatment was also included as an endpoint for the analysis of pooled data from Studies 1237.5 and 1237.6, which follow the design identical to each other [see "4.(ii).A.(2).3) The pooled analysis of Studies 1237.5 and 1237.6 (5.3.5.3-3)"].

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[35] Patients who had a diagnosis of COPD with relatively stable symptoms and who met the following criteria: (1) post-bronchodilator FEV_1 of <80% of predicted value at screening visit (GOLD II to IV); (2) post-bronchodilator FEV_1/FVC <70%; (3) aged ≥40 years; and (4) a current or former smoker with a smoking history of >10 pack years.

[36] Subjects who were found to have been enrolled in another clinical study of Tio, Olo, or Tio + Olo.

[37] A value calculated as the area under the FEV_1-time curve from 0 to 3 hours after administration using the trapezoidal rule, and adjusted to area per unit.

[38] The baseline was defined as the mean of FEV_1 values measured 1 hour before, and 10 minutes before the first inhalation of the study drug. Trough FEV_1 was defined as the mean of FEV_1 values measured 1 hour before, and 10 minutes before the inhalation of the study drug on the next day.

[39] The SGRQ total score was calculated as the total score of the 2 components of the questionnaire: Symptoms score, and Activity and Impacts score, each consisting of 8 questions.

Table 25 shows the changes from baseline in the FEV_1AUC_{0-3} and trough FEV_1 values after 24 weeks of treatment, the co-primary efficacy endpoints. The differences were statistically significant between the Tio + Olo 5/5 µg and Olo 5 µg groups, and between the Tio + Olo 5/5 µg and Tio 5 µg groups; and between the Tio + Olo 2.5/5 µg and Olo 5 µg groups, Tio + Olo 2.5/5 µg and Tio 2.5 µg groups. The results demonstrated the superiority of Tio + Olo 5/5 µg and Tio + Olo 2.5/5 µg, over the individual components, Olo 5 µg, Tio 5 µg, and Tio 2.5 µg.

Table 25. Changes from baseline in the FEV_1AUC_{0-3} and trough FEV_1 values (L) after 24 weeks of treatment (FAS, WOCF)

	Tio+Olo 2.5/5 µg	Tio+Olo 5/5 µg	Tio 2.5 µg	Tio 5 µg	Olo 5 µg
FEV_1AUC_{0-3}					
Baseline	1.172 ± 0.467 (521)	1.110 ± 0.462 (522)	1.203 ± 0.493 (524)	1.148 ± 0.491 (526)	1.159 ± 0.519 (525)
After 24 weeks of treatment	1.408 ± 0.513 (491)	1.363 ± 0.517 (498)	1.359 ± 0.515 (488)	1.298 ± 0.527 (489)	1.314 ± 0.575 (475)
Change	0.241 ± 0.218 (491)	0.258 ± 0.211 (498)	0.146 ± 0.229 (488)	0.140 ± 0.188 (489)	0.138 ± 0.207 (475)
Difference from Tio+Olo 5 /5 µg group [95% CI],[a)] p-value[a), b)]				0.117 [0.094, 0.140] p<0.0001	0.123 [0.100, 0.146] p<0.0001
Difference from Tio+Olo 2.5 /5 µg [95% CI],[a)] p-value[a), b)]			0.093 [0.070, 0.116] p<0.0001		0.109 [0.086, 0.132] p<0.0001
Trough FEV_1					
Baseline	1.172 ± 0.467 (521)	1.110 ± 0.462 (522)	1.203 ± 0.493 (524)	1.148 ± 0.491 (526)	1.159 ± 0.519 (525)
After 24 weeks of treatment	1.260 ± 0.487 (491)	1.223 ± 0.491 (498)	1.257 ± 0.493 (488)	1.210 ± 0.500 (489)	1.212 ± 0.541 (476)
Change	0.093 ± 0.203 (491)	0.118 ± 0.183 (498)	0.044 ± 0.214 (488)	0.052 ± 0.176 (489)	0.035 ± 0.180 (476)
Difference from Tio+Olo 5/5 µg group [95% CI],[a)] p-value[a), b)]				0.071 [0.047, 0.094] p<0.0001	0.082 [0.059, 0.106] p<0.0001
Difference from Tio+Olo 2.5/5 µg [95% CI],[a)] p-value[a), b)]			0.029 [0.005, 0.052] p=0.0174		0.058 [0.034, 0.081] p<0.0001

Mean ± standard deviation (number of subjects)

[a)] The analysis was based on a mixed effect model with repeated measures (MMRM), with a spatial power covariance structure for within subject variation. The model included treatment group, treatment day, treatment group-by-treatment day interaction, baseline, and baseline-by-treatment day interaction as fixed effect; and subject a random effect.

[b)] The p-values were adjusted for multiplicity by a step-down multiple comparison procedure in the following prespecified hierarchical order: Tio + Olo 5/5 µg versus Olo 5 µg, Tio + Olo 5 /5 µg versus Tio 5 µg for FEV_1AUC_{0-3} after 24 weeks of treatment; Tio + Olo 5/5 µg versus Olo 5 µg, Tio + Olo 5/5 µg versus Tio 5 µg for trough FEV_1 values 24 weeks of treatment; Tio + Olo 5/5 µg versus Olo 5 µg, Tio + Olo 5/5 µg versus Tio 5 µg for the pooled SGRQ total score after 24 weeks of treatment; Tio + Olo 2.5/5 µg versus Olo 5 µg, Tio + Olo 2.5/5 µg versus Tio 2.5 µg for FEV_1AUC_{0-3} after 24 weeks of treatment; Tio + Olo 2.5/5 µg versus Olo 5 µg, Tio + Olo 2.5/5 µg versus Tio 2.5 µg for trough FEV_1 values after 24 weeks of treatment; Tio + Olo 2.5/5 µg versus Olo 5 µg, Tio + Olo 2.5/5 µg versus Tio 2.5 µg for the pooled SGRQ total score after 24 weeks of treatment.

Table 26 shows the FEV_1AUC_{0-3} and trough FEV_1 values for the Japanese subpopulation after 24 weeks of treatment.

Table 26. Changes from baseline in the FEV_1AUC_{0-3} and trough FEV_1 values (L) after 24 weeks of treatment (Japanese subpopulation, WOCF)

	Tio+Olo 2.5/5 µg	Tio+Olo 5/5 µg	Tio 2.5 µg	Tio 5 µg	Olo 5 µg
FEV_1AUC_{0-3}					
Baseline	1.102 ± 0.424 (35)	0.989 ± 0.394 (45)	1.209 ± 0.462 (33)	1.070 ± 0.432 (38)	1.094 ± 0.486 (53)
After 24 weeks of treatment	1.311 ± 0.487 (32)	1.307 ± 0.458 (42)	1.364 ± 0.494 (30)	1.194 ± 0.440 (38)	1.290 ± 0.545 (48)
Change	0.235 ± 0.190 (32)	0.315 ± 0.169 (42)	0.154 ± 0.191 (30)	0.125 ± 0.134 (38)	0.158 ± 0.273 (48)
Difference from Tio+Olo 5/5 µg group [95% CI] [a)]				0.184 [0.112, 0.256]	0.155 [0.087, 0.222]
Difference from Tio+Olo 2.5/5 µg [95% CI] [a)]			0.079 [−0.002, 0.160]		0.076 [0.003, 0.148]
Trough FEV_1					
Baseline	1.102 ± 0.424 (35)	0.989 ± 0.394 (45)	1.209 ± 0.462 (33)	1.070 ± 0.432 (38)	1.094 ± 0.486 (53)
After 24 weeks of treatment	1.206 ± 0.471 (32)	1.199 ± 0.438 (42)	1.271 ± 0.486 (30)	1.125 ± 0.434 (38)	1.214 ± 0.524 (48)
Change	0.130 ± 0.157 (32)	0.207 ± 0.147 (42)	0.061 ± 0.149 (30)	0.055 ± 0.143 (38)	0.083 ± 0.240 (48)
Difference from Tio+Olo 5/5 µg group [95% CI] [a)]				0.152 [0.085, 0.218]	0.134 [0.072, 0.196]
Difference from Tio+Olo 2.5/5 µg [95% CI] [a)]			0.066 [−0.008, 0.141]		0.043 [−0.023, 0.110]

Mean ± standard deviation (number of subjects)

[a)] The analysis was based on mixed effect models with repeated measures (MMRM), with a spatial power covariance structure for within subject variation. The model included treatment group, treatment day, treatment group-by-treatment day interaction, baseline, and baseline-by-treatment day interaction as fixed effects; and subject as a random effect..

The incidence of adverse events was 75.7% (395 of 522 subjects) in the Tio + Olo 2.5/5 µg group, 74.1% (387 of 522 subjects) in the Tio + Olo 5/5 µg group, 71.2% (374 of 525 subjects) in the Tio 2.5 µg group, 72.3% (381 of 527 subjects) in the Tio 5 µg group, and 73.9% (390 of 528 subjects) in the Olo 5 µg group. Table 27 shows the adverse events with an incidence of ≥2% in any group.

A total of 10 deaths occurred in the Tio + Olo 2.5/5 µg group (cardio-respiratory arrest, glioblastoma multiforme, pancreatitis acute, oesophageal carcinoma, ventricular fibrillation, lung cancer metastatic, pulmonary mass, death, respiratory failure,[40] and pneumonia[40] in 1 subject each), 10 in the Tio + Olo 5/5 µg group (pulmonary mass, peripheral vascular disorder, cardiopulmonary failure, cardiac arrest, brain neoplasm, sudden death, cardio-respiratory arrest, haemorrhagic stroke, death, and respiratory failure[40] in 1 subject each), 11 in the Tio 2.5 µg group (cardiac failure in 2 subjects, pancreatitis acute, bronchial carcinoma, pulmonary oedema, haematemesis, cerebrovascular accident, respiratory failure, injury,[40] pneumonia,[40] and death[40] in 1 subject each), 12 in the Tio 5 µg group (lung neoplasm malignant in 4 subjects,[41] and renal cancer, amyotrophic lateral sclerosis, COPD, cardiac failure acute, multi-organ failure, death, and post procedural sepsis[40] in 1 subject each), and 5 in the Olo 5 µg group (oesophageal carcinoma, cerebral infarction, arteriosclerosis coronary artery, COPD, and lung neoplasm malignant[40] in 1 subject each). A causal relationship to the study drug was ruled out for all deaths except for 1 subject (pancreatitis acute) in the Tio 2.5 µg group.

[40] The adverse event was observed after the completion of treatment period, or after the completion of the study.

[41] Two subjects had the event after the completion of treatment period, or after completion of the study.

Serious adverse events occurred in 81 of 522 subjects (15.5%) in the Tio + Olo 2.5/5 µg group, 87 of 522 subjects (16.7%) in the Tio + Olo 5/5 µg group, 66 of 525 subjects (12.6%) in the Tio 2.5 µg group, 79 of 527 subjects (15.0%) in the Tio 5 µg group, and 75 of 528 subjects (14.2%) in the Olo 5 µg group. Common serious adverse events include COPD and pneumonia. COPD occurred in 20 of 522 subjects (3.8%) in the Tio + Olo 2.5/5 µg group, 36 of 522 subjects (6.9%) in the Tio + Olo 5/5 µg group, 25 of 525 subjects (4.8%) in the Tio 2.5 µg group, 24 of 527 subjects (4.6%) in the Tio 5 µg group, 27 of 528 subjects (5.1%) in the Olo 5 µg group. Pneumonia occurred in 10 of 522 subjects (1.9%) in the Tio + Olo 2.5/5 µg group, 9 of 522 subjects (1.7%) in the Tio + Olo 5/5 µg group, 5 of 525 subjects (1.0%) in the Tio 2.5 µg group, 5 of 527 subjects (0.9%) in the Tio 5 µg group, and 8 of 528 subjects (1.5%) in the Olo 5 µg group. A causal relationship to the study drug could not be ruled out for the events experienced by 4 subjects in the Tio + Olo 2.5/5 µg group (suicidal ideation, cardiac failure chronic, urinary retention, and benign prostatic hyperplasia in 1 subject each), 5 subjects in the Tio + Olo 5/5 µg group (acute myocardial infarction, acute respiratory failure/COPD, COPD, benign prostatic hyperplasia, and femoral neck fracture in 1 subject each), 2 subjects in the Tio 2.5 µg group (pancreatitis acute, and cerebrovascular accident in 1 subject each), 4 subjects in the Tio 5 µg group (cerebral infarction, gout, atrial fibrillation, and urinary tract obstruction in 1 subject each), and 2 subjects in the Olo 5 µg group (confusional state and COPD in 1 subject each).

Adverse events leading to the discontinuation of treatment occurred in 29 of 522 subjects (5.6%) in the Tio + Olo 2.5/5 µg group, 37 of 522 subjects (7.1%) in the Tio + Olo 5/5 µg group, 37 of 525 subjects (7.0%) in the Tio 2.5 µg group, 42 of 527 subjects (8.0%) in the Tio 5 µg group, and 49 of 528 subjects (9.3%) in the Olo 5 µg group.

Adverse reactions occurred in 30 of 522 subjects (5.7%) in the Tio + Olo 2.5/5 µg group, 36 of 522 subjects (6.9%) in the Tio + Olo 5/5 µg group, 24 of 525 subjects (4.6%) in the Tio 2.5 µg group, 25 of 527 subjects (4.7%) in the Tio 5 µg group, 32 of 528 subjects (6.1%) in the Olo 5 µg group.

Table 27. Adverse events with an incidence of ≥2% in any group (safety analysis population)

Event	Tio+Olo 2.5/5 µg (522 subjects)	Tio+Olo 5/5 µg (522 subjects)	Tio 2.5 µg (525 subjects)	Tio 5 µg (527 subjects)	Olo 5 µg (528 subjects)
COPD	153 (29.3)	170 (32.6)	169 (32.2)	175 (33.2)	182 (34.5)
Nasopharyngitis	64 (12.3)	67 (12.8)	64 (12.2)	67 (12.7)	65 (12.3)
Upper respiratory tract infection	40 (7.7)	25 (4.8)	30 (5.7)	30 (5.7)	24 (4.5)
Pneumonia	20 (3.8)	19 (3.6)	11 (2.1)	19 (3.6)	22 (4.2)
Hypertension	16 (3.1)	18 (3.4)	18 (3.4)	19 (3.6)	22 (4.2)
Dyspnoea	15 (2.9)	17 (3.3)	20 (3.8)	22 (4.2)	18 (3.4)
Bronchitis	14 (2.7)	17 (3.3)	11 (2.1)	14 (2.7)	11 (2.1)
Cough	14 (2.7)	16 (3.1)	19 (3.6)	20 (3.8)	14 (2.7)
Influenza	13 (2.5)	15 (2.9)	14 (2.7)	10 (1.9)	12 (2.3)
Headache	15 (2.9)	14 (2.7)	12 (2.3)	16 (3.0)	16 (3.0)
Back pain	20 (3.8)	13 (2.5)	10 (1.9)	11 (2.1)	20 (3.8)
Diarrhoea	16 (3.1)	12 (2.3)	11 (2.1)	13 (2.5)	18 (3.4)
Dry mouth	6 (1.1)	11 (2.1)	5 (1.0)	8 (1.5)	3 (0.6)
Urinary tract infection	13 (2.5)	9 (1.7)	10 (1.9)	14 (2.7)	10 (1.9)
Chest pain	7 (1.3)	5 (1.0)	4 (0.8)	12 (2.3)	7 (1.3)
Constipation	11 (2.1)	4 (0.8)	8 (1.5)	7 (1.3)	7 (1.3)
Rhinorrhoea	2 (0.4)	0	5 (1.0)	3 (0.6)	11 (2.1)

Number of subjects (%)

The incidence of adverse events for the Japanese subpopulation was 85.7% (30 of 35 subjects) in the Tio + Olo 2.5/5 µg group, 82.2% (37 of 45 subjects) in the Tio + Olo 5/5 µg group, 72.7% (24 of 33 subjects) in the Tio 2.5 µg group, 78.9% (30 of 38 subject) in the Tio 5 µg group, and 83.0% (44 of 53 subjects) in the Olo 5 µg group. Table 28 shows the adverse events that occurred in ≥3 subjects in any 1 group.

In the Japanese subpopulation, 1 death occurred in the Tio + Olo 5/5 µg group (sudden death), and a causal relationship to the study drug was ruled out for the death.

In the Japanese subpopulation, serious adverse events occurred in 11 of 35 subjects (31.4%) in the Tio + Olo 2.5/5 µg group (gastric cancer, pneumonia/organising pneumonia, bronchitis, bladder cancer, gastric cancer/metastases to lymph nodes, prostate cancer, cardiac failure acute, cardiac failure chronic, COPD, inguinal hernia, and rectal ulcer in 1 subject each), 9 of 45 subjects (20.0%) in the Tio + Olo 5/5 µg group (COPD in 3 subjects, pneumonia/influenza, pneumonia/bronchitis, extradural abscess/post herpetic neuralgia, pneumonia pneumococcal, small cell lung cancer, and sudden death in 1 subject each), 3 of 33 subjects (9.1%) in the Tio 2.5 µg group (pneumonia, COPD, pancreatic duct dilatation/pancreatitis and acute/ pancreatitis chronic/biliary dilatation in 1 subject each), 9 of 38 subjects (23.7%) in the Tio 5 µg group (pneumonia, bronchitis, bronchopneumonia, exacerbation of COPD due to infection, gastric cancer, lung neoplasm malignant/metastases to central nervous system, myocardial ischaemia, large intestine polyp, and arthritis in 1 subject each), and 8 of 53 subjects (15.1%) in the Olo 5 µg group (COPD and pneumonia in 3 subjects each; prostatic specific antigen increased, and brain contusion/cervical spine fracture/fall/radius fracture/skull fracture/thoracic vertebral fracture in 1 subject each). A causal relationship to the study drug could not be ruled out for cardiac failure chronic in 1 subject in the Tio + Olo 2.5/5 µg group.

In the Japanese subpopulation, adverse events leading to the discontinuation of treatment occurred in 4 of 35 subjects (11.4%) in the Tio + Olo 2.5/5 µg group, 6 of 45 subjects (13.3%) in the Tio + Olo 5/5 µg

group, 2 of 33 subjects (6.1%) in the Tio 2.5 μg group, 3 of 38 subjects (7.9%) in the Tio 5 μg group, and 6 of 53 subjects (11.3%) in the Olo 5 μg group.

Adverse reactions occurred in 4 of 35 subjects (11.4%) in the Tio + Olo 2.5/5 μg group, 4 of 45 subjects (8.9%) in the Tio + Olo 5/5 μg group, 1 of 33 subjects (3.0%) in the Tio 2.5 μg group, 3 of 38 subjects (7.9%) in the Tio 5 μg group, and 4 of 53 subjects (7.5%) in the Olo 5 μg group.

Table 28. Adverse events that occurred in ≥3 subjects in any group (Japanese subpopulation)

Event	Tio+Olo 2.5/5 μg (43 subjects)	Tio+Olo 5/5 μg (34 subjects)	Tio 2.5 μg (39 subjects)	Tio 5 μg (38 subjects)	Olo 5 μg (55 subjects)
COPD	6 (17.1)	15 (33.3)	5 (15.2)	6 (15.8)	13 (24.5)
Nasopharyngitis	10 (28.6)	14 (31.1)	9 (27.3)	10 (26.3)	14 (26.4)
Bronchitis	4 (11.4)	7 (15.6)	1 (3.0)	5 (13.2)	4 (7.5)
Pneumonia	2 (5.7)	4 (8.9)	1 (3.0)	2 (5.3)	4 (7.5)
Diarrhoea	1 (2.9)	3 (6.7)	1 (3.0)	1 (2.6)	4 (7.5)
Dry mouth	0	3 (6.7)	0	0	1 (1.9)
Upper respiratory tract inflammation	2 (5.7)	2 (4.4)	3 (9.1)	0	7 (13.2)
Constipation	4 (11.4)	1 (2.2)	1 (3.0)	1 (2.6)	4 (7.5)
Insomnia	2 (5.7)	1 (2.2)	1 (3.0)	1 (2.6)	3 (5.7)
Vomiting	1 (2.9)	1 (2.2)	0	3 (7.9)	0
Influenza	0	1 (2.2)	3 (9.1)	1 (2.6)	0
Dental caries	0	1 (2.2)	1 (3.0)	0	3 (5.7)
Pruritus	3 (8.6)	0	0	1 (2.6)	1 (1.9)
Hypertension	2 (5.7)	0	2 (6.1)	2 (5.3)	3 (5.7)
Dizziness	0	0	0	0	3 (5.7)

Number of subjects (%)

4.(ii).A.(2).2) Multiregional phase III study (5.3.5.1-13, Study 1237.6 [September 2011 to November 2013])

A randomized, double-blind, active-controlled, parallel-group study was conducted in patients with COPD[35] (target sample size, 2500 [500 subjects/group]) in 24 countries including Japan, the US, China, and Germany to evaluate the efficacy and safety of Tio + Olo FDC.

This study was conducted using a design that was identical to that of the multiregional phase III study (1237.5) in patients with COPD.

Of 2539 subjects randomized, 2538 received the study drug and were included in the safety analysis population (508 subjects [Tio + Olo 2.5/5 μg], 507 subjects [Tio + Olo 5/5 μg], 507 subjects [Tio 2.5 μg], 506 subjects [Tio 5 μg], and 510 subjects [Olo 5 μg]). Of these, 2528 subjects (who had baseline data and efficacy measurements obtained at ≥1 time point during the treatment period) were included in the FAS and efficacy analysis population (508 subjects [Tio + Olo 2.5/5 μg], 505 subjects [Tio + Olo 5/5 μg], 505 subjects [Tio 2.5 μg], 503 subjects [Tio 5 μg], and 507 subjects [Olo 5 μg]). The study drug was discontinued in 12.4% (63 of 508) of subjects in the Tio + Olo 2.5/5 μg group, 15.2% (77 of 507) of subjects in the Tio + Olo 5/5 μg group, 19.3% (98 of 507) of subjects in the Tio 2.5 μg group, 19.0% (96 of 506) of subjects in the Tio 5 μg group, 19.2% (98 of 510) of subjects in the Olo 5 μg group.

In the FAS, the Japanese subpopulation consisted of 209 subjects (43 subjects [Tio + Olo 2.5/5 μg], 34 subjects [Tio + Olo 5/5 μg], 39 subjects [Tio 2.5 μg], 38 subjects [Tio 5 μg], and 55 subjects [Olo 5 μg]).

In the Japanese subpopulation, the study drug was discontinued in 7.0% (3 of 43) of subjects in the Tio + Olo 2.5/5 μg group, 17.6% (6 of 34) of subjects in the Tio + Olo 5/5 μg group, 15.4% (6 of 39) of subjects in the Tio 2.5 μg group, 15.8% (6 of 38) of subjects in the Tio 5 μg group, and 14.5% (8 of 55) of subjects in the Olo 5 μg group.

Table 29 shows the changes from baseline in FEV_1AUC_{0-3} and trough FEV_1 values after 24 weeks of treatment, which were co-primary efficacy endpoints. The differences were statistically significant between the Tio + Olo 5/5 μg and Olo 5 μg groups and between the Tio + Olo 5/5 μg and Tio 5 μg groups; and between the Tio + Olo 2.5/5 μg and Olo 5 μg groups and between the Tio + Olo 2.5/5 μg and Tio 2.5 μg groups. The results demonstrated the superiority of Tio + Olo 5/5 μg and Tio + Olo 2.5/5 μg over Olo 5 μg, Tio 5μg, and Tio 2.5 μg.

Table 29. Changes from baseline in the FEV_1AUC_{0-3} and trough FEV_1 values (L) after 24 weeks of treatment (FAS, WOCF)

	Tio+Olo 2.5/5 μg	Tio+Olo 5/5 μg	Tio 2.5 μg	Tio 5 μg	Olo 5 μg
FEV_1AUC_{0-3}					
Baseline	1.150 ± 0.458 (506)	1.154 ± 0.516 (502)	1.127 ± 0.487 (504)	1.146 ± 0.499 (500)	1.173 ± 0.490 (507)
After 24 weeks of treatment	1.417 ± 0.522 (466)	1.413 ± 0.569 (455)	1.259 ± 0.506 (453)	1.307 ± 0.555 (460)	1.325 ± 0.527 (452)
Change	0.256 ± 0.245 (466)	0.271 ± 0.240 (455)	0.126 ± 0.214 (453)	0.166 ± 0.222 (460)	0.139 ± 0.210 (452)
Difference from Tio+Olo 5/5 μg group [95% CI],[a)] p-value[a), b)]				0.103 [0.078, 0.127] p<0.0001	0.132 [0.108, 0.157] p<0.0001
Difference from Tio+Olo 2.5/5 μg [95% CI],[a)] p-value[a), b)]			0.131 [0.106, 0.155] p<0.0001		0.121 [0.096, 0.145] p<0.0001
Trough FEV_1					
Baseline	1.150 ± 0.458 (506)	1.154 ± 0.516 (502)	1.127 ± 0.487 (504)	1.146 ± 0.499 (500)	1.173 ± 0.490 (507)
After 24 weeks of treatment	1.270 ± 0.488 (467)	1.265 ± 0.530 (455)	1.178 ± 0.486 (453)	1.213 ± 0.526 (460)	1.219 ± 0.505 (452)
Change	0.110 ± 0.212 (467)	0.123 ± 0.213 (455)	0.045 ± 0.206 (453)	0.073 ± 0.199 (460)	0.033 ± 0.196 (452)
Difference from Tio+Olo 5/5 μg group [95% CI],[a)] p-value[a), b)]				0.050 [0.024, 0.075] p=0.0001	0.088 [0.063, 0.113] p<0.0001
Difference from Tio+Olo 2.5/5 μg [95% CI],[a)] p-value[a), b)]			0.062 [0.037, 0.087] p<0.0001		0.067 [0.042, 0.092] p<0.0001

Mean ± standard deviation (number of subjects)
[a)] See note [a)] of Table 25 for the models.
[b)] See note [b)] of Table 25 for multiplicity.

Table 30 shows the FEV_1AUC_{0-3} and trough FEV_1 values after 24 weeks of treatment in the Japanese subpopulation.

Table 30. Changes from baseline in the FEV_1AUC_{0-3} and trough FEV_1 values (L) after 24 weeks of treatment (Japanese subpopulation, WOCF)

	Tio+Olo 2.5/5 µg	Tio+Olo 5/5 µg	Tio 2.5 µg	Tio 5 µg	Olo 5 µg
FEV_1AUC_{0-3}					
Baseline	1.158 ± 0.473 (43)	1.185 ± 0.588 (34)	1.057 ± 0.402 (39)	1.146 ± 0.507 (37)	1.207 ± 0.418 (54)
After 24 weeks of treatment	1.382 ± 0.561 (40)	1.414 ± 0.530 (30)	1.215 ± 0.407 (35)	1.361 ± 0.550 (36)	1.369 ± 0.394 (49)
Change	0.230 ± 0.177 (40)	0.279 ± 0.203 (30)	0.164 ± 0.132 (35)	0.201 ± 0.145 (36)	0.138 ± 0.209 (49)
Difference from Tio+Olo 5/5 µg group [95% CI],[a)]				0.078 [0.006, 0.150]	0.143 [0.076, 0.211]
Difference from Tio+Olo 2.5/5 µg [95% CI],[a)]			0.064 [−0.003, 0.132]		0.097 [0.035, 0.159]
Trough FEV_1					
Baseline	1.158 ± 0.473 (43)	1.185 ± 0.588 (34)	1.057 ± 0.402 (39)	1.146 ± 0.507 (37)	1.207 ± 0.418 (54)
After 24 weeks of treatment	1.288 ± 0.546 (40)	1.311 ± 0.507 (30)	1.151 ± 0.399 (35)	1.290 ± 0.555 (36)	1.286 ± 0.390 (49)
Change	0.137 ± 0.160 (40)	0.176 ± 0.161 (30)	0.100 ± 0.125 (35)	0.129 ± 0.145 (36)	0.055 ± 0.203 (49)
Difference from Tio+Olo 5/5 µg group [95% CI],[a)]				0.059 [−0.014, 0.131]	0.124 [0.056, 0.192]
Difference from Tio+Olo 2.5/5 µg [95% CI],[a)]			0.034 [−0.034, 0.102]		0.075 [0.012, 0.137]

Mean ± standard deviation (number of subjects)
[a)] See note [a)] of Table 26 for the models.

Adverse events occurred in 73.6% (374 of 508) of subjects in the Tio + Olo 2.5/5 µg group, 73.8% (374 of 507) of subjects in the Tio + Olo 5/5 µg group, 75.7% (384 of 507) of subjects in the Tio 2.5 µg group, 74.3% (376 of 506) of subjects in the Tio 5 µg group, and 79.4% (405 of 510) of subjects in the Olo 5 µg group. Table 31 shows the adverse events with an incidence of ≥2% in any group.

A total of 8 deaths occurred in the Tio + Olo 2.5/5 µg group (ventricular fibrillation, pulmonary embolism, pneumonia, acute myocardial infarction, COPD, cardiac arrest, septic shock,[42] and acute kidney failure[42] in 1 subject each), 11 in the Tio + Olo 5/5 µg group (COPD in 2 subjects;[43] small cell lung cancer, prostate cancer metastatic, biliary sepsis, pulmonary oedema, drowning, aortic aneurysm rupture, dyspnoea, lung neoplasm malignant, [42] and cardiopulmonary failure[42] in 1 subject each), 5 in the Tio 2.5 µg group (cardio-respiratory arrest, pancreatic carcinoma, COPD, death, and cardiac arrest[42] in 1 subject each), 11 in the Tio 5 µg group (haemorrhage intracranial, cardiac arrest, small cell lung cancer, sudden death, COPD, prostate cancer, respiratory failure, femoral neck fracture, [42] death, [42] cardio-respiratory arrest,[42] and myocardial infarction[42] in 1 subject each), and 13 in the Olo 5 µg group (cerebral haemorrhage and death in 2 subjects each,[43] and shock, cardiac arrest, multi-organ failure, cardiac failure, cardiac failure acute, ileus, COPD, delirium, and duodenal ulcer perforation[42] in 1 subject each). A causal relationship to the study drug was ruled out for all events except for that occurring1 subject (aortic aneurysm rupture) in the Tio + Olo 5/5 µg group, and 1 subject (death[42]) in the Tio 5 µg group.

[42] The adverse event was observed after the completion of treatment period, or after the completion of the study.
[43] One of the events was observed after the completion of treatment period, or after the completion of the study.

Serious adverse events occurred in 87 of 508 subjects (17.1%) in the Tio + Olo 2.5/5 µg group, 82 of 507 subjects (16.2%) in the Tio + Olo 5/5 µg group, 90 of 507 subjects (17.8%) in the Tio 2.5 µg group, 93 of 506 subjects (18.4%) in the Tio 5 µg group, and 106 of 510 subjects (20.8%) in the Olo 5 µg group. Common serious adverse events include COPD and pneumonia. COPD occurred in 30 of 508 subjects (5.9%) in the Tio + Olo 2.5/5 µg group, 33 of 507 subjects (6.5%) in the Tio + Olo 5/5 µg group, 37 of 507 subjects (7.3%) in the Tio 2.5 µg group, 33 of 506 subjects (6.5%) in the Tio 5 µg group, and 41 of 510 subjects (8.0%) in the Olo 5 µg group. Pneumonia occurred in 9 of 508 subjects (1.8%) in the Tio + Olo 2.5/5 µg group, 9 of 507 subjects (1.8%) in the Tio + Olo 5/5 µg group, 6 of 507 subjects (1.2%) in the Tio 2.5 µg group, 2 of 506 subjects (0.4%) in the Tio 5 µg group, and 6 of 510 subjects (1.2%) in the Olo 5 µg group. A causal relationship to the study drug could not be ruled out for the events experienced by 3 subjects in the Tio + Olo 2.5/5 µg group (myocardial infarction, COPD/nephritis, and COPD in 1 subject each), 5 subjects in the Tio + Olo 5/5 µg group (COPD, extrasystoles, aortic aneurysm rupture, benign prostatic hyperplasia, and pneumonia in 1 subject each), 3 subjects in the Tio 2.5 µg group (lung neoplasm malignant, lung neoplasm malignant, and COPD in 1 subject each), 6 subjects in the Tio 5 µg group (acute polyneuropathy, atrial fibrillation, COPD/benign prostatic hyperplasia, dysuria, benign prostatic hyperplasia, and chest discomfort in 1 subject each), and 1 subject in the Olo 5 µg group (angina pectoris).

Adverse events leading to the discontinuation of treatment occurred in 28 of 508 subjects (5.5%) in the Tio + Olo 2.5/5 µg group, 39 of 507 subjects (7.7%) in the Tio + Olo 5/5 µg group, 53 of 507 subjects (10.5%) in the Tio 2.5 µg group, 51 of 506 subjects (10.1%) in the Tio 5 µg group, and 54 of 510 subjects (10.6%) in the Olo 5 µg group.

Adverse reactions occurred in 32 of 508 subjects (6.3%) in the Tio + Olo 2.5/5 µg group, 37 of 507 subjects (7.3%) in the Tio + Olo 5/5 µg group, 38 of 507 subjects (7.5%) in the Tio 2.5 µg group, 38 of 506 subjects (7.5%) in the Tio 5 µg group, and 37 of 510 subjects (7.3%) in the Olo 5 µg group.

Table 31. Adverse events with an incidence of ≥2% in any group (safety analysis population)

Event	Tio+Olo 2.5/5 µg (508 subjects)	Tio+Olo 5/5 µg (507 subjects)	Tio 2.5 µg (507 subjects)	Tio 5 µg (506 subjects)	Olo 5 µg (510 subjects)
COPD	148 (29.1)	162 (32.0)	183 (36.1)	165 (32.6)	188 (36.9)
Nasopharyngitis	70 (13.8)	61 (12.0)	59 (11.6)	54 (10.7)	66 (12.9)
Upper respiratory tract infection	29 (5.7)	29 (5.7)	31 (6.1)	27 (5.3)	32 (6.3)
Cough	29 (5.7)	24 (4.7)	27 (5.3)	25 (4.9)	17 (3.3)
Back pain	20 (3.9)	24 (4.7)	13 (2.6)	8 (1.6)	15 (2.9)
Dyspnoea	22 (4.3)	22 (4.3)	24 (4.7)	29 (5.7)	20 (3.9)
Influenza	15 (3.0)	16 (3.2)	11 (2.2)	12 (2.4)	13 (2.5)
Pneumonia	11 (2.2)	15 (3.0)	13 (2.6)	7 (1.4)	14 (2.7)
Bronchitis	14 (2.8)	14 (2.8)	12 (2.4)	9 (1.8)	22 (4.3)
Headache	15 (3.0)	13 (2.6)	11 (2.2)	25 (4.9)	15 (2.9)
Urinary tract infection	10 (2.0)	13 (2.6)	8 (1.6)	16 (3.2)	3 (0.6)
Hypertension	19 (3.7)	12 (2.4)	10 (2.0)	11 (2.2)	26 (5.2)
Diarrhoea	13 (2.6)	12 (2.4)	12 (2.4)	14 (2.8)	15 (2.9)
Sinusitis	11 (2.2)	11 (2.2)	12 (2.4)	5 (1.0)	10 (2.0)
Fall	6 (1.2)	10 (2.0)	6 (1.2)	8 (1.6)	8 (1.6)
Constipation	11 (2.2)	9 (1.8)	9 (1.8)	9 (1.8)	9 (1.8)
Arthralgia	11 (2.2)	9 (1.8)	6 (1.2)	7 (1.4)	5 (1.0)
Dizziness	10 (2.0)	9 (1.8)	8 (1.6)	7 (1.4)	7 (1.4)
Nausea	9 (1.8)	9 (1.8)	2 (0.4)	13 (2.6)	2 (0.4)
Chest pain	8 (1.6)	9 (1.8)	13 (2.6)	10 (2.0)	10 (2.0)
Oedema peripheral	8 (1.6)	9 (1.8)	4 (0.8)	8 (1.6)	10 (2.0)
Rhinitis	6 (1.2)	8 (1.6)	10 (2.0)	7 (1.4)	4 (0.8)
Abdominal pain	4 (0.8)	6 (1.2)	11 (2.2)	6 (1.2)	3 (0.6)
Dry mouth	7 (1.4)	5 (1.0)	9 (1.8)	11 (2.2)	7 (1.4)
Oropharyngeal pain	11 (2.2)	4 (0.8)	11 (2.2)	11 (2.2)	7 (1.4)
Insomnia	8 (1.6)	4 (0.8)	3 (0.6)	7 (1.4)	12 (2.4)
Pharyngitis	5 (1.0)	4 (0.8)	4 (0.8)	10 (2.0)	9 (1.8)
Muscle spasms	9 (1.8)	3 (0.6)	5 (1.0)	4 (0.8)	12 (2.4)
Gastroenteritis	4 (0.8)	3 (0.6)	7 (1.4)	7 (1.4)	10 (2.0)
Pain in extremity	12 (2.4)	2 (0.4)	12 (2.4)	8 (1.6)	1 (0.2)

Number of subjects (%)

Adverse events occurred in 83.7% (36 of 43) of subjects in the Tio + Olo 2.5/5 µg group, 79.4% (27 of 34) of subjects in the Tio + Olo 5/5 µg group, 79.5% (31 of 39) of subjects in the Tio 2.5 µg group, 86.8% (33 of 38) of subjects in the Tio 5 µg group, and 85.5% (47 of 55) of subjects in the Olo 5 µg group. Table 32 shows the adverse events that occurred in ≥3 subjects in any group.

One death occurred in the Tio + Olo 5/5 µg group (aortic aneurysm rupture), and a causal relationship to the study drug could not be ruled out for the deaths.

In the Japanese subpopulation, serious adverse events occurred in 7 of 43 subjects (16.3%) in the Tio + Olo 2.5/5 µg group (lumbar spinal stenosis, pneumonia, lung neoplasm malignant, rectal cancer, lumbar spinal stenosis/spondylitic myelopathy, vocal cord polyp, and melaena in 1 subject each), 6 of 34 subjects (17.6%) in the Tio + Olo 5/5 µg group (COPD in 2 subjects; and bronchitis, aortic aneurysm rupture, hypercapnia, and pulmonary granuloma in 1 subject each), 4 of 39 subjects (10.3%) in the Tio 2.5 µg group (gastroenteritis/tendon rupture, influenza, gastric cancer, and lung neoplasm malignant in 1 subject each), 5 of 38 subjects (13.2%) in the Tio 5 µg group (bronchitis/analgesic asthma syndrome/nasal polyps/renal vasculitis, gastroenteritis, sweat gland tumour, anti-neutrophil cytoplasmic antibody positive vasculitis, and COPD in 1 subject each), 8 of 55 subjects (14.5%) in the Olo 5 µg group (pneumonia in 3 subjects; and COPD, influenza, cataract, pneumonia/COPD/cardiac failure/pulmonary embolism, and mesenteric artery stenosis in 1 subject each). A causal relationship to

the study drug could not be ruled out for the events experienced by 1 subject in the Tio + Olo 5/5 μg group (aortic aneurysm rupture) and 1 subject in the Tio 2.5 μg group (lung neoplasm malignant).

In the Japanese subpopulation, adverse events leading to the discontinuation of treatment occurred in 3 of 43 subjects (7.0%) in the Tio + Olo 2.5/5 μg group, 4 of 34 subjects (11.8%) in the Tio + Olo 5/5 μg group, 3 of 39 subjects (7.7%) in the Tio 2.5 μg group, 3 of 38 subjects (7.9%) in the Tio 5 μg group, and 3 of 55 subjects (5.5%) in the Olo 5 μg group.

Adverse reactions occurred in 3 of 43 subjects (7.0%) in the Tio + Olo 2.5/5 μg group, 5 of 34 subjects (14.7%) in the Tio + Olo 5/5 μg group, 4 of 39 subjects (10.3%) in the Tio 2.5 μg group, 1 of 38 subjects (2.6%) in the Tio 5 μg group, and 6 of 55 subjects (10.9%) in the Olo 5 μg group.

Table 32. Adverse events that occurred in ≥3 subjects in any group (Japanese subpopulation)

Event	Tio+Olo 2.5/5 μg (43 subjects)	Tio+Olo 5/5 μg (34 subjects)	Tio 2.5 μg (39 subjects)	Tio 5 μg (38 subjects)	Olo 5 μg (55 subjects)
Nasopharyngitis	10 (23.3)	10 (29.4)	14 (35.9)	5 (13.2)	14 (25.5)
Bronchitis	1 (2.3)	5 (14.7)	0	4 (10.5)	5 (9.1)
COPD	3 (7.0)	4 (11.8)	9 (23.1)	7 (18.4)	8 (14.5)
Insomnia	0	2 (5.9)	0	2 (5.3)	3 (5.5)
Back pain	2 (4.7)	1 (2.9)	1 (2.6)	1 (2.6)	3 (5.5)
Gastroenteritis	2 (4.7)	1 (2.9)	3 (7.7)	1 (2.6)	1 (1.8)
Hypertension	1 (2.3)	1 (2.9)	0	1 (2.6)	4 (7.3)
Diabetes mellitus	1 (2.3)	1 (2.9)	3 (7.7)	0	1 (1.8)
Upper respiratory tract infection	0	1 (2.9)	2 (5.1)	2 (5.3)	6 (10.9)
Constipation	3 (7.0)	0	1 (2.6)	3 (7.9)	3 (5.5)
Oropharyngeal pain	2 (4.7)	0	1 (2.6)	3 (7.9)	0
Influenza	2 (4.7)	0	2 (5.1)	2 (5.3)	3 (5.5)
Pneumonia	2 (4.7)	0	1 (2.6)	0	5 (9.1)
Dermatitis contact	0	0	0	4 (10.5)	1 (1.8)

Number of subjects (%)

4.(ii).A.(2).3) The pooled analysis of Studies 1237.5 and 1237.6 (5.3.5.3-3)

Table 33 shows the SGRQ total score after 24 weeks of treatment, the co-primary endpoint for the pooled data analysis of the replicate studies (Studies 1237.5 and 1237.6). The results suggest that the difference was statistically significant between the Tio + Olo 5/5 μg and Olo 5 μg groups and between the Tio + Olo 5/5 μg and Tio 5 μg groups. In contrast, the difference was not statistically significant between the Tio + Olo 2.5/5 μg and Olo 5 μg groups, or between the Tio + Olo 2.5/5 μg and Tio 2.5 μg groups.

Table 33. The SGRQ total score after 24 weeks of treatment (FAS, WOCF)

	Tio+Olo 2.5/5 μg	Tio+Olo 5/5 μg	Tio 2.5 μg	Tio 5 μg	Olo 5 μg
Baseline	43.841 ± 17.831 (990)	44.225 ± 17.921 (979)	43.300 ± 17.789 (960)	43.298 ± 18.138 (955)	42.849 ± 18.312 (954)
After 24 weeks of treatment	37.586 ± 18.576 (947)	37.314 ± 18.004 (940)	37.532 ± 17.378 (921)	37.604 ± 18.275 (910)	37.341 ± 18.474 (897)
Difference from Tio+Olo 5/5 μg group [95% CI],[a)] p-value[a), b)]				−1.233 [−2.313, −0.153] p=0.0252	−1.693 [−2.778, −0.608] p=0.0022
Difference from Tio+Olo 2.5/5 μg group [95% CI],[a)] p-value[a), b)]			−0.456 [−1.531, 0.618]		−1.031 [−2.113, 0.052] p=0.0620

Mean ± standard deviation (number of subjects)
[a)] See note [a)] of Table 25 for the models.
[b)] See note [b)] of Table 25 for multiplicity.

Table 34 shows the SGRQ total score after 24 weeks of treatment in the Japanese subpopulation.

Table 34. The SGRQ total score after 24 weeks of treatment (Japanese subpopulation, WOCF)

	Tio+Olo 2.5/5 μg	Tio+Olo 5/5 μg	Tio 2.5 μg	Tio 5 μg	Olo 5 μg
Baseline	34.336 ± 16.744 (76)	36.374 ± 15.082 (76)	32.277 ± 15.985 (68)	34.791 ± 16.373 (74)	31.463 ± 14.986 (103)
After 24 weeks of treatment	28.570 ± 14.420 (73)	29.217 ± 16.232 (71)	29.835 ± 16.297 (65)	31.325 ± 17.774 (73)	27.359 ± 15.672 (97)
Difference from Tio+Olo 5/5 μg group [95% CI][a)]				−3.604 [−6.712, −0.497]	−3.331 [−6.334, −0.328]
Difference from Tio+Olo 2.5/5 μg group [95% CI][a)]			−2.947 [−6.132, 0.238]		−1.973 [−4.891, 0.945]

Mean ± standard deviation (number of subjects)
[a)] See note [a)] of Table 26 for the models.

4.(ii).A.(2).4) Japanese phase III study (5.3.5.1-14, Study 1237.22 [February 2012 to September 2013])

A randomized, double-blind, active-controlled, parallel-group study was conducted in patients with COPD[44] (target sample size, 120 [40 subjects/group]) to evaluate the efficacy and safety of Tio + Olo FDC.

Subjects received a once-daily inhaled dose of Tio + Olo FDC 2.5/5 μg, Tio + Olo FDC 5/5 μg, or Olo 5 μg for 52 weeks.

All 122 randomized subjects were included in the FAS and safety analysis population and the efficacy analysis population (40 subjects [Tio + Olo 2.5/5 μg], 41 subjects [Tio + Olo 5/5 μg], and 41 subjects [Olo 5 μg]). The study drug was discontinued in 5.0% (2 of 40) of subjects in the Tio + Olo 2.5/5 μg group, 4.9% (2 of 41) of subjects in the Tio + Olo 5/5 μg group, and 19.5% (8 of 41) of subjects in the Olo 5 μg group.

[44] Patients with a diagnosis of COPD, relatively stable, meeting the following criteria: (1) post-bronchodilator FEV_1 of <80% of predicted value at the time of screening visit (GOLD II to IV); (2) post-bronchodilator FEV_1/FVC <70%; (3) aged ≥40 years; and (4) a current or former smoker with a smoking history of >10 pack years.

Adverse events occurred in 30 of 40 subjects (75.0%) in the Tio + Olo 2.5/5 μg group, 35 of 41 subjects (85.4%) in the Tio + Olo 5/5 μg group, and 33 of 41 subjects (80.5%) in the Olo 5 μg group. Table 35 shows the adverse events that occurred in ≥2 subjects in any group.

No deaths occurred.

Serious adverse events occurred in 6 of 40 subjects (15.0%) in the Tio + Olo 2.5/5 μg group, 3 of 41 subjects (7.3%) in the Tio + Olo 5/5 μg group, and 5 of 41 subjects (12.2%) in the Olo 5 μg group. The serious adverse event that occurred in ≥2 subjects in any group was COPD (3 of 40 subjects [7.5%] in the Tio + Olo 2.5/5 μg group; 2 of 41 subjects [4.9%] in the Tio + Olo 5/5 μg group; and 2 of 41 subjects [4.9%] in the Olo 5 μg group). A causal relationship to the study drug could not be ruled out for the event in 1 subject (interstitial lung disease) in the Olo 5 μg group.

Adverse events leading to the discontinuation of treatment occurred in 1 of 40 subjects (2.5%) in the Tio + Olo 2.5/5 μg group, 2 of 41 subjects (4.9%) in the Tio + Olo 5/5 μg group, and 6 of 41 subjects (14.6%) in the Olo 5 μg group.

Adverse reactions occurred in 2 of 40 subjects (5.0%) in the Tio + Olo 2.5/5 μg group, 3 of 41 subjects (7.3%) in the Tio + Olo 5/5 μg group, and 2 of 41 subjects (4.9%) in the Olo 5 μg group.

Table 35. Adverse event that occurred in ≥2 subjects in any group (safety analysis population)

Event	Tio+Olo 2.5/5 μg (40 subjects)	Tio+Olo 5/5 μg (41 subjects)	Olo 5 μg (41 subjects)
Nasopharyngitis	11 (27.5)	11 (26.8)	17 (41.5)
COPD	7 (17.5)	9 (22.0)	6 (14.6)
Bronchitis	5 (12.5)	6 (14.6)	3 (7.3)
Constipation	1 (2.5)	4 (9.8)	3 (7.3)
Gastroenteritis	3 (7.5)	2 (4.9)	0
Pharyngitis	3 (7.5)	2 (4.9)	1 (2.4)
Hyperuricaemia	2 (5.0)	2 (4.9)	0
Eczema	2 (5.0)	2 (4.9)	0
Back pain	2 (5.0)	2 (4.9)	1 (2.4)
Rhinitis allergic	0	2 (4.9)	1 (2.4)
Infected dermal cyst	0	2 (4.9)	1 (2.4)
Hypertension	0	2 (4.9)	0
Musculoskeletal stiffness	2 (5.0)	1 (2.4)	0
Upper respiratory tract infection	1 (2.5)	1 (2.4)	2 (4.9)
Abdominal pain upper	1 (2.5)	1 (2.4)	2 (4.9)
Diarrhoea	1 (2.5)	1 (2.4)	2 (4.9)
Pneumonia	0	1 (2.4)	2 (4.9)
Benign prostatic hyperplasia	0	1 (2.4)	2 (4.9)
Spinal osteoarthritis	2 (5.0)	0	1 (2.4)
Oral herpes	2 (5.0)	0	0
Periarthritis	2 (5.0)	0	0
Gastritis	0	0	2 (4.9)

Number of subjects (%)

Table 36 shows the change from baseline in the trough FEV_1 values.[45]

[45] The baseline was defined as the mean of FEV_1 values measured 1 hour before and 10 minutes before the first inhalation of the study drug. Trough FEV_1 was defined as the mean of FEV_1 values measured 1 hour before and 10 minutes before the inhalation of the study drug on the next day.

Table 36. Change from baseline in trough FEV_1 values (FAS, WOCF)

	Tio+Olo 2.5 /5 μg	Tio+Olo 5/5 μg	Olo 5 μg
After 12 weeks of treatment	0.198 ± 0.179 (40)	0.259 ± 0.132 (41)	0.106 ± 0.146 (38)
After 24 weeks of treatment	0.206 ± 0.210 (40)	0.185 ± 0.165 (40)	0.093 ± 0.153 (37)
After 52 weeks of treatment	0.168 ± 0.193 (39)	0.143 ± 0.157 (39)	0.075 ± 0.156 (34)

Mean ± standard deviation (number of subjects)

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

4.(ii).B.(1) Efficacy

The applicant's explanation on the submitted clinical data package for Tio + Olo FDC:

In Japan, the clinical data package in support of the application for Tio + Olo FDC was prepared based on the results of the multiregional phase III studies involving Japanese patients (Studies 1237.5 and 1237.6) and other studies, which evaluated the synergistic effect of the FDC of Olo and Tio, an approved LAMA as compared with its constituent products. Because the Olo alone is unapproved in Japan, a bridging approach was employed so that its efficacy and safety could be demonstrated based on the data extrapolated from foreign phase III studies, if bridging between the Japanese phase II study (Study 1222.22, bridging study) and a foreign phase II study (Study 1222.5, study to be bridged) was successful. The extrapolated data would be supplementarily used as the rationale for the dosage and administration of Olo as a component of Tio + Olo FDC.

There are no significant differences between Japan and other countries in the disease definition, diagnostic criteria, and therapeutic system for COPD including classes and dosage of drugs, and no clinically significant differences in the pharmacokinetic profile of Tio + Olo FDC between Japanese and non-Japanese patients [see "4.(i).B.(1) Ethnic differences in pharmacokinetics of Olo"], etc. Olo monotherapy can thus be evaluated based on the results of foreign clinical studies in accordance with the ICH E5 guideline entitled "Ethnic Factors in the Acceptability of Foreign Clinical Data" (PMSB/ELD Notification No. 672 dated August 11, 1998), and Tio + Olo FDC can be evaluated based on the results of multiregional phase III studies (Studies 1237.5 and 1237.6) as confirmatory studies in accordance with "Basic principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007).

4.(ii).B.(1).1) Efficacy of Olo monoproduct

The applicant's explanation on the extrapolation of data from the foreign phase III studies to evaluate the efficacy of Olo alone in Japanese COPD patients:

Table 37 shows changes from baseline in trough FEV_1 after 4 weeks of treatment in a Japanese phase II study (Study 1222.22, bridging study) and a foreign phase II study (Study1222.5, study to be bridged). As a result of pairwise comparison with placebo, the Olo groups showed a statistically significant difference, but in both Japanese and foreign studies, the change from baseline in trough FEV_1 was smaller in the Olo 2 μg group than in the 5 μg and 10 μg groups.

Table 37. Changes from baseline in trough FEV_1 (L) after 4 weeks of treatment

	Olo 2 μg	Olo 5 μg	Olo 10 μg	Olo 20 μg	Placebo
Japanese phase II (1222.22)[a)]	0.059 ± 0.145 (84) 0.091 [0.051, 0.131]	0.102 ± 0.121 (79) 0.132 [0.091, 0.172]	0.103 ± 0.146 (86) 0.132 [0.092, 0.172]		−0.030 ± 0.117 (79)
Foreign phase II (1222.5)[a)]	0.035 ± 0.158 (81) 0.061 [0.008, 0.113]	0.072 ± 0.188 (80) 0.097 [0.044, 0.149]	0.100 ± 0.229 (86) 0.123 [0.072, 0.175]	0.107 ± 0.161 (79) 0.132 [0.080, 0.185]	−0.025 ± 0.139 (79)

Upper, change from baseline; mean ± standard deviation (number of subjects); lower, difference from placebo [95% CI]
[a)] Based on the linear mixed effect models, with treatment group and baseline as fixed effects, and center as a random effect.

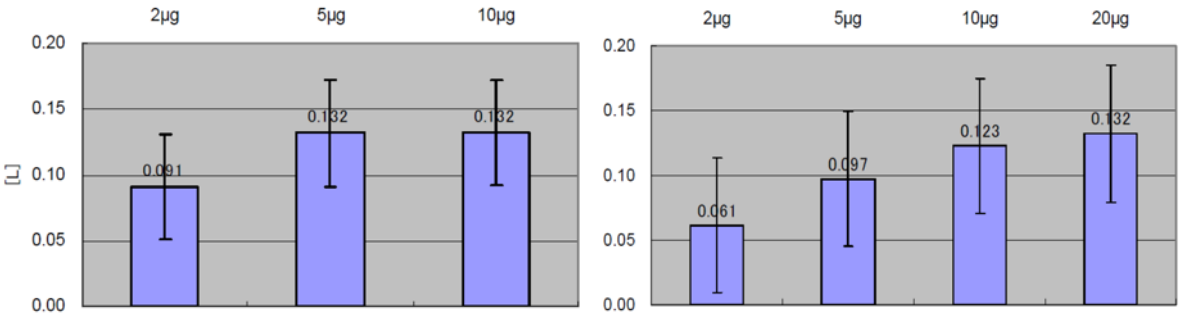

Figure 2. Changes from baseline in trough FEV_1 (L) after 4 weeks of treatment in the Japanese phase II study (left) and foreign phase II study (right) (Difference from placebo, mean and 95% CI)

In the Japanese phase II study, the incidence of adverse events was 33.3% (28 of 84 subjects) in the Olo 2 μg group, 31.6% (25 of 79 subjects) in the Olo 5 μg group, 41.9% (36 of 86 subjects) in the Olo 10 μg group, and 35.4% (28 of 79 subjects) in the placebo group. The incidence of adverse events in the foreign phase II study was 37.0% (30 of 81 subjects) in the Olo 2 μg group, 41.3% (33 of 80 subjects) in the Olo 5 μg group, 30.2% (26 of 86 subjects) in the Olo 10 μg group, 38.0% (30 of 79 subjects) in the Olo 20 μg group, and 36.7% (29 of 79 subjects) in the placebo group, indicating similarity to those in the Japanese study. The types of adverse events were also similar between the 2 studies, and the safety profile of Olo showed no clear dose dependence up to 10 μg in both studies.

Patient characteristics were compared between the populations of the Japanese and foreign phase II studies. Background factors including the proportion of male subjects, age, and body weight tended to differ, but the subgroup analysis of the effects of these factors on the change from baseline in trough FEV_1 revealed no apparent differences between subgroups in both Japanese and foreign studies. The differences in these factors were therefore unlikely to have affected the efficacy evaluation.

Based on these findings and discussions, the applicant concluded that the foreign phase III study data as a whole may be extrapolated to Japanese patients with COPD.

The applicant's explanation on the efficacy of the Olo alone and the justification for the dosage and administration of Olo as a component of Tio + Olo FDC based on the data from foreign phase III studies (Studies 1222.11, 1222.12, 1222.13, and 1222.14):

The change from baseline in trough FEV_1 after 12 to 24 weeks of treatment, one of the primary efficacy endpoints of these studies, was analyzed. As a result of pairwise comparison with placebo, the Olo 5 μg and Olo 10 μg groups of the Studies 1222.11, 1222.13, and 1222.14, showed statistically significant differences, while the Olo 5 μg or Olo 10 μg group of the Study 1222.12 did not. However, the

differences from the placebo groups in the 4 studies were 33 to 84 mL for the Olo 5 μg groups and 45 to 80 mL for the Olo 10 μg groups [see "4.(ii).A Summary of the submitted data"], showing the similarity of bronchodilating effects of Olo 5 μg and Olo 10 μg. Change from baseline in FEV_1AUC_{0-3}, another primary efficacy endpoint showed similar results. In Studies 1222.13 and 1222.14, in both of which formoterol, an approved LABA, was used as the comparator, differences from the placebo group in the change from baseline in trough FEV_1 after 24 weeks of treatment were similar between the Olo 5 μg groups (78 and 53 mL, respectively) and the formoterol groups (54 and 42 mL, respectively) [see "4.(ii).A Summary of the submitted data"]. Furthermore, given that no difference was found between the 2 dose levels in terms of safety [see "4.(ii).B.(2) Safety"], 5 μg is considered the appropriate dose of Olo.

As explained, trough FEV_1 measured 24 hours after dosing showed consistently improving pulmonary function. Once-daily inhalation of Olo may therefore be sufficient, as with Tio.

On the basis of the above findings, The dosage of 5 μg once daily for Olo as a component of Tio + Olo FDC is considered the appropriate, and is also appropriate for Japanese patients with COPD given a similar trend seen in the efficacy results from the Japanese and foreign phase II studies.

PMDA accepted the applicant's explanations and concluded that the data on Olo monotherapies such as those from the foreign phase III studies can be extrapolated to Japanese patients with COPD, and that The proposed dosage of 5 μg once daily is appropriate for Olo as a component of Tio + Olo FDC in Japanese as well as in foreign patients with COPD, based on the results of foreign phase III studies (Studies 1222.11, 1222.12, 1222.13, and 1222.14),.

4.(ii).B.(1).2) Efficacy of Tio + Olo FDC

The applicant's explanation on the efficacy of Tio + Olo FDC:

The change from baseline in trough FEV_1 after 24 weeks of treatment, the primary efficacy endpoint of the multiregional phase III studies (Studies 1237.5 and 1237.6), demonstrated the superiority of the FDC doses, Tio + Olo 2.5/5 μg and 5/5 μg, over the individual components in the entire population of both studies (Table 38). The change from baseline in FEV_1AUC_{0-3}, another primary efficacy endpoint, also showed similar results. These indicate that the efficacy of Tio + Olo FDC in patients with COPD has been demonstrated. Furthermore, the results of both multiregional studies showed consistency between the entire study population and the Japanese subpopulation and, therefore the efficacy of Tio + Olo FDC in Japanese patients with COPD may be evaluated based on the data from Studies 1237.5 and 1237.6. The SGRQ total score after 24 weeks of treatment, the primary endpoint of the pooled data analysis of Studies 1237.5 and 1237.6 was analyzed. As a result of pairwise comparison with the individual FDC components (Tio and Olo), the Tio + Olo 5/5 μg group showed statistically significant differences, while the Tio + Olo 2.5/5 μg group did not [see "4.(ii).A Summary of the submitted data"].

Table 38. Changes from baseline in the trough FEV_1 values (L) after 24 weeks of treatment in Studies 1237.5 and 1237.6

	Study 1237.5			Study 1237.6		
	Tio 2.5 µg	Tio 5 µg	Olo 5 µg	Tio 2.5 µg	Tio 5 µg	Olo 5 µg
Entire study population						
Difference from Tio+Olo 2.5/5 µg group [95% CI], [a] p-value[a), b)]	0.029 [0.005, 0.052] p=0.0174		0.058 [0.034, 0.081] p<0.0001	0.062 [0.037, 0.087] p<0.0001		0.067 [0.042, 0.092] p<0.0001
Difference from Tio+Olo 5/5 µg group [95% CI], [a] p-value[a), b)]		0.071 [0.047, 0.094] p<0.0001	0.082 [0.059, 0.106] p<0.0001		0.050 [0.024, 0.075] p=0.0001	0.088 [0.063, 0.113] p<0.0001
Japanese subpopulation						
Difference from Tio+Olo 2.5/5 µg group [95% CI][a)]	0.066 [−0.008, 0.141]		0.043 [−0.023, 0.110]	0.034 [−0.034, 0.102]		0.075 [0.012, 0.137]
Difference from Tio+Olo 5/5 µg group [95% CI][a)]		0.152 [0.085, 0.218]	0.134 [0.072, 0.196]		0.059 [−0.014, 0.131]	0.124 [0.056, 0.192]

[a)] See note [a)] of Table 25 for the models
[b)] See note [b)] of Table 25 for multiplicity

Patient characteristics of Studies 1237.5 and 1237.6 were compared between the entire study population and the Japanese subpopulation. The comparisons identified different trends in the distribution of the factors listed below. Then, a subgroup analysis was performed based on pooled data of Studies 1237.5 and 1237.6 to investigate the effects of these factors on the change from baseline in trough FEV_1. No significant difference was observed among subpopulations for these factors in both studies (Table 39), and they were therefore unlikely to have affected the efficacy evaluation.

- Age (entire population, 64.2 years [Study 1237.5] and 63.8 years [Study 1237.6]; Japanese subpopulation, 69.3 years [Study 1237.5] and 68.9 years[Study 1237.6])
- Proportion of male subjects (entire population, 73.7% [Study 1237.5] and 72.0% [Study 1237.6]; Japanese subpopulation, 95.1% [Study 1237.5] and 91.9% [Study 1237.6])
- Proportion of current smokers (entire population, 37.5% [Study 1237.5] and 36.4% [Study 1237.6]; Japanese subpopulation, 17.2% [Study 1237.5] and 18.7% [Study 1237.6])
- Proportion of subjects with GOLD stages II, III and IV (entire population, 50.2%, 39.1% and 10.7%, respectively [Study 1237.5], 50.1%, 37.9%, and 11.8%, respectively [Study 1237.6]; Japanese subpopulation, 55.9%, 36.8%, and 7.4%, respectively [Study 1237.5], 63.6%, 30.6%, and 5.7%, respectively [Study 1237.6])
- Proportion of subjects previously treated with LAMA (entire population, 36.5% [Study 1237.5] and 34.7% [Study 1237.6]; Japanese subpopulation, 62.7% [Study 1237.5] and 66.5% [Study 1237.6])
- Percentages of subjects previously treated with short-acting muscarinic antagonist (SAMA) (entire population, 10.3% [Study 1237.5] and 15.6% [Study 1237.6]; Japanese subpopulation, 2.9% [Study 1237.5] and 1.0% [Study 1237.6])
- Proportion of subjects with previous treatment with LABA (entire population, 48.1% [Study 1237.5] and 44.6% [Study 1237.6]; Japanese subpopulation, 28.9% [Study 1237.5] and 25.4% [Study 1237.6])

Table 39. The results of the subgroup analysis of the changes from baseline in the trough FEV_1 values (L) after 24 weeks of treatment

		Number of subjects (Tio+Olo [2.5/5 μg] / Tio 2.5 μg / Olo 5 μg)	Difference between Tio+Olo 2.5/5 μg and Tio 2.5 μg groups [95% CI]	Difference between Tio+Olo 2.5/5 μg and Olo 5 μg groups [95% CI]	Number of subjects (Tio+Olo [5/5 μg] / Tio 5 μg / Olo 5 μg)	Difference between Tio+Olo 5/5 μg and Tio 5 μg groups [95% CI]	Difference between Tio+Olo 5/5 μg and Olo 5 μg groups [95% CI]
Sex	Male	752/746/753	0.048 [0.027, 0.069]	0.071 [0.050, 0.092]	724/745/753	0.060 [0.039, 0.081]	0.088 [0.067, 0.109]
	Female	266/272/269	0.035 [0.006, 0.064]	0.039 [0.010, 0.068]	293/273/269	0.060 [0.031, 0.088]	0.076 [0.047, 0.104]
Age	<65 years	528/528/515	0.055 [0.029, 0.081]	0.076 [0.049, 0.102]	520/529/515	0.070 [0.044, 0.097]	0.100 [0.073, 0.127]
	≥65 years and <75 years	387/374/399	0.037 [0.012, 0.062]	0.041 [0.017, 0.066]	403/380/399	0.058 [0.033, 0.083]	0.062 [0.037, 0.087]
	≥75 years	103/116/108	0.023 [−0.018, 0.063]	0.071 [0.030, 0.112]	94/109/108	0.014 [−0.028, 0.056]	0.089 [0.047, 0.132]
Body weight	<50 kg	64/54/43	0.063 [0.005, 0.120]	0.094 [0.033, 0.155]	55/53/43	0.059 [−0.000, 0.118]	0.110 [0.047, 0.173]
	≥50 kg and <70 kg	401/410/429	0.050 [0.024, 0.075]	0.072 [0.047, 0.097]	437/405/429	0.037 [0.012, 0.062]	0.087 [0.062, 0.112]
	≥70 kg	540/544/537	0.040 [0.015, 0.065]	0.053 [0.028, 0.078]	511/553/537	0.081 [0.056, 0.106]	0.085 [0.059, 0.110]
Smoking status	Former	652/635/652	0.059 [0.038, 0.079]	0.054 [0.034, 0.074]	619/655/652	0.044 [0.024, 0.065]	0.069 [0.049, 0.089]
	Current	366/383/370	0.022 [−0.009, 0.053]	0.078 [0.047, 0.110]	398/363/370	0.086 [0.055, 0.117]	0.111 [0.081, 0.142]
GOLD stage	II	514/513/526	0.045 [0.019, 0.071]	0.052 [0.026, 0.078]	496/512/526	0.069 [0.042, 0.095]	0.083 [0.057, 0.109]
	III and IV	503/503/496	0.045 [0.023, 0.067]	0.073 [0.051, 0.095]	521/505/496	0.052 [0.030, 0.073]	0.087 [0.065, 0.109]
LABA	Not used	533/548/539	0.060 [0.037, 0.084]	0.063 [0.039, 0.087]	535/570/539	0.070 [0.046, 0.093]	0.090 [0.067, 0.114]
	Used	485/470/483	0.027 [0.002, 0.052]	0.062 [0.038, 0.087]	482/448/483	0.049 [0.024, 0.075]	0.078 [0.053, 0.103]
LAMA	Not used	619/672/664	0.038 [0.016, 0.061]	0.057 [0.034, 0.079]	641/675/664	0.063 [0.041, 0.085]	0.084 [0.062, 0.106]
	Used	399/346/358	0.057 [0.030, 0.083]	0.072 [0.046, 0.099]	376/343/358	0.054 [0.028, 0.081]	0.086 [0.060, 0.113]
SAMA	Not used	884/878/890	0.045 [0.026, 0.063]	0.061 [0.042, 0.079]	895/889/890	0.058 [0.040, 0.077]	0.085 [0.067, 0.104]
	Used	134/140/132	0.046 [−0.001, 0.093]	0.075 [0.028, 0.122]	122/129/132	0.065 [0.016, 0.114]	0.077 [0.029, 0.126]

PMDA concluded that the efficacy of Tio + Olo FDC in patients with COPD has been demonstrated in the multiregional phase III studies (Studies 1237.5 and 1237.6), and that based on the results of these studies, Tio + Olo FDC is expected to be effective in Japanese patients with COPD for the following reasons:

- Superiority of Tio + Olo FDC (Tio + Olo 2.5/5 μg and Tio + Olo 5/5 μg) over Tio 2.5 and 5 μg, and Olo 5 μg was demonstrated in changes from baseline in trough FEV_1 values.
- Consistency in changes from baseline in trough FEV_1 values between the entire study population and Japanese subpopulation was demonstrated. In the subgroup analysis, some patient background factors showed different distribution trends between the entire population and the Japanese subpopulation, but none of these factors were not likely to affect the efficacy evaluation of Tio + Olo FDC. Furthermore, in terms of exposure to Tio or Olo, there was no clinically important difference between non-Japanese and Japanese subjects [see the Review Report of "Spiriva 2.5 μg

Respimat 60 Puffs," dated November 10, 2009 (in Japanese only), and "4.(i).B.(1) Ethnic differences in pharmacokinetics of Olo"].

4.(ii).B.(2) Safety

The applicant's explanation on the safety of Olo alone and Tio + Olo FDC from the results of the 4 foreign phase III studies (Studies 1222.11, 1222.12, 1222.13, and 1222.14) of Olo (pooled data of the Olo monotherapies) and 2 multiregional phase III studies (Studies 1237.5 and 1237.6) and Japanese phase III study (Study 1237.22) of Tio + Olo FDC (pooled data of Tio + Olo FDC):

Tables 40 and 42 show common adverse events observed in the pooled data of the Olo monotherapies and the Tio + Olo FDC, respectively. There were no significant differences in the incidences of adverse events among placebo, Tio alone, Olo alone, and Tio + Olo FDC.

Table 41 summarizes the adverse events in the pooled data of the Olo monotherapies. Adverse events that resulted in death include: respiratory system-related events including exacerbation of COPD (8 subjects in the Olo 5 μg group, 3 subjects in the Olo 10 μg group, 2 subjects in the formoterol group, and 4 subjects in the placebo group); and neoplasm benign or malignant including lung cancer (2 subjects in the Olo 5 μg group, 7 subjects in the Olo 10 μg group, and 1 subject in the formoterol group). Common serious adverse events (including deaths) included respiratory system-related events including exacerbation of COPD and infections including pneumonia. Respiratory system-related events including exacerbation of COPD occurred in 48 of 876 subjects (5.5%) in the Olo 5 μg group, 70 of 883 subjects (7.9%) in the Olo 10 μg group, 31 of 460 subjects (6.7%) in the formoterol group, and 64 of 885 subjects (7.2%) in the placebo group. Infections including pneumonia occurred in 34 of 876 subjects (3.9%) in the Olo 5 μg group, 32 of 883 subjects (3.6%) in the Olo 10 μg group, 13 of 460 subjects (2.8%) in the formoterol group, and 31 of 885 subjects (3.5%) in the placebo group.

Table 43 summarizes the adverse events in the pooled data of the Tio + Olo FDC. Adverse events that resulted in death include: neoplasm benign or malignant including lung cancer (3 subjects in the Tio + Olo 2.5/5 μg group, 4 subjects in the Tio + Olo 5/5 μg group, 2 subjects in the Tio 2.5 μg group, 7 subjects in the Tio 5 μg group, and 1 subject in the Olo 5 μg group); and respiratory system-related events including exacerbation of COPD (4 subjects in the Tio + Olo 2.5/5 μg group, 4 subjects in the Tio + Olo 5/5 μg group, 4 subjects in the Tio 2.5 μg group, 6 subjects in the Tio 5 μg group, and 2 subjects in the Olo 5 μg group). Common serious adverse events (including deaths) include respiratory system-related events including exacerbation of COPD and infections including pneumonia. Respiratory system-related events including exacerbation of COPD occurred in 63 of 1070 subjects (5.9%) in the Tio + Olo 2.5/5 μg group, 80 of 1070 subjects (7.5%) in the Tio + Olo 5/5 μg group, 74 of 1032 subjects (7.2%) in the Tio 2.5 μg group, 69 of 1033 subjects (6.7%) in the Tio 5 μg group, and 75 of 1079 subjects (7.0%) in the Olo 5 μg group. Infections including pneumonia occurred in 31 of 1070 subjects (2.9%) in the Tio + Olo 2.5/5 μg group, 35 of 1070 subjects (3.3%) in the Tio + Olo 5/5 μg group, 23 of 1032

subjects (2.2%) in the Tio 2.5 μg group, 23 of 1033 subjects (2.2%) in the Tio 5 μg group, and 39 of 1079 subjects (3.6%) in the Olo 5 μg group.

Table 40. Adverse events with an incidence of ≥2% in any group in the pooled data of Olo

	Olo 5 μg (876 subjects)	Olo 10 μg (883 subjects)	Formoterol (460 subjects)	Placebo (885 subjects)
Total	622 (71.0)	642 (72.7)	318 (69.1)	627 (70.8)
Chronic obstructive pulmonary disease	227 (25.9)	266 (30.1)	131 (28.5)	255 (28.8)
Nasopharyngitis	99 (11.3)	91 (10.3)	46 (10.0)	68 (7.7)
Upper respiratory tract infection	72 (8.2)	62 (7.0)	32 (7.0)	66 (7.5)
Bronchitis	41 (4.7)	31 (3.5)	13 (2.8)	32 (3.6)
Cough	37 (4.2)	35 (4.0)	27 (5.9)	35 (4.0)
Dyspnoea	35 (4.0)	25 (2.8)	25 (5.4)	37 (4.2)
Back pain	31 (3.5)	28 (3.2)	18 (3.9)	24 (2.7)
Headache	25 (2.9)	30 (3.4)	15 (3.3)	32 (3.6)
Diarrhoea	25 (2.9)	22 (2.5)	11 (2.4)	22 (2.5)
Hypertension	23 (2.6)	26 (2.9)	8 (1.7)	30 (3.4)
Pneumonia	22 (2.5)	35 (4.0)	14 (3.0)	24 (2.7)
Urinary tract infection	22 (2.5)	16 (1.8)	5 (1.1)	9 (1.0)
Dizziness	20 (2.3)	18 (2.0)	7 (1.5)	19 (2.1)
Arthralgia	18 (2.1)	14 (1.6)	6 (1.3)	7 (0.8)
Influenza	16 (1.8)	9 (1.0)	11 (2.4)	16 (1.8)
Pyrexia	12 (1.4)	20 (2.3)	12 (2.6)	17 (1.9)
Muscle spasms	12 (1.4)	8 (0.9)	10 (2.2)	11 (1.2)
Chest pain	11 (1.3)	16 (1.8)	13 (2.8)	16 (1.8)
Gastroenteritis	10 (1.1)	8 (0.9)	10 (2.2)	11 (1.2)
Sinusitis	8 (0.9)	20 (2.3)	1 (0.2)	21 (2.4)
Constipation	5 (0.6)	19 (2.2)	3 (0.7)	15 (1.7)

Number of subjects (%)

Table 41. Summary of adverse events for the pooled data of Olo

	Olo 5 μg (876 subjects)	Olo 10 μg (883 subjects)	Formoterol (460 subjects)	Placebo (885 subjects)
All adverse events	622 (71.0)	642 (72.7)	318 (69.1)	627 (70.8)
Adverse events related to study drug	63 (7.2)	52 (5.9)	52 (11.3)	79 (8.9)
Adverse events leading to the discontinuation of study or of treatment with study drug	54 (6.2)	66 (7.5)	37 (8.0)	74 (8.4)
Serious adverse events (including death)	138 (15.8)	147 (16.6)	69 (15.0)	145 (16.4)
Adverse events that resulted in death	13 (1.5)	17 (1.9)	10 (2.2)	13 (1.5)

Table 42. Adverse events with an incidence of ≥2% in any group in the pooled data of Tio + Olo FDC

	Tio+Olo 2.5/5 μg (1070 subjects)	Tio+Olo 5/5 μg (1070 subjects)	Tio 2.5 μg (1032 subjects)	Tio 5 μg (1033 subjects)	Olo 5 μg (1079 subjects)
Total	799 (74.7)	796 (74.4)	758 (73.4)	757 (73.3)	828 (76.7)
Chronic obstructive pulmonary disease	308 (28.8)	341 (31.9)	352 (34.1)	340 (32.9)	376 (34.8)
Nasopharyngitis	145 (13.6)	139 (13.0)	123 (11.9)	121 (11.7)	148 (13.7)
Upper respiratory tract infection	70 (6.5)	55 (5.1)	61 (5.9)	57 (5.5)	58 (5.4)
Cough	43 (4.0)	41 (3.8)	46 (4.5)	45 (4.4)	31 (2.9)
Dyspnoea	37 (3.5)	39 (3.6)	44 (4.3)	51 (4.9)	38 (3.5)
Back pain	42 (3.9)	39 (3.6)	23 (2.2)	19 (1.8)	36 (3.3)
Pneumonia	31 (2.9)	35 (3.3)	24 (2.3)	26 (2.5)	38 (3.5)
Bronchitis	33 (3.1)	37 (3.5)	23 (2.2)	23 (2.2)	36 (3.3)
Influenza	29 (2.7)	31 (2.9)	25 (2.4)	22 (2.1)	25 (2.3)
Hypertension	35 (3.3)	32 (3.0)	28 (2.7)	30 (2.9)	48 (4.4)
Headache	30 (2.8)	28 (2.6)	23 (2.2)	41 (4.0)	31 (2.9)
Diarrhoea	30 (2.8)	25 (2.3)	23 (2.2)	27 (2.6)	35 (3.2)
Oropharyngeal pain	21 (2.0)	10 (0.9)	17 (1.6)	16 (1.5)	17 (1.6)
Urinary tract infection	23 (2.1)	22 (2.1)	18 (1.7)	30 (2.9)	13 (1.2)
Sinusitis	19 (1.8)	21 (2.0)	22 (2.1)	13 (1.3)	18 (1.7)
Chest pain	15 (1.4)	14 (1.3)	17 (1.6)	22 (2.1)	17 (1.6)
Constipation	23 (2.1)	17 (1.6)	17 (1.6)	16 (1.5)	19 (1.8)

Number of subjects (%)

Table 43. Summary of adverse events in the entire population and Japanese subpopulation in the pooled data of Tio + Olo FDC

		Tio+Olo 2.5/5 μg (1070 subjects)	Tio+Olo 5/5 μg (1070 subjects)	Tio 2.5 μg (1032 subjects)	Tio 5 μg (1033 subjects)	Olo 5 μg (1079 subjects)
Entire population	All adverse events	799 (74.7)	796 (74.4)	758 (73.4)	757 (73.3)	828 (76.7)
	Adverse events related to study drug	64 (6.0)	76 (7.1)	62 (6.0)	63 (6.1)	71 (6.6)
	Adverse events leading to the discontinuation of study or treatment with study drug	58 (5.4)	78 (7.3)	90 (8.7)	93 (9.0)	109 (10.1)
	Serious adverse events (including death)	174 (16.3)	172 (16.1)	156 (15.1)	172 (16.7)	186 (17.2)
	Adverse events that resulted in death	14 (1.3)	18 (1.7)	12 (1.2)	17 (1.6)	14 (1.3)
		Tio+Olo 2.5/5 μg (118 subjects)	Tio+Olo 5/5 μg (120 subjects)	Tio 2.5 μg (72 subjects)	Tio 5 μg (76 subjects)	Olo 5 μg (149 subjects)
Japanese subpopulation	All adverse events	96 (81.4)	99 (82.5)	55 (76.4)	63 (82.9)	124 (83.2)
	Adverse events related to study drug	9 (7.6)	12 (10.0)	5 (6.9)	4 (5.3)	12 (8.1)
	Adverse events leading to the discontinuation of study or treatment with study drug	8 (6.8)	12 (10.0)	5 (6.9)	6 (7.9)	15 (10.1)
	Serious adverse events (including death)	24 (20.3)	18 (15.0)	7 (9.7)	14 (18.4)	21 (14.1)
	Adverse events that resulted in death	0	2 (1.7)	0	0	0

Number of subjects (%)

Table 43 summarizes the adverse events of the Japanese subpopulation in the pooled data of Tio + Olo FDC. Common adverse events in the Japanese subpopulation include nasopharyngitis, COPD, and bronchitis. Nasopharyngitis occurred in 31 of 118 subjects (26.3%) in the Tio + Olo 2.5/5 μg group, 35 of 120 subjects (29.2%) in the Tio + Olo 5/5 μg group, 23 of 72 subjects (31.9%) in the Tio 2.5 μg group, 15 of 76 subjects (19.7%) in the Tio 5 μg group, and 45 of 149 subjects (30.2%) in the Olo 5 μg group. COPD occurred in 16 of 118 subjects (13.6%) in the Tio + Olo 2.5/5 μg group, 28 of 120 subjects (23.3%) in the Tio + Olo 5/5 μg group, 14 of 72 subjects (19.4%) in the Tio 2.5 μg group, 13 of 76

subjects (17.1%) in the Tio 5 µg group, 27 of 149 subjects (18.1%) in the Olo 5 µg group. Bronchitis occurred in 10 of 118 subjects (8.5%) in the Tio + Olo 2.5/5 µg group, 18 of 120 subjects (15.0%) in the Tio + Olo 5/5 µg group, 1 of 72 subjects (1.4%) in the Tio 2.5 µg group, 9 of 76 subjects (11.8%) in the Tio 5 µg group, and 12 of 149 subjects (8.1%) in the Olo 5 µg group.

A limited number of Japanese subjects precluded rigorous comparison. Nevertheless, the occurrence of adverse events in the Japanese subpopulation tended to be similar to that in the entire population.

The applicant further explained the occurrence of adverse cardiovascular events attributable to the class effects of LAMA or LABA and LAMA- or LABA-related adverse events, based on the pooled data of Olo monotherapies and Tio + Olo FDC. The details are presented in the sections below.

4.(ii).B.(2).1) LAMA- or LABA-related adverse events

(a) Adverse cardiovascular events

The occurrence of adverse cardiovascular events of arrhythmia, torsade de pointes/QT prolonged, ischaemic heart disease, cardiac failure, cerebrovascular disorder, and hypertension were investigated.

Tables 44 and 45 show the incidences of serious adverse cardiovascular events and adverse cardiovascular events in the pooled data of Olo monotherapies and Tio + Olo FDC, respectively. The incidences of events did not differ significantly between treatment groups. The incidence of serious adverse cardiovascular events was 3% or less in all Olo groups and Tio + Olo FDC groups.

Table 44. Incidences of adverse cardiovascular events in the pooled data of Olo

	Olo 5 µg (876 subjects)	Olo 10 µg (883 subjects)	Formoterol (460 subjects)	Placebo (885 subjects)
Adverse cardiovascular events	101 (11.5)	101 (11.4)	43 (9.3)	111 (12.5)
Arrhythmia	57 (6.5)	52 (5.9)	28 (6.1)	48 (5.4)
Torsade de pointes/QT prolonged	11 (1.3)	4 (0.5)	5 (1.1)	6 (0.7)
Ischaemic heart disease	14 (1.6)	26 (2.9)	7 (1.5)	22 (2.5)
Cardiac failure	11 (1.3)	7 (0.8)	1 (0.2)	5 (0.6)
Cerebrovascular disorder	7 (0.8)	7 (0.8)	1 (0.2)	15 (1.7)
Hypertension	27 (3.1)	30 (3.4)	10 (2.2)	36 (4.1)
Serious adverse cardiovascular events	26 (3.0)	20 (2.3)	9 (2.0)	37 (4.2)
Arrhythmia	10 (1.1)	7 (0.8)	7 (1.5)	9 (1.0)
Torsade de pointes/QT prolonged	1 (0.1)	0	1 (0.2)	0
Ischaemic heart disease	6 (0.7)	12 (1.4)	3 (0.7)	14 (1.6)
Cardiac failure	8 (0.9)	4 (0.5)	1 (0.2)	2 (0.2)
Cerebrovascular disorder	5 (0.6)	3 (0.3)	0	12 (1.4)
Hypertension	2 (0.2)	1 (0.1)	0	2 (0.2)

Number of subjects (%)

Table 45. Incidences of adverse cardiovascular events in the pooled data of Tio + Olo FDC

	Tio+ Olo 2.5/5 μg (1070 subjects)	Tio+Olo 5/5 μg (1070 subjects)	Tio 2.5 μg (1032 subjects)	Tio 5 μg (1033 subjects)	Olo 5 μg (1079 subjects)
Adverse cardiovascular events	117 (10.9)	105 (9.8)	109 (10.6)	104 (10.1)	125 (11.6)
Arrhythmia	52 (4.9)	42 (3.9)	49 (4.7)	47 (4.5)	42 (3.9)
Torsade de pointes/QT prolonged	3 (0.3)	5 (0.5)	3 (0.3)	3 (0.3)	5 (0.5)
Ischaemic heart disease	21 (2.0)	22 (2.1)	23 (2.2)	22 (2.1)	27 (2.5)
Cardiac failure	9 (0.8)	6 (0.6)	8 (0.8)	8 (0.8)	12 (1.1)
Cerebrovascular disorder	10 (0.9)	8 (0.7)	12 (1.2)	9 (0.9)	11 (1.0)
Hypertension	42 (3.9)	38 (3.6)	34 (3.3)	35 (3.4)	53 (4.9)
Serious adverse events cardiovascular	26 (2.4)	28 (2.6)	23 (2.2)	28 (2.7)	30 (2.8)
Arrhythmia	9 (0.8)	8 (0.7)	6 (0.6)	8 (0.8)	7 (0.6)
Torsade de pointes/QT prolonged	0	1 (0.1)	0	0	1 (0.1)
Ischaemic heart disease	8 (0.7)	13 (1.2)	7 (0.7)	11 (1.1)	10 (0.9)
Cardiac failure	3 (0.3)	3 (0.3)	5 (0.5)	5 (0.5)	4 (0.4)
Cerebrovascular disorder	7 (0.7)	5 (0.5)	6 (0.6)	6 (0.6)	9 (0.8)
Hypertension	1 (0.1)	0	0	4 (0.4)	2 (0.2)

Number of subjects (%)

An analysis of pooled data of the Tio + Olo FDC group showed that the incidences of serious adverse cardiovascular events and adverse cardiovascular events in the Japanese subpopulation were similar to those in the entire population. In the Japanese subpopulation, the incidence of adverse events was 11.0% (13 of 118 subjects) in the Tio + Olo 2.5/5 μg group, 6.7% (8 of 120 subjects) in the Tio + Olo 5/5 μg group, 12.5% (9 of 72 subjects) in the Tio 2.5 μg group, 7.9% (6 of 76 subjects) in the Tio 5 μg group, and 11.4% (17 of 149 subjects) in the Olo 5 μg group. Hypertension, one of the common adverse events, occurred in 5 of 118 subjects (4.2%) in the Tio + Olo 2.5/5 μg group, 3 of 120 subjects (2.5%) in the Tio + Olo 5/5 μg group, 4 of 72 subjects (5.6%) in the Tio 2.5 μg group, 4 of 76 subjects (5.3%) in the Tio 5 μg group, and 8 of 149 subjects (5.4%) in the Olo 5 μg group. Serious adverse cardiovascular events occurred in 3 subjects in the Tio + Olo 2.5/5 μg group (cardiac failure chronic, acute myocardial infarction, and cardiac failure acute), 3 subjects in the Tio + Olo 5/5 μg group (aortic aneurysm rupture, cardiac failure chronic/cardiac failure acute, and sudden death), 1 subject in the Tio 5 μg group (myocardial ischaemia), and 1 subject in the Olo 5 μg group (cardiac failure).

A subgroup analysis was conducted based on the presence or absence of baseline cardiovascular risk factors (e.g., diabetes mellitus and dyslipidaemia) or concurrent cardiovascular diseases to investigate the relationship between the onset of adverse cardiovascular events and risk factors. Although a limited number of subjects experiencing adverse cardiovascular events precluded rigorous comparison, serious adverse cardiovascular events tended to occur more frequently in the subpopulation with cardiovascular risk factors or cardiovascular complications. However, the trend toward increased incidence of serious cardiovascular events in the Tio + Olo FDC groups was not significant as compared with the Olo or Tio group.

Common electrocardiogram-related adverse events observed in the pooled data of Tio Olo FDC include QT prolonged and T wave inversion. QT prolonged occurred in 3 of 1070 subjects (0.3%) in the Tio + Olo 2.5/5 μg group, 3 of 1070 subjects (0.3%) in the Tio + Olo 5/5 μg group, 2 of 1032 subjects (0.2%) in the Tio 2.5 μg group, 3 of 1033 subjects (0.3%) in the Tio 5 μg group, 2 of 1079 subjects (0.2%) in the Olo 5 μg group. T wave inversion occurred in 1 of 1070 subjects (0.1%) in the Tio + Olo 2.5/5 μg

group, 1 of 1070 subjects (0.1%) in the Tio + Olo 5/5 μg group, 1 of 1032 subjects (0.1%) in the Tio 2.5 μg group, 3 of 1079 subjects (0.3%) in the Olo 5 μg group. No consistent trend was observed among treatment groups or treatment durations, and the incidence of the adverse events in the Japanese subpopulation was similar to that of the entire population.

Table 46 shows the incidences of adverse cardiovascular events in the pooled data of Tio + Olo FDC by time to onset of a cardiovascular event (Months 0 to 3, Months 4 to 6, Months 7 to 9, Months 10 to 12, and Month 13 or later). The results did not show increased adverse cardiovascular events in any treatment group after long-term treatment.

Table 46. Incidences of adverse cardiovascular events in the pooled data of Tio + Olo by time to event onset

	Tio+Olo 2.5/5 μg (1070 subjects)	Tio+Olo 5/5 μg (1070 subjects)	Tio 2.5 μg (1032 subjects)	Tio 5 μg (1033 subjects)	Olo 5 μg (1079 subjects)
Months 0 to 3	38/1070 (3.6)	31/1070 (2.9)	43/1032 (4.2)	50/1033 (4.8)	50/1079 (4.6)
Months 4 to 6	36/1046 (3.4)	35/1036 (3.4)	37/984 (3.8)	27/980 (2.8)	39/1018 (3.8)
Months 7 to 9	20/1012 (2.0)	14/1001 (1.4)	14/935 (1.5)	14/933 (1.5)	13/952 (1.4)
Months 10 to 12	25/973 (2.6)	26/959 (2.7)	17/889 (1.9)	17/900 (1.9)	20/922 (2.2)
Month 13 or later	8/951 (0.8)	8/939 (0.9)	7/865 (0.8)	6/870 (0.7)	14/886 (1.6)

Number of subjects (%)

Further, major adverse cardiac events (MACEs) were analyzed based on the pooled data of Olo monotherapies and Tio + Olo FDC. As shown in Tables 47 and 48, the incidences of MACEs were low in all treatment groups. No trend toward increased incidence of adverse cardiovascular events was seen in the Tio + Olo FDC groups as compared with the Tio or Olo alone group, or in the Olo groups as compared with the placebo groups. In the Japanese subpopulation of the pooled data of the Tio + Olo FDC, the incidence of MACEs was 2.5% (3 of 118 subjects) in the Tio + Olo 2.5/5 μg group, 2.5% (3 of 120 subjects) in the Tio + Olo 5/5 μg group, 2.8% (2 of 72 subjects) in the Tio 2.5 μg group, 0% (0 of 76 subjects) in the Tio 5 μg group, and 1.3% (2 of 149 subjects) in the Olo 5 μg group, showing no significant difference from that in the entire population. Two deaths occurred in the Tio + Olo 5/5 μg group due to MACEs.

Table 47. Incidences of MACEs in the pooled data of Olo

	Olo 5 μg (876 subjects)	Olo 10 μg (883 subjects)	Formoterol (460 subjects)	Placebo (885 subjects)
MACE	10 (1.1)	16 (1.8)	9 (2.0)	24 (2.7)
Cardiac disorder	2 (0.2)	1 (0.1)	3 (0.7)	3 (0.3)
Angiopathy	0	0	1 (0.2)	1 (0.1)
Myocardial infarction	4 (0.5)	12 (1.4)	4 (0.9)	9 (1.0)
Stroke	3 (0.3)	3 (0.3)	1 (0.2)	11 (1.2)
Sudden death	0	0	1 (0.2)	1 (0.1)
Sudden cardiac death	1 (0.1)	1 (0.1)	0	0
Fetal MACE	3 (0.3)	2 (0.2)	5 (1.1)	6 (0.7)
Cardiac disorder	2 (0.2)	1 (0.1)	3 (0.7)	3 (0.3)
Angiopathy	0	0	1 (0.2)	1 (0.1)
Myocardial infarction	0	0	1 (0.2)	1 (0.1)
Stroke	0	0	0	1 (0.1)
Sudden death	0	0	1 (0.2)	1 (0.1)
Sudden cardiac death	1 (0.1)	1 (0.1)	0	0
Death	0	1 (0.1)	1 (0.2)	2 (0.2)

Number of subjects (%)

Table 48. Incidences of MACE in the pooled data of Tio + Olo FDC

	Tio+Olo 2.5/5 µg (1070 subjects)	Tio+Olo 5/5 µg (1070 subjects)	Tio 2.5 µg (1032 subjects)	Tio 5 µg (1033 subjects)	Olo 5 µg (1079 subjects)
MACE	22 (2.1)	24 (2.2)	21 (2.0)	19 (1.8)	26 (2.4)
Cardiac disorder	5 (0.5)	3 (0.3)	4 (0.4)	3 (0.3)	4 (0.4)
Angiopathy	0	2 (0.2)	0	1 (0.1)	1 (0.1)
Myocardial infarction	14 (1.3)	11 (1.0)	10 (1.0)	8 (0.8)	11 (1.0)
Stroke	4 (0.4)	7 (0.7)	7 (0.7)	7 (0.7)	10 (0.9)
Sudden death	0	1 (0.1)	0	1 (0.1)	0
Fetal MACE	5 (0.5)	7 (0.7)	5 (0.5)	5 (0.5)	7 (0.6)
Cardiac disorder	5 (0.5)	3 (0.3)	4 (0.4)	3 (0.3)	4 (0.4)
Angiopathy	0	2 (0.2)	0	1 (0.1)	1 (0.1)
Myocardial infarction	1 (0.1)	0	0	0	0
Stroke	0	1 (0.1)	1 (0.1)	1 (0.1)	2 (0.2)
Sudden death	0	1 (0.1)	0	1 (0.1)	0
Death	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)

Number of subjects (%)

(b) LABA-related adverse events

The incidences of the following LABA-related, non-cardiovascular adverse events were analyzed: metabolism and nutrition disorders (hypokalaemia, hyperglycaemia, and lactic acidosis), musculoskeletal and connective tissue disorders (arthralgia, myalgia, muscular weakness, muscle spasms, and blood creatinine phosphokinase increased), nervous system disorders (dizziness, tremor, spasm and sleep disorder), and psychiatric disorders (restlessness and nervousness).

The pooled data of Olo monotherapies (Table 49) or Tio + Olo FDC (Table 50) were analyzed. The incidences of LABA-related adverse events did not differ significantly among the treatment groups.

In the Japanese subpopulation in the pooled data of Tio + Olo FDC, the incidence of LABA-related adverse events was 24.6% (29 of 118 subjects) in the Tio + Olo 2.5/5 µg group, 15.0% (18 of 120 subjects) in the Tio + Olo 5/5 µg group, 16.7% (12 of 72 subjects) in the Tio 2.5 µg group, 15.8% (12 of 76 subjects) in the Tio 5 µg group, and 18.8% (28 of 149 subjects) in the Olo 5 µg group, showing no significant difference from that in the entire population.

Table 49. Incidences of LABA-related adverse events in the pooled data of Olo

	Olo 5 µg (876 subjects)	Olo 10 µg (883 subjects)	Formoterol (460 subjects)	Placebo (885 subjects)
Total	144 (16.4)	145 (16.4)	72 (16.3)	118 (13.3)
Metabolism and nutrition disorders	17 (1.9)	16 (1.8)	4 (0.9)	17 (1.3)
Musculoskeletal and connective tissue disorders	108 (12.3)	104 (11.8)	61 (13.3)	84 (9.5)
Nervous system disorders	35 (4.0)	43 (4.9)	15 (3.3)	31 (3.5)
Psychiatric disorders	1 (0.1)	1 (0.1)	1 (0.2)	2 (0.2)

Number of subjects (%)

Table 50. Incidences of LABA-related adverse events in the pooled data of Tio + Olo FDC

	Tio+Olo 2.5/5 µg (1070 subjects)	Tio+Olo 5/5 µg (1070 subjects)	Tio 2.5 µg (1032 subjects)	Tio 5 µg (1033 subjects)	Olo 5 µg (1079 subjects)
Total	205 (19.2)	178 (16.6)	152 (14.7)	157 (15.2)	174 (16.1)
Metabolism and nutrition disorders	28 (2.6)	21 (2.0)	30 (2.9)	28 (2.7)	21 (1.9)
Musculoskeletal and connective tissue disorders	144 (13.5)	134 (12.5)	102 (9.9)	104 (10.1)	121 (11.2)
Nervous system disorders	53 (5.0)	41 (3.8)	32 (3.1)	39 (3.8)	50 (4.6)
Psychiatric disorders	3 (0.3)	0	0	1 (0.1)	1 (0.1)

Number of subjects (%)

(c) LAMA-related adverse events

The incidences of the following LAMA-related, non-cardiovascular adverse events were analyzed: eye disorders (glaucoma, vision blurred, and lens disorder), gastrointestinal disorders (dry mouth, stomatitis, gingivitis, constipation, and intestinal obstruction), renal or urinary disorders (urinary retention, and prostatic disorder), skin and subcutaneous tissue disorders (dry skin).

The incidences of LAMA-related events did not differ significantly among the treatment groups in the pooled data of Tio + Olo FDC (Table 51).

In the Japanese subpopulation in the pooled data of Tio + Olo FDC, the incidence of LAMA-related events was 13.6% (16 of 118 subjects) in the Tio + Olo 2.5/5 μg group, 12.5% (15 of 120 subjects) in the Tio + Olo 5/5 μg group, 12.5% (9 of 72 subjects) in the Tio 2.5 μg group, 13.2% (10 of 76 subjects) in the Tio 5 μg group, and 13.4% (20 of 149 subjects) in the Olo 5 μg group, showing no significant difference from that in the entire population.

Table 51. Incidences of LAMA-related adverse events in the pooled data of Tio + Olo FDC

	Tio+Olo 2.5/5 μg (1070 subjects)	Tio+Olo 5/5 μg (1070 subjects)	Tio 2.5 μg (1032 subjects)	Tio 5 μg (1033 subjects)	Olo 5 μg (1079 subjects)
Total	79 (7.4)	82 (7.7)	73 (7.1)	81 (7.8)	76 (7.0)
Eye disorders	17 (1.6)	17 (1.6)	15 (1.5)	16 (1.5)	22 (2.0)
Gastrointestinal disorders	42 (3.9)	43 (4.0)	35 (3.4)	43 (4.2)	39 (3.6)
Renal or urinary disorders	19 (1.8)	19 (1.8)	16 (1.6)	19 (1.8)	17 (1.6)
Skin and subcutaneous tissue disorders	4 (0.4)	2 (0.2)	3 (0.3)	3 (0.3)	0

Number of subjects (%)

PMDA's view:

The submitted study data showed no trend toward greater risk of adverse cardiovascular events associated with Tio + Olo FDC than that associated with Tio or Olo alone. The risk of adverse cardiovascular events associated with associated with Olo alone did not tend to greater than that associated with placebo, or formoterol, an approved LABA. These findings suggest no significant difference in the risk of adverse cardiovascular events between Tio + Olo FDC and Tio or Olo alone, or other similar drugs. However,β_2-agonists are known to have a potential risk of cardiovascular events caused by β-receptor stimulation, and an increased risk of adverse cardiovascular events including death and other major events associated with the inhalation of an anticholinergic agent has been reported (Singh S et al. *JAMA*. 300: 1439-1450, 2008; Singh S et al. *BMJ*. 342.d3215[online], 2011). Given these facts, the possibility that the coadministration of LAMA and LABA may increase the risk of adverse cardiovascular events cannot be denied. Therefore, the incidence of adverse cardiovascular events following the administration of Tio + Olo FDC should be carefully investigated based further on accumulated post-marketing safety data in and outside Japan, including a relationship to the presence of a risk factor or other patient characteristics. LAMA- or LABA-related non-cardiovascular events, although no particular concerns were indicated, at present, the occurrence of these events associated with the combination of LAMA and LABA in clinical use should also be further investigated via post-marketing surveillance. The package insert of Tio + Olo FDC should include precautionary statements on the risk of adverse cardiovascular events and LAMA- or LABA-related events.

4.(ii).B.(2).2) Effects of age and body weight on safety

In Japanese patients with COPD, the proportion of the elderly with low body weight is relatively large. PMDA therefore asked the applicant to explain the safety of Tio + Olo FDC in the elderly or lower body-weight patients by showing the incidence of adverse events by age and by body weight

The applicant's explanation:

Table 52 shows the incidences of adverse events by age in the pooled data of Tio + Olo FDC. While the incidences of adverse events and serious adverse events tended to be high in subjects aged ≥75 years, there was no trend towards significant difference among treatment groups. The high incidences were therefore attributed to increased onset of diseases due to aging. The incidences of adverse cardiovascular events, LABA-related, and LAMA-related events did not differ significantly between age groups, or between treatment groups.

Table 53 shows the incidences of adverse events by body weight in the pooled data of Tio + Olo FDC. The incidences of adverse events and serious adverse events tended to be high in patients with body weight of <50 kg in the Tio + Olo 5/5 μg group. Serious adverse events tended to occur more frequently in patients with body weight of <50 kg. The incidences of adverse cardiovascular events, LABA- or LAMA-related events did not differ significantly among body-weight groups, or between treatment groups.

Table 52. Incidences of adverse events by age in the pooled data of Tio + Olo FDC

	Age group	Tio+Olo 2.5/5 μg (1070 subjects)	Tio+Olo 5/5 μg (1070 subjects)	Tio 2.5 μg (1032 subjects)	Tio 5 μg (1033 subjects)	Olo 5 μg (1079 subjects)
Adverse events	<65 years	395/545 (72.5)	389/538 (72.3)	389/534 (72.8)	376/540 (69.6)	394/527 (74.8)
	65-74 years	303/409 (74.1)	322/427 (75.4)	281/379 (74.1)	290/383 (75.7)	334/427 (78.2)
	≥75 years	101/116 (87.1)	85/105 (81.0)	88/119 (73.9)	91/110 (82.7)	100/125 (80.0)
Serious adverse events	<65 years	79/545 (14.5)	75/538 (13.9)	69/534 (12.9)	67/540 (12.4)	84/527 (15.9)
	65-74 years	68/409 (16.6)	68/427 (15.9)	69/379 (18.2)	76/383 (19.8)	68/427 (15.9)
	≥75 years	27/116 (23.3)	29/105 (27.6)	18/119 (15.1)	29/110 (26.4)	34/125 (27.2)
Adverse events leading to treatment discontinuation	<65 years	26/545 (4.8)	22/538 (4.1)	44/534 (8.2)	34/540 (6.3)	47/527 (8.9)
	65-74 years	23/409 (5.6)	44/427 (10.3)	31/379 (8.2)	46/383 (12.0)	44/427 (10.3)
	≥75 years	9/116 (7.8)	12/105 (11.4)	15/119 (12.6)	13/110 (11.8)	18/125 (14.4)
Adverse cardiovascular events	<65 years	52/545 (9.5)	53/538 (9.9)	46/534 (8.6)	53/540 (9.8)	45/527 (8.5)
	65-74 years	44/409 (10.8)	37/427 (8.7)	47/379 (12.4)	36/383 (9.4)	59/427 (13.8)
	≥75 years	21/116 (18.1)	15/105 (14.3)	16/119 (13.4)	15/110 (13.6)	21/125 (16.8)
LAMA-related events	<65 years	33/545 (6.1)	29/538 (5.4)	22/534 (4.1)	23/540 (4.3)	32/527 (6.1)
	65-74 years	33/409 (8.1)	40/427 (9.4)	37/379 (9.8)	40/383 (10.4)	34/427 (8.0)
	≥75 years	13/116 (11.2)	13/105 (12.4)	14/119 (11.8)	18/110 (16.4)	10/125 (8.0)
LABA-related events	<65 years	91/545 (16.7)	87/538 (16.2)	68/534 (12.7)	73/540 (13.5)	78/527 (14.8)
	65-74 years	83/409 (20.3)	71/427 (16.6)	68/379 (17.9)	68/383 (17.8)	70/427 (16.4)
	≥75 years	31/116 (26.7)	20/105 (19.0)	16/119 (13.4)	16/110 (14.5)	26/125 (20.8)

Number of subjects (%)

Table 53. Incidences of adverse events by body weight in the pooled data of Tio + Olo FDC

	Body weight group	Tio+Olo 2.5/5 μg (1070 subjects)	Tio+Olo 5/5 μg (1070 subjects)	Tio 2.5 μg (1032 subjects)	Tio 5 μg (1033 subjects)	Olo 5 μg (1079 subjects)
Adverse events	<50 kg	57/72 (79.2)	49/62 (79.0)	41/54 (75.9)	48/54 (88.9)	43/52 (82.7)
	≥50 kg and <70 kg	329/430 (76.5)	350/467 (74.9)	305/415 (73.5)	286/412 (69.4)	364/460 (79.1)
	≥70 kg	403/553 (72.9)	386/527 (73.2)	405/553 (73.2)	418/560 (74.6)	410/554 (74.0)
Serious adverse events	<50 kg	10/72 (13.9)	20/62 (32.3)	7/54 (13.0)	11/54 (20.4)	10/52 (19.2)
	≥50 kg and <70 kg	72/430 (16.7)	64/467 (13.7)	62/415 (14.9)	59/412 (14.3)	83/460 (18.0)
	≥70 kg	89/553 (16.1)	86/527 (16.3)	87/553 (15.7)	99/560 (17.7)	91/554 (16.4)
Adverse events leading to treatment discontinuation	<50 kg	1/72 (1.4)	9/62 (14.5)	7/54 (13.0)	6/54 (11.1)	7/52 (13.5)
	≥50 kg and <70 kg	21/430 (4.9)	36/467 (7.7)	39/415 (9.4)	34/412 (8.3)	51/460 (11.1)
	≥70 kg	36/553 (6.5)	33/527 (6.3)	44/553 (8.0)	50/560 (8.9)	50/554 (9.0)
Cardiovascular events	<50 kg	5/72 (6.9)	12/62 (19.4)	8/54 (14.8)	3/54 (5.6)	8/52 (15.4)
	≥50 kg and <70 kg	41/430 (9.5)	35/467 (7.5)	38/415 (9.2)	47/412 (11.4)	52/460 (11.3)
	≥70 kg	70/553 (12.7)	56/527 (10.6)	63/553 (11.4)	52/560 (9.3)	64/554 (11.6)
LAMA-related events	<50 kg	10/72 (13.9)	8/62 (12.9)	5/54 (9.3)	6/54 (11.1)	6/52 (11.5)
	≥50 kg and <70 kg	29/430 (6.7)	35/467 (7.5)	31/415 (7.5)	36/412 (8.7)	36/460 (7.8)
	≥70 kg	39/553 (7.1)	38/527 (7.2)	37/553 (6.7)	38/560 (6.8)	34/554 (6.1)
LABA-related events	<50 kg	16/72 (22.2)	12/62 (19.4)	7/54 (13.0)	11/54 (20.4)	6/52 (11.5)
	≥50 kg and <70 kg	71/430 (16.5)	71/467 (15.2)	66/415 (15.9)	51/412 (12.4)	71/460 (15.4)
	≥70 kg	115/553 (20.8)	93/527 (17.6)	77/553 (13.9)	94/560 (16.8)	94/554 (17.0)

Number of subjects (%)

PMDA's view:

The safety of Tio + Olo FDC based on age and body weight cannot be definitely concluded due to the lack of accumulated patient data. Further investigation should be conducted via post-marketing surveillance and other programs to evaluate the safety of Tio + Olo FDC in elderly patients, specifically, elderly patients with low body weight, cardiovascular risk factors, or concurrent cardiovascular diseases, in view of the following issues: the incidences of adverse events and serious adverse events tended to be higher in subjects aged ≥75 years and in subjects with body weight of <50 kg than in subjects aged <75 years or those with medium to high body-weight in the Tio + Olo FDC groups. The elderly accounts for a large proportion of the entire patients with COPD in Japan, and many of them are assumed to have relatively low body weight and high risk of adverse cardiovascular events. Therefore, the possibility cannot be denied that elderly patients are likely to experience systemic adverse events associated with Tio + Olo FDC.

4.(ii).B.(3) Dosage and administration

The applicant's explanation:

As discussed earlier [see "4.(ii).B.(1).2) Efficacy of Tio + Olo FDC"], the changes from baseline in $FEV_1AUC_{0\text{-}3}$ and trough FEV_1, the primary endpoints of multiregional phase III studies involving Japanese patients (Studies 1237.5 and 1237.6), demonstrated the superiority of Tio + Olo FDC 2.5/5 μg and 5/5 μg over Tio or Olo alone. Moreover, the comparison of the primary endpoints between the FDC doses showed the consistent superiority of the Tio + Olo 5/5 μg group over the Tio + Olo 2.5/5 μg group. As mentioned earlier [see "4.(ii).B.(2) Safety"], the safety profiles of the Tio + Olo 2.5/5 μg and Tio + Olo 5/5 μg were similar, and Tio + Olo FDC did not differ significantly from those of Tio or Olo alone. Tio 5 μg has been widely used to treat patients with COPD in and outside Japan, and so far no major safety concerns have been reported. Further, the safety profile of Tio + Olo FDC 5/5 μg was demonstrated to be similar to that of Tio alone in the clinical studies. Based on these findings and discussions, the dose of Tio + Olo FDC 5/5 μg, which was found to be more effective than Tio + Olo FDC 2.5/5 μg, is appropriate for treatment of patients with COPD.

PMDA's view

Based on the submitted clinical study data and the above discussions by the applicant, 2 puffs once daily (5 μg of tiotropium and 5 μg of olodaterol) proposed as the dosage and administration of Tio + Olo FDC are acceptable.

4.(ii).B.(4) Indications

PMDA's view:

Tio + Olo FDC should be prescribed exclusively to patients with COPD who require a LABA/LAMA combination therapy, and should not be indiscriminately used in all patients with COPD for the following reasons: (1) although a specific condition of patients may require Tio + Olo FDC for early-stage treatment of COPD, Japanese guidelines, etc. recommend that, in principle, the therapy be stepped up according to the severity of the patient's condition; and (2) the risk of serious adverse cardiovascular events associated with long-term use of LAMA/LABA is yet to be fully elucidated. Therefore, the indication should be revised as shown below, in a similar way to the approved LAMA/LABA combination drugs, with the addition of the phrase "who require a combination therapy with a long-acting inhaled anticholinergic agent and a long-acting inhaled β_2-agonist."

[Indication] Relief of symptoms of airflow obstruction in patients with chronic obstructive pulmonary disease (~~COPD;~~ chronic bronchitis and emphysema) who require a combination therapy with a long-acting inhaled anticholinergic agent and a long-acting inhaled β_2-agonist

(Revised from the proposed indication by deleting the words stricken through and adding the underlined phrase)

4.(ii).B.(5) Post-marketing investigations

The applicant plans to conduct post-marketing surveillance to investigate the long-term safety and efficacy of Tio + Olo FDC in clinical use after the market launch.

Based on the earlier discussions ["4.(ii).B.(2) Safety"], PMDA considers that the safety of Tio + Olo FDC in long-term use and in elderly patients, adverse cardiovascular events that may be induced by LAMA and LABA, and the occurrence of LAMA- and LABA-related adverse events should be further investigated through post-marketing surveillance.

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

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

The inspections are currently underway. The results and PMDA's conclusion will be reported in Review Report (2).

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

The inspections are currently underway. The results and PMDA's conclusion will be reported in Review Report (2).

IV. Overall Evaluation

Having reviewed the submitted data, PMDA considers that the efficacy of Tio + Olo FDC (Spiolto Respimat) in patients with COPD has been proven, combining tiotropium bromide hydrate with olodaterol hydrochloride has been justified, and the safety of Tio + Olo FDC is acceptable in light of the demonstrated benefits. Tio + Olo FDC is a LAMA/LABA combination inhaler that may serve as a new therapeutic option for COPD. PMDA therefore considers that the safety of Tio + Olo FDC in long-term use and in elderly patients, the occurrence of adverse cardiovascular events and other issues should be further investigated through post-marketing surveillance.

This application may be approved if Tio + Olo FDC is not considered to have any problems based on the comments from the Expert Discussion.

Review Report (2)

July 22, 2015

I. Product Submitted for Registration

[Brand name]	Spiolto Respimat 28 puffs, Spiolto Respimat 60 puffs
[Non-proprietary name]	Tiotropium Bromide Hydrate/Olodaterol Hydrochloride
[Name of applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	October 17, 2014

II. Content of the Review

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

(1) Efficacy, indications, dosage, and administration

The PMDA's conclusion on the efficacy, indications, dosage and administration of "Spiolto Respimat 28 Puffs and Spiolto Respimat 60 Puffs" ("Spiolto Respimat" or "Tio + Olo FDC"), which is described in the Review Report (1), was supported by the expert advisors.

(2) Safety and risk management plan (proposed)

The PMDA's conclusion on the safety of Tio + Olo FDC, which is described in the Review Report (1), was supported by the expert advisors. The expert advisors commented that the risk of adverse cardiovascular events associated with Tio + Olo FDC should be closely monitored, in view of the reports on approved LAMAs and LABAs. The expert advisors also noted that the risk of cardiovascular events should be communicated to healthcare professionals through the package insert, etc., and the occurrence of these events should be carefully and continuously monitored through post-marketing surveillance, etc. Further, the expert advisors pointed out that the occurrence of LAMA- or LABA-related non-cardiovascular adverse events associated with Tio + Olo FDC in clinical use should also be monitored through post-marketing surveillance, etc.

Based on the discussions in ["4.(ii).B.(5) Post-marketing investigations" in the Review Report (1)], the comments of the expert advisors, and the safety data of similar drugs, PMDA concluded that the applicant should determine safety and efficacy specifications (Table 54) in the proposed risk management plan, and implement additional pharmacovigilance actions and risk minimization actions shown in Table 55.

Table 54. Safety specifications and efficacy specifications for the risk management plan (proposed)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Cardiac failure, atrial fibrillation, and extrasystoles • Ileus • Angle closure glaucoma • Anaphylaxis	• Cardiac disorders (myocardial ischaemia and arrhythmia) • Asthma-related intubation or death	• None
Efficacy specifications		
• Efficacy under actual use conditions		

Table 55. Summary of additional pharmacovigilance and risk minimization actions for the risk management plan (proposed)

Additional pharmacovigilance actions	Additional risk minimization actions
• Early post-marketing phase vigilance • Specified use-results survey (long-term use)	• Information provision by implementing an early post-marketing phase vigilance program

PMDA instructed the applicant to implement post-marketing surveillance to investigate the above issues.

The applicant's response:

A specified use-results survey will be conducted in patients with COPD with a target sample size of 1000 and an observation period of 1 year (Table 56). In order to evaluate the safety of Tio + Olo FDC in clinical use, the survey will focus primarily on adverse cardiovascular events, anticholinergic effect-related events, and β_2 stimulation-related events, and will facilitate the collection of data from patients on long-term treatment and from elderly patients, because only a limited number of these patient population participated in the clinical studies.

Table 56. Outline of specified use-results survey (proposed)

Objectives	Compilation of safety and efficacy information under actual use conditions
Survey method	Continuous prospective surveillance
Patient population	Patients with COPD
Observation period	1 year
Planned number of subjects	1000 subjects
Focused survey items	Adverse cardiovascular events, anticholinergic effect-related events, and β_2 stimulation-related events
Main survey items	Patient characteristics (severity of COPD, smoking history, age, complications, etc.) Status of treatment with Tio + Olo FDC Treatment history Combination administration/combined treatment Efficacy evaluation Adverse events

PMDA considers that the survey should be conducted as promptly as possible, and the results should be provided to healthcare professionals.

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

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

Document-based compliance inspection of the data submitted in the new drug application was conducted in accordance with the provisions of the Pharmaceutical Affairs Act. PMDA concluded that there should be no problem in conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the New Drug Application (5.3.5.1-4, 5.3.5.1-12, 5.3.5.1-13, and 5.3.5.1-14). The results showed satisfactory overall GCP compliance in the conduct of clinical studies, and PMDA therefore concluded that there should be no problem in conducting a regulatory review based on the submitted application documents. However, the following issues were found at some study sites (medical institutions) and the sponsor, albeit with no major impact on the overall study evaluation, and were notified to the heads of the medical institutions in question and the applicant (sponsor) as issues that need to be improved.

Issues to be improved

Medical institutions

- A protocol deviation (missed urinalysis)

Sponsor

- The monitor failed to detect the protocol deviation (missed urinalysis) in a timely manner

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that Tio + Olo FDC (Spiolt Respimat) may be approved for the indication and dosage and administration shown below, with the conditions added to the end of this section. As Spiolt Respimat contains a new active ingredient, the re-examination period is 8 years. One of the drug substances (olodaterol hydrochloride) is classified as a powerful drug. The drug product is classified as neither poisonous nor powerful, and is also classified as neither a biological product nor a specified biological product.

[Indication]

Relief of symptoms of airflow obstruction in patients with chronic obstructive pulmonary disease (chronic bronchitis and emphysema) who require a combination therapy with a long-acting inhaled anticholinergic agent and a long-acting inhaled β_2-agonist

[Dosage and administration]

The usual adult dosage is 2 inhalations once daily (5 μg of tiotropium and 5 μg of olodaterol).

[Conditions for approval]

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