Original Article

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Real-World Safety of Fluticasone Furoate/Umeclidinium/Vilanterol in Patients with Asthma or Chronic Obstructive Pulmonary Disease (COPD), and Clinical Outcomes in COPD: Post-marketing Surveillance in Korea

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Abstract

Background: Fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) is a single-inhaler triple therapy administered via the ELLIPTA inhaler (GSK). FF/UMEC/VI 100/62.5/25 μg was approved in Korea to treat chronic obstructive pulmonary disease (COPD) in 2018 and asthma in 2022 (100/62.5/25 and 200/62.5/25 μg). Safety and efficacy of FF/UMEC/VI are well established in global clinical trials, though Korean real-world evidence remains limited.

Methods: This Korean multicentre post-marketing surveillance assessed safety and clinical outcomes of FF/UMEC/VI 100/62.5/25 μg in COPD (May 2018–May 2024) and safety of FF/UMEC/VI in asthma (100/62.5/25 μg: August 2022–May 2024; 200/62.5/25 μg: September 2022–May 2024). Safety was assessed by total, serious, and unexpected adverse event and adverse drug reaction (ADR) incidence. For COPD, physicians assessed within-patient improvement in clinical outcomes (lung function [forced expiratory volume in 1 second, forced vital capacity], exacerbations and symptoms [modified Medical Research Council dyspnoea, COPD Assessment Test]).

Results: Overall, 606 patients with COPD and 132 patients with asthma were evaluated. Mean±standard deviation administration for FF/UMEC/VI 100/62.5/25 μg was 254.11±119.97 days overall; 271.83±104.99 for COPD; 20.74±10.87 for integrated asthma; 34.17±13.06 days for asthma with FF/UMEC/VI 200/62.5/25 μg. ADRs occurred in 2.64% (16/606) of patients with COPD and 3.79% (5/132) with asthma. Most ADRs were mild; all serious/unexpected ADRs resolved. Of 33 patients with COPD who reported pneumonia, all events were considered unlikely to be treatment-related. Physicians determined improvement in 74.87% (283/378) of patients with COPD post- versus pre-FF/UMEC/VI administration.

Conclusion: FF/UMEC/VI was well tolerated in Korean patients with asthma or COPD, with no new safety concerns identified. In COPD, within-patient improvement was observed in clinical outcomes post-administration. These results support continued FF/UMEC/VI use in real-world clinical practice in Korea.

Keywords: Adrenergic Beta-2 Agonist; Asthma; Chronic Obstructive Pulmonary Disease; Corticosteroids; Drug Surveillance, Post-marketing; Inhalation Therapy; Korea; Muscarinic Antagonists

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are prevalent chronic respiratory diseases that impose significant socioeconomic burdens[1-4]. In Korea, asthma affects an estimated 3.2%–4.7% of the population[5], whilst COPD affects approximately 13.1%–14.6% of the population[6]. Korean guidelines and international recommendations advise stepwise inhaled pharmacological therapy for effective treatment of both diseases. The 2025 Global Initiative for Asthma (GINA) strategy report, 2024 Korean Academy of Tuberculosis and Respiratory Diseases (KATRD) clinical guidelines and 2021 Korean Guideline for Asthma recommend escalation to inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β_2-agonist (ICS/LAMA/LABA) triple therapy in adults with inadequately controlled asthma despite ICS/LABA maintenance therapy[5,7,8]. For patients at continued risk of COPD exacerbations and a blood eosinophil count ≥300 cells/μL, the 2026 Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy report recommends ICS/LAMA/LABA triple therapy, and the KATRD 2024 clinical guidelines recommend triple therapy for patients with a blood eosinophil count ≥300 cell/μL and history of ≥2 moderate or ≥1 severe exacerbation[9,10]. Despite these recommendations, a substantial proportion of patients with asthma (20%–55%) continue to have uncontrolled disease with ICS/LABA dual therapy globally[11,12], highlighting a persistent gap in treatment optimisation.

The ICS/LAMA/LABA fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI; Trelegy ELLIPTA, GSK, London, UK) is a once-daily single-inhaler triple therapy (SITT) approved for use in Korea. The 100/62.5/25 μg dose was approved in May 2018 for patients with moderate-severe COPD inadequately controlled on ICS/LABA or LABA/LAMA dual therapy[13]; for patients with uncontrolled asthma despite ICS/LABA, FF/UMEC/VI 100/62.5/25 μg was approved for use in August 2022[13], and the 200/62.5/25 μg dose was approved in September 2022[14]. The safety and efficacy of FF/UMEC/VI versus dual therapy has been demonstrated in global randomised clinical trials for both asthma[15] and COPD[16,17]. Beyond controlled clinical trials, real-world studies have begun to provide valuable insights into its safety profile in routine clinical practice[18-20].

Evidence is limited regarding overall safety and clinical outcomes in patients with asthma or COPD under routine clinical settings. Here, we present results of post-marketing surveillance assessing real-world safety of FF/UMEC/VI therapy in Korean patients with uncontrolled COPD or asthma despite dual therapy in clinical practice, and clinical outcomes with FF/UMEC/VI 100/62.5/25 μg in adult patients with COPD.

Materials and Methods

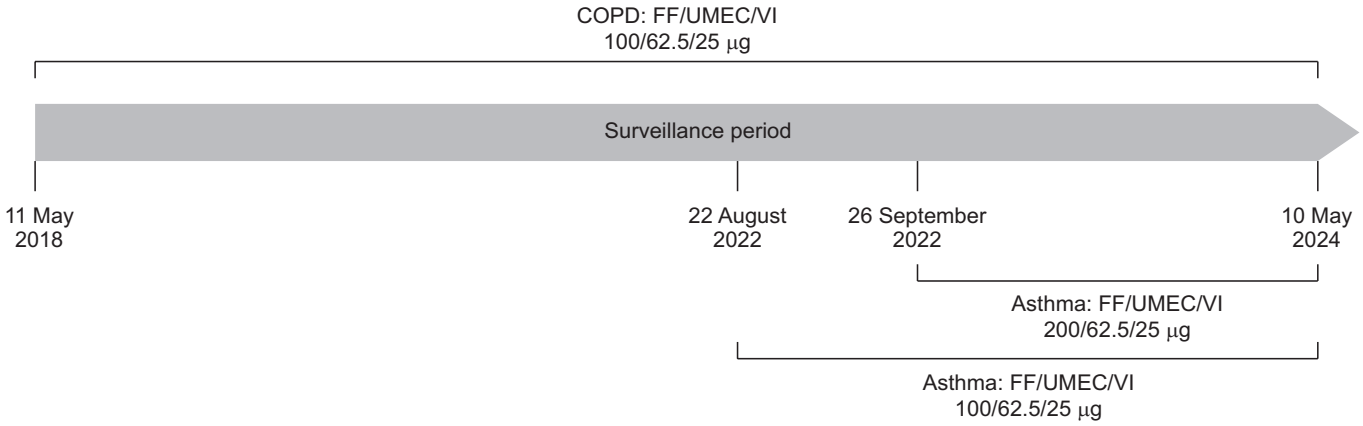
1. Study design

Prospective, multicentre, open-label, post-marketing surveillance was undertaken in Korea to assess the safety of on-label FF/UMEC/VI 100/62.5/25 μg use (n=652) in adult patients with asthma or COPD, and on-label FF/UMEC/VI 200/62.5/25 μg use (n=86) in adult patients with asthma, as maintenance treatment administered via the ELLIPTA dry-powder inhaler. Clinical outcomes with FF/UMEC/VI 100/62.5/25 μg in adult patients with COPD (n=378) were also assessed. Patients <18 years of age were excluded. Data regarding the on-label use of FF/UMEC/VI 100/62.5/25 μg in the treatment of COPD in usual clinical practice was collected via electronic case report forms between May 11, 2018 and May 10, 2024. For FF/UMEC/VI 100/62.5/25 μg treatment in asthma, data were collected between August 22, 2022 and May 10, 2024; for FF/UMEC/VI 200/62.5/25 μg treatment in asthma, data were collected between September 26, 2022 and May 10, 2024 (Figure 1). These studies were reviewed, and ethical approval was provided by the Institutional Review Board of Hanyang University Hospital (PMS 2021-009, June 10, 2021).

2. Study endpoints and objectives

The primary objective was to assess the safety of FF/UMEC/VI 100/62.5/25 μg and 200/62.5/25 μg in patients with asthma or COPD after initiation of treatment. Safety was assessed by the incidence of total, serious and unexpected adverse events (AEs) and adverse drug reactions (ADRs), all of which were recorded by the investigator throughout the study period, whether related or unrelated to FF/UMEC/VI, as defined by the World Health Organization (WHO)[21]. AEs related to FF/UMEC/VI treatment (as assessed by the investigator) were referred to as suspected ADRs; the causal relationship with FF/UMEC/VI was described as being certain, likely, possible, unlikely or unassessable, as defined by the WHO-Uppsala Monitoring Centre[22]. Serious ADRs and serious adverse events (SAEs) were defined as when the event was life-threatening/fatal, resulted in hospitalization or an extension of the hospitalization period, severe or persistent disabilities or function declines, congenital deformities or abnormalities or was an otherwise medically important situation[21]. Unexpected AEs and ADRs were defined as those not currently listed in the local prescription

Figure 1. Study design. COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.



information labels for FF/UMEC/VI 100/62.5/25 and 200/62.5/25 μg[21].

The secondary objective was to assess clinical outcomes with FF/UMEC/VI in patients with asthma >10 weeks post-treatment initiation (100/62.5/25 μg and 200/62.5/25 μg)[7] or COPD >40 weeks post-initiation (100/62.5/25 μg)[18] compared with the pre-initiation period (exacerbations and blood eosinophil counts: ≤12 months prior to initiation; lung function: last recorded forced expiratory volume in 1 second [FEV_1] measurement prior to initiation). However, due to a short administration period for asthma, clinical outcomes could not be assessed for patients with asthma and results were not specified by physicians. Therefore, clinical outcomes with FF/UMEC/VI were only reported in patients with COPD. In patients with COPD, physicians provided their clinical judgement of within-patient improvement post-versus pre-treatment[23-25], based on lung function, history of exacerbations and modified Medical Research Council (mMRC) dyspnoea and COPD Assessment Test (CAT) scores. Mean pre- and post-administration and mean change in lung function was assessed by FEV_1 and forced vital capacity (FVC). COPD exacerbation history was determined by frequency of moderate (requiring treatment with systemic corticosteroids or antibiotics) and severe (requiring hospitalization or emergency department [ED] visit) exacerbations with ≥2 symptoms (increased difficulty in breathing, increased sputum volume or purulent) for ≥2 consecutive days. Mean pre- and post-administration and mean change in mMRC dyspnoea and CAT scores was assessed. Post-administration values were collected at the timepoint closest to the completion of follow-up (52 weeks post-administration ±12-week), and a mean change in score from pre-initiation was calculated.

3. Data analysis

Descriptive statistics were performed to summarise the proportion of patients or mean±standard deviation (SD) for demographics, baseline patient characteristics, treatment and medical history, and administration data for the FF/UMEC/VI 100 population (patients with asthma or COPD receiving FF/UMEC/VI 100/62.5/25 μg), COPD subgroup (patients with COPD receiving FF/UMEC/VI 100/62.5/25 μg) and integrated asthma subgroup (patients with asthma receiving FF/UMEC/VI 100/62.5/25 μg or 200/62.5/25 μg). Descriptive statistics were also performed to summarise the incidence of AEs and ADRs in patients with COPD or asthma. All AEs reported were included in the analysis, regardless of causal relationship with FF/UMEC/VI. All AEs were classified by system organ class (SOC) and preferred term as defined by the International Medical Dictionary for Regulatory Activities (version 27.0). To identify patient demographics and characteristics associated with AEs or ADRs in patients with COPD or asthma, either chi-square tests or Fisher's exact tests were applied. For factors where a significant association was detected, odds ratios (ORs) were estimated using simple or multiple logistic regression analyses. Additionally, in the COPD subgroup, change in lung function and CAT and mMRC scores from the pre- to post-treatment periods were assessed using Wilcoxon signed rank tests.

4. Ethical approval

These studies were reviewed and approved by the Institutional Review Board of Hanyang University (2021-009, June 10, 2021) and complied with all applicable laws regarding subject privacy. No direct subject contact or primary collection of individual human subject data occurred, and all data used in this study were

anonymised. Study results are presented as aggregate analyses that omit subject identification. Institutional Review Board approval was obtained from all study sites. All patients provided written, informed consent.

Results

1. Patient population

In the FF/UMEC/VI 100 population (patients with asthma or COPD receiving FF/UMEC/VI 100/62.5/25 μg), 652 patients were assessed overall across 16 investigation sites, including 46 patients with asthma and 606 patients with COPD; 86 patients with asthma across five investigational sites were included in the FF/UMEC/VI 200/62.5/25 μg subgroup (Figure 2). Baseline characteristics were similar in the FF/UMEC/VI 100 population compared with the COPD subgroup (patients with COPD receiving FF/UMEC/VI 100/62.5/25 μg), with

Figure 2. Patient disposition in (A) fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 μg and (B) 200/62.5/25 μg studies. COPD: chronic obstructive pulmonary disease.

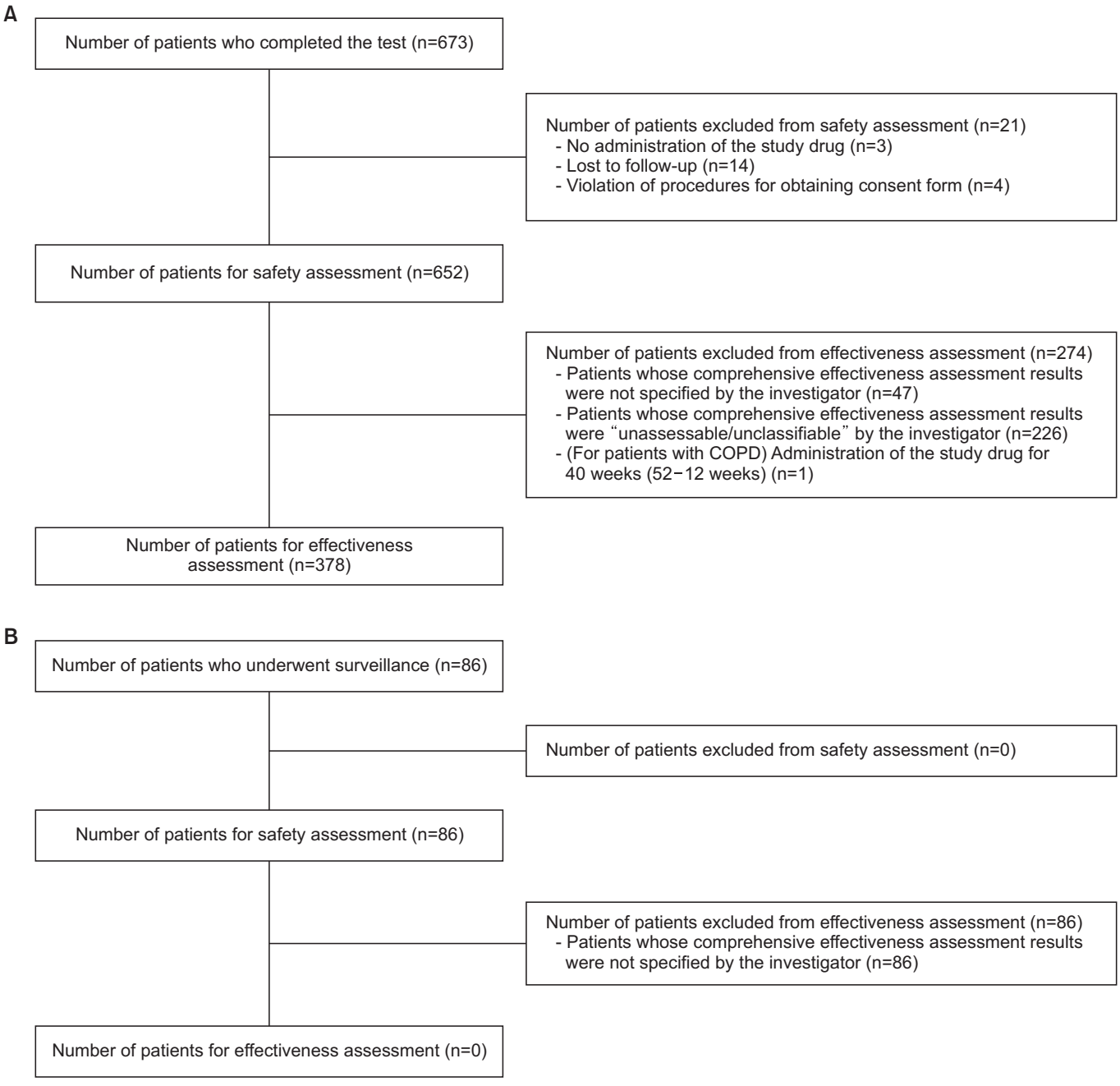


Table 1. Patient demographics and baseline characteristics in patients receiving on-label FF/UMEC/VI

Characteristic	FF/UMEC/VI 100 population* (n=652)	COPD subgroup† (n=606)	Integrated asthma subgroup‡ (n=132)
Male sex	557 (85.43)	522 (86.14)	76 (57.58)
Age			
Mean±SD, yr	70.94±9.61	71.23±8.95	65.86±14.82
<19 years	0	0	1 (0.76)
≥19–<65 years	143 (21.93)	127 (20.96)	49 (37.12)
≥65 years	509 (78.07)	479 (79.04)	82 (62.12)
BMI			
Number	641	595	132
Mean±SD, kg/m^2	23.14±3.89	22.97±3.75	25.00±4.83
Smoking history			
Smoker	105 (16.10)	96 (15.84)	18 (13.64)
Ex-smoker	395 (60.58)	381 (62.87)	36 (27.27)
Non-smoker	152 (23.31)	129 (21.29)	78 (59.09)
COPD diagnosis	606 (92.94)	606 (100)	-
COPD duration§			
Number		601	–
Mean±SD, yr		6.76±5.09	–
Median (min–max), yr		6.00 (0–41.00)	–
COPD severity‖			
Number		597	
Mild		8 (1.32)	–
Moderate		336 (55.45)	–
Severe		182 (30.03)	–
Very severe		71 (11.72)	–
Asthma diagnosis	46 (7.06)	-	132 (100.00)
Asthma duration§			
Number	46	-	131
Mean±SD, yr	5.02±5.09	-	8.08±7.94
Median (min–max), yr	3.50 (0–19.00)	-	6.00 (0–32.00)
Asthma severity¶			
Number	46		132
Mild	23 (50.00)	-	23 (17.42)
Moderate	23 (50.00)	-	78 (59.09)
Severe	0	-	31 (23.48)
Blood eosinophils			
Number	472 (72.62)	435 (71.78)	79 (59.85)
Mean±SD, cells/μL	251.70±256.99	244.77±233.22	338.48±545.50
Treatment history**			
Previous COPD or asthma treatment	648 (99.39)	602 (99.34)	132 (100.00)
Asthma- or COPD-related concomitant medication	408 (62.58)	370 (61.06)	114 (86.36)
Other concomitant medication	460 (70.55)	419 (69.14)	93 (70.45)

Table 1. Continued

Characteristic	FF/UMEC/VI 100 population* (n=652)	COPD subgroup† (n=606)	Integrated asthma subgroup‡ (n=132)
Medical history			
Hepatic impairment	48 (7.36)	45 (7.43)	7 (5.30)
Renal impairment	62 (9.51)	55 (9.08)	11 (8.33)
Other	584 (89.57)	541 (89.27)	114 (86.36)
Total FF/UMEC/VI administration period, day			
100/62.5/25 μg	254.11±119.97	271.83±104.99	20.74±10.87
200/62.5/25 μg	-	-	34.17±13.06

Values are presented as number (%), mean±standard deviation, or median (range).
*Population included patients with asthma or COPD receiving FF/UMEC/VI 100/62.5/25 μg; †Subgroup included patients with COPD receiving FF/UMEC/VI 100/62.5/25 μg (200/62.5/25 μg dose not indicated for COPD); ‡Subgroup included patients with asthma receiving FF/UMEC/VI 100/62.5/25 μg or 200/62.5/25 μg; §Disease duration was calculated by year of informed consent minus year of diagnosis; ‖COPD severity was classified based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric classification as follows: mild (forced expiratory volume in 1 second [FEV_1] ≥80% predicted), moderate (FEV_1 ≥50–<80% predicted), severe (FEV_1 ≥30–<50% predicted), very severe (FEV_1 <30% predicted). Of the 606 patients with sufficient EMR data for COPD severity assessment, COPD severity was collected and classified in the study dataset for 597 patients; ¶Asthma severity was assessed by the investigator based on the Korean Asthma Management Guidelines 2021[8]; **Previous treatments for asthma or COPD can be found in Supplementary Table S1.
FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; COPD: chronic obstructive pulmonary disease; SD: standard deviation; BMI: body mass index.

approximately 85% of patients being male and a mean age of approximately 71 years (Table 1). In the integrated asthma subgroup (patients with asthma receiving FF/UMEC/VI 100/62.5/25 μg or 200/62.5/25 μg), most patients were male (n=76 [57.58%]) with a mean±SD age of 65.86±14.82 years. Most patients had moderate disease (COPD subgroup: n=336/606 [55.45%]; integrated asthma subgroup: n=78/132 [59.09%]). Almost all patients had a history of previous COPD or asthma treatment (FF/UMEC/VI 100 population: n=648/652 [99.39%]; COPD subgroup: n=602/606 [99.34%]; integrated asthma subgroup: n=132/132 [100.00%]), with three quarters of patients with asthma previously receiving ICS/LABA dual therapy (n=99/132 [75%]) (Supplementary Table S1). The mean±SD total administration period for FF/UMEC/VI 100/62.5/25 μg was 254.11±119.97 days for the FF/UMEC/VI 100 population, 271.83±104.99 days for the COPD subgroup and 20.74±10.87 days for the integrated asthma subgroup. For patients with asthma receiving FF/UMEC/VI 200/62.5/25 μg, the mean±SD administration period was 34.17±13.06 days.

2. Patients with COPD

1) Safety

Among the 606 patients with COPD receiving FF/UMEC/VI 100/62.5/25 μg, 2.64% (n=16) experienced a total of 17 ADRs, most of which were mild (Table 2). Respiratory, thoracic and mediastinal disorders were the most commonly reported ADRs (11 events in 10 patients), of which three events were dyspnoea and three events were sore throat. One patient reported two serious ADRs (exacerbation of COPD and dyspnoea), both of which had resolved by the end of the surveillance period. Four unexpected ADRs occurred; all were mild and resolved by the end of the surveillance period. No unexpected serious ADRs were reported, and no new safety concerns were identified.

Overall, 38.61% (number/total number [n/N]= 234/606) of patients with COPD reported 368 AEs and 14.85% (n/N=90/606) reported 115 SAEs (Supplementary Table S2), the majority of which were deemed unlikely to be causally related to FF/UMEC/VI. Three AEs were deemed likely to have a causal relationship with FF/UMEC/VI (sore throat: n=2, oesophageal candidiasis: n=1). One patient experienced two SAEs (dyspnoea and COPD exacerbation), which were considered to have a possible causal relationship with treatment. Most SAEs were moderate (n=58/90 [9.57%] patients) and 75% (n=175/234) of patients experiencing AEs had recovered by the end of the surveillance period, including the severe dyspnoea event. By SOC, the most frequent AEs were respiratory, thoracic and mediastinal

Table 2. ADR occurrence in patients with COPD*

Variable	No. of patients (%) (n=606)
Any ADR	16 (2.64)†
Severity	
Mild	11 (1.82)
Moderate	4 (0.66)
Severe	1 (0.17)
Causal relationship with FF/UMEC/VI	
Certain	0
Probable/likely	3 (0.50)
Possible	9 (1.49)
Unlikely	0
Unclassified	2 (0.33)
Unassessable	2 (0.33)
System organ class‡	
Respiratory, thoracic and mediastinal disorders§	10 (1.65)
Dyspnoea	3 (0.50)
Oropharyngeal pain	3 (0.50)
Gastrointestinal disorders‖	4 (0.66)
Dry mouth	2 (0.33)
Infections and infestations	1 (0.17)
Oesophageal candidiasis	1 (0.17)
Nervous system disorders	1 (0.17)
Dizziness	1 (0.17)

*Patients were receiving FF/UMEC/VI 100/62.5/25 μg; †One patient reported two serious ADRs (COPD exacerbation and dyspnoea), both of which had resolved by the end of the surveillance period. If there were ≥2 different types of serious ADRs reported in the same patient, the patient was counted multiple times; ‡Most commonly reported ADR by preferred term shown; §Other ADRs reported were throat tightness, COPD exacerbation, dysphonia and haemoptysis; ‖Other ADRs reported were oral pain and stomatitis.
ADR: adverse drug reaction; COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

disorder (n=102/606 patients [16.83%]), with COPD exacerbations (n=46/606 patients [7.59%]) and dyspnoea (n=24/606 [3.96%]) occurring most frequently. Most COPD exacerbations were of mild (n=18/46 patients) or moderate (n=24/46 patients) severity, all of which were considered unlikely to have a causal relationship with FF/UMEC/VI. The next most frequent AEs by SOC were infections and infestations, of which pneumonia events were reported in 33 patients (5.45%); of these, 27 patients had recovered by the end of the surveillance period. Most patients experienced mild (n=11/33) or moderate (n=18/33) pneumonia events. Overall, 25 events in 21 patients were classed as SAEs. All pneumonia events were considered unlikely to be related to treatment with FF/UMEC/VI. A total of 17 patients had died by the end of the surveillance period; all AEs occurring in these patients were deemed unlikely to be related to FF/UMEC/VI.

Unexpected AEs were reported in 122/606 patients (20.13%), with the most common being coronavirus disease 2019 (COVID-19) infection that was considered unlikely to be related to treatment. Overall, most unexpected AEs were deemed unlikely to be related to FF/UMEC/VI (n=118). Three events were considered possibly related to treatment (throat tightness: n=2, oral pain: n=1) and one event was deemed likely related to treatment (oesophageal candidiasis), all of which had resolved by the end of the surveillance period. Unexpected SAEs occurred in 49 patients (8.09%), all of which were considered unlikely to be related to FF/UMEC/VI.

2) Factors associated with adverse drug reactions and adverse events

In patients with COPD receiving FF/UMEC/VI 100/62.5/25 μg, ADRs occurred more frequently in those with a duration of administration less than the median (307 days) compared with ≥307 days (p=0.0023) (Table 3). The odds of reporting an ADR were greater when FF/UMEC/VI was administered for <307 days versus ≥307 days (OR, 7.340; 95% Wald confidence interval [CI], 1.654 to 32.577; p=0.0088). The frequency of reporting an ADR did not significantly differ with sex, age, smoking history, duration of COPD or concomitant medications. AEs occurred more frequently in patients with smoking history (p=0.0017), duration of COPD less than the median number of years (6 years; p=0.0161), concomitant medications (COPD-related: p<0.0001; other: p<0.0001) and with hepatic (p=0.0022) or renal (p=0.0109) impairment or other medical history (p<0.0001) (Supplementary Table S3). The odds of experiencing an AE were significantly lower in patients with a duration of COPD of at least the median number of years (6 years) versus <6 years (OR, 0.689; 95% Wald CI, 0.480 to 0.987; p=0.0423) and significantly higher in patients with polypharmacy versus no concomitant medication (COPD-related medication [OR, 2.683; 95% Wald CI, 1.769 to 4.069; p<0.0001]; other medication [OR, 2.334; 95% Wald CI, 1.452 to 3.751; p=0.0005]) and with hepatic impairment versus no hepatic dysfunction (OR, 2.436; 95% Wald CI, 1.227 to 4.835; p=0.0109) (Supplementary Figure S1).

Table 3. ADR occurrence by characteristics in patients with COPD*

Characteristic	Patients with characteristic (n=606)	Patients with ≥1 ADR (n=16)	Patients with no ADRs (n=590)	p-value
Sex				
Male	522/606 (86.14)	14/522 (2.68)	508/522 (97.32)	1.0000†
Female	84/606 (13.86)	2/84 (2.38)	82/84 (97.62)	
Age, yr				
<19	0 (0)	0 (0)	0 (0)	0.1176†
≥19–<65	127/606 (20.96)	6/127 (4.72)	121/127 (95.28)	
≥65	479/606 (79.04)	10/479 (2.09)	469/479 (97.91)	
Smoking history				
Smoker	96/606 (15.84)	1/96 (1.04)	95/96 (98.96)	0.4666†
Ex-smoker	381/606 (62.87)	10/381 (2.62)	371/381 (97.38)	
Non-smoker	129/606 (21.29)	5/129 (3.88)	124/129 (96.12)	
Duration of COPD, yr				
<6	275/606 (45.38)	8/275 (2.91)	267/275 (97.09)	0.7299‡
≥6	326/606 (53.80)	8/326 (2.45)	318/326 (97.55)	
Duration of FF/UMEC/VI				
<Median (307 days)	302/606 (49.83)	14/302 (4.64)	288/302 (95.36)	0.0023‡
≥Median (307 days)	304/606 (50.17)	2/304 (0.66)	302/304 (99.34)	
Concomitant medications				
COPD-related				
Yes	370/606 (61.06)	8/370 (2.16)	362/370 (97.84)	0.3580‡
No	236/606 (38.94)	8/236 (3.39)	228/236 (96.61)	
Other				
Yes	419/606 (69.14)	7/419 (1.67)	412/419 (98.33)	0.0500†
No	187/606 (30.86)	9/187 (4.81)	178/187 (95.19)	

Values are presented as number/total number (%).
*Patients were receiving FF/UMEC/VI 100/62.5/25 μg; †Fisher's exact test; ‡Chi-square test.
ADR: adverse drug reaction; COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

3) Clinical outcomes

Overall, 378 patients with COPD receiving FF/UMEC/VI 100/62.5/25 μg were assessed for within-patient improvement in clinical outcomes (Table 4). Lung function was similar in the pre- and post-administration periods, though showed a numerical improvement (mean±SD change in FEV_1/FVC ratio: 0.92%±5.42%). The number of patients experiencing an exacerbation was lower in the post-administration period (n=42/378 [11.11%]) compared with pre-administration (n=76/378 [20.11%]), with the mean±SD frequency of exacerbations also lower post- (1.19±0.59) versus pre-administration (1.59±1.19). The mean±SD mMRC dyspnoea score was significantly improved post- versus pre-administration (mean change: −0.52±0.96; p<0.0001). Health status was similar in pre- and post-administration periods (mean±SD change in CAT score: 1.06±6.53; p=0.2281).

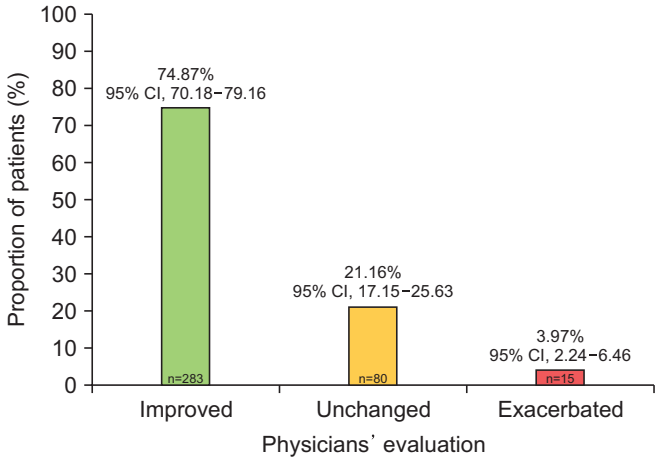
Taken together, using their own clinical judgement based on lung function, history of exacerbations and mMRC dyspnoea and CAT scores, physicians evaluated approximately 75% of patients (n=283/378) to have improved from the pre- to post-administration periods, 21% of patients (n=80/378) to have unchanged disease status and 4% of patients (n=15/378) to have worsened (Figure 3). By disease severity, 87.50% of patients with mild COPD (n=7/8), 75.60% of patients with moderate COPD (n=158/209), 72.48% of patients with severe COPD (n=79/109), and 75.00% of patients with very severe COPD (n=36/48) were deemed by physicians to have improved post-administration of FF/UMEC/VI, though disease severity was not associated with patient improvement (p=0.7845).

Table 4. Clinical outcomes with FF/UMEC/VI 100/62.5/25 μg in patients with COPD (n=378) in the post-administration period (>40 weeks) versus the pre-administration period (≤12 months)

Endpoint	No. of patients (%)	Mean±SD
Lung function*		
FEV_1, L		
Pre-administration	349	1.40±0.51
Post-administration	144	1.41±0.54
Change from pre-administration†	140	0.03±0.24, p=0.6503‡
FEV_1, % predicted		
Pre-administration	349	53.58±17.08
Post-administration	143	53.59±17.29
Change from pre-administration†	139	1.24±8.10, p=0.1627‡
FVC, L		
Pre-administration	348	2.76±0.83
Post-administration	144	2.83±0.78
Change from pre-administration†	140	−0.02±0.31, p=0.1257‡
FEV_1/FVC ratio		
Pre-administration	348	51.72±14.03
Post-administration	144	49.94±14.52
Change from pre-administration†	140	0.92±5.42, p=0.1332‡
Exacerbations		
Moderate and severe exacerbations during surveillance period		
Pre-administration	76 (20.11)	1.59±1.19
Post-administration	42 (11.11)	1.19±0.59
Hospitalizations/ED visits		
Pre-administration	27 (7.14)	1.11±0.32
Post-administration	19 (5.03)	1.26±0.45
Symptom control		
mMRC dyspnoea score		
Pre-administration	254	2.14±0.91
Post-administration	156	1.51±0.94§
Change from pre-administration†	149	−0.52±0.96, p<0.0001‡
CAT score		
Pre-administration	140	16.31±7.93
Post-administration	104	17.06±9.09
Change from pre-administration†	87	1.06±6.53, p=0.2281‡

*Baseline FEV_1 values were available in the electronic medical records (EMR) and used to classify COPD severity according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric criteria. Pulmonary function testing was not mandated by the study protocol, and baseline FEV_1 values were recorded in the case report form (CRF) only for patients with corresponding post-treatment measurements within the 52-week window (±12 weeks). Although 606 patients had sufficient EMR data for severity assessment, only 349 patients had baseline FEV_1 recorded in the CRF because these were the patients with paired pre- and post-treatment measurements. Patients without qualifying follow-up measurements were not included in the CRF per protocol; †Analyses conducted for patients with data in both pre- and post-administration periods; ‡Wilcoxon signed rank test; §Values collected at timepoint closest to completion of follow-up.
FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; COPD: chronic obstructive pulmonary disease; SD: standard deviation; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ED: emergency department; mMRC: modified Medical Research Council; CAT: COPD Assessment Test.

Figure 3. Within-patient improvement in patients with chronic obstructive pulmonary disease (COPD) post- versus pre-administration of fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 μg. As determined by physicians' clinical judgement based on pulmonary function test results, frequency of moderate and severe exacerbations, hospitalizations/emergency department visits due to exacerbations, modified Medical Research Council dyspnoea score and COPD Assessment Test score. CI: confidence interval.



3. Patients with asthma

1) Safety

Among 132 patients with asthma receiving FF/UMEC/VI 100/62.5/25 μg or 200/62.5/25 μg, 3.79% (n=5/132) reported a total of five ADRs, all of which were mild and resolving by the end of surveillance (Table 5). The most commonly reported ADRs were respiratory, thoracic and mediastinal disorders (n=4), of which three events were dysphonia. No unexpected ADRs were reported.

During the observation period, 11.36% (n=15/132) of patients experienced AEs, most of which were mild (n=14/15) (Supplementary Table S4). Five AEs were deemed possibly related to FF/UMEC/VI treatment, all of which were resolving by the end of the surveillance period. Respiratory, thoracic and mediastinal disorders were the most common AE by SOC (n=9/15), with three dysphonia events. There was one asthma exacerbation event, which was deemed mild, unlikely to be causally related to FF/UMEC/VI, and was resolving by the end of the surveillance period. Two hepatobiliary disorder events occurred (cholangitis: n=1; jaundice: n=1), of which jaundice was an unexpected SAE. The jaundice event was of mild severity and was resolved by the end of the surveillance period. The cholangitis event was of moderate severity and was resolving by the end of the surveillance period. Both these hepatobiliary disorder events were deemed unlikely to be related to FF/UMEC/VI. No deaths during the surveillance period were reported.

Table 5. ADR occurrence in integrated asthma population*

Variable	No. of patients (%) (n=132)
Any ADR	5 (3.79)
Severity	
Mild	5 (3.79)
Moderate	0
Severe	0
Causal relationship with FF/UMEC/VI	
Certain	0
Probable/likely	0
Possible	5 (3.79)
Unlikely	0
Unclassified	0
Unassessable	0
System organ class†	
Respiratory, thoracic and mediastinal disorders‡	4 (3.03)
Dysphonia	3 (2.27)
General disorders and administration site conditions	1 (0.76)
Sensation of foreign body	1 (0.76)

*Patients with asthma receiving FF/UMEC/VI 100/62.5/25 μg or 200/62.5/25 μg; †Most commonly reported ADR by preferred term shown; ‡The other ADR reported was oropharyngeal pain.
ADR: adverse drug reaction; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

2) Factors associated with adverse drug reactions and adverse events

In patients with asthma, ADRs were more frequently reported in patients with a duration of asthma less than the median (6 years) compared with ≥6 years (p=0.0256) (Table 6), though the odds of reporting an ADR were not significantly different between the groups (OR, infinity [Inf]; 95% Wald CI, 0.00 to Inf; p=0.9564), with the small sample size of this group limiting analysis. ADRs were also reported less frequently in patients receiving concomitant asthma-related medication compared with patients who were not (p=0.0012), and the odds of reporting an ADR when receiving concomitant asthma-medication were significantly lower (OR, 0.045;

Table 6. ADR occurrence by characteristics in integrated asthma population*

Characteristic	Patients with characteristic (n=132)	Patients with ≥1 ADR (n=5)	Patients with no ADRs (n=127)	p-value†
Sex				
Male	76/132 (57.58)	4/76 (5.26)	72/76 (94.74)	0.3946
Female	56/132 (42.42)	1/56 (1.79)	55/56 (98.21)	
Age, yr				
<19	1/132 (0.76)	0/1 (0.00)	1/1 (100.00)	0.1002
≥19–<65	49/132 (37.12)	4/49 (8.16)	45/49 (91.84)	
≥65	82/132 (62.12)	1/82 (1.22)	81/82 (98.78)	
Smoking history				
Smoker	18/132 (13.64)	1/18 (5.56)	17/18 (94.44)	0.5197
Ex-smoker	36/132 (27.27)	2/36 (5.56)	34/36 (94.44)	
Non-smoker	78/132 (59.09)	2/78 (2.56)	76/78 (97.44)	
Duration of asthma, yr				
<6	64/132 (48.48)	5/64 (7.81)	59/64 (92.19)	0.0256
≥6	67/132 (50.76)	0/67 (0.00)	67/67 (100.00)	
Duration of FF/UMEC/VI				
100/62.5/25 μg				
Number	46	2	44	
<Median (22 days)	22/46 (47.83)	1/22 (4.55)	21/22 (95.45)	1.0000
≥Median (22 days)	24/46 (52.17)	1/24 (4.17)	23/24 (95.83)	
200/62.5/25 μg				
Number	86	3	83	
<32 days	42/86 (48.84)	2/42 (4.76)	40/42 (95.24)	0.6118
≥32 days	44/86 (51.16)	1/44 (2.27)	43/44 (97.73)	
Concomitant medications				
Asthma-related				
Yes	114/132 (86.36)	1/114 (0.88)	113/114 (99.12)	0.0012
No	18/132 (13.64)	4/18 (22.22)	14/18 (77.78)	
Other				
Yes	93/132 (70.45)	2/93 (2.15)	91/93 (97.85)	0.1530
No	39/132 (29.55)	3/39 (7.69)	36/39 (92.31)	

Values are presented as number/total number (%).
*Patients with asthma receiving FF/UMEC/VI 100/62.5/25 μg or 200/62.5/25 μg; †Fisher's exact test.
ADR: adverse drug reaction; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

95% Wald CI, 0.004 to 0.450; p=0.0083). AEs occurred more frequently in patients with asthma who were younger (p=0.0078) and those without concomitant asthma medication (p=0.0336) (Supplementary Table S5). The odds of experiencing an AE were significantly lower when patients were receiving concomitant asthma medication compared with patients who were not (OR, 0.251; 95% Wald CI, 0.071 to 0.893; p=0.0328), whilst patient age did not significantly affect the odds of AE occurrence (reference: ≥65 years; <19 years [Inf; 95% Wald CI, 0 to Inf; p=0.9862]; ≥19–<65 years [3.170; 95% Wald CI, 0.972 to 10.345; p=0.0559]) (Supplementary Figure S2).

Discussion

This real-world post-marketing surveillance of FF/UMEC/VI 100/62.5/25 μg and 200/62.5/25 μg in patients with

asthma or COPD did not identify any new safety concerns in a Korean population. ADRs were reported in approximately 3% of patients with COPD and 4% of patients with asthma, and in both patient populations, respiratory, thoracic, and mediastinal disorders were the most common ADRs. No unexpected serious ADRs were reported in either patient population; for all deaths reported during the studies, the causal relationship with the study drug was considered unlikely. Overall, incidence of ADRs and AEs in these patient populations were consistent with the known safety profile of FF/UMEC/VI at both doses of FF[15-17,26]. The overall safety profile observed in these studies is largely consistent with data from pivotal randomised controlled trials (IMPACT[17], FULFIL[16], and CAPTAIN[15]), which demonstrated that FF/UMEC/VI was generally well tolerated.

In the COPD subgroup, the frequency of the most common AEs reported were within the range of those reported in previous clinical trials[16,17]. Specifically, COPD exacerbations were reported as SAEs in 2%–11% of patients receiving FF/UMEC/VI in the IMPACT[17] and FULFIL[16] trials, and approximately 7.6% of patients with COPD in the population assessed here reported COPD exacerbations, one event of which was classed as an SAE. A subgroup analysis of Asian patients from the IMPACT trial, which included patients from Korea, demonstrated that FF/UMEC/VI was well tolerated in Asian patients with COPD, though noted a higher incidence of AEs, including pneumonia, in the Asian population compared with non-Asian patients[26]. Interestingly, whilst a higher number of AEs were reported in the current post-marketing surveillance compared with the IMPACT trial, the incidence of pneumonia was notably lower compared with IMPACT (5.5% vs 7.6%). This may be reflective of differences in the baseline characteristics of these patient populations. Furthermore, differences in trial settings, specifically the controlled and closely monitored environment of a randomised clinical trial versus routine clinical practice in real-world post-marketing surveillance, may contribute to the variation in AE detection and reporting.

Reported pneumonia events were in line with the known safety profile of FF/UMEC/VI for patients with COPD. Pneumonia occurred in approximately 5.5% of the patients assessed in this post-marketing surveillance, consistent with the incidence observed in the pivotal trials of FF/UMEC/VI: IMPACT (7.6%)[17] and FULFIL (2.2%)[16]. Within the patient population with COPD assessed here, the incidence of pneumonia aligned with the expected ranges for SITT from randomised controlled trials which range from 1.9% to 7.6%[16,17,27-31]. Incidence of pneumonia is likely to be higher in real-world settings compared with randomised controlled trials due to the diverse patient population captured in real-world studies. Whilst ICS-containing regimens are known to increase the risk of pneumonia compared with dual bronchodilator therapy[17,28,32], this risk is considered a class effect without definitive intraclass differences, as highlighted by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee in 2016[33]. The class effect is well-supported by both a clinical meta-analysis and real-world studies which concluded that pneumonia risk was similar across triple therapy combinations[34-36]. In a pre-specified analysis of the IMPACT trial, the risk of combined pneumonia was reduced with FF/UMEC/VI compared with FF/VI or UMEC/VI, supporting a favourable benefit-risk profile of once-daily triple therapy compared with dual therapy in symptomatic patients with COPD who are at risk of exacerbation[37]. It should also be noted that COPD is a known independent risk factor for pneumonia[38]. Taken together, the manageable pneumonia risk in our COPD subgroup, together with previously published real-world data, provides further reassurance for clinicians regarding the use of FF/UMEC/VI in this population.

In patients with asthma, the incidence of AEs was comparable with the CAPTAIN trial and previous real-world studies[15,39]. The most commonly experienced AEs differed between these studies of real-world use in Korea and the CAPTAIN study, with the most common AEs in CAPTAIN being nasopharyngitis (13%), headache, upper respiratory tract infection and bronchitis (5% each), whereas dysphonia (approximately 2%), cough and oropharyngeal discomfort (approximately 1.5% each) were the most common AEs here. These differences may reflect the different patient populations studied as CAPTAIN was a multinational clinical trial whilst our studies focused on a Korean population. In a real-world study of FF/UMEC/VI safety in Japanese patients with asthma, the most common ADRs reported were similar to those reported here in a Korean population, with dysphonia reported in approximately 3% of patients and oropharyngeal pain/discomfort in approximately 0.7% of patients in both studies[39].

The tolerability of both doses of FF/UMEC/VI was demonstrated in the analysis of patients with asthma or COPD in these studies. The absence of serious unexpected ADRs over the median exposure period may inform the utility of FF/UMEC/VI for continued use in clinical practice in Korea. Additionally, logistic regression analyses assessed risk factors for AEs and ADRs and highlighted the potential need for individualised risk stratification, particularly for older patients

with asthma, those with polypharmacy for treatment of asthma or COPD, long-term use of FF/UMEC/VI 100/62.5/25 μg in COPD and in patients with COPD and hepatic impairment. Associations between increasing age and ADRs have been previously established and are likely due to age-related changes, such as reduced metabolism, in older patients[40,41]. Additionally, older patients are more likely to be receiving concomitant medications[41], which is also associated with increased risk of AEs and ADRs[42]. Patients with hepatic impairment have a reduced ability to effectively metabolise and clear drugs, increasing the risk of ADRs[43]. Our results highlight that these considerations should be applied when assessing treatment options for Korean patients with asthma or COPD.

Whilst this study was not designed to assess efficacy outcomes, clinical outcomes were assessed in patients with COPD receiving FF/UMEC/VI 100/62.5/25 μg and identified real-world clinical benefits in symptom control and exacerbation reduction. Approximately 75% of patients improved post-initiation of treatment, as assessed by physicians. Dyspnoea, as measured by mMRC score, significantly improved from baseline (mean change: −0.52; p<0.0001), and the proportion of patients experiencing moderate-severe COPD exacerbations fell from 20.11% to 11.11% between the pre- and post-administration periods, accompanied by a reduction in hospitalizations/ED visits. The pre-administration COPD exacerbation rates align with previous reports of exacerbation rates in Korean populations (19.8%–21.9%)[44,45] and the observed reductions in exacerbations post-administration of FF/UMEC/VI align with pivotal clinical trials, IMPACT and FULFIL[16,17], which demonstrated the efficacy of FF/UMEC/VI in reducing exacerbations and improving lung function in diverse populations, including Asian populations[26]. Real-world studies further support these outcomes, with studies of United States populations identifying lower asthma and COPD exacerbation rates post-FF/UMEC/VI initiation[46,47]. Although the clinical outcomes for FF/UMEC/VI could not be assessed in Korean patients with asthma, real-world studies of United States and Japanese populations have demonstrated the effectiveness of both 100/62.5/25 μg and 200/62.5/25 μg doses in the treatment of asthma[20,48,49]. Taken with the acceptable safety profile demonstrated here, these data underscore the important role of FF/UMEC/VI in treating Korean patients with COPD or asthma.

One notable strength of this post-marketing surveillance is the robust generation of real-world evidence based on a large and diverse patient population recruited from multiple centers across Korea (FF/UMEC/VI 100/62.5/25 μg study: n=673, 16 centers; FF/UMEC/VI 200/62.5/25 μg study: n=86, 5 centers), ensuring broad representation of clinical practice settings nationwide. This comprehensive coverage enhances the generalisability of the findings to routine clinical practice. Additionally, for COPD, the longitudinal nature of the follow-up (median FF/UMEC/VI administration period of approximately 307 days) allowed comprehensive assessment of safety and tolerability over time.

Whilst these studies provide robust real-world evidence, their observational nature inherently carries limitations, including the potential for selection bias and reliance on spontaneous AE reporting. In patients with asthma receiving FF/UMEC/VI 200/62.5/25 μg, the treatment administration period was relatively short for assessing long-term safety, resulting in a smaller sample size compared with the FF/UMEC/VI 100/62.5/25 μg study that included patients with asthma or COPD. As small sample sizes can reduce statistical power and increase the potential for random variation, it is difficult to draw reliable conclusions about any observed associations between AEs, ADRs and baseline characteristics. In addition, the small sample size meant that clinical outcomes with FF/UMEC/VI could not be assessed in patients with asthma. Additionally, some clinical outcomes data were subjective based on clinical judgement by physicians and self-report questionnaires, introducing the potential for subjectivity and variability. As a result, findings should be interpreted with caution, as they may not fully reflect objective outcomes. Finally, neither study contained a comparator treatment or placebo and so the efficacy of FF/UMEC/VI cannot be assessed, and the safety and clinical outcomes results reported here cannot be compared with other COPD or asthma therapies.

In conclusion, this large-scale post-marketing surveillance assessed the real-world safety and clinical outcomes with FF/UMEC/VI in Korean patients with asthma or COPD. FF/UMEC/VI was well tolerated for both doses, and no new safety concerns were identified for either patient population. Notably, clinical benefits in reducing the burden of disease in COPD with FF/UMEC/VI 100/62.5/25 μg were identified. These results support the role of FF/UMEC/VI as a well-tolerated treatment in Korean patients with asthma and COPD and in improving clinical outcomes in Korean patients with COPD.

Authors' Contributions

Conceptualization: Lee EB, Cho JE. Methodology: Lee EB, Cho JE. Formal analysis: Lee EB, Cho JE, Kwon E,

Ko K. Data curation: Kim SH (Sang Heon Kim), Kim SH (Sang-Ha Kim). Funding acquisition: Lee EB, Cho JE. Project administration: Lee EB, Cho JE. Visualization: Lee EB, Cho JE. Software: Lee EB, Cho JE. Validation: Lee EB, Cho JE. Investigation: Kim SH (Sang Heon Kim), Kim SH (Sang-Ha Kim). Writing - original draft preparation: all authors. Writing - review and editing: all authors. Approval of final manuscript: all authors.

Conflicts of Interest

Eun-Bin Lee, Jung-Eun Cho, and Eunsun Kwon are employees of GSK Korea. Karam Ko was an employee of GSK Korea at the time of the study. Sang Heon Kim and Sang-Ha Kim have no competing interests to declare.

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Please refer to GSK weblink to access GSK's data sharing policies and as applicable seek anonymised subject level data via the link https://www.gsk-studyregister.com/en/.

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Supplementary Material

Supplementary material can be found in the journal homepage (http://www.e-trd.org).

Supplementary Table S1. Asthma or COPD treatment history pre-administration of FF/UMEC/VI.

Supplementary Table S2. AE occurrence in patients with COPD.

Supplementary Table S3. AE occurrence by characteristics in patients with COPD.

Supplementary Table S4. AE occurrence in integrated asthma population.

Supplementary Table S5. AE occurrence by characteristics in the integrated asthma population.

Supplementary Figure S1. Odds of experiencing an adverse event (AE) by characteristics in patients with chronic obstructive pulmonary disease (COPD).

Supplementary Figure S2. Odds of experiencing an adverse event (AE) by characteristics in integrated asthma population.

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