Evaluation of Safety and Clinical Outcomes of FF/UMEC/VI therapy in patients with Asthma in Japan

Interim Analysis of General Drug Use Investigation

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ABSTRACT

Background: Following approval for asthma treatment in Japan, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) maintenance treatment was included in the Japanese guidelines for adult asthma 2021.

Objective: To assess safety, including cardiovascular (CV) event risk, and clinical outcomes in routine clinical practice in Japanese patients with asthma initiating treatment with FF/UMEC/VI.

Methods: This prospective, observational, post-marketing surveillance study in Japan assessed patients with asthma who were prescribed once-daily single-inhaler triple therapy with FF/UMEC/VI (100/62.5/25 μg or 200/62.5/25 μg) for the first time. Adverse drug reactions (ADRs; investigator assessed events related to FF/UMEC/VI), effectiveness (investigator assessment of course of clinical outcomes; respiratory function, asthma control test score, and asthma exacerbations), and patient characteristics at baseline and end of observation period were collected using an electronic data capture system. Results are presented descriptively.

Results: For these interim results, at data cut-off, 143 patients received FF/UMEC/VI initial doses of 100/62.5/25 μg (n=30, 21.0%) and 200/62.5/25 μg (n=113, 79.0%). ADRs were reported in 15 (10.5%) patients, including one non-serious CV-related ADR (palpitations) and one serious ADR (urinary retention, resolved); cough and dysphonia were the most common ADRs (each: n=4, 2.8%). Across 138 patients assessed for effectiveness, treatment was deemed effective in 130 (94.2%).

Key words: Asthma, Japan, Post-marketing surveillance, Safety, Single-inhaler triple therapy

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Conclusion: This interim analysis identified no new safety concerns and demonstrated effectiveness of FF/UMEC/VI for asthma treatment in Japanese routine clinical practice. The final study readout will provide additional data on safety and effectiveness of FF/UMEC/VI.

INTRODUCTION

Asthma is a common respiratory disease, usually characterized by chronic airway inflammation, which affects 1–29% of the population in different countries[1]. In 2019, the global prevalence of asthma was estimated at 262 million cases[2]. The mean prevalence of asthma in adults in Japan has been reported to range between 6 and 10%, highlighting the importance to the healthcare system of effectively managing this disease[3].

The Japanese guidelines for adult asthma 2021 classify asthma severity into four categories, based on the clinical presentation of the disease[3]. These categories correspond to a four step treatment approach for long-term asthma management ; the first step consists of low-dose inhaled corticosteroids (ICS) with escalation to higher dose of ICS and the addition of concomitant long-acting β_2-agonist (LABA) and/or long-acting muscarinic antagonist (LAMA) therapy if asthma symptoms are not controlled[3]. The 2023 Practical Guidelines for Asthma Management (PGAM) recommend the addition of LAMA to ICS/LABA therapy, i.e., triple therapy, if cough symptoms, sputum or dyspnea remain after ICS/LABA treatment. For patients whose cough, sputum or severe dyspnea are predominant, triple therapy is listed as an initial maintenance therapy (IMT) treatment option to achieve symptom control[4].

Historically, triple therapy for asthma maintenance was only available for administration by multiple inhalers. Real-world data from Japan in 2016 suggest that adherence to triple therapy administered by multiple inhalers is low (38.5%) in patients with asthma[5]. In November 2020, the single-inhaler triple therapy fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) was approved for the treatment of bronchial asthma in Japan[6]. Two ICS dose strengths, FF/UMEC/VI 100/62.5/25 μg and 200/62.5/25 μg, were approved based on the results of a global Phase 3A clinical trial, CAPTAIN (NCT02924688), which assessed the safety and efficacy of the addition of UMEC to medium- or high-dose ICS/LABA treatment (FF/VI) in patients with uncontrolled asthma[7]. In CAPTAIN, the combination of FF/UMEC/VI at either FF dose strength met the primary endpoint, demonstrating significant improvements in least squares mean change from baseline in clinic trough forced expiratory volume in 1 second (FEV_1) at 24 weeks compared with FF/VI therapy (difference of 110 mL [95% confidence interval {CI}: 66–153] and 92 mL [95% CI: 49–135], respectively; $p<0.0001$ for both). Improvements in asthma control were seen as early as 4 weeks across all FF/UMEC/VI dose strengths (including lower dose UMEC [31.25 μg] and pooled analyses), which was sustained throughout the total length of the study (note that these were not adjusted for multiplicity at Week 4).

Across a range of chronic respiratory diseases, including asthma and chronic obstructive pulmonary disease (COPD), the use of LABA and LAMA, either alone or in combination, has been shown to be associated with an increased risk of cardiovascular (CV) events in some stud-

ies[8–12]. In a Taiwanese study using claims data from 284,220 patients with COPD across 2007–2011, the risk of a severe CV event within 30 days of first LABA or LAMA therapy initiation increased by approximately 1.5-fold[9]. In a Phase 3 uncontrolled, open-label clinical trial assessing the safety of once-daily FF/UMEC/VI treatment (100/62.5/25 μg and 200/62.5/25 μg) in 111 Japanese patients with asthma reported no serious adverse events (AEs) related to treatment, CV events were reported in 4.5% (5/111) of patients during 52 weeks of follow-up, although none of these events were major[12]. In consideration of the evidence, CV events were noted as an important identified risk as part of the risk management plan for treatment of COPD with FF/UMEC/VI in the European Union and in Japan, requiring CV events to be monitored alongside triple therapy use in routine clinical practice[13, 14]. As such, further studies on the risk of CV events associated with FF/UMEC/VI in routine clinical practice are necessary.

This interim analysis of an ongoing post-marketing surveillance (PMS) study is the first of its kind to assess the overall safety and clinical outcomes of first-time treatment with FF/UMEC/VI in patients with asthma in routine clinical practice in Japan.

METHODS

1 Study design and patient population

This is a prospective, observational, non-interventional, multicenter, PMS study investigating the safety and effectiveness of once-daily single-inhaler triple therapy with FF/UMEC/VI 100/62.5/25 μg or 200/62.5/25 μg in patients with asthma. The registration period for this study was July 2021—May 2022. To be eligible, patients with diagnosed bronchial asthma were to be prescribed FF/UMEC/VI for the first time per physician's decision, according to package insert information and their usual clinical practice, which was to be administered via the ELLIPTA dry-powder inhaler. Patients were followed from the day of, or day before FF/UMEC/VI initiation (baseline) throughout the observation period of up to 1 year, or until treatment withdrawal/study termination (end of observation period); to reflect routine clinical practice no further patient inclusion or exclusion criteria were applied. Data were captured using the electronic data capture system and the investigator was responsible for imputing the relevant information; patients with fixed Case Report Form (CRF) data were included in the analyses. All patients provided informed, written consent.

This PMS study was reviewed and approved (approval number: GSK08027) by the Ethics Review Board of Kitamachi Clinic (central ethics committee) and conducted in accordance with Japanese Good Post-Marketing Study Practice.

2 Data collection and clinical observations

Patient baseline demographics and clinical characteristics, as well as safety and clinical effectiveness data throughout the observation period, were collected and assessed. All AEs were recorded by the investigator, regardless of whether the AE was related to FF/UMEC/VI treatment. Among the AEs reported, those corresponding to the events in the standard search formula of "CV events" in the Medical Dictionary for Regulatory Activities (MedDRA) were picked-up as a safety specification. AEs assessed by the investigator as related to FF/UMEC/VI were referred to as suspected adverse drug reaction (ADR). ADRs were reported as serious or non-serious, with serious referring to any ADR that may result in death, be life-threatening, result in/prolong existing hospitalization, or result in significant incapacity/disability. Safety was assessed in terms of occurrence and nature of ADRs and the proportion of patients with

ADRs (e.g., CV events) and infections reported during the observation period.

Overall effectiveness for each patient was assessed by investigators based on the course of clinical outcomes throughout the observation period, which included the distribution and change from baseline in respiratory function and asthma control test (ACT) score, and occurrence of events related to asthma exacerbations. Respiratory function tests included peak expiratory flow (PEF), FEV_1, and forced vital capacity (FVC). The ACT is a clinically validated test, patient-based index of asthma control that uses a 5-item scale in which higher scores indicate better asthma control[15]. Asthma-related exacerbations were defined as hospitalization, emergency room visit, ≧3 days oral corticosteroid (OCS) use, unscheduled visit to a medical institution, or 1 day absence from work or school. All effectiveness outcome data were collected at baseline and at the end of the observation period. In addition, PEF and ACT data were collected at 1 month, 3 months, 6 months and 1 year (or at end of observation period) following baseline, and FEV_1, FVC and asthma-related exacerbation events data at 1 year (or the last test during the observation period) following baseline ; baseline asthma-related exacerbations included events in the 1-year period prior to the day of (or day before) FF/UMEC/VI initiation. Change from baseline for these parameters was calculated for each timepoint for those patients who had available data both from the specified timepoint during the observation period and at baseline.

3 Statistical analysis

The proportion of patients with ADRs was calculated for the total safety population (safety analysis set; all patients who initiated treatment and had at least one post-baseline visit) ; ADRs were classified by system organ class and preferred term per MedDRA v25.1[16]. The proportion of patients with ADRs was also reported according to patient baseline characteristics, where the percentage calculations used the number of patients in each patient characteristic subgroup as the denominator.

Overall effectiveness was calculated as the proportion of patients for whom treatment was evaluated as effective in the effectiveness analysis set (effective/not effective). The overall effectiveness analysis set included all patients in the safety analysis set.

For analysis of FEV_1 and FVC, mean (SD) were calculated for the value at baseline and at 1 year (or the last test during the observation period), and value changed from the baseline (changes in each patient) at 1 year (or the last test in the observation period). In respiratory function PEF and ACT, patients with both data at baseline and at each timepoint were eligible for analysis. The proportion of patients who experienced asthma-related exacerbation events were calculated by each event at baseline and 1 year (or at end of observation period if patient withdrew/terminated treatment

ACT score and FEV_1 were also reported according to patient characteristics, including sex, comorbidities, asthma duration, asthma severity, type of asthma, and prior maintenance treatment for asthma. Results are presented descriptively.

RESULTS

1 Patient disposition

At the data cut-off date for this interim analysis of March 17, 2023, 314 patients were enrolled at 62 registered sites. Of those who had a fixed CRF, 143 were included in the safety analysis set, and 138 were included in the effectiveness analysis set (**Table 1**).

Table 1 Patient enrollment

Patient enrollment and the associated study sites	Patients excluded in this analysis
Registered: 314 patients, 62 registered sites	59 patients, no CRF available 1 patient, withdrawal from study
CRF data collected: 254 patients, 53 registered sites	104 patients, no fixed CRF
With CRF data fixed: 150 patients, 37 registered sites	7 patients excluded[a]
Safety analysis set: 143 patients, 37 registered sites	5 patients excluded[b]
Effectiveness analysis set: 138 patients	—

[a] There was no revisit after first prescription date [b] patient was deemed "unevaluable for effectiveness" and effectiveness could not be assessed
CRF: case report form

2 Patient baseline characteristics and daily ICS administration

Patient baseline characteristics were generally balanced between the safety analysis set and the effectiveness analysis set (**Table 2**). Overall, for the 143 patients in the safety analysis set, mean (SD) age was 59.0 (17.3) years, with 85 (59.4%) patients under 65 years of age. The proportions of male and female patients were similar. Comorbid COPD was reported in 13 (9.1%) patients and smoking history showed that 11 (7.7%) patients were previous, and 43 (30.1%) patients were current smokers. The majority of patients had mild or moderate persistent asthma (n=104, 72.7%) and there were 40 (28.0%) patients who were not prescribed maintenance treatment for asthma prior to FF/UMEC/VI initiation (**Table 2**).

Of the 143 patients in the safety analysis set, 21.0% (n=30) of patients received FF/UMEC/VI 100/62.5/25 μg, while 79.0% (n=113) received FF/UMEC/VI 200/62.5/25 μg as initial doses. Overall, during the observation period, a large proportion of patients (n=94, 65.7%) were taking concomitant medications, and 1 (0.7%) patient was taking concomitant therapies other than asthma medication (**Table 3**).

3 Safety profile of FF/UMEC/VI

During the observation period, 15/143 (10.5%) patients in the safety analysis set had ADRs (**Table 4**); serious ADRs were reported in 1/143 (0.7%) patient (urinary retention), which resolved approximately 1 month after FF/UMEC/VI termination. Of the total ADRs, respiratory, thoracic and mediastinal disorders were reported in 9/143 (6.3%) patients, and cardiac disorders (palpitations) were reported in 1/143 (0.7%) patient, with all ADRs resolved or resolving at cut-off. Of the respiratory, thoracic and mediastinal ADRs, cough and dysphonia were the most common, each experienced by 4/143 (2.8%) patients (**Table 4**).

Based on patient demographics, the proportions of patients with ADRs of those aged 65 years or over were 17.2% (10/58), for patients with comorbid COPD 15.4% (2/13) and for those who were current smokers 18.6% (8/43). In terms of clinical characteristics, the proportion of patients with ADRs who had mild intermittent asthma was 21.1% (4/19). ADRs were experienced in 11.7% (12/103) of patients with prior maintenance treatment for asthma, and more specifically, in 12.6% (12/95) of the patients with a treatment history of ICS or ICS/LABA (**Table 5**).

4 Clinical outcomes of FF/UMEC/VI

In the effectiveness analysis set (n=138), 94.2% of patients had treatment assessed as

Table 2　Patient baseline demographics and clinical characteristics

Patient characteristics	Safety analysis set (*n*＝143)	Effectiveness analysis set (*n*＝138)
Sex, *n*（%）		
Male	64（44.8）	63（45.7）
Female	79（55.2）	75（54.3）
Age, years, mean（SD）	59.0（17.3）	58.7（17.5）
Age groups, years, *n*（%）		
＜15	0	0
15－＜65	85（59.4）	83（60.1）
≧65	58（40.6）	55（39.9）
BMI, kg/m^2, mean（SD）	23.98（4.23）	24.00（4.23）
BMI groups, kg/m^2, *n*（%）		
＜18.5	8.0（5.6）	7（5.1）
≧18.5－＜25	49.0（34.3）	48（34.8）
≧25	34.0（23.8）	33（23.9）
Unknown	52.0（36.4）	50（36.2）
Any comorbidity, *n*（%）	79（55.2）	76（55.1）
Renal	2（1.4）	2（1.4）
Hepatic	3（2.1）	3（2.2）
COPD	13（9.1）	13（9.4）
Pregnancy（female patients）, *n*	0	0
Smoking history, *n*（%）		
Never smoked	78（54.5）	76（55.1）
Has ever smoked	11（7.7）	11（8.0）
Current smoker	43（30.1）	40（29.0）
Unknown	11（7.7）	11（8.0）
Duration of asthma, years, *n*（%）		
≦2	35（24.5）	34（24.6）
＞2－≦5	25（17.5）	23（16.7）
＞5－≦10	23（16.1）	23（16.7）
＞10	49（34.3）	47（34.1）
Unknown	11（7.7）	11（8.0）
Asthma severity, *n*（%）		
Mild intermittent	19（13.3）	17（12.3）
Mild persistent	33（23.1）	32（23.2）
Moderate persistent	71（49.7）	69（50.0）
Severe persistent	19（13.3）	19（13.8）
Most severe persistent	1（0.7）	1（0.7）

BMI：body mass index, COPD：chronic obstructive pulmonary disease, SD：standard deviation

Table 2　Patient baseline demographics and clinical characteristics（Continued）

Patient characteristics	Safety analysis set (*n*＝143)	Effectiveness analysis set (*n*＝138)
Type of asthma, *n*（%）		
Atopic	61（42.7）	59（42.8）
Non-atopic	62（43.4）	60（43.5）
Unknown	20（14.0）	19（13.8）
Prior maintenance treatment for asthma[a], *n*（%）		
Yes	103（72.0）	98（71.0）
No	40（28.0）	40（29.0）
Prior medication for asthma[a], *n*（%）		
ICS or ICS/LABA	95（66.4）	91（65.9）
Leukotriene receptor antagonist	44（30.8）	43（31.2）
LAMA	20（14.0）	20（14.5）
Theophylline	11（7.7）	10（7.2）
LABA	5（3.5）	5（3.6）
OCS	2（1.4）	2（1.4）
ICS/LABA/LAMA	3（2.1）	3（2.2）

[a] maintenance treatment within the 6 weeks prior to FF/UMEC/VI initiation
FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol, ICS: inhaled corticosteroid, LABA: long-acting β_2-agonist, LAMA: long-acting muscarinic antagonist, OCS: oral corticosteroid

effective（**Table 6**）.

In patients with respiratory function data at baseline and at the end of the observation period, mean（SD）PEF increased from baseline by 35.2（45.6）L/min in the morning（*n*＝32）and 33.6（45.1）L/min at night（*n*＝19）; a change from baseline in morning PEF score was observed using the 1-year timepoint（morning: 42.6［47.4］L/min［*n*＝25］, night: 30.3［42.6］L/min［*n*＝14］）（**e-Table 1**）. Similarly, mean（SD）FEV_1 changed from baseline by 0.201（0.257）L（*n*＝34）at the end of the observation period（**e-Fig. 1**）; mean（SD）FVC changed by 0.198（0.338）L（*n*＝34）（**e-Table 1**）.

In the 99 patients with baseline ACT score data（**e-Fig. 2**）, mean（SD）score was 17.0（5.2）, which increased over months 1（*n*＝76）and 3（*n*＝57）to 20.6（4.1）and 21.8（3.5）, respectively; after which, mean（SD）score remained consistent until the end of the observation period（21.9［3.7］, *n*＝88）. For patients with ACT score data at baseline and each time period, the change in score over time equated to a 3.5（3.9）change at 1 month（*n*＝76）up to a 6.0（5.1）change at 1 year（*n*＝62）; an increase from baseline in ACT was observed at end of the observation period（4.9［5.3］, *n*＝88）（**Fig. 1**）.

In the year prior to initiating FF/UMEC/VI therapy, 28（20.3%）patients experienced an asthma-related exacerbation event, which reduced to 3（2.2%）patients at the end of the observation period（**Table 7**）. A similar trend was seen in patients with data at 1 year（15［17.6%］and 2［2.4%］, respectively［*n*＝85］）（**e-Table 2**）.

5　Clinical outcomes stratified by prior asthma medication

Mean（SD）ACT score and mean（SD）FEV_1（L）stratified by individual patient characteristics at baseline and last measurement are reported in

Table 3　Treatment administration during the observation period

	Safety analysis set (*n*＝143)
Initial ICS dose of FF/UMEC/VI/day, μg, *n* (%)	
100	30 (21.0)
200	113 (79.0)
Maximum ICS dose of FF/UMEC/VI/day during the observation period[a], μg, *n* (%)	
100	29 (20.3)
200	114 (79.7)
Total duration of treatment, days, mean (SD)	256.2 (146.2)
Duration of treatment groups, days, *n* (%)	
＜28	13 (9.1)
≧28－＜84	20 (14.0)
≧84－＜168	14 (9.8)
≧168－＜252	4 (2.8)
≧252－＜365	22 (15.4)
≧365	70 (49.0)
Treatment status at end of observation period[a], *n* (%)	
Continued	85 (59.4)
Withdrawn/terminated	58 (40.6)
Concomitant medications[b], *n* (%)	94 (65.7)
Concomitant therapies[c], *n* (%)	1 (0.7)

[a] Number of patients who continued with FF/UMEC/IV after the study, regardless of whether this was for≧365 days, [b] presence of concomitant medications during the observation period, [c] presence of concomitant asthma therapies other than medications during the observation period
FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol, ICS: inhaled corticosteroid, SD: standard deviation

e-Table 3. Of the 62 patients in the effectiveness analysis set with ACT data available, 24 (38.7%) had received no prior maintenance treatment for asthma; for those patients mean (SD) ACT score changed from 12.5 (3.8) at baseline to 22.6 (2.9) at 1 year. A similar change in ACT score over time was observed in patients who had received prior maintenance treatment, with a score of 18.2 (5.0) at baseline and 21.7 (3.9) at 1 year. In patients with prior ICS＋LABA use (*n*＝32), ACT score changed from 18.1 (5.0) at baseline to 21.9 (3.8) after 1 year. A similar change in ACT score was observed for patients with prior ICS＋LABA＋LAMA use (*n*＝6), changing from 18.7 (5.8) at baseline to 20.2 (4.4) after 1 year.

Of the 34 patients in the effectiveness analysis set with FEV_1 data available, 16 (47.1%) had received no prior maintenance treatment for asthma (**e-Table 3**); of those, mean (SD) FEV_1 changed from 2.2 (0.7) L at baseline to 2.3 (0.7) L after observation period. For patients who had

Table 4 Occurrence of ADRs during the observation period (safety analysis set, *n*=143)

	Total ADRs	Serious ADRs
Patients with ADRs, *n* (%)	15 (10.5)	1 (0.7)
Type of ADRs, *n* (%)[a]		
Respiratory, thoracic and mediastinal disorders	9 (6.3)	0
Cough	4 (2.8)	0
Dysphonia	4 (2.8)	0
Oropharyngeal discomfort	1 (0.7)	0
Gastrointestinal disorders	2 (1.4)	0
Glossitis	1 (0.7)	0
Nausea	1 (0.7)	0
Infections and infestations	1 (0.7)	0
Oropharyngeal candidiasis	1 (0.7)	0
Nervous system disorders	1 (0.7)	0
Taste disorder	1 (0.7)	0
Cardiac disorders	1 (0.7)	0
Palpitations	1 (0.7)	0
Skin and subcutaneous tissue disorders	1 (0.7)	0
Eczema	1 (0.7)	0
Renal and urinary disorders	1 (0.7)	1 (0.7)
Urinary retention	1 (0.7)	1 (0.7)
General disorders and administration site conditions	1 (0.7)	0
Thirst	1 (0.7)	0

[a] Percentage value given is the percentage of the total safety analysis set
ADR: adverse drug reaction

received prior maintenance treatment (*n*=18), a change in FEV_1 was seen from 2.0 (0.7) L at baseline to 2.2 (0.6) L after observation period. In patients with prior ICS+LABA use (*n*=14), FEV_1changed from 2.1 (0.8) to 2.3 (0.6) L after observation period. In patients with prior ICS+LABA+LAMA use (*n*=4), FEV_1 changed from 1.6 (0.3) to 1.8 (0.4) L after observation period.

DISCUSSION

This interim analysis of a PMS study of FF/UMEC/VI therapy in patients with asthma demonstrated that FF/UMEC/VI treatment in routine clinical practice is well tolerated, with no serious CV events reported following treatment initiation. Furthermore, following FF/UMEC/VI initiation, patients had improved respiratory function and symptom control paralleled by reduced asthma-related exacerbation events than before initiating FF/UMEC/VI. Together, our data suggest that FF/UMEC/VI is well tolerated and is of potential clinical benefit to patients with asthma in Japan.

There was one serious ADR (urinary reten-

Table 5　Proportion of patients with ADRs by patient characteristic (safety analysis set, *n*＝143)

Patient characteristics	Patients, *n*	Patients with ADRs, *n* (%)[a]
Total	143	15 (10.5)
Sex		
Male	64	7 (10.9)
Female	79	8 (10.1)
Age groups, years		
＜15	0	0
15－＜65	85	5 (5.9)
≧65	58	10 (17.2)
BMI groups, kg/m^2		
＜18.5	8	1 (12.5)
≧18.5－＜25	49	5 (10.2)
≧25	34	4 (11.8)
Unknown	52	5 (9.6)
Any comorbidity	79	10 (12.7)
Renal	2	0
Hepatic	3	0
COPD	13	2 (15.4)
Pregnancy (female patients)	0	0
Smoking history		
Never smoked	78	6 (7.7)
Has ever smoked	11	1 (9.1)
Current smoker	43	8 (18.6)
Unknown	11	0
Duration of asthma, years		
≦2	35	4 (11.4)
＞2－≦5	25	4 (16.0)
＞5－≦10	23	1 (4.3)
＞10	49	6 (12.2)
Unknown	11	0
Asthma severity		
Mild intermittent	19	4 (21.1)
Mild persistent	33	5 (15.2)
Moderate persistent	71	6 (8.5)
Severe persistent	19	0
Most severe persistent	1	0
Type of asthma		
Atopic	61	5 (8.2)
Non-atopic	62	8 (12.9)
Unknown	20	2 (10.0)
Prior maintenance treatment for asthma[b]		
Yes	103	12 (11.7)
No	40	3 (7.5)
Treatment history of ICS or ICS/LABA[b]	95	12 (12.6)

[a] The percentage values given are the percentage of the number of patients with that characteristic, rather than the safety analysis set　[b] maintenance treatment within the 6 weeks prior to FF/UMEC/VI initiation

ADR: adverse drug reaction, BMI: body mass index, COPD: chronic obstructive pulmonary disease, FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol, ICS: inhaled corticosteroid, LABA: long-acting β_2-agonist

Table 6 Proportion of patients with treatment assessed as effective in overall assessment (effectiveness analysis set, *n*＝138)

Patient characteristics	Patients, *n*	Patients with treatment assessed as effective, *n* (%)[a]
Total	138	130 (94.2)
Sex		
Male	63	60 (95.2)
Female	75	70 (93.3)
Age group, years		
＜15	0	0
15－＜65	83	81 (97.6)
≧65	55	49 (89.1)
BMI groups, kg/m^2		
＜18.5	7	7 (100.0)
≧18.5－＜25	48	45 (93.8)
≧25	33	31 (93.9)
Unknown	50	47 (94.0)
Any comorbidity	76	70 (92.1)
Renal	2	2 (100.0)
Hepatic	3	3 (100.0)
COPD	13	11 (84.6)
Pregnancy (female patients)	0	0
Smoking history		
Never smoked	76	71 (93.4)
Has ever smoked	11	11 (100.0)
Current smoker	40	37 (92.5)
Unknown	11	11 (100.0)
Duration of asthma, years		
≦2	34	32 (94.1)
＞2－≦5	23	22 (95.7)
＞5－≦10	23	22 (95.7)
＞10	47	44 (93.6)
Unknown	11	10 (90.9)
Asthma severity		
Mild intermittent	17	15 (88.2)
Mild persistent	32	30 (93.8)
Moderate persistent	69	66 (95.7)
Severe persistent	19	18 (94.7)
Most severe persistent	1	1 (100.0)
Type of asthma		
Atopic	59	57 (96.6)
Non-atopic	60	55 (91.7)
Unknown	19	18 (94.7)
Prior maintenance treatment for asthma[b]		
Yes	98	90 (91.8)
No	40	40 (100.0)

[a] The percentage values given for patients with treatment deemed as effective by the investigator was calculated from the number of patients within each specified characteristic sub-category [b] maintenance treatment within the 6 weeks prior to FF/UMEC/VI initiation

ADR: adverse drug reaction, BMI: body mass index, COPD: chronic obstructive pulmonary disease, FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol, ICS: inhaled corticosteroid, LABA: long-acting β_2-agonist

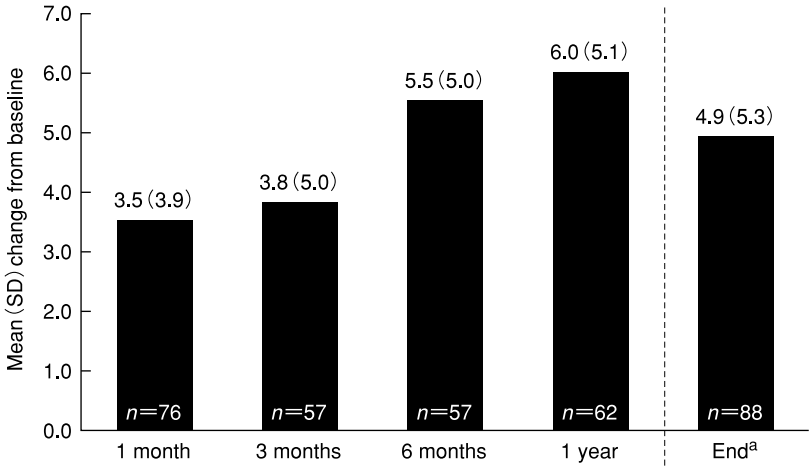

Fig. 1 Change from baseline in ACT score following FF/UMEC/VI initiation
Change from baseline (day of, or day before FF/UMEC/VI initiation) was calculated for each timepoint for those patients who had available data both from that timepoint and at baseline.
[a] End of observation period, 1 year after the initiation of treatment or at withdrawal/termination of treatment with FF/UMEC/VI
ACT: Asthma Control Test, FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol, SD: standard deviation

Table 7 Asthma-related exacerbation events in the year prior to FF/UMEC/VI initiation and at end of observation period (effectiveness analysis set, *n*=138)

Patients who experienced asthma-related exacerbation events, *n* (%)	1 year prior to FF/UMEC/VI initiation0	End of observation period[a]
Any asthma-related exacerbation event	28 (20.3)	3 (2.2)
Hospitalization	3 (2.2)	0
ER treatment	1 (0.7)	0
≧3 days OCS use	15 (10.9)	3 (2.2)
Unscheduled visit to a medical institution	21 (15.2)	3 (2.2)
1 day absence from work or school	6 (4.3)	1 (0.7)

[a] End of observation period, 1 year after the initiation of treatment or at withdrawal/termination of treatment with FF/UMEC/VI
ER: emergency room, FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol, OCS: oral corticosteroid

tion) reported in this study and other non-serious ADRs reported, including taste disorder and eczema (one of each), which are consistent with those described by Hozawa, et al. in the subset of Japanese patients of the Phase 3 CAPTAIN trial[12]. In our study, CV-related ADRs, palpitations, were reported in<1% of patients, a lower proportion than the 4.5% of Japanese patients with asthma that experienced an AE of special interest associated with CV effects in CAPTAIN[12]. Further efficacy studies have also reported low CV event occurrences (<1-3%) associated with FF/UMEC/VI therapy in patients with asthma[7, 17] suggestive of a favorable

safety profile. In contrast to previous reports about the risks of CV events associated with LABA use[8–12], the low proportion of reported CV events during this PMS study may suggest that there is no increased CV event risk associated with FF/UMEC/VI therapy in routine clinical practice.

This is the first prospective, observational study to assess the safety and overall effectiveness of FF/UMEC/VI therapy in daily clinical practice in a general population of Japanese patients with asthma. In this study, 94.2% of patients had treatment assessed as effective.

Lung function has previously been assessed in an open-label study of patients with asthma in Japan[18]. Results showed that FEV_1 and FVC were improved following treatment escalation from ICS/LABA to FF/UMEC/VI (200/62.5/25 μg). Similarly, in our study, patient respiratory function, as measured by PEF, FEV_1 and FVC, tended to be higher, indicating improvement, at the end of the observation period than from baseline measurements, though no formal statistical analysis was performed. Given the small sample size in our study, further evidence is required to draw conclusions on changes in respiratory function following FF/UMEC/VI treatment initiation in routine clinical practice.

Patient asthma control in our study tended to improve over time, as indicated by a higher mean ACT score, after FF/UMEC/VI treatment initiation, though no formal statistical analysis was performed. This expands on the findings of the Umeda, et al. study that reported significant increases in ACT score in 104 patients with asthma in Japan treated with FF/UMEC/VI[18]. Baseline ACT scores were lower in our study compared with the Umeda, et al. study suggesting that asthma symptoms in our patient population were less well controlled. Nonetheless, our data showed that patient lung function and symptom control improved following FF/UMEC/VI treatment, in the small number of patients with data available, suggesting FF/UMEC/VI is of benefit to a range of patients with varying levels of symptom control. Despite treatment guidance to optimize control[19], evidence from routine clinical practice suggests that there are still patients who are not optimally controlled[5].

Results from this study indicate that patients with asthma had reduced numbers of asthma-related exacerbation events 1 year after initiating FF/UMEC/VI therapy from the previous year. These data expand on the findings from the Phase 3A CAPTAIN clinical trial that reported dose-related reductions in the annualized rate of moderate and/or severe exacerbations in patients prescribed FF/UMEC/VI 100/62.5/25 or 100/31.25/25 μg[7], and highlight the potential benefit of FF/UMEC/VI in reducing asthma exacerbations in patients with inadequately controlled asthma in the real world.

This interim study has several limitations. It was not powered to assess clinical outcomes and as such all results are descriptive; therefore, further larger real-world studies investigating the effectiveness of FF/UMEC/VI in clinical practice are required to confirm the findings. Additionally, as this is a single-arm study, no conclusions regarding the benefits of FF/UMEC/VI compared with other treatment options can be made. The non-interventional, observational nature of this study means that the data reported were limited to measures and/or outcomes that could be collected by a physician in a general practice. Particular clinical sites were selected for this study and, as such, they may not be reflective of the wider Japanese healthcare environment; similarly, FF/UMEC/VI treatment initiation, and therefore patient data collection, was at the discretion of the prescribing physician, so the resulting patient population

in this study may not be representative of the general patient population in Japan. Lastly, as the results reported are from an interim analysis with a relatively small sample size, data, in particular ACT score, FEV_1 and FVC, may not be a full reflection of effectiveness outcomes of FF/UMEC/VI. Results from the final analysis and the full patient population are required to confirm these findings.

CONCLUSIONS

This interim analysis in Japanese patients in routine clinical practice showed that FF/UMEC/VI is well tolerated and is an effective treatment option for patients with asthma. No new safety signals were identified. Additionally, the low proportion of patients experiencing drug-related CV events and other ADRs support the safety profile of FF/UMEC/VI reported in clinical trials. Completion of this PMS study will provide further data on the safety and effectiveness of FF/UMEC/VI for the treatment of patients with asthma in routine clinical practice in Japan.

CONFLICTS OF INTEREST

HM, RI, IM, YM, MK, LY, and NT are employees of GSK. RI, YM, MK, LY, and NT own stocks/shares in GSK.

ELLIPTA is owned by/licensed to the GSK group of companies.

DATA AVAILABILITY STATEMENT

GSK makes available anonymized individual participant data and associated documents from interventional clinical studies that evaluate medicines, upon approval of proposals submitted to : https://www.gsk-studyregister.com/en/.

AUTHOR CONTRIBUTIONS

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published. All authors take complete responsibility for the integrity of the data and accuracy of the data analysis. YM was involved in study concept or design, data analysis and interpretation. HM, RI, IM, MK, LY, and NT were involved in data interpretation.

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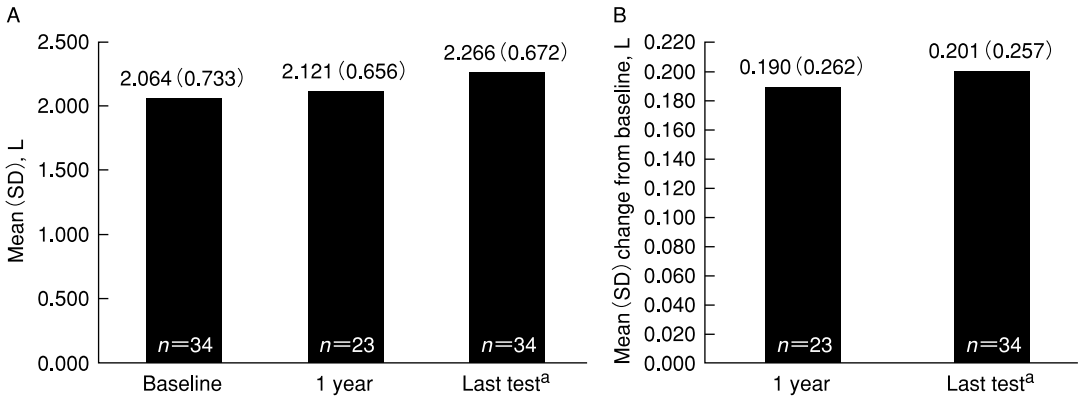
e-Table 1　Respiratory function during the observation period

Clinical outcome	Patients, *n*	Mean（SD）［95% CI］
PEF（morning）, L/min		
Baseline	33	381.1（105.7）
1 month	24	410.2（115.5）
3 months	17	421.5（126.4）
6 months	22	412.4（83.0）
1 year	25	412.6（98.2）
End of observation period[a]	32	423.5（104.3）
PEF change from baseline（morning）, L/min		
1 month	24	20.5（35.2）［5.6-35.4］
3 months	17	43.8（52.6）［16.7-70.8］
6 months	22	43.3（56.4）［18.3-68.3］
1 year	25	42.6（47.4）［23.0-62.2］
End of observation period[a]	32	35.2（45.6）［18.8-51.6］
PEF（night）, L/min		
Baseline	19	395.9（90.1）
1 month	10	438.3（113.8）
3 months	8	466.3（126.7）
6 months	15	422.3（105.8）
1 year	14	409.4（90.5）
End of observation period[a]	19	429.6（100.3）
PEF change from baseline（night）, L/min		
1 month	10	19.4（43.1）［−11.4-50.2］
3 months	8	45.6（66.3）［−9.8-101.1］
6 months	15	31.8（49.1）［4.6-59.0］
1 year	14	30.3（42.6）［5.7-54.9］
End of observation period[a]	19	33.6（45.1）［11.9-55.4］
FVC, L		
Baseline	34	2.730（1.000）
1 year	23	2.677（0.817）
Last test during observation period	34	2.928（0.918）
Amount of FVC change, L		
1 year	23	0.221（0.398）［0.049-0.393］
Last test during observation period	34	0.198（0.338）［0.080-0.316］

[a] End of observation period, 1 year after the initiation of FF/UMEC/VI treatment or at treatment withdrawal/study termination

CI：confidence interval, FF/UMEC/VI：fluticasone furoate/umeclidinium/vilanterol, FVC：forced vital capacity, PEF：peak expiratory flow

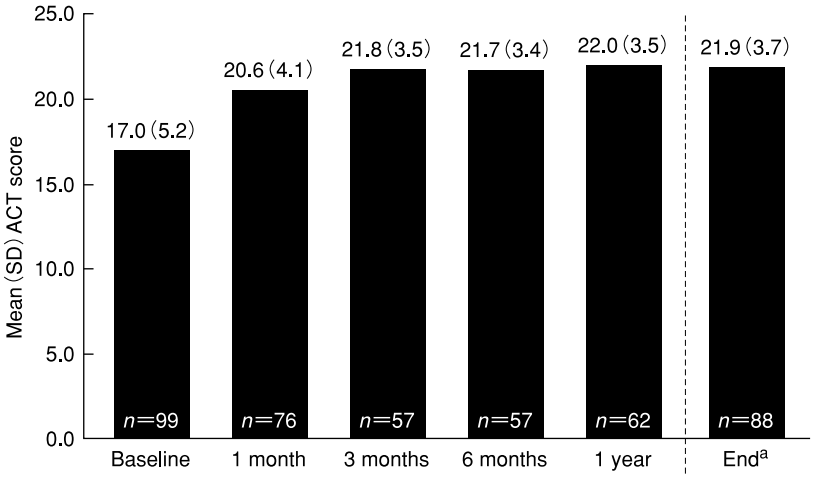


e-Fig. 1 Mean FEV_1 measurements (A) and mean change from baseline in FEV_1 (B) following FF/UMEC/VI initiation

Change from baseline (day of, or day before FF/UMEC/VI initiation) was calculated for each timepoint for those patients who had available data both from that timepoint and at baseline.

[a] Last test, 1 year after the initiation of treatment or at withdrawal/termination of treatment with FF/UMEC/VI

FEV_1: forced expiratory volume in 1 second, FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol, SD: standard deviation



e-Fig. 2 Mean ACT score following FF/UMEC/VI initiation

[a] End of observation period, 1 year after the initiation of treatment or at withdrawal/termination of treatment with FF/UMEC/VI

ACT: Asthma Control Test, FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol, SD: standard deviation

e-Table 2　Asthma-related exacerbation events in the year prior to and after FF/UMEC/VI initiation（*n*＝85）

Patients who experienced asthma-related exacerbation events, *n*（%）	1 year prior to FF/UMEC/VI initiation	1 year after FF/UMEC/VI initiation
Any asthma-related exacerbation event	15（17.6）	2（2.4）
Hospitalization	3（3.5）	0
ER treatment	1（1.2）	0
≧3 days OCS use	7（8.2）	2（2.4）
Unscheduled visit to a medical institution	12（14.1）	2（2.4）
1 day absence from work or school	4（4.7）	1（1.2）

ER：emergency room, FF/UMEC/VI：fluticasone furoate/umeclidinium/vilanterol, OCS：oral corticosteroid

e-Table 3 ACT score and FEV_1 following FF/UMEC/VI initiation by patient characteristics (effectiveness analysis set, $n=138$)

Patient characteristics	ACT score			FEV_1 (L)		
	Patients, *n*	Baseline, mean (SD)	1 year, mean (SD)	Patients, *n*	Baseline, mean (SD)	Last test during observation period, mean (SD)
Effectiveness analysis set	62	16.0 (5.3)	22.0 (3.5)	34	2.1 (0.7)	2.3 (0.7)
Sex						
Male	31	17.2 (5.4)	22.5 (3.3)	19	2.4 (0.6)	2.6 (0.5)
Female	31	14.8 (5.1)	21.5 (3.8)	15	1.6 (0.7)	1.9 (0.7)
Any comorbidity						
Yes	28	17.5 (5.5)	21.9 (4.0)	22	2.1 (0.7)	2.3 (0.7)
No	34	14.8 (4.9)	22.1 (3.2)	12	2.0 (0.8)	2.2 (0.7)
Duration of asthma, years						
≦2	14	12.8 (3.8)	22.2 (3.0)	10	2.1 (0.8)	2.3 (0.8)
>2－≦5	11	15.2 (6.5)	21.8 (4.1)	2	2.6 (0.1)	2.7 (0.0)
>5－≦10	11	14.1 (3.4)	20.8 (4.5)	6	2.0 (0.6)	2.1 (0.6)
>10	24	19.4 (4.6)	22.9 (3.0)	14	2.0 (0.8)	2.2 (0.7)
Unknown	2	12.5 (4.9)	18.5 (2.1)	2	2.3 (1.1)	2.6 (1.0)
Asthma severity						
Mild intermittent	7	16.1 (5.7)	22.4 (2.0)	6	2.2 (0.9)	2.2 (0.9)
Mild persistent	15	17.9 (5.8)	22.7 (2.3)	10	2.1 (0.7)	2.2 (0.6)
Moderate persistent	32	15.1 (5.1)	22.4 (3.7)	15	2.1 (0.8)	2.4 (0.7)
Severe persistent	8	16.0 (5.3)	18.8 (4.7)	3	2.0 (0.7)	2.0 (0.8)
Most severe persistent	0	—	—	0	—	—
Type of asthma						
Atopic	32	14.6 (5.4)	22.1 (4.2)	12	1.9 (0.7)	2.2 (0.6)
Non-atopic	23	17.0 (5.4)	22.2 (3.0)	20	2.1 (0.7)	2.2 (0.7)
Unknown	7	19.0 (3.1)	21.3 (2.3)	2	2.5 (0.7)	2.8 (0.8)
Prior maintenance treatment for asthma[a]						
No	24	12.5 (3.8)	22.6 (2.9)	16	2.2 (0.7)	2.3 (0.7)
Yes	38	18.2 (5.0)	21.7 (3.9)	18	2.0 (0.7)	2.2 (0.6)
ICS	0	—	—	0	—	—
ICS+LABA[b]	32	18.1 (5.0)	21.9 (3.8)	14	2.1 (0.8)	2.3 (0.6)
ICS+LAMA	0	—	—	0	—	—
ICS+LABA+LAMA[a]	6	18.7 (5.8)	20.2 (4.4)	4	1.6 (0.3)	1.8 (0.4)
ICS/LABA combination+LAMA	6	18.7 (5.8)	20.2 (4.4)	4	1.6 (0.3)	1.8 (0.4)
Other	0	—	—	0	—	—

[a] maintenance treatment within the 6 weeks prior to FF/UMEC/VI initiation [b]combination product is included

ACT: Asthma Control Test, FEV_1: forced expiratory volume in 1 second, FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol, ICS: inhaled corticosteroid, LABA: long-acting β_2-agonist, LAMA: long-acting muscarinic antagonist, SD: standard deviation