Report on the Deliberation Results

May 16, 2014
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Anoro Ellipta 7 doses, Anoro Ellipta 30 doses
[Non-proprietary name]	Umeclidinium Bromide/Vilanterol Trifenatate (JAN*)
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	April 22, 2013

[Results of deliberation]
In the meeting held on April 30, 2014, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years. The drug substance (umeclidinium bromide) is classified as a powerful drug, while the product is not classified as a poisonous drug or a powerful drug. The product is not classified as a biological product or a specified biological product.

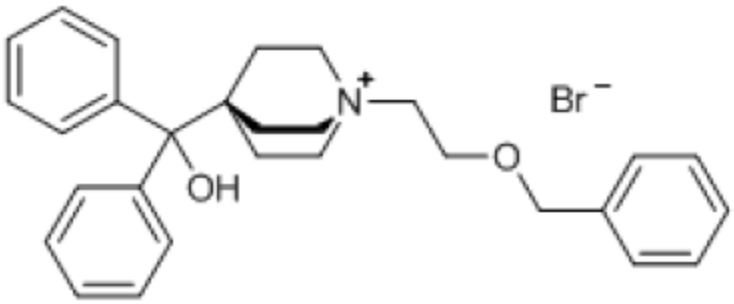
**Japanese Accepted Name (modified INN)*

Review Report

April 14, 2014
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]	Anoro Ellipta 7 doses, Anoro Ellipta 30 doses
[Non-proprietary name]	Umeclidinium Bromide/Vilanterol Trifenatate
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	April 22, 2013
[Dosage form/Strength]	Inhalation powder with a metered-dose inhaler containing 74.2 μg of Umeclidinium Bromide (62.5 μg as umeclidinium) and 40 μg of Vilanterol Trifenatate (25 μg as vilanterol) per blister
[Application classification]	Prescription drug (1) Drug with a new active ingredient, (2) New combination drug
[Chemical structure]	Umeclidinium bromide



Molecular formula: $C_{29}H_{34}BrNO_2$
Molecular mass: 508.49
Chemical name:
1-[2-(Benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo [2.2.2]octane bromide

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

Review Results

April 14, 2014

[Brand name]	Anoro Ellipta 7 doses, Anoro Ellipta 30 doses
[Non-proprietary name]	Umeclidinium Bromide/Vilanterol Trifenatate
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	April 22, 2013

[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in patients with chronic obstructive pulmonary disease (COPD) has been demonstrated, and the safety of the product is acceptable in view of its observed benefits. The safety of the product in patients receiving long-term treatment and elderly patients, the incidence of cardiovascular adverse events, the efficacy of the product in patients who have switched from monotherapy of an approved long-acting muscarinic antagonist (LAMA) or long-acting β_2 adrenergic agonist (LABA) or concomitant use of LAMA and LABA, etc. need to be further investigated via post-marketing surveillance.

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

[Indication]	Relief of symptoms of obstructive airway disorder due to chronic obstructive pulmonary disease (chronic bronchitis and pulmonary emphysema) (Only in the case where combination of a long-acting inhaled anticholinergic drug and a long-acting inhaled β_2-agonist is required.)
[Dosage and administration]	The usual adult dosage is 1 inhalation of Umeclidinium Bromide/Vilanterol Trifenatate (62.5 μg as umeclidinium, 25 μg as vilanterol) administered once daily.

Review Report (1)

February 28, 2014

I. Product Submitted for Registration

[Brand name]	Anoro 62.5 Ellipta 7 doses, Anoro 62.5 Ellipta 30 doses, Anoro 125 Ellipta 7 doses, Anoro 125 Ellipta 30 doses (as proposed in the application)
[Non-proprietary name]	Umeclidinium Bromide/Vilanterol Trifenatate
[Name of applicant]	GlaxoSmithKline K.K.
[Application]	April 22, 2013
[Dosage form/Strength]	Inhalation powder with a metered-dose inhaler containing 74.2 μg of Umeclidinium Bromide (62.5 μg as umeclidinium) and 40 μg of Vilanterol Trifenatate (25 μg as vilanterol) per blister, or containing 148.3 μg of Umeclidinium Bromide (125 μg as umeclidinium) and 40 μg of Vilanterol Trifenatate (25 μg as vilanterol) per blister (as proposed in the application)
[Proposed indication]	Relief of symptoms of obstructive airway disorder due to chronic obstructive pulmonary disease (chronic bronchitis and pulmonary emphysema)
[Proposed dosage and administration]	The usual adult dosage is 1 inhalation of Umeclidinium Bromide/Vilanterol Trifenatate 62.5 (62.5 μg as umeclidinium, 25 μg as vilanterol) administered once daily. Where necessary, 1 inhalation of Umeclidinium Bromide/Vilanterol Trifenatate 125 (125 μg as umeclidinium, 25 μg as vilanterol) may be administered once daily.

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

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

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

Umeclidinium Bromide/Vilanterol Trifenatate is a combination product for treatment of chronic obstructive pulmonary disease (COPD) (a metered-dose dry powder inhaler) developed by GlaxoSmithKline plc. (UK) and contains umeclidinium bromide (UMEC), a long-acting muscarinic antagonist (LAMA), and vilanterol trifenatate (VI), a long-acting β_2 adrenergic agonist (LABA), as the active ingredients.

UMEC has not been approved in Japan while VI was approved in September 2013 as an active ingredient in combination products with fluticasone furoate (FF), a steroid, ("Relvar 100 Ellipta 14 doses," "Relvar 100 Ellipta 30 doses," "Relvar 200 Ellipta 14 doses," "Relvar 200 Ellipta 30 doses" [hereinafter referred to as "Relvar"]), which were developed by the applicant and are indicated for treatment of bronchial asthma.

COPD is an inflammatory disease in the lungs caused by long-term exposure to hazardous substances contained mainly in tobacco smoke, and causes progressive airflow obstruction. COPD is clinically characterized by shortness of breath with daily activities and chronic cough and sputum. The drug therapy for COPD at a stable condition mainly consists of bronchodilators including short-acting β_2 adrenergic agonists (SABAs), LABAs, and LAMAs, which are used

stepwise according to the severity. For treatment of moderate or severer COPD, periodic use of LABA or LAMA is recommended, however, if the therapeutic effect of such monotherapy is not sufficient or if the symptom is even severer, concomitant use of 2 or more bronchodilators may be administered (Japanese Respiratory Society, Guidelines for the Diagnosis and Treatment of COPD [Chronic Obstructive Pulmonary Disease] 4th edition 2013; Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, 2011).

LAMA and LABA have different mechanisms of actions and concomitant use of inhalation products of LAMA and LABA have been used widely in clinical practice. Combination product of a LAMA and a LABA has been needed because, by combining the 2 drugs, administration of LAMA and LABA once daily by inhaler is considered to improve the medication adherence and convenience of the patients. Therefore, the combination product containing UMEC and VI (hereinafter referred to as UMEC/VI), which are novel LAMA and LABA, respectively, for the treatment of COPD, was developed.

Outside of Japan, UMEC/VI was approved for the indication of COPD in the US in December 2013 and is under review in Europe as of February 2014.

In Japan, clinical development of UMEC/VI for treatment of COPD was initiated in September 2008 by GlaxoSmithKline K.K. A marketing application has been filed based on data including the results from global clinical studies that included Japanese subjects. [redacted].

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance (UMEC)

2.A.(1).1) Characterization

UMEC, one of the drug substances, is white powder and its properties, including description, solubility, hygroscopicity, melting point, thermal analysis, pH, dissociation constant (pKa), partition coefficient, crystalline polymorphism, and particle shape, have been determined. [redacted].

Its chemical structure has been elucidated by elementary analysis, mass spectrometry, ultraviolet-visible spectrophotometry (UV), infrared spectrophotometry (IR), nuclear magnetic resonance spectroscopy (^{1}H-, ^{13}C-NMR), and single-crystal X ray crystallography.

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

[redacted].

In addition, in consideration of the “Pharmaceutical Development” (PFSB/ELD Notification No. 0628-1 dated June 28, 2010, ICH Q8 Guideline), the “Quality Risk Management” (PFSB/ELD Notification No. 0901004 dated September 1, 2006, ICH Q9 Guideline), and the “Pharmaceutical Quality System” (PFSB/ELD Notification No. 0219-1 dated February 19, 2010, ICH Q10 Guideline), the following investigations have been mainly performed by the Quality by design (QbD) approach.

- [redacted]
- Identification of critical process parameters (CPPs) based on quality risk assessment and design of experiment
- Verification of control strategy

[redacted].

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

[redacted].

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

The stability studies for the drug substance (UMEC) are as shown in Table 1. Photostability data showed that the drug substance is photostable.

Table 1. Stability studies of UMEC

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long term	3 batches on a commercial scale	30°C	65% RH	Polyethylene bag + aluminum bag + plastic container	24 months
Accelerated	3 batches on a commercial scale	40°C	75% RH		6 months

Based on the above, a re-test period of 36 months has been proposed for the drug substance when stored at room temperature in a polyethylene bag and aluminum bag in accordance with the "Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003, ICH Q1E Guideline). Long-term testing is planned to be continued up to 60 months.

2.A.(2) Drug substance (VI)

VI, one of the drug substances, is identical to the drug substance contained in Relvar, an approved product.

2.A.(3) Drug product

2.A.(3).1) Description and composition of the drug product and formulation development

UMEC/VI (the drug product) is an inhalation powder containing UMEC and VI as the drug substances. The proposed drug products include 4 formulations (UMEC/VI) at 2 strengths of 62.5/25 μg and 125/25 μg[1] and in 2 sizes of 7 doses and 30 doses for each strength. The multiple-dose type metered-dose powder inhaler (Figure 1), an inhaler dedicated to the product, has the same configuration as that of Relvar, an approved product. Each drug product contains 2 double-aluminum blister strips with 7 or 30 blisters. In one strip, a mixed powder containing 74.2 μg or 148.3 μg of UMEC (62.5 μg or 125 μg as umeclidinium) per blister is filled, and in the other strip, a mixed powder containing 40 μg of VI (25 μg as vilanterol) per blister is filled. The UMEC strip and VI strip contain lactose hydrate and magnesium stearate as the excipients.

[redacted]

Figure 1. Inside of an inhaler

2.A.(3).2) Manufacturing process

[redacted].

In consideration of the ICH Q8 Guideline, ICH Q9 Guideline, and ICH Q10 Guideline, the following investigations have been mainly performed by the QbD approach.

- [redacted]
- [redacted]
- Identification of CPPs based on quality risk assessment and design of experiment

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

The proposed specifications for the drug product include the contents (UMEC, VI), description, identification (UMEC [HPLC, UV], VI [HPLC]), purity (related substances; UMEC, VI [HPLC]), uniformity of delivery dose (HPLC), particle amount (next-generation impactor), microbial limit test (UMEC, VI), and assay (UMEC, VI [HPLC]).

2.A.(3).4) Stability of drug product

The stability studies for the drug product are as shown in Table 2.

[1] Both contents of the product are expressed as free base.

Table 2. Stability studies on the drug product

Study	Drug product	Primary batches	Temperature	Humidity	Storage form	Storage period
Long term	62.5/25 μg, 30 doses	3 batches on a commercial scale	25°C	60% RH	Aluminum tray	24 months
	125/25 μg, 30 doses	3 batches on a commercial scale				
Accelerated	62.5/25 μg, 30 doses	3 batches on a commercial scale	40°C	75% RH		6 months
	125/25 μg, 30 doses	3 batches on a commercial scale				
Relative comparison	62.5/25 μg, 7 doses	1 batch on a commercial scale	40°C	75% RH	Aluminum tray	3 months
	125/25 μg, 7 doses	1 batch on a commercial scale				
	62.5/25 μg, 30 doses	3 batches on a commercial scale				
	125/25 μg, 30 doses	3 batches on a commercial scale				

Three batches of the drug product with 30 doses were set as the primary batches for the stability data. The relative comparison study has shown comparable stability of the drug product with 30 doses and the product with 7 doses. Based on the above, a shelf life of 24 months has been proposed for the drug product when stored at room temperature in an aluminum tray package. Long-term testing is planned to be continued up to 36 months.

2.B Outline of the review by PMDA

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

2.B.(1) Control strategy of UMEC drug substance and quality management system

The applicant explained a justification for the control strategy of UMEC drug substance as follows:

[redacted].

[redacted].

The applicant explained as follows:

[redacted]. In addition, even when continuous monitoring throughout the post-marketing product lifecycle indicates that a new factor would affect the control strategy, the investigation will be performed to take appropriate actions.

PMDA has accepted the above responses and has concluded that the quality management system is appropriately constructed.

2.B.(2) Difference in [redacted] particle amount between UMEC alone and UMEC/VI

[redacted].

The applicant explained as follows:

[redacted]. Variations among the batches due to limited data sets may be involved as a factor.

The difference in [redacted] particle amount between the single-strip formulation and the dual-strip formulation was small up to approximately [redacted]%. In a clinical study (Study AC4115487) comparing the UMEC single-strip formulation and dual-strip formulation, both formulations provided comparable specific airway conductance (sGaw) and forced expiratory volume in 1 second (FEV_1) during a period from baseline (0 hours) to 24 hours after the single dose [see "4.(i) Summary of biopharmaceutic data and associated analytical methods"]. The difference in [redacted] particle amount between the single-strip formulation and the dual-strip formulation is therefore considered unlikely to affect the efficacy evaluation of UMEC/VI.

PMDA accepted the above applicant's explanation.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

The pharmacology data of VI were previously evaluated in the application of Relvar. For the application of UMEC/VI, *in vitro* primary pharmacodynamic studies were conducted to investigate binding affinity, selectivity, cellular function activity, and persistence of action of UMEC to the muscarinic receptors, and the airway contraction relieving effect was also investigated *in vitro* and *in vivo*. The secondary pharmacology studies were also conducted to investigate the effects of UMEC on receptors, ion channels, and transporters as well as those on bradycardia. In addition, the safety pharmacology studies were conducted to investigate the effects of UMEC on the central nervous system, respiratory system, and cardiovascular system as

well as effects of concomitant use of UMEC with VI on the cardiovascular system. No pharmacodynamic drug interaction studies have been performed. The doses and concentrations of UMEC and VI are expressed as free base.

3.(i).A.(1) Primary pharmacodynamics (4.2.1.1)

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

(a) Binding affinity to human muscarinic receptor subtype (CH2006/00020/00, 2012N138876_01)

Membrane preparations from Chinese hamster ovary (CHO) cells expressing recombinant human muscarinic M1, M2, M3, M4, or M5 receptor were used to investigate the inhibitory activity (K_i) of UMEC against each receptor. UMEC inhibited the binding of ^{3}H-N-methylscopolamine to M1, M2, M3, M4, and M5 receptors at the K_i (mean) value of 0.159, 0.151, 0.062, 0.050, and 0.131 nmol/L, respectively. Although the dissociation constant (K_d) of ^{3}H-N-methylscopolamine to the M3 receptor increased with the increasing concentration of UMEC (0.21-0.55 nmol/L), the maximum binding value (B_{max}) remained unchanged (5.49-6.11 pmol/mL), suggesting that UMEC competitively inhibits the binding of ^{3}H-N-methylscopolamine to the M3 receptor.

Membrane preparations from CHO cells expressing recombinant human muscarinic M2 or M3 receptor were used to compare characteristics in binding of UMEC and tiotropium (TIO) to each receptor. The K_d value of UMEC to the M2 and M3 receptors was 0.16 and 0.03 nmol/L, respectively, and that of TIO was 0.05 and 0.02 nmol/L, respectively. The binding selectivity factor to the M2 and M3 receptors (K_d to the M2 receptor/K_d to the M3 receptor) was approximately 5 for UMEC compared to 2.5 for TIO. The B_{max} value (mean) to the M2 and M3 receptors was 2.53 and 5.01 pmol/mg, respectively, for UMEC and 1.98 and 3.93 pmol/mg, respectively, for TIO. Furthermore, the dissociation rate constant (k_{off}, mean) to the M2 and M3 receptors in the presence of atropine (10 μmol/L) was 0.074 and 0.0089, respectively, for UMEC and 0.023 and 0.0026, respectively, for TIO. As with TIO, the dissociation of UMEC from the M2 receptor was faster than that from the M3 receptor.

(b) Effects on acetylcholine-induced calcium mobilization response (CH2006/00020/00, CH2009/00016/00)

The inhibitory effect of UMEC against acetylcholine (0.033-1,000,000 nmol/L)-induced calcium mobilization response was investigated in CHO cells expressing recombinant human muscarinic M1, M2, or M3 receptor. UMEC inhibited acetylcholine-induced calcium mobilization response via the M1, M2, and M3 receptors. The absolute common logarithm value (pA_2, mean) of the molar concentration of a competitive antagonist required for a parallel shift of the concentration reaction curve toward a 2-fold higher concentration range than that with an agonist alone was 9.59, 10.11, and 10.62, respectively. In addition, the slope of Schild plot for the M1, M2, and M3 receptors was 0.829, 0.928, and 0.963, respectively, which were close to 1, indicating that UMEC and acetylcholine competitively act on the M1 to M3 receptors.

Persistence of the inhibitory effects of UMEC and TIO against the acetylcholine (0.033-10,000 nmol/L)-induced calcium mobilization response was investigated and compared in CHO cells expressing recombinant human muscarinic M3 receptor. Pre-treatment of either UMEC or TIO inhibited acetylcholine-induced calcium mobilization response. When the cells pre-treated with UMEC or TIO were washed for 180 or 90 minutes, respectively, the inhibitory effect against acetylcholine-induced calcium mobilization response was reduced compared with that before washing, but was not fully restored. The above results showed that the M3 receptor antagonistic effects of both UMEC and TIO were persistent for long periods.

The inhibitory effect of UMEC metabolites against acetylcholine (3.3, 10, and 1.0 nmol/L for the M1, M2, and M3 receptors, respectively)-induced calcium mobilization response was investigated in CHO cells expressing recombinant human muscarinic M1, M2, or M3 receptor.

M33 (hydroxylated form) inhibited acetylcholine-induced calcium mobilization response via the M1 and M3 receptors [2] (pIC_{50}, >8.00). The pA_2 value calculated from the acetylcholine concentration reaction curve in the cells expressing the M3 receptor was 9.87, which was approximately one-fifth of the inhibitory effect of unchanged UMEC (pA_2, 10.62). M14 (O-dealkylated form) also inhibited acetylcholine-induced calcium mobilization response via the M1, M2, and M3 receptors, and the pIC_{50} value in cells expressing each receptor was 5.92, 5.78, and 6.25, respectively, which were less than one-fiftieth of the inhibitory effect of M33. As for the antagonistic effect of M33 against M1 and M3 receptors, the applicant explained that the antagonistic effect of M33 is unlikely to affect muscarinic receptors in the non-lung tissues pharmacologically in the clinical setting, because in healthy adult subjects who received UMEC once daily at the dose of 1000 μg for 7 days through inhalation, the plasma M33 concentration was less than the lower limit of quantitation.

(c) Effect against carbachol-induced contraction in human isolated bronchus preparations (CH2006/00014/01, CH2006/00015/00)

The inhibitory effect of UMEC, TIO, and ipratropium against carbachol (0.01-10,000 μmol/L)-induced contraction was investigated and compared using human isolated bronchus preparations. UMEC (1, 10 or 100 nmol/L), TIO (0.1, 1 or 10 nmol/L), and ipratropium (1, 10 or 100 nmol/L) inhibited the carbachol-induced contraction in a concentration-dependent manner. The pA_2 value of UMEC and ipratropium was 9.5 and 9.2, respectively, indicating a comparable inhibitory effect on bronchoconstriction. The pA_2 value of TIO could not be calculated because it inhibited the maximum carbachol-induced contraction significantly.

Human isolated bronchus perfusion preparations were used to investigate and compare the onset time and persistence of the inhibitory effect of UMEC, TIO, and ipratropium against carbachol (1 μmol/L)-induced contraction. UMEC, TIO or ipratropium was added at the final concentrations of 1, 10, and 100 nmol/L to human isolated bronchus preparations in which contraction was induced by carbachol treatment. The time to reduce the inhibitory effect to 50% of the maximum effect (On $t_{1/2}$, mean), an index of the effect onset, was 14 to 63 for UMEC, 2 to 17 for TIO, and 4 to 29 minutes for ipratropium, indicating that UMEC acted slower than TIO or ipratropium. The time to restore the inhibitory effect to 50% of the maximum effect after removal of the test article from the perfusate (Off $t_{1/2}$, mean), an index of duration of the effect, was 119 to 299, 106 to 435, and 20 to 86 minutes for UMEC, TIO, and ipratropium, respectively, indicating that the duration of the effect of UMEC was longer than that of ipratropium and comparable to that of TIO.

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

(a) Effect on mouse methacholine-induced bronchoconstriction (CH2006/00018/00)

The pulmonary flow resistance was measured in male mice (n = 4/group) which received a single intranasal dose of UMEC at 0.005 to 5 μg followed by methacholine spray at a dose of 30 mg/mL at a flow rate of 1.6 mL/min for 2 minutes at 5 hours post-dose. UMEC inhibited the methacholine-induced bronchoconstriction in a dose-dependent manner with ED_{50} of 0.02 μg.

In addition, the pulmonary flow resistance was measured in male mice (n = 8/group) which received a single intranasal dose of UMEC or TIO at 0.05 μg followed by methacholine spray at 15 minutes, 5, 24, 30, and 48 hours post-dose and then every 24 hours until Day 7. UMEC presented the maximum inhibitory effect on methacholine-induced bronchoconstriction at 30 hours post-dose, and the inhibitory effect (24%-80%) continued until Day 6. TIO presented the maximum inhibitory effect on methacholine-induced bronchoconstriction at 5 hours post-dose, and the inhibitory effect (13%-98%) continued until Day 6.

[2] The inhibitory effect of M33 (hydroxylated form) on M2 receptor-mediated acetylcholine-induced calcium mobilization response has not been investigated.

Furthermore, the pulmonary flow resistance was measured in male mice (n = 8/group) which received intranasal doses of UMEC 0.025 μg once daily for 5 days and methacholine spray at 24 hours after each of the intranasal doses on Day 1 to Day 5. The methacholine-induced bronchoconstriction inhibitory effect increased over time and then almost disappeared following 5-day withdrawal. Following re-administration of UMEC on Day 10 after the first dose, the methacholine-induced bronchoconstriction inhibitory effect (35%) on Day 11 (Day 1 of re-administration) was comparable to that on Day 1 (34%). Based on the above results, the applicant explained that repeated administration of UMEC is unlikely to cause resistance to its bronchoconstriction inhibitory effect.

(b) Effect on guinea pig acetylcholine-induced bronchoconstriction (CH2005/00954/00, CH2005/00953/00)

The pulmonary flow resistance was measured in male guinea pigs (n = 6/group) which received a single intratracheal dose of UMEC at 0.25 to 25 μg followed by acetylcholine spray at a dose of 3.5 mg/mL at a flow rate of 0.6 mL/min for 36 seconds at 4 and 24 hours post-dose and then every 24 hours until Day 8. At 4 hours post-dose, acetylcholine-induced bronchoconstriction was almost completely inhibited. The duration of UMEC's inhibitory effect on acetylcholine-induced bronchoconstriction extended in a dose-dependent manner, and in the 2.5 and 25 μg groups, the ≥50% contraction inhibitory effect continued until Days 2 and 5, respectively.

In addition, the pulmonary flow resistance was measured in male guinea pigs (n = 18/group) which received a single intratracheal dose of UMEC or TIO at 2.5 μg followed by acetylcholine spray at 4 and 24 hours post-dose and then every 24 hours until Day 5. Acetylcholine-induced bronchoconstriction was inhibited by ≥90% at 4 hours after the dosing of UMEC or TIO, and the ≥50% contraction inhibitory effect continued in UMEC and TIO groups until Days 1 and 2, respectively.

Furthermore, the airway resistance was measured in male guinea pigs (n = 6/group) which received a single intratracheal dose of UMEC at 0.025 to 2.5 μg or TIO at 25 μg, and were left to ensure stable airway resistance for 5 minutes followed by intravenous dose of acetylcholine at 10 to 100 μg/kg. UMEC inhibited the increase in acetylcholine-induced airway resistance in a dose-dependent manner, and in the UMEC 2.5 μg group and TIO group, the increase was almost completely inhibited.

3.(i).A.(2) Secondary pharmacodynamics (4.2.1.2)

3.(i).A.(2).1) Effects on receptors, ion channels and transporters (CH2006/00030/00)

The effects of UMEC at 1 μmol/L on 46 types of receptors, ion channels, and transporters were investigated *in vitro*. The inhibitory effects were observed against ligand binding of the guinea pig κ opioid receptor, rat σ (non-selective) receptor, rat L-type Ca^{2+} channel, rat Na^{+} channel (site 2), and human dopamine transporter. As a result, K_i was 69, 220, 330, 170, and 780 nmol/L, respectively, which were ≥370 times the expected C_{max} (0.185 nmol/L) in Japanese COPD patients (treated with UMEC/VI 62.5/25 μg once daily).

3.(i).A.(2).2) Effect on acetylcholine-induced bradycardia following intravenous dose (CH2005/00953/00)

Since cardiovascular adverse events were reported by COPD patients treated with existing muscarinic receptor antagonists (Singh S et al. *BMJ*. 2011;342:d3215 [online]), the effect on the heart rate was investigated in male guinea pigs (n = 6-8/group) which received a single intratracheal dose of UMEC at 0.025 to 2.5 μg and were left to ensure stable airway resistance for 5 minutes followed by intravenous dose of acetylcholine at 10 to 100 μg/kg. UMEC at the dose range above did not show the dose-dependent or consistent effect on acetylcholine-induced bradycardia. The applicant explained that UMEC/VI at a clinical dose is unlikely to affect the heart rate because UMEC at the dose leading to almost complete inhibition against the

acetylcholine-induced airway resistance increase did not inhibit acetylcholine-induced bradycardia.

3.(i).A.(3) Safety pharmacology (4.2.1.3)

3.(i).A.(3).1) Effect on the central nervous system (VD2005/00625/01)

Following single inhalation dose of UMEC at 36, 322 or 1994 μg/kg administered over 1 hour to male rats (n = 8/group), the effects on the behavior observation (functional observational battery) and locomotor activity were investigated. In the 36 μg/kg group, there were no effects on the behavior observation or locomotor activity. In 2 animals in the 322 μg/kg group and 6 animals in the 1994 μg/kg group, moderate mydriasis was observed at 1.25 to 9 hours and at 1.25 to 3 hours, respectively, after the start of the treatment. In any dose group, there were no effects on the other peripheral or central nervous system activity, rectal temperature, or locomotor activity. In a 7-day inhalation dose toxicity study in rats (WD2005/01063/01), C_{max} was 4.88 ng/mL in the 325 μg/kg group, the dose comparable to that (322 μg/kg) led to mydriasis. This C_{max} was approximately 60 times the expected value (79.4 pg/mL) in Japanese COPD patients (treated with UMEC/VI 62.5/25 μg once daily).

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

(a) Effect on the hERG current (FD2005/00109/00)

Effects of UMEC on hERG currents were evaluated in HEK293 cells expressing hERG channels by whole-cell patch clamping. UMEC at 1 μmol/L (0.4286μg/mL), 3 μmol/L (1.286μg/mL), and 10 μmol/L (4.286 μg/mL) inhibited hERG tail current by 9.6%, 25.8%, and 56.3%, respectively, with IC_{50} of 9.41 μmol/L (4.033 μg/mL). This IC_{50} value was approximately 50,000 times the expected C_{max} in Japanese COPD patients (treated with UMEC/VI 62.5/25 μg once daily).

(b) *In vivo studies*

Study of UMEC (FD2005/00167/00)

Following a single intravenous dose of 0.3, 3 or 10 μg/kg of UMEC to male beagle dogs (n = 4/group), the effects on the cardiovascular system were investigated. In the 0.3 and 3 μg/kg groups, no effects on the arterial blood pressure, heart rate, electrocardiogram (ECG) parameters, or ECG waveform were observed. In the 10 μg/kg group, mildly decreased pulse pressure (maximum, 7 mmHg), increased heart rate (maximum, 49 bpm), prolonged PR interval, and shortened RR interval were observed after the administration but resolved by 30 to 35 minutes post-dose. In 3 animals in the 10 μg/kg group, independent P wave was observed, suggesting second-degree atrioventricular block. However, there were no effects on the clinical conditions in any dose group. C_{max} in the 10 μg/kg group was 86.1 ng/mL, which was approximately 1000 times the expected C_{max} in Japanese COPD patients (treated with UMEC/VI 62.5/25 μg once daily).

Study of UMEC and VI (FD2008/00365/00)

Following a single intravenous dose of UMEC 0.3 μg/kg alone, VI 0.3 μg/kg alone, or concomitant use of the drugs to male beagle dogs (n = 4/group), the effects on the cardiovascular system were investigated. In the UMEC/VI concomitant use group, the mean blood pressure, systolic blood pressure, and diastolic blood pressure increased (by up to 11, 14, and 9 mmHg, respectively) from 126 minutes post-dose to 3 hours post-dose (at the end of measurement period). In addition, in the VI group and the UMEC/VI concomitant use group, the heart rate increased by 33 and 34 bpm, respectively, at 6 minutes post-dose. There were no observed effects on the clinical conditions in any dose group. C_{max} in the UMEC 0.3 μg/kg group and VI 0.3 μg/kg group was 1.24 and 4.25 ng/mL, respectively, which were approximately 15 and 33 times, respectively, the expected C_{max} values (79.4 and 126.8 pg/mL, respectively) in Japanese COPD patients (treated with UMEC/VI 62.5/25 μg once daily).

3.(i).A.(3).3) Effects on the respiratory system (CD2005/01385/02)

Following a single inhalation dose of UMEC at 36, 215, or 2260 μg/kg administered over 1 hour to male rats (n = 6/group), the effects on the respiratory system were investigated. There were no observed effects on the respiratory system in the 36 μg/kg group. In the 215 and 2260 μg/kg groups, increase in respiratory rate (by 18%-45%) associated with the tidal volume decrease (by 3%-17%) was observed during the treatment, but there was no apparent effect on the minute volume. Using C_{max} (4.88 ng/mL) in the 325 μg/kg group in a 7-day inhalation dose toxicity study in rats (WD2005/01063/01), C_{max} at the dose of 215 μg/kg was calculated to be 3.23 ng/mL, which was approximately 40 times the expected C_{max} value in Japanese COPD patients (treated with UMEC/VI 62.5/25 μg once daily).

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

The applicant explained the pharmacological significance of concomitant use of UMEC and VI as follows:

Reports on concomitant use of muscarinic antagonist and β_2 adrenergic agonist have shown that the β_2 adrenergic agonist stimulates the β_2 receptor in the airway, thereby leading to decreased release of acetylcholine mediated by transmission regulation in the adjacent parasympathetic nerve, which then intensifies muscarinic antagonist-induced bronchus smooth muscle dilatation (Cazzola M and Molimard M. *Pulm Pharmacol Ther*. 2010;23:257-267), and that concomitant intratracheal use of muscarinic antagonist and β_2 adrenergic agonist has an additive inhibitory effect on the acetylcholine-induced bronchoconstriction reaction in guinea pigs (Rossoni G et al. *Pulm Pharmacol Ther*. 2007;20:250-257). These reports thus indicate that concomitant use of muscarinic antagonist and β_2 adrenergic agonist directly and indirectly relaxes the airway smooth muscle, presenting the additive effect of the concomitant use.

PMDA considers that, based on the submitted data, the effect of UMEC against COPD can be explained because bronchodilation of UMEC has been demonstrated.

Furthermore, taking account of the available findings including publications, the pharmacological significance of the concomitant use of UMEC and VI has been indicated.

3.(ii) Summary of pharmacokinetic studies

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

The pharmacokinetic data of VI were already evaluated in the application of Relvar. For the application of UMEC/VI, the data from inhalation, oral, intraportal, and intravenous dose studies of UMEC in rats and dogs were submitted as the data on absorption, distribution, metabolism, excretion, and drug interaction. UMEC, radiolabeled umeclidinium trifluoroacetate (^{14}C-umeclidinium trifluoroacetate), and radiolabeled UMEC (^{14}C-UMEC) were used to investigate the pharmacokinetics of UMEC. The plasma umeclidinium level was determined by liquid chromatography tandem mass spectrometry (LC-MS/MS) (lower limit of quantitation; 0.02 or 0.1 ng/mL in rat plasma, 0.1 ng/mL in dog plasma), and the radioactivity by a liquid scintillation counter (LSC) (lower limit of quantitation, 0.007 μg eq./g) and tissue radioactivity by quantitative whole-body autoradiography (QWBA).

Unless otherwise specified, the doses and concentrations are expressed as free base, and the pharmacokinetic parameters are expressed as the mean or mean ± standard deviation (SD).

3.(ii).A.(1) Absorption (4.2.2.2)

3.(ii).A.(1).1) Single-dose study of UMEC

Table 3 shows the pharmacokinetic parameters of plasma umeclidinium concentrations in male rats (WD2006/00073/00) and male dogs (CH2006/00001/00) following single intravenous infusion of UMEC administered over 1 hour.

Table 3. Pharmacokinetic parameters in rats and dogs following a single intravenous dose of UMEC

Animal	Dose (mg/kg)	No. of animals	Route of administration	C_{max} (ng /mL)	T_{max} (h)	AUC (ng·h/mL)	$t_{1/2}$ (h)	CL (mL/min/kg)	Vss (L/kg)
Rat	0.5	3 males	i.v.	30.3 ± 1.56	0.33-0.67	25.2 ± 1.59[a]	3.35 ± 1.00	328 ± 22.5	14.6 ± 6.59
Dog	1.0	3 males	i.v.	651 ± 194	0.75-1.0	502 ± 74[b]	11.6 ± 1.7	32.5 ± 4.53	4.67 ± 1.73

Mean ± SD, T_{max} expressed as a range

C_{max}: Maximum plasma concentration, T_{max}: Time to reach the maximum plasma concentration, AUC: Area under the concentration-time curve, $t_{1/2}$: Elimination half-life, CL: Plasma clearance, Vss: Distribution volume at steady state, i.v.: Intravenous, a: $AUC_{0-\infty}$, b: AUC_{0-t}

Following a single oral dose of 2 mg/kg of UMEC to male rats (n = 3), the plasma umeclidinium concentration was less than the lower limit of quantitation (1.0 ng/mL), and in the portal plasma, umeclidinium was detected at the concentration of 1.08 ng/mL in 1 of 3 animals 5 minutes post-dose. Following continuous intraportal infusion of UMEC 0.5 mg/kg for 30 minutes, the plasma umeclidinium concentration reached the maximum of 15.6 ng/mL at 33 minutes after the initiation of the infusion and then was less than the lower limit of quantitation (1.0 ng/mL) at 45 minutes after the initiation and thereafter (CH2006/00012/00). Following a single oral dose of UMEC 2 mg/kg or ^{14}C-UMEC 1 mg/kg to male dogs (n = 3), the plasma umeclidinium concentration was less than the lower limit of quantitation (1.0 ng/mL) (CH2006/00001/00, FD2005/00164/00). The above data suggested a large first-pass effect following the oral administration in rats and dogs.

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

(a) Study on UMEC monotherapy

The toxicokinetics following repeated inhalation doses of UMEC was investigated in rat 14-day (WD2006/03225/00) and 26-week (FD2009/00467/00) as well as dog 14-day (WD2006/03669/00) and 39-week repeated inhalation toxicity studies (FD2009/00466/02). Table 4 shows the plasma umeclidinium pharmacokinetic parameters. The plasma concentration varied largely but increased with the increasing dose. No apparent accumulation of UMEC due to the repeated doses was observed. There were no apparent gender-related differences.

Table 4. Pharmacokinetic parameters in rats and dogs following repeated inhalation doses of UMEC

	Treatment period	Estimated dose (μg/kg)	No. of animals	Time point	Male		Female	
					C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)
Rat	14 days	1400[a]	3	Day 1	161 ± 184	182	146 ± 51.7	223
				Day 14	96.8 ± 70.3	214	145 ± 148	315
	26 weeks	87.1	3	Week 4	1.32 ± 0.140	6.24 ± 0.801	1.57 ± 0.263	9.59 ± 4.00
				Week 26	0.914 ± 0.0735	9.18 ± 1.86	1.72 ± 0.477	10.4 ± 3.12
		289	2-3	Week 4	7.36 ± 2.95	30.9 ± 9.16	9.93 ± 1.89	38.0 ± 1.34
				Week 26	4.38 ± 0.176	18.3 ± 5.56	6.57	23.5
		987	2-3	Week 4	28.8 ± 17.4	87.8 ± 15.8	29.8 ± 12.1	84.5 ± 25.3
				Week 26	14.1 ± 3.29	48.3 ± 4.19	13.0	41.6
Dog	14 days	1000[b]	3	Day 1	33.4 ± 17.5	26.1 ± 14.8	52.2 ± 19.8	26.5 ± 5.49
				Day 14	98.3 ± 89.5	99.2 ± 34.7	84.3 ± 48.5	88.9 ± 25.4
	39 weeks	109	4-6	Week 4	11.1 ± 10.0	11.7 ± 6.18	12.2 ± 6.61	13.3 ± 5.87
				Week 39	3.13 ± 0.701	4.65 ± 1.48	3.92 ± 1.72	7.13 ± 2.03
		421	4-6	Week 4	45.0 ± 26.9	39.5 ± 19.2	44.2 ± 20.2	44.6 ± 9.63
				Week 39	14.3 ± 5.30	23.0 ± 7.84	16.5 ± 9.58	29.5 ± 6.89
		1002	4-6	Week 4	86.0 ± 63.6	85.7 ± 28.7	128 ± 28.9	113 ± 20.5
				Week 39	17.9 ± 12.9	47.0 ± 32.6	35.2 ± 20.8	41.2 ± 11.5

Mean ± SD, Vehicle consists of lactose and magnesium stearate. a: Target dose (estimated dose on Days 1 and 14; 1510 and 1610 μg/kg for males, 1650 and 1770 μg/kg for females, respectively), b: Target dose (estimated dose on Days 1 and 14; 721 and 1270 μg/kg for males, 812 and 1140 μg/kg for females, respectively)

(b) UMEC/VI concomitant therapy study

The toxicokinetics following repeated inhalation doses of UMEC/VI were investigated in rat 4-week (FD2009/00392/00), dog 4-week (FD2009/00391/00), and dog 13-week repeated inhalation toxicity studies (WD2010/00677/01). Table 5 shows the plasma umeclidinium and vilanterol pharmacokinetic parameters. The plasma concentration of UMEC or VI following concomitant administration varied largely, but was not largely different from that of each drug administered alone with no apparent accumulation due to the repeated inhalation doses being observed.

Table 5. Pharmacokinetic parameters in rats and dogs following repeated inhalation of UMEC/VI

	No. of animals	Time point	Umeclidinium					Vilanterol				
			Estimated dose (μg/kg)	Male		Female		Estimated dose (μg/kg)	Male		Female	
				C_{max} (ng/mL)	$AUC_{0\text{-}t}$ (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}t}$ (ng·h/mL)		C_{max} (ng/mL)	$AUC_{0\text{-}t}$ (ng·h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}t}$ (ng·h/mL)
Rat 4-week	2-3	Day 1	Male 898 Female 998	10.8	28.3	7.27	29.7	Male 4.69 Female 5.21	-		-	
	2-3	Week 4	Male 837 Female 928	6.57	29.0	4.77	20.7	Male 4.54 Female 5.03	-		-	
	3	Day 1	Male 1020 Female 1140	5.83	18.9	7.24	25.4	Male 54.5 Female 60.8	0.886	2.13	1.13	6.16
	3	Week 4	Male 1400 Female 1550	5.50	32.3	5.09	28.8	Male 70.3 Female 78.2	1.56	3.47	2.07	2.84
	2-3	Day 1	Male 952 Female 1060	26.4	54.2	19.6	41.6	Male 930 Female 1040	29.5	111	22.9	112
	3	Week 4	Male 1450 Female 1610	13.0	42.6	10.3	26.0	Male 1130 Female 1260	14.9	77.1	11.1	43.4
	2-3	Day 1	Male 660 Female 741	7.48	19.5	6.52	22.8					
	3	Week 4	Male 656 Female 734	4.78	24.5	5.59	28.0					
	3	Day 1						Male 702 Female 786	24.6	123	21.5	127
	3	Week 4						Male 688 Female 769	23.1	98.2	19.5	81.5
Dog 4-week	3	Day 1	Male 1083 Female 1181	150	85.8	64.8	54.1	Male 5.9 Female 6.5	11.4	12.5	10.0	14.5
	2-3	Week 4	Male 1157 Female 1259	115	113	50.5	70.4	Male 7.5 Female 8.1	7.71	12.9	5.53	10.1
	3	Day 1	Male 181 Female 195	9.25	5.35	5.11	4.23	Male 202 Female 218	73.9	219	42.7	89.0
	3	Week 4	Male 224 Female 243	16.7	18.3	11.6	13.0	Male 240 Female 261	174	294	83.7	186
	3	Day 1	Male 1087 Female 1182	71.4	65.3	53.1	39.8					
	3	Week 4	Male 1241 Female 1340	151	125	124	88.8					
	1	Day 1						Male 231 Female 250	29.0	66.5	71.7	133
	3	Week 4						Male 195 Female 212	68.0	185	76.9	219
Dog 13-week	3-4	Week 4	1070	56.0	55.1	34.5	52.2	7.50	3.70	8.11	5.98	14.5
	4	Week 13	1070	59.9	83.8	27.0	61.0	7.50	4.14	8.83	4.04	13.3
	3-4	Week 4	23.3	0.689	0.427	1.98	2.35	28.7	15.8	33.6	43.5	96.7

	No. of animals	Time point	Umeclidinium					Vilanterol				
			Estimated dose (μg/kg)	Male		Female		Estimated dose (μg/kg)	Male		Female	
				C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)		C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng·h/mL)
	3-4	Week 13	23.3	0.896	0.466	1.37	2.00	28.7	18.0	42.3	30.8	94.5
	3-4	Week 4	60.2	2.78	4.35	3.49	4.92	71.6	46.9	97.3	75.1	128
	4	Week 13	60.2	3.64	7.89	2.44	4.49	71.6	72.3	173	59.8	163
	4	Week 4	177	8.50	11.1	8.14	8.32	183	90.2	142	116	198
	3-4	Week 13	177	4.42	10.6	2.56	9.37	183	74.2	168	49.8	200
	4	Week 4	1048	55.2	58.8	86.4	81.5					
	4	Week 13	1048	28.3	53.2	104	116					
	4	Week 4						180	119	208	80.1	156
	4	Week 13						180	67.2	223	75.4	205

Mean, Vehicle consists of lactose and magnesium stearate. "-": Less than the lower limit of quantitation. The blank field indicates a failure of calculation.

3.(ii).A.(2) Distribution (4.2.2.3)

3.(ii).A.(2).1) Tissue distribution (FD2005/00236/00)

Following a single intravenous dose of ^{14}C-UMEC (1000 μg/kg) to male pigmented rats (n = 1/time point), the radioactivity was distributed throughout the body at 30 minutes and reached the maximum value in most of the tissues investigated at 0.5 or 1.5 hours. At 1.5 hours, the radioactivity in most of the tissues was detected to be ≥2 times the level in blood. Especially, high radioactivities were detected in the renal cortex, small intestinal wall, pancreas, thyroid, salivary gland, renal medulla, pineal gland, preputial gland, pituitary gland, gastric wall, adrenal medulla, choroid plexus, adrenal cortex, large intestinal wall, cecal wall, tongue, liver, mucus gland, and myocardium. The radioactivity was detected in the renal medulla, mucus gland, skeletal muscle, tongue, and melanin-containing tissues (uvea/retina) 35 days post-dose.

Following single oral dose of ^{14}C-UMEC (1000 μg/kg) to male pigmented rats (n = 1/time point), the radioactivity was not detected in most of the tissues except for the gastrointestinal tract.

3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells (WD2008/00503/00, 2012N144582_00)

The plasma protein binding rate of UMEC at the concentrations of 5, 25, and 200 ng/mL was 86.7% to 88.8% for mice, 84.3% to 86.9% for rats, 74.8% to 78.8% for rabbits, 77.2% to 83.0% for dogs, and 87.1% to 88.8% for humans, which were almost constant irrespective of the concentration. At the concentration of 1 ng/mL, the binding rates of UMEC to human serum albumin (40 mg/mL), α_1-acid glycoprotein (0.8 mg/mL), and γ-globulin (7 mg/mL) were 67.2%, 84.9%, and 64.6%, respectively.

At the concentrations of 50, 200, and 500 ng/mL, the blood/plasma concentration ratio of UMEC was 0.732 to 0.778 for mice, 0.670 to 0.691 for rats, 0.729 to 0.747 for rabbits, 0.520 to 0.533 for dogs, and 0.541 to 0.560 for humans, which were almost constant irrespective of the concentration.

3.(ii).A.(3) Metabolism (4.2.2.4)

3.(ii).A.(3).1) *In vitro* studies (WD2006/03367/00, WD2006/00147/00, WD2005/01195/00)

Following incubation of ^{14}C-UMEC (0.075 μM) in human liver microsome, unchanged UMEC (48.5%), O-dealkylated form (M14, 19.3%), hydroxylated form (M33, 20.0%), dihydroxylated forms (M56 and M61, 4.5% and 3.8%, respectively), 1 unidentified metabolite (2.8%) were detected. Production of M14 was inhibited by 90% in the presence of quinidine (1 μM, CYP2D6 inhibitor) and 52% in the presence of azamulin (5 μM, CYP3A4 inhibitor) and production of M33 was inhibited by 100% in the presence of quinidine.

CYP isoenzymes involved in the metabolism of ^{14}C-UMEC (0.075 μM) were investigated using recombinant human CYP expression system. M14, M33, M56, and M61 were detected in the CYP2D6 expression system, indicating that UMEC is mainly metabolized by CYP2D6. In addition, only M14 was detected in both CYP1A1 and CYP3A4 expression systems.

^{14}C-UMEC (10 or 50 μM) was incubated in rat, dog, or human hepatocytes. As a result, metabolites were detected in the human hepatocytes as follows: M14 (22.9% of the total metabolites), M33/M34 (methoxyhydroxylated form) (18.4%), M13 (glutathione conjugate)/M60 (cysteine conjugate) (8.9%), M21 (glucuronate conjugate)/M22/M51 (dihydrodiol form) (7.5%), M45 (glutathione conjugate)/M59 (cysteine conjugate) (5.2%), M53 (cysteine conjugate) (4.5%), M52 (cysteine conjugate) (3.5%), etc.. In the rat hepatocytes, M14 (37.9%), M13/M60 (16.4%), and M27 (glucuronate conjugate)/M53 (16.2%) were mainly detected. In the dog hepatocytes, M22/M51 (30.8%), M14 (25.9%), and M33/M34 (18.0%) were mainly detected. In the rat and dog hepatocytes, M45/M59 and M52 were below the lower limit of quantitation or not detected.

^{14}C-UMEC at 10 mg/kg was perfused in rat (n = 1/sex) liver. As a result, 11%, 24%, and 51% of the radioactivity dose were detected in the bile, perfusate, and liver extract, respectively, in the male, and 37%, 26%, and 36%, respectively, in the female. Main metabolites detected included unchanged UMEC, M21/M22, and M27 in the bile, M27, M21/M22, and unchanged UMEC in the perfusate, and unchanged UMEC, M14, and M18 in the liver extract.

3.(ii).A.(3).2) *In vivo* studies (WD2006/00172/00, WD2006/00250/00, WD2009/00030/00)

Following a single intravenous dose of ^{14}C-UMEC (1000 μg/kg) to male rats (n = 3), unchanged UMEC was mainly detected in the plasma at 0.5 and 2 hours. Unchanged UMEC, M14, and M33 were detected in the urine collected up to 24 hours post-dose, and unchanged UMEC, M14, M33, M34, and M37 were detected in the feces collected up to 48 hours post-dose.

Following a single intravenous dose of ^{14}C-UMEC (1000 μg/kg) to male dogs (n = 3), unchanged UMEC, M14, M33, M34, and M51 were detected in the plasma at 1 and 3 hours. Unchanged UMEC, M14, M33, M34, M51, and 2 unidentified metabolites were detected in the urine collected up to 48 hours post-dose. Unchanged UMEC, M14, M33, M34, M37, M51, M56, M57, M58, and 1 unidentified metabolite were detected in the feces collected up to 72 hours post-dose. A single dose of ^{14}C-UMEC (200 μg/kg) was intravenously administered over 10 minutes to bile duct-cannulated male dogs (n = 2). Unchanged UMEC, M14, M33/M34, M37/M54, M58, M63, M65, and M66 were detected in the bile collected up to 48 hours post-dose, and unchanged UMEC, M14, M33, M34, and M51 were detected in the urine collected up to 48 hours post-dose.

Following 7-day multiple inhalation doses of UMEC at 1000 μg to humans (8 male subjects, 8 female subjects), unchanged UMEC and M14 were detected in the plasma at 5 minutes and at 1 hour.

Based on the above investigations, possible metabolic pathways of UMEC are as shown in Figure 2.

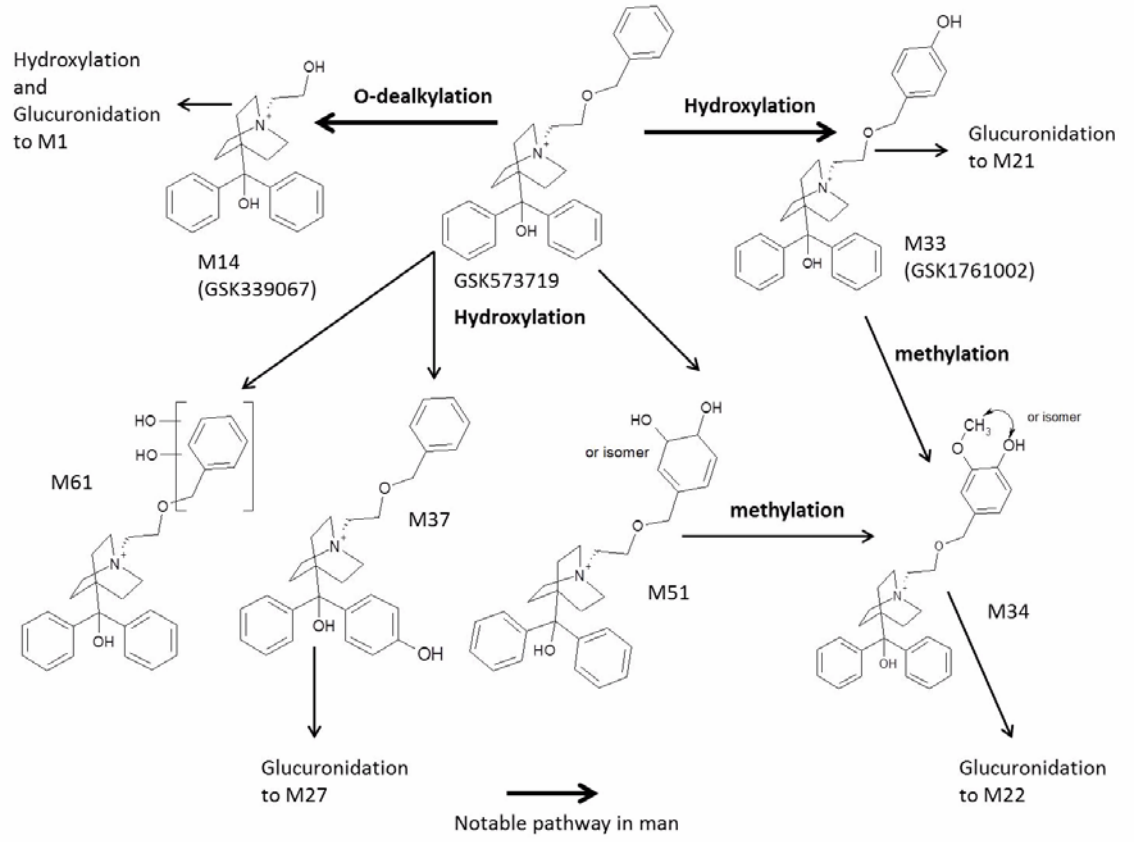


Figure 2. Possible metabolic pathways of UMEC in human and animals

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

3.(ii).A.(4).1) Excretion into feces, urine, and bile (4.2.2.5) (FD2005/00164/00, FD2005/00208/00, WD2007/01907/00)

Following a single intravenous dose of ^{14}C-UMEC (1000 μg/kg) to male rats (n = 3), the urinary and fecal excretion rates (percentage of the radioactivity dose) until 96 hours post-dose were 16.9% and 65.3%, respectively.

Following a single oral dose of ^{14}C-UMEC (1000 μg/kg) to male rats (n = 3), the urinary and fecal excretion rates until 96 hours post-dose were 0.10% and 96.4%, respectively. Following a single oral dose of ^{14}C-UMEC (1000 μg/kg) to bile duct-cannulated male rats (n = 3), the urinary, fecal, and biliary excretion rates until 48 hours post-dose were 0.13%, 92.9%, and 0.17%, respectively.

Following a single intravenous dose of ^{14}C-UMEC (1000 μg/kg) to male dogs (n = 3), the urinary and fecal excretion rates until 168 hours post-dose were 11.9% and 61.8%, respectively. Following a single intravenous dose of ^{14}C-UMEC (10 μg/kg) to bile duct-cannulated male dogs (n = 2), the urinary, fecal, and biliary excretion rates until 48 hours post-dose were 14.2%, 3.30%, and 55.6%, respectively.

Following a single oral dose of ^{14}C-UMEC (1000 μg/kg) to male dogs (n = 3), the urinary and fecal excretion rates until 168 hours post-dose were 0.43% and 95.2%, respectively.

3.(ii).A.(4).2) Excretion in milk (4.2.2.3) (2011N118595_00)

Following subcutaneous doses of UMEC at 10, 60, or 180 μg/kg to female rats (n = 24/group) from Gestation day 6 to Lactation day 20, the plasma umeclidinium concentrations in the

offspring aged 10 days (n = 54) were measured. As a result, 0.02 ng/mL of plasma umeclidinium as the concentration in offspring was detected in 1 animal in the 60 μg/kg group, and 0.03 ng/mL of that in 1 animal in the 180 μg/kg group, suggesting that UMEC is possibly excreted into milk.

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

3.(ii).A.(5).1) Enzyme inhibition and enzyme induction (4.2.2.4; CH2005/00950/00, WD2005/01627/00)

The inhibitory effect of UMEC (0.03-33 μM) against CYPs was investigated in recombinant human CYP expression system. The IC_{50} value against CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (substrate, diethoxyfluorescein), and CYP3A4 (substrate, 7-benzyloxyquinoline) was >33, >33, 14, 0.1, 1.0, and 8.0 μM, respectively, suggesting that UMEC inhibits CYP2D6 and CYP3A4.

The CYP mRNA expression level was investigated in rats (n = 3/sex/group) which received UMEC at 30, 200, or 2000 μg/kg/day once daily through 1-hour inhalation for 4 weeks. In females in the 2000 μg/kg/day group, the mRNA level of CYP1A1 increased 7.7 times, but the increase occurred in 1 of 3 animals. In males, the mRNA level of CYP4A1 increased 3.6 times at the maximum in the 30 and 200 μg/kg/day groups, but did not increase in the 2000 μg/kg/day group. Based on the above, no apparent CYP induction by UMEC was observed.

3.(ii).A.(5).2) Transporters (4.2.2.3)

(a) UMEC (WD2006/02657/00, WD2006/02596/00, WD2008/00001/00, WD2010/00669/00)

The UMEC transport by P-glycoprotein (P-gp) was investigated using Madin-Darby Canine Kidney (MDCK) II cells expressing MDR1. The Efflux Ratio (basolateral→apical/apical→basolateral) at the UMEC concentration of 3 μM was 7 to 17, while the Efflux Ratio in the presence of GF120918A at 2 μM, a P-gp inhibitor, was approximately 1, suggesting that umeclidinium serves as a substrate for P-gp.

The inhibitory effect of UMEC (0.1-100 μM) against ^{3}H-digoxin transport was investigated using MDCKII cells expressing MDR1. As a result, umeclidinium did not inhibit the transport.

Following a single oral dose of ^{14}C-umeclidinium trifluoroacetate at 40 μg/kg to MDR1a/1b gene knockout mice (n = 3/time point), C_{max} and AUC_{0-t} of the portal blood radioactivity were 17 and 20 times, respectively, those in wild-type mice, and C_{max} and AUC_{0-t} of the plasma radioactivity were 13 and 18 times, respectively, those in wild-type mice, suggesting that P-gp is involved in absorption of umeclidinium through the gastrointestinal tract.

The transport of UMEC (1.8 μM) was investigated using HEK293 cells expressing an organic cation transporter (OCT1, OCT2, OCT3, OCTN1, or OCTN2). Cells expressing OCT1 and OCT2 were found to have high transport capability of UMEC, which was inhibited by MPP (1-1000 μM, OCT1 inhibitor) and cimetidine (10-10,000 μM, OCT2 inhibitor), suggesting that umeclidinium serves as a substrate for OCT1 and OCT2.

(b) VI (Reference 2012N145447_00)

The transport of VI (3.7 μM) was investigated using HEK293 cells expressing an organic cation transporter (OCT1, OCT3, OCTN1, or OCTN2). The results suggested that vilanterol do not serve as a substrate for OCT1, OCT3, OCTN1, or OCTN2.

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

A distribution study of UMEC in pigmented rats showed slow elimination of the radioactivity from the melanin-containing tissues (uvea/retina) and renal medulla, mucus gland, skeletal

muscle, and tongue. PMDA thus asked the applicant if toxicity studies and clinical studies have presented any findings or adverse events in the melanin-containing eye tissues and other tissues potentially related to accumulation of UMEC.

The applicant explained as follows:
In the toxicity studies in which rats and dogs received inhalation administration of UMEC for up to 26 and 39 weeks, respectively, no effects of UMEC were observed at the ophthalmological or histopathological examination. Based on the primary efficacy study combined data,[3] etc. from the clinical studies in COPD patients, the incidence of eye-related adverse events was ≤1% in any dose group, and there were no events of which the incidence in the UMEC group was higher than that in the placebo group or in patients treated with a similar drug. Although in the Japanese long-term treatment study (Study DB2115362), cataract (4 subjects [3%]) occurred as an eye-related adverse event, the event was considered to be incidental to aging, because the incidence of cataract increases with aging; the age distribution in the Japanese long-term treatment study (70.4 ± 7.9 years) was higher than that in the primary efficacy study combined data (63.3 ± 8.7 years); and all of the subjects with cataract were ≥60 years of age, and 2 of them were ≥80 years of age. Based on the above, it is considered unlikely that clinical use of UMEC/VI results in development of adverse events related to melanin binding of UMEC in the uvea/retina.

In the distribution study of UMEC in pigmented rats, radioactivity was detected in the renal medulla, mucus gland, skeletal muscle, and tongue at 35 days post-dose. As a finding related to these tissues, inflammation of the laryngeal mucus gland (1 of 4 males in the 1002 μg/kg/day group) was observed in the 39-week inhalation toxicity study in dogs and was considered to be related to irritation of UMEC. The finding is, however, not considered to be a critical change, because it was mild in severity and was reversible after a recovery period. Based on the primary efficacy study combined data from the clinical studies, the incidence of adverse events classified into musculoskeletal and connective tissue disorders of system organ class in the UMEC group (10%-11%) was comparable to that in the placebo group (10%). The incidences of adverse events related to the mucus gland, kidney, and tongue (salivary gland pain, tongue ulceration, glossitis, dysuria, haematuria, etc.) in the UMEC group were <1% and comparable to those in the placebo group. Base on the above, the results of investigation in pigmented rats indicated that UMEC is distributed into the renal medulla, mucus gland, skeletal muscle, and tongue, and it remains for long periods. It is, however, considered unlikely that clinical use of UMEC/VI results in development of adverse events related to accumulation of UMEC in the tissues.

PMDA accepted the above response and concludes that the currently available data do not suggest specific safety concerns attributable to accumulation of UMEC in the melanin-containing tissues and other tissues in which elimination of UMEC was slow in the distribution study of UMEC in pigmented rats. PMDA, however, considers it necessary to continue the investigation via post-marketing surveillance, because UMEC/VI is expected to be used for long periods, and patients receiving long-term treatment in the clinical studies were limited.

3.(iii) Summary of toxicology studies

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

The toxicity data of VI were already evaluated in the application of Relvar. For the application of UMEC/VI, the data from repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, local tolerance, and other toxicity studies (skin sensitization study, toxicity studies of the impurities) were submitted as the toxicity data of UMEC; and the data from repeat-dose toxicity and reproductive and developmental toxicity studies (study on embryo-fetal development) of concomitant use of UMEC and VI were submitted as the toxicity data of the concomitant use. The doses and concentrations of UMEC and VI are expressed as free base.

[3] Studies DB2113361, DB2113373, DB2113360, and DB2113374

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

Although no single dose toxicity studies of UMEC have been conducted, the acute toxicity was evaluated in the 7-day inhalation toxicity study in rats (WD2005/01063/01 Reference data, non-GLP) and 14-day repeated inhalation toxicity study in dogs (WD2006/03228/00 Reference data, non-GLP). Post-dose symptoms in rats included changes in the nasal cavity and larynx such as degeneration, regeneration, hyperplasia, inflammation, erosion, and ulcer. Post-dose symptoms in dogs included thirst, panting, writhing, gasping, mydriasis, and increased heart rate, changes in the trachea and larynx such as degeneration, regeneration, hyperplasia, inflammation, erosion, and ulcer, epithelial degeneration and regeneration in the bronchus and bronchiole, and lymph atrophy in the thymus. Writhing, gasping, mydriasis, and increased heart rate were observed in 1 female dog in the 3430 μg/kg/day group (1 of 1 animal in this group) during the inhalation on Day 8 and thus the animal was sacrificed moribund. The histopathological findings in the animal included inflammation in the myocardium, mineralization in the kidney, fibrosis in the pleura pulmonalis, necrosis in the laryngeal mucosa, and exudates in the larynx lumen. Based on the above, the approximate lethal dose was determined to be >3418 μg/kg for rats and >3430 μg/kg for dogs.

3.(iii).A.(2) Repeat-dose toxicity studies (4.2.3.2)

Inhalation toxicity studies of UMEC in rats (13 and 26 weeks) and dogs (13 and 39 weeks) and inhalation toxicity studies of concomitant use of UMEC and VI in rats (4 weeks) and dogs (4 and 13 weeks) were conducted as repeat-dose toxicity studies.

Major toxicity findings following administration of UMEC alone included irritative changes in the upper airway (rats, dogs), alveolar macrophage accumulation (rats), increased heart rate (dogs), and effects on the blood vessels (dogs). Of the irritative changes in the upper airway, moderate changes were assessed as toxicity, and thereby the no observed adverse effect level (NOAEL) was determined.

Following concomitant use of UMEC and VI in rats, the irritative changes in the upper airway were slightly intensified compared with those following administration of UMEC alone, but the concomitant use did not lead to intensified toxicity of either single agent or development of new toxicity findings, which could cause clinical issues.

The exposures at the NOAEL (87.1 μg/kg/day) in the 26-week inhalation toxicity study of UMEC in rats and at the NOAEL (109 μg/kg/day) in the 39-week inhalation toxicity study of UMEC in dogs were compared with the estimated exposure (AUC, 365 pg·h/mL; C_{max}, 79.4 pg/mL) in Japanese COPD patients receiving multiple inhalation of UMEC 62.5 μg once daily (concomitantly with VI 25 μg). AUC in rats and in dogs were 22 times and 31 times, respectively, the estimated value in the patients, and C_{max} in rats and dogs were 20 times and 96 times, respectively, the estimated value in the patients. The lung delivery amount at the NOAEL in the 26-week inhalation toxicity study of UMEC in rats and in the 39-week inhalation toxicity study of UMEC in dogs was estimated to be 23 times and 40 times, respectively, that in humans receiving inhalation administration of UMEC 62.5 μg/day.[4]

3.(iii).A.(2).1) Study on UMEC monotherapy

(a) Thirteen-week inhalation toxicity study in rats (WD2007/02012/00)

UMEC (0 [vehicle, lactose containing 1%w/w MgSt], 38, 102, 288, or 924 μg/kg/day) was administered to SD rats by nose inhalation for 13 weeks. One of 12 males in the 102 μg/kg/day

[4] Lung delivery ratio = concentration in the animal lung/concentration in the human lung, Concentration in the animal lung = delivery rate (10% for rodent or 25% for dogs) × dose (μg/kg) × animal body weight (kg)/animal lung weight (g), Concentration in the human lung = delivery rate in humans (100%) × dose (125 μg)/human lung weight (1000 g)

group and 1 of 12 females in the 288 μg/kg/day group died on Days 74 and 27, respectively, but the deaths were assessed to be unrelated to UMEC. Findings included irritative changes in the larynx (ventral squamous metaplasia, cartilage necrosis) and in the nasal/paranasal cavity (hyperplasia/hypertrophy of goblet cells) in males and females in the ≥38 μg/kg/day groups; decreased food consumption and reduced body weight gain as well as inflammation and exudates in the nasal/paranasal cavity in males in the ≥102 μg/kg/day groups; irritative changes in the larynx (squamous metaplasia and inflammation of the submucosal gland) and in the nasal/paranasal cavity (degeneration/regeneration of the respiratory epithelium or olfactory epithelium, hyperplasia of the transitional epithelium) in the ≥288 μg/kg/day groups; and irritative changes in the nasal/paranasal cavity (moderate degeneration/regeneration of the respiratory epithelium) in males and females and decreased food consumption, reduced body weight gain, and decreased reticulocyte count in females in the 924 μg/kg/day group. These changes showed a reversible trend after a 4-week recovery period. Based on the above finding that moderate degeneration of the respiratory epithelium in the nasal/paranasal cavity was observed in the 924 μg/kg group, the NOAEL in this study was determined to be 288 μg/kg/day.

(b) Twenty-six-week inhalation toxicity study in rats (FD2009/00467/00)

UMEC (0 [vehicle, lactose containing 1%w/w MgSt], 87.1, 289, or 987 μg/kg/day) was administered to SD rats by nose inhalation for 26 weeks. Although 2 animals in the control group, 1 animal in the 289 μg/kg/day group, and 1 animal in the 987 μg/kg/day group died, these deaths were assessed to be unrelated to UMEC. Findings included reduced body weight gain, irritative changes in the nasal/paranasal cavity (hyperplasia and hypertrophy of the goblet cells) and in the larynx (ventral cartilage degeneration and necrosis, squamous metaplasia and hyperplasia, inflammation, exudate) and macrophage accumulation in the lung in males and females in the ≥87.1 μg/kg/day groups; moderate or severer irritative changes in the larynx (ventral cartilage degeneration/necrosis) and squamous metaplasia in the carina in males and females, irritative changes in the nasal/paranasal cavity (exudate and inflammation, acidophil granules in the olfactory epithelium, degeneration/regeneration of the respiratory epithelium) in males, and irritative changes in the nasal/paranasal cavity (degeneration/regeneration of the olfactory epithelium, squamous metaplasia of the respiratory epithelium) in females in the ≥289 μg/kg/day groups; irritative changes in the nasopharynx (inflammation or hyperplasia/hypertrophy of the goblet cells) in males and females, increases in neutrophil count and blood urea, irritative changes in the nasal/paranasal cavity (degeneration/regeneration of the olfactory epithelium, squamous metaplasia of the respiratory epithelium), and degeneration and regeneration of the goblet cells in the nasopharynx in males, and discolouration in the lung and irritative changes in the nasal/paranasal cavity (exudate and inflammation, acidophil granules of the olfactory epithelium, degeneration/regeneration of the respiratory epithelium) in females in the 987 μg/kg/day group. These changes showed a reversible trend after a 6-week recovery period. Based on the above finding that moderate or severer irritative changes in the larynx were observed in the ≥289 μg/kg/day groups, the NOAEL in this study was determined to be 87.1 μg/kg/day.

(c) Thirteen-week inhalation toxicity study in dogs (WD2007/01512/00)

UMEC (0 [vehicle, lactose containing 1%w/w MgSt], 40.7, 187, or 1070 μg/kg/day) was administered to beagle dogs by inhalation for 13 weeks. Findings included thirst, dry nose, and decreased lacrimal fluid in the ≥40.7 μg/kg/day groups; and increased heart rate, disappeared respiratory sinus arrhythmia (RSA), and increased cardiac troponin I (cTnI) in the 1070 μg/kg/day group and description changes of the bile (black/granular) in males in the same group. All of the findings were reversibile after a 4-week recovery period. In addition, all of them were assessed to have little toxicological significance, because the thirst, dry nose, and decreased lacrimal fluid were considered to be changes related to the anticholinergic effect of UMEC; the effects on the cardiovascular system were mild changes without histological changes in the heart; and for the description changes of the bile, no related histological changes were observed in the gallbladder. Based on the above, the NOAEL in this study was determined to be 1070 μg/kg/day.

(d) Thirty-nine-week inhalation toxicity study in dogs (FD2009/00466/02)

UMEC (0 [vehicle, lactose containing 1%w/w MgSt], 109, 421, or 1002 μg/kg/day) was administered to beagle dogs by inhalation for 39 weeks. Findings included thirst, decreased incidences of loose stool/watery stool/mucous feces, decreased lacrimal fluid, increases in pulse rate and heart rate in males and females, and disappeared RSA and decreases in hemoglobin, hematocrit, and red blood cell count in males in the ≥109 μg/kg/day groups; increased cTnI, irritative changes in the larynx (erosion/ulcer of the mucosal epithelium, inflammation/squamous hyperplasia of the mucus gland) and in the turbinate (squamous metaplasia of the respiratory epithelium) in males and females, necrotizing arteritis in the external wall of the coronary artery in males, and disappeared RSA in females in the ≥421 μg/kg/day groups; and increased blood urea nitrogen in the 1002 μg/kg/day group, decreased thymus weight in males, and necrotizing arteritis of the coronary artery and focal mononuclear inflammatory cell infiltration of the pulmonary arteriole in females in the same dose group. Except for changes in erythroid parameters, all of the findings were reversible after a 6-week recovery period. In addition, both changes in erythroid parameters and increased blood urea nitrogen were assessed to have little toxicological significance, because they were slight without any related histological changes. Based on the above finding that vascular lesions in the heart and lung were observed in the ≥421 μg/kg/day groups, the NOAEL in this study was determined to be 109 μg/kg/day.

3.(iii).A.(2).2) UMEC/VI concomitant therapy study

(a) Four-week concomitant inhalation toxicity study in rats (FD2009/00392/00)

UMEC/VI (0/0 [vehicle, lactose containing 1%w/w MgSt], 757/0, 0/869, 817/4.37, 1200/60.7, or 1060/1040 μg/kg/day) was administered to SD rats by nose inhalation for 4 weeks. The findings in the UMEC alone group included reduced body weight gain, increased red blood cell count, decreases in mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration, increases in aspartate aminotransferase (AST) and creatinine, increases in potassium and chloride, decreases in calcium and phosphorus, increased glucose, irritative changes in the turbinate (degeneration/regeneration of the respiratory epithelium), in the vomeronasal organ (degeneration/regeneration, squamous metaplasia of the respiratory epithelium and olfactory epithelium), in the larynx (squamous metaplasia and epithelial keratinization of the ventral/lateral wall or necrosis of ventral cartilage, squamous hyperplasia of the arytenoids), and in the carina (deciliation/basophilic change/flat cells) in males and females; and increased urine pH and irritative changes in the turbinate (squamous metaplasia of the respiratory epithelium) in males. Findings in the VI alone group included increased body weight gain, decreases in mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration, increases in alanine aminotransferase (ALT)/AST/creatinine, increases in potassium and chloride, decreases in calcium and phosphorus, increased urine volume, increased urine creatinine, and irritative changes in the larynx (squamous hyperplasia of the arytenoids) in males and females; increased urine pH, decreased urine specific gravity, and decreased liver weight in males; and increased red blood cell count in females. Findings that were observed in the concomitant use groups but not in the single agent groups included increased blood urea in males in the ≥817/4.37 μg/kg/day concomitant use groups and in females in the 1060/1040 μg/kg/day concomitant use group; irritative changes in the nasopharynx (degeneration/regeneration of the respiratory epithelium) in males in the 817/4.37 μg/kg/day concomitant use group and in males and females in the 1060/1040 μg/kg/day concomitant use group; irritative changes in the pharynx (keratinization of the arytenoids) in males in the 1060/1040 μg/kg/day concomitant use group and in females in the 1200/60.7 μg/kg/day concomitant use group; and irritative changes in the turbinate (atrophy/abnormal arrangement of the olfactory epithelium, olfactory nerve fiber atrophy) in males and females in the ≥817/4.37 μg/kg/day concomitant use groups.

(b) Four-week concomitant inhalation toxicity study in dogs (FD2009/00391/00)

UMEC/VI (0/0 [vehicle, lactose containing 1%w/w MgSt], 997/0, 0/174, 996/6.46,

190/205 μg/kg/day) was administered to beagle dogs by inhalation for 4 weeks. VI was expected to affect the cardiovascular system. Thus, to enable to administer high dose repeatedly in the 190/205 μg/kg/day group and 0/174 μg/kg/day group, UMEC/VI was administered at the dose of 40/40 or 0/40 μg/kg/day by inhalation for 3 days for tachyphylaxis induction before administration of the test drug. Findings in the UMEC alone group included neck swelling, thirst, decreased lacrimal fluid, increased pulse rate, increased heart rate, disappeared RSA, increased cTnI, increases in glutamate dehydrogenase/blood urea nitrogen/phosphorus/triglyceride, decreased thymus weight, regression/atrophy of the thymus, irritative changes in the larynx (epithelial erosion/ulcer, acute/subacute inflammation associated with squamous hyperplasia). Findings in the VI alone group included neck swelling, thirst, salivation, increased body weight gain, increased pulse rate, increased heart rate, increased cTnI, increases in potassium/glutamate dehydrogenase/blood urea nitrogen/phosphorus/triglyceride, regression/atrophy of the thymus. As a finding that was observed in the concomitant use groups but not in the single agent groups, focal fibrosis associated with mineralization in the myocardial papillary muscle occurred in 1 female in the 190/205 μg/kg/day concomitant use group. Fibrosis of the myocardial papillary muscle was a change also observed following the VI alone administration and was assessed to be a change expected from β_2 adrenergic agonists attributable to hypoxic condition resulted from vasodilation and tachycardia. Any finding was not intensified by concomitant administration.

(c) Thirteen-week concomitant inhalation toxicity study in dogs (WD2010/00677/01)

UMEC/VI (0/0 [vehicle, lactose containing 1%w/w MgSt], 1048/0, 0/180, 1070/7.5, 23/29, 60/72, 177/183 μg/kg/day) was administered to beagle dogs by inhalation for 13 weeks. VI was expected to affect the cardiovascular system. Thus, to enable to administer high dose repeatedly in the 177/183 μg/kg/day group and 0/180 μg/kg/day group, UMEC/VI was administered at the dose of 40/40 or 0/40 μg/kg/day by inhalation for 3 days for tachyphylaxis induction before administration of the test drug. Findings in the UMEC alone group included neck swelling, decreased lacrimal fluid, and disappeared RSA in males and females and irritative changes in the larynx (mixed cell infiltration in the laryngeal mucosa) in females. Findings in the VI alone group included neck swelling, increased body weight gain, increased pulse rate, increased heart rate, and increased cTnI in males and females. Subacute or chronic inflammation in the lung was observed in all dose groups including the vehicle group and was apparent in 1 male in the 1070/7.5 μg/kg/day group. Findings in either concomitant use group were similar to those in the single agent groups, and their incidence and severity did not show any clear relationship with the dose. The concomitant administration was thus considered not to intensify the changes observed.

3.(iii).A.(3) Genotoxicity studies (4.2.3.3.1 to 4.2.3.3.2; WD2005/00750/00, WD2005/00751/00, WD2005/01079/00)

Bacteria reverse mutation assay, mouse lymphoma TK assay, and micronucleus assay in rat were conducted for genotoxicity studies of UMEC, and none of the assays indicated genotoxicity.

3.(iii).A.(4) Carcinogenicity study (4.2.3.4.1)

A carcinogenicity study of UMEC was conducted in mice and rats which received the test drug through inhalation. Neither proliferative nor neoplastic changes attributable to UMEC were observed.

3.(iii).A.(4).1) Carcinogenicity study in mice (2012N131664_00)

UMEC was administered to male CD-1 mice at doses of 0 (vehicle, lactose containing 1%w/w MgSt), 58.6, 188, 533 μg/kg/day by inhalation until Week 66 and then 0 (vehicle), 32.2, 102, or 295 μg/kg/day from Week 67 and thereafter; and to female CD-1 mice at doses of 0 (vehicle), 20.8, 63.7, or 200 μg/kg/day for 104 weeks. In males, decreased food consumption and reduced body weight gain were observed, and thus the dose was decreased from Week 67.

The incidence of neoplastic lesions related to UMEC did not increase.

Non-neoplastic lesions included deciliation in the carina in all dose groups; irritative changes in the larynx (squamous metaplasia/hyperplasia), in the nasal cavity (eosinophilic inclusion bodies in the respiratory epithelium, olfactory epithelium, and subepithelial mucosal gland, subepithelial mucosal gland dilatation) in females in the ≥20.8 μg/kg/day groups; irritative changes in the larynx (ventral cartilage necrosis, ventral epithelial erosion/ulcer) in females in the ≥63.7 μg/kg/day groups; irritative changes in the larynx (squamous metaplasia/hyperplasia) in males in the ≥188 μg/kg/day groups; changes in the nasal cavity (atrophy and abnormal arrangement of the olfactory epithelium) in females in the 200 μg/kg/day group; and irritative changes in the larynx (ventral cartilage necrosis, ventral epithelial erosion/ulcer), in the nasal cavity (eosinophilic inclusion bodies in the respiratory epithelium, olfactory epithelium, and subepithelial mucosal gland, atrophy/abnormal arrangement of the olfactory epithelium, respiratory epithelium metaplasia in the olfactory epithelium, subepithelial mucosal gland dilatation, subepithelial mucosal gland inflammation) in males in the 533 μg/kg/day group.

3.(iii).A.(4).2) Carcinogenicity study in rats (2012N131619_00)

UMEC (0 [vehicle, lactose containing 1%w/w MgSt], 30.1, 101, 276 μg/kg/day) was administered to SD rats by inhalation until Week 72. In both males and females of all dose groups, reduced body weight gain was observed, and therefore the dose was decreased to 0 (vehicle), 14.7, 45.0, or 137 μg/kg/day from Week 73 and thereafter. The treatment period in total was 104 weeks.

Benign granular cell tumor in the brain was observed in males in the 30.1 μg/kg/day group, but the incidence in the other dose groups was within the background data and did not correlate with the dose. The finding was therefore assessed to be unrelated to UMEC.

Non-neoplastic lesions observed were irritative changes in the larynx (ventral cartilage necrosis, squamous metaplasia/hyperplasia) and foaming of the alveolar macrophage in males and females and porphyrin pigmentation of the Harderian gland in males in the ≥30.1 μg/kg/day groups; porphyrin pigmentation of the Harderian gland in females in the ≥101 μg/kg/day groups; and eosinophilic inclusion bodies in the turbinate olfactory epithelium in males and females in the 276 μg/kg/day group.

3.(iii).A.(5) Reproductive and developmental toxicity studies (4.2.3.5.1 to 4.2.3.5.3)

For single use of UMEC, a study of male fertility and study of female fertility and early embryonic development to implantation (in rats), studies on embryo-fetal development (in rats and rabbits), and a study for effects on pre- and postnatal development including maternal function (in rats) were conducted. For concomitant use of UMEC/VI, a study on embryo-fetal development (in rabbits) was conducted. As a major finding related to UMEC, decreased body weight in maternal animals during the pregnancy period and in offspring was observed, but no finding indicating teratogenicity was observed. Although the placental transfer of UMEC has not been investigated, a repeated subcutaneous dose study of UMEC in rats suggests its excretion in milk [see "3.(ii) Summary of pharmacokinetic studies"].

3.(iii).A.(5).1) Study on UMEC monotherapy

(a) Study of male fertility (CD2010/00187/01)

UMEC (0 [vehicle, saline], 30, 60, 180 μg/kg/day) was subcutaneously administered to male SD rats from 14 days prior to mating for 49 to 53 days. Untreated female rats that mated with the male rats underwent cesarean section on Gestation day 20. Reduced body weight gain in the ≥30 μg/kg/day groups and decreased food consumption in the 180 μg/kg/day group were observed, but there were no effects observed on the fertility. As the reduced body weight gain did not correlate with the dose, the NOAEL for general toxicity and fertility in paternal animals was determined to be 180 μg/kg/day.

(b) Study of female fertility (WD2007/00763/00)

UMEC (0 [vehicle, lactose containing 1%w/w MgSt], 3.37, 29.1, 100, 294 μg/kg/day) was administered to female SD rats by inhalation from 14 days prior to mating to Gestation day 7, and the animals underwent cesarean section on Gestation day 20. There were no effects of UMEC observed on the maternal animals or fertility or early embryonic development to implantation. Increased fetal body weight was observed in the 294 μg/kg/day group, but no fetal appearance abnormalities were observed. Based on the above, the NOAELs for maternal general toxicity as well as fertility and early embryonic development were all determined to be 294 μg/kg/day.

(c) Embryo-fetal development in rats (WD2007/00764/00)

UMEC (0 [vehicle, lactose containing 1%w/w MgSt], 31.7, 96.9, 278 μg/kg/day) was administered to pregnant SD rats by inhalation from Gestation day 6 to Gestation day 17, and the animals underwent cesarean section on Gestation day 21. In maternal animals, reduced body weight gain were observed in the ≥96.9 μg/kg/day groups and decreased food consumption in the 278 μg/kg/day group, but the findings showed a reversible trend at the end of the treatment period. There were no observed effects of UMEC on the numbers of corpora lutea, implantation sites, dead resorptions, dead fetuses and live fetuses, sex ratio or fetal morphology. Based on the above, the NOAELs for maternal general toxicity as well as reproductive potential and embryo-fetal development were all determined to be 278 μg/kg/day.

(d) Embryo-fetal development in rabbits (WD2007/00762/00)

UMEC (0 [vehicle, lactose containing 1%w/w MgSt], 28.5, 88.9, 306 μg/kg/day) was administered to pregnant NZW rabbits by inhalation from Gestation day 7 to Gestation day 19, and the animals underwent cesarean section on Gestation day 29. Abortion occurred in 1 of 22 animals in the 306 μg/kg/day group, but no impact of the abortion was seen on fetal survival. It was thus assessed to be unrelated to UMEC. Decreased food consumption was observed in maternal animals in the ≥28.5 μg/kg/day groups, but there were no observed effects on the numbers of corpora lutea, implantation sites, dead resorptions, dead fetuses and live fetuses, sex ratio or fetal morphology. Based on the above, the NOAELs for maternal general toxicity as well as reproductive potential and embryo-fetal development were all determined to be 306 μg/kg/day.

(e) Study on pre- and postnatal development, including maternal function (2011N118595_00)

UMEC (0 [vehicle, saline], 10, 60, 180 μg/kg/day) was subcutaneously administered to pregnant SD rats from Gestation day 6 to Lactation day 20. In maternal animals, decreased food consumption was observed in the ≥60 μg/kg/day groups and reduced body weight gain during the pregnancy period in the 180 μg/kg/day group, but the body weight at Lactation day 21 was comparable to that in the control group. Decreased body weight was observed in F1 offspring in the 180 μg/kg/day group. Based on the above, the NOAEL was determined to be 180 μg/kg/day for maternal reproductive potential and 60 μg/kg/day for pre- and postnatal development of the offspring.

3.(iii).A.(5).2) UMEC/VI concomitant therapy study

(a) Embryo-fetal development in rabbits (CD2009/00970/00)

UMEC/VI (0/0 [vehicle, mixture of PEG400 and 8% 2-hydroxypropyl-β-cyclodextrin], 100/0, 100/100 μg/kg/day) was subcutaneously administered to pregnant NZW rabbits from Gestation day 7 to Gestation day 19. There were no observed effects of UMEC alone or UMEC/VI concomitant use on the maternal general toxicity or embryo-fetal development in any group.

3.(iii).A.(6) Local tolerance study (4.2.3.6)

Eye irritability of UMEC was evaluated in a reconstructed human corneal epithelium model. The cell viability after 10- and 60-minute treatment with UMEC at 30 mg was 80.2% and 10.6%,

respectively, of that in the negative control. UMEC was therefore assessed to have mild or moderate eye irritation.

3.(iii).A.(7) Other toxicity studies (4.2.3.7.7)

3.(iii).A.(7).1) Skin sensitization study (2011N123962_00)

UMEC (50 μL of 25% w/w in propylene glycol, 25 μL/pinna) was applied to each auricle of female CBA/Ca mice (n = 5/group) once daily for 3 days. ^{3}H-methylthymidine was then intravenously administered 6 days after the start of the study to evaluate the sensitizing property using uptake of thymidine in the auricular lymph nodes as an indicator. As a result, UMEC was not classified as a skin sensitizer.

3.(iii).A.(7).2) Qualification of impurities in the UMEC drug substance

In the UMEC drug substance, 8 impurities have their acceptance criteria set beyond the qualification threshold (0.15%). The estimated exposure of each of the 8 impurities in the batches used in the repeat-dose toxicity studies, genotoxicity studies, and carcinogenicity studies was above the estimated exposure of that in humans at the maximum clinical dose. Thus, the 8 impurities were considered to be qualified.

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

3.(iii).B.(1) Local effects of UMEC or UMEC/VI concomitant use on the respiratory tract

Squamous hyperplasia in the larynx was observed in a 26-week inhalation toxicity study in rats and a 39-week inhalation toxicity study in dogs and was considered attributable to the irritative changes caused by UMEC. The exposure at the dose not leading to this finding in dogs (109 μg/kg/day) was 31 times that at the proposed dose in the application (62.5 μg/day). On the other hand, in rats, the finding was observed even in the low dose group (87.1 μg/kg/day, the exposure is 22 times that at the proposed dose of 62.5 μg/day) and the dose not leading to the finding was not identified. PMDA therefore asked the applicant to discuss the concerned finding in terms of the extrapolation to humans and the safety.

The applicant explained as follows:

The rat larynx is known to be anatomically predisposed to histological changes (Osimitz TG et al. *Toxicology and Applied Pharmacology.* 2007;225:229-237). This animal species is therefore considered to be readily affected by inhalation administration of UMEC. In general, the squamous hyperplasia in the upper airway is considered attributable to long-term inhalation exposure (Wagner JG et al. *Toxicology of the Nose and Upper Airways.* 2010;243). The exposure of UMEC studied in rats lasted for a long time (1 hour), while a short-duration oral inhalation is to be administered to humans. In the clinical studies, the incidences of adverse events considered related to local stimulation in the UMEC 125 μg group based on the primary efficacy study combined data were 5% (29 of 629 subjects) for cough, 7% (43 of 629 subjects) for nasopharyngitis, and 2% (12 of 629 subjects) for oropharyngeal pain, which were comparable to those in the placebo group (4% [23 of 555 subjects], 9% [48 of 555 subjects], 2% [9 of 555 subjects], respectively) [see "4.(iii).B.(3) Safety"]. Based on the above, changes in the upper airway attributable to UMEC, which were observed in the non-clinical studies, are considered unlikely to develop in humans.

In the 4-week concomitant inhalation toxicity study in rats, atrophy of the turbinate olfactory nerve fiber was observed only in the concomitant use group. PMDA asked the applicant to discuss this finding in terms of the toxicological significance and extrapolation to humans.

The applicant explained as follows:

In the 4-week concomitant inhalation toxicity study in rats, the animals with atrophy of the turbinate olfactory nerve fiber were frequently found to have degeneration/regeneration,

hyperplasia of the goblet cells, or inflammatory cell infiltration in the respiratory epithelium in the turbinate, and atrophy/abnormal arrangement or inflammatory cell infiltration of the olfactory epithelium. Cells comprising the olfactory epithelium are highly sensitive to stimulation. The atrophy of the olfactory nerve fiber bundle occurs in association with changes in the olfactory epithelium (Sells DM et al. *Toxicol Pathol.* 2007;35:170-177). Based on the above, it is considered that the degeneration of olfactory cells spreads through the axon, resulting in the atrophy of nerve fibers in the lower layer. The atrophy of turbinate olfactory nerve fibers is considered as a consequence of irritative changes caused by each of UMEC and VI being intensified by the concomitant use. This finding is, however, considered unlikely to occur in humans because rats were exposed by the nose inhalation at a high concentration for a long time (1 hour), while humans are to be exposed by oral inhalation in a short duration; in clinical studies, the severities of cough, nasopharyngitis, and oropharyngeal pain considered related to local stimulation were not increased in the UMEC group compared with those in the placebo group [see "4.(iii).B.(3) Safety"].

In the 13-week concomitant inhalation toxicity study in dogs, marked subacute or chronic inflammation in the lung was observed in the 1070/7.5 μg/kg/day concomitant use group. PMDA asked the applicant to discuss whether this finding is related to UMEC/VI and extrapolated to humans.

The applicant explained as follows:
Subacute or chronic inflammation in the lung was observed in all of the groups including the control group, and the findings differed in severity between the concomitant use groups and the vehicle group. The difference is considered to be caused by the secondary changes resulted from the effects of UMEC anticholinergic activity on the relevant organs such as thirst due to sialoschesis, decreased mucociliary clearance due to mucostasis in the airway, gastric regurgitation due to the effect on the esophageal sphincter, and enhanced invasion of inhaled foreign matters into the deep lung due to bronchodilation. These changes are, however, considered unlikely to occur in humans because the study showed no findings indicating direct effects on the lung parenchyma; and the dose of 1070/7.5 μg/kg/day, which led to marked inflammation, is far above the clinical dose; and there were no findings in the lung considered related to UMEC and VI in clinical studies [see "4.(iii).B.(3) Safety"].

3.(iii).B.(2) Effects of UMEC/VI concomitant use on the heart

The applicant explained the effects of concomitant use of UMEC and VI on the heart as follows:
In the 39-week inhalation toxicity study of UMEC in dogs, the pulse rate and heart rate increased in association with disappeared RSA. These findings are expected changes considered attributable to the block of the parasympathetic nerves that resulted from UMEC anticholinergic effects against sinoatrial node M2 receptor (Brown JH and Taylor P. *The Pharmacological Basis of Therapeutics* [Volume 1]. 2007;230-236). They showed reversibility after a recovery period. The heart rate increased in the 13-week concomitant inhalation toxicity study in dogs, but there was no considerable difference between single agent groups and concomitant use group. In the safety pharmacology study, the increased heart rate and variations in ECG in each single agent group as well as increased blood pressure in the concomitant use group were observed, but all of these findings were observed at the exposure levels above the clinical dose. Based on the above, the clinical dose of UMEC/VI is considered unlikely to cause clinically relevant effects on the heart.

Based on the discussions in (1) and (2), PMDA considers that no particular issues for clinical use of UMEC/VI are suggested from a toxicological viewpoint, because data from the toxicity studies of UMEC alone and concomitant use of UMEC and VI show that the toxicity profile of UMEC is similar to those of existing LAMAs, and combination of UMEC and VI has not led to increased or new toxicity concerns about the clinical use. However, in a series of toxicity studies and the safety pharmacology studies in which UMEC and VI were separately or concomitantly

administered, effects on the heart such as increases in pulse rate and heart rate were observed even in the low dose group as the treatment period was extended, and the effects on the heart are changes expected from the pharmacologic actions of UMEC and VI. Thus, it is considered necessary to investigate the clinical effects of UMEC/VI on the cardiovascular system carefully based on the clinical data and post-marketing surveillance data.

4. Clinical data

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

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

As the evaluation data, the results from absolute bioavailability studies (5.3.1.1; AC4112008, AC4115487) were submitted.

Plasma and urine umeclidinium concentrations as well as vilanterol concentrations were measured by high performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS) (lower limit of quantitation of the plasma umeclidinium concentration, 0.01 or 0.02 ng/mL; lower limit of quantitation of the urine umeclidinium concentration, 0.01 or 0.10 ng/mL; lower limit of quantitation of the plasma vilanterol concentration, 0.01 or 0.03 ng/mL; lower limit of quantitation of the urine vilanterol concentration, 0.50 ng/mL).

Unless otherwise specified, the doses and concentrations are expressed as free base, and the measured values and pharmacokinetic parameters are expressed as the mean or mean ± SD.

4.(i).A.(1) Absolute bioavailability of UMEC (Reference 5.3.1.1, Study AC4112008 [April to June 2010])

The absolute bioavailability of UMEC following single inhalation administration was investigated in an open-label, sequential crossover study in foreign healthy adult subjects (10 subjects). Table 6 shows pharmacokinetic parameters of plasma umeclidinium following single inhalation of UMEC 1000 μg (i.e. 2 inhalations of 500 μg) using a new dry powder inhaler (NDPI), single oral dose of UMEC 1000 μg, or single intravenous dose of UMEC 20, 50, or 65 μg. The absolute bioavailability of umeclidinium [95% confidence interval (CI)] following the inhalation administration was 12.8% [9.0, 18.2]. The plasma umeclidinium concentration following the oral administration was less than the lower limit of quantitation [0.02 ng/mL] at all sampling points.

Table 6. Pharmacokinetic parameters of plasma umeclidinium in foreign healthy adult subjects following single inhalation dose 1000 μg, single oral dose 1000 μg, or single intravenous dose 20, 50, 65 μg

Dose	Route of administration	Number of subjects	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-t} (h·ng/mL)	$AUC_{0-\infty}$ (h·ng/mL)	$t_{1/2}$ (h)
1000 μg	i.h.	9	1.82 ± 0.84	0.083 (0.08-0.25)	1.26 ± 0.33	1.38 ± 0.40	3.20 ± 2.64
1000 μg	p.o.	10	-	-	-	-	-
20 μg	i.v.	10	0.39 ± 0.12	0.48 (0.33-0.53)	0.17 ± 0.06	0.15 ± 0.08	0.06 ± 0.01 [b]
50 μg	i.v.	9	1.16 ± 0.21 [a]	0.48 (0.48-0.53) [a]	0.52 ± 0.12 [a]	0.54 ± 0.17 [a]	0.80 ± 2.02 [a]
65 μg	i.v.	9	1.62 ± 0.44	0.48 (0.33-0.48)	0.81 ± 0.31	0.67 ± 0.30	0.33 ± 0.28 [a]

Mean ± SD, t_{max} was expressed as median (range). "-": No data available, C_{max}: Maximum plasma concentration, t_{max}: Time to reach the maximum plasma concentration, AUC: Area under the plasma concentration-time curve, $t_{1/2}$: Elimination half-life, a) N = 8, b) N = 7

4.(i).A.(2) Comparison between single and dual-strip formulations of UMEC (Reference 5.3.1.1, Study AC4115487 [October to December 2011])

In a randomized, double-blind, 5-period crossover study in foreign healthy adult subjects (12 male subjects, 3 female subjects), single inhalation dose of UMEC in the single- and dual-strip formulations were administered to compare the pharmacokinetic and pharmacodynamic effects. Table 7 shows the pharmacokinetic parameters of plasma umeclidinium following single

inhalation dose of UMEC 62.5 or 125 μg using a single- or dual-strip NDPI. The pharmacokinetic parameters[5] of these formulations were compared and the geometric mean ratio of C_{max} (single-strip formulation/dual-strip formulation) was 0.86 to 0.88, those of $AUC_{(0-1)}$ was 0.91, and $AUC_{(0-2)}$ was 0.93.

Table 7. Pharmacokinetic parameters of plasma umeclidinium in foreign healthy adult subjects following single inhalation dose in the single and dual-strip formulations

Dose	Formulation	Number of subjects	C_{max} (pg/mL)	t_{max} (h)	$AUC_{(0-1)}$ (h·pg/mL)	$AUC_{(0-2)}$ (h·pg/mL)	AUC_{0-t} (h·pg/mL)
62.5 μg	Single	15	121.41 ± 60.43	0.08 (0.08-0.10)	36.59 ± 15.28	-	35.52 ± 17.29
62.5 μg	Dual	15	131.17 ± 71.29	0.08 (0.08-0.10)	38.60 ± 16.52	-	38.41 ± 21.16
125 μg	Single	14	289.99 ± 149.11	0.08 (0.08-0.13)	-	118.26 ± 45.19	131.32 ± 61.18
125 μg	Dual	15	300.79 ± 141.66	0.08 (0.08-0.50)	-	118.11 ± 35.83	126.77 ± 46.98

Mean ± SD, t_{max} was expressed as median (range). "-": No data available

The bronchodilation following use of the single- and dual-strip formulations was compared using sGaw and FEV_1 as indicators. The geometric mean ratio (single-strip formulation/dual-strip formulation [90% CI]) of the sGaw weighted mean during a period from baseline (0 hours) to 24 hours post-dose was 1.02 [0.97, 1.07] at the dose of 62.5 μg and 0.99 [0.94, 1.05] at the dose of 125 μg. The difference (between the single-strip formulation and the dual-strip formulation [90% CI]) in the adjusted mean of weighted mean FEV_1 during a period from baseline (0 hours) to 24 hours post-dose was -0.03 [-0.09, 0.03] at the dose of 62.5 μg and -0.01 [-0.07, 0.05] at the dose of 125 μg.[6]

4.(ii) Summary of clinical pharmacology studies

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

As the evaluation data, the results from multiple dose study of UMEC in Japanese healthy adult subjects (5.3.3.1, Study AC4113377), multiple dose study of UMEC in foreign healthy adult subjects and subjects with CYP2D6 poor metabolizers (5.3.3.4, Study AC4110106), mass balance study of UMEC (5.3.1.1, Study AC4112014), single dose study of each agent and their combination drug in Japanese healthy adult subjects (5.3.3.1, Study DB2113208), population pharmacokinetic analysis in COPD patients (5.3.5.3, 2012N155790_00), intrinsic factor studies in foreign subjects (5.3.3.3, Studies DB2114636 and DB2114637), drug interaction study (5.3.3.4, Study DB2113950), and pharmacodynamic study (5.3.4.1, Study DB2114635) were submitted.

Unless otherwise specified, the doses and concentrations are expressed as free base, and the pharmacokinetic parameters are expressed as a mean or mean ± SD.

4.(ii).A.(1) UMEC alone

4.(ii).A.(1).1) Single and multiple dose study of UMEC in Japanese healthy adult subjects (5.3.3.1, Study AC4113377 [October to December 2009])

The pharmacokinetic profiles of UMEC following single and multiple inhalation administrations were investigated in a placebo-controlled, randomized, double-blind, dose escalation study in Japanese healthy adult subjects (12 subjects per group). Table 8 shows the pharmacokinetic parameters of plasma umeclidinium when UMEC at 250, 500, or 1000 μg was administered as a single inhalation dose using NDPI followed by 2-day washout and then 7-day once-daily multiple inhalation doses of UMEC 250, 500, or 1000 μg. C_{max} and AUC following both single and multiple doses increased in a dose-dependent manner.

[5] Since subjects with $AUC_{0-\infty}$ calculable were limited, the exposures were compared among the formulations using $AUC_{(0-1)}$ or $AUC_{(0-2)}$ based on t_{last} (median) at each dose level.

[6] The dual-strip formulations were used in the UMEC group and the VI group in the phase II studies and in the UMEC/VI group in phase III studies, while the single-strip formulations were used in the UMEC group and VI group in the phase III studies.

Table 8. Pharmacokinetic parameters of plasma umeclidinium following single and 7-day multiple inhalation doses

Dose	Day of administration	Number of subjects	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng·h/mL)	AUC_{0-last} (ng·h/mL)	t_{max} (h)
250 μg	Single dose	12	0.40 ± 0.14	-	0.18 ± 0.07	0.08 (0.08-0.25)
	Day 7 of multiple dose		0.73 ± 0.23 [a)]	1.10 ± 0.21	1.40 ± 0.59 [a)]	0.08 (0.08-0.08) [a)]
500 μg	Single dose	12	0.96 ± 0.29	-	0.44 ± 0.18	0.08 (0.08-0.08)
	Day 7 of multiple dose		1.42 ± 0.54	2.26 ± 0.57	3.46 ± 0.87	0.08 (0.08-0.08)
1000 μg	Single dose	12	2.57 ± 0.72	2.05 ± 0.21 [b)]	2.06 ± 0.58	0.08 (0.08-0.08)
	Day 7 of multiple dose		3.77 ± 0.95	5.06 ± 1.40	7.54 ± 2.17	0.08 (0.08-0.08)

Mean ± SD, t_{max} was expressed as median (minimum-maximum). C_{max}: Maximum plasma concentration, AUC: Area under the plasma concentration-time curve, t_{max}: Time to reach the maximum plasma concentration, "-": Not calculated. a) N = 11, b) N = 10

4.(ii).A.(1).2) Multiple dose study of UMEC in foreign healthy adult subjects and those with CYP2D6 poor metabolizers (5.3.3.4, Study AC4110106 [May to October 2008])

The pharmacokinetic profiles following single and multiple inhalation doses of UMEC using NDPI were investigated in a placebo-controlled, randomized, double-blind, dose escalation study in foreign healthy adult subjects with active CYP2D6 (healthy adult subjects) (16 subjects) and healthy adult subjects with CYP2D6 poor metabolizers (CYP2D6 poor metabolizer subjects) (12 subjects).

In healthy adult subjects, UMEC 100, 500, and 1000 μg were administered in a dose escalation manner by inhalation with ≥7-day washout periods between the dosing sessions; after a single dose of 1000 μg administration followed by a ≥7-day washout, multiple doses of either UMEC 500 or 1000 μg were administered once daily by inhalation for 7 days. In CYP2D6 poor metabolizer subjects, in Cohort 1 (6 subjects), after single inhalation of UMEC 100 μg followed by a ≥14-day washout, multiple inhalation doses of UMEC 100 μg were administered once-daily for 7 days, and then after a ≥14-day washout, single inhalation of UMEC 500 μg was administered followed by a ≥14-day washout, and then a 7-day once-daily multiple inhalation doses of UMEC 500 μg was administered; and in Cohort 2 (6 subjects), after single inhalation of UMEC 500 μg followed by a ≥14-day washout, multiple inhalation doses of UMEC 500 μg were administered once-daily for 7 days, and then after a ≥14-day washout, single inhalation of UMEC 1000 μg was administered followed by a ≥14-day washout, and then a 7-day once-daily multiple inhalation doses of UMEC 1000 μg was administered. Tables 9 and 10 show the pharmacokinetic parameters of plasma umeclidinium in healthy adult subjects and CYP2D6 poor metabolizer subjects. The pharmacokinetic parameters were compared between the 2 subject groups. The geometric mean ratios of C_{max} and $AUC_{0-\tau}$ following the multiple inhalation doses (CYP2D6 poor metabolizer subjects/healthy adult subjects [90% CI]) were 0.80 [0.59, 1.08] and 1.03 [0.79, 1.34], respectively, at 500 μg and 1.07 [0.76, 1.51] and 1.33 [0.98, 1.81], respectively, at 1000 μg. No clear difference in exposure was observed in CYP2D6 poor metabolizer subjects.

Table 9. Pharmacokinetic parameters of plasma umeclidinium in foreign healthy adult subjects following single and 7-day multiple inhalation doses

Dose	Day of administration	Number of subjects	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng·h/mL)	AUC_{0-t} (ng·h/mL)	t_{max} (h)
100 μg	Single dose	16	0.09 ± 0.05	-	0.02 ± 0.01	0.08 (0.08-0.25) [a)]
500 μg	Single dose	16	0.70 ± 0.28	-	0.47 ± 0.29	0.08 (0.08-0.25)
	Day 7 of multiple doses	8	1.54 ± 0.58	2.49 ± 0.66	-	0.08 (0.08-0.08)
1000 μg	Single dose	16	1.65 ± 0.53	1.97 ± 1.02	2.25 ± 1.11	0.08 (0.08-0.25)
	Day 7 of multiple doses	8	2.04 ± 1.18	3.72 ± 1.13	-	0.08 (0.08-0.08)

Mean ± SD, t_{max} was expressed as median (minimum-maximum). "-": Not calculated, a) N = 15

Table 10. Pharmacokinetic parameters of plasma umeclidinium in foreign CYP2D6 poor metabolizer subjects following single and 7-day multiple inhalation doses

Dose	Day of administration	Number of subjects	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng·h/mL)	AUC_{0-t} (ng·h/mL)	t_{max} (h)
100 μg	Single dose	6	0.12 ± 0.06	-	0.03 ± 0.03	0.08 (0.08-0.08)
	Day 7 of multiple dose	6	0.18 ± 0.07	0.09 ± 0.04	-	0.08 (0.08-0.17)
500 μg	Single dose	12	0.81 ± 0.20	-	0.54 ± 0.25	0.08 (0.08-0.12)
	Day 7 of multiple doses	11	1.20 ± 0.39	2.50 ± 0.56	-	0.08 (0.08-0.08)
1000 μg	Single dose	6	1.70 ± 0.72	2.07 ± 0.75	2.60 ± 1.13	0.08 (0.08-0.12)
	Day 7 of multiple doses	6	2.01 ± 0.92	4.91 ± 1.43	-	0.08 (0.08-0.08)

Mean ± SD, t_{max} was expressed as median (minimum-maximum). "-": Not calculated

4.(ii).A.(1).3) Mass balance study of UMEC in humans (Reference 5.3.1.1, Study AC4112014 [April to June 2011])

A mass balance of UMEC was investigated in an open-label study in foreign healthy adult subjects (6 subjects). C_{max} of total radioactivity following single intravenous dose of ^{14}C-UMEC 65 μg was 1.55 ng eq./mL, AUC_{0-t} was 1.39 ng eq.·h/mL, and t_{max} (median) was 0.53 hours. C_{max} of total radioactivity following single oral dose of ^{14}C-UMEC 1000 μg was 0.11 ng eq./mL, AUC_{0-t} was 1.26 ng eq.·h/mL, and t_{max} (median) was 4.0 hours.

The mean total radioactivity recovery rate with respect to the dose (% of the dosed radioactivity) was 80.72% at 192 hours after the intravenous dose including 22.26% from the urine and 58.46% from the feces. At 168 hours after the oral dose, 93.10% was recovered including 0.75% from the urine and 92.35% from the feces.

4.(ii).A.(2) UMEC/VI concomitant use

4.(ii).A.(2).1) Single dose study of UMEC monotherapy, VI monotherapy, and UMEC/VI concomitant therapy in Japanese healthy adult subjects (5.3.3.1, Study DB2113208 [July to September 2009])

The pharmacokinetic profiles following single inhalation dose of UMEC alone or VI alone or UMEC/VI combination were investigated in a placebo-controlled, randomized, double-blind, 4-period crossover study in Japanese healthy adult subjects (16 subjects). Table 11 shows the pharmacokinetic parameters of plasma umeclidinium and vilanterol following single inhalation dose of UMEC 500 μg or/and VI 50 μg as a single agent or in combination using NDPI. The adjusted geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ during the concomitant use to those during the single agent use were 1.30 [1.04, 1.64] and 1.08 [0.74, 1.59], respectively, for UMEC and 1.01 [0.70, 1.45] and 1.39 [1.07, 1.80], respectively, for VI (in a mixed-effects model using the dosing period and dose group as the fixed effects and the subject as the random effect).

Table 11. Pharmacokinetic parameters following single inhalation dose of UMEC 500 μg or/and VI 50 μg

		Number of subjects	UMEC/VI 500/50 μg concomitant use	UMEC 500 μg	VI 50 μg
UMEC	C_{max} (pg/mL)	15	1417.71 ± 604.39	1057.33 ± 733.46	
	t_{max} (h)		0.08 (0.08, 0.08)	0.08 (0.08, 0.13) [c]	
	AUC_{0-t} (pg·h/mL)		615.11 ± 268.43	511.11 ± 292.69	
	$AUC_{0-\infty}$ (pg·h/mL)		713.14 ± 350.77	543.21 ± 334.01	
	$t_{1/2}$ (h)		2.64 ± 3.96	1.62 ± 0.39 [d]	
VI	C_{max} (pg/mL)	16	582.41 ± 234.54 [a]		536.43 ± 211.61
	t_{max} (h)		0.08 (0.08, 0.08) [a]		0.08 (0.08, 0.10)
	AUC_{0-t} (pg·h/mL)		297.26 ± 106.63 [a]		258.65 ± 119.56
	$AUC_{0-\infty}$ (pg·h/mL)		346.75 ± 128.58 [a]		262.66 ± 124.62
	$t_{1/2}$ (h)		0.83 ± 0.55 [b]		0.44 ± 0.13 [a]

Mean ± SD, t_{max} was expressed as median (range). a) N = 15, b) N = 14, c) N = 13, d) N = 12

4.(ii).A.(3) Studies in patients

4.(ii).A.(3).1) Population pharmacokinetic analysis (5.3.3.5, DB2116975 pooled analysis)

Population pharmacokinetic analysis was performed using data of the plasma umeclidinium concentration (1635 subjects, 8498 measurement points) and plasma vilanterol concentration (1637 subjects, 8405 measurement points) from the global phase III studies in Japanese and foreign COPD patients (Studies DB2113361 and DB2113373) by NONMEM Version 7.1.2. The dosage and administration in the clinical studies were UMEC/VI 62.5/25 or 125/25 μg, UMEC 62.5 or 125 μg, and VI 25 μg once daily.

The analysis indicated that the pharmacokinetics of UMEC was based on a two-compartment model with the first-order absorption. As a result of the covariate selection,[7] the body weight, age, and CLcr were selected for the apparent clearance (CL/F), and the body weight was selected for the apparent volume of distribution (V2/F). The population parameters (inter-individual variability [%CV]) in COPD patients estimated in the final model were 218 L/h (42.5%) for CL/F and 1160 L (32.1%) for V2/F. CL/F in patients weighing 140 kg and aged 60 years was estimated to be approximately 10% to 12% higher than that in those weighing 70 kg and aged 60 years. The dose adjustment based on these covariates is, however, determined to be unnecessary because their effects on the exposure of UMEC are limited.

The analysis indicated that the pharmacokinetics of VI was also based on a two-compartment model with the first-order absorption. As a result of the covariate selection,[7] the body weight and age were selected for CL/F. The population parameters (inter-individual variability [%CV]) in COPD patients estimated in the final model were 40.9 L/h (30.8%) for CL/F and 268.0 L/h (26.9%) for V2/F. CL/F in patients weighing 140 kg and aged 60 years was estimated to be approximately 14% higher than that in those weighing 70 kg and aged 60 years. The dose adjustment based on these covariates is, however, determined to be unnecessary because their effects on the exposure of VI are limited.

Table 12 shows predicted values of C_{max} and AUC (geometric mean [95% CI]) at the steady state. Both predicted values of the plasma umeclidinium and vilanterol concentrations following administration of each single agent were comparable to those following administration of the combination drug. It was therefore considered that no drug interaction occurs between UMEC and VI.

Table 12. Pharmacokinetic parameters at the steady state following multiple inhalation doses of each single agent or combination drug (predicted value)

		UMEC/VI 62.5/25 μg	UMEC 62.5 μg	UMEC/VI 125/25 μg	UMEC 125 μg	VI 25 μg
UMEC	C_{max} (pg/mL)	68.5 [65.2, 71.9]	70.3 [67.0, 73.8]	138.0 [131.6, 144.9]	138.8 [132.2, 146.0]	
	AUC (pg·h/mL)	307.6 [293.2, 322.7]	317.6 [303.1, 333.5]	627.5 [597.8, 658.9]	622.9 [593.4, 653.0]	
VI	C_{max} (pg/mL)	128.2 [122.1, 134.6]		128.4 [122.3, 135.0]		128.2 [122.0, 134.6]
	AUC (pg·h/mL)	612.3 [588.6, 636.7]		616.7 [592.1, 642.1]		612.8 [589.3, 637.3]

Geometric mean [95% CI]

[7] As covariates, effects of age, body weight, sex, race, %FEV_1 predicted values, dose group, use of inhaled corticosteroids, reversibility to salbutamol, reversibility to salbutamol and ipratropium, smoking history, and creatinine clearance on CL/F, Q/F, V2/F, V3/F, and KA were investigated.

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

4.(ii).A.(4).1) Pharmacokinetics in subjects with renal impairment (5.3.3.3, Study DB2114636 [March to June 2012])

Pharmacokinetic profiles following single inhalation dose of UMEC/VI or UMEC alone were investigated in a single-blind study in foreign patients with severe renal impairment (CLcr <30 mL/min) and foreign healthy adult subjects in whom the sex, ethnicity, age, and BMI were matched to those in the patients with renal impairment (9 subjects per group). Following single inhalation dose of UMEC 125 μg using NDPI, C_{max} of plasma umeclidinium in healthy adult subjects and patients with severe renal impairment was 142.03 and 127.46 pg/mL, respectively, and AUC_{0-2} was 64.24 and 65.90 pg·h/mL, respectively. The geometric mean ratios [90% CI] of C_{max} and AUC_{0-2} in patients with renal impairment to those in the healthy adult subjects were 0.89 [0.58, 1.35] for C_{max} and 0.90 [0.64, 1.26] for AUC_{0-2}. Following single inhalation dose of UMEC/VI 125/25 μg after a ≥7-day washout, C_{max} of plasma umeclidinium in healthy adult subjects and patients with severe renal impairment was 168.04 and 164.51 pg/mL, respectively, and AUC_{0-2}, 64.50 and 70.62 pg·h/mL, respectively, while for those of plasma vilanterol, C_{max} was 81.41 and 82.57 pg/mL, respectively, and AUC_{0-1} was 31.14 and 37.06 pg·h/mL, respectively.[8] The geometric mean ratios [90% CI] of C_{max} and AUC_{0-2} or AUC_{0-1} in the patients with renal impairment to those in the healthy adult subjects were 0.98 [0.64, 1.49] and 1.10 [0.79, 1.52], respectively, for UMEC and 1.03 [0.73, 1.46] and 1.21 [0.87, 1.70], respectively, for VI, indicating that neither the exposure of UMEC nor that of VI increased in patients with renal impairment. The applicant therefore claimed that no dose adjustment of UMEC/VI is required for patients with severe renal impairment.

4.(ii).A.(4).2) Pharmacokinetics in subjects with hepatic impairment (5.3.3.3, Study DB2114637 [March to June 2012])

Pharmacokinetic profiles following single inhalation dose of UMEC/VI 125/25 μg and multiple inhalation doses of UMEC 125 μg were investigated in an open-label study in foreign patients with moderate hepatic impairment (Child-Pugh score, 7-9) and foreign healthy adult subjects in whom the sex, ethnicity, age, and BMI were matched to those in the patients with hepatic impairment (9 subjects per group). Following single inhalation dose of UMEC/VI 125/25 μg using NDPI, C_{max} of plasma umeclidinium in healthy adult subjects and patients with moderate hepatic impairment was 225.70 and 168.30 pg/mL, respectively, and AUC_{0-t} was 85.96 and 70.87 pg·h/mL, respectively, while C_{max} of plasma vilanterol was 135.23 and 103.37 pg/mL, respectively, and AUC_{0-t} was 61.27 and 41.90 pg·h/mL, respectively. The geometric mean ratios [90% CI] of C_{max} and AUC_{0-t} in the patients with moderate hepatic impairment to those in the healthy adult subjects were 0.85 [0.56, 1.28] and 0.94 [0.62, 1.43], respectively, for UMEC, and 0.78 [0.54, 1.11] and 0.74 [0.46, 1.19], respectively, for VI. Subsequently, following a washout period (7-14 days), multiple inhalation doses of UMEC at 125 μg was administered once daily for 7 days. As a result, C_{max} of plasma umeclidinium in healthy adult subjects and patients with moderate hepatic impairment was 296.47 and 258.66 pg/mL, respectively, and AUC_{0-t} was 542.71 and 545.74 pg·h/mL, respectively. The geometric mean ratios [90% CI] of C_{max} and AUC_{0-t} in the patients with moderate hepatic impairment to those in the healthy adult subjects were 0.85 [0.56, 1.28] and 0.94 [0.62, 1.43], respectively, for UMEC, and 0.78 [0.54, 1.11] and 0.74 [0.46, 1.19], respectively, for VI, indicating that neither the exposure of UMEC nor that of VI increased in patients with hepatic impairment. The applicant therefore claimed that no dose adjustment of UMEC/VI is required for patients with moderate hepatic impairment.

[8] For both UMEC and VI, $AUC_{0-\infty}$, AUC_{0-24}, and $t_{1/2}$ could not be calculated.

4.(ii).A.(5) Drug interaction study

4.(ii).A.(5).1) Effects of verapamil on UMEC single agent and UMEC/VI combination drug (5.3.3.4, Study DB2113950 [March to April 2010])

Pharmacokinetic interactions of UMEC/VI combination drug or UMEC single agent with verapamil, which inhibits CYP3A4 and P-gp, were investigated in a randomized, open-label, comparative study in foreign healthy adult subjects (16 subjects per cohort). UMEC 500 μg (Cohort 1) or UMEC/VI 500/25 μg (Cohort 2) was administered once daily for 13 days by inhalation using NDPI, and from Day 9 to Day 13 of the UMEC or UMEC/VI treatment, verapamil 240 mg was orally administered once daily for 5 days. In the Cohort 1, C_{max} of plasma umeclidinium during the UMEC monotherapy and during the concomitant use of UMEC with verapamil was 1294.59 and 1335.88 pg/mL, respectively, $AUC_{0-\tau}$ was 1953.22 and 2629.65 pg·h/mL, respectively, t_{max} (median) was 0.08 and 0.08 hours, respectively, and $t_{1/2}$ was 12.69 and 26.52 hours, respectively. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\tau}$ during the concomitant use of UMEC and verapamil to those during UMEC monotherapy were 1.05 [0.90, 1.22] for C_{max} and 1.39 [1.18, 1.64] for $AUC_{0-\tau}$. In the Cohort 2, C_{max} of plasma umeclidinium during the UMEC/VI treatment and during the concomitant use of UMEC/VI with verapamil was 1519.29 and 1236.47 pg/mL, respectively, $AUC_{0-\tau}$ was 1946.40 and 2681.62 pg·h/mL, respectively, t_{max} (median) was 0.08 and 0.08 hours, respectively, and $t_{1/2}$ was 15.70 and 28.10 hours, respectively, while for those of plasma vilanterol, C_{max} was 256.05 and 257.79 pg/mL, respectively, AUC_{0-2} was 97.26 and 124.84 pg·h/mL, respectively, and t_{max} (median) was 0.08 and 0.08 hours, respectively. The geometric mean ratios [90% CI] of C_{max} and AUC[9] during the concomitant use of UMEC/VI and verapamil to those during the UMEC/VI treatment were 0.89 [0.73, 1.07] and 1.37 [1.29, 1.46], respectively, for UMEC and 1.05 [0.90, 1.22] and 1.14 [0.94, 1.37], respectively, for VI.

The applicant explained that although the concomitant use with verapamil increased AUC of UMEC by approximately 40%, clinically relevant pharmacokinetic interaction is unlikely to occur during concomitant use of UMEC/VI and verapamil, taking into account that the weighted mean heart rate during a period from baseline (0 hours) to 4 hours after the UMEC/VI treatment and after the verapamil concomitant treatment was 64.43 and 65.04 bpm, respectively, which were comparable.

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

4.(ii).A.(6).1) TQT study of UMEC single agent and UMEC/VI combination drug in foreign healthy adult subjects (5.3.4.1, Study DB2114635 [January to June 2012])

The effect of UMEC or UMEC/VI on QTc interval was investigated in a placebo-controlled, randomized, 4-period, incomplete block design crossover study in foreign healthy adult subjects (103 subjects). UMEC/VI 125/25 μg, UMEC/VI 500/100 μg, UMEC 500 μg, and placebo were administered once daily for 10 days each by inhalation using NDPI. Single dose of moxifloxacin 400 mg (positive control) or placebo tablet was orally administered on Day 10 of treatment of the study drugs above. Washout periods between treatments were ≥10 days. The difference in mean QTc(F) change from baseline between UMEC/VI 125/25 μg and placebo (adjusted mean [two-sided 90% CI]) was up to 4.3 [2.2, 6.4] msec (repeated measure analysis of the covariance model using the treatment period, duration, dose group, and interaction effect of the duration with the dose group as fixed effects, subject, and baseline value in the treatment period as the covariates, and subject as the random effect), while the difference between UMEC 500 μg and placebo was up to -0.8 [-2.8, 1.1] msec (at 30 minutes post-dose). Thus, the difference between UMEC/VI 125/25 μg or UMEC 500 μg and placebo was <5 msec at any time point up to 24 hours post-dose, and additionally, the upper limit of the two-sided 90% CI was <10 msec, indicating that neither

[9] $AUC_{0-\tau}$and AUC_{0-2} were used for UMEC and VI, respectively, in the calculations.

UMEC/VI 125/25 μg nor UMEC 500 μg affects QTc(F) interval. On the other hand, the difference between UMEC/VI 500/100 μg and placebo (adjusted mean [two-sided 90% CI]) was up to 8.2 [6.2, 10.2] msec (at 30 minutes post-dose). Although the upper limit of the two-sided 90% CI exceeded 10 msec, such a value was obtained only at 1 time point (at 30 minutes post-dose), and the difference between UMEC/VI 500/100 μg and placebo rapidly decreased afterwards. The difference in QTc(F) change from baseline between moxifloxacin and placebo (adjusted mean [two-sided 90% CI]) was up to 9.7 [8.0, 11.3] msec (at 4 hours post-dose). Following multiple doses of UMEC/VI 125/25 μg or 500/100 μg or UMEC 500 μg, C_{max} of plasma umeclidinium was 366.68, 1486.70, and 1637.90 pg/mL, respectively, and $AUC_{0-\tau}$ was 560.52, 2264.58, and 2547.08 pg·h/mL, respectively. Following multiple doses of UMEC/VI 125/25 μg or 500/100 μg, C_{max} of plasma vilanterol was 361.48 and 1576.96 pg/mL, respectively, and $AUC_{0-\tau}$ was 468.51 and 1870.92 pg·h/mL, respectively.

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

4.(ii).B.(1) Ethnic difference in UMEC pharmacokinetics

The applicant explained the difference in UMEC pharmacokinetics in terms of ethnicity as follows:

Following once daily 7-day multiple inhalation doses of UMEC 500 or 1000 μg in Japanese healthy adult subjects, C_{max} (geometric mean [95% CI]) was 1318 [1007, 1724] and 3672 [3166, 4259] pg/mL, respectively, and $AUC_{0-\tau}$ was 2196 [1860, 2594] and 4894 [4139, 5788] pg·h/mL, respectively. Following the same regimen as the above in foreign healthy adult subjects, C_{max} was 1458 [1095, 1942] for UMEC 500 μg and 1756 [1073, 2873] pg/mL for UMEC 1000 μg, and $AUC_{0-\tau}$ was 2415 [1930, 3022] and 3575 [2795, 4574] pg·h/mL, respectively. Except for the C_{max} at the dose of 1000 μg, there were no clear differences between the Japanese and foreign healthy adult subjects. Additionally, the exposure of UMEC at the steady state following multiple inhalation doses of UMEC/VI 62.5/25 or 125/25 μg was estimated by the population pharmacokinetic analysis based on the results from the late phase II study and global phase III study. In the Japanese COPD patient population, C_{max} was 79.4 [64.8, 99.7] pg/mL following administration at 62.5/25 μg and 161.6 [130.0, 204.1] pg/mL following administration at 125/25 μg, and AUC_{0-24} was 365.3 [299.2, 450.4] and 737.2 [588.9, 928.5] pg·h/mL, respectively, while in the overall COPD patient population, C_{max} was 68.5 [65.2, 71.9] and 138.0 [131.6, 144.9] pg/mL, respectively, and AUC_{0-24} was 307.6 [293.2, 322.7] and 627.5 [597.8, 658.9] pg·h/mL, respectively, suggesting that the parameter values in the Japanese patient population were slightly higher than those in the overall population. Such higher values were, however, considered partially attributable to low creatinine clearance because the Japanese patient population was characterized by lower body weight and higher age compared with the overall population. Based on the above, the applicant considered that no clinically relevant ethnic differences have been observed in UMEC pharmacokinetics.

PMDA accepted the applicant's explanation. Moreover, no clinically relevant ethnic differences in VI pharmacokinetics were suggested (see the Review Report for Relvar). PMDA thus concluded from a viewpoint of the pharmacokinetics that it is acceptable to use the results from the global study including Japanese COPD patients as the evidence of the efficacy and safety of UMEC/VI in Japanese COPD patients.

4.(ii).B.(2) Drug interaction

The applicant explained pharmacokinetic interactions between UMEC and VI as follows:

In Study DB2113208, single dose of UMEC 500 μg as monotherapy or the concomitant use of UMEC 500 μg and VI 50 μg was administered to Japanese healthy adult subjects by inhalation. The adjusted geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\infty}$ of plasma umeclidinium following the concomitant use to those following the monotherapy were 1.30 [1.04, 1.64] and 1.08 [0.74, 1.59] (mixed-effects model using the treatment period and dose group as the fixed

effects and the subject as the random effect), indicating that C_{max} following the concomitant use tended to be higher than that following the monotherapy. In Study DB2114635, the pharmacokinetic parameters (geometric mean) of plasma umeclidinium following multiple inhalation doses of UMEC 500 μg or UMEC/VI 500/100 μg in foreign healthy adult subjects were C_{max} of 1637.90 and 1486.70 pg/mL, respectively, and $AUC_{0-\tau}$ of 2547.08 and 2264.58 pg·h/mL, respectively, showing that these parameter values following the monotherapy were comparable to those following the concomitant use. The population pharmacokinetic analysis based on the results from the global phase III studies (Studies DB2113361 and DB2113373) also indicated that C_{max} and AUC (estimated value) of plasma umeclidinium and vilanterol at the steady state following administration of each single agent were comparable to those following administration of UMEC/VI (Table 12). The above data show that no clear differences have been observed in the pharmacokinetics between each single agent and combination drug. Pharmacokinetic interactions between UMEC and VI are thus considered unlikely to occur.

PMDA has concluded that the applicant's explanation that pharmacokinetic interaction between UMEC and VI is unlikely to occur is acceptable, because the exposures of UMEC and VI in foreign subjects following use of each single agent were comparable to those following use of UMEC/VI; and no clinically relevant ethnic differences in pharmacokinetics were suggested for UMEC or VI as described in "4.(ii).B.(1) Ethnic difference in UMEC pharmacokinetics," although the factor causing the trend of higher C_{max} following the UMEC/VI concomitant use compared with that following the UMEC monotherapy in Study DB2113208 in Japanese healthy adult subjects remains unknown.

Concomitant use of UMEC/VI with verapamil increased AUC of UMEC by approximately 40%. Taking into account that the expected AUC of UMEC following concomitant use of UMEC/VI at the proposed dose of 62.5/25 μg with verapamil do not exceed AUC following UMEC/VI 125/25 μg, and that no considerable safety issues were suggested following use of UMEC/VI 125/25 μg [see "4.(iii).B.(3) Safety"], PMDA concluded that the applicant's explanation that the concomitant use of the proposed drug with verapamil is unlikely to cause clinically relevant pharmacokinetic interactions is acceptable.

4.(iii) Summary of clinical efficacy and safety

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

The results from the phase II studies for dose-response relationship of UMEC in foreign COPD patients (AC4113073 [5.3.5.1], AC4115321 [5.3.5.1], AC4113589 [5.3.5.1]), global phase III studies for the efficacy and safety of UMEC/VI in COPD patients (including Japanese) (DB2113361 [5.3.5.1], DB2113373 [5.3.5.1]), and phase III long-term treatment study in Japanese COPD patients (DB2115362 [5.3.5.2]) were submitted for the efficacy and safety evaluation.

Unless otherwise specified, the doses are expressed as free base. In the phase II and III studies, UMEC/VI, UMEC single agent, VI single agent, or placebo was administered using NDPI.

4.(iii).A.(1) UMEC monotherapy study

4.(iii).A.(1).1) Foreign phase II study (5.3.5.1, Study AC4113073 [September 2009 to March 2010])

A placebo-controlled, randomized, double-blind, 3-period, incomplete block design crossover study[10] was conducted in the 2 countries of the US and Germany to investigate the efficacy and

[10] The randomization was designed so that patients would receive the placebo during one of the 3 study treatment periods and 2 of 9 active drugs during the remaining 2 study treatment periods.

safety of UMEC monotherapy in foreign COPD patients[11] (target sample size, 170).

In a double-blind manner, UMEC 62.5 μg, 125 μg, 250 μg, 500 μg, or 1000 μg, or placebo was administered once daily in the morning (QD) by inhalation, or UMEC 62.5 μg, 125 μg, or 250 μg, or placebo was administered twice daily in the morning and evening (BD) by inhalation; or in an open-label manner, TIO 18 μg was administered once daily in the morning by inhalation. Each treatment period was 14 days and separated from the next treatment by a washout period of 10 to 14 days. The subjects who had been receiving inhaled corticosteroid (ICS) treatment at a constant dose equivalent to ≤1000 μg of fluticasone propionate (FP) for ≥30 days until the screening (Visit 1) were allowed to use the drug concomitantly during the study period.

Of 179 randomized[12] subjects, 176[13] subjects who received the study drug were included in the modified intent-to-treat (mITT) population (35 subjects in the UMEC 62.5 μg QD group, 34 subjects in the UMEC 62.5 μg BD group, 34 subjects in the UMEC 125 μg QD group, 37 subjects in the UMEC 125 μg BD group, 36 subjects in the UMEC 250 μg QD group, 33 subjects in the UMEC 250 μg BD group, 38 subjects in the UMEC 500 μg QD group, 32 subjects in the UMEC 1000 μg QD group, 35 subjects in the TIO group, 158 subjects in the placebo group). This population was also included in the safety analysis set and efficacy analysis set.

Discontinuation of the study occurred in 3% (1 of 35 subjects) in the UMEC 62.5 μg QD group, 6% (2 of 34 subjects) in the UMEC 62.5 μg BD group, 3% (1 of 34 subjects) in the UMEC 125 μg QD group, 11% (4 of 37 subjects) in the UMEC 125 μg BD group, 3% (1 of 36 subjects) in the UMEC 250 μg QD group, 3% (1 of 33 subjects) in the UMEC 250 μg BD group, 3% (1 of 38 subjects) in the UMEC 500 μg group, 9% (3 of 32 subjects) in the UMEC 1000 μg group, 3% (1 of 35 subjects) in the TIO group, and 4% (6 of 158 subjects) in the placebo group, and the main reason for discontinuation was adverse events (3% [1 of 35 subjects] in the UMEC 62.5 μg QD group, 3% [1 of 34 subjects] in the UMEC 62.5 μg BD group, 3% [1 of 37 subjects] in the UMEC 125 μg BD group, 8% [3 of 36 subjects] in the UMEC 250 μg QD group, 3% [1 of 38 subjects] in the UMEC 500 μg QD group, 6% [2 of 32 subjects] in the UMEC 1000 μg QD group, 3% [5 of 158 subjects] in the placebo group).

Table 13 shows results on the primary efficacy endpoint, a change from baseline in trough FEV_1[14] at Day 15. Statistically significant differences were observed in pairwise comparisons between the placebo group and each of the UMEC 62.5 μg QD group, UMEC 125 μg QD group, UMEC 250 μg QD group, UMEC 500 μg QD group, and UMEC 1000 μg QD group.

[11] Patients who have been diagnosed with COPD in accordance with the Standards for the Diagnosis and Management of Patients with COPD issued by the American Thoracic Society (ATS)/European Respiratory Society and who meet the following criteria: (a) who currently smoke or smoked in the past, having a smoking history of ≥10 pack-years; (b) in whom the FEV_1/forced vital capacity (FVC) ratio following administration of a bronchodilator is ≤0.7, and the FEV_1 following administration of a bronchodilator is between 35% and 70% of the FEV_1 predicted value according to the standard formula of the National Health and Nutrition Examination Survey (NHANES) III at Visit 1 (screening); and (c) who are aged 40 to 80 years.

[12] Subjects who meet the inclusion criteria for randomization; i.e., neither aggravation of COPD nor lower respiratory tract infection is observed during the screening period.

[13] Although 3 subjects were randomized by mistake, the study drug was not administered. Of 34 subjects assigned to the UMEC 250 μg BD group, 1 subject received the wrong study drug (UMEC 250 μg QD) during the study treatment Period 2. The concerned subject was thus handled as the UMEC 250 μg QD group in the tabulation and analysis of the mITT population.

[14] The baseline was defined as the measured value before dosing on Day 1 of each study treatment period, and trough FEV_1 was defined as the FEV_1 value measured at 24 hours after dosing in the morning on Day 14.

Table 13. Change from baseline in trough FEV_1 (L) at Day 15 (mITT population, OC)

	UMEC 62.5 μg QD group	UMEC 125 μg QD group	UMEC 250 μg QD group	UMEC 500 μg QD group	UMEC 1000 μg QD group
Baseline	1.465 ± 0.567 (35)	1.400 ± 0.498 (34)	1.368 ± 0.451 (36)	1.479 ± 0.418 (38)	1.372 ± 0.415 (32)
Day 15	1.552 ± 0.585 (34)	1.527 ± 0.523 (33)	1.467 ± 0.434 (35)	1.540 ± 0.490 (37)	1.556 ± 0.430 (29)
Change	0.073 ± 0.279 (34)	0.135 ± 0.233 (33)	0.087 ± 0.220 (35)	0.054 ± 0.291 (37)	0.157 ± 0.234 (29)
Difference from the placebo group [95% CI] [a)]	0.128 [0.060, 0.196]	0.147 [0.077, 0.216]	0.095 [0.027, 0.162]	0.140 [0.074, 0.205]	0.186 [0.113, 0.259]
P-value [a), b)]	$P < 0.001$	$P < 0.001$	$P = 0.006$	$P < 0.001$	$P < 0.001$
	UMEC 62.5 μg BD group	UMEC 125 μg BD group	UMEC 250 μg BD group	TIO group	Placebo group
Baseline	1.469 ± 0.519 (34)	1.376 ± 0.457 (37)	1.484 ± 0.604 (33)	1.415 ± 0.497 (35)	1.449 ± 0.497 (158)
Day 15	1.546 ± 0.495 (31)	1.511 ± 0.400 (33)	1.661 ± 0.520 (32)	1.426 ± 0.562 (34)	1.380 ± 0.461 (150)
Change	0.024 ± 0.299 (31)	0.126 ± 0.301 (33)	0.152 ± 0.256 (32)	0.034 ± 0.261 (34)	-0.071 ± 0.235 (150)
Difference from the placebo group [95% CI] [a)]	0.079 [0.008, 0.151]	0.134 [0.064, 0.204]	0.172 [0.101, 0.242]	0.105 [0.037, 0.173]	

Mean ± SD (number of subjects)

a) Mixed model with baseline value during the treatment period, mean baseline value, dose group, and treatment period as fixed effects and subject as a random effect

b) In pairwise comparisons between the placebo group and each of the UMEC QD groups, multiplicity of the test was adjusted by the step-down method in which the groups were stratified in descending order of the dose. The pairwise comparisons between the placebo group and each of the UMEC BD groups or TIO group were handled as exploratory analyses, and thus multiplicity of the test was not considered.

Adverse events occurred in 23% (8 of 35 subjects) in the UMEC 62.5 μg QD group, 18% (6 of 34 subjects) in the UMEC 62.5 μg BD group, 18% (6 of 34 subjects) in the UMEC 125 μg QD group, 22% (8 of 37 subjects) in the UMEC 125 μg BD group, 39% (14 of 36 subjects) in the UMEC 250 μg QD group, 30% (10 of 33 subjects) in the UMEC 250 μg BD group, 37% (14 of 38 subjects) in the UMEC 500 μg QD group, 41% (13 of 32 subjects) in the UMEC 1000 μg QD group, 17% (6 of 35 subjects) in the TIO group, and 16% (25 of 158 subjects) in the placebo group. The major adverse events are shown in Table 14.

No deaths were reported. Serious adverse events occurred in 3% (1 of 37 subjects, chronic obstructive pulmonary disease) in the UMEC 125 μg BD group and 6% (2 of 36 subjects, chronic obstructive pulmonary disease and concussion in 1 subject each) in the UMEC 250 μg QD group, but a causal relationship to the study drug was ruled out for all the events.

Adverse events leading to discontinuation of the study occurred in 3% (1 of 35 subjects) in the UMEC 62.5 μg QD group, 3% (1 of 34 subjects) in the UMEC 62.5 μg BD group, 3% (1 of 37 subjects) in the UMEC 125 μg BD group, 8% (3 of 36 subjects) in the UMEC 250 μg QD group, 3% (1 of 38 subjects) in the UMEC 500 μg QD group, 6% (2 of 32 subjects) in the UMEC 1000 μg QD group, and 3% (5 of 158 subjects) in the placebo group.

Adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) occurred in 6% (2 of 35 subjects) in the UMEC 62.5 μg QD group, 3% (1 of 34 subjects) in the UMEC 62.5 μg BD group, 3% (1 of 34 subjects) in the UMEC 125 μg QD group, 11% (4 of 37 subjects) in the UMEC 125 μg BD group, 8% (3 of 36 subjects) in the UMEC 250 μg QD group, 18% (6 of 33 subjects) in the UMEC 250 μg BD group, 18% (7 of 38 subjects) in the UMEC 500 μg QD group, 19% (6 of 32 subjects) in the UMEC 1000 μg QD group, 3% (1 of 35 subjects) in the TIO group, and 6% (9 of 158 subjects) in the placebo group.

Table 14. Adverse events reported by ≥2 subjects in any group (mITT population)

	Placebo group (N = 158)	UMEC 62.5 μg QD group (N = 35)	UMEC 125 μg QD group (N = 34)	UMEC 250 μg QD group (N = 36)	UMEC 500 μg QD group (N = 38)	UMEC 1000 μg QD group (N = 32)	UMEC 62.5 μg BD group (N = 34)	UMEC 125 μg BD group (N = 37)	UMEC 250 μg BD group (N = 33)	TIO group (N = 35)
Headache	4 (3)	1 (3)	1 (3)	3 (8)	1 (3)	2 (6)	0	1 (3)	3 (9)	2 (6)
Cough	1 (<1)	1 (3)	0	1 (3)	4 (11)	2 (6)	0	0	2 (6)	0
Nasopharyngitis	2 (1)	0	0	2 (6)	0	4 (13)	2 (6)	0	0	0
Dry mouth	1 (<1)	0	0	0	1 (3)	2 (6)	0	1 (3)	3 (9)	1 (3)
Dysgeusia	0	0	0	2 (6)	0	2 (6)	1 (3)	0	2 (6)	0
Oropharyngeal pain	2 (1)	0	0	0	1 (3)	0	0	1 (3)	2 (6)	0
Dysphonia	1 (<1)	0	0	0	0	0	0	2 (5)	0	0
Hypertension	0	0	2 (6)	1 (3)	0	0	0	0	0	0

Number of subjects (%)

4.(iii).A.(1).2) Foreign phase II study (5.3.5.1, Study AC4115321 [July to October 2011])

A placebo-controlled, randomized, double-blind, 3-period, incomplete block design crossover study[15] was conducted in the US to investigate the efficacy and safety of UMEC monotherapy in foreign COPD patients[16] (target sample size, 160).

In a double-blind manner, UMEC 15.6 μg, 31.25 μg, 62.5 μg, 125 μg, or placebo was administered once daily in the morning (QD) by inhalation, or UMEC 15.6 μg or 31.25 μg, or placebo was administered twice daily in the morning and evening (BD) by inhalation; or in an open-label manner, TIO 18 μg was administered once daily in the morning by inhalation. Each treatment period was 7 days and separated from the next treatment by a washout period of 10 to 14 days. The subjects who had been receiving ICS treatment at a constant dose equivalent to ≤1000 μg of FP for ≥30 days until the screening (Visit 1) were allowed to use the drug concomitantly during the study period.

Of 163 randomized[17] subjects, 163 subjects who received the study drug were included in the mITT[18] population (60 subjects in the UMEC 15.6 μg QD group, 56 subjects in the UMEC 15.6 μg BD group, 57 subjects in the UMEC 31.25 μg QD group, 58 subjects in the UMEC 31.25 μg BD group, 59 subjects in the UMEC 62.5 μg QD group, 60 subjects in the UMEC 125 μg QD group, 56 subjects in the TIO group, 60 subjects in the placebo group). This population was also included in the safety analysis set and efficacy analysis set.

Discontinuation of the study occurred in 3% (2 of 60 subjects) in the UMEC 15.6 μg QD group, 2% (1 of 56 subjects) in the UMEC 15.6 μg BD group, 2% (1 of 57 subjects) in the UMEC 31.25 μg QD group, 5% (3 of 58 subjects) in the UMEC 31.25 μg BD group, 7% (4 of 60 subjects) in the UMEC 125 μg QD group, 5% (3 of 56 subjects) in the TIO group, 3% (2 of 60 subjects) in the placebo group. The main reasons for discontinuation were consent withdrawal (3% [2 of 58 subjects] in the UMEC 31.25 μg BD group, 2% [1 of 60 subjects] in the UMEC 125 μg QD group, 4% [2 of 56 subjects] in the TIO group, 2% [1 of 60 subjects] in the placebo group), adverse events (2% [1 of 60 subjects] in the UMEC 15.6 μg QD group, 2% [1 of 57 subjects] in the UMEC

[15] The subjects were randomized to the pre-determined treatment orders, which were designed to include 3 of 8 study treatment conditions.

[16] Patients who have been diagnosed with COPD in accordance with the Standards for the Diagnosis and Management of Patients with COPD issued by the ATS/European Respiratory Society and who meet the following criteria: (a) who currently smoke or smoked in the past, having a smoking history of ≥10 pack-years; (b) in whom the FEV_1/FVC ratio following administration of a bronchodilator is <0.7, and the FEV_1 following administration of a bronchodilator is between 35% and 70% of the FEV_1 predicted value according to the standard formula of the NHANES III at Visit 1 (screening); and (c) who are aged 40 to 80 years.

[17] Subjects who meet the inclusion criteria for randomization; i.e., aggravation of COPD is not observed during the run-in period or at Visit 2 (at the start of the treatment period).

[18] Subjects who were randomized and received the study drug during the treatment period at least once were included in the study patient population. Subjects who received the study drug different from the scheduled drug (when randomized) were included into the dose group of the actually administered study drug.

31.25 μg QD group, 2% [1 of 58 subjects] in the UMEC 31.25 μg BD group, 2% [1 of 60 subjects] in the UMEC 125 μg QD group), and lack of efficacy (2% [1 of 60 subjects] in the UMEC 15.6 μg QD group, 2% [1 of 60 subjects] in the UMEC 125 μg QD group, 2% [1 of 56 subjects] in the TIO group, 2% [1 of 60 subjects] in the placebo group).

Table 15 shows data on the primary efficacy endpoint of the trough FEV_1[19] at Day 8 and results from the analysis based on a dose-response model.

Table 15. Changes from baseline in trough FEV_1 (L) at Day 8 and results from the analysis based on a dose-response model (mITT population, OC)

	UMEC 15.6 μg QD group	UMEC 31.25 μg QD group	UMEC 62.5 μg QD group	UMEC 125 μg QD group
Baseline	1.371 ± 0.556 (60)	1.412 ± 0.578 (57)	1.392 ± 0.565 (59)	1.409 ± 0.562 (60)
Day 8	1.419 ± 0.607 (58)	1.470 ± 0.576 (56)	1.442 ± 0.624 (59)	1.541 ± 0.597 (59)
Change	0.040 ± 0.195 (58)	0.054 ± 0.256 (56)	0.051 ± 0.212 (59)	0.123 ± 0.233 (59)
	UMEC 15.6 μg BD group	UMEC 31.25 μg BD group	TIO group	Placebo group
Baseline	1.433 ± 0.588 (56)	1.398 ± 0.461 (58)	1.425 ± 0.453 (56)	1.474 ± 0.585 (60)
Day 8	1.475 ± 0.594 (55)	1.475 ± 0.491 (57)	1.429 ± 0.468 (56)	1.376 ± 0.580 (59)
Change	0.053 ± 0.224 (55)	0.068 ± 0.205 (57)	0.004 ± 0.256 (56)	-0.098 ± 0.165 (59)
Parameters in the dose-response model [a)]				
	E_{max} (L)	ED_{50} (μg)	E_0 (L)	Mean baseline value for E_0 (L)
Point estimate [95% CI]	0.185 [0.154, 0.216]	37.4 [17.8, 57.0]	1.24 [1.21, 1.27]	0.691 [0.65, 0.73]

Mean ± SD (number of subjects)

a) Dose-E_{max} model with the mean baseline value during each treatment period as a covariate of E_0 (L)

E_{max} (L) is defined as the maximum difference of trough FEV_1 (L) on Day 8 from that in the placebo group; ED_{50} (μg) is defined as a dose providing an effect equivalent to 50% of the E_{max} (L); E_0 (L) is defined as trough FEV_1 (L) at Day 8 in the placebo group; and mean baseline value for E_0 (L) is defined as an effect of the mean baseline value, a covariate for E_0 (L).

Adverse events occurred in 10% (6 of 60 subjects) in the UMEC 15.6 μg QD group, 7% (4 of 56 subjects) in the UMEC 15.6 μg BD group, 5% (3 of 57 subjects) in the UMEC 31.25 μg QD group, 12% (7 of 58 subjects) in the UMEC 31.25 μg BD group, 5% (3 of 59 subjects) in the UMEC 62.5 μg QD group, 18% (11 of 60 subjects) in the UMEC 125 μg QD group, 4% (2 of 56 subjects) in the TIO group, 8% (5 of 60 subjects) in the placebo group. Table 16 shows the major adverse events.

No deaths were reported. Serious adverse events occurred in 2% (1 of 60 subjects, acute respiratory failure) in the UMEC 15.6 μg QD group and 2% (1 of 57 subjects, myocardial infarction) in the UMEC 31.25 μg QD group, but a causal relationship to the study drug was ruled out for all the events.

Adverse events leading to discontinuation of the study occurred in 2% (1 of 60 subjects) in the UMEC 15.6 μg QD group, 2% (1 of 57 subjects) in the UMEC 31.25 μg QD group, 2% (1 of 58 subjects) in the UMEC 31.25 μg BD group, and 2% (1 of 60 subjects) in the UMEC 125 μg QD group.

[19] Trough FEV_1 was defined as the mean of measured FEV_1 values at 23 hours and 24 hours after dosing in the morning on Day 7 of the study treatment period.

Adverse drug reactions occurred in 2% (1 of 60 subjects) in the UMEC 15.6 μg QD group, 2% (1 of 56 subjects) in the UMEC 15.6 μg BD group, and 5% (3 of 60 subjects) in the UMEC 125 μg QD group.

Table 16. Adverse events reported by ≥3% of subjects in any group (mITT population)

	Placebo group (N = 60)	UMEC 15.6 μg QD group (N = 60)	UMEC 15.6 μg BD group (N = 56)	UMEC 31.25 μg QD group (N = 57)	UMEC 31.25 μg BD group (N = 58)	UMEC 62.5 μg QD group (N = 59)	UMEC 125 μg QD group (N = 60)	TIO group (N = 56)
Headache	2 (3)	1 (2)	4 (7)	0	1 (2)	0	3 (5)	0
Nasopharyngitis	0	1 (2)	0	0	0	0	1 (2)	2 (4)
Dysgeusia	0	1 (2)	0	0	0	0	2 (3)	0
Sinusitis	0	0	0	0	0	0	2 (3)	0

Number of subjects (%)

4.(iii).A.(1).3) Foreign phase II study (5.3.5.1, Study AC4113589 [December 2009 to July 2010])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of UMEC monotherapy in foreign COPD patients[20] (target sample size, 224 [56 subjects per group]) in the 4 countries of the US, Germany, Estonia, and Poland.

UMEC 125 μg, 250 μg, or 500 μg, or placebo was administered once daily in the morning by inhalation. The treatment period was 28 days. The subjects who had been receiving ICS treatment at a constant dose equivalent to ≤1000 μg of FP for ≥30 days until the screening (Visit 1) were allowed to use the drug concomitantly during the study period.

Of 288 randomized[21] subjects, 285 subjects who received the study drug (71 subjects in the UMEC 125 μg group, 72 subjects in the UMEC 250 μg group, 71 subjects in the UMEC 500 μg group, 71 subjects in the placebo group) were included in the ITT population, which was also included in the safety analysis set and efficacy analysis set.

Discontinuation of the study occurred in 8% (6 of 71 subjects) in the UMEC 125 μg group, 6% (4 of 72 subjects) in the UMEC 250 μg group, 10% (7 of 71 subjects) in the UMEC 500 μg group, and 6% (4 of 71 subjects) in the placebo group. The main reason for discontinuation was lack of efficacy (3% [2 of 71 subjects] in the UMEC 125 μg group, 4% [3 of 71 subjects] in the UMEC 500 μg group, 4% [3 of 71 subjects] in the placebo group).

Table 17 shows the results on the primary efficacy endpoint, a change from baseline in trough FEV_1[22] at Day 29. Statistically significant differences were observed in pairwise comparisons between the placebo group and each of the UMEC 125 μg group, UMEC 250 μg group, and UMEC 500 μg group.

[20] Patients who have been diagnosed with COPD in accordance with the Standards for the Diagnosis and Management of Patients with COPD issued by the ATS/European Respiratory Society and who meet the following criteria: (a) who currently smoke or smoked in the past, having a smoking history of ≥10 pack-years; (b) in whom the FEV_1/FVC ratio following administration of a bronchodilator is ≤0.7, and the FEV_1 following administration of a bronchodilator is between 35% and 70% of the FEV_1 predicted value according to the standard formula of the NHANES III at Visit 1 (screening); and (c) who are aged 40 to 80 years.

[21] Subjects who meet the inclusion criteria for randomization; i.e., neither aggravation of COPD nor lower respiratory tract infection is observed during the run-in period or at Visit 2 (at the start of the treatment period).

[22] The baseline was defined as the mean of 2 measured values at 30 minutes and just before dosing on Day 1. Trough FEV_1 at Day 29 was defined as the mean of measured FEV_1 values at 23 and 24 hours after dosing on Day 28.

Table 17. Change from baseline in trough FEV_1 (L) at Day 29 (ITT population, OC)

	UMEC 125 μg group	UMEC 250 μg group	UMEC 500 μg group	Placebo group
Baseline	1.466 ± 0.474 (71)	1.480 ± 0.577 (72)	1.320 ± 0.424 (71)	1.349 ± 0.444 (70)
Day 29	1.637 ± 0.515 (64)	1.673 ± 0.553 (68)	1.511 ± 0.455 (64)	1.378 ± 0.415 (68)
Change	0.163 ± 0.237 (64)	0.172 ± 0.215 (68)	0.174 ± 0.206 (64)	0.016 ± 0.183 (67)
Difference between groups [95% CI] [a)] *P*-value [a), b)]	0.159 [0.088, 0.229] *P* < 0.001	0.168 [0.099, 0.238] *P* < 0.001	0.150 [0.080, 0.220] *P* < 0.001	

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with the baseline value, dose group, country, sex, age, smoking status, day of administration, interaction between day of administration and the baseline value, and interaction between day of administration and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

b) Multiplicity of the test was adjusted by the step-down method in which the groups were stratified in descending order of the dose.

Adverse events occurred in 25% (18 of 71 subjects) in the UMEC 125 μg group, 24% (17 of 72 subjects) in the UMEC 250 μg group, 34% (24 of 71 subjects) in the UMEC 500 μg group, and 23% (16 of 71 subjects) in the placebo group. Table 18 shows the major adverse events.

No deaths were reported. Serious adverse events occurred in 1% (1 of 71 subjects, retinal detachment) in the UMEC 125 μg group, 1% (1 of 72 subjects, chronic obstructive pulmonary disease) in the UMEC 250 μg group, and 1% (1 of 71 subjects, gastroenteritis viral) in the UMEC 500 μg group, but a causal relationship to the study drug was ruled out for all the events.

Adverse events leading to discontinuation of the study occurred in 1% (1 of 71 subjects) in the UMEC 125 μg group, 3% (2 of 72 subjects) in the UMEC 250 μg group, and 1% (1 of 71 subjects) in the UMEC 500 μg group.

Adverse drug reactions occurred in 3% (2 of 71 subjects) in the UMEC 125 μg group, 11% (8 of 72 subjects) in the UMEC 250 μg group, 17% (12 of 71 subjects) in the UMEC 500 μg group, and 3% (2 of 71 subjects) in the placebo group.

Table 18. Adverse events reported by ≥3% of subjects in any group (ITT population)

	Placebo group (N = 71)	UMEC 125 μg group (N = 71)	UMEC 250 μg group (N = 72)	UMEC 500 μg group (N = 71)
Cough	2 (3)	0	6 (8)	8 (11)
Headache	3 (4)	3 (4)	4 (6)	6 (8)
Nasopharyngitis	3 (4)	2 (3)	1 (1)	2 (3)
Back pain	0	2 (3)	1 (1)	0
Hypertension	2 (3)	1 (1)	0	0
Sputum increased	0	0	2 (3)	0

Number of subjects (%)

4.(iii).A.(1).4) Global phase III study (5.3.5.1, Study AC4115408 [July 2011 to February 2012])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of UMEC monotherapy in Japanese and foreign COPD patients[23] (target sample size, 198 [66 subjects per group]) in the 3 countries of Japan, the US, and Germany.

[23] Patients who have been diagnosed with COPD in accordance with the Standards for the Diagnosis and Management of Patients with COPD issued by the ATS/European Respiratory Society and who meet the following criteria: (a) who currently smoke or smoked in the past, having a smoking history of ≥10 pack-years; (b) in whom the FEV_1/FVC ratio following administration of a bronchodilator is <0.7, and the FEV_1 following administration of a bronchodilator is ≤70% of the FEV_1 predicted value according to the standard formula of the NHANES III at Visit 1 (screening); (c) who have a score of ≥2 on the modified Medical Research Council (mMRC) Dyspnea Scale; and (d) who are aged ≥40 years.

UMEC at 62.5 μg or 125 μg or placebo was administered once daily in the morning by inhalation. The treatment period was 12 weeks. The subjects who had been receiving ICS treatment at a constant dose equivalent to ≤1000 μg of FP for ≥30 days until the screening (Visit 1) were allowed to use the drug concomitantly during the study period.

Of 206 randomized[24] subjects, 206 subjects who received the study drug (69 subjects in the UMEC 62.5 μg group, 69 subjects in the UMEC 125 μg group, 68 subjects in the placebo group) were included in the ITT population, which was also included in the safety analysis set and efficacy analysis set.

Discontinuation of the study occurred in 10% (7 of 69 subjects) in the UMEC 62.5 μg group, 19% (13 of 69 subjects) in the UMEC 125 μg group, 26% (18 of 68 subjects) in the placebo group. The main reason for discontinuation was lack of efficacy (7% [5 of 69 subjects] in the UMEC 62.5 μg group, 6% [4 of 69 subjects] in the UMEC 125 μg group, 12% [8 of 68 subjects] in the placebo group).

The ITT population included 21 Japanese subjects (7 subjects in the UMEC 62.5 μg group, 6 subjects in the UMEC 125 μg group, 8 subjects in the placebo group) as the Japanese subpopulation. In the Japanese subpopulation, discontinuation occurred in 50% (4 of 8 subjects) in the placebo group and the main reason for discontinuation was lack of efficacy (25% [2 of 8 subjects] in the placebo group).

Table 19 shows the results on the primary efficacy endpoint, a change from baseline in trough FEV_1[25] at Week 12. Statistically significant differences were observed in pairwise comparisons between the UMEC 62.5 μg group and the placebo group and between the UMEC 125 μg group and the placebo group.

Table 19. Change from baseline in trough FEV_1 (L) at Week 12 (ITT population, OC)

	UMEC 62.5 μg group	UMEC 125 μg group	Placebo group
Baseline	1.255 ± 0.566 (69)	1.248 ± 0.441 (69)	1.214 ± 0.431 (68)
Week 12	1.379 ± 0.632 (61)	1.426 ± 0.453 (55)	1.249 ± 0.457 (50)
Change	0.119 ± 0.214 (61)	0.156 ± 0.151 (55)	0.000 ± 0.238 (50)
Difference between groups [95% CI] [a)] *P*-value [a), b)]	0.127 [0.052, 0.202] $P < 0.001$	0.152 [0.076, 0.229] $P < 0.001$	

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with the baseline value, dose group, smoking status, center group, day of administration, interaction between day of administration and the baseline value, and interaction between day of administration and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

b) Multiplicity of the test was adjusted by the step-down method in which the groups were stratified in descending order of the dose.

Table 20 shows trough FEV_1 at Week 12 in the Japanese subpopulation.

[24] Subjects who meet the inclusion criteria for randomization; i.e., neither aggravation of COPD nor lower respiratory tract infection is observed during the run-in period or at Visit 2 (at the start of the treatment period).

[25] Trough FEV_1 at Week 12 (Day 85) was defined as the mean of measured FEV_1 values at 23 and 24 hours after dosing on Day 84.

Table 20. Change from baseline in trough FEV_1 (L) at Week 12 in the Japanese subpopulation (ITT population, OC)

	UMEC 62.5 μg group	UMEC 125 μg group	Placebo group
Baseline	1.424 ± 0.540 (7)	1.187 ± 0.521 (6)	1.079 ± 0.421 (8)
Week 12	1.514 ± 0.594 (7)	1.341 ± 0.580 (6)	1.109 ± 0.436 (4)
Change [a)]	0.089 ± 0.116 (7)	0.154 ± 0.131 (6)	-0.165 ± 0.384 (4)
Difference between groups [95% CI] [a)]	0.243 [0.006, 0.481]	0.292 [0.047, 0.538]	

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with the baseline value, dose group, smoking status, region (Japan/outside Japan), day of administration, interaction between day of administration and the baseline value, interaction between day of administration and dose group, interaction between the region and dose group, and interaction among the region, day of administration, and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

Adverse events occurred in 39% (27 of 69 subjects) in the UMEC 62.5 μg group, 41% (28 of 69 subjects) in the UMEC 125 μg group, and 35% (24 of 68 subjects) in the placebo group. Table 21 showed the major adverse events.

No deaths were reported. Serious adverse events occurred in 1% (1 of 69 subjects, lung neoplasm malignant) in the UMEC 62.5 μg group, 3% (2 of 69 subjects, chronic obstructive pulmonary disease and coronary artery stenosis in 1 subject each) in the UMEC 125 μg group, and 1% (1 of 68 subjects, non-cardiac chest pain) in the placebo group, but a causal relationship to the study drug was ruled out for all the events.

Adverse events leading to discontinuation of the study occurred in 1% (1 of 69 subjects) in the UMEC 62.5 μg group and 4% (3 of 69 subjects) in the UMEC 125 μg group.

Adverse drug reactions occurred in 3% (2 of 69 subjects) in the UMEC 62.5 μg group, 1% (1 of 69 subjects) in the UMEC 125 μg group, and 1% (1 of 68 subjects) in the placebo group.

Table 21. Adverse events reported by ≥3% of subjects in any group (ITT population)

	UMEC 62.5 μg group (N = 69)	UMEC 125 μg group (N = 69)	Placebo group (N = 68)
Headache	5 (7)	10 (14)	7 (10)
Nasopharyngitis	8 (12)	7 (10)	7 (10)
Back pain	2 (3)	0	4 (6)
Cough	0	5 (7)	1 (1)
Upper respiratory tract infection	2 (3)	2 (3)	0
Oropharyngeal pain	0	2 (3)	1 (1)
Bursitis	2 (3)	0	0
Chronic obstructive pulmonary disease	0	2 (3)	0

Number of subjects (%)

In the Japanese subpopulation, adverse events occurred in 43% (3 of 7 subjects) in the UMEC 62.5 μg group, 33% (2 of 6 subjects) in the UMEC 125 μg group, and 63% (5 of 8 subjects) in the placebo group. No deaths were reported. A serious adverse event occurred in 14% (1 of 7 subjects, lung neoplasm malignant) in the UMEC 62.5 μg group, but a causal relationship to the study drug was ruled out for the event. No adverse events leading to discontinuation of the study occurred.

An adverse drug reaction was reported by 13% (1 of 8 subjects) in the placebo group.

4.(iii).A.(2) VI monotherapy study

4.(iii).A.(2).1) Foreign phase II study (5.3.5.1, Study B2C111045 [February to October 2008])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of VI monotherapy in foreign COPD patients[26] (target sample size, 480 [80 subjects per group]) in the 14 countries of the US, Canada, Denmark, Estonia, Germany, Poland, Russia, Slovakia, Argentina, Chile, Korea, Mexico, Peru, and Philippines.

VI 3 μg, 6.25 μg, 12.5 μg, 25 μg, or 50 μg, or placebo was administered once daily in the morning by inhalation, and the treatment period was 28 days. The subjects who had been receiving ICS treatment at a constant dose equivalent to ≤1000 μg of FP for ≥4 weeks until the screening (Visit 1) were allowed to use the drug concomitantly during the study period.

Of 605 randomized[27] subjects, 602 subjects who received the study drug (99 subjects in the VI 3 μg group, 101 subjects in the VI 6.25 μg group, 101 subjects in the VI 12.5 μg group, 101 subjects in the VI 25 μg group, 99 subjects in the VI 50 μg group, 101 subjects in the placebo group) were included in the ITT population, which was also included in the safety analysis set and efficacy analysis set.

Discontinuation of the study occurred in 11% (11 of 99 subjects) in the VI 3 μg group, 10% (10 of 101 subjects) in the VI 6.25 μg group, 9% (9 of 101 subjects) in the VI 12.5 μg group, 9% (9 of 101 subjects) in the VI 25 μg group, 8% (8 of 99 subjects) in the VI 50 μg group, and 16% (16 of 101 subjects) in the placebo group. The main reason for discontinuation was protocol deviation (5% [5 of 99 subjects] in the VI 3 μg group, 3% [3 of 101 subjects] in the VI 6.25 μg group, 3% [3 of 101 subjects] in the VI 25 μg group, 4% [4 of 99 subjects] in the VI 50 μg group, 5% [5 of 101 subjects] in the placebo group).

Table 22 shows the results on the primary efficacy endpoint, a change from baseline in trough FEV_1[28] at Day 29. Statistically significant differences were observed in pairwise comparisons between the placebo group and each of the VI groups, indicating the presence of dose-response relationship.

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[26] Patients who have been diagnosed with COPD in accordance with the Standards for the Diagnosis and Management of Patients with COPD issued by the ATS/European Respiratory Society and who meet the following criteria: (a) who currently smoke or smoked in the past, having a smoking history of ≥10 pack-years; (b) in whom the FEV_1/FVC ratio following administration of a bronchodilator is ≤0.7, and the FEV_1 following administration of a bronchodilator is between 35% and 70% of the FEV_1 predicted value according to the standard formula of the NHANES III at Visit 1 (screening); and (c) who are aged 40 to 80 years.

[27] Subjects who meet the following inclusion criteria for randomization: (a) neither aggravation of COPD nor lower respiratory tract infection is observed during the run-in period or at Visit 2 (at the start of the treatment period); (b) who present no clinically significant abnormal findings in the ECG, hematology, clinical chemistry, or urinalysis at the screening; (c) who present no clinically significant abnormal signs of the activity in 12-lead ECG at Visit 2 (at the start of the treatment period) (myocardial ischaemia, arrhythmia, etc.); (d) who had had a history of ICS treatment and were using ICS at a constant dose during the run-in period and will use the drug at the constant dose throughout the study period.

[28] Trough FEV_1 at Day 29 was defined as the mean of measured FEV_1 values at 23 and 24 hours after dosing on Day 28. The baseline FEV_1 was defined as the mean of 2 measured values at ≤30 minutes and just before dosing of the study drug on Day 1.

Table 22. Change from baseline in trough FEV_1 (L) at Day 29 (ITT population, LOCF)

	VI 3 μg group	VI 6.25 μg group	VI 12.5 μg group	VI 25 μg group	VI 50 μg group	Placebo group
Baseline	1.299 ± 0.459 (99)	1.242 ± 0.431 (101)	1.222 ± 0.427 (100)	1.182 ± 0.483 (100)	1.330 ± 0.487 (99)	1.255 ± 0.467 (101)
Day 29	1.421 ± 0.501 (99)	1.362 ± 0.414 (100)	1.3655 ± 0.466 (99)	1.348 ± 0.531 (100)	1.521 ± 0.502 (99)	1.283 ± 0.464 (101)
Change	0.122 ± 0.179 (99)	0.127 ± 0.155 (100)	0.137 ± 0.207 (99)	0.169 ± 0.195 (99)	0.190 ± 0.206 (99)	0.029 ± 0.199 (101)
Difference between groups [95% CI] [a)] *P*-value [a), b)]	0.092 [0.039, 0.144] *P* < 0.001	0.098 [0.046, 0.150] *P* < 0.001	0.110 [0.057, 0.162] *P* < 0.001	0.137 [0.085, 0.190] *P* < 0.001	0.165 [0.112, 0.217] *P* < 0.001	

Mean ± SD (number of subjects)

a) Analysis of the covariance model with stratum of the baseline value, dose group, sex, age, smoking status, and reversibility (cutoff values were 12% and 200 mL change in FEV_1 value before and after salbutamol inhalation) and dose group as explanatory variables

b) Multiplicity of the test was adjusted by the step-down method in which the groups were stratified in descending order of the dose.

Adverse events occurred in 24% (24 of 99 subjects) in the VI 3 μg group, 32% (32 of 101 subjects) in the VI 6.25 μg group, 24% (24 of 101 subjects) in the VI 12.5 μg group, 33% (33 of 101 subjects) in the VI 25 μg group, 28% (28 of 99 subjects) in the VI 50 μg group, and 36% (36 of 101 subjects) in the placebo group. Table 23 shows the major adverse events.

Death was reported in 1 subject in the VI 6.25 μg group (subdural haematoma) during the follow-up period, but a causal relationship to the study drug was ruled out. Serious adverse events occurred in 1% (1 of 99 subjects, syncope vagovagal) in the VI 3 μg group, <1% (1 of 101 subjects, aortic aneurysm) in the VI 6.25 μg group, and 2% (2 of 101 subjects, atrial fibrillation/chronic obstructive disease and pneumonia in 1 subject each) in the VI 12.5 μg group, but no events occurred in ≥2 subjects of any dose group. A causal relationship to the study drug was ruled out for all of the serious adverse events.

Adverse events leading to discontinuation of the study occurred in 3% (3 of 99 subjects) in the VI 3 μg group, 4% (4 of 101 subjects) in the VI 6.25 μg group, 2% (2 of 101 subjects) in the VI 12.5 μg group, 1% (1 of 99 subjects) in the VI 50 μg group, and 3% (3 of 101 subjects) in the placebo group.

Adverse drug reactions occurred in 5% (5 of 99 subjects) in the VI 3 μg group, 5% (5 of 101 subjects) in the VI 6.25 μg group, 5% (5 of 101 subjects) in the VI 12.5 μg group, 5% (5 of 101 subjects) in the VI 25 μg group, 7% (7 of 99 subjects) in the VI 50 μg group, and 10% (10 of 101 subjects) in the placebo group.

Table 23. Adverse events reported by ≥3% of subjects in any group (ITT population)

	VI 3 μg group (N = 99)	VI 6.25 μg group (N = 101)	VI 12.5 μg group (N = 101)	VI 25 μg group (N = 101)	VI 50 μg group (N = 99)	Placebo group (N = 101)
Headache	6 (6)	5 (5)	3 (3)	3 (3)	7 (7)	10 (10)
Nausea	1 (1)	3 (3)	2 (2)	2 (2)	1 (1)	4 (4)
Nasopharyngitis	2 (2)	5 (5)	0	1 (<1)	0	3 (3)
Blood potassium increased	0	1 (<1)	2 (2)	2 (2)	2 (2)	3 (3)
Diarrhoea	2 (2)	1 (<1)	1 (<1)	3 (3)	0	1 (<1)
Blood glucose increased	0	1 (<1)	3 (3)	1 (<1)	0	3 (3)
Ventricular extrasystoles	0	1 (<1)	0	0	3 (3)	2 (2)
Nasal congestion	0	2 (2)	0	0	0	3 (3)
Oropharyngeal pain	0	3 (3)	0	0	1 (1)	0

Number of subjects (%)

4.(iii).A.(3) UMEC/VI concomitant therapy study

4.(iii).A.(3).1) Global phase III study (5.3.5.1, Study DB2113361 [March 2011 to April 2012])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of UMEC/VI in Japanese and foreign COPD patients[29] (target sample size, 1463 [399 subjects in each active drug group, 266 subjects in the placebo group]) in the 14 countries of Japan, the US, Belgium, Denmark, Estonia, France, Germany, Hungary, Netherlands, Norway, Slovakia, Sweden, Ukraine, and Philippines.

UMEC/VI 125/25 μg, UMEC 125 μg, VI 25 μg, or placebo was administered once daily in the morning by inhalation. The treatment period was 24 weeks. The subjects who had been receiving ICS treatment at a constant dose equivalent to ≤1000 μg of FP for ≥30 days until the screening (Visit 1) were allowed to use the drug concomitantly during the study period.

Of 1493 randomized[30] subjects, 1489 subjects who received the study drug (403 subjects in the UMEC/VI 125/25 μg group, 407 subjects in the UMEC 125 μg group, 404 subjects in the VI 25 μg group, 275 subjects in the placebo group) were included in the ITT population, which was also included in the safety analysis set and efficacy analysis set.

Discontinuation of the study occurred in 19% (78 of 403 subjects) in the UMEC/VI 125/25 μg group, 23% (95 of 407 subjects) in the UMEC 125 μg group, 26% (106 of 404 subjects) in the VI 25 μg group, 33% (92 of 275 subjects) in the placebo group. The main reason for discontinuation was lack of efficacy (6% [24 of 403 subjects] in the UMEC/VI 125/25 μg group, 9% [38 of 407 subjects] in the UMEC 125 μg group, 9% [37 of 404 subjects] in the VI 25 μg group, 16% [44 of 275 subjects] in the placebo group).

The ITT population included 74 Japanese subjects (19 subjects in the UMEC/VI 125/25 μg group, 21 subjects in the UMEC 125 μg group, 21 subjects in the VI 25 μg group, 13 subjects in the placebo group) as the Japanese subpopulation. In the Japanese subpopulation, discontinuation of

[29] Patients who have been diagnosed with COPD in accordance with the Standards for the Diagnosis and Management of Patients with COPD issued by the ATS/European Respiratory Society and who meet the following criteria: (a) who currently smoke or smoked in the past, having a smoking history of ≥10 pack-years; (b) in whom the FEV_1/FVC ratio following administration of a bronchodilator is <0.7, and the FEV_1 following administration of a bronchodilator is ≤70% of the FEV_1 predicted value according to the standard formula of the NHANES III at Visit 1 (screening); (c) who have a score of ≥2 on the mMRC; and (d) who are aged ≥40 years.

[30] Subjects who meet the following inclusion criteria for randomization: (a) neither aggravation of COPD nor lower respiratory tract infection has been observed during the run-in period; and (b) electronic diary has been entered on ≥4 days during the last 7days of the run-in period.

the study occurred in 16% (3 of 19 subjects) in the UMEC/VI 125/25 μg group, 14% (3 of 21 subjects) in the UMEC 125 μg group, 38% (8 of 21 subjects) in the VI 25 μg group, and 46% (6 of 13 subjects) in the placebo group, and the main reason for discontinuation was lack of efficacy (14% [3 of 21 subjects] in the UMEC 125 μg group, 5% [1 of 21 subjects] in the VI 25 μg group, 38% [5 of 13 subjects] in the placebo group).

Table 24 shows the results on the primary efficacy endpoint, a change from baseline in trough FEV_1[31] at Week 24. Statistically significant differences were observed in pairwise comparisons between the placebo group and each of the UMEC/VI 125/25 μg group, UMEC 125 μg group, and VI 25 μg group, verifying the superiority of UMEC/VI 125/25 μg, UMEC 125 μg, and VI 25 μg to placebo. In addition, statistically significant differences were observed in pairwise comparisons between the UMEC/VI 125/25 μg group and the UMEC 125 μg group and between the UMEC/VI 125/25 μg group and the VI 25 μg group, verifying superiority of UMEC/VI 125/25 μg to UMEC 125 μg or VI 25 μg.

Table 24. Change from baseline in trough FEV_1 (L) at Week 24 (ITT population, OC)

	UMEC/VI 125/25 μg group	UMEC 125 μg group	VI 25 μg group	Placebo group
Baseline	1.257 ± 0.481 (402)	1.299 ± 0.488 (406)	1.279 ± 0.487 (403)	1.259 ± 0.473 (274)
Week 24	1.503 ± 0.524 (324)	1.469 ± 0.516 (312)	1.418 ± 0.520 (300)	1.337 ± 0.504 (183)
Change	0.214 ± 0.222 (323)	0.139 ± 0.212 (312)	0.100 ± 0.223 (299)	-0.024 ± 0.226 (182)
Difference from the placebo group [95% CI],[a)] *P*-value [a), b)]	0.238 [0.200, 0.276] *P* < 0.001	0.160 [0.122, 0.198] *P* < 0.001	0.124 [0.086, 0.162] *P* < 0.001	
Difference from UMEC/VI 125/25 μg group [95% CI],[a)] *P*-value [a), b)]		0.079 [0.046, 0.112] *P* < 0.001	0.114 [0.081, 0.148] *P* < 0.001	

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with the baseline value, dose group, smoking status, center group, day of administration, interaction between day of administration and the baseline value, and interaction between day of administration and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

b) Multiplicity of the test was adjusted by the step-down method in which pairwise comparisons between the UMEC/VI 125/25 μg group and the placebo group, between the UMEC 125 μg group and the placebo group, between the VI 25 μg group and the placebo group, between the UMEC/VI 125/25 μg group and the VI 25 μg group, and between the UMEC/VI 125/25 μg group and the UMEC 125 μg group were stratified in this order.

Table 25 shows trough FEV_1 at Week 24 in the Japanese subpopulation.

Table 25. Change from baseline in trough FEV_1 (L) at Week 24 in the Japanese subpopulation (ITT population, OC)

	UMEC/VI 125/25 μg group	UMEC 125 μg group	VI 25 μg group	Placebo group
Baseline	0.947 ± 0.400 (19)	0.981 ± 0.312 (21)	0.926 ± 0.335 (21)	1.038 ± 0.214 (13)
Week 24	1.093 ± 0.398 (16)	1.104 ± 0.329 (18)	1.030 ± 0.316 (13)	1.111 ± 0.165 (7)
Change	0.138 ± 0.185 (16)	0.139 ± 0.141 (18)	0.071 ± 0.177 (13)	-0.11 ± 0.152 (7)
Difference from placebo group [95% CI] [a)]	0.174 [-0.008, 0.356]	0.188 [0.009, 0.366]	0.131 [-0.053, 0.315]	
Difference from UMEC/VI 125/25 μg group [95% CI] [a)]		-0.014 [-0.160, 0.131]	0.043 [-0.109, 0.195]	

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with the baseline value, dose group, smoking status, region (Japan/outside Japan), day of administration, interaction between day of administration and the baseline value, interaction between day of administration and dose group, interaction between the region and dose group, and interaction among the region, day of administration, and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

[31] Trough FEV_1 at Week 24 (Day 169) was defined as the mean of measured FEV_1 values at 23 and 24 hours after dosing on Day 168.

Adverse events occurred in 52% (211 of 403 subjects) in the UMEC/VI 125/25 μg group, 53% (217 of 407 subjects) in the UMEC 125 μg group, 53% (215 of 404 subjects) in the VI 25 μg group, and 49% (134 of 275 subjects) in the placebo group. Table 26 shows the major adverse events.

Deaths were reported in 2 subjects (pancreatic cancer metastatic and metastases to bone/metastases to central nervous system/non-small cell lung cancer in 1 subject each) in the UMEC 125 μg group, 2 subjects (acute myocardial infarction and lung neoplasm malignant/metastases to bone in 1 subject each) in the VI 25 μg group, and 2 subjects (arteriosclerosis and pneumonia in 1 subject each) in the placebo group, but a causal relationship to the study drug was ruled out for all of the deaths.

Serious adverse events occurred in 6% (23 of 403 subjects) in the UMEC/VI 125/25 μg group, 5% (22 of 407 subjects) in the UMEC 125 μg group, 5% (20 of 404 subjects) in the VI 25 μg group, and 6% (17 of 275 subjects) in the placebo group. Events reported by ≥2 subjects in any treatment group included chronic obstructive pulmonary disease (1% [5 of 403 subjects] in the UMEC/VI 125/25 μg group, <1% [4 of 407 subjects] in the UMEC 125 μg group, <1% [3 of 404 subjects] in the VI 25 μg group, 3% [8 of 275 subjects] in the placebo group), pneumonia (<1% [3 of 403 subjects] in the UMEC/VI 125/25 μg group, <1% [2 of 407 subjects] in the UMEC 125 μg group, 1% [4 of 275 subjects] in the placebo group), acute myocardial infarction (<1% [1 of 407 subjects] in the UMEC 125 μg group, <1% [2 of 404 subjects] in the VI 25 μg group), atrial fibrillation (<1% [2 of 407 subjects] in the UMEC 125 μg group, <1% [1 of 404 subjects] in the VI 25 μg group), ventricular extrasystoles (<1% [2 of 407 subjects] in the UMEC 125 μg group), and lung neoplasm malignant (<1% [2 of 403 subjects] in the UMEC/VI 125/25 μg group, <1% [1 of 404 subjects] in the VI 25 μg group). Of these, the events occurred in 2 subjects (atrial fibrillation and chest pain in 1 subject each) in the UMEC 125 μg group and 1 subject (atrial fibrillation) in the VI 25 μg group were assessed as causally related to the study drug.

Adverse events leading to discontinuation of the study occurred in 5% (19 of 403 subjects) in the UMEC/VI 125/25 μg group, 6% (24 of 407 subjects) in the UMEC 125 μg group, 6% (25 of 404 subjects) in the VI 25 μg group, and 6% (17 of 275 subjects) in the placebo group.

Adverse drug reactions occurred in 9% (36 of 403 subjects) in the UMEC/VI 125/25 μg group, 8% (34 of 407 subjects) in the UMEC 125 μg group, 7% (30 of 404 subjects) in the VI 25 μg group, and 4% (12 of 275 subjects) in the placebo group.

Table 26. Adverse events reported by ≥3% of subjects in any group (ITT population)

	UMEC/VI 125/25 μg group (N = 403)	UMEC 125 μg group (N = 407)	VI 25 μg group (N = 404)	Placebo group (N = 275)
Nasopharyngitis	47 (12)	37 (9)	55 (14)	32 (12)
Headache	41 (10)	37 (9)	41 (10)	32 (12)
Cough	29 (7)	15 (4)	18 (4)	16 (6)
Back pain	10 (2)	17 (4)	10 (2)	13 (5)
Pyrexia	13 (3)	9 (2)	9 (2)	7 (3)
Hypertension	8 (2)	9 (2)	12 (3)	4 (1)
Toothache	4 (<1)	12 (3)	10 (2)	7 (3)
Arthralgia	11 (3)	5 (1)	8 (2)	5 (2)
Upper respiratory tract infection	7 (2)	6 (1)	9 (2)	7 (3)
Dyspnoea	4 (<1)	5 (1)	10 (2)	9 (3)
Pain in extremity	3 (<1)	8 (2)	12 (3)	5 (2)
Chronic obstructive pulmonary disease	6 (1)	6 (1)	4 (<1)	11 (4)

Number of subjects (%)

In the Japanese subpopulation, adverse events occurred in 58% (11 of 19 subjects) in the UMEC/VI 125/25 μg group, 52% (11 of 21 subjects) in the UMEC 125 μg group, 81% (17 of 21 subjects) in the VI 25 μg group, and 62% (8 of 13 subjects) in the placebo group. Death was reported in 1 subject (acute myocardial infarction) in the VI 25 μg group, but a causal relationship to the study drug was ruled out. Serious adverse events occurred in 5% (1 of 19 subjects, chronic obstructive pulmonary disease) in the UMEC/VI 125/25 μg group, 14% (3 of 21 subjects; chronic obstructive pulmonary disease in 2 subjects, acute myocardial infarction in 1 subject) in the VI 25 μg group, and 15% (2 of 13 subjects, chronic obstructive pulmonary disease and pneumothorax in 1 subject each) in the placebo group, but a causal relationship to the study drug was ruled out for all the events. Adverse events leading to discontinuation of the study occurred in 5% (1 of 19 subjects, chronic obstructive pulmonary disease) in the UMEC/VI 125/25 μg group, 19% (4 of 21 subjects; chronic obstructive pulmonary disease in 2 subjects, pneumonia and acute myocardial infarction in 1 subject each) in the VI 25 μg group, and 8% (1 of 13 subjects, chronic obstructive pulmonary disease) in the placebo group, but a causal relationship to the study drug was ruled out for all the events.

Adverse drug reactions occurred in 16% in the UMEC/VI 125/25 μg group and 10% in the UMEC 125 μg group.

4.(iii).A.(3).2) Global phase III study (5.3.5.1, Study DB2113373 [March 2011 to April 2012])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of UMEC/VI in Japanese and foreign COPD patients[32] (target sample size, 1463 [399 subjects in each active drug group, 266 subjects in the placebo group]) in the 13 countries of Japan, the US, Canada, Chile, Mexico, Bulgaria, Czech Republic, Greece, Poland, Russia, Spain, South Africa, and Thailand.

UMEC/VI 62.5/25 μg, UMEC 62.5 μg, VI 25 μg, or placebo was administered once daily in the morning by inhalation. The treatment period was 24 weeks. The subjects who had been receiving

[32] Patients who have been diagnosed with COPD in accordance with the Standards for the Diagnosis and Management of Patients with COPD issued by the ATS/European Respiratory Society and who meet the following criteria: (a) who currently smoke or smoked in the past, having a smoking history of ≥10 pack-years; (b) in whom the FEV_1/FVC ratio following administration of a bronchodilator is <0.7, and the FEV_1 following administration of a bronchodilator is ≤70% of the FEV_1 predicted value according to the standard formula of the NHANES III at Visit 1 (screening); (c) who have a score of ≥2 on the mMRC; and (d) who are aged ≥40 years.

ICS treatment at a constant dose equivalent to ≤1000 μg of FP for ≥30 days until the screening (Visit 1) were allowed to use the drug concomitantly during the study period.

Of 1536 randomized[33] subjects, 1532 subjects who received the study drug (413 subjects in the UMEC/VI 62.5/25 μg group, 418 subjects in the UMEC 62.5 μg group, 421 subjects in the VI 25 μg group, 280 subjects in the placebo group) were included in the ITT population, which was also included in the safety analysis set and efficacy analysis set.

Discontinuation of the study occurred in 20% (81 of 413 subjects) in the UMEC/VI 62.5/25 μg group, 22% (94 of 418 subjects) in the UMEC 62.5 μg group, 24% (103 of 421 subjects) in the VI 25 μg group, and 27% (76 of 280 subjects) in the placebo group. The main reason for discontinuation was lack of efficacy (5% [20 of 413 subjects] in the UMEC/VI 62.5/25 μg group, 5% [20 of 418 subjects] in the UMEC 62.5 μg group, 8% [32 of 421 subjects] in the VI 25 μg group, 13% [37 of 280 subjects] in the placebo group).

The ITT population included 68 subjects (20 subjects in the UMEC/VI 62.5/25 μg group, 18 subjects in the UMEC 62.5 μg group, 18 subjects in the VI 25 μg group, 12 subjects in the placebo group) as the Japanese subpopulation. In the Japanese subpopulation, discontinuation of the study occurred in 5% (1 of 20 subjects) in the UMEC/VI 62.5/25 μg group, 28% (5 of 18 subjects) in the UMEC 62.5 μg group, and 33% (4 of 12 subjects) in the placebo group., The main reason for discontinuation was lack of efficacy (17% [3 of 18 subjects] in the UMEC 62.5 μg group, 17% [2 of 12 subjects] in the placebo group).

Table 27 shows the results on the primary efficacy endpoint, a change from baseline in trough FEV_1[34] at Week 24. Statistically significant differences were observed in pairwise comparisons between the placebo group and each of the UMEC/VI 62.5/25 μg group, UMEC 62.5 μg group, and VI 25 μg group, verifying the superiority of UMEC/VI 62.5/25 μg, UMEC 62.5 μg, and VI 25 μg to placebo. In addition, statistically significant differences were observed in pairwise comparisons between the UMEC/VI 62.5/25 μg group and the UMEC 62.5 μg group and between the UMEC/VI 62.5/25 μg group and the VI 25 μg group, verifying superiority of UMEC/VI 62.5/25 μg to UMEC 62.5 μg or VI 25 μg.

[33] Subjects who meet the following inclusion criteria for randomization: (a) neither aggravation of COPD nor lower respiratory tract infection has been observed during the run-in period or Visit 2 (at the start of the treatment period); and (b) electronic diary has been entered on ≥4 days during the last 7 days of the run-in period.

[34] Trough FEV_1 at Week 24 (Day 169) was defined as the mean of measured FEV_1 values at 23 and 24 hours after dosing on Day 168.

Table 27. Change from baseline in trough FEV_1 (L) at Week 24 (ITT population, OC)

	UMEC/VI 62.5/25 μg group	UMEC 62.5 μg group	VI 25 μg group	Placebo group
Baseline	1.282 ± 0.556 (413)	1.199 ± 0.488 (417)	1.247 ± 0.485 (421)	1.200 ± 0.469 (280)
Week 24	1.461 ± 0.557 (330)	1.357 ± 0.516 (322)	1.358 ± 0.492 (317)	1.226 ± 0.475 (201)
Change	0.164 ± 0.246 (330)	0.123 ± 0.225 (322)	0.083 ± 0.234 (317)	0.004 ± 0.230 (201)
Difference from placebo group [95% CI], [a] *P*-value [a), b)]	0.167 [0.128, 0.207] *P* < 0.001	0.115 [0.076, 0.155] *P* < 0.001	0.072 [0.032, 0.112] *P* < 0.001	
Difference from UMEC/VI 62.5/25 μg group [95% CI], [a] *P*-value [a), b)]		0.052 [0.017, 0.087] *P* = 0.004	0.095 [0.060, 0.130] *P* < 0.001	

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with the baseline value, dose group, smoking status, center group, day of administration, interaction between day of administration and the baseline value, and interaction between day of administration and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

b) Multiplicity of the test was adjusted by the step-down method in which pairwise comparisons between the UMEC/VI 62.5/25 μg group and the placebo group, between the UMEC 62.5 μg group and the placebo group, between the VI 25 μg group and the placebo group, between the UMEC/VI 62.5/25 μg group and the VI 25 μg group, and between the UMEC/VI 62.5/25 μg group and the UMEC 62.5 μg group were stratified in this order.

Table 28 shows trough FEV_1 at Week 24 in the Japanese subpopulation.

Table 28. Change from baseline in trough FEV_1 (L) at Week 24 in the Japanese subpopulation (ITT population, OC)

	UMEC/VI 62.5/25 μg group	UMEC 62.5 μg group	VI 25 μg group	Placebo group
Baseline	0.890 ± 0.328 (20)	1.118 ± 0.349 (18)	1.094 ± 0.450 (18)	1.204 ± 0.508 (12)
Week 24	1.079 ± 0.342 (19)	1.329 ± 0.453 (13)	1.184 ± 0.509 (18)	1.286 ± 0.564 (8)
Change	0.201 ± 0.153 (19)	0.205 ± 0.144 (13)	0.091 ± 0.170 (18)	-0.006 ± 0.140 (8)
Difference from placebo group [95% CI] [a]	0.201 [0.013, 0.388]	0.215 [0.018, 0.412]	0.114 [-0.076, 0.303]	
Difference from UMEC/VI 62.5/25 μg group [95% CI] [a]		-0.014 [-0.177, 0.149]	0.087 [-0.067, 0.241]	

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with the baseline value, dose group, smoking status, region (Japan/outside Japan), day of administration, interaction between day of administration and the baseline value, interaction between day of administration and dose group, interaction between the region and dose group, and interaction among the region, day of administration, and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

Adverse events occurred in 51% (212 of 413 subjects) in the UMEC/VI 62.5/25 μg group, 52% (216 of 418 subjects) in the UMEC 62.5 μg group, 48% (204 of 421 subjects) in the VI 25 μg group, and 46% (130 of 280 subjects) in the placebo group. Table 29 shows the major adverse events.

Deaths were reported in 2 subjects (chronic obstructive pulmonary disease/respiratory failure and myocardial infarction in 1 subject each) in the UMEC/VI 62.5/25 μg group, 1 subject (acute respiratory failure/chronic obstructive pulmonary disease) in the UMEC 62.5 μg group, 3 subjects (sudden death in 1 subject, chronic obstructive pulmonary disease in 2 subjects) in the VI 25 μg group, and the death in 1 subject in the VI 25 μg group (sudden death) was assessed as causally related to the study drug.

Serious adverse events occurred in 5% (21 of 413 subjects) in the UMEC/VI 62.5/25 μg group, 6% (27 of 418 subjects) in the UMEC 62.5 μg group, 6% (24 of 421 subjects) in the VI 25 μg group, and 3% (9 of 280 subjects) in the placebo group. Of them, events reported by ≥2 subjects in any treatment group included chronic obstructive pulmonary disease (2% [7 of 413 subjects] in the UMEC/VI 62.5/25 μg group, 3% [12 of 418 subjects] in the UMEC 62.5 μg group, 2% [8 of 421 subjects] in the VI 25 μg group, 1% [3 of 280 subjects] in the placebo group), respiratory

failure (<1% [2 of 413 subjects] in the UMEC/VI 62.5/25 μg group, <1% [1 of 418 subjects] in the UMEC 62.5 μg group), bronchitis (<1% [2 of 413 subjects] in the UMEC/VI 62.5/25 μg group, <1% [1 of 421 subjects] in the VI 25 μg group), pneumonia (<1% [2 of 413 subjects] in the UMEC/VI 62.5/25 μg group, <1% [1 of 421 subjects] in the VI 25 μg group), infective exacerbation of chronic obstructive airways disease (<1% [2 of 418 subjects] in the UMEC 62.5 μg group), coronary artery disease (<1% [2 of 418 subjects] in the UMEC 62.5 μg group, <1% [1 of 421 subjects] in the VI 25 μg group), cerebrovascular accident (<1% [2 of 421 subjects] in the VI 25 μg group, <1% [1 of 280 subjects] in the placebo group), and cholecystitis chronic (<1% [2 of 418 subjects] in the UMEC 62.5 μg group). Events reported in 1 subject (atrial fibrillation) in the UMEC/VI 62.5/25 μg group, 1 subject (tachycardia) in the UMEC 62.5 μg group, and 1 subject (sudden death) in the VI 25 μg group were assessed as causally related to the study drug.

Adverse events leading to discontinuation of the study occurred in 5% (22 of 413 subjects) in the UMEC/VI 62.5/25 μg group, 7% (31 of 418 subjects) in the UMEC 62.5 μg group, 6% (24 of 421 subjects) in the VI 25 μg group, and 3% (9 of 280 subjects) in the placebo group.

Adverse drug reactions occurred in 6% (25 of 413 subjects) in the UMEC/VI 62.5/25 μg group, 8% (34 of 418 subjects) in the UMEC 62.5 μg group, 6% (26 of 421 subjects) in the VI 25 μg group, and 7% (19 of 280 subjects) in the placebo group.

Table 29. Adverse events reported by ≥3% of subjects in any group (ITT population)

	UMEC/VI 62.5/25 μg group (N = 413)	UMEC 62.5 μg group (N = 418)	VI 25 μg group (N = 421)	Placebo group (N = 280)
Headache	35 (8)	32 (8)	25 (6)	26 (9)
Nasopharyngitis	39 (9)	29 (7)	26 (6)	16 (6)
Upper respiratory tract infection	13 (3)	21 (5)	18 (4)	14 (5)
Cough	6 (1)	16 (4)	15 (4)	7 (3)
Oropharyngeal pain	13 (3)	6 (1)	14 (3)	4 (1)
Back pain	13 (3)	8 (2)	7 (2)	7 (3)
Chronic obstructive pulmonary disease	7 (2)	12 (3)	8 (2)	3 (1)
Arthralgia	4 (<1)	12 (3)	2 (<1)	3 (1)

Number of subjects (%)

In the Japanese subpopulation, adverse events occurred in 50% (10 of 20 subjects) in the UMEC/VI 62.5/25 μg group, 56% (10 of 18 subjects) in the UMEC 62.5 μg group, 50% (9 of 18 subjects) in the VI 25 μg group, and 67% (8 of 12 subjects) in the placebo group. No deaths were reported. A serious adverse event occurred in 6% (1 of 18 subjects, ankle fracture) in the UMEC 62.5 μg group, but a causal relationship to the study drug was ruled out. No adverse events leading to discontinuation of the study occurred.

Adverse drug reactions occurred in 11% in the UMEC 62.5 μg group and 6% in the VI 25 μg group.

4.(iii).A.(3).3) Foreign phase III study (5.3.5.1, Study DB2113360 [March 2011 to April 2012])

A randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of UMEC/VI in foreign COPD patients[35] (target sample size, 832 [208 subjects per group])

[35] Patients who have been diagnosed with COPD in accordance with the Standards for the Diagnosis and Management of Patients with COPD issued by the ATS/European Respiratory Society and who meet the following criteria: (a) who currently smoke or smoked in the past, having a smoking history of ≥10 pack-years; (b) in whom the FEV_1/FVC ratio following administration of a bronchodilator is <0.7, and the FEV_1 following administration of a bronchodilator is ≤70% of the FEV_1 predicted value according to the standard formula of the NHANES III at Visit 1 (screening); (c) who have a score of ≥2 on the mMRC; and (d) who are aged ≥40 years.

in the 9 countries of the US, Germany, Italy, Poland, Romania, Russia, Ukraine, Mexico, and Peru.

UMEC/VI 62.5/25 μg, UMEC/VI 125/25 μg, VI 25 μg, or TIO 18 μg was administered once daily in the morning by inhalation. The treatment period was 24 weeks. The subjects who had been receiving ICS treatment at a constant dose equivalent to ≤1000 μg of FP for ≥30 days until the screening (Visit 1) were allowed to use the drug concomitantly during the study period.

Of 846 randomized[36] subjects, 843 subjects who received the study drug (212 subjects in the UMEC/VI 62.5/25 μg group, 214 subjects in the UMEC/VI 125/25 μg group, 209 subjects in the VI 25 μg group, 208 subjects in the TIO group) were included in the ITT population, which was also included in the safety analysis set. Of these subjects, 823 subjects were included in the efficacy analysis set.[37]

Discontinuation of the study occurred in 15% (31 of 212 subjects) in the UMEC/VI 62.5/25 μg group, 19% (41 of 214 subjects) in the UMEC/VI 125/25 μg group, 21% (44 of 209 subjects) in the VI 25 μg group, and 15% (31 of 208 subjects) in the TIO group. The main reason for discontinuation was lack of efficacy (4% [9 of 212 subjects] in the UMEC/VI 62.5/25 μg group, 2% [5 of 214 subjects] in the UMEC/VI 125/25 μg group, 8% [17 of 209 subjects] in the VI 25 μg group, 3% [7 of 208 subjects] in the TIO group).

Table 30 shows the results on the primary efficacy endpoint, a change from baseline in trough FEV_1[38] at Week 24. Statistically significant differences were observed in pairwise comparisons between the UMEC/VI 125/25 μg group and the VI 25 μg group, between the UMEC/VI 62.5/25 μg group and the VI 25 μg group, between the UMEC/VI 125/25 μg group and the TIO group, and between the UMEC/VI 62.5/25 μg group and the TIO group, verifying the superiority ofUMEC/VI 62.5/25 μg to VI 25 μg or TIO 18 μg, and superiority of UMEC/VI 125/25 μg to VI 25 μg or TIO 18 μg.

[36] Subjects who meet the following inclusion criteria for randomization: (a) neither aggravation of COPD nor lower respiratory tract infection has been observed during the run-in period or Visit 2 (at the start of the treatment period); and (b) electronic diary has been entered on ≥4 days during the last 7 days of the run-in period.

[37] Population excluding the subjects included by the investigator 040688. This population was defined before unblinding and used as the primary evaluation population for the efficacy and health outcomes data.

[38] Trough FEV_1 at Week 24 (Day 169) was defined as the mean of measured FEV_1 values at 23 and 24 hours after dosing on Day 168.

Table 30. Change from baseline in trough FEV_1 (L) at Week 24 (efficacy analysis set, OC)

	UMEC/VI 125/25 μg group	UMEC/VI 62.5/25 μg group	VI 25 μg group	TIO group
Baseline	1.296 ± 0.481 (207)	1.319 ± 0.526 (207)	1.353 ± 0.541 (204)	1.289 ± 0.531 (203)
Week 24	1.505 ± 0.523 (168)	1.545 ± 0.539 (177)	1.532 ± 0.578 (163)	1.426 ± 0.559 (173)
Change [a)]	0.212 ± 0.252 (167)	0.209 ± 0.246 (177)	0.125 ± 0.259 (162)	0.130 ± 0.270 (173)
Difference from VI 25 μg group [95% CI],[a)] *P*-value [a), b)]	0.088 [0.036, 0.140] *P* < 0.001	0.090 [0.039, 0.142] *P* < 0.001		
Difference from TIO group [95% CI],[a)] *P*-value [a), b)]	0.088 [0.036, 0.140] *P* < 0.001	0.090 [0.039, 0.141] *P* < 0.001		

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with the baseline value, dose group, smoking status, center group, day of administration, interaction between day of administration and the baseline value, and interaction between day of administration and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

b) Multiplicity of the test was adjusted by the step-down method in which pairwise comparisons were stratified in the following order: Between the UMEC/VI 125/25 μg group and the TIO group, and between the UMEC/VI 125/25 μg group and the VI 25 μg group in terms of the primary endpoint; between the UMEC/VI 125/25 μg group and the TIO group, and between the UMEC/VI 125/25 μg group and the VI 25 μg group in terms of weighted mean FEV_1 (L) over 0 to 6 hours post-dose at Week 24, the secondary endpoint; and between the UMEC/VI 62.5/25 μg group and the TIO group, and between the UMEC/VI 62.5/25 μg group and the VI 25 μg group in terms of the primary endpoint.

Adverse events occurred in 51% (108 of 212 subjects) in the UMEC/VI 62.5/25 μg group, 44% (94 of 214 subjects) in the UMEC/VI 125/25 μg group, 47% (99 of 209 subjects) in the VI 25 μg group, and 39% (82 of 208 subjects) in the TIO group. Table 31 shows the major adverse events.

Deaths occurred in 1 subject (cardiac failure acute) in the VI 25 μg group during the treatment period and 1 subject (chronic obstructive pulmonary disease/cardiac arrest) in the UMEC/VI 62.5/25 μg group during the follow-up period, but a causal relationship to the study drug was ruled out for all the deaths. Serious adverse events occurred in 3% (7 of 212 subjects) in the UMEC/VI 62.5/25 μg group, 2% (5 of 214 subjects) in the UMEC/VI 125/25 μg group, 7% (15 of 209 subjects) in the VI 25 μg group, and 6% (13 of 208 subjects) in the TIO group. Events reported by ≥2 subjects in any treatment group included chronic obstructive pulmonary disease (2% [5 of 212 subjects] in the UMEC/VI 62.5/25 μg group, 1% [3 of 214 subjects] in the UMEC/VI 125/25 μg group, <1% [2 of 209 subjects] in the VI 25 μg group, 1% [3 of 208 subjects] in the TIO group), pneumonia (<1% [1 of 209 subjects] in the VI 25 μg group, <1% [2 of 208 subjects] in the TIO group), and non-cardiac chest pain (<1% [2 of 208 subjects] in the TIO group). Of these, the events reported in 3 subjects (supraventricular extrasystoles, acute myocardial infarction, and chronic obstructive pulmonary disease in 1 subject each) in the VI 25 μg group were assessed as causally related to the study drug.

Adverse events leading to discontinuation of the study occurred in 4% (8 of 212 subjects) in the UMEC/VI 62.5/25 μg group, 7% (14 of 214 subjects) in the UMEC/VI 125/25 μg group, 5% (10 of 209 subjects) in the VI 25 μg group, and 4% (9 of 208 subjects) in the TIO group.

Adverse drug reactions occurred in 5% (11 of 212 subjects) in the UMEC/VI 62.5/25 μg group, 4% (9 of 214 subjects) in the UMEC/VI 125/25 μg group, 6% (12 of 209 subjects) in the VI 25 μg group, and 3% (7 of 208 subjects) in the TIO group.

Table 31. Adverse events reported by ≥3% of subjects in any group (ITT population)

	UMEC/VI 62.5/25 μg group (N = 212)	UMEC/VI 125/25 μg group (N = 214)	VI 25 μg group (N = 209)	TIO group (N = 208)
Nasopharyngitis	21 (10)	14 (7)	17 (8)	16 (8)
Headache	20 (9)	14 (7)	21 (10)	9 (4)
Upper respiratory tract infection	8 (4)	7 (3)	5 (2)	8 (4)
Back pain	10 (5)	7 (3)	3 (1)	4 (2)
Cough	7 (3)	7 (3)	4 (2)	5 (2)
Oropharyngeal pain	1 (<1)	6 (3)	5 (2)	2 (<1)
Hypertension	3 (1)	3 (1)	6 (3)	1 (<1)
Urinary tract infection	0	0	2 (<1)	6 (3)

Number of subjects (%)

4.(iii).A.(3).4) Foreign phase III study (5.3.5.1, Study DB2113374 [March 2011 to April 2012])

A randomized, double-blind, parallel-group study was conducted to investigate the efficacy and safety of UMEC/VI in foreign COPD patients[39] (target sample size, 832 [208 subjects per group]) in the 10 countries of the US, Argentina, Australia, Canada, Chile, Germany, Korea, Mexico, Romania, and South Africa.

UMEC/VI 62.5/25 μg, UMEC/VI 125/25 μg, UMEC 125 μg, or TIO 18 μg was administered once daily in the morning by inhalation. The treatment period was 24 weeks. The subjects who had been receiving ICS treatment at a constant dose equivalent to ≤1000 μg of FP for ≥30 days until the screening (Visit 1) were allowed to use the drug concomitantly during the study period.

Of 872 randomized[40] subjects, 869 subjects who received the study drug (217 subjects in the UMEC/VI 62.5/25 μg group, 215 subjects in the UMEC/VI 125/25 μg group, 222 subjects in the UMEC 125 μg group, 215 subjects in the TIO group) were included in the ITT population, which was also included in the safety analysis set and efficacy analysis set.

Discontinuation of the study occurred in 25% (54 of 217 subjects) in the UMEC/VI 62.5/25 μg group, 23% (49 of 215 subjects) in the UMEC/VI 125/25 μg group, 26% (57 of 222 subjects) in the UMEC 125 μg group, and 18% (39 of 215 subjects) in the TIO group. The main reason for discontinuation was adverse events (9% [20 of 217 subjects] in the UMEC/VI 62.5/25 μg group, 7% [15 of 215 subjects] in the UMEC/VI 125/25 μg group, 8% [17 of 222 subjects] in the UMEC 125 μg group, and 5% [11 of 215 subjects] in the TIO group).

Table 32 shows the results on the primary efficacy endpoint, a change from baseline in trough FEV_1[41] at Week 24. A statistically significant difference was observed in a pairwise comparison between the UMEC/VI 125/25 μg group and the TIO group, verifying the superiority of UMEC/VI 125/25 μg to TIO 18 μg. No statistically significant difference was, however, observed in any pairwise comparison between the UMEC/VI 125/25 μg group and the UMEC 125 μg group, between the UMEC/VI 62.5/25 μg group and the TIO group, or between the UMEC/VI 62.5/25 μg group and the UMEC 125 μg group, resulting in a failure to verify the superiority of

[39] Patients who have been diagnosed with COPD in accordance with the Standards for the Diagnosis and Management of Patients with COPD issued by the ATS/European Respiratory Society and who meet the following criteria: (a) who currently smoke or smoked in the past, having a smoking history of ≥10 pack-years; (b) in whom the FEV_1/FVC ratio following administration of a bronchodilator is <0.7, and the FEV_1 following administration of a bronchodilator is ≤70% of the FEV_1 predicted value according to the standard formula of the NHANES III at Visit 1 (screening); (c) who have a score of ≥2 on the mMRC; and (d) who are aged ≥40 years.

[40] Subjects who meet the following inclusion criteria for randomization: (a) neither aggravation of COPD nor lower respiratory tract infection has been observed during the run-in period or Visit 2 (at the start of the treatment period); and (b) electronic diary has been entered on ≥4 days during the last 7 days of the run-in period.

[41] Trough FEV_1 at Week 24 (Day 169) was defined as the mean of measured FEV_1 values at 23 and 24 hours after dosing on Day 168.

UMEC/VI 125/25 μg to UMEC 125 μg or that of UMEC/VI 62.5/25 μg to TIO 18 μg or UMEC 125 μg.

Table 32. Change from baseline in trough FEV_1 (L) at Week 24 (ITT population, OC)

	UMEC/VI 62.5/25 μg group	UMEC/VI 125/25 μg group	UMEC 125 μg group	TIO group
Baseline	1.162 ± 0.479 (216)	1.142 ± 0.473 (215)	1.119 ± 0.443 (221)	1.158 ± 0.449 (215)
Week 24	1.394 ± 0.508 (162)	1.373 ± 0.505 (164)	1.341 ± 0.483 (164)	1.325 ± 0.498 (175)
Change	0.210 ± 0.205 (161)	0.218 ± 0.245 (164)	0.194 ± 0.214 (163)	0.150 ± 0.287 (175)
Difference from UMEC 125 μg group [95% CI],[a)] *P*-value [a), b)]	0.022 [-0.027, 0.072]	0.037 [-0.012, 0.087] *P* = 0.142		
Difference from TIO group [95% CI],[a)] *P*-value [a), b)]	0.060 [0.010, 0.109]	0.074 [0.025, 0.123] *P* = 0.003		

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with the baseline value, dose group, smoking status, center group, day of administration, interaction between day of administration and the baseline value, and interaction between day of administration and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

b) Multiplicity of the test was adjusted by the step-down method in which pairwise comparisons were stratified in the following order: Between the UMEC/VI 125/25 μg group and the TIO group, and between the UMEC/VI 125/25 μg group and the UMEC 125 μg group in terms of the primary endpoint; between the UMEC/VI 125/25 μg group and the TIO group, and between the UMEC/VI 125/25 μg group and the UMEC 125 μg group in terms of weighted mean FEV_1 (L) over 0 to 6 hours post-dose at Week 24, the secondary endpoint; and between the UMEC/VI 62.5/25 μg group and the TIO group, and between the UMEC/VI 62.5/25 μg group and the UMEC 125 μg group in terms of the primary endpoint.

Adverse events occurred in 59% (127 of 217 subjects) in the UMEC/VI 62.5/25 μg group, 62% (133 of 215 subjects) in the UMEC/VI 125/25 μg group, 59% (131 of 222 subjects) in the UMEC 125 μg group, and 59% (126 of 215 subjects) in the TIO group. Table 33 shows the major adverse events.

Deaths were reported in 1 subject (haemorrhagic stroke) in the UMEC/VI 62.5/25 μg group and 2 subjects (upper gastrointestinal haemorrhage and respiratory arrest in 1 subject each) in the TIO group during the treatment period and 1 subject (upper gastrointestinal haemorrhage) in the UMEC/VI 125/25 μg group during the follow-up period, but a causal relationship to the study drug was ruled out for all the deaths. Serious adverse events occurred in 10% (22 of 217 subjects) in the UMEC/VI 62.5/25 μg group, 7% (15 of 215 subjects) in the UMEC/VI 125/25 μg group, 7% (15 of 222 subjects) in the UMEC 125 μg group, and 4% (9 of 215 subjects) in the TIO group. Events reported by ≥2 subjects in any treatment group included pneumonia (<1% [2 of 217 subjects] in the UMEC/VI 62.5/25 μg group, 1% [3 of 215 subjects] in the UMEC/VI 125/25 μg group, <1% [2 of 222 subjects] in the UMEC 125 μg group, <1% [2 of 215 subjects] in the TIO group), infective exacerbation of chronic obstructive airways disease (<1% [2 of 217 subjects] in the UMEC/VI 62.5/25 μg group), chronic obstructive pulmonary disease (3% [7 of 217 subjects] in the UMEC/VI 62.5/25 μg group, 3% [6 of 215 subjects] in the UMEC/VI 125/25 μg group, <1% [2 of 222 subjects] in the UMEC 125 μg group, <1% [1 of 215 subjects] in the TIO group), and coronary artery disease (<1% [2 of 215 subjects] in the UMEC/VI 125/25 μg group).

Adverse events leading to discontinuation of the study occurred in 9% (20 of 217 subjects) in the UMEC/VI 62.5/25 μg group, 7% (14 of 215 subjects) in the UMEC/VI 125/25 μg group, 8% (17 of 222 subjects) in the UMEC 125 μg group, and 5% (11 of 215 subjects) in the TIO group.

Adverse drug reactions occurred in 7% (16 of 217 subjects) in the UMEC/VI 62.5/25 μg group, 8% (17 of 215 subjects) in the UMEC/VI 125/25 μg group, 13% (28 of 222 subjects) in the UMEC 125 μg group, and 7% (16 of 215 subjects) in the TIO group.

Table 33. Adverse events reported by ≥3% of subjects in any group (ITT population)

	UMEC/VI 62.5/25 μg group (N = 217)	UMEC/VI 125/25 μg group (N = 215)	UMEC 125 μg group (N = 222)	TIO group (N = 215)
Headache	21 (10)	20 (9)	25 (11)	15 (7)
Nasopharyngitis	14 (6)	16 (7)	6 (3)	17 (8)
Upper respiratory tract infection	6 (3)	10 (5)	17 (8)	14 (7)
Back pain	8 (4)	6 (3)	10 (5)	11 (5)
Cough	5 (2)	8 (4)	14 (6)	6 (3)
Hypertension	1 (<1)	4 (2)	9 (4)	7 (3)
Oropharyngeal pain	3 (1)	6 (3)	8 (4)	3 (1)
Diarrhoea	4 (2)	1 (<1)	8 (4)	5 (2)
Gastritis	6 (3)	5 (2)	6 (3)	1 (<1)
Pain in extremity	7 (3)	6 (3)	1 (<1)	4 (2)
Urinary tract infection	2 (<1)	5 (2)	6 (3)	4 (2)
Chronic obstructive pulmonary disease	7 (3)	6 (3)	2 (<1)	1 (<1)
Influenza	3 (1)	2 (<1)	6 (3)	5 (2)
Lower respiratory tract infection	9 (4)	3 (1)	1 (<1)	2 (<1)
Dyspnoea	1 (<1)	0	6 (3)	3 (1)

Number of subjects (%)

4.(iii).A.(3).5) Foreign phase III study (5.3.5.1, Study DB2114417 [March 2011 to June 2012])

A placebo-controlled, randomized, double-blind, 2-period, incomplete block design crossover study[42] was conducted to investigate the efficacy and safety of UMEC/VI in foreign COPD patients[43] (target sample size, 312) in the 6 countries of the US, Germany, the UK, Bulgaria, Estonia, and Russia.

UMEC/VI 62.5/25 μg, UMEC/VI 125/25 μg, UMEC 62.5 μg, UMEC 125 μg, VI 25 μg, or placebo was administered once daily in the morning by inhalation. Each treatment period was 12 weeks and separated from the next treatment period by a washout period of 2 weeks. The subjects who had been receiving ICS treatment at a constant dose equivalent to ≤1000 μg of FP for ≥30 days until the screening (Visit 1) were allowed to use the drug concomitantly during the study period.

Of 349 randomized[44] subjects, 348 subjects who received the study drug (152 subjects in the UMEC/VI 62.5/25 μg group, 144 subjects in the UMEC/VI 125/25 μg group, 49 subjects in the UMEC 62.5 μg group, 50 subjects in the UMEC 125 μg group, 76 subjects in the VI 25 μg group, 170 subjects in the placebo group) were included in the ITT population, which was also included in the safety analysis set and efficacy analysis set.

Discontinuation of the study occurred in 14% (22 of 152 subjects) in the UMEC/VI 62.5/25 μg group, 9% (13 of 144 subjects) in the UMEC/VI 125/25 μg group, 12% (6 of 49 subjects) in the UMEC 62.5 μg group, 12% (6 of 50 subjects) in the UMEC 125 μg group, 17% (13 of 76 subjects)

[42] The subjects were randomized to the pre-determined treatment orders (including 2 of 6 study drugs). Since the treatment order was designed to optimize the power of comparisons between UMEC/VI and placebo, the number of subjects is not consistent among the dose groups.

[43] Patients who have been diagnosed with COPD in accordance with the Standards for the Diagnosis and Management of Patients with COPD issued by the ATS/European Respiratory Society and who meet the following criteria: (a) who currently smoke or smoked in the past, having a smoking history of ≥10 pack-years; (b) in whom the FEV_1/FVC ratio following administration of a bronchodilator is <0.7, and the FEV_1 following administration of a bronchodilator is between 35% and 70% of the FEV_1 predicted value according to the standard formula of the NHANES III at Visit 1 (screening); (c) who have a score of ≥2 on the mMRC; (d) in whom the functional residual capacity (FRC) is ≥120% of the predicted value; and (e) who are aged ≥40 years.

[44] Subjects who meet the following inclusion criteria for randomization: (a) neither aggravation of COPD nor lower respiratory tract infection is observed during the run-in period or at Visit 4 (at the start of the treatment period); (b) endurance shuttle walk test (ESWT) can be performed at Visit 3 (7 days before the start of the treatment period) or Visit 4; (c) the exercise endurance time (EET) measured using the ESWT does not exceed 15 minutes at Visit 3 or Visit 4; (d) the difference in EET using the ESWT between Visit 3 and Visit 4 does not exceed 2 minutes; (e) the oxygen saturation during the ESWT at Visit 3 is ≥85%; and (f) no oxygen supplementation is needed to perform the ESWT.

in the VI 25 μg group, and 13% (22 of 170 subjects) in the placebo group. The main reason for discontinuation was lack of efficacy (6% [9 of 152 subjects] in the UMEC/VI 62.5/25 μg group, 4% [6 of 144 subjects] in the UMEC/VI 125/25 μg group, 4% [2 of 49 subjects] in the UMEC 62.5 μg group, 4% [2 of 50 subjects] in the UMEC 125 μg group, 4% [3 of 76 subjects] in the VI 25 μg group, 6% [11 of 170 subjects] in the placebo group).

Table 34 shows the results on one of the co-primary efficacy endpoints, a change from baseline in exercise endurance time (EET) 3 hours post-dose at Week 12. The EET was measured using the endurance shuttle walk test. No statistically significant differences were observed in any pairwise comparison between the UMEC/VI 62.5/25 μg group and the placebo group or between the UMEC/VI 125/25 μg group and the placebo group.

Table 34. Change from baseline in EET(s) 3 hours post-dose at Week 12 (ITT population, OC)

	UMEC/VI 62.5/25 μg group	UMEC/VI 125/25 μg group	UMEC 62.5 μg group	UMEC 125 μg group	VI 25 μg group	Placebo group
Baseline	293.7 ± 161.1 (152)	307.7 ± 165.9 (144)	280.5 ± 152.7 (49)	322.6 ± 182.6 (50)	295.2 ± 112.0 (76)	316.1 ± 171.8 (170)
Week 12	355.7 ± 232.0 (131)	388.2 ± 233.9 (130)	330.2 ± 205.2 (43)	389.3 ± 225.6 (44)	313.7 ± 148.2 (63)	347.6 ± 245.8 (146)
Change	55.8 ± 139.1 (131)	67.7 ± 207.3 (130)	54.6 ± 120.7 (43)	52.5 ± 192.2 (44)	17.5 ± 106.5 (63)	34.2 ± 174.5 (146)
Difference from placebo group [95% CI] [a)] *P*-value [a), b)]	21.9 [-14.2, 58.0]	32.4 [-3.9, 68.8] *P* = 0.080	26.5 [-25.9, 78.9]	13.1 [-38.9, 65.1]	-10.0 [-55.5, 35.4]	
Difference from UMEC/VI 125/25 μg group [95% CI] [a)]				19.3 [-33.4, 71.9]	42.4 [-3.8, 88.7]	
Difference from UMEC/VI 62.5/25 μg group [95% CI] [a)]			-4.6 [-57.6, 48.4]		31.9 [-14.1, 77.9]	

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with treatment period baseline walking speed, mean baseline walking speed, treatment period, dose group, visit, smoking status, center group, interaction between visit and treatment period baseline walking speed, interaction between visit and mean baseline walking speed, and interaction between visit and dose group as fixed effects and the subject as a random effect on the hypothesis of unstructured covariance structure in the subjects in each treatment period

b) Multiplicity of the test was adjusted by the step-down method in which pairwise comparisons between the UMEC/VI 125/25 μg group and the placebo group in terms of 3 hours post-dose EET at Week 12 ([a]), between the UMEC/VI 125/25 μg group and the placebo group in terms of a change from baseline in trough FEV_1 (L) at Week 12 ([b]), between the UMEC/VI 62.5/25 μg group and the placebo group in terms of (a), and between the UMEC/VI 62.5/25 μg group and the placebo group in terms of (b) were stratified in this order.

Table 35 shows the results on the other co-primary endpoint, a change from baseline in trough FEV_1 [45] at Week 12. No statistically significant differences were observed in any pairwise comparisons between the UMEC/VI 62.5/25 μg group and the placebo group or between the UMEC/VI 125/25 μg group and the placebo group.

[45] Trough FEV_1 at Week 12 (Day 85) was defined as the FEV_1 value measured at 24 hours after dosing on Day 84.

Table 35. Change from baseline in trough FEV_1 (L) at Week 12 (ITT population, OC)

	UMEC/VI 62.5/25 μg group	UMEC/VI 125/25 μg group	UMEC 62.5 μg group	UMEC 125 μg group	VI 25 μg group	Placebo group
Treatment period baseline	1.462 ± 0.523 (151)	1.408 ± 0.465 (144)	1.417 ± 0.419 (49)	1.471 ± 0.475 (50)	1.368 ± 0.443 (76)	1.443 ± 0.462 (170)
Week 12	1.606 ± 0.508 (131)	1.610 ± 0.517 (132)	1.506 ± 0.424 (43)	1.606 ± 0.432 (44)	1.444 ± 0.462 (64)	1.419 ± 0.485 (148)
Change	0.167 ± 0.264 (130)	0.178 ± 0.240 (132)	0.079 ± 0.243 (43)	0.113 ± 0.223 (44)	0.059 ± 0.236 (64)	-0.052 ± 0.199 (148)
Difference from placebo group [95% CI] [a)] *P*-value [a), b)]	0.211 [0.172, 0.249] -	0.169 [0.129, 0.209] -	0.087 [0.030, 0.143]	0.140 [0.084, 0.196]	0.099 [0.050, 0.148]	
Difference from UMEC/VI 125/25 μg group [95% CI] [a)]				0.029 [-0.028,0.086]	0.070 [0.019, 0.120]	
Difference from UMEC/VI 62.5/25 μg group [95% CI] [a)]			0.124 [0.067, 0.181]		0.111 [0.062, 0.161]	

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with treatment period baseline value, mean baseline value, treatment period, dose group, visit, smoking status, center group, interaction between visit and treatment period baseline value, interaction between visit and mean baseline value, and interaction between visit and dose group as fixed effects and the subject as a random effect on the hypothesis of unstructured covariance structure in the subjects in each treatment period

b) As defined in Table 34

Adverse events occurred in 23% (35 of 152 subjects) in the UMEC/VI 62.5/25 μg group, 32% (46 of 144 subjects) in the UMEC/VI 125/25 μg group, 12% (6 of 49 subjects) in the UMEC 62.5 μg group, 28% (14 of 50 subjects) in the UMEC 125 μg group, 29% (22 of 76 subjects) in the VI 25 μg group, and 27% (46 of 170 subjects) in the placebo group. Table 36 shows the major adverse events.

Death was reported in 1 subject in the UMEC 125 μg group, but a causal relationship to the study drug was ruled out. Serious adverse events occurred in 3% (4 of 152 subjects) in the UMEC/VI 62.5/25 μg group, 3% (4 of 144 subjects) in the UMEC/VI 125/25 μg group, 6% (3 of 50 subjects) in the UMEC 125 μg group, 9% (7 of 76 subjects) in the VI 25 μg group, and 4% (6 of 170 subjects) in the placebo group. There were no serious adverse events reported by ≥2 subjects in any treatment group. The most commonly reported events included pneumonia (<1% [1 of 144 subjects] in the UMEC/VI 125/25 μg group, 1% [1 of 76 subjects] in the VI 25 μg group), non-cardiac chest pain (1% [1 of 76 subjects] in the VI 25 μg group, <1% [1 of 170 subjects] in the placebo group), and chronic obstructive pulmonary disease (<1% [1 of 144 subjects] in the UMEC/VI 125/25 μg group, <1% [1 of 170 subjects] in the placebo group). There were no serious adverse events considered related to the study drug.

Adverse events leading to discontinuation of the study occurred in 3% (5 of 152 subjects) in the UMEC/VI 62.5/25 μg group, 1% (2 of 144 subjects) in the UMEC/VI 125/25 μg group, 2% (1 of 49 subjects) in the UMEC 62.5 μg group, 4% (2 of 50 subjects) in the UMEC 125 μg group, 4% (3 of 76 subjects) in the VI 25 μg group, and 5% (9 of 170 subjects) in the placebo group.

Adverse drug reactions occurred in 3% (4 of 152 subjects) in the UMEC/VI 62.5/25 μg group, 2% (3 of 144 subjects) in the UMEC/VI 125/25 μg group, 6% (3 of 50 subjects) in the UMEC 125 μg group, 5% (4 of 76 subjects) in the VI 25 μg group, and 4% (7 of 170 subjects) in the placebo group.

Table 36. Adverse events reported by ≥3% of subjects in any group (ITT population)

	UMEC/VI 62.5/25 μg group (N = 152)	UMEC/VI 125/25 μg group (N = 144)	UMEC 62.5 μg group (N = 49)	UMEC 125 μg group (N = 50)	VI 25 μg group (N = 76)	Placebo group (N = 170)
Nasopharyngitis	5 (3)	8 (6)	1 (2)	1 (2)	3 (4)	10 (6)
Headache	3 (2)	2 (1)	0	1 (2)	4 (5)	7 (4)
Sinusitis	0	4 (3)	0	2 (4)	0	3 (2)
Dry mouth	0	0	0	2 (4)	0	0

Number of subjects (%)

4.(iii).A.(3).6) Foreign phase III study (5.3.5.1, Study DB2114418 [March 2011 to July 2012])

A placebo-controlled, randomized, double-blind, 2-period, incomplete block design crossover study[46] was conducted to investigate the efficacy and safety of UMEC/VI in foreign COPD patients[47] (target sample size, 312) in the 7 countries of the US, Czech Republic, South Africa, Denmark, Canada, Ukraine, and the UK.

UMEC/VI 62.5/25 μg or 125/25 μg, UMEC 62.5 μg, UMEC 125 μg, VI 25 μg, or placebo was administered once daily in the morning by inhalation. The treatment period was 12 weeks and separated from the next treatment period by a washout period of 2 weeks. The subjects who had been receiving ICS treatment at a constant dose equivalent to ≤1000 μg of FP for ≥30 days until the screening (Visit 1) were allowed to use the drug concomitantly during the study period.

Of 308 randomized[48] subjects, 307 subjects who received the study drug were included in the ITT population (130 subjects in the UMEC/VI 62.5/25 μg group, 128 subjects in the UMEC/VI 125/25 μg group, 40 subjects in the UMEC 62.5 μg group, 41 subjects in the UMEC 125 μg group, 64 subjects in the VI 25 μg group, 151 subjects in the placebo group).This population was also included in the safety analysis set and efficacy analysis set.

Discontinuation of the study occurred in 11% (14 of 130 subjects) in the UMEC/VI 62.5/25 μg group, 13% (16 of 128 subjects) in the UMEC/VI 125/25 μg group, 5% (2 of 40 subjects) in the UMEC 62.5 μg group, 20% (8 of 41 subjects) in the UMEC 125 μg group, 13% (8 of 64 subjects) in the VI 25 μg group, 21% (31 of 151 subjects) in the placebo group. The main reason for discontinuation was lack of efficacy (2% [2 of 130 subjects] in the UMEC/VI 62.5/25 μg group, 5% [6 of 128 subjects] in the UMEC/VI 125/25 μg group, 10% [4 of 41 subjects] in the UMEC 125 μg group, 3% [2 of 64 subjects] in the VI 25 μg group, 10% [15 of 151 subjects] in the placebo group).

Table 37 shows the results on one of the co-primary efficacy endpoints, a change from baseline in EET 3 hours post-dose at Week 12. Statistically significant differences were observed in pairwise comparisons between the UMEC/VI 62.5/25 μg group and the placebo group, and

[46] The subjects were randomized to any of the pre-determined treatment orders (including 2 of 6 study drugs). Since the treatment order was designed to optimize the power of comparisons between UMEC/VI and placebo, the number of subjects is not consistent among the dose groups.

[47] Patients who have been diagnosed with COPD in accordance with the Standards for the Diagnosis and Management of Patients with COPD issued by the ATS/European Respiratory Society and who meet the following criteria: (a) who currently smoke or smoked in the past, having a smoking history of ≥10 pack-years; (b) in whom the FEV_1/FVC ratio following administration of a bronchodilator is <0.7, and the FEV_1 following administration of a bronchodilator is between 35% and 70% of the FEV_1 predicted value according to the standard formula of the NHANES III at Visit 1 (screening); (c) who have a score of ≥2 on the mMRC; (d) in whom the FRC is ≥120% of the predicted value; and (e) who are aged ≥40 years.

[48] Subjects who meet the following inclusion criteria for randomization: (a) neither aggravation of COPD nor lower respiratory tract infection is observed during the run-in period or at Visit 4 (at the start of the treatment period); (b) ESWT can be performed at Visit 3 (7 days before the start of the treatment period) or Visit 4; (c) the EET does not exceed 15 minutes at Visit 3 or Visit 4; (d) the difference in EET using the ESWT between Visit 3 and Visit 4 does not exceed 2 minutes; (e) the oxygen saturation during the ESWT at Visit 3 is ≥85%; and (f) no oxygen supplementation is needed to perform the ESWT.

between the UMEC/VI 125/25 μg group and the placebo group.

Table 37. Change from baseline in EET(s) 3 hours post-dose at Week 12 (ITT population, OC)

	UMEC/VI 62.5/25 μg group	UMEC/VI 125/25 μg group	UMEC 62.5 μg group	UMEC 125 μg group	VI 25 μg group	Placebo group
Treatment period baseline	323.2 ± 163.0 (130)	303.5 ± 159.8 (128)	318.0 ± 167.0 (39)	278.3 ± 155.6 (40)	309.9 ± 148.0 (64)	339.7 ± 193.0 (150)
Week 12	395.3 ± 258.3 (115)	370.3 ± 236.1 (110)	329.9 ± 232.3 (38)	350.6 ± 194.6 (32)	337.2 ± 163.5 (56)	351.5 ± 212.6 (118)
Change	72.9 ± 243.2 (115)	60.3 ± 180.7 (110)	19.6 ± 155.8 (37)	79.8 ± 146.3 (32)	31.8 ± 127.5 (56)	-0.4 ± 167.4 (118)
Difference from placebo group [95% CI] [a)] *P*-value [a), b)]	69.4 [24.5, 114.4] *P* = 0.003	65.8 [20.3, 111.3] *P* = 0.005	25.0 [-41.0, 91.0]	74.7 [6.0, 143.4]	30.6 [-26.8, 88.0]	
Difference from UMEC/VI 125/25 μg group [95% CI] [a)]				-8.9 [-77.8, 60.1]	35.2 [-22.7, 93.1]	
Difference from UMEC/VI 62.5/25 μg group [95% CI] [a)]			44.4 [-21.8, 110.6]		38.8 [-18.9, 96.5]	

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with treatment period baseline walking speed, mean baseline walking speed, treatment period, dose group, visit, smoking status, center group, interaction between visit and treatment period baseline walking speed, interaction between visit and mean baseline walking speed, and interaction between visit and dose group as fixed effects and the subject as a random effect on the hypothesis of unstructured covariance structure in the subjects in each treatment period

b) Multiplicity of the test was adjusted by the step-down method in which pairwise comparisons between the UMEC/VI 125/25 μg group and the placebo group in terms of 3 hours post-dose EET at Week 12 ([a]), between the UMEC/VI 125/25 μg group and the placebo group in terms of a change from baseline in trough FEV_1 (L) at Week 12 ([b]), between the UMEC/VI 62.5/25 μg group and the placebo group in terms of (a), and between the UMEC/VI 62.5/25 μg group and the placebo group in terms of (b) were stratified in this order.

Table 38 shows the results on the other co-primary endpoint, a change from baseline in trough FEV_1[49] at Week 12. Statistically significant differences were observed in pairwise comparisons between the UMEC/VI 62.5/25 μg group and the placebo group and between the UMEC/VI 125/25 μg group and the placebo group.

[49] Trough FEV_1 at Week 12 (Day 85) was defined as the measured FEV_1 value at 24 hours after dosing on Day 84.

Table 38. Change from baseline in trough FEV_1 (L) at Week 12 (ITT population, OC)

	UMEC/VI 62.5/25 μg group	UMEC/VI 125/25 μg group	UMEC 62.5 μg group	UMEC 125 μg group	VI 25 μg group	Placebo group
Treatment period baseline	1.319 ± 0.396 (130)	1.283 ± 0.396 (128)	1.358 ± 0.401 (40)	1.156 ± 0.386 (41)	1.455 ± 0.493 (64)	1.321 ± 0.434 (150)
Week 12	1.525 ± 0.450 (117)	1.533 ± 0.458 (112)	1.481 ± 0.416 (38)	1.405 ± 0.447 (33)	1.503 ± 0.490 (56)	1.260 ± 0.416 (119)
Change	0.211 ± 0.220 (117)	0.232 ± 0.223 (112)	0.120 ± 0.216 (38)	0.273 ± 0.228 (33)	0.043 ± 0.182 (56)	-0.083 ± 0.161 (119)
Difference from placebo group [95% CI] [a)] *P*-value [a), b)]	0.243 [0.202, 0.284] *P* < 0.001	0.261 [0.220, 0.303] *P* < 0.001	0.144 [0.086, 0.203]	0.255 [0.193, 0.318]	0.112 [0.061, 0.163]	
Difference from UMEC/VI 125/25 μg group [95% CI] [a)]				0.006 [-0.055, 0.067]	0.150 [0.098, 0.201]	
Difference from UMEC/VI 62.5/25 μg group [95% CI] [a)]			0.099 [0.041, 0.157]		0.132 [0.081, 0.183]	

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with treatment period baseline value, mean baseline value, treatment period, dose group, visit, smoking status, center group, interaction between visit and treatment period baseline value, interaction between visit and mean baseline value, and interaction between visit and dose group as fixed effects and the subject as a random effect on the hypothesis of unstructured covariance structure in the subjects in each treatment period

b) As defined in Table 37

Adverse events occurred in 44% (57 of 130 subjects) in the UMEC/VI 62.5/25 μg group, 41% (52 of 128 subjects) in the UMEC/VI 125/25 μg group, 30% (12 of 40 subjects) in the UMEC 62.5 μg group, 54% (22 of 41 subjects) in the UMEC 125 μg group, 36% (23 of 64 subjects) in the VI 25 μg group, and 39% (59 of 151 subjects) in the placebo group. Table 39 shows the major adverse events.

Death was reported in 1 subject assigned to the UMEC 62.5 μg group for Period 1 and UMEC/VI 62.5/25 μg group for Period 2. In this subject, lung neoplasm malignant and metastases to the central nervous system occurred during Period 2, but a causal relationship to the study drug was ruled out for the death. Serious adverse events occurred in 2% (3 of 130 subjects) in the UMEC/VI 62.5/25 μg group, 4% (5 of 128 subjects) in the UMEC/VI 125/25 μg group, 3% (1 of 40 subjects) in the UMEC 62.5 μg group, 2% (1 of 41 subjects) in the UMEC 125 μg group, 3% (2 of 64 subjects) in the VI 25 μg group, and 3% (4 of 151 subjects) in the placebo group. Events reported by ≥2 subjects in any treatment group included chronic obstructive pulmonary disease (2% [2 of 128 subjects] in the UMEC/VI 125/25 μg group, <1% [1 of 151 subjects] in the placebo group). Leukocytoclastic vasculitis reported by 1 subject in the VI 25 μg group was assessed as causally related to the study drug.

Adverse events leading to discontinuation of the study occurred in 4% (5 of 130 subjects) in the UMEC/VI 62.5/25 μg group, 4% (5 of 128 subjects) in the UMEC/VI 125/25 μg group, 3% (1 of 40 subjects) in the UMEC 62.5 μg group, 2% (1 of 41 subjects) in the UMEC 125 μg group, 6% (4 of 64 subjects) in the VI 25 μg group, and 5% (8 of 151 subjects) in the placebo group.

Adverse drug reactions occurred in 6% (8 of 130 subjects) in the UMEC/VI 62.5/25 μg group, 5% (7 of 128 subjects) in the UMEC/VI 125/25 μg group, 2% (1 of 41 subjects) in the UMEC 125 μg group, 2% (1 of 64 subjects) in the VI 25 μg group, and 5% (7 of 151 subjects) in the placebo group.

Table 39. Adverse events reported by ≥3% of subjects in any group (ITT population)

	UMEC/VI 62.5/25 µg group (N = 130)	UMEC/VI 125/25 µg group (N = 128)	UMEC 62.5 µg group (N = 40)	UMEC 125 µg group (N = 41)	VI 25 µg group (N = 64)	Placebo group (N = 151)
Nasopharyngitis	8 (6)	2 (2)	4 (10)	4 (10)	1 (2)	10 (7)
Headache	3 (2)	6 (5)	1 (3)	4 (10)	1 (2)	8 (5)
Cough	2 (2)	5 (4)	0	1 (2)	2 (3)	3 (2)
Arthralgia	6 (5)	0	1 (3)	1 (2)	0	2 (1)
Back pain	0	2 (2)	0	1 (2)	2 (3)	5 (3)
Sinusitis	2 (2)	0	0	2 (5)	3 (5)	3 (2)
Dyspnoea	0	1 (<1)	0	1 (2)	1 (2)	6 (4)
Upper respiratory tract infection	3 (2)	3 (2)	0	0	2 (3)	1 (<1)
Musculoskeletal pain	0	1 (<1)	0	1 (2)	2 (3)	0
Rhinitis	1 (<1)	1 (<1)	1 (3)	0	0	1 (<1)
Toothache	1 (<1)	0	0	2 (5)	0	1 (<1)
Osteoarthritis	0	0	1 (3)	0	0	2 (1)
Deep vein thrombosis	0	0	1 (3)	1 (2)	0	0
Dermatitis	0	0	1 (3)	0	1 (2)	0
Neutrophil count increased	0	1 (<1)	1 (3)	0	0	0
Oedema peripheral	0	0	1 (3)	0	1 (2)	0
White blood cell count increased	0	1 (<1)	1 (3)	0	0	0
Cataract operation	0	0	1 (3)	0	0	0
Constipation	0	0	1 (3)	0	0	0
Dehydration	0	0	1 (3)	0	0	0
Diverticulitis	0	0	1 (3)	0	0	0
Genital herpes	0	0	1 (3)	0	0	0
Migraine	0	0	1 (3)	0	0	0
Pulmonary embolism	0	0	1 (3)	0	0	0

Number of subjects (%)

4.(iii).A.(3).7) Japanese long-term treatment study (5.3.5.2, Study DB2115362 [August 2011 to December 2012])

An open-label, uncontrolled study was conducted to investigate the safety and tolerability of UMEC/VI in Japanese COPD patients[50] (target sample size, 120).

UMEC/VI 125/25 µg was administered once daily in the morning by inhalation. The treatment period was 52 weeks. Subjects were allowed to use ICS concomitantly at a constant dose unless they received a new ICS therapy during the treatment period (from Visit 2 to the end of the evaluation at Visit 8).

Of the 131 treated subjects,[51] 1 subject who did not comply with the GCP[52] was excluded, and the remaining 130 subjects were included in the ITT population, which was also included in the safety analysis set.

Discontinuation of the study occurred in 14% (18 of 130 subjects) and the main reason for discontinuation was adverse events (10% [13 of 130 subjects]).

[50] Patients who have been diagnosed with COPD in accordance with Guidelines for the Diagnosis and Treatment of COPD in Japan (Committee for the Third Edition of the COPD Guidelines of the Japanese Respiratory Society, 2009), and patients who meet the following criteria: (a) who have a smoking history of ≥10 pack-years; (b) in whom the FEV_1/FVC ratio following administration of a bronchodilator is <0.7, and the FEV_1 following administration of a bronchodilator is <80% of the predicted value; (c) who have no comorbidities causing another air flow obstruction; and (d) who are Japanese aged ≥40 years.

[51] Subjects who meet the inclusion criteria at the start of the study treatment; i.e., neither aggravation of COPD nor lower respiratory tract infection is observed during the run-in period or at Visit 2 (at the start of the treatment period).

[52] The subject discontinued the clinical study due to non-compliance to the GCP in which a physician without the study contract saw the subject at the scheduled visit (Visit 3).

Adverse events occurred in 87% of the subjects (113 of 130 subjects). Table 40 shows the major adverse events.

Deaths were reported in 3 subjects (malignant ascites/metastases to spine/metastases to pelvis, chronic obstructive pulmonary disease, and sudden death in 1 subject each), but a causal relationship to the study drug was ruled out for all the deaths. Serious adverse events occurred in 13% of subjects (17 of 130 subjects). Events reported by ≥2 subjects included chronic obstructive pulmonary disease (4%, 5 of 130 subjects) and pneumonia (3%, 4 of 130 subjects). A causal relationship to the study drug was ruled out for all the serious adverse events.

Adverse events leading to discontinuation of the study occurred in 10% of the subjects (13 of 130 subjects).

Adverse drug reactions occurred in 6% of the subjects (8 of 130 subjects).

Table 40. Adverse events reported by ≥3% of subjects (ITT population, N = 130)

Nasopharyngitis	50 (38)
Bronchitis	13 (10)
Pharyngitis	9 (7)
Constipation	7 (5)
Pneumonia	6 (5)
Upper respiratory tract inflammation	6 (5)
Chronic obstructive pulmonary disease	5 (4)
Hypertension	5 (4)
Gastrooesophageal reflux disease	4 (3)
Muscle spasms	4 (3)
Cataract	4 (3)

Number of subjects (%)

In terms of the other endpoint, changes from baseline in trough FEV_1 at Weeks 12, 24, 36, and 52 (mean ± SD [number of subjects]) were 0.082 ± 0.157 (127), 0.087 ± 0.175 (122), 0.082 ± 0.168 (116), and 0.046 ± 0.189 (112) L, respectively.

4.(iii).A.(3).8) Foreign phase III study (5.3.5.1, Study DB2113359 [January 2011 to July 2012])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted to investigate the safety and tolerability of UMEC/VI in foreign COPD patients[53] (target sample size, 500 [200 subjects per group, 100 subjects in the placebo group]) in 6 countries in the US, Chile, Romania, Russia, Slovakia, and South Africa.

UMEC/VI 125/25 μg, UMEC 125 μg, or placebo was administered once daily in the morning by inhalation. The treatment period was 52 weeks. The subjects who had been receiving ICS treatment at a constant dose equivalent to ≤1000 μg of FP for ≥30 days until the screening (Visit 1) were allowed to use the drug concomitantly during the study period.

Of 563 randomized[54] subjects, 562 who received the study drug (226 subjects in the UMEC/VI

[53] Patients who have been diagnosed with COPD in accordance with the Standards for the Diagnosis and Management of Patients with COPD issued by the ATS/European Respiratory Society and who meet the following criteria: (a) who currently smoke or smoked in the past, having a smoking history of ≥10 pack-years; (b) in whom the FEV_1/FVC ratio following administration of a bronchodilator is <0.7, and the FEV_1 following administration of a bronchodilator is between 35% and 80% of the FEV_1 predicted value according to the standard formula of the NHANES III at Visit 1 (screening); and (c) who are aged ≥40 years.

[54] Subjects who meet the inclusion criteria for randomization; i.e., neither aggravation of COPD nor lower respiratory tract infection is observed during the run-in period or at Visit 2 (at the start of the treatment period).

125/25 μg group, 227 subjects in the UMEC 125 μg group, 109 subjects in the placebo group) were included in the ITT population, which was also included in the safety analysis set.

Discontinuation of the study occurred in 37% (83 of 226 subjects) in the UMEC/VI 125/25 μg group, 41% (94 of 227 subjects) in the UMEC 125 μg group, 39% (43 of 109 subjects) in the placebo group. The main reason for discontinuation was violation against the discontinuation criteria (16% [36 of 226 subjects] in the UMEC/VI 125/25 μg group, 16% [37 of 227 subjects] in the UMEC 125 μg group, 7% [8 of 109 subjects] in the placebo group).

Table 41 shows changes in trough FEV_1 over time.

Table 41. Trough FEV_1 (L) (ITT population, OC)

	UMEC/VI 125/25 μg group (N = 226)	UMEC 125 μg group (N = 227)	Placebo group (N = 109)
Baseline	1.506 ± 0.551 (225)	1.445 ± 0.495 (225)	1.557 ± 0.575 (109)
Week 4	1.678 ± 0.554 (216)	1.598 ± 0.541 (215)	1.551 ± 0.597 (103)
Week 13	1.694 ± 0.570 (208)	1.598 ± 0.575 (197)	1.551 ± 0.622 (90)
Week 26	1.674 ± 0.577 (178)	1.600 ± 0.590 (164)	1.609 ± 0.650 (79)
Week 39	1.679 ± 0.583 (153)	1.537 ± 0.569 (143)	1.531 ± 0.608 (71)
Week 52	1.683 ± 0.598 (143)	1.563 ± 0.560 (133)	1.540 ± 0.609 (66)

Mean ± SD (number of subjects)

Adverse events occurred in 53% (120 of 226 subjects) in the UMEC/VI 125/25 μg group, 58% (132 of 227 subjects) in the UMEC 125 μg group, and 52% (57 of 109 subjects) in the placebo group. Table 42 shows the major adverse events.

Deaths occurred in 2 subjects (metastases to spine and pneumonia in 1 subject each) in the UMEC 125 μg group during the treatment period, 2 subjects (cardiac failure acute and metastases to liver in 1 subject each) in the UMEC 125 μg group during the follow-up period, and 1 subject (coronary artery insufficiency) in the placebo group during the follow-up period, but a causal relationship to the study drug was ruled out for all the deaths. Serious adverse events occurred in 6% (14 of 226 subjects) in the UMEC/VI 125/25 μg group, 7% (17 of 227 subjects) in the UMEC 125 μg group, and 6% (7 of 109 subjects) in the placebo group. Events reported by ≥2 subjects in any treatment group included chronic obstructive pulmonary disease (<1% [2 of 226 subjects] in the UMEC/VI 125/25 μg group, 2% [4 of 227 subjects] in the UMEC 125 μg group, 3% [3 of 109 subjects] in the placebo group), coronary artery disease (<1% [2 of 226 subjects] in the UMEC/VI 125/25 μg group, <1% [1 of 227 subjects] in the UMEC 125 μg group, <1% [1 of 109 subjects] in the placebo group), pneumonia (1% [3 of 227 subjects] in the UMEC 125 μg group), and urinary tract infection (<1% [2 of 227 subjects] in the UMEC 125 μg group). Of the serious adverse events, rhythm idioventricular (1 subject) in the UMEC 125 μg group was assessed as causally related to the study drug.

Adverse events leading to discontinuation of the study occurred in 8% (17 of 226 subjects) in the UMEC/VI 125/25 μg group, 9% (20 of 227 subjects) in the UMEC 125 μg group, and 11% (12 of 109 subjects) in the placebo group.

Adverse drug reactions occurred in 12% (26 of 226 subjects) in the UMEC/VI 125/25 μg group, 12% (28 of 227 subjects) in the UMEC 125 μg group, and 13% (14 of 109 subjects) in the placebo group.

Table 42. Adverse events reported by ≥3% of subjects in any group (ITT population)

	UMEC/VI 125/25 μg group (N = 226)	UMEC 125 μg group (N = 227)	Placebo group (N = 109)
Headache	20 (9)	25 (11)	9 (8)
Nasopharyngitis	11 (5)	20 (9)	5 (5)
Ventricular extrasystoles	11 (5)	12 (5)	5 (5)
Extrasystoles	10 (4)	10 (4)	4 (4)
Back pain	10 (4)	9 (4)	3 (3)
Hypertension	8 (4)	4 (2)	5 (5)
Sinusitis	8 (4)	6 (3)	3 (3)
Influenza	6 (3)	5 (2)	5 (5)
Cough	6 (3)	6 (3)	1 (<1)
Upper respiratory tract infection	2 (<1)	8 (4)	3 (3)
Chronic obstructive pulmonary disease	3 (1)	6 (3)	3 (3)
Ventricular tachycardia	4 (2)	3 (1)	4 (4)
Supraventricular tachycardia	2 (<1)	6 (3)	1 (<1)
Supraventricular extrasystoles	1 (<1)	6 (3)	1 (<1)
Sinus tachycardia	0	6 (3)	1 (<1)
Dyspnoea	3 (1)	0	3 (3)
Pneumonia	0	6 (3)	0

Number of subjects (%)

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

4.(iii).B.(1) Dosage regimen in phase III studies

4.(iii).B.(1).1) Dosage regimen of UMEC

The applicant explained the rationale of the dosage regimen of UMEC used in phase III studies as follows:

In a foreign phase II study (Study AC4115321), UMEC was administered once daily at a dose of 15.6 to 125 μg or twice daily at a dose of 15.6 to 31.25 μg. In another foreign phase II study (Study AC4113073), UMEC was administered once daily at a dose of 62.5 to 1000 μg or twice daily at a dose of 62.5 to 250 μg. Table 15 and Table 13 show the results on the primary efficacy endpoint, trough FEV_1, in these studies. A statistically significant difference was observed in comparison of any UMEC group with the placebo group. The trough FEV_1 following the twice-daily regimens did not largely exceed that following the once-daily regimens as long as the daily dose was the same [see 4.(iii).A "Summary of the submitted data"]. Table 43 shows the 0 to 24 hours post-dose weighted mean FEV_1 over time on Day 7 or Day 14, the secondary endpoint. The improved pulmonary function in once-daily regimen groups continued for 24 hours in comparison with the placebo group, and the benefit of the twice-daily regimen did not exceed that of the once-daily regimen.

Table 43. Changes from baseline in weighted mean FEV_1 (L) over 0 to 24 hours post-dose on Day 7 (Study AC4115321, upper) and on Day 14 (Study AC4113073, lower) (mITT population, OC)

	UMEC 15.6 μg QD group	UMEC 31.25 μg QD group	UMEC 62.5 μg QD group	UMEC 125 μg QD group	UMEC 15.6 μg BD group	UMEC 31.25 μg BD group	TIO group	Placebo group		
Day 7	1.427 ± 0.576 (56)	1.441 ± 0.576 (51)	1.400 ± 0.566 (54)	1.529 ± 0.570 (56)	1.510 ± 0.560 (52)	1.462 ± 0.470 (55)	1.474 ± 0.469 (53)	1.350 ± 0.507 (54)		
Change	0.041 ± 0.139 (56)	0.071 ± 0.245 (51)	0.066 ± 0.164 (54)	0.101 ± 0.183 (56)	0.077 ± 0.208 (52)	0.063 ± 0.155 (55)	0.061 ± 0.210 (53)	-0.090 ± 0.158 (54)		
Difference from placebo group [95% CI][a)]	0.116 [0.072, 0.160]	0.118 [0.073, 0.163]	0.132 [0.087, 0.178]	0.173 [0.129, 0.217]	0.136 [0.091, 0.181]	0.142 [0.098, 0.186]	0.157 [0.113, 0.202]			
	UMEC 62.5 μg QD group	UMEC 125 μg QD group	UMEC 250 μg QD group	UMEC 500 μg QD group	UMEC 1000 μg QD group	UMEC 62.5 μg BD group	UMEC 125 μg BD group	UMEC 250 μg BD group	TIO group	Placebo group
Day 14	1.579 ± 0.563 (33)	1.514 ± 0.511 (33)	1.509 ± 0.437 (34)	1.528 ± 0.461 (36)	1.485 ± 0.431 (29)	1.604 ± 0.474 (30)	1.486 ± 0.415 (32)	1.600 ± 0.534 (31)	1.446 ± 0.521 (33)	1.376 ± 0.459 (143)
Change	0.083 ± 0.210 (33)	0.122 ± 0.215 (33)	0.126 ± 0.219 (34)	0.035 ± 0.240 (36)	0.086 ± 0.230 (29)	0.077 ± 0.227 (30)	0.107 ± 0.272 (32)	0.091 ± 0.260 (31)	0.050 ± 0.177 (33)	-0.087 ± 0.215 (143)
Difference from placebo group [95% CI] [a)]	0.143 [0.093, 0.194]	0.136 [0.085, 0.187]	0.136 [0.086, 0.186]	0.131 [0.083, 0.179]	0.138 [0.085, 0.192]	0.120 [0.068, 0.173]	0.142 [0.090, 0.193]	0.133 [0.081, 0.185]	0.127 [0.078, 0.177]	

Mean ± SD (number of subjects)

a) Mixed model with baseline value of the treatment period, mean baseline value, dose group, and treatment period as fixed effects and subject as a random effect

Table 15 and Table 43 show the results on the primary efficacy endpoint, a change from baseline in trough FEV_1 at Day 8, and the secondary endpoint, weighted mean FEV_1 over 0 to 24 hours post-dose on Day 7, in Study AC4115321. The improvements following the once-daily administration of UMEC at doses of 15.6 μg and 31.25 μg were smaller than those at doses of ≥62.5 μg.

In Study AC4113073, statistically significant differences were observed in all of the once-daily UMEC groups at 62.5 to 1000 μg in comparison with the placebo group in terms of the primary efficacy endpoint, a change from baseline in trough FEV_1 at Day 15, and the secondary endpoint, weighted mean FEV_1 over 0 to 24 hours post-dose on Day 14. The improvements in the UMEC 62.5 μg and 125 μg groups were almost comparable to those in the UMEC ≥250 μg groups (Table 13, Table 43), but in the UMEC ≥250 μg groups, the incidences of adverse events such as cough and headache increased.

In a foreign phase II study (Study AC4113589) in which UMEC was administered once daily at doses of 125 to 500 μg, statistically significant differences were observed in all of the dose groups in comparison with the placebo group in terms of the primary efficacy endpoint, a change from baseline in trough FEV_1 at Day 29 (Table 17), and the secondary endpoint, weighted mean FEV_1 over 0 to 6 hours post-dose on Day 28, but no clear dose-response relationship was observed. The incidences of adverse events of cough and headache increased dose-dependently.

Based on the above results, the dosage regimens of UMEC for phase III studies were chosen to be at 62.5 μg and 125 μg administered once daily.

PMDA considers it acceptable for the applicant to have selected the once-daily regimen for UMEC at doses of 62.5 μg and 125 μg in phase III studies based on the results from foreign late phase II studies (Studies AC4115321, AC4113073, and AC4113589).

4.(iii).B.(1).2) Dosage regimen of VI

The applicant explained the rationale of the dosage regimen of VI used in phase III studies as follows:

In Study HZA113310 of VI in asthma patients, the benefit observed with the twice-daily regimen did not exceed that with the once-daily regimen (see Review Report for Relvar) as long as the daily dose was the same. In consideration of the finding, it was considered acceptable to set the once-daily regimen for VI in clinical studies in COPD patients.

In a foreign phase II study (Study B2C111045), VI at 3 to 50 μg was administered once daily to COPD patients. As shown in Table 22, statistically significant differences were observed in any of the dose groups at 3 to 50 μg in comparison with the placebo group in terms of the primary efficacy endpoint, trough FEV_1 at Day 29, but the clinically significant differences in the endpoint from the placebo group of ≥100 mL were observed only at the doses of ≥12.5 μg. As shown in Table 44, large improvements were observed in the VI 25 μg and 50 μg groups in comparison with the VI ≤12.5 μg groups in terms of the secondary endpoint, weighted mean FEV_1 over 0 to 24 hours post-dose on Day 28. The dose of 25 μg of VI was thus considered appropriate as the recommended dose. Additionally, in Study B2C109575 in which VI at 3 to 50 μg was administered once daily to asthma patients, a dose-response relationship similar to that in COPD patients was also observed, leading to determination of the recommended dose of VI at 25 μg (see Review Report for Relvar). Responsiveness to bronchodilation effects of β-agonists in asthma patients is generally higher than that in COPD patients. In consideration of the above findings, the results of Study B2C109575 was also considered to suggest appropriateness of setting the recommended dose of 25 μg of VI in COPD patients.

Based on the above results, the dosage regimen of VI for phase III studies was chosen to be at 25 μg administered once daily.

Table 44. Weighted mean FEV_1 (L) over 0 to 24 hours on Day 28 in foreign Study B2C111045

	VI 3 μg group	VI 6.25μg group	VI 12.5 μg group	VI 25 μg group	VI 50 μg group	Placebo group
Day 28	1.430 ± 0.500 (88)	1.378 ± 0.447 (91)	1.362 ± 0.471 (92)	1.364 ± 0.541 (92)	1.507 ± 0.488 (91)	1.308 ± 0.461 (84)
Change	0.120 ± 0.162 (88)	0.132 ± 0.173 (91)	0.145 ± 0.204 (92)	0.174 ± 0.176 (92)	0.187 ± 0.205 (91)	0.016 ± 0.181 (84)
Difference from placebo group [a)] [95% CI]	0.105 [0.052, 0.157]	0.125 [0.073, 0.177]	0.142 [0.090, 0.194]	0.158 [0.106, 0.210]	0.177 [0.125, 0.229]	

Mean ± SD (number of subjects)

a) Mixed model for repeated measures with the baseline value, dose group, sex, age, smoking status, stratum of the reversibility (cut-off values of 12% and 200 mL change in FEV_1 before and after salbutamol inhalation), visit, interaction between visit and dose group, and interaction between visit and baseline value as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

PMDA has concluded that, although the dosing regimen of VI has not been investigated in COPD patients except for the once-daily regimen, it is acceptable that the applicant selected the once-daily regimen for VI in phase III studies because an improvement in the trough FEV_1 value in any of the VI groups exceeded that in the placebo group in Study B2C111045, in which VI was administered once daily to COPD patients; and the once-daily regimen was convenient for patients when the drug was administered by inhalation. PMDA has also concluded that it is acceptable that the applicant set the dose of VI at 25 μg in phase III studies because the results on the primary and secondary endpoints in Study B2C111045 suggest an improving trend of

respiratory function at the doses of 25 μg and 50 μg exceeding that at the other doses; and the results from a dose-finding study in asthma patients support this conclusion.

4.(iii).B.(2) Efficacy

4.(iii).B.(2).1) Results of the overall population including Japanese in global phase III studies (Studies DB2113361 and DB2113373)

In a global phase III study (Study DB2113361), the efficacy and safety of UMEC/VI 125/25 μg were investigated, and in the other global phase III study (Study DB2113373), the efficacy and safety of UMEC/VI 62.5/25 μg were investigated. In these studies, study discontinuation occurred in 24.9% (371 of 1489 subjects) and 23.1% (354 of 1532 subjects), respectively. PMDA thus investigated the effect of the discontinuation on the results of the overall population based on the results from scheduled sensitivity analysis and from additional analysis separately submitted by the applicant on a request from PMDA.

As shown in Table 45, the results from an analysis in a mixed model for repeated measures (MMRM) without imputation were comparable to those from sensitivity analysis performed by each imputation method for missing data due to discontinuation, demonstrating that the results from the main analysis were robust for the effects of the discontinuation.

Table 45. Difference in trough FEV_1 (L) at Week 24 between UMEC/VI group and the other dose groups in Studies DB2113361 and DB2113373

Imputation method	Dose group	Study DB2113361		Study DB2113373	
		No. of subjects UMEC/VI group/control group	Difference from UMEC/VI group [95% CI]	No. of subjects UMEC/VI group/control group	Difference from UMEC/VI group [95% CI]
MMRM [a] (main analysis, without imputation)	Placebo group	323/182	0.238 [0.200, 0.276]	330/201	0.167 [0.128, 0.207]
	UMEC group	323/312	0.079 [0.046, 0.112]	330/322	0.052 [0.017, 0.087]
	VI group	323/299	0.114 [0.081, 0.148]	330/317	0.095 [0.060, 0.130]
ANCOVA [b] (MI: MAR [c])	Placebo group	401/269	0.238 [0.198, 0.277]	411/278	0.165 [0.126, 0.205]
	UMEC group	401/404	0.077 [0.044, 0.111]	411/416	0.051 [0.015, 0.087]
	VI group	401/402	0.114 [0.080, 0.148]	411/419	0.096 [0.062, 0.131]
ANCOVA [b] (MI: CDC [d])	Placebo group	401/269	0.233 [0.194, 0.271]	411/278	0.168 [0.129, 0.206]
	UMEC group	401/404	0.079 [0.045, 0.112]	411/416	0.051 [0.015, 0.087]
	VI group	401/402	0.115 [0.082, 0.149]	411/419	0.094 [0.060, 0.128]
ANCOVA [b] (MI: LMCF [e] [0 mL/year])	Placebo group	401/269	0.230 [0.192, 0.269]	411/278	0.168 [0.130, 0.207]
	UMEC group	401/404	0.079 [0.046, 0.112]	411/416	0.051 [0.016, 0.087]
	VI group	401/402	0.114 [0.080, 0.148]	411/419	0.094 [0.060, 0.128]
ANCOVA [b] (MI: LMCF [e] [25 mL/year])	Placebo group	401/269	0.230 [0.192, 0.268]	411/278	0.168 [0.130, 0.207]
	UMEC group	401/404	0.079 [0.046, 0.112]	411/416	0.051 [0.015, 0.087]
	VI group	401/402	0.114 [0.080, 0.147]	411/419	0.094 [0.060, 0.128]
MMRM [a] (LOCF [f])	Placebo group	401/269	0.234 [0.200, 0.268]	411/278	0.171 [0.134, 0.207]
	UMEC group	401/404	0.083 [0.053, 0.114]	411/416	0.051 [0.019, 0.084]
	VI group	401/402	0.114 [0.083, 0.145]	411/419	0.093 [0.061, 0.126]
MMRM [a] (BOCF [g])	Placebo group	401/269	0.189 [0.158, 0.220]	411/278	0.135 [0.103, 0.166]
	UMEC group	401/404	0.064 [0.036, 0.092]	411/416	0.041 [0.013, 0.070]
	VI group	401/402	0.098 [0.070, 0.125]	411/419	0.071 [0.042, 0.099]
MMRM [a] (WOCF [h])	Placebo group	401/269	0.230 [0.196, 0.263]	411/278	0.175 [0.140, 0.210]
	UMEC group	401/404	0.086 [0.056, 0.116]	411/416	0.055 [0.024, 0.087]
	VI group	401/402	0.114 [0.084, 0.144]	411/419	0.090 [0.059, 0.121]
ANCOVA [b] (reason for discontinuation considered [i])	Placebo group	401/269	0.225 [0.194, 0.256]	411/278	0.159 [0.128, 0.190]
	UMEC group	401/404	0.079 [0.051, 0.106]	411/416	0.041 [0.013, 0.069]
	VI group	401/402	0.104 [0.078, 0.131]	411/419	0.096 [0.068, 0.124]

MI: Multiple Imputation

a) MMRM with the baseline value, dose group, smoking status, center group, day of administration, interaction between day of administration and the baseline value and interaction between day of administration and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

b) Analysis of the covariance model with the baseline value, dose group, smoking status, and center group as explanatory variables

c) On the hypothesis of random discontinuation (Missing At Random) that occurs only depending on the measured data (patient demographic characteristic, baseline value, dose group, FEV_1 over time to discontinuation) but not on unmeasured FEV_1 over time after the discontinuation

d) On the hypothesis that discontinuation occurs depending on unmeasured FEV_1 over time after the discontinuation, and that the FEV_1 over time after the discontinuation is comparable to that in the placebo group (Copy Differences from Control)

e) On the hypothesis that discontinuation occurs depending on unmeasured FEV_1 over time after the discontinuation, and that the reduction rate in FEV_1 after the discontinuation is constant (0 or 25 mL/year) (Last Mean Carried Forward)

f) Imputation using the FEV_1 value at the last time point (Last Observation Carried Forward)

g) Imputation using the FEV_1 value at baseline (Baseline Observation Carried Forward)

h) Imputation using the worst FEV_1 value measured (Worst Observation Carried Forward)

i) For the subjects who discontinued the study due to COPD aggravation, imputation using the mean trough FEV1 at Week 24 in the placebo group on the assumption that the discontinuation occurs depending on unmeasured FEV1 over time after the discontinuation; for the subjects who discontinued due to other reasons, MI was applied on the assumption of MAR

PMDA has concluded that, in consideration of the results from the main analysis and the above investigations, the efficacy of UMEC/VI against COPD is demonstrated because the results on the primary efficacy endpoint, a change from baseline in trough FEV_1, in both Studies DB2113361 and DB2113373 show superiority of UMEC/VI and both single agents of UMEC and VI to placebo in the overall population as well as superiority of UMEC/VI to each single agent, which is essential to the efficacy evaluation of a combination drug.

4.(iii).B.(2).2) Results in Japanese subpopulation

Results in the Japanese subpopulation in global phase III studies (Studies DB2113361 and DB2113373) are shown in Table 46. In terms of the primary efficacy endpoint, a change from baseline in trough FEV_1 at Week 24, a trend observed in comparison between the VI group and

the UMEC/VI group was similar to that in the overall population. However, in pairwise comparison between the UMEC group and the UMEC/VI group in the Japanese subpopulation, the drug effect in the UMEC/VI group did not tend to exceed that in the UMEC group in either study, indicating that the results in the overall population were not consistent with those in the Japanese subpopulation. In terms of the profile of a change from baseline in trough FEV_1 over time and the secondary endpoint, a change from baseline in weighted mean FEV_1 over 0 to 6 hours post-dose on Week 24, the results in the overall population were not consistent with those in the Japanese subpopulation.

In principle, the efficacy evaluation in a global study is based on the results in the overall population. Figures 3 and 4 show the forest plots of differences in change from baseline in trough FEV_1 at Week 24 between groups in Studies DB2113361 and DB2113373 by country. The results varied in each subpopulation, and although the results in the Japanese subpopulation were not largely different from those in the other subpopulation, the results in the Japanese subpopulation were inconsistent with those in the overall population. PMDA investigated as described in (a) to (d) below, in order to explore the cause of the above findings and to confirm the efficacy of UMEC/VI in Japanese COPD patients based on the application documents and results from additional analysis separately submitted by the applicant on a request from PMDA.

Table 46. Trough FEV_1 (L) at Week 24 in the overall population and Japanese subpopulation in Studies DB2113361 and DB2113373

	Study DB2113361			Study DB2113373		
	UMEC/VI 125/25 μg group	UMEC 125 μg group	VI 25 μg group	UMEC/VI 62.5/25 μg group	UMEC 62.5 μg group	VI 25 μg group
Overall population						
Difference from placebo group [95% CI], *P*-value [a)]	0.238 [0.200, 0.276] *P* < 0.001	0.160 [0.122, 0.198] *P* < 0.001	0.124 [0.086, 0.162] *P* < 0.001	0.167 [0.128, 0.207] *P* < 0.001	0.115 [0.076, 0.155] *P* < 0.001	0.072 [0.032, 0.112] *P* < 0.001
Difference from UMEC/VI group [95% CI], *P*-value [a)]		0.079 [0.046, 0.112] *P* < 0.001	0.114 [0.081, 0.148] *P* < 0.001		0.052 [0.017, 0.087] *P* = 0.004	0.095 [0.060, 0.130] *P* < 0.001
Japanese subpopulation						
Difference from placebo group [95% CI] [a)]	0.174 [-0.008, 0.356]	0.188 [0.009, 0.366]	0.131 [-0.053, 0.315]	0.201 [0.013, 0.388]	0.215 [0.018, 0.412]	0.114 [-0.076, 0.303]
Difference from UMEC/VI group [95% CI] [a)]		-0.014 [-0.160, 0.131]	0.043 [-0.109, 0.195]		-0.014 [-0.177, 0.149]	0.087 [-0.067, 0.241]

a) MMRM with the baseline value, dose group, smoking status, center group, day of administration, interaction between day of administration and the baseline value, and interaction between day of administration and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

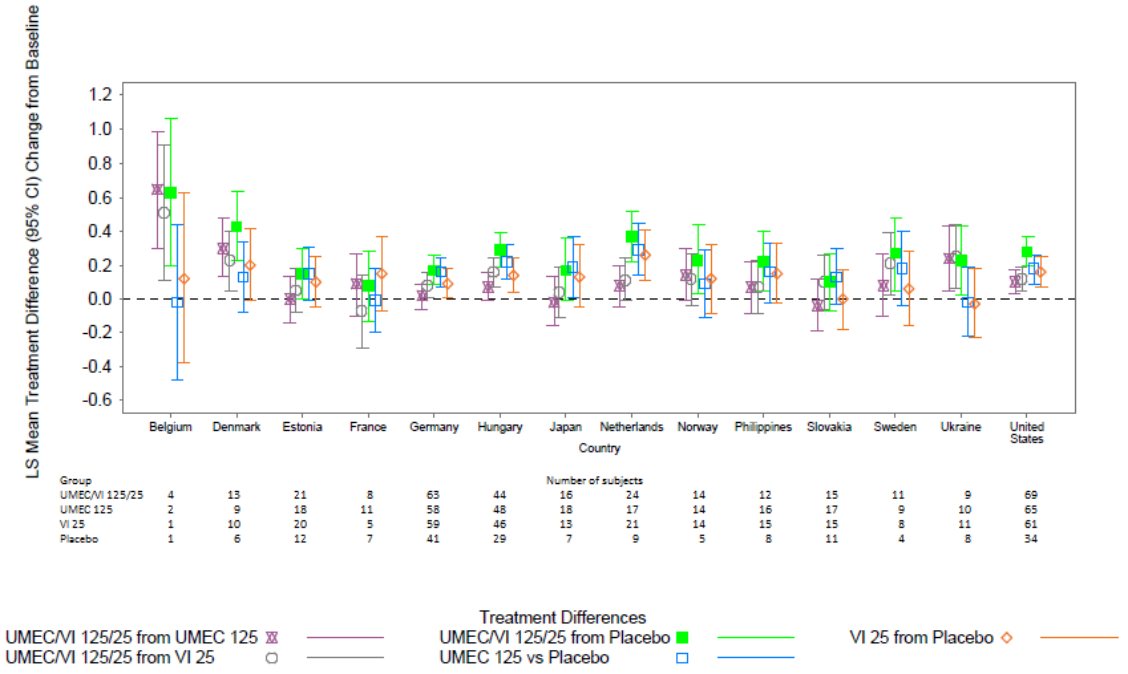

Figure 3. Change from baseline in trough FEV_1 in Study DB2113361 by country (adjusted mean, 95% CI)

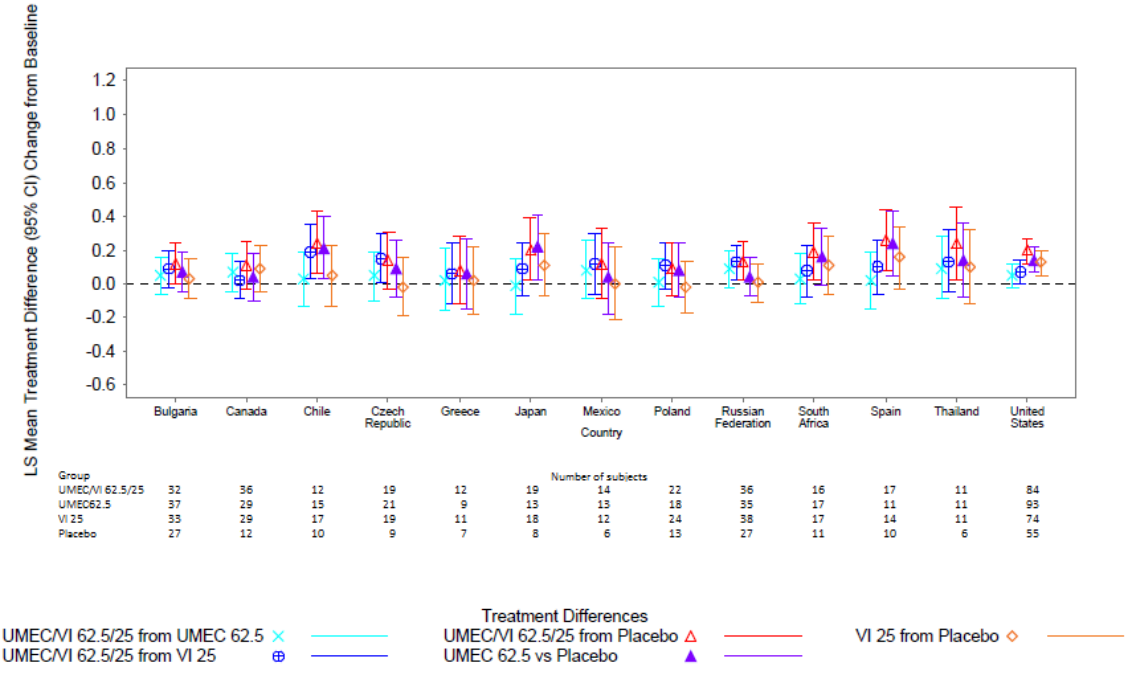

Figure 4. Change from baseline in trough FEV_1 in Study DB2113373 by country (adjusted mean, 95% CI)

(a) Patient demographic characteristics of the overall population and Japanese subpopulation

The patient demographic characteristics were compared between the Japanese subpopulation and overall population in Studies DB2113361 and DB2113373. As shown in Table 47, the Japanese subpopulation in both studies was characterized by, in comparison with the overall population,

older age, higher percentage of males, lower height and body weight, lower FEV_1 before salbutamol inhalation, higher percentage of the patients at Stage II and lower percentage of the patients at Stage III according to the severity classification of the GOLD, and higher percentage of former smokers and lower percentage of current smokers. As shown in Table 48, however, there were no trends indicating interactions between any of these patient demographic characteristics above and the dose group in the overall population of either Study DB2113361 or DB2113373. Subpopulation analysis in either study did not show any clear differences in the efficacy among the subpopulations. It is therefore unlikely that the differences in patient demographic characteristics between the overall population and Japanese subpopulation affected the results on the efficacy in Japanese subpopulation.

Table 47. Patient demographic characteristics in the overall population and Japanese subpopulation

	Study DB2113361		Study DB2113373	
	Japanese	Overall	Japanese	Overall
Age	70.2 ± 7.0 (74)	62.9 ± 8.5 (1489)	67.4 ± 7.4 (68)	63.1 ± 8.9 (1532)
Sex				
Males	95 (70)	65 (974)	93 (63)	71 (1083)
Females	5 (4)	35 (515)	7 (5)	29 (449)
Height	162.4 ± 6.3 (74)	169.7 ± 9.0 (1489)	165.6 ± 7.5 (68)	168.4 ± 9.4 (1532)
Body weight	57.6 ± 10.7 (74)	77.1 ± 18.9 (1488)	59.3 ± 11.8 (68)	76.4 ± 19.1 (1531)
GOLD classification				
Stage II	61 (45)	47 (699)	56 (38)	46 (708)
Stage III	32 (24)	45 (660)	34 (23)	43 (650)
Stage IV	7 (5)	8 (124)	10 (7)	11 (171)
Smoking status				
Current smokers	26 (19)	52 (769)	40 (27)	50 (759)
Former smokers	74 (55)	48 (720)	60 (41)	50 (773)
FEV_1 before salbutamol inhalation	0.965 ± 0.314 (74)	1.283 ± 0.484 (1485)	1.070 ± 0.393 (67)	1.233 ± 0.488 (1530)

Mean ± SD (number of subjects) or % (number of subjects)

Table 48. Trough FEV_1 (L) at Week 24 by subpopulation analysis based on the MMRM [a)] by patient demographic characteristic

Demographic characteristics		Study DB2113361			Study DB2113373		
		No. of subjects UMEC/VI group/UMEC group	Difference between UMEC/VI 125/25 μg group and UMEC 125 μg group [95% CI]	*P* value of interaction between each demographic characteristic and dose group	No. of subjects UMEC/VI group/UMEC group	Difference between UMEC/VI 62.5/25 μg group and UMEC 62.5 μg group [95% CI]	*P* value of interaction between each demographic characteristic and dose group
Age	<65 years	167/181	0.088 [0.043, 0.133]	*P* = 0.905	176/171	0.035 [-0.013, 0.082]	*P* = 0.162
	≥65 years and <75 years	135/109	0.060 [0.007, 0.114]		124/116	0.087 [0.029, 0.144]	
	≥75 years and <85 years	21/21	0.097 [-0.027, 0.221]		29/33	0.040 [-0.071, 0.150]	
Sex	Males	213/211	0.092 [0.051, 0.132]	*P* = 0.415	243/224	0.039 [-0.002, 0.080]	*P* = 0.334
	Females	110/101	0.053 [-0.004, 0.109]		87/98	0.083 [0.017, 0.149]	
Height	≤ Median [b)]	174/163	0.054 [0.010, 0.099]	*P* = 0.021	161/172	0.045 [-0.004, 0.094]	*P* = 0.721
	> Median [b)]	149/149	0.106 [0.058, 0.154]		169/150	0.059 [0.009, 0.109]	
Body weight	≤ Median [c)]	160/155	0.050 [0.003, 0.096]	*P* = 0.248	150/168	0.061 [0.011, 0.111]	*P* = 0.603
	> Median [c)]	163/157	0.107 [0.061, 0.154]		180/154	0.042 [-0.007, 0.091]	
GOLD classification	Stage I/II	152/156	0.084 [0.036, 0.131]	*P* = 0.379	164/161	0.014 [-0.036, 0.064]	*P* = 0.064
	Stage III/IV	170/155	0.074 [0.029, 0.120]		165/160	0.092 [0.044, 0.141]	
Smoking status	Current smokers	162/171	0.081 [0.035, 0.126]	*P* = 0.498	167/159	0.049 [-0.001, 0.098]	*P* = 0.967
	Former smokers	161/141	0.077 [0.030, 0.125]		163/163	0.055 [0.005, 0.104]	
Baseline FEV_1	≤ Median [d)]	156/140	0.063 [0.015, 0.111]	*P* = 0.035	157/159	0.075 [0.025, 0.125]	*P* = 0.452
	> Median [d)]	167/172	0.096 [0.050, 0.142]		173/163	0.022 [-0.028, 0.071]	

a) MMRM with the baseline value, dose group, smoking status, region (Japan/outside Japan), day of administration, each demographic characteristic, interaction between day of administration and the baseline value, interaction between day of administration and dose group, interaction between each demographic characteristic and dose group, and interaction among each demographic characteristic, day of administration, and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

b) Study DB2113361, 170 cm; Study DB2113373, 168 cm

c) Study DB2113361, 76 kg; Study DB2113373, 74.5 kg

d) Study DB2113361, 1.215 L; Study DB2113373, 1.145 L

(b) Biases in patient demographic characteristics among dose groups in the Japanese subpopulation

There were no differences in patient demographic characteristics among the dose groups in the overall population in Studies DB2113361 and DB2113373. The patient demographic characteristics in the Japanese subpopulation were compared among the dose groups. As shown in Table 49, biases were observed among the dose groups in terms of severity of COPD according to the GOLD classification, use of ICS, smoking status, reversibility to salbutamol, a short-acting β_2 agonist (increase in FEV_1 ≥12% and ≥200 mL from baseline), and baseline FEV_1. Of the above patient demographic characteristic variables, severity of COPD according to the GOLD classification, use of ICS, reversibility to salbutamol (change from baseline in FEV_1 following administration of salbutamol [%]) were not included in the explanatory variables of the MMRM in the Japanese subpopulation analysis. To investigate the effect of biases in these excluded variables among the dose groups, the Japanese subpopulation analysis was performed by adding each of these variables to the explanatory variables. Table 50 shows the results of the additional analyses. As with the results before the addition, the results of additional analyses in the

UMEC/VI groups did not tend to exceed those in the UMEC groups. It is unlikely that the biases in patient demographic characteristics among the dose groups affected the efficacy results in the Japanese subpopulation.

Table 49. Patient demographic characteristics in the Japanese subpopulation at baseline by dose group

	Study DB2113361				Study DB2113373			
	UMEC/VI 125/25 μg group (N = 19)	UMEC 125 μg group (N = 21)	VI 25 μg group (N = 21)	Placebo group (N = 13)	UMEC/VI 62.5/25 μg group (N = 20)	UMEC 62.5 μg group (N = 18)	VI 25 μg group (N = 18)	Placebo group (N = 12)
GOLD classification Stage II Stage III Stage IV	53 (10/19) 42 (8/19) 5 (1/19)	57 (12/21) 38 (8/21) 5 (1/21)	57 (12/21) 29 (6/21) 14 (3/21)	85 (11/13) 15 (2/13) 0	40 (8/20) 50 (10/20) 10 (2/20)	67 (12/18) 22 (4/18) 11 (2/18)	61 (11/18) 28 (5/18) 11 (2/18)	58 (7/12) 33 (4/12) 8 (1/12)
ICS users	47 (9/19)	48 (10/21)	48 (10/21)	69 (9/13)	50 (10/20)	28 (5/18)	28 (5/18)	42 (5/12)
Smoking status Current smokers Former smokers	42 (8/19) 58 (11/19)	24 (5/21) 76 (16/21)	24 (5/21) 76 (16/21)	8 (1/13) 92 (12/13)	45 (9/20) 55 (11/20)	28 (5/18) 72 (13/18)	28 (5/18) 72 (13/18)	67 (8/12) 33 (4/12)
Reversibility to salbutamol	16 (3/19)	38 (8/21)	24 (5/21)	23 (3/13)	30 (6/20)	28 (5/18)	44 (8/18)	18 (2/11)
Baseline FEV_1	0.947 ± 0.400 (19)	0.981 ± 0.312 (21)	0.926 ± 0.335 (21)	1.038 ± 0.214 (13)	0.890 ± 0.328 (20)	1.118 ± 0.349 (18)	1.094 ± 0.450 (18)	1.204 ± 0.508 (11)

Mean ± SD (number of subjects) or % (number of subjects)

Table 50. Change from baseline in trough FEV_1 (L) at Week 24 in the Japanese subpopulation based on a model[a)] in which each patient demographic characteristic is added to the MMRM in the Japanese subpopulation analysis as an explanatory variable

Added demographic characteristics	Study DB2113361			Study DB2113373		
	UMEC/VI 125/25 μg group (N = 19)	UMEC 125 μg group (N = 21)	Difference between groups [95% CI]	UMEC/VI 62.5/25 μg group (N = 20)	UMEC 62.5 μg group (N = 18)	Difference between groups [95% CI]
No addition	0.115	0.129	-0.014 [-0.160, 0.131]	0.171	0.185	-0.014 [-0.177, 0.149]
GOLD classification	0.098	0.110	-0.012 [-0.157, 0.133]	0.166	0.173	-0.008 [-0.170, 0.155]
ICS use status	0.115	0.129	-0.014 [-0.160, 0.131]	0.170	0.178	-0.008 [-0.172, 0.155]
Reversibility to salbutamol (%)	0.120	0.122	-0.002 [-0.146, 0.142]	0.168	0.186	-0.018 [-0.182, 0.147]

a) MMRM with the baseline value, dose group, smoking status, region (Japan/outside Japan), day of administration, interaction between day of administration and the baseline value, interaction between day of administration and dose group, interaction between the region and dose group, interaction among the region, day of administration, and dose group, and each demographic characteristic as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

(c) Effects of discontinuation

In Studies DB2113361 and DB2113373, discontinuation of the study frequently occurred in the overall population. As described in "4.(iii).B.(2).1) Results of the overall population including Japanese in global phase III studies (Studies DB2113361 and DB2113373)," the study results did not suggest that the efficacy evaluation was affected by discontinuation in the overall population. However, in a subpopulation with limited number of patients, the efficacy evaluation may be largely affected by discontinuation. The potential effect of discontinuation on the results in the Japanese subpopulation was thus investigated.

Table 51 shows the incidence of discontinuation in the Japanese subpopulation in Studies DB2113361 and DB2113373. In the comparison between the UMEC/VI group and UMEC group, only 1 subject in the UMEC/VI 62.5/25 μg group discontinued, while 5 subjects in the UMEC 62.5 μg group did in Study DB2113373. Of the subjects, COPD aggravation tended to be commonly reported as the reason for discontinuation in the UMEC 62.5 μg group. There was no difference in the number of subjects who discontinued the study between the UMEC/VI 125/25

μg group and the UMEC 125 μg group in Study DB2113361, but of them, more subjects in the UMEC 125 μg group tended to discontinue due to COPD aggravation compared with the UMEC/VI 125/25 μg group.

Table 51. Change from baseline in trough FEV_1 at each visit (L), reason for discontinuation, and day of the event leading to discontinuation in the Japanese subpopulation

	Change from baseline in trough FEV_1								Reason for discontinuation	Day of the event leading to discontinuation
	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9		
	Day 1	Day 2	Day 28	Day 56	Day 84	Day 112	Day 168	The following day of Visit 8		
Study DB2113361										
Placebo group (N = 6)	0	-0.37	-0.31	-0.39	-0.34				COPD aggravation[a)]	87
	0	-0.05							COPD aggravation[a)]	10
	0	-0.07							COPD aggravation[a)]	7
	0	-0.09	0.06						Adverse event (COPD aggravation)[b)]	38
	0	-0.05	-0.05	-0.12	-0.14				COPD aggravation[a)]	88
	0	0.10							COPD aggravation[a)]	7
UMEC 125 μg group (N = 3)	0	0.01							COPD aggravation[a)]	18
	0	0.04	0.00	0.04					COPD aggravation[a)]	64
	0	0.49	0.09	0.08	0.39				COPD aggravation[a)]	100
VI 25 μg group (N = 8)	0	-0.06	-0.04	0.14	0.15				Violation against discontinuation criteria (ECG abnormal)	
	0	0.22							Adverse event (acute myocardial infarction)	6
	0	-0.02	0.06	-0.05	-0.12				Adverse event (pneumonia)	82
	0	0.06	0.07						Adverse event (COPD aggravation)[b)]	34
	0	0.32	0.22	0.29					Consent withdrawal	
	0	0.08							Consent withdrawal	
	0	0.11	0.10	0.03					COPD aggravation[a)]	64
	0	0.16	0.10	0.04	0.13	0.14			Adverse event (COPD aggravation)	169
UMEC/VI 125/25 μg group (N = 3)	0	0.25	0.13	0.09	0.07				Consent withdrawal	
	0	0.00	0.05						Adverse event (COPD aggravation)[b)]	57
	0	0.17							Violation against discontinuation criteria (ECG abnormal)	
Study DB2113373										
Placebo group (N = 4)	0		-0.05	-0.10	-0.03				Consent withdrawal	
	0	0.01	-0.22	-0.05	-0.06	-0.14			Consent withdrawal	
	0	0.01							Lack of efficacy	
	0	0							Lack of efficacy	
UMEC 62.5 μg group (N = 5)	0	0.20							Protocol violation	
	0	0.06	0.16	0.23	0.51	0.33			COPD aggravation[a)]	158
	0	0.10	-0.08						COPD aggravation[a)]	32
	0	0.08	-0.05						Consent withdrawal	
	0	0.15	0.20						COPD aggravation[a)]	17
UMEC/VI 62.5/25 μg group (N = 1)	0	0.19							Violation against discontinuation criteria (ECG abnormal)	

Blank indicates missing data.

a) Acute aggravation of COPD symptoms requiring therapeutic drugs other than the study drug or rescue drug specified in the discontinuation criteria in the study protocol

b) Adverse event (COPD aggravation) means COPD aggravation collected as a serious adverse event specified in the study protocol.

Therefore, PMDA asked the applicant to perform the sensitivity analysis based on the imputation method for missing data due to the discontinuation and the responder analysis, which is considered to be relatively resistant to the effects of discontinuation and the imputation method, and reviewed the effect of discontinuation on the efficacy results in the Japanese subpopulation. As shown in Table 52, the efficacy of UMEC/VI did not tend to exceed that of the UMEC single agent in either study in any of the MMRM analysis (without imputation of missing data), ANCOVA analysis according to each of the multiple imputation methods on the hypothesis of Missing At Random (MAR),[55] Copy Differences from Control (CDC),[56] and Last Mean Carried Forward (LMCF),[57] and MMRM analysis (with imputation according to LOCF method[58]). On the other hand, from a clinical viewpoint that the bronchodilation effect of UMEC/VI is reversible and the effect cannot be expected to be maintained after treatment discontinuation, more conservative imputation methods for the missing data were adopted in the analyses. As a result, the MMRM analyses with imputation according to BOCF method[59] and WOCF method[60] as well as ANCOVA with imputation in consideration of reason for discontinuation[61] showed that there was no consistent trend in Study DB2113361, but the efficacy in the UMEC/VI 62.5/25 μg group tended to exceed that of the UMEC 62.5 μg group in Study DB2113373. As shown in Table 53, the responder analysis showed that the percentage of responders in the UMEC/VI 125/25 μg group tended to be higher than that in the UMEC 125 μg group irrespective of the imputation method in Study DB2113361, but in Study DB2113373, the percentage of responders in the UMEC/VI 62.5/25 μg group did not exceed that in the UMEC 62.5 μg group in any of the MMRM analysis (without imputation of missing data), ANCOVA analyses according to various multiple imputation methods on the hypothesis of MAR, CDC, and LMCF, and MMRM analysis (imputation according to LOCF method). In the MMRM analyses with imputation according to the BOCF method and WOCF method as well as ANCOVA with imputation in consideration of reason for discontinuation, which are considered to be more conservative methods, the percentage of responders in the UMEC/VI 62.5/25 μg group tended to be higher than that in the UMEC 62.5 μg group. In addition, this sensitivity analysis and responder analysis showed similar trends in terms of the time course of changes from baseline in trough FEV_1 and the change from baseline in weighted mean FEV_1 over 0 to 6 hours post-dose at Week 24, the secondary endpoint.

On the other hand, with more conservative imputation methods, the add-on effect of UMEC/VI to UMEC was suggested in the Japanese subpopulation as observed in the overall population. In consideration of the above, one of the potential causes for the finding that the efficacy of UMEC/VI did not tend to exceed that of UMEC in the Japanese subpopulation was considered to be overestimation of the efficacy of UMEC as explained in the following: in the subjects who discontinued due to COPD aggravation which was potentially related to the lack of efficacy of the study drug, the FEV_1 value is expected to worsen over time after discontinuation, while in the MMRM analysis (without imputation of missing data), which was used to process the data in the Japanese subpopulation, the missing data in the subjects who discontinued were excluded. Thus, it should be noted that the effect of the missing data cannot be clearly identified as the cause of the finding that the efficacy of UMEC/VI did not tend to exceed that of UMEC in the Japanese subpopulation, taking into account that the trough FEV_1 values just before COPD aggravation and afterward were not actually measured in the subjects who discontinued and that COPD

[55] On the hypothesis of random discontinuation that occurs only depending on the measured data (patient demographic characteristic, baseline value, FEV_1 over time to discontinuation) but not on unmeasured FEV_1 over time after the discontinuation

[56] On the hypothesis that discontinuation occurs depending on unmeasured FEV_1 over time after the discontinuation, and that the FEV_1 over time after the discontinuation is comparable to that in the placebo group

[57] On the hypothesis that discontinuation occurs depending on unmeasured FEV_1 over time after the discontinuation, and that the reduction rate in FEV_1 after the discontinuation is constant (0 or 25 mL/year)

[58] Imputation using the FEV_1 value at the last time point

[59] Imputation using the FEV_1 value at baseline

[60] Imputation using the worst FEV_1 value measured

[61] For the subjects who discontinued the study due to COPD aggravation, imputation using the mean trough FEV_1 at Week 24 in the placebo group, while for the subjects who discontinued due to other reasons, imputation using the multiple imputation method on the assumption of MAR.

aggravation was not necessarily attributed to the lack of efficacy of the bronchodilator.

Table 52. Sensitivity analysis of changes from baseline in trough FEV_1 (L) at Week 24 in the Japanese subpopulation

Imputation method	Study DB2113361			Study DB2113373		
	UMEC/VI 125/25 µg group	UMEC 125 µg group	Difference between groups [95% CI]	UMEC/VI 62.5/25 µg group	UMEC 62.5 µg group	Difference between groups [95% CI]
MMRM [a] (without imputation)	0.115	0.129	-0.014 [-0.160, 0.131]	0.171	0.185	-0.014 [-0.177, 0.149]
ANCOVA [b] (MI: MAR [c])	0.123	0.129	-0.006 [-0.151, 0.139]	0.174	0.180	-0.006 [-0.167, 0.155]
ANCOVA [b] (MI: CDC [d])	0.122	0.125	-0.003 [-0.150, 0.143]	0.173	0.186	-0.014 [-0.175, 0.148]
ANCOVA [b] (MI: LMCF [e] [0 mL/year])	0.124	0.128	-0.003 [-0.148, 0.141]	0.177	0.185	-0.008 [-0.170, 0.153]
ANCOVA [b] (MI: LMCF [e] [25 mL/year])	0.125	0.127	-0.002 [-0.147, 0.143]	0.176	0.183	-0.007 [-0.169, 0.154]
MMRM [a] (LOCF [f])	0.122	0.134	-0.013 [-0.150, 0.124]	0.176	0.178	-0.002 [-0.155, 0.150]
MMRM [a] (BOCF [g])	0.111	0.117	-0.006 [-0.131, 0.118]	0.170	0.145	0.025 [-0.108, 0.158]
MMRM [a] (WOCF [h])	0.119	0.118	0.001 [-0.133, 0.135]	0.175	0.160	0.015 [-0.131, 0.162]
ANCOVA [b] (reason for discontinuation considered [i])	0.126	0.109	0.017 [-0.123, 0.157]	0.176	0.154	0.022 [-0.131, 0.176]

MI: Multiple Imputation

a) MMRM with the baseline value, dose group, smoking status, region (Japan/outside Japan), day of administration, interaction between day of administration and the baseline value, interaction between day of administration and dose group, interaction between the region and dose group, and interaction among the region, day of administration, and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

b) Analysis of the covariance model with the baseline value, dose group, smoking status, region (Japan/outside Japan), day of administration, and interaction between region and dose group as explanatory variables

c) On the hypothesis of random discontinuation (Missing At Random) that occurs only depending on the measured data (patient demographic characteristic, baseline value, dose group, FEV_1 over time to discontinuation) but not on unmeasured FEV_1 over time after the discontinuation

d) On the hypothesis that discontinuation occurs depending on unmeasured FEV_1 over time after the discontinuation, and that the FEV_1 over time after the discontinuation is comparable to that in the placebo group (Copy Differences from Control)

e) On the hypothesis that discontinuation occurs depending on unmeasured FEV_1 over time after the discontinuation, and that the reduction rate in FEV_1 after the discontinuation is constant (0 or 25 mL/year) (Last Mean Carried Forward)

f) Imputation using the FEV_1 value at the last time point (Last Observation Carried Forward)

g) Imputation using the FEV_1 value at baseline (Baseline Observation Carried Forward)

h) Imputation using the worst FEV_1 value measured (Worst Observation Carried Forward)

i) For the subjects who discontinued the study due to COPD aggravation, imputation using the mean trough FEV_1 at Week 24 in the placebo group on the assumption that the discontinuation occurs depending on unmeasured FEV_1 over time after the discontinuation; for the subjects who discontinued due to other reasons, MI was applied on the assumption of MAR

Table 53. Responder analysis on changes from baseline in trough FEV_1 (L) at Week 24 in the Japanese subpopulation

Imputation method	Study DB2113361			Study DB2113373		
	UMEC/VI 125/25 μg group	UMEC 125 μg group	Difference between groups [95% CI]	UMEC/VI 62.5/25 μg group	UMEC 62.5 μg group	Difference between groups [95% CI]
MMRM [a] (without imputation)	75 (12/16) 75 (12/16) 75 (12/16)	61 (11/18) 61 (11/18) 50 (9/18)	14 [-17, 45] 14 [-17, 45] 25 [-6, 56]	74 (14/19) 74 (14/19) 74 (14/19)	77 (10/13) 77 (10/13) 69 (9/13)	-3 [-34, 27] -3 [-34, 27] 4 [-28, 36]
ANCOVA [b] (MI: MAR [c])	73 72 71	61 60 50	12 [-17, 41] 11 [-18, 41] 21 [-9, 50]	74 73 73	73 72 65	1 [-27, 29] 2 [-27, 30] 9 [-21, 38]
ANCOVA [b] (MI: CDC [d])	72 71 70	60 59 49	12 [-17, 41] 12 [-18, 41] 21 [-8, 51]	74 73 73	74 73 66	-1 [-29, 27] 0 [-28, 28] 7 [-23, 36]
ANCOVA [b] (MI: LMCF [e] [0 mL/year])	73 72 71	61 60 50	12 [-17, 41] 12 [-18, 41] 21 [-9, 50]	74 73 73	73 72 66	0 [-28, 28] 1 [-27, 29] 8 [-22, 37]
ANCOVA [b] (MI: LMCF [e] [25 mL/year])	73 72 71	60 60 50	12 [-17, 41] 12 [-17, 41] 21 [-8, 51]	73 73 73	73 72 65	0 [-28, 28] 1 [-27, 30] 8 [-22, 37]
MMRM [a] (LOCF [f])	68 (13/19) 68 (13/19) 68 (13/19)	57 (12/21) 57 (12/21) 48 (10/21)	11 [-18, 41] 11 [-18, 41] 21 [-9, 51]	75 (15/20) 75 (15/20) 75 (15/20)	72 (13/18) 72 (13/18) 67 (12/18)	3 [-25, 31] 3 [-25, 31] 8 [-21, 37]
MMRM [a] (BOCF [g])	63 (12/19) 63 (12/19) 63 (12/19)	52 (11/21) 52 (11/21) 43 (9/21)	11 [-20, 41] 11 [-20, 41] 20 [-10, 51]	70 (14/20) 70 (14/20) 70 (14/20)	56 (10/18) 56 (10/18) 50 (9/18)	14 [-16, 45] 14 [-16, 45] 20 [-11, 51]
MMRM [a] (WOCF [h])	68 (13/19) 68 (13/19) 68 (13/19)	57 (12/21) 52 (11/21) 43 (9/21)	11 [-18, 41] 16 [-14, 46] 26 [-4, 55]	75 (15/20) 75 (15/20) 75 (15/20)	67 (12/18) 67 (12/18) 61 (11/18)	8 [-21, 37] 8 [-21, 37] 14 [-16, 43]
ANCOVA [b] (reason for discontinuation considered [i])	73 72 71	52 52 43	20 [-9, 49] 19 [-10, 49] 28 [-1, 57]	74 73 73	62 61 55	12 [-18, 42] 12 [-18, 42] 18 [-12, 48]

% (number of subjects), MI: Multiple imputation (% only, because the number of responders differs among the imputation data sets)
Cut-off value for responders; 0.075 (top), 0.10 (middle), 0.125 (bottom) (L)
a) to i): As defined in Table 52

(d) Efficacy of single agent administration of UMEC or VI

PMDA investigated if the efficacy trend of single agent of UMEC or VI in the Japanese subpopulation was different from that in the overall population or in the subpopulation in the other countries in Studies DB2113361 and DB2113373.

As shown in Table 46, in terms of the change from baseline in trough FEV_1 at Week 24, the primary efficacy endpoint, the values in the UMEC and VI monotherapy groups exceeded those in the placebo group in the Japanese subpopulation as observed in the overall population in both Studies DB2113361 and DB2113373, suggesting the efficacy of UMEC and VI in Japanese patients. As the forest plots by country in Studies DB2113361 and DB2113373 indicate (Figures 3 and 4), the values in the UMEC 62.5 μg group in the Japanese subpopulation tended to be slightly higher than those in the overall population in Study DB2113373, but the values in each monotherapy group in the Japanese subpopulation were not largely different from those in the other countries.

Furthermore, PMDA reviewed the data from the global phase III study including Japanese (Study AC4115408) in which the efficacy and safety of UMEC 62.5 μg and 125 μg were investigated. As shown in Tables 19 and 20, the results in the Japanese subpopulation showed similar trends to those in the overall population. As shown in Table 54, the results from Japanese subjects were not largely different from those from the subjects in the other regions.

In conclusion, the difference in responsiveness to UMEC or VI between Japanese patients and the overall population is unlikely to have caused the finding that the efficacy of UMEC/VI did not exceed that of UMEC alone in the Japanese subpopulation.

Table 54. Trough FEV_1 in Study AC4115408 by country

	No. of subjects UMEC 62.5 μg group/placebo group	Difference between placebo group and UMEC 62.5 μg group [95% CI][a)]	No. of subjects UMEC 125 μg group/placebo group	Difference between placebo group and UMEC 125 μg group [95% CI][a)]	No. of subjects UMEC 125 μg group/UMEC 62.5 μg group	Difference between UMEC 62.5 μg group and UMEC 125 μg group [95% CI][a)]
Germany	42/35	0.090 [0.000, 0.180]	36/35	0.156 [0.064, 0.249]	36/42	0.067 [-0.022, 0.156]
Japan	7/4	0.243 [0.006, 0.481]	6/4	0.292 [0.047, 0.538]	6/7	0.049 [-0.174, 0.273]
U.S.	12/11	0.212 [0.052, 0.372]	13/11	0.098 [-0.062, 0.257]	13/12	-0.114 [-0.268, 0.040]

a) MMRM with the baseline value, dose group, smoking status, country, day of administration, interaction between day of administration and the baseline value, interaction between day of administration and dose group, interaction between country and dose group, and interaction among country, day of administration, and dose group as explanatory variables on the hypothesis of unstructured covariance structure in the subjects

PMDA concluded on the efficacy of UMEC/VI in Japanese COPD patients as follows:
In Studies DB2113361 and DB2113373, the efficacy of UMEC/VI did not exceed that of UMEC in the Japanese subpopulation. Results from a series of sensitivity analyses suggested that data in the subjects who discontinued might have partly affected the results in the Japanese subpopulation, but such potential cause could not be clearly confirmed.

Given the efficacy of single agent of UMEC or VI observed in the Japanese subpopulation as with the overall population, it is unlikely that an add-on effect of the combination of UMEC and VI is not seen in Japanese patients, from the following aspects: comparisons among the UMEC and VI monotherapy groups and the placebo group in Studies DB2113361 and DB2113373 showed that the results in the overall population were consistent with those in the Japanese subpopulation, leading to a conclusion that the efficacy of single agent of UMEC or VI is indicated in the Japanese COPD patients and that the efficacy trend of each single agent in the Japanese subpopulation was not largely different from those in the subpopulations of the other countries; LAMA and LABA, which act on muscarinic receptor and β_2 receptor, respectively, dilate the bronchial smooth muscle through different mechanisms of action; a clinical study in COPD patients reported that a combination therapy of approved LAMA and LABA showed the efficacy exceeding that of each single agent (Mahler DA et al. *Thorax.* 2012;67:781-788); and based on these findings, the combination therapy of LAMA and LABA has been included in the guidelines for the diagnosis and treatment of COPD in both Japan and overseas, indicating that consensus on the clinical significance of the combination has been obtained.

Based on the above, the finding that the efficacy of UMEC/VI did not exceed that of UMEC in the Japanese subpopulation in Studies DB2113361 or DB2113373 is likely to be incidental, and thus it has been concluded that the efficacy of UMEC/VI can be expected in Japanese COPD patients as observed in the overall population.

The above conclusion of PMDA will be discussed at the Expert Discussion.

4.(iii).B.(3) Safety

The applicant has positioned 4 phase III confirmatory studies (Studies DB2113361, DB2113373, DB2113360, and DB2113374) as the pivotal clinical studies for the safety evaluation in the application. These studies also serve as the pivotal efficacy studies in COPD patients and were conducted in comparable subject populations in a similar study design (24-week, randomized,

double-blind, parallel-group study). The applicant explained the safety of UMEC/VI based on the combined data from these 4 studies (pivotal efficacy study combined data) as follows:
Tables 55 and 56 show the major adverse events and summary of adverse events, respectively, in the pivotal efficacy study combined data.

The major adverse events with high incidences in the UMEC/VI group included headache, nasopharyngitis, cough, upper respiratory tract infection, and back pain, and their incidences were not largely different from those in the placebo group or each monotherapy group.

Deaths occurred in 5 subjects in the UMEC/VI 62.5/25 µg group, 1 subject in the UMEC/VI 125/25 µg group, 3 subjects in the UMEC 62.5 µg group, 2 subjects in the UMEC 125 µg group, 6 subjects in the VI 25 µg group, 2 subjects in the TIO group, and 3 subjects in the placebo group. The causes of deaths included cardiovascular adverse events (including sudden death) in 2 subjects in the UMEC/VI 62.5/25 µg group, 2 subjects in the VI 25 µg group, and 1 subject in the placebo group; respiratory adverse events (including COPD aggravation) in 2 subjects in the UMEC/VI 62.5/25 µg group, 1 subject in the UMEC 62.5 µg group, 1 subject in the VI 25 µg group, and 1 subject in the placebo group; and cancer-related adverse events in 2 subjects in the UMEC 125 µg group and 1 subject in the VI 25 µg group. Serious adverse events not resulting in death occurred in 6% (49 of 842 subjects) in the UMEC/VI 62.5/25 µg group, 5% (45 of 832 subjects) in the UMEC/VI 125/25 µg group, 6% (27 of 418 subjects) in the UMEC 62.5 µg group, 6% (37 of 629 subjects) in the UMEC 125 µg group, 6% (57 of 1034 subjects) in the VI 25 µg group, 5% (20 of 423 subjects) in the TIO group, 5% (25 of 555 subjects) in the placebo group. These serious adverse events not resulting in death included cardiovascular adverse events in <1% (7 of 842 subjects) in the UMEC/VI 62.5/25 µg group, <1% (8 of 832 subjects) in the UMEC/VI 125/25 µg group, <1% (4 of 418 subjects) in the UMEC 62.5 µg group, 2% (11 of 629 subjects) in the UMEC 125 µg group, 1% (13 of 1034 subjects) in the VI 25 µg group, and <1% (2 of 423 subjects) in the TIO group, <1% (2 of 555 subjects) in the placebo group; and respiratory adverse events (including COPD aggravation) in 3% (27 of 842 subjects) in the UMEC/VI 62.5/25 µg group, 2% (20 of 832 subjects) in the UMEC/VI 125/25 µg group, 3% (13 of 418 subjects) in the UMEC 62.5 µg group, 2% (10 of 629 subjects) in the UMEC 125 µg group, 2% (22 of 1034 subjects) in the VI 25 µg group, 2% (9 of 423 subjects) in the TIO group, and 2% (13 of 555 subjects) in the placebo group.

Table 55. Adverse events reported by ≥3% of subjects in any group in the pivotal efficacy study combined data

	UMEC/VI 62.5/25 µg group (N = 842)	UMEC/VI 125/25 µg group (N = 832)	UMEC 62.5 µg group (N = 418)	UMEC 125 µg group (N = 629)	VI 25 µg group (N = 1034)	TIO group (N = 423)	Placebo group (N = 555)
Total	447 (53)	438 (53)	216 (52)	348 (55)	518 (50)	208 (49)	264 (48)
Headache	76 (9)	75 (9)	32 (8)	62 (10)	87 (8)	24 (6)	58 (10)
Nasopharyngitis	74 (9)	77 (9)	29 (7)	43 (7)	98 (9)	33 (8)	48 (9)
Cough	18 (2)	44 (5)	16 (4)	29 (5)	37 (4)	11 (3)	23 (4)
Upper respiratory tract infection	27 (3)	24 (3)	21 (5)	23 (4)	32 (3)	22 (5)	21 (4)
Back pain	31 (4)	23 (3)	8 (2)	27 (4)	20 (2)	15 (4)	20 (4)
Hypertension	13 (2)	15 (2)	10 (2)	18 (3)	24 (2)	8 (2)	10 (2)
Oropharyngeal pain	17 (2)	17 (2)	6 (1)	12 (2)	29 (3)	5 (1)	9 (2)
Chronic obstructive pulmonary disease	19 (2)	15 (2)	12 (3)	8 (1)	14 (1)	6 (1)	14 (3)
Arthralgia	10 (1)	17 (2)	12 (3)	10 (2)	14 (1)	7 (2)	8 (1)
Dyspnoea	10 (1)	4 (<1)	4 (<1)	11 (2)	20 (2)	3 (<1)	14 (3)

Number of subjects (%)

Table 56. Summary of adverse events in the overall population and Japanese subpopulation in the pivotal efficacy study combined data

		UMEC/VI 62.5/25 µg group (N = 842)	UMEC/VI 125/25 µg group (N = 832)	UMEC 62.5 µg group (N = 418)	UMEC 125 µg group (N = 629)	VI 25 µg group (N = 1034)	Placebo group (N = 555)
Overall population	Overall adverse events	447 (53)	438 (53)	216 (52)	348 (55)	518 (50)	264 (48)
	Adverse events related to study drug	52 (6)	62 (7)	34 (8)	62 (10)	68 (7)	31 (6)
	Adverse events leading to study discontinuation or study drug discontinuation	50 (6)	47 (6)	31 (7)	41 (7)	59 (6)	26 (5)
	Serious adverse events other than death	49 (6)	45 (5)	27 (6)	37 (6)	57 (6)	25 (5)
	Adverse events resulting in death	5 (<1)	1 (<1)	3(<1)	2 (<1)	6(<1)	3 (<1)
		UMEC/VI 62.5/25 µg group (N = 20)	UMEC/VI 125/25 µg group (N = 19)	UMEC 62.5 µg group (N = 18)	UMEC 125 µg group (N = 21)	VI 25 µg group (N = 39)	Placebo group (N = 25)
Japanese subpopulation	Overall adverse events	10 (50)	11 (58)	10 (56)	11 (52)	26 (67)	16 (64)
	Adverse events related to study drug	0	3 (16)	2 (11)	2 (10)	1 (3)	0
	Adverse events leading to study discontinuation or study drug discontinuation	0	1 (5)	0	0	4 (10)	1 (4)
	Serious adverse events other than death	0	1 (5)	1 (6)	0	2 (5)	2 (8)
	Adverse events resulting in death	0	0	0	0	1 (3)	0

Table 56 shows the summary of adverse events in the Japanese subpopulation in the pivotal efficacy study combined data. The major adverse events in Japanese in the combined data included nasopharyngitis (25% [5 of 20 subjects] in the UMEC/VI 62.5/25 µg group, 16% [3 of 19 subjects] in the UMEC/VI 125/25 µg group, 22% [4 of 18 subjects] in the UMEC 62.5 µg group, 29% [6 of 21 subjects] in the UMEC 125 µg group, 26% [10 of 39 subjects] in the VI 25 µg group, 8% [2 of 25 subjects] in the placebo group) and upper respiratory tract infection (0% [0 of 20 subjects] in the UMEC/VI 62.5/25 µg group, 5% [1 of 19 subjects] in the UMEC/VI 125/25 µg group, 6% [1 of 18 subjects] in the UMEC 62.5 µg group, 5% [1 of 21 subjects] in the UMEC 125 µg group, 13% [5 of 39 subjects] in the VI 25 µg group, 20% [5 of 25 subjects] in the placebo group). Although it is difficult to make detailed comparisons due to the limited number of Japanese subjects, the incidence trends of adverse events in the Japanese subpopulation were comparable to those in the overall population.

4.(iii).B.(3).1) Cardiovascular adverse events

The applicant explained cardiovascular adverse events related to UMEC/VI as follows:
COPD patients are likely to have concomitant cardiac disorders, and LAMAs and LABAs are considered to have cardiovascular effects as class effects. Therefore, cardiovascular adverse events reported were classified into any of predefined events, i.e., long QT acquired, arrhythmia, cardiac failure, myocardial ischaemia, hypertension, sudden death, and cerebrovascular accident for investigation.

Table 57 shows the incidence of cardiovascular adverse events in the pivotal efficacy study combined data. The incidence trend of any event did not differ among the dose groups. The incidences of serious cardiovascular adverse events were <2% in any dose group, and no major difference was observed in incidence of any serious adverse event among the dose groups. Percentage of subjects who had risk factors [62] of cardiovascular diseases or concurrent

[62] Angina pectoris, diabetes mellitus, hyperlipidaemia, hypertension, myocardial infarction, cerebrovascular accident

cardiovascular diseases at the time of screening did not largely differ among the dose groups. In any dose group, more than half of the subjects who reported serious cardiovascular adverse events had the risk factors or concurrent diseases.

The incidence of cardiovascular adverse events in the Japanese subpopulation was 10% (2 of 20 subjects, oedema peripheral and blood pressure increased [1 subject each]) in the UMEC/VI 62.5/25 µg group, 0% (0 of 19 subjects) in the UMEC/VI 125/25 µg group, 11% (2 of 18 subjects, palpitations and hypertension [1 subject each]) in the UMEC 62.5 µg group, 0% (0 of 21 subjects) in the UMEC 125 µg group, 3% (1 of 39 subjects, acute myocardial infarction) in the VI 25 µg group, and 8% (2 of 25 subjects, supraventricular tachycardia and hypertension [1 subject each]) in the placebo group. Of these, the serious adverse event was only acute myocardial infarction in the VI 25 µg group.

Table 57. Incidence of cardiovascular adverse events in the pivotal efficacy study combined data

	UMEC/VI 62.5/25 µg group (N = 842)	UMEC/VI 125/25 µg group (N = 832)	UMEC 62.5 µg group (N = 418)	UMEC 125 µg group (N = 629)	VI 25 µg group (N = 1034)	TIO group (N = 423)	Placebo group (N = 555)
Cardiovascular adverse events							
Total	70 (8) 202.4	55 (7) 163.6	41 (10) 244.2	52 (8) 208.9	95 (9) 231.0	27 (6) 156.0	40 (7) 192.7
Long QT acquired	0 0	2 (<1) 5.9	1 (<1) 6.0	0 0	0 0	0 0	0 0
Arrhythmia	24 (3) 69.4	19 (2) 56.5	20 (5) 119.1	20 (3) 80.4	46 (4) 111.9	9 (2) 52.0	18(3) 86.7
Cardiac failure	11 (1) 31.8	11 (1) 32.7	7 (2) 41.7	7 (1) 28.1	12 (1) 29.2	5 (1) 28.9	6 (1) 28.9
Myocardial ischaemia	11 (1) 31.8	12 (1) 35.7	7 (2) 41.7	5 (<1) 20.1	12 (1) 29.2	4 (<1) 23.1	5 (<1) 24.1
Hypertension	25 (3) 72.3	17 (2) 50.6	12 (3) 71.5	21 (3) 84.4	29 (3) 70.5	11 (3) 63.6	11 (2) 53.0
Sudden death	0 0	0 0	0 0	0 0	1 (<1) 2.4	0 0	0 0
Cerebrovascular accident	1 (<1) 2.9	1 (<1) 3.0	1 (<1) 6.0	1 (<1) 4.0	3 (<1) 7.3	1 (<1) 5.8	2 (<1) 9.6
Serious cardiovascular adverse events							
Total	8 (<1) 23.1	7 (<1) 20.8	7 (2) 41.7	9 (1) 36.2	18 (2) 43.8	3 (<1) 17.3	2 (<1) 9.6
Long QT acquired	0 0	0 0	1 (<1) 6.0	0 0	0 0	0 0	0 0
Arrhythmia	1 (<1) 2.9	2 (<1) 5.9	4 (<1) 23.8	4 (<1) 16.1	6 (<1) 14.6	1 (<1) 5.8	0 0
Cardiac failure	0 0	1 (<1) 3.0	0 0	0 0	3 (<1) 7.3	0 0	0 0
Myocardial ischaemia	6 (<1) 17.3	3 (<1) 8.9	4 (<1) 23.8	3 (<1) 12.1	6 (<1) 14.6	1 (<1) 5.8	1 (<1) 4.8
Hypertension	0 0	0 0	0 0	1 (<1) 4.0	1 (<1) 2.4	0 0	0 0
Sudden death	0 0	0 0	0 0	0 0	1 (<1) 2.4	0 0	0 0
Cerebrovascular accident	1 (<1) 2.9	1 (<1) 3.0	0 0	1 (<1) 4.0	3 (<1) 7.3	1 (<1) 5.8	1 (<1) 4.8

Upper, number of subjects (%); lower, incidence adjusted according to the exposure (number of subjects with the event/1000 subject-years)

The incidence adjusted according to the exposure was determined by the formula of (1000 × number of subjects with the adverse event)/(total number of days of exposure/365.25).

Electrocardiogram (ECG) findings in the pivotal efficacy study combined data were investigated. As shown in Table 58, the incidences of ECG abnormalities after baseline related to “atrial arrhythmia” (e.g., ectopic supraventricular contraction, ectopic supraventricular rhythm, atrial fibrillation with rapid ventricular response [heart rate >100 bpm], supraventricular tachycardia)

in the UMEC/VI group tended to be higher than those in the placebo group, but did not tend to exceed those in either UMEC or VI monotherapy group. Most of the subjects with the ECG abnormality of atrial fibrillation or supraventricular tachycardia observed after baseline did not report clinically significant adverse events, and the clinical impact of such a finding was considered to be limited.

Table 58. Incidence of ECG abnormality in the pivotal efficacy study combined data

	UMEC/VI 62.5/25 µg group (N = 842)	UMEC/VI 125/25 µg group (N = 832)	UMEC 62.5 µg group (N = 418)	UMEC 125 µg group (N = 629)	VI 25 µg group (N = 1034)	TIO group (N = 423)	Placebo group (N = 555)
ST segment depression	50 (6)	49 (6)	27 (6)	27 (4)	50 (5)	22 (5)	32 (6)
Frequent ventricular premature depolarization (≥3 times)	40 (5)	35 (4)	16 (4)	23 (4)	39 (4)	16 (4)	25 (5)
Ectopic supraventricular contraction	30 (4)	35 (4)	14 (3)	21 (3)	34 (3)	15 (4)	16 (3)
Bundle branch block right with QTc(F) <530 msec	22 (3)	28 (3)	9 (2)	19 (3)	32 (3)	12 (3)	23 (4)
T wave flat	22 (3)	16 (2)	9 (2)	16 (3)	28 (3)	14 (3)	14 (3)
PR interval shortened	18 (2)	18 (2)	12 (3)	9 (1)	27 (3)	8 (2)	15 (3)
T wave inversion	21 (2)	24 (3)	11 (3)	5 (<1)	22 (2)	10 (2)	14 (3)
Infrequent ventricular premature depolarization (<3 times)	21 (2)	20 (2)	11 (3)	12 (2)	19 (2)	7 (2)	11 (2)
Ectopic supraventricular rhythm	12 (1)	25 (3)	8 (2)	15 (2)	21 (2)	7 (2)	10 (2)
AV block first degree (PR interval, >240 msec)	9 (1)	16 (2)	3 (<1)	10 (2)	22 (2)	9 (2)	7 (1)
Myocardial infarction (old)	12 (1)	12 (1)	2 (<1)	4 (<1)	12 (1)	8 (2)	11 (2)
AV block first degree (PR interval, >200 msec)	8 (<1)	14 (2)	4 (<1)	7 (1)	13 (1)	5 (1)	5 (<1)
Sinus tachycardia ≥110 bpm	6 (<1)	11 (1)	6 (1)	6 (<1)	11 (1)	3 (<1)	10 (2)
T wave biphasic	9 (1)	12 (1)	6 (1)	3 (<1)	11 (1)	7 (2)	3 (<1)
Left anterior hemiblock	4 (<1)	2 (<1)	2 (<1)	4 (<1)	14 (1)	5 (1)	2 (<1)
Multifocal ventricular extrasystoles	4 (<1)	7 (<1)	2 (<1)	4 (<1)	11 (1)	2 (<1)	2 (<1)
Multiple ventricular couplets	4 (<1)	4 (<1)	1 (<1)	6 (<1)	11 (1)	1 (<1)	3 (<1)

Number of subjects (%)

The incidence of cardiovascular adverse events was 12% (15 of 130 subjects) and the incidence of serious cardiovascular adverse events was 2% (3 of 130 subjects) in the Japanese long-term treatment study (Study DB2115362), and 15% (34 of 226 subjects) and 2% (4 of 226 subjects), respectively, in the foreign long-term treatment study (Study DB2113359). The incidences in the UMEC/VI group did not largely differ between Japanese and foreign patients in these studies. Furthermore, Table 59 shows the incidence of cardiovascular adverse events by time of onset (Week 0-12, Week 13-24, Week 25-36, Week 37 and thereafter). In the Japanese long-term treatment study, the incidence of arrhythmia in the UMEC/VI group tended to increase slightly with the increasing treatment period, and in the foreign long-term treatment study, the incidences of overall adverse events and arrhythmia in the UMEC/VI group tended to increase slightly with the increasing treatment period as well. Similar trends, however, were also observed in the placebo group and more than half of the subjects (58% [76 of 130 subjects] in Study DB2115362, 67% [151 of 226 subjects] in Study DB2113359) were found to have cardiovascular diseases concurrently. These increases were therefore considered potentially attributable to effects of the natural history of the disease.

Table 59. Cardiovascular adverse events in the Japanese long-term study (DB2115362) and foreign long-term study (DB2113359) by time of onset

	Study DB2113359												Study DB2115362			
	UMEC/VI 125/25 μg group (N = 226)				UMEC 125 μg group (N = 227)				Placebo group (N = 109)				UMEC/VI 125/25 μg group (N = 130)			
	Week 0-12 (N = 226)	Week 13-24 (N = 210)	Week 25-36 (N = 180)	Week 37- (N = 160)	Week 0-12 (N = 227)	Week 13-24 (N = 199)	Week 25-36 (N = 169)	Week 37- (N = 154)	Week 0-12 (N = 109)	Week 13-24 (N = 93)	Week 25-36 (N = 81)	Week 37- (N = 73)	Week 0-12 (N = 130)	Week 13-24 (N = 126)	Week 25-36 (N = 122)	Week 37- (N = 116)
Cardiovascular adverse events	12 (5)	7 (3)	9 (5)	11 (7)	13 (6)	16 (8)	10 (6)	17 (11)	6 (6)	9 (10)	6 (7)	9 (12)	6 (5)	4 (3)	2 (2)	6 (5)
Long QT acquired	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Arrhythmia	9 (4)	4 (2)	7 (4)	9 (6)	9 (4)	12 (6)	9 (5)	14 (9)	3 (3)	6 (6)	5 (6)	7 (10)	1 (<1)	2 (2)	1 (<1)	3 (3)
Cardiac failure	1 (<1)	0	1 (<1)	0	2 (<1)	0	1 (<1)	1 (<1)	0	0	0	1 (1)	1 (<1)	0	1 (<1)	1 (<1)
Myocardial ischaemia	1 (<1)	0	2 (1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (3)	0	0	1 (1)	0	0	0	3 (3)
Hypertension	1 (<1)	3 (1)	1 (<1)	3 (2)	1 (<1)	3 (2)	1 (<1)	2 (1)	2 (2)	3 (3)	1 (1)	1 (1)	4 (3)	1 (<1)	0	0
Sudden death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (<1)
Cerebrovascular accident	0	0	0	0	1 (<1)	0	0	0	0	0	0	0	0	1 (<1)	0	0

Number of subjects (%)

Combined data from 8 phase III studies[63] in which UMEC/VI or UMEC was administered for ≥12 weeks were subjected to investigation of Major Adverse Cardiac Events (MACEs).[64] As shown in Table 60, the incidence of MACEs was low in any dose group. Compared to the placebo group, all treatment groups of the UMEC/VI, UMEC monotherapy, and VI monotherapy showed no increasing trend in the risk for MACEs.

Table 60. Incidence of MACEs in the combined data from 8 phase III studies

	UMEC/VI 62.5/25 μg group (N = 1124)	UMEC/VI 125/25 μg group (N = 1330)	UMEC 62.5 μg group (N = 576)	UMEC 125 μg group (N = 1016)	VI 25 μg group (N = 1174)	TIO group (N = 423)	Placebo group (N = 1053)
Broadly defined MACEs	15 (1) 36.8	22 (2) 38.4	9 (2) 44.5	14 (1) 31.2	17 (1) 38.5	6 (1) 34.7	20 (2) 54.3
Narrowly defined MACEs	5 (<1) 12.3	6 (<1) 10.5	2 (<1) 9.9	7 (<1) 15.6	8 (<1) 18.1	1 (<1) 5.8	7 (<1) 19.0
Death assessed as related to cardiovascular effects	2 (<1) 4.9	0 0	0 0	1 (<1) 2.2	2 (<1) 4.5	0 0	2 (<1) 5.4
AESI in the subgroup of subjects with “myocardial ischaemia” not resulting in death	13 (1) 31.9	19 (1) 33.2	8 (1) 39.5	11 (1) 24.5	12 (1) 27.2	5 (1) 28.9	14 (1) 38.0
Myocardial infarction not resulting in death	3 (<1) 7.4	3 (<1) 5.2	1 (<1) 4.9	4 (<1) 8.9	2 (<1) 4.5	0 0	1 (<1) 2.7
AESI in the subgroup of subjects with “cerebrovascular accident” not resulting in death	0 0	3 (<1) 5.2	1 (<1) 4.9	2 (<1) 4.5	4 (<1) 9.1	1 (<1) 5.8	4 (<1) 10.9

Upper, number of subjects (%); lower, incidence adjusted according to the exposure (number of subjects with the event/1000 subject-years)

The incidence adjusted according to the exposure was determined by the formula of (1000 × number of subjects with the adverse event)/(total number of days of exposure/365.25).

[63] Studies DB2113361, DB2113373, DB2113360, DB2113374, DB2114417, DB2114418, DB2113359, and AC4115408

[64] Broad definition of MACEs includes non-fatal “myocardial ischaemia” subgroup, non-fatal “cerebrovascular accident” subgroup, and deaths assessed as related to cardiovascular adverse events. Narrow definition of MACEs includes non-fatal myocardial infarction (acute myocardial infarction, myocardial infarction), non-fatal “cerebrovascular accident” subgroup, and deaths assessed as related to cardiovascular adverse events.

PMDA considers as follows:
The clinical data in the application do not suggest a trend toward greater risk of cardiovascular adverse events in subjects treated with UMEC/VI compared to those treated with UMEC or VI as a single agent, or similar drugs. It is, however, necessary to continue to carefully investigate the incidence of cardiovascular adverse events in patients treated with UMEC/VI as well as the relationship between the incidence and the demographic characteristics (e.g., presence/absence of risk factors) by collecting sufficient post-marketing safety information from Japanese and non-Japanese populations, because the number of subjects receiving long-term treatment with UMEC/VI is limited, and it cannot be ruled out that concomitant use of LAMA and LABA increases the risk of cardiovascular adverse events for the following reasons: β_2 agonists have a potential cardiovascular risk through the β agonist activity; and inhalation of anticholinergics has been reported to increase the risk of deaths due to cardiovascular events (Singh S et al. *JAMA*. 2008;300:1439-1450, Singh S et al. *BMJ*. 2011;342.d3215[online]). It is also appropriate to provide cautions for the cardiovascular risk in the package insert as provided for similar drugs.

4.(iii).B.(3).2) Adverse events related to LAMA and LABA

The applicant explained adverse events related to the LAMA and LABA contained in UMEC/VI as follows:

(a) Adverse events related to LAMA

The incidences of adverse events related to "anticholinergic effects" (e.g., dry mouth, dizziness, dysphagia), "urinary retention," "ocular effects" (e.g., vision blurred), "gallbladder disorder," and "intestinal obstruction," which are non-cardiovascular pharmacological class effects of LAMAs, were investigated based on the pivotal efficacy study combined data as shown in Table 61. The number of subjects reported "urinary retention," "gallbladder disorder," and "intestinal obstruction" was limited. The incidences of the events related to "anticholinergic effects" and "ocular effects" in each active drug group did not largely exceed those in the placebo group while the incidences in the UMEC/VI group were comparable to those in either UMEC or VI monotherapy group.

In the Japanese subpopulation, adverse events related to "anticholinergic effects" occurred in 5% (1 of 19 subjects) in the UMEC/VI 125/25 μg group, 5% (1 of 21 subjects) in the UMEC 125 μg group, and 4% (1 of 25 subjects) in the placebo group; and adverse events related to "ocular effects" occurred in 4% (1 of 25 subjects) in the placebo group.

Table 61. Adverse events related to LAMA in the pivotal efficacy study combined data

	UMEC/VI 62.5/25 μg group (N = 842)	UMEC/VI 125/25 μg group (N = 832)	UMEC 62.5 μg group (N = 418)	UMEC 125 μg group (N = 629)	VI 25 μg group (N = 1034)	TIO group (N = 423)	Placebo group (N = 555)
Overall population							
Anticholinergic effect	25 (3) 72.3	43 (5) 127.9	18 (4) 107.2	29 (5) 116.5	40 (4) 97.3	15 (4) 86.7	22 (4) 106.0
Urinary retention	1 (<1) 2.9	0 0	0 0	2 (<1) 8.0	1 (<1) 2.4	2 (<1) 11.6	0 0
Ocular effects	7 (<1) 20.2	7 (<1) 20.8	3 (<1) 17.9	8 (1) 32.1	6 (<1) 14.6	1 (<1) 5.8	5 (<1) 24.1
Gallbladder disorder	2 (<1) 5.8	0 0	3 (<1) 17.9	0 0	2 (<1) 4.9	0 0	1 (<1) 4.8
Intestinal obstruction	1 (<1) 2.9	0 0	0 0	0 0	0 0	0 0	2 (<1) 9.6

Upper, number of subjects (%); lower, incidence adjusted according to the exposure (number of subjects with the event/1000 subject-years)

The incidence adjusted according to the exposure was determined by the formula of (1000 × number of subjects with the adverse event)/(total number of days of exposure/365.25).

Table 62 shows the incidence of each adverse event related to “anticholinergic effects.” The incidences of dry mouth, which is classified as an event related to the anticholinergic effects, in the UMEC/VI groups (11.6 for 62.5/25 µg group; 41.6 for 125/25 µg group) and the UMEC groups (17.9 for 62.5 µg group; 20.1 for 125 µg group) were higher than that in the placebo group (9.6) and tended to increase with the increasing dose of UMEC, but were comparable to that in the TIO group (40.4). For severity, all of the dry mouth were moderate or milder except for a severe dry mouth in 1 subject in the UMEC 125 µg group, which resolved following the treatment discontinuation. None of the dry mouth was found to be clinically relevant. The incidences of dizziness, which is classified as an event related to the anticholinergic effects, in the UMEC/VI groups (28.9 for 62.5/25 µg group; 29.7 for 125/25 µg group) and the UMEC groups (17.9 for 62.5 µg group; 20.1 for 125 µg group) were higher than that in the TIO group (11.6), but lower than that in the placebo group (38.5).

In addition, cataract, which is classified as an event related to the “ocular effects,” occurred in all groups (8.7 for UMEC/VI 62.5/25 µg group; 5.9 for UMEC/VI 125/25 µg group; 6.0 for UMEC 62.5 µg group; 8.0 for UMEC 125 µg group; 4.9 for VI 25 µg group; 0 for TIO group; 4.8 for placebo group), but was considered attributable to the high percentage of the elderly in the COPD patients enrolled in the studies.

In the Japanese subpopulation, dry mouth and pyrexia, which are classified as events related to the anticholinergic effects, occurred in 5% (1 of 21 subjects) in the UMEC 125 µg group for dry mouth and 5% (1 of 19 subjects) in the UMEC/VI 125/25 µg group for pyrexia while vision blurred, which is classified as an event related to the anticholinergic effects and ocular effects, occurred in 4% (1 of 25 subjects) in the placebo group.

Table 62. Adverse events related to "anticholinergic effects" in the pivotal efficacy study combined data

	UMEC/VI 62.5/25 µg group (N = 842)	UMEC/VI 125/25 µg group (N = 832)	UMEC 62.5 µg group (N = 418)	UMEC 125 µg group (N = 629)	VI 25 µg group (N = 1034)	TIO group (N = 423)	Placebo group (N = 555)
Total	25 (3) 72.3	43 (5) 127.9	18 (4) 107.2	29 (5) 116.5	40 (4) 97.3	15 (4) 86.7	22 (4) 106.0
Agitation	0 0	0 0	1 (<1) 6.0	0 0	0 0	0 0	0 0
Balance disorder	1 (<1) 2.9	0 0	0 0	0 0	0 0	0 0	0 0
Confusional state	0 0	1 (<1) 3.0	0 0	0 0	0 0	0 0	0 0
Delirium	0 0	0 0	0 0	1 (<1) 4.0	1 (<1) 2.4	0 0	0 0
Dizziness	10 (1) 28.9	10 (1) 29.7	3 (<1) 17.9	5 (<1) 20.1	11 (1) 26.8	2 (<1) 11.6	8 (1) 38.5
Dry eye	0 0	2 (<1) 5.9	0 0	0 0	0 0	1 (<1) 5.8	0 0
Dry mouth	4 (<1) 11.6	14 (2) 41.6	3 (<1) 17.9	5 (<1) 20.1	6 (<1) 14.6	7 (2) 40.4	2 (<1) 9.6
Dysphagia	0 0	0 0	0 0	0 0	1 (<1) 2.4	0 0	1 (<1) 4.8
Loss of consciousness	0 0	0 0	1 (<1) 6.0	2 (<1) 8.0	0 0	1 (<1) 5.8	0 0
Presyncope	0 0	0 0	1 (<1) 6.0	0 0	1 (<1) 2.4	0 0	0 0
Pyrexia	5 (<1) 14.5	14 (2) 41.6	3 (<1) 17.9	9 (1) 36.2	14 (1) 34.0	2 (<1) 11.6	8 (1) 38.5
Restlessness	1 (<1) 2.9	0 0	0 0	1 (<1) 4.0	0 0	0 0	0 0
Somnolence	0 0	1 (<1) 3.0	0 0	1 (<1) 4.0	0 0	0 0	0 0
Tachycardia	2 (<1) 5.8	4 (<1) 11.9	5 (1) 29.8	2 (<1) 8.0	5 (<1) 12.2	1 (<1) 5.8	2 (<1) 9.6
Urinary retention	1 (<1) 2.9	0 0	0 0	2 (<1) 8.0	1 (<1) 2.4	1 (<1) 5.8	0 0
Vision blurred	0 0	2 (<1) 5.9	1 (<1) 6.0	1 (<1) 4.0	3 (<1) 7.3	0 0	2 (<1) 9.6
Visual acuity reduced	2 (<1) 5.8	0 0	0 0	1 (<1) 4.0	0 0	0 0	0 0

Upper, number of subjects (%); lower, incidence adjusted according to the exposure (number of subjects with the event/1000 subject-years)

The incidence adjusted according to the exposure was determined by the formula of (1000 × number of subjects with the adverse event)/(total number of days of exposure/365.25).

Table 63 shows the incidence of adverse events related to LAMA in the Japanese long-term treatment study (Study DB2115362) and foreign long-term treatment study (Study DB2113359) by time of onset (Week 0-12, Week 13-24, Week 25-36, Week 37 and thereafter). Although the incidence of the adverse events related to "anticholinergic effects" and "ocular effects" tended to be high in the Japanese long-term treatment study, all of the events were moderate or mild in severity except for dysphagia (1 subject), which is classified as an event related to the "anticholinergic effects." A causal relationship of the dysphagia to UMEC/VI was ruled out. The incidence of any adverse event did not tend to increase largely with the increasing treatment period in either Japanese or foreign patients.

Table 63. Adverse events related to LAMA in the Japanese long-term treatment study (DB2115362) and foreign long-term treatment study (DB2113359) by time of onset

	Study DB2113359												Study DB2115362			
	UMEC/VI 125/25 μg group (N = 226)				UMEC 125 μg group (N = 227)				Placebo group (N = 109)				UMEC/VI 125/25 μg group (N = 130)			
	Week 0-12 (N = 226)	Week 13-24 (N = 210)	Week 25-36 (N = 180)	Week 37- (N = 160)	Week 0-12 (N = 227)	Week 13-24 (N = 199)	Week 25-36 (N = 169)	Week 37- (N = 154)	Week 0-12 (N = 109)	Week 13-24 (N = 93)	Week 25-36 (N = 81)	Week 37- (N = 73)	Week 0-12 (N = 130)	Week 13-24 (N = 126)	Week 25-36 (N = 122)	Week 37- (N = 116)
Anticholinergic effects	3 (1)	2 (<1)	0	0	3 (1)	1 (<1)	0	1 (<1)	2 (2)	0	0	0	2 (2)	4 (3)	1 (<1)	3 (3)
Urinary retention	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ocular effects	0	0	0	1 (<1)	0	1 (<1)	0	0	0	1 (1)	0	0	1 (<1)	0	3 (2)	0
Gallbladder disorder	0	0	0	0	0	1 (<1)	1 (<1)	0	0	0	0	0	0	0	0	0
Intestinal obstruction	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (<1)	0	0

Number of subjects (%)

(b) Adverse events related to LABA

The incidences of metabolism-related events (low potassium, glucose increased) and tremor, which are non-cardiovascular pharmacological class effects of LABA, were investigated based on the pivotal efficacy study combined data. As shown in Table 64, the incidence of any adverse event did not largely differ among the dose groups.

None of the adverse events occurred in the Japanese subpopulation.

Table 64. Adverse events related to LABA in the pivotal efficacy study combined data

	UMEC/VI 62.5/25 μg group (N = 842)	UMEC/VI 125/25 μg group (N = 832)	UMEC 62.5 μg group (N = 418)	UMEC 125 μg group (N = 629)	VI 25 μg group (N = 1034)	TIO group (N = 423)	Placebo group (N = 555)
Overall population							
Effects on glucose level	11 (1) 31.8	4 (<1) 11.9	7 (2) 41.7	11 (2) 44.2	17 (2) 41.3	6 (1) 34.7	2 (<1) 9.6
Effects on potassium level	0 0	2 (<1) 5.9	0 0	1 (<1) 4.0	1 (<1) 2.4	1 (<1) 5.8	1 (<1) 4.8
Tremor	1 (<1) 2.9	0 0	3 (<1) 17.9	1 (<1) 4.0	1 (<1) 2.4	1 (<1) 5.8	2 (<1) 9.6

Upper, number of subjects (%); lower, incidence adjusted according to the exposure (number of subjects with the event/1000 subject-years)

The incidence adjusted according to the exposure was determined by the formula of (1000 × number of subjects with the adverse event)/(total number of days of exposure/365.25).

Table 65 shows the incidence of adverse events related to LABA in the Japanese long-term treatment study (Study DB2115362) and foreign long-term treatment study (Study DB2113359) by time of onset (Week 0-12, Week 13-24, Week 25-36, Week 37 and thereafter). The trend was similar between Japanese and foreign patients, and the incidence did not tend to increase largely with an increasing treatment period.

Table 65. Adverse events related to LABA in the Japanese long-term treatment study (DB2115362) and foreign long-term treatment study (DB2113359) by time of onset

	Study DB2113359												Study DB2115362			
	UMEC/VI 125/25 μg group (N = 226)				UMEC 125 μg group (N = 227)				Placebo group (N = 109)				UMEC/VI 125/25 μg group (N = 130)			
	Week 0-12 (N = 226)	Week 13-24 (N = 210)	Week 25-36 (N = 180)	Week 37- (N = 160)	Week 0-12 (N = 227)	Week 13-24 (N = 199)	Week 25-36 (N = 169)	Week 37- (N = 154)	Week 0-12 (N = 109)	Week 13-24 (N = 93)	Week 25-36 (N = 81)	Week 37- (N = 73)	Week 0-12 (N = 130)	Week 13-24 (N = 126)	Week 25-36 (N = 122)	Week 37- (N = 116)
Effects on glucose level	3 (1)	1 (<1)	3 (2)	2 (1)	0	0	0	1 (<1)	0	0	0	0	0	1 (<1)	1 (<1)	0
Effects on potassium level	0	0	0	0	1 (<1)	0	0	0	0	0	0	0	0	1 (<1)	1 (<1)	0
Tremor	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of subjects (%)

PMDA considers as follows:
The clinical study data in the application do not suggest a trend toward greater risk of adverse events related to pharmacological class effects of LAMA or LABA in subjects treated with UMEC/VI compared to the subjects treated with UMEC or VI as a single agent or similar drugs. However, the incidence of the adverse events in routine use, as well as the effects of patient demographic characteristics, should be further investigated via post-marketing surveillance. It is also appropriate to provide cautions for the concerned risk in the package insert as provided for similar drugs.

4.(iii).B.(3).3) Effects of age and body weight

Many of the COPD patients in Japan are relatively elderly people with low body weight. PMDA asked the applicant to tabulate the incidence of adverse events by age and body weight and to explain whether or not the safety profile of UMEC/VI tended to differ in elderly or low body weight patients.

The applicant explained as follows:
Table 66 shows the incidence of adverse events in the pivotal efficacy study combined data tabulated by age. The incidence of overall adverse events in the UMEC/VI 62.5/25 μg group and the incidence of the adverse events leading to discontinuation in the UMEC/VI 62.5/25 μg group and the UMEC groups tended to be higher in the ≥75-year old subpopulation than those in the other age subpopulations. Although increased incidences were observed in the ≥75-year old subpopulation for lower respiratory tract infection and pneumonia in the UMEC/VI 62.5/25 μg group and for adverse events related to the cardiovascular effects in the UMEC groups, no particular problems with the safety of UMEC/VI treatment in the elderly have been suggested compared with UMEC single agent, VI single agent, or similar drugs, because the increased incidences of overall adverse events, adverse events leading to discontinuation, and lower respiratory tract infection and pneumonia were also observed in the ≥75-year old subpopulation in the TIO group; in the UMEC/VI groups, the incidence of adverse events related to the cardiovascular effects in the ≥75-year old subpopulation was comparable to that in the other age subpopulations; and types of the adverse events did not largely differ among age subpopulations.

Table 66. Incidence of adverse events in the pivotal efficacy study combined data by age

	Age bracket	UMEC/VI 62.5/25 µg group (N = 842)	UMEC/VI 125/25 µg group (N = 832)	UMEC 62.5 µg group (N = 418)	UMEC 125 µg group (N = 629)	VI 25 µg group (N = 1034)	TIO group (N = 423)	Placebo group (N = 555)
Overall adverse events	<65 years	224/453 (49)	222/445 (50)	110/217 (51)	185/335 (55)	299/592 (51)	103/213 (48)	158/335 (47)
	≥65 years and <75 years	167/300 (56)	175/309 (57)	78/148 (53)	128/232 (55)	173/346 (50)	76/160 (48)	81/170 (48)
	≥75 years	56/89 (63)	41/78 (53)	28/53(53)	35/62 (56)	46/96 (48)	29/50 (58)	25/50 (50)
Serious adverse events	<65 years	23/45 (5)	16/445 (4)	15/217 (7)	12/335 (4)	37/592 (6)	13/213 (6)	10/335 (3)
	≥65 years and <75 years	19/300 (6)	22/309 (7)	11/148 (7)	21/232 (9)	16/346 (5)	7/160 (4)	12/170 (7)
	≥75 years	8/89 (9)	5/78 (6)	1/53 (2)	4/62 (6)	6/96 (6)	2/50 (4)	4/50 (8)
Adverse events leading to discontinuation	<65 years	23/453 (5)	24/445 (5)	17/217 (8)	21/335 (6)	40/592 (7)	11/213 (5)	9/335 (3)
	≥65 years, and <75 years	18/300 (6)	19/309 (6)	8/148 (5)	14/232 (6)	15/346 (4)	5/160 (3)	14/170 (8)
	≥75 years	9/89 (10)	4/78 (5)	6/53 (11)	6/62 (10)	4/96 (4)	4/50 (8)	3/50 (6)
Cardiovascular effects	<65 years	33/453 (7)	31/445 (7)	19/217 (9)	24/335 (7)	58/592 (10)	14/213 (7)	28/335 (8)
	≥65 years and <75 years	30/300 (10)	19/309 (6)	15/148 (10)	18/232 (8)	33/346 (10)	11/160 (7)	8/170 (5)
	≥75 years	7/89 (8)	5/78 (6)	7/53 (13)	10/62 (16)	4/96 (4)	2/50 (4)	4/50 (8)
Anticholinergic effects	<65 years	12/453 (3)	22/445 (5)	12/217 (6)	14/335 (4)	20/592 (3)	6/213 (3)	12/335 (4)
	≥65 years and <75 years	11/300 (4)	16/309 (5)	4/148 (3)	12/232 (5)	17/346 (5)	5/160 (3)	9/170 (5)
	≥75 years	2/89 (2)	5/78 (6)	2/53 (4)	3/62 (5)	3/96 (3)	4/50 (8)	1/50 (2)
Urinary retention	<65 years	0	0	0	1/335 (<1)	0	0	0
	≥65 years and <75 years	1/300 (1)	0	0	1/232 (<1)	0	1/160 (<1)	0
	≥75 years	0	0	0	0	1/96 (1)	1/50 (2)	0
Ocular effects	<65 years	3/453 (<1)	4/445 (<1)	0	4/335 (1)	3/592 (<1)	1/213 (<1)	2/335 (<1)
	≥65 years and <75 years	3/300 (<1)	2/309 (<1)	1/148 (<1)	3/232 (1)	3/346 (<1)	0	3/170 (2)
	≥75 years	1/89 (1)	1/78 (1)	2/53 (4)	1/62 (2)	0	0	0
Gallbladder disorder	<65 years	0	0	1/217 (<1)	0	0	0	1/335 (<1)
	≥65 years and <75 years	2/300 (<1)	0	2/148 (1)	0	1/346 (<1)	0	0
	≥75 years	0	0	0	0	1/96 (1)	0	0
Intestinal obstruction	<65 years	0	0	0	0	0	0	1/335 (<1)
	≥65 years and <75 years	1/300 (<1)	0	0	0	0	0	1/170 (<1)
	≥75 years	0	0	0	0	0	0	0
Effects on glucose level	<65 years	3/453 (<1)	2/445 (<1)	1/217 (<1)	3/335 (<1)	13/592 (2)	3/213 (1)	1/335 (<1)
	≥65 years and <75 years	7/300 (2)	2/309 (<1)	6/148 (4)	8/232 (3)	4/346 (1)	3/160 (2)	1/170 (<1)
	≥75 years	1/89 (1)	0	0	0	0	0	0
Effects on potassium level	<65 years	0	1/445 (<1)	0	0	1/592 (<1)	1/213 (<1)	1/335 (<1)
	≥65 years and <75 years	0	0	0	1/232 (<1)	0	0	0
	≥75 years	0	1/78 (1)	0	0	0	0	0
Tremor	<65 years	0	0	1/217 (<1)	0	0	1/213 (<1)	1/335 (<1)
	≥65 years and <75 years	0	0	1/148 (<1)	0	0	0	1/170 (<1)
	≥75 years	1/89 (1)	0	1/53 (2)	1/62 (2)	1/96 (1)	0	0

Number of subjects (%)

Table 67 shows the incidence of adverse events in the pivotal efficacy study combined data by body weight. The incidence of overall adverse events in the UMEC/VI 62.5/25 µg group tended to be higher in the <50 kg body weight subpopulation than in the other body weight subpopulations. Although in the UMEC/VI 62.5/25 µg group and UMEC 125 µg group, the incidence of adverse events related to the anticholinergic effects tended to increase in the <50 kg body weight subpopulation, no particular problems with the safety of UMEC/VI in low body weight patients have been suggested because marked difference in the incidence was not observed compared with the other groups; and types of the adverse events did not largely differ among different body weight subpopulations.

Table 67. Incidence of adverse events in the pivotal efficacy study combined data by body weight

	Body weight bracket	UMEC/VI 62.5/25 µg group (N = 842)	UMEC/VI 125/25 µg group (N = 832)	UMEC 62.5 µg group (N = 418)	UMEC 125 µg group (N = 629)	VI 25 µg group (N = 1034)	TIO group (N = 423)	Placebo group (N = 555)
Overall adverse events	<50 kg	27/40 (68)	20/36 (56)	12/21 (57)	20/35 (57)	21/37 (57)	11/21 (52)	18/40 (45)
	≥50 kg and <70 kg	142/256 (55)	148/275 (54)	81/159 (51)	115/219 (53)	174/356 (49)	71/153 (46)	91/177 (51)
	≥70 kg and <90 kg	168/337 (50)	170/349 (49)	77/151 (51)	137/235 (58)	184/387 (48)	72/149 (48)	99/211 (47)
	≥90 kg	110/209 (53)	100/172 (58)	46/87 (53)	76/140 (54)	139/254 (55)	54/100 (54)	56/127 (44)
Serious adverse events	<50 kg	1/40 (3)	3/36 (8)	2/21 (10)	2/35 (6)	3/37 (8)	1/21 (5)	5/40 (13)
	≥50 kg and <70 kg	17/256 (7)	11/275 (4)	10/159 (6)	16/219 (7)	22/356 (6)	8/153 (5)	8/177 (5)
	≥70 kg and <90 kg	17/337 (5)	16/349 (5)	11/151 (7)	9/235 (4)	18/387 (5)	6/149 (4)	9/211 (4)
	≥90 kg	15/209 (7)	13/172 (8)	4/87 (5)	10/140 (7)	16/254 (6)	7/100 (7)	4/127 (3)
Adverse events leading to discontinuation	<50 kg	1/40 (3)	1/36 (3)	2/21 (10)	2/35 (6)	0	1/21 (5)	5/40 (13)
	≥50 kg and <70 kg	23/256 (9)	16/275 (6)	10/159 (6)	16/219 (7)	22/356 (6)	8/153 (5)	5/177 (3)
	≥70 kg and <90 kg	17/337 (5)	15/349 (4)	12/151 (8)	15/235 (6)	22/387 (6)	5/149 (3)	10/211 (5)
	≥90 kg	9/209 (4)	14/172 (8)	7/87 (8)	7/140 (5)	15/254 (6)	6/100 (6)	6/127 (5)
Cardiovascular effects	<50 kg	3/40 (8)	4/36 (11)	1/21 (5)	4/35 (11)	3/37 (8)	1/21 (5)	3/40 (8)
	≥50 kg and <70 kg	17/256 (7)	14/275 (5)	13/159 (8)	15/219 (7)	24/356 (7)	8/153 (5)	8/177 (5)
	≥70 kg and <90 kg	25/337 (7)	21/349 (6)	13/151 (9)	22/235 (9)	36/387 (9)	10/149 (7)	20/211 (9)
	≥90 kg	25/209 (12)	16/172 (9)	14/87 (16)	11/140 (8)	32/254 (13)	8/100 (8)	9/127 (7)
Anticholinergic effects	<50 kg	5/40 (13)	2/36 (6)	1/21 (5)	6/35 (17)	2/37 (5)	1/21 (5)	2/40 (5)
	≥50 kg and <70 kg	7/256 (3)	10/275 (4)	10/159 (6)	8/219 (4)	14/356 (4)	7/153 (5)	8/177 (5)
	≥70 kg and <90 kg	4/337 (1)	19/349 (5)	3/151 (2)	10/235 (4)	12/387 (3)	4/149 (3)	6/211 (3)
	≥90 kg	9/209 (4)	12/172 (7)	4/87 (5)	5/140 (4)	12/254 (5)	3/100 (3)	6/127 (5)
Urinary retention	<50 kg	0	0	0	0	0	0	0
	≥50 kg and <70 kg	0	0	0	0	1/356 (<1)	1/153 (<1)	0
	≥70 kg and <90 kg	0	0	0	1/235 (<1)	0	0	0
	≥90 kg	1/209 (<1)	0	0	1/140 (<1)	0	1/100 (1)	0
Ocular effects	<50 kg	0	0	1/21 (5)	0	0	0	0
	≥50 kg and <70 kg	4/256 (2)	3/275 (1)	1/159 (<1)	4/219 (2)	2/356 (<1)	0	2/177 (1)
	≥70 kg and <90 kg	2/337 (<1)	1/349 (<1)	1/151 (<1)	2/235 (<1)	3/387 (<1)	0	1/211 (<1)
	≥90 kg	1/209 (<1)	3/172 (2)	0	2/140 (1)	1/254 (<1)	1/100 (1)	2/127 (2)
Gallbladder disorder	<50 kg	0	0	0	0	0	0	0
	≥50 kg and <70 kg	1/256 (<1)	0	1/159 (<1)	0	1/356 (<1)	0	0
	≥70 kg and <90 kg	0	0	2/151 (1)	0	0	0	0
	≥90 kg	1/209 (<1)	0	0	0	1/254 (<1)	0	1/127 (<1)
Intestinal obstruction	<50 kg	0	0	0	0	0	0	0
	≥50 kg and <70 kg	0	0	0	0	0	0	0
	≥70 kg and <90 kg	0	0	0	0	0	0	2/211 (<1)
	≥90 kg	1/209 (<1)	0	0	0	0	0	0
Effects on glucose level	<50 kg	0	0	0	0	0	0	0
	≥50 kg and <70 kg	2/256 (<1)	0	1/159 (<1)	1/219 (<1)	2/356 (<1)	1/153 (<1)	1/177 (<1)
	≥70 kg and <90 kg	5/337 (1)	2/349 (<1)	2/151 (1)	5/235 (2)	6/387 (2)	1/149 (<1)	0
	≥90 kg	4/209 (2)	2/172 (1)	4/87 (5)	5/140 (4)	9/254 (4)	4/100 (4)	1/127 (<1)
Effects on potassium level	<50 kg	0	0	0	0	0	0	0
	≥50 kg and <70 kg	0	1/275 (<1)	0	1/219 (<1)	0	0	0
	≥70 kg and <90 kg	0	0	0	0	0	0	1/211 (<1)
	≥90 kg	0	1/172 (<1)	0	0	1/254 (<1)	1/100 (1)	0
Tremor	<50 kg	0	0	0	0	0	0	0
	≥50 kg and <70 kg	1/256 (<1)	0	3/159 (2)	0	0	0	1/177 (<1)
	≥70 kg and <90 kg	0	0	0	0	1/387 (<1)	1/149 (<1)	1/211 (<1)
	≥90 kg	0	0	0	1/140 (<1)	0	0	0

Number of subjects (%)

PMDA considers as follows:

The safety of UMEC/VI in patients aged ≥75 years or who weighed <50 kg cannot be judged definitely because of the insufficient number of the subjects. The safety in elderly patients and low body weight patients should continue to be investigated through post-marketing surveillance for the following reasons: in the UMEC/VI group, the incidences of overall adverse events and adverse events leading to discontinuation in the ≥75-year old subpopulation tended to be higher than those in the other age subpopulations; the incidences of adverse events related to the anticholinergic effects in the <50 kg subpopulation tended to be higher than those in the other body weight subpopulations; and in Japan, a large percentage of the COPD patients are elderly,

and in general, elderly patients are supposed to be weighed low and/or have cardiovascular risk factors, and thus, the possibility of increased incidence of adverse events related to UMEC/VI cannot be ruled out in such patients.

4.(iii).B.(4) Dosage and administration

As described in "1. Origin or history of discovery and usage conditions in foreign countries etc.," the application of UMEC/VI 125/25 μg was withdrawn in the course of the review, and the dosage and administration were changed as shown below.

PMDA has concluded that the changed dosage and administration have no particular problem because, based on the submitted data, the efficacy of UMEC/VI 62.5/25 μg in COPD patients can be expected [see "4.(iii).B.(2) Efficacy"], and no clinically relevant issues are suggested in terms of safety [see "4.(iii).B.(3) Safety"].

[Dosage and administration]	The usual adult dosage is 1 inhalation of Umeclidinium Bromide/Vilanterol Trifenatate 62.5 (62.5 μg as umeclidinium, 25 μg as vilanterol) administered once daily. ~~Where necessary, 1 inhalation of Umeclidinium Bromide/Vilanterol Trifenatate 125 (125 μg as umeclidinium, 25 μg as vilanterol) may be administered once daily.~~ (The strikeout part were excluded from the proposed dosage and administration.)

4.(iii).B.(5) Indication

The proposed indication was "Relief of symptoms of obstructive airway disorder due to chronic obstructive pulmonary disease (chronic bronchitis and pulmonary emphysema)", and UMEC/VI may be needed in the early phase of treatment depending on the condition of the patient. PMDA considers, however, that it is not appropriate to use UMEC/VI in COPD patients uniformly and that UMEC/VI should be positioned as a drug product used only in patients who require concomitant use of LAMA and LABA, for the following reasons: the Japanese guideline recommends that intensity of the treatment be increased step by step based on the severity of the patient's condition in principle; and the risk of serious cardiovascular adverse events associated with long-term combination therapy with LAMA and LABA remains to be fully characterized. Therefore, the indication should include a statement to the effect that "only in the case where combination of a long-acting inhaled anticholinergic drug and a long-acting inhaled β_2-agonist is required."

[Indication]	Relief of symptoms of obstructive airway disorder due to chronic obstructive pulmonary disease (chronic bronchitis and pulmonary emphysema) <u>(Only in the case where combination of a long-acting inhaled anticholinergic drug and a long-acting inhaled β_2-agonist is required.)</u> (The underlined part were added to the proposed indication.)

4.(iii).B.(6) Doses for Japanese long-term treatment study

The only dose used in the Japanese long-term treatment study (Study DB2115362) was UMEC/VI 125/25 μg, not the dose (62.5/25 μg) that PMDA considered appropriate in "4.(iii).B.(4) Dosage and administration." The incidence of adverse events in patients treated with UMEC/VI 125/25 μg did not tend to be higher than that in patients treated with UMEC/VI 62.5/25 μg; the incidences of cardiovascular adverse events and adverse events related to LAMA did not largely differ among different dose levels; and the safety profile did not largely differ among different dose levels [see "4.(iii).B.(3) Safety"]. PMDA therefore considers it acceptable to evaluate the long-

term safety of UMEC/VI 62.5/25 μg based on the long-term treatment data of UMEC/VI 125/25 μg.

4.(iii).B.(7) Post-marketing investigations

The applicant plans to conduct a post-marketing surveillance to confirm the safety and efficacy of UMEC/VI in routine use including long-term treatment.

PMDA considers as follows:

The clinical study data did not suggest an exceeding safety issues of UMEC compared to the approved LAMAs, and the safety profile of UMEC/VI does not indicate an exceeding trend of adverse events compared to UMEC single agent, VI single agent, and similar drugs. However, as discussed in "4.(iii).B.(3) Safety," the safety of UMEC/VI should be further investigated via the post-marketing surveillance in patients receiving long-term treatment and elderly patients, of whom only limited number was included in the clinical studies. The incidence of cardiovascular adverse events, which are possible events for patients treated with LAMA and LABA, should also be investigated.

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

A document-based compliance inspection and data integrity assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted 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 for DB2113361, 5.3.5.1 for DB2113373, 5.3.5.1 for AC4115408, 5.3.5.2 for DB2115362). As a result, protocol deviations (enrollment of subjects who met the exclusion criteria) were found at some trial sites. Although these findings requiring improvement were noted, the concerned patients were appropriately handled. PMDA therefore has concluded that the clinical studies as a whole were performed in compliance with GCP and there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data, it is concluded that the efficacy of UMEC/VI in patients with COPD has been demonstrated and its safety is acceptable in view of its observed benefits. The significance of the combination drug has also been suggested. UMEC/VI is considered to offer a new option in treatment of COPD as a LAMA/LABA combination inhaler administered once daily. The safety of UMEC/VI in patients receiving long-term treatment and elderly patients, of whom only limited number was included in the clinical studies, and incidence of cardiovascular adverse events should be further investigated via post-marketing surveillance. PMDA considers that UMEC/VI may be approved if the product is considered to have no problem based on comments from the Expert Discussion.

Review Report (2)

April 11, 2014

I. Product Submitted for Registration

[Brand name]	Anoro Ellipta 7 doses, Anoro Ellipta 30 doses
[Non-proprietary name]	Umeclidinium Bromide/Vilanterol Trifenatate
[Name of applicant]	GlaxoSmithKline K.K.
[Date of application]	April 22, 2013

II. Content of the Review

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

(1) Efficacy

In the global phase III studies in COPD patients including Japanese patients (Studies DB2113361 and DB2113373), the efficacy of UMEC/VI did not exceed that of UMEC in the Japanese subpopulation. However, PMDA concluded that the efficacy of UMEC/VI can be expected in Japanese COPD patients as with the result in the overall population, as described in "4.(iii).B.(2) Efficacy" of Review Report (1). The conclusion by PMDA was discussed at the Expert Discussion.

The following comments were raised from the expert advisors, concerning whether or not it is acceptable to conclude that the efficacy of UMEC/VI can be expected in Japanese COPD patients despite the inconsistent study results between the overall population and the Japanese subpopulation:
In general, if the add-on effect of the combination therapy is sufficiently large, consistent results can be obtained. On the other hand, in the treatment with UMEC/VI, the add-on effect of VI to UMEC is not large, that is, the bronchodilation effect of UMEC (change from baseline in trough FEV_1) is more potent than that of VI. Consequently, it is possible that the subpopulation analysis based on the point estimates shows UMEC/VI to be inferior in efficacy to UMEC due to variable results between individuals. In addition to the above viewpoint, in the forest plots by country in Studies DB2113361 and DB2113373 (Figures 3 and 4), treatment difference (UMEC/VI, UMEC, VI, placebo) and the 95% CIs for each country including Japan did not indicate more specific trend than the variability of the point estimates, supporting the interpretation that differences of the race or medical environment was unlikely to affect the results. It is therefore considered appropriate for PMDA to conclude that the efficacy of UMEC/VI can be expected in Japanese COPD patients as observed in the overall population.

Besides, LAMA act on muscarinic M3 receptors and LABA on β_2 receptors; M3 and β_2 receptors are differently distributed in the airway. To provide bronchodilation throughout the lungs, therefore, combination of LAMA and LABA is effective, and a consensus exists on the clinical significance of the combination therapy of LAMA and LABA. PMDA's conclusion that the efficacy of UMEC/VI can be expected in Japanese COPD patients is appropriate, based on the results in the overall population and the results in the Japanese subpopulation receiving UMEC or VI monotherapy. Furthermore, clinical usefulness of UMEC/VI can be expected for the following reasons: LAMA is the main treatment of COPD, but the selection of existing LAMAs

is limited and thus novel LAMA is highly required in clinical practice; and combination of LAMA with LABA can improve the adherence to the clinical use.

On the other hand, the following comment was raised from some of the expert advisors: It is agreed that the efficacy can be expected in Japanese COPD patients, but the number of Japanese subjects evaluated was limited; the results in the Japanese subpopulation have not shown adequate evidence for the efficacy of UMEC/VI in Japanese COPD patients. A post-marketing clinical study should therefore be conducted to obtain definite evidence.

PMDA has concluded, taking account of the comments from the Expert Discussion, as follows: The global phase III studies (Studies DB2113361 and DB2113373) in COPD patients including Japanese patients demonstrated the efficacy of UMEC/VI, and thus the efficacy of UMEC/VI can be expected in Japanese COPD patients as observed in the overall population. Some expert advisors commented that the post-marketing clinical study should be conducted in Japan to obtain definite evidence of the efficacy of UMEC/VI. Meanwhile, other expert advisors commented that the post-marketing clinical study is not necessary because the efficacy of UMEC/VI can be expected in Japanese COPD patients; based on this comment, the post-marketing clinical study is judged to be unnecessary. However, information about the efficacy (changes in FEV_1, etc.) should be collected from patients who have switched from monotherapy of approved LAMA or LABA or concomitant use of LAMA and LABA to UMEC/VI therapy via post-marketing surveillance to confirm the efficacy of UMEC/VI in routine use.

(2) Safety

The conclusion of PMDA described in Review Report (1) was supported by the expert advisors.

The expert advisors presented the following comments: Based on the reports on the approved LAMAs and LABAs, attention should be paid to the risk of cardiovascular adverse events in patients treated with UMEC/VI. The package insert, etc. should provide sufficient cautions about the risk of cardiovascular adverse events in particular and their incidences after market launch should be carefully investigated; and adverse events related to the pharmacological class effects of UMEC and VI should be investigated via post-marketing surveillance since UMEC and VI are novel LAMA and LABA, respectively, with the limited use experience in Japanese COPD patients. Based on the above comments, actions have been taken as described in "(3) Draft risk management plan" to control the risk of UMEC/VI treatment.

(3) Draft risk management plan

Taking account of "4.(iii).B.(7) Post-marketing investigations" of Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA has concluded that it is appropriate that the safety and the efficacy specifications as shown in Table 68 will be included in the draft risk management plan and that additional pharmacovigilance activities and risk minimization actions as shown in Table 69 will be implemented. As for non-Japanese patients with bronchial asthma, a higher incidence of asthma-related deaths has been reported in those receiving salmeterol (LABA) than in those receiving placebo. UMEC/VI may be administered to COPD patients complicated with bronchial asthma. Therefore, PMDA considered it appropriate to specify asthma-related intubation and death as important potential risks.

Table 68. Safety specifications and efficacy specifications of draft risk management plan

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Cardiovascular events	• Asthma-related intubation and death	• None
Efficacy specifications		
• Efficacy in routine use		

Table 69. Summary of additional pharmacovigilance activities and risk minimization actions in the risk management plan

Additional pharmacovigilance activities	Additional risk minimization actions
• Early post-marketing phase vigilance • Drug use-results survey	• Early post-marketing phase vigilance

PMDA instructed the applicant to plan post-marketing surveillance to investigate the safety specifications in the above draft risk management plan and the efficacy (changes in FEV_1, etc.) in the patients who have switched from monotherapy of approved LAMA or LABA or concomitant use of LAMA and LABA to UMEC/VI therapy.

The applicant explained as follows:
As shown in Table 70, the use-results survey with a 1-year observation period in 2000 patients with COPD will be conducted to investigate the safety in routine use. The priority investigation items are the adverse events related to the pharmacological class effect of UMEC and VI such as cardiovascular adverse events. This survey is also designed to appropriately collect data from patients receiving long-term treatment with UMEC/VI and elderly patients, of whom limited number was included in the clinical studies. Furthermore, the efficacy in the patients who have switched from monotherapy of approved LAMA or LABA or concomitant use of LAMA and LABA to UMEC/VI therapy will be investigated by collecting data on FEV_1 pre- and post-dose of UMEC/VI.

Table 70. Outline of drug use-results survey (draft)

Objective	Information collection for the safety and efficacy in routine use
Survey method	Central registration system
Patient population	COPD patients
Observation period	1 year
Target sample size	2000
Priority investigation items	Cardiovascular adverse events, effects on glucose level, effects on potassium level, tremor, urinary retention, ocular effects, gallbladder disorder, intestinal obstruction, anticholinergic effects, lower respiratory tract infection, and pneumonia
Major investigation items	Patient demographic characteristics (severity of COPD, smoking history, age, prior treatment history, complications, etc.) Use status of UMEC/VI Concomitant drug or therapy Efficacy evaluation (FEV_1, etc.) Adverse events

PMDA considers it necessary to conduct the survey promptly and provide the collected information appropriately to the clinical practice.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the following indication and dosage and administration. The re-examination period is 8 years; the

drug substance (umeclidinium bromide) is classified as a powerful drug, while the drug product is not classified as a poisonous drug or a powerful drug. The drug product is not classified as a biological product or a specified biological product.

[Indication]	Relief of symptoms of obstructive airway disorder due to chronic obstructive pulmonary disease (chronic bronchitis and pulmonary emphysema) (Only in the case where combination of a long-acting inhaled anticholinergic drug and a long-acting inhaled β_2-agonist is required.)
[Dosage and administration]	The usual adult dosage is 1 inhalation of Umeclidinium Bromide/Vilanterol Trifenatate (62.5 μg as umeclidinium, 25 μg as vilanterol) administered once daily.