# Supplementary materials for:

**Safety of once-daily single-inhaler triple therapy with fluticasone furoate/umeclidinium/vilanterol in Japanese patients with asthma: a long-term (52-week) Phase III open-label study**

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## Inclusion and exclusion criteria

Patients were eligible to be included in the study only if all of the following criteria applied:

1. Patients had to be 18 years of age or older at the time of signing the informed consent.
2. Race: Japanese.
3. Patients with a diagnosis of asthma as defined by the National Institute of Health at least 1 year prior to providing informed consent.1
4. Outpatients were eligible if they had received inhaled corticosteroid/long-acting β2-agonist (ICS/LABA) with or without long-acting muscarinic antagonist (LAMA) as inhaled medications for asthma in stable regimen and dosage for at least 4 weeks prior to Screening Visit (Visit 1) (with medium to high dose of ICS defined by the Japanese Guidelines2) and had control status as shown in the table below. Asthma Control Questionnaire (ACQ)-6 was used for the assessment of control status of asthma at Visit 1 (Screening Visit) (ie, ≤0.75 points showed controlled and >0.75 showed not well controlled).

**Asthma therapy and control status**

|  |  |
| --- | --- |
| **Pre-screening inhaled asthma therapy** | **Control status of asthmaa** |
| ICS+LABA | Not well controlled with ICS (mid-dose)+LABA  Not well controlled with ICS (high-dose)+LABA |
| ICS+LABA+LAMA | Controlled with ICS (mid-dose)+LABA+LAMA  Not well controlled with ICS (mid-dose)+LABA+LAMA  Controlled with ICS (high-dose)+LABA+LAMA |

aACQ-6 at Screening and ACQ-7 at Week 0, Week 24, and Week 52/Withdrawal were to be used for the assessment of control status of asthma (ie, ≤0.75 points showed controlled and >0.75 showed not well controlled).

ACQ, Asthma Control Questionnaire; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist.

1. All patients had to be able to replace their current short-acting β2-agonist (SABA) inhaler with salbutamol aerosol inhaler at Visit 1 as needed for the duration of the study. Patients were able to withhold salbutamol for at least 6 hours prior to clinic visit.
2. Both male and female patients were included. A female patient was eligible to participate if she was not pregnant and not breastfeeding.
3. All patients had to be capable of giving signed informed consent.

Patients were excluded from the study if any of the following criteria applied:

1. Chest X-ray documented pneumonia in the 6 weeks prior to Visit 1.
2. Any asthma exacerbation requiring a change in maintenance asthma therapy in the 6 weeks prior to Visit 1. Note: Patients requiring a temporary change in asthma therapy (eg, oral corticosteroids or increased dose of ICS) to treat an exacerbation in the 6 weeks prior to Visit 1 were not to be explicitly excluded at Visit 1 provided that, at the investigator’s discretion, the patient’s condition was stable after they had resumed their pre-exacerbation maintenance asthma therapy (without modification) and they were considered appropriate for enrollment into this study of up to 12 months’ duration.
3. Patients with the diagnosis of chronic obstructive pulmonary disease (COPD), as per Global Initiative for Chronic Obstructive Lung Disease guidelines,3 including all of the following:

* History of exposure to risk factors (ie, especially tobacco smoke, occupational dusts and chemicals, smoke from home cooking and heating fuels) (for tobacco smoke, see Exclusion Criterion 16);

and

* A post-salbutamol forced expiratory volume in 1 second (FEV1)/forced vital capacity ratio of <0.70 and a post-salbutamol FEV1 of ≤70% of predicted normal values (diagnosis prior to Visit 1 acceptable);   
  and
* Onset of disease ≥40 years of age.

1. Patients with current evidence of pneumonia, active tuberculosis, lung cancer, significant bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases, or other active pulmonary diseases or abnormalities other than asthma.
2. Immune suppression (eg, human immunodeficiency virus or lupus) or other risk factors for pneumonia (eg, neurological disorders affecting control of the upper airway, such as Parkinson’s disease or myasthenia gravis). Patients at potentially high risk (eg, very low body mass index [BMI], severely malnourished, or very low FEV1) were to be only included at the discretion of the investigator.
3. Patients with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, urogenital, nervous system, musculoskeletal, skin, sensory, endocrine (including uncontrolled diabetes or thyroid disease), or hematological abnormalities that are uncontrolled. Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the patient at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
4. Unstable liver disease as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, cirrhosis, or known biliary abnormalities (with the exception of Gilbert’s syndrome or asymptomatic gallstones). Note: Chronic stable hepatitis B and C were acceptable if the patient otherwise met entry criteria.
5. Evidence of a clinically significant abnormality in the 12-lead electrocardiogram (ECG) performed during Screening. The investigator determined the clinical significance of each abnormal ECG finding in relation to the patient’s medical history and excluded patients who would be at undue risk by participating in the trial. An abnormal and clinically significant finding was defined as a 12-lead tracing that was interpreted as, but not limited to, any of the following:

* atrial fibrillation with rapid ventricular rate >120 beats per minute
* sustained or non-sustained ventricular tachycardia
* second-degree heart block Mobitz type II and third-degree heart block (unless pacemaker or defibrillator had been inserted)
* QT interval corrected for heart rate by Fridericia’s formula (QTcF) ≥500 msec in patients with QRS <120 msec and QTcF ≥530 msec in patients with QRS ≥120 msec.

1. Patients with any of the following at Screening (Visit 1) were excluded:

* myocardial infarction or unstable angina in the last 6 months
* unstable or life-threatening cardiac arrhythmia requiring intervention in the last 3 months
* New York Heart Association Class IV heart failure.

1. Patients with a medical condition such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy, or bladder neck obstruction were to be included only if in the opinion of the investigator the benefit outweighed the risk and that the condition did not contraindicate study participation.
2. Patients with carcinoma that had not been in complete remission for at least 5 years. Patients who had had carcinoma in situ of the cervix, squamous cell carcinoma, and basal cell carcinoma of the skin were not to be excluded based on the 5-year waiting period if the patient had been considered cured by treatment.
3. Patients with a history of psychiatric disease, intellectual deficiency, poor motivation, or other conditions that could limit the validity of informed consent to participate in the study.
4. Medication prior to spirometry: Patients who were medically unable to withhold their salbutamol for the 6-hour period required prior to spirometry testing at each study visit.
5. Patients with a known or suspected history of alcohol or drug abuse within the last 2 years.
6. A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, β2-agonist, lactose/severe milk protein, or magnesium stearate.
7. Patients who were current smokers (defined as patients who had used inhaled tobacco products within the 12 months prior to Visit 1 [ie, cigarettes, e-cigarettes/vaping, cigars, or pipe tobacco]), or former smokers with a smoking history of ≥10 pack years (eg, ≥20 cigarettes/day for 10 years).
8. Patients at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that could limit compliance for scheduled visits.
9. Study investigators, sub-investigators, study coordinators, employees of a participating investigator or study site, or immediate family members of the aforementioned that were involved with this study.
10. In the opinion of the investigator, any patient who was unable to read study related materials and/or was not able to complete the study.

**Supplementary Table 1.** Summary of shifts from baseline relative to normal range in clinical chemistry (A) and hematology (B) (ITT population).

**A**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Change category** | **Group 1a**  **(n=47)** | **Step-up groupb**  **(n=9)** | **Group 2c**  **(n=55)** | **Total (N=111)** |
| **Alanine aminotransferase (IU/L)** | |  |  |  |  |
| Worst case post baseline, n (%)d | To low | 0 | 0 | 0 | 0 |
| To normal or no change | 45 (96) | 9 (100) | 51 (93) | 105 (95) |
| To high | 2 (4) | 0 | 4 (7) | 6 (5) |
| **Albumin (g/L)** |  |  |  |  |  |
| Worst case post baseline, n (%)d | To low | 1 (2) | 0 | 1 (2) | 2 (2) |
| To normal or no change | 45 (96) | 9 (100) | 53 (96) | 107 (96) |
|  | To high | 1 (2) | 0 | 1 (2) | 2 (2) |
| **Alkaline phosphatase (IU/L)** | |  |  |  |  |
| Worst case post baseline, n (%)d | To low | 1 (2) | 0 | 1 (2) | 2 (2) |
| To normal or no change | 45 (96) | 9 (100) | 52 (95) | 106 (95) |
| To high | 1 (2) | 0 | 2 (4) | 3 (3) |
|  |  |  |  |  |  |
| **Aspartate aminotransferase (IU/L)** | |  |  |  |  |
| Worst case post baselined | To low | 0 | 0 | 0 | 0 |
| To normal or no change | 46 (98) | 9 (100) | 52 (95) | 107 (96) |
|  | To high | 1 (2) | 0 | 3 (5) | 4 (4) |
| **Bilirubin (µmol/L)** |  |  |  |  |  |
| Worst case post baseline, n (%)d | To low | 2 (4) | 0 | 2 (4) | 4 (4) |
| To normal or no change | 43 (91) | 9 (100) | 53 (96) | 105 (95) |
|  | To high | 2 (4) | 0 | 0 | 2 (2) |
| **Calcium (mmol/L)** |  |  |  |  |  |
| Worst case post baseline, n (%)d | To low | 0 | 0 | 1 (2) | 1 (<1) |
| To normal or no change | 47 (100) | 9 (100) | 53 (96) | 109 (98) |
| To high | 0 | 0 | 1 (2) | 1 (<1) |
| **Creatinine (µmol/L)** |  |  |  |  |  |
| Worst case post baseline, n (%)d | To low | 3 (6) | 0 | 3 (5) | 6 (5) |
| To normal or no change | 41 (87) | 7 (78) | 47 (85) | 95 (86) |
|  | To high | 3 (6) | 2 (22) | 5 (9) | 10 (9) |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Direct bilirubin (µmol/L)** | |  |  |  |  |
| Worst case post baseline, n (%)d | To low | 0 | 0 | 0 | 0 |
| To normal or no change | 46 (98) | 9 (100) | 55 (100) | 110 (>99) |
| To high | 1 (2) | 0 | 0 | 1 (<1) |
| **Glucose (mmol/L)** |  |  |  |  |  |
| Worst case post baseline, n (%)d | To low | 0 | 1 (11) | 0 | 1 (<1) |
| To normal or no change | 34 (72) | 7 (78) | 41 (75) | 82 (74) |
|  | To high | 13 (28) | 1 (11) | 14 (25) | 28 (25) |
| **Potassium (mmol/L)** |  |  |  |  |  |
| Worst case post baseline, n (%)d | To low | 1 (2) | 0 | 4 (7) | 5 (5) |
| To normal or no change | 45 (96) | 9 (100) | 50 (91) | 104 (94) |
| To high | 1 (2) | 0 | 1 (2) | 2 (2) |
| **Protein (g/L)** |  |  |  |  |  |
| Worst case post baseline, n (%)d | To low | 7 (15) | 3 (33) | 8 (15) | 18 (16) |
| To normal or no change | 40 (85) | 6 (67) | 47 (85) | 93 (84) |
|  | To high | 0 | 0 | 0 | 0 |
| **Sodium (mmol/L)** |  |  |  |  |  |
| Worst case post baseline, n (%)d | To low | 0 | 0 | 0 | 0 |
| To normal or no change | 47 (100) | 9 (100) | 54 (98) | 110 (>99) |
|  | To high | 0 | 0 | 1 (2) | 1 (<1) |
| **Urea (mmol/L)** |  |  |  |  |  |
| Worst case post baseline, n (%)d | To low | 3 (6) | 0 | 4 (7) | 7 (6) |
| To normal or no change | 42 (89) | 9 (100) | 50 (91) | 101 (91) |
|  | To high | 2 (4) | 0 | 1 (2) | 3 (3) |

**B**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Change category** | **Group 1†**  **(n=47)** | | **Step-up group‡**  **(n=9)** | | **Group 2§**  **(n=55)** | | **Total (N=111)** | |
| **Basophils/leukocytes (%)** | |  |  | |  | |  | |
| Worst case post baseline, n (%)d | To low | 0 | | 0 | | 0 | | 0 | |
| To normal or no change | 46 (98) | | 9 (100) | | 52 (95) | | 107 (96) | |
| To high | 1 (2) | | 0 | | 3 (5) | | 4 (4) | |
| **Eosinophils/leukocytes (%)** | |  |  | |  | |  | |
| Worst case post baseline, n (%)d | To low | 0 | | 0 | | 0 | | 0 | |
| To normal or no change | 35 (74) | | 7 (78) | | 47 (85) | | 89 (80) | |
|  | To high | 12 (26) | | 2 (22) | | 8 (15) | | 22 (20) | |
| **Erythrocyte mean corpuscular hemoglobin (pg)** | |  |  | |  | |  | |
| Worst case post baseline, n (%)d | To low | 1 (2) | | 0 | | 2 (4) | | 3 (3) | |
| To normal or no change | 45 (96) | | 9 (100) | | 53 (96) | | 107 (96) | |
|  | To high | 1 (2) | | 0 | | 0 | | 1 (<1) | |
| **Erythrocyte mean corpuscular volume (fL)** | |  |  | |  | |  | |
| Worst case post baseline, n (%)d | To low | 0 | | 0 | | 1 (2) | | 1 (<1) | |
| To normal or no change | 46 (98) | | 9 (100) | | 51 (93) | | 106 (95) | |
|  | To high | 1 (2) | | 0 | | 3 (5) | | 4 (4) | |
| **Erythrocytes (1012/L)** |  |  | |  | |  | |  | |
| Worst case post baseline, n (%)d | To low | 4 (9) | | 0 | | 4 (7) | | 8 (7) | |
| To normal or no change | 43 (91) | | 9 (100) | | 50 (91) | | 102 (92) | |
|  | To high | 0 | | 0 | | 1 (2) | | 1 (<1) | |
| **Hematocrit (fraction of 1)** | |  |  | |  | |  | |
| Worst case post baseline, n (%)d | To low | 2 (4) | | 0 | | 0 | | 2 (2) | |
| To normal or no change | 45 (96) | | 9 (100) | | 53 (96) | | 107 (96) | |
|  | To high | 0 | | 0 | | 2 (4) | | 2 (2) | |
| **Hemoglobin (g/L)** |  |  | |  | |  | |  | |
| Worst case post baseline, n (%)d | To low | 5 (11) | | 0 | | 3 (5) | | 8 (7) | |
| To normal or no change | 42 (89) | | 9 (100) | | 51 (93) | | 102 (92) | |
|  | To high | 0 | | 0 | | 1 (2) | | 1 (<1) | |
| **Leukocytes (109/L)** |  |  | |  | |  | |  | |
| Worst case post baseline, n (%)d | To low | 6 (13) | | 0 | | 3 (5) | | 9 (8) | |
| To normal or no change | 39 (83) | | 8 (89) | | 50 (91) | | 97 (87%) | |
|  | To high | 2 (4) | | 1 (11) | | 2 (4) | | 5 (5) | |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Lymphocytes/leukocytes (%)** | |  |  | |  | |  | |
| Worst case post baseline, n (%)d | To low | 7 (15) | | 2 (22) | | 8 (15) | | 17 (15) | |
| To normal or no change | 40 (85) | | 7 (78) | | 47 (85) | | 94 (85) | |
|  | To high | 0 | | 0 | | 0 | | 0 | |
| **Monocytes/leukocytes (%)** | |  |  | |  | |  | |
| Worst case post baseline, n (%)d | To low | 0 | | 0 | | 0 | | 0 | |
| To normal or no change | 40 (85) | | 8 (89) | | 49 (89) | | 97 (87) | |
|  | To high | 7 (15) | | 1 (11) | | 6 (11) | | 14 (13) | |
| **Neutrophils/leukocytes (%)** | |  |  | |  | |  | |
| Worst case post baseline, n (%)d | To low | 0 | | 0 | | 2 (4) | | 2 (2) | |
| To normal or no change | 41 (87) | | 7 (78) | | 46 (84) | | 94 (85) | |
|  | To high | 6 (13) | | 2 (22) | | 7 (13) | | 15 (14) | |
| **Platelets (109/L)** |  |  | |  | |  | |  | |
| Worst case post baseline, n (%)d | To low | 0 | | 0 | | 0 | | 0 | |
| To normal or no change | 46 (98) | | 9 (100) | | 50 (91) | | 105 (95) | |
|  | To high | 1 (2) | | 0 | | 5 (9) | | 6 (5) | |

aPatients allocated to receive FF/UMEC/VI 100/62.5/25mcg; bPatients switching medication from FF/UMEC/VI 100/62.5/25mcg to 200/62.5/25mcg at Week 24; cPatients allocated to receive FF/UMEC/VI 200/62.5/25mcg; dAny patient with a shift from baseline to outside the normal range at any time post baseline throughout the study.

FF, fluticasone furoate; ITT, intention-to-treat; UMEC, umeclidinium; VI, vilanterol.

**Supplementary Table 2.** On-treatment LS mean change from baseline in efficacy parameters by dose group (ITT population).

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | |  | **Group 1a**  **(n=47)** | | **Step-up groupb**  **(n=9)** | | **Group 2c**  **(n=55)** | | **Total  (N=111)** |
| **FEV1 (L)** | |  |  | |  | |  | |  |
| Baseline | | n | 47 | | 9 | | 55 | | 111 |
| Mean (SD) | 2.4 (0.71) | | 2.3 (0.68) | | 2.3 (0.72) | | 2.3 (0.71) |
| Week 24 | | n | 46 | | 9 | | 52 | | 107 |
| Mean (SD) | 2.7 (0.75) | | 2.2 (0.70) | | 2.4 (0.79) | | 2.5 (0.78) |
| Change from baseline | | Mean (SD) | 0.3 (0.31) | | -0.1 (0.31) | | 0.1 (0.27) | | 0.2 (0.30) |
| Week 52 | | n | 46 | | 8 | | 51 | | 105 |
| Mean (SD) | 2.7 (0.70) | | 2.4 (0.80) | | 2.4 (0.76) | | 2.5 (0.74) |
| Change from baseline | | Mean (SD) | 0.2 (0.34) | | 0.1 (0.24) | | 0.1 (0.25) | | 0.2 (0.29) |
| **ACQ-7 total score** | | | |  | |  | |  | |
| Baseline | | n | 47 | | 9 | | 55 | | 111 |
|  | | Mean (SD) | 1.5 (0.44) | | 1.7 (0.75) | | 1.5 (0.63) | | 1.5 (0.57) |
| Week 24 | | n | 46 | | 9 | | 52 | | 107 |
| Mean (SD) | 0.7 (0.47) | | 1.8 (0.66) | | 1.1 (0.72) | | 1.0 (0.68) |
| Change from baseline | | Mean (SD) | -0.7 (0.50) | | 0.1 (1.15) | | -0.4 (0.73) | | -0.5 (0.72) |
| Week 52 | | n | 46 | | 8 | | 51 | | 105 |
| Mean (SD) | 0.7 (0.57) | | 1.0 (0.45) | | 1.0 (0.72) | | 0.9 (0.64) |
| Change from baseline | | Mean (SD) | -0.72 (0.67) | | -0.82 (0.83) | | -0.52 (0.67) | | -0.63 (0.68) |
| **SGRQ total score** |  | | |  | |  | |  | |
| Baseline | | n | 47 | | 9 | | 55 | | 111 |
|  | | Mean (SD) | 27.4 (11.36) | | 23.8 (9.74) | | 31.3 (15.96) | | 29.0 (13.85) |
| Week 24 | | n | 46 | | 9 | | 52 | | 107 |
| Mean (SD) | 16.7 (9.53) | | 22.1 (12.78) | | 24.4 (15.18) | | 20.9 (13.25) |
| Change from baseline | | Mean (SD) | -10.3 (10.32) | | -1.7 (11.01) | | -7.7 (12.72) | | -8.3 (11.74) |
| Week 52 | | n | 46 | | 8 | | 51 | | 105 |
| Mean (SD) | 15.8 (9.54) | | 16.1 (8.03) | | 22.8 (15.55) | | 19.2 (13.12) |
| Change from baseline | | Mean (SD) | -11.2 (10.41) | | -9.8 (9.09) | | -9.1 (13.22) | | -10.1 (11.73) |
| **AQLQ total score** |  | | |  | |  | |  | |
| Baseline | | n | 47 | | 9 | | 55 | | 111 |
|  | | Mean (SD) | 5.5 (0.50) | | 5.3 (0.28) | | 5.2 (0.90) | | 5.3 (0.72) |
| Week 24 | | n | 46 | | 9 | | 52 | | 107 |
| Mean (SD) | 6.1 (0.57) | | 5.4 (0.84) | | 5.5 (0.86) | | 5.7 (0.79) |
| Change from baseline | | Mean (SD) | 0.6 (0.58) | | 0.1 (0.76) | | 0.3 (0.74) | | 0.4 (0.69) |
| Week 52 | | n | 46 | | 8 | | 51 | | 105 |
| Mean (SD) | 6.0 (0.60) | | 5.7 (0.67) | | 5.7 (0.90) | | 5.9 (0.78) |
| Change from baseline | | Mean (SD) | 0.6 (0.57) | | 0.5 (0.41) | | 0.5 (0.79) | | 0.6 (0.67) |

aPatients allocated to receive FF/UMEC/VI 100/62.5/25mcg; bPatients switching medication from FF/UMEC/VI 100/62.5/25mcg to 200/62.5/25mcg at Week 24; cPatients allocated to receive FF/UMEC/VI 200/62.5/25mcg.  
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 second; FF, fluticasone furoate; ITT, intention-to-treat; LS, least squares; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

## References

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