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ORIGINAL RESEARCH

# Effectiveness of FF/UMEC/VI versus ICS/LABA in Patients with Uncontrolled Asthma Treated in Routine Clinical Practice (PERFORM): A Pragmatic Randomized Controlled Trial

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**Purpose:** Asthma guidelines recommend stepwise escalation of inhaled corticosteroid/long-acting $\beta_2$-agonist (ICS/LABA) therapy, yet many patients remain uncontrolled. Randomized controlled trials (RCTs) show that single-inhaler triple therapy improves lung function, with varying effects on symptoms and exacerbations. However, highly controlled explanatory RCTs with selective populations may not reflect real-world care. PERFORM evaluated the effectiveness and safety of initiating once-daily fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) ELLIPTA versus usual care non-ELLIPTA ICS/LABA in routine clinical practice.

**Methods:** PERFORM (GSK219912/NCT06372496) is a randomized, open-label, active-controlled, 52-week, global pragmatic trial including adults (18–75 years) with uncontrolled, infrequently exacerbating asthma, previously untreated or treated with non-ELLIPTA ICS or ICS/LABA in the 3-months pre-randomization. Powered primary and secondary endpoints were change from baseline in trough forced expiratory volume in 1 second ($FEV_1$) and asthma control (Asthma Control Questionnaire [ACQ]-7 responder analysis) at Week 24 (W24). Safety was assessed throughout the trial.

**Results:** Overall, 1236 patients (mean age: 48.9 years; 68.6% female) were included in this W24 primary analysis (FF/UMEC/VI: N=619; ICS/LABA: N=617). At baseline mean $FEV_1$%predicted was 85.7; mean ACQ-7 score was 2.46. At W24, FF/UMEC/VI statistically significantly improved trough $FEV_1$ from baseline versus ICS/LABA (least squares mean difference [95% confidence interval]: +68mL [36–99], $P<0.001$). $FEV_1$ improvement from baseline was 178mL (139–217) with FF/UMEC/VI and 110mL (72–149) with ICS/LABA. Odds of a clinically meaningful response in ACQ-7 score (≥0.5-point improvement from baseline) were significantly greater with FF/UMEC/VI versus ICS/LABA (odds ratio [95% confidence interval]: 1.47 [1.13–1.92], $P<0.004$); 79.0% of patients achieved a response with FF/UMEC/VI and 71.8% with ICS/LABA. Safety profile to W24 aligned with previous studies.

**Conclusion:** This pragmatic RCT demonstrated significant improvements in lung function and asthma control with FF/UMEC/VI versus ICS/LABA in uncontrolled and infrequently exacerbating patients treated in a routine practice setting. These findings further inform the evidence base for optimized use of FF/UMEC/VI.

**Keywords:** asthma control, lung function, real-world setting, single-inhaler triple therapy

## Introduction

Asthma treatment guidelines recommend inhaled corticosteroid/long-acting $\beta_2$-agonist (ICS/LABA) maintenance therapy as part of a stepwise approach.[1–3] Yet many patients treated with ICS/LABA continue to experience considerable disease burden,

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including lung function impairment, exacerbations, and poor symptom control,[4–6] with approximately 30% unable to achieve asthma control even after increasing ICS dose.[7] Moreover, among patients adherent to medium- and high-dose ICS/LABA, 63.8% and 70.0% remain uncontrolled.[8]

For patients with uncontrolled asthma receiving ICS/LABA, the Global Initiative for Asthma (GINA) currently recommends addition of a long-acting muscarinic antagonist (LAMA) as triple therapy,[1] noting that evidence from explanatory Phase 3 randomized controlled trials (RCTs) of single-inhaler triple therapy (SITT) versus ICS/LABA in moderate-to-severe asthma is mixed.[1] Of the four ICS/LAMA/LABA SITT combinations that have been evaluated in RCTs (CAPTAIN, IRIDIUM, TRIMARAN/TRIGGER and KALOS/LOGOS), significant improvements in lung function versus dose-matched ICS/LABA comparators were consistently reported in all.[9–12] However, the benefit of SITT versus ICS/LABA for other clinical outcomes vary: CAPTAIN showed no significant reduction in moderate/severe exacerbation rates and nominally significant improvements in symptom control;[10] IRIDIUM showed no significant reduction in exacerbations or symptom control;[9] TRIMARAN/TRIGGER demonstrated significant reductions in moderate/severe exacerbations in TRIMARAN but not TRIGGER;[11] and KALOS/LOGOS showed varying improvements in severe exacerbations, depending on the analytic approach, and no significant improvements in symptom control.[12] Meanwhile, evidence from real-world studies shows significant reductions in exacerbation rates and oral corticosteroid (OCS) dispensing after initiation of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) SITT versus pre-initiation.[13]

Explanatory Phase 3 RCTs are designed to assess trial interventions under highly controlled conditions, with selective patient populations and strict treatment criteria that may not be representative of routine clinical practice.[14–16] Previous studies have found that over 90% of real-world patients with asthma would be ineligible for such RCTs.[15,17] Indeed, prior Phase 3 RCTs of SITT in asthma included patients with moderate-to-severe disease and impaired lung function,[9–12] and generally required a history of exacerbations,[9–11] representing only a small subset of real-world patients,[18–20] who are increasingly considered eligible for biologic therapy.[21–23] Furthermore, double-blind, double-dummy RCTs primarily focus on the pharmacologic effects of treatment; in the aforementioned asthma RCTs, SITT was evaluated versus dose- and formulation-matched ICS/LABA, generally via the same inhaler device.[9–12] However, in routine practice, physicians base treatment choice on the combined effects of the available therapeutic agent, inhaler device and dosing strategy.

There is a need for randomized evidence evaluating the clinical effectiveness of SITT in a real-world asthma population. Pragmatic RCTs offer a solution to this evidence gap. These trials assess the effectiveness of interventions in conditions representative of real-world care: they include broad eligibility criteria to reflect real-world populations and are designed to allow physician-guided prescribing based on routine care and local guidelines, while encouraging usual patient behavior.[24] Pragmatic RCTs apply the robust control of explanatory Phase 3 RCTs to routine practice settings with evidence that can be directly applicable to real-world clinical decision-making.[24]

There is a clear unmet need for improved symptom control in patients with asthma who are eligible for ICS/LABA therapy,[4–6,8] yet based on varying evidence from Phase 3 RCTs,[9–12] escalation to SITT is reserved for patients who remain uncontrolled and are at risk of exacerbating.[1] We therefore conducted the global Phase 4 PERFORM (Pragmatic Evaluation of Randomized FF/UMEC/VI vs Open-label ICS-LABA for Regular asthma Management) trial to evaluate the effectiveness and safety of FF/UMEC/VI ELLIPTA compared with usual care ICS/LABA in patients with uncontrolled asthma and infrequent exacerbations in a routine practice setting. Herein, we report the primary analysis of PERFORM after 24 weeks of treatment.

# Materials and Methods

## Trial Design

PERFORM is an ongoing 52-week, stratified, randomized, open-label, active-controlled, pragmatic trial conducted at 101 sites across Argentina, Australia, Canada, Japan, South Korea, Taiwan, and the United States. For the primary analysis at Week 24, the trial ran from 04/16/2024 to 07/28/2025.

Following screening (Visit 1), patients underwent randomization (Visit 2), either directly or within 7 days (Supplementary Figure 1). Patients were randomized 1:1 to initiate FF/UMEC/VI delivered via the ELLIPTA inhaler or to initiate or continue any licensed non-ELLIPTA ICS/LABA. An open-label approach was taken to reflect regional availability of ICS/LABA formulations at the time of the trial and encourage prescribing as per usual care, to try to best

capture real-world data. This approach allowed a pragmatic evaluation of FF/UMEC/VI versus usual care non-ELLIPTA ICS/LABA, based on the combined effect of therapeutic agent, inhaler device and dosing strategy. For patients randomized to usual care ICS/LABA, choice of ICS/LABA (including dose and frequency of use) was at the investigator's discretion, according to usual clinical practice and availability. Randomization was stratified by pre-trial asthma maintenance therapy (untreated, ICS alone, ICS/LABA) and pre-trial ICS dose (high, low). ICS dose tapering was not required for patients previously treated with ICS-containing maintenance therapy. Throughout the trial, patients prescribed FF/UMEC/VI 100/62.5/25 µg or low-dose ICS/LABA could be escalated to FF/UMEC/VI 200/62.5/25 µg or high-dose ICS/LABA, respectively, at the physician's discretion. Trial intervention crossover was not permitted.

The primary analysis was completed at Week 24, with the prespecified final analysis to be completed at Week 52, and a telephone safety follow-up to be completed at Week 53. Trial intervention/treatment-related adverse events (AEs) and all serious AEs were documented throughout the trial via questioning at scheduled clinic visits or via spontaneous reporting.

This was an open-label trial designed to reflect routine clinical practice, therefore, site-level personnel and patients were unblinded; however, to maintain data integrity, data review and preparations for statistical analysis were conducted using blinded data. In addition, to encourage patients' usual behavior and medication use, required trial visits were kept to a minimum and adherence reminders were omitted. Further trial design details are included in the Supplementary Material and have been published separately.[25]

PERFORM was sponsored by GSK (219912; NCT06372496) and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guideline for Good Clinical Practice, as well as applicable local regulations. Trial documents and protocol amendments received approval by relevant local Institutional Review Boards and/or Independent Ethics Committees.[25] All patients provided written, informed consent.

## Trial Population

Eligible patients were aged 18–75 years with physician-diagnosed asthma (defined by GINA 2023 recommendations)[26] at screening, had uncontrolled symptomatic asthma (Asthma Control Questionnaire [ACQ]-6 score ≥1.5) at randomization, and were currently untreated (no ICS-containing therapy in the 3 months pre-randomization) or treated with non-ELLIPTA ICS or ICS/LABA maintenance therapy (including formoterol-containing ICS/LABA maintenance and reliever therapy [MART] formulations) for ≥3 months pre-randomization. Patients were excluded if they had >1 severe exacerbation in the 12 months pre-randomization; had exposure to LAMA-containing or biologic therapies in the 12 months pre-randomization; were currently treated with FF or FF/VI (ELLIPTA); or had chronic obstructive pulmonary disease (COPD) or other uncontrolled/clinically significant disease. Full eligibility criteria are presented in Supplementary Table 1.

## Outcomes

The primary endpoint was change from baseline (CFB) in trough forced expiratory volume in 1 second ($FEV_1$) at Week 24. The trial was also powered to assess a response in ACQ-7 total score at Week 24 as the key secondary endpoint, defined as an improvement (decrease) from baseline beyond the 0.5-point minimum clinically important difference (MCID).[27]

Other secondary endpoints evaluated CFB in trough $FEV_1$ ≥100 mL and ≥0 mL at Week 24; a response in ACQ-5 and ACQ-6 total score (≥0.5-point decrease from baseline) at Week 24; and CFB at Week 24 in ACQ-5, ACQ-6 and ACQ-7 total scores, and Asthma Control Test (ACT) score.

The trial assessed response to an exploratory composite endpoint at Week 24, defined as no OCS use, no severe exacerbations, controlled asthma (ACQ-5 total score <1.50), and either optimized or stabilized lung function (CFB in trough $FEV_1$ ≥100 mL or ≥0 mL). Patients will continue in the trial to evaluate the same components within a composite endpoint at Week 52, representing clinical remission. Patients' OCS use (daily dose) and incidence of severe exacerbations over 24 weeks were also assessed as exploratory endpoints. A detailed summary of effectiveness endpoints is included in Supplementary Table 2.

Safety endpoints included incidence of trial intervention/treatment-related treatment-emergent AEs (TEAEs) and serious TEAEs, assessed to Week 24 (Supplementary Material).

## Statistical Analyses

The sample size was calculated to power both the primary endpoint and key secondary endpoint for the primary treatment comparison. Assuming a true odds ratio (OR) between FF/UMEC/VI and ICS/LABA of 1.48 for an ACQ-7 response at Week 24, and assuming that 55% of patients achieved a response with ICS/LABA versus 65% with FF/UMEC/VI, a total of 1136 patients (568 per treatment arm) was required to provide 90% power to observe significance at the 2-sided 5% level. For the primary endpoint, a sample size of 568 patients per treatment arm provided 99% power to observe significance at the 2-sided 5% level, with a minimum detectable treatment difference of 46.5 mL.

Effectiveness and safety analyses included randomized patients who received ≥1 prescription of FF/UMEC/VI or ICS/LABA. Effectiveness analyses (modified full analysis set 1 [FAS-Modified-1]) were assessed according to randomized trial intervention. Safety analyses (modified safety analysis set 1 [SAF-Modified-1]) were assessed according to actual treatment prescribed. Two sites were closed by the sponsor for good clinical practice concerns. After a trial-wide investigation, one of these sites showed evidence of patient falsification, therefore, these patients were excluded from both the FAS-Modified-1 and SAF-Modified-1. No evidence of falsification was identified at the second site, therefore, patients from this site were included in the primary analysis sets. No other misconduct was identified. Further details are reported in the Supplementary Material. Supportive analyses excluding patients from both closed sites (FAS-Modified-2 and SAF-Modified-2) and including all patients (FAS and SAF) were also performed (Supplementary Table 3).

The primary endpoint (CFB in trough $FEV_1$ at Week 24) was assessed using an analysis of covariance, with covariates of actual pre-trial asthma maintenance therapy (untreated, ICS alone, ICS/LABA), pre-trial ICS dose (high, low), baseline $FEV_1$ value, age, sex and region. Least squares (LS) mean and 95% confidence intervals (CIs) are reported. Intercurrent events of interest (trial intervention discontinuation, use of prohibited medications, ICS dose escalation) were handled using a treatment policy approach. If patients withdrew from the trial before Week 24, missing $FEV_1$ data were not imputed. Supportive analyses using different strategies to handle intercurrent events and using the FAS are described in the Supplementary Material.

The key secondary endpoint (ACQ-7 response at Week 24) was analyzed using a generalized linear model (logistic regression), with covariates of treatment group, sex, region, actual pre-trial asthma maintenance therapy (untreated, ICS alone, ICS/LABA), pre-trial ICS dose (high, low), age, and baseline value, using a logit link function. Results are expressed as the number and percentage of responders and non-responders, and OR (95% CI) of a response with FF/UMEC/VI versus ICS/LABA. Intercurrent events were handled per the primary endpoint. Patients with a missing baseline ACQ-7 score were considered as having a missing responder status. Patients with a missing Week 24 ACQ-7 score were considered non-responders. Further information on the statistical methods used, including supportive analyses and handling of missing data, is included in the Supplementary Material.

A prespecified step-down closed testing approach (0.05 significance level) was used to control for multiplicity for the primary endpoint and key powered secondary endpoint. Subsequent endpoints in the step-down approach include a composite endpoint at Week 52 and CFB in trough $FEV_1$ at Week 24 stratified by patients treated with ICS/LABA or untreated pre-randomization. Only the primary endpoint and key secondary endpoint are included in the Week 24 analysis. Other Week 24 endpoints not included in the step-down approach are unadjusted for multiplicity and *P* values should be considered descriptive.

# Results

## Trial Population

A total of 1349 patients were randomized and received ≥1 prescription of trial intervention. Upon discovery of misconduct and evidence of falsification at a trial site, the site was closed by the sponsor and all 113 patients were withdrawn from the trial prior to the Week 24 visit. In total, 1236 patients were included in the primary analysis set (FAS-Modified-1) (FF/UMEC/VI: N=619; ICS/LABA: N=617). Overall, 1155 patients completed 24 weeks of trial intervention and completed the Week 24 study visit (Figure 1 and Supplementary Table 3). Most patients who were randomized to ICS/LABA received budesonide/formoterol (43.8% [n=265]), fluticasone propionate/salmeterol (32.7% [n=198]) or fluticasone propionate/formoterol (18.8% [n=114]) (Supplementary Table 4).

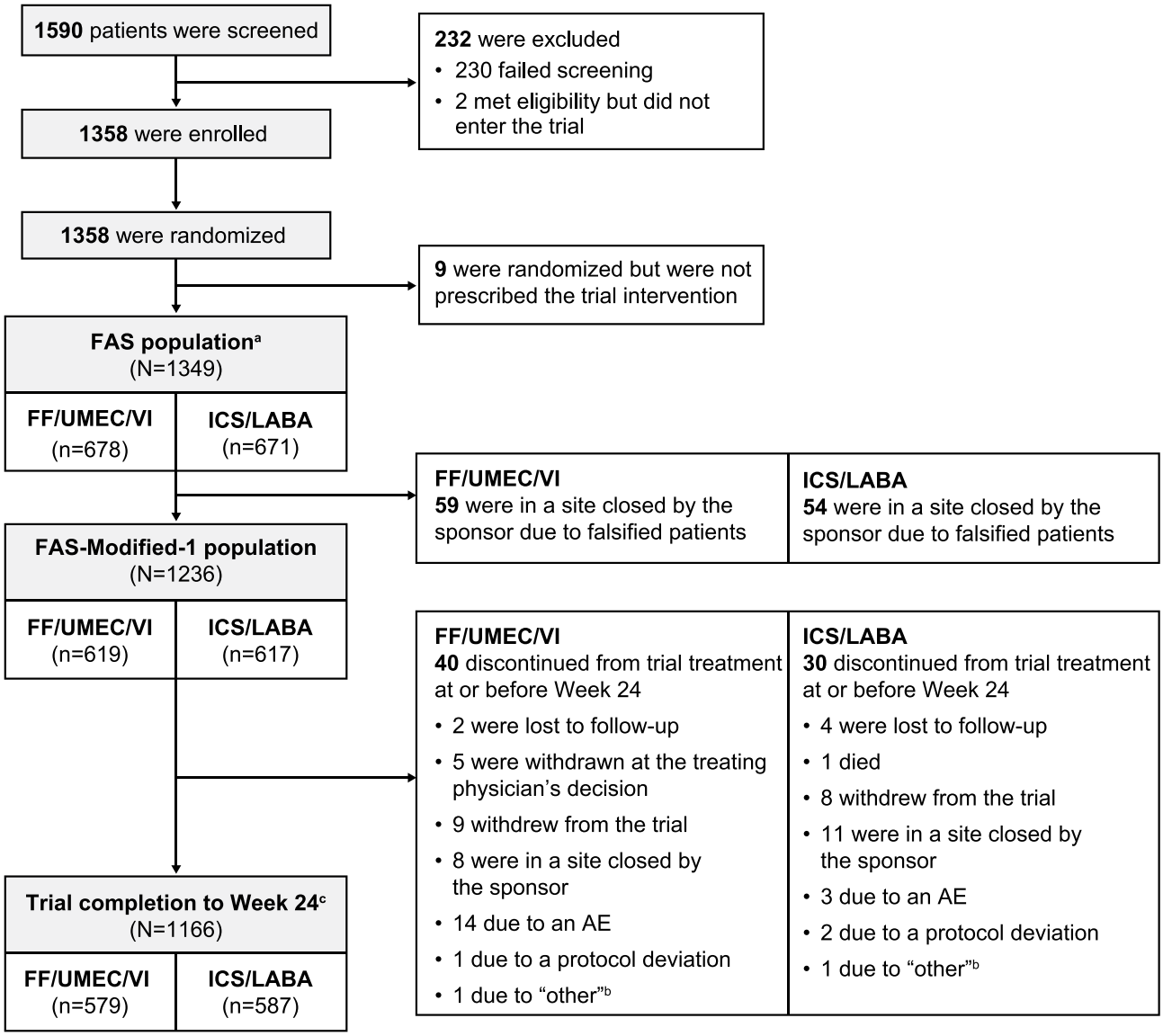


**Figure 1** Patient disposition. [a]All randomized patients who received ≥1 prescription of trial intervention; [b] "other" was provided as an option in the eCRF if alternative discontinuation reasons were not applicable (adverse event, death, lack of efficacy, lost to follow-up, physician decision, pregnancy, progressive disease, protocol deviation, site closed by sponsor, sponsor terminated trial treatment, trial terminated by sponsor, withdrawal by participant); [c]patients who completed 24 weeks of trial intervention and completed the Week 24 study visit. Treatment groups are presented according to randomized trial intervention.

**Abbreviations**: eCRF, electronic case report form; FAS, full analysis set; FAS-Modified-1, modified full analysis set 1; FF, fluticasone furoate; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; UMEC, umeclidinium; VI, vilanterol.

Baseline characteristics were generally similar across treatment groups (Table 1). Mean (standard deviation [SD]) age was 48.9 (15.09) years, 68.6% (n=848/1236) of patients were female, and 7.0% (n=87/1236) were current smokers. Most patients were White (61.1% [n=755/1236]) or Asian (31.1% [n=384/1236]) ethnicity. Mean (SD) $FEV_1$% predicted was 85.74% (19.56) and ACQ-7 score was 2.46 (0.76); 0.5% (n=6/1236) of patients were taking OCS at baseline and 17.9% (n=221/1236) had a severe exacerbation in the previous 12 months. Pre-randomization, 63.3% of patients (n=782/1236) were taking ICS/LABA, 32.0% (n=395/1236) were untreated, and 4.8% (n=59/1236) were taking ICS alone. Among patients receiving ICS-containing medications pre-randomization, 37.1% (n=459/1236) received low-dose ICS and 30.9% (n=382/1236) high-dose ICS. Concomitant medications and medical history are presented in Supplementary Tables 5–6.


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**Table 1** Baseline Patient Characteristics (FAS-Modified-1)

| | FF/UMEC/VI (N=619) | ICS/LABA (N=617) | Overall Population (N=1236) |
|---|---|---|---|
| Age, years, mean (SD) | 48.7 (15.01) | 49.1 (15.17) | 48.9 (15.09) |
| Female, n (%) | 429 (69.3) | 419 (67.9) | 848 (68.6) |
| Country, n (%) | | | |
| Argentina | 216 (34.9) | 204 (33.1) | 420 (34.0) |
| United States | 182 (29.4) | 186 (30.1) | 368 (29.8) |
| Japan | 165 (26.7) | 161 (26.1) | 326 (26.4) |
| Australia | 29 (4.7) | 39 (6.3) | 68 (5.5) |
| Canada | 10 (1.6) | 14 (2.3) | 24 (1.9) |
| Taiwan | 8 (1.3) | 10 (1.6) | 18 (1.5) |
| South Korea | 9 (1.5) | 3 (0.5) | 12 (1.0) |
| Ethnicity, n (%) | | | |
| White | 376 (60.7) | 379 (61.4) | 755 (61.1) |
| Asian | 193 (31.2) | 191 (31.0) | 384 (31.1) |
| Black or African American | 41 (6.6) | 38 (6.2) | 79 (6.4) |
| Native Hawaiian or Other Pacific Islander | 4 (0.6) | 2 (0.3) | 6 (0.5) |
| Multiple | 2 (0.3) | 4 (0.6) | 6 (0.5) |
| Native American or Native Alaskan[a] | 2 (0.3) | 3 (0.5) | 5 (0.4) |
| Not reported/Unknown | 1 (0.2) | 0 | 1 (0.1) |
| Smoking status, n (%) | | | |
| Current smoker | 42 (6.8) | 45 (7.3) | 87 (7.0) |
| Former smoker | 111 (17.9) | 119 (19.3) | 230 (18.6) |
| Never-smoker | 466 (75.3) | 453 (73.4) | 919 (74.4) |
| Smoking pack years, mean (SD) | n=149<br>11.3 (12.79) | n=163<br>12.0 (14.53) | n=312<br>11.6 (13.71) |
| Pre-trial asthma maintenance therapy, n (%) | | | |
| ICS/LABA | 391 (63.2) | 391 (63.4) | 782 (63.3) |
| Untreated | 199 (32.1) | 196 (31.8) | 395 (32.0) |
| ICS alone | 29 (4.7) | 30 (4.9) | 59 (4.8) |
| Pre-trial ICS dose, n (%) | | | |
| Low | 230 (37.2) | 229 (37.1) | 459 (37.1) |
| High | 190 (30.7) | 192 (31.1) | 382 (30.9) |
| Time since asthma diagnosis at randomization, years, mean (SD)[b] | 20.50 (18.57) | 21.97 (19.27) | 21.23 (18.93) |
| Patients taking OCS at baseline, n (%) | 2 (0.3) | 4 (0.6) | 6 (0.5) |
| Patients with a severe asthma exacerbation during the 12 months pre-randomization, n (%) | 107 (17.3) | 114 (18.5) | 221 (17.9) |
| Trough $FEV_1$, mL, mean (SD) | 2449 (801) | 2504 (785) | 2476 (793) |
| $FEV_1$% predicted, mean (SD) | 85.12 (19.872) | 86.36 (19.241) | 85.74 (19.562) |
| FVC, mL, mean (SD) | 3362 (938) | 3451 (968) | 3406 (954) |
| ACQ-5 total score, mean (SD) | 2.79 (0.793) | 2.80 (0.806) | 2.80 (0.799) |
| ACQ-6 total score, mean (SD) | 2.55 (0.777) | 2.56 (0.775) | 2.56 (0.776) |
| ACQ-7 total score, mean (SD) | 2.46 (0.768) | 2.46 (0.758) | 2.46 (0.762) |
| ACT total score, mean (SD) | 14.7 (4.12) | 14.7 (4.07) | 14.7 (4.09) |

**Notes**: [a]Data were collected as "American Indian or Alaska Native" in the eCRF; [b]FF/UMEC/VI: n=617; ICS/LABA: n=617; Overall: n=1234.

**Abbreviations**: ACQ-5/-6/-7, Asthma Control Questionnaire-5/-6/-7; ACT, Asthma Control Test; eCRF, electronic case report form; FAS-Modified-1, modified full analysis set 1; $FEV_1$, forced expiratory volume in 1 second; FF, fluticasone furoate; FVC, forced vital capacity; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; OCS, oral corticosteroid; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

## Primary Endpoint and Key Secondary Endpoint

### Lung Function

Improvements in lung function (trough $FEV_1$) at Week 24 from baseline were statistically significantly greater after initiating FF/UMEC/VI versus usual care ICS/LABA (LS mean treatment difference [95% CI]: 68 mL [36, 99], $P<0.001$). Improvements (LS mean change [95% CI]) in $FEV_1$ from baseline were 178 mL (139, 217) with FF/UMEC/VI and 110 mL (72, 149) with usual care ICS/LABA (Table 2).

## Asthma Control

The odds of achieving a clinically meaningful response to therapy in ACQ-7 total score at Week 24 (≥0.5-point improvement [decrease] from baseline) were statistically significantly greater after initiating FF/UMEC/VI versus usual care ICS/LABA (OR [95% CI]: 1.47 [1.13, 1.92], $P=0.004$). A response in ACQ-7 score at Week 24 was achieved by 79.0% (n=489/619) of patients with FF/UMEC/VI and 71.8% (n=443/617) with usual care ICS/LABA (Table 2).

**Table 2** Primary and Secondary Effectiveness Endpoints (FAS-Modified-1)

| | FF/UMEC/VI (N=619) | ICS/LABA (N=617) |
|---|---|---|
| **Primary endpoint** | | |
| CFB in trough $FEV_1$ at Week 24, mL | n=562 | n=546 |
| LS mean (95% CI) CFB | 178 (139, 217) | 110 (72, 149) |
| LS mean treatment difference (95% CI), *P* value | 68 (36, 99); <0.001 | REF |
| **Key secondary endpoint** | | |
| ACQ-7 response at Week 24[a] | | |
| Responders, n (%) | 489 (79.0) | 443 (71.8) |
| Non-responders, n (%) | 130 (21.0) | 174 (28.2) |
| Non-responder due to missing data, n (%)[b] | 61 (46.9) | 72 (41.4) |
| OR (95% CI), *P* value | 1.47 (1.13, 1.92); 0.004 | REF |
| **Other secondary endpoints** | | |
| **Lung function** | | |
| CFB in trough $FEV_1$ ≥100 mL at Week 24 | | |
| Responders, n (%) | 285 (46.0) | 182 (29.5) |
| Non-responders, n (%) | 334 (54.0) | 435 (70.5) |
| Non-responder due to missing data, n (%)[b] | 57 (17.1) | 71 (16.3) |
| O.R (95% CI), *P* value[c] | 2.01 (1.58, 2.56); <0.001 | REF |
| CFB in trough $FEV_1$ ≥0 mL at Week 24 | | |
| Responders, n (%) | 408 (65.9) | 318 (51.5) |
| Non-responders, n (%) | 211 (34.1) | 299 (48.5) |
| Non-responder due to missing data, n (%)[b] | 57 (27.0) | 71 (23.7) |
| OR (95% CI), *P* value[c] | 1.77 (1.41, 2.24); <0.001 | REF |
| **Asthma control** | | |
| CFB in ACQ-7 total score at Week 24 | n=558 | n=545 |
| LS mean (95% CI) CFB | −1.42 (−1.52, −1.31) | −1.25 (−1.35, −1.14) |
| LS mean treatment difference (95% CI), *P* value[c] | −0.17 (−0.25, −0.08); <0.001 | REF |
| ACQ-5 response at Week 24[a] | | |
| Responders, n (%) | 496 (80.1) | 464 (75.2) |
| Non-responders, n (%) | 123 (19.9) | 153 (24.8) |
| Non-responder due to missing data, n (%)[b] | 59 (48.0) | 69 (45.1) |
| OR (95% CI), *P* value[c] | 1.33 (1.01, 1.75); 0.04 | REF |

(*Continued*)

**Table 2** (Continued).

| | FF/UMEC/VI (N=619) | ICS/LABA (N=617) |
|---|---|---|
| ACQ-6 response at Week 24[a] | | |
| Responders, n (%) | 501 (80.9) | 475 (77.0) |
| Non-responders, n (%) | 118 (19.1) | 142 (23.0) |
| Non-responder due to missing data, n (%)[b] | 59 (50.0) | 69 (48.6) |
| OR (95% CI), *P* value[c] | 1.26 (0.95, 1.67), 0.10 | REF |
| CFB in ACQ-5 total score at Week 24 | n=560 | n=548 |
| LS mean (95% CI) CFB | −1.76 (−1.88, −1.63) | −1.60 (−1.72, −1.48) |
| LS mean treatment difference (95% CI), *P* value[c] | −0.16 (−0.26, −0.06); 0.002 | REF |
| CFB in ACQ-6 total score at Week 24 | n=560 | n=548 |
| LS mean (95% CI) CFB | −1.58 (−1.70, −1.46) | −1.42 (−1.54, −1.31) |
| LS mean treatment difference (95% CI), *P* value[c] | −0.16 (−0.25, −0.06); 0.001 | REF |
| CFB in ACT score at Week 24 | n=560 | n=548 |
| LS mean (95% CI) CFB | 5.92 (5.39, 6.44) | 5.35 (4.83, 5.87) |
| LS mean treatment difference (95% CI), *P* value[c] | 0.57 (0.14, 1.00); 0.01 | REF |
| **Exploratory endpoints** | | |
| Composite endpoint at Week 24 (lung function optimization) | | |
| Responders, n (%) | 210 (33.9) | 117 (19.0) |
| No OCS use since baseline | 587 (94.8) | 564 (91.4) |
| No severe asthma exacerbations since baseline | 579 (93.5) | 564 (91.4) |
| ACQ-5 total score <1.50 | 421 (68.0) | 365 (59.2) |
| CFB in trough $FEV_1$ ≥100 mL | 285 (46.0) | 182 (29.5) |
| Non-responders, n (%) | 409 (66.1) | 500 (81.0) |
| Non-responder due to missing data, n (%)[b] | 61 (14.9) | 72 (14.4) |
| OR (95% CI), *P* value[c] | 2.18 (1.66, 2.85); <0.001 | REF |
| Composite endpoint at Week 24 (lung function stabilization), n (%) | | |
| Responders, n (%) | 297 (48.0) | 198 (32.1) |
| No OCS use since baseline | 587 (94.8) | 564 (91.4) |
| No severe asthma exacerbations since baseline | 579 (93.5) | 564 (91.4) |
| ACQ-5 total score <1.50 | 421 (68.0) | 365 (59.2) |
| CFB in trough $FEV_1$ ≥0 mL | 408 (65.9) | 318 (51.5) |
| Non-responders, n (%) | 322 (52.0) | 419 (67.9) |
| Non-responder due to missing data, n (%)[b] | 61 (18.9) | 72 (17.2) |
| OR (95% CI), *P* value[c] | 1.96 (1.54, 2.49), <0.001 | REF |
| OCS use at Week 24 | | |
| n | 32 | 53 |
| Mean (SD) daily dose, mg/day | 2.19 (3.147) | 2.44 (4.822) |
| Incidence of severe exacerbations at Week 24 | | |
| Patients with ≥1 event, n (%) | 40 (6.5) | 53 (8.6) |
| Number of events | 48 | 56 |

**Notes**: [a]A response was defined as a ≥0.5-point improvement (decrease) from baseline to Week 24. Patients with a missing baseline score had their responder status set as missing. Patients with missing data at Week 24 or who withdrew from the trial prior to Week 24 were considered non-responders; [b]percentages based on the number of non-responders; [c]endpoint not included in the statistical hierarchy; the *P* value was not adjusted for multiplicity and is considered descriptive.

**Abbreviations**: ACQ-5/-6/-7, Asthma Control Questionnaire-5/-6/-7; ACT, Asthma Control Test; CFB, change from baseline; CI, confidence interval; FAS-Modified-1, modified full analysis set 1; $FEV_1$, forced expiratory volume in 1 second; FF, fluticasone furoate; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LS, least squares; OCS, oral corticosteroid; OR, odds ratio; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.


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## Other Secondary Endpoints and Exploratory Endpoints

Endpoints listed below were not included in the prespecified testing hierarchy and were therefore not adjusted for multiplicity.

## Lung Function

The odds of achieving lung function optimization, defined as CFB in trough $FEV_1$ ≥100 mL at Week 24, were greater after initiating FF/UMEC/VI versus usual care ICS/LABA (OR [95% CI]: 2.01 [1.58, 2.56], $P$<0.001). Lung function optimization was achieved by 46.0% (n=285/619) of patients with FF/UMEC/VI versus 29.5% (n=182/617) with ICS/LABA. Other secondary lung function endpoints are presented in Table 2.

## Asthma Control

Improvements (decreases) from baseline in ACQ-7 score at Week 24 were greater after initiating FF/UMEC/VI versus usual care ICS/LABA (LS mean [95% CI]: −0.17 [−0.25, −0.08], $P$<0.001). Initiating FF/UMEC/VI led to an LS mean (95% CI) improvement from baseline at Week 24 in ACQ-7 total score of −1.42 (−1.52, −1.31), almost triple the 0.5-point MCID, while initiating or continuing usual care ICS/LABA led to a −1.25 (−1.35, −1.14) improvement from baseline (Table 2).

Other secondary asthma control endpoints are reported in Table 2. As part of exploratory analyses, the proportion of patients with an ACQ-5 total score <1.50 at Week 24 was 68.0% (n=421/619) with FF/UMEC/VI and 59.2% (n=365/617) with ICS/LABA.

## Other Exploratory Endpoints

At Week 24, the odds of meeting the exploratory composite endpoint (no OCS use, no exacerbations, symptom control [ACQ-5 <1.50] and optimized lung function [CFB in $FEV_1$ ≥100 mL]) were greater after initiating FF/UMEC/VI compared with usual care ICS/LABA (OR [95% CI]: 2.18 [1.66, 2.85], $P$<0.001) (Table 2). The proportion of patients meeting the composite endpoint at Week 24 was 33.9% (n=210/619) with FF/UMEC/VI and 19.0% (n=117/617) with ICS/LABA. Results for the exploratory composite endpoint using lung function stabilization (CFB in $FEV_1$ ≥0 mL) are presented in Table 2.

The mean (SD) daily OCS dose was 2.19 mg (3.15) with FF/UMEC/VI and 2.44 mg (4.82) with ICS/LABA, and 6.5% (n=40/619) of patients had ≥1 severe exacerbation with FF/UMEC/VI and 8.6% (n=53/617) with ICS/LABA by Week 24 (Table 2).

## Supportive Analyses

Supportive analyses for the primary endpoint and key secondary endpoint showed similar results to the primary analysis (Supplementary Tables 7–10), confirming its robustness.

## Safety Profile

Overall, 5.3% (n=65/1236) of patients experienced ≥1 TEAE (FF/UMEC/VI: 7.0% [n=44/631]; ICS/LABA: 3.5% [n=21/605]); 4.0% (n=50/1236) had a trial intervention/treatment-related TEAE (FF/UMEC/VI: 5.7% [n=36/631]; ICS/LABA: 2.3% [n=14/605]); 1.4% (n=17/1236) of patients had ≥1 serious TEAE (FF/UMEC/VI: 1.6% [n=10/631]; ICS/LABA: 1.2% [n=7/605]); and 0.3% (n=4/1236) had a cardiovascular (CV) event of any kind (FF/UMEC/VI: 0.6% [n=4/631]; ICS/LABA: 0% [0/605]) (Table 3). Similar safety findings were observed in the SAF.

# Discussion

PERFORM is the first pragmatic RCT to evaluate a SITT in asthma, and the first to provide randomized evidence demonstrating significant improvements in lung function and symptom control with FF/UMEC/VI versus usual care ICS/LABA in patients with uncontrolled asthma and infrequent exacerbations in a routine practice setting.

**Table 3** Treatment-Emergent Adverse Events During the 24-Week Treatment Period (SAF-Modified-1)

| Patients, n (%) | FF/UMEC/VI (N=631) | ICS/LABA (N=605) | Overall Population (N=1236) |
|---|---|---|---|
| Any TEAE[a] | 44 (7.0) | 21 (3.5) | 65 (5.3) |
| Respiratory, thoracic, and mediastinal disorders | 25 (4.0) | 8 (1.3) | 33 (2.7) |
| Infections and infestations | 9 (1.4) | 2 (0.3) | 11 (0.9) |
| Gastrointestinal disorders | 5 (0.8) | 2 (0.3) | 7 (0.6) |
| Nervous system disorders | 3 (0.5) | 2 (0.3) | 5 (0.4) |
| Neoplasms benign, malignant, and unspecified (including cysts and polyps) | 2 (0.3) | 1 (0.2) | 3 (0.2) |
| General disorders and administration site conditions | 1 (0.2) | 2 (0.3) | 3 (0.2) |
| Hepatobiliary disorders | 1 (0.2) | 0 | 1 (0.1) |
| Injury, poisoning and procedural complications | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| Investigations – sputum abnormal | 1 (0.2) | 0 | 1 (0.1) |
| Musculoskeletal and connective tissue disorders | 1 (0.2) | 0 | 1 (0.1) |
| Psychiatric disorders | 1 (0.2) | 0 | 1 (0.1) |
| Skin and subcutaneous tissue disorders | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| Cardiac disorders | 0 | 2 (0.3) | 2 (0.2) |
| Vascular disorders | 0 | 1 (0.2) | 1 (0.1) |
| Any trial intervention/treatment-related TEAE[b] | 36 (5.7) | 14 (2.3) | 50 (4.0) |
| Respiratory, thoracic, and mediastinal disorders | 21 (3.3) | 7 (1.2) | 28 (2.3) |
| Infections and infestations | 7 (1.1) | 1 (0.2) | 8 (0.6) |
| Gastrointestinal disorders | 4 (0.6) | 0 | 4 (0.3) |
| Nervous system disorders | 2 (0.3) | 2 (0.3) | 4 (0.3) |
| General disorders and administration site conditions | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| Injury, poisoning and procedural complications | 1 (0.2) | 0 | 1 (0.1) |
| Investigations – sputum abnormal | 1 (0.2) | 0 | 1 (0.1) |
| Psychiatric disorders | 1 (0.2) | 0 | 1 (0.1) |
| Skin and subcutaneous tissue disorders | 1 (0.2) | 1 (0.2) | 2 (0.2) |
| Cardiac disorders | 0 | 2 (0.3) | 2 (0.2) |
| Any serious TEAE | 10 (1.6) | 7 (1.2) | 17 (1.4) |
| Respiratory, thoracic, and mediastinal disorders | 4 (0.6) | 1 (0.2) | 5 (0.4) |
| Infections and infestations | 3 (0.5) | 1 (0.2) | 4 (0.3) |
| Neoplasms benign, malignant, and unspecified (including cysts and polyps) | 2 (0.3) | 1 (0.2) | 3 (0.2) |
| Gastrointestinal disorders | 1 (0.2) | 2 (0.3) | 3 (0.2) |
| Hepatobiliary disorders | 1 (0.2) | 0 | 1 (0.1) |
| Musculoskeletal and connective tissue disorders | 1 (0.2) | 0 | 1 (0.1) |
| Nervous system disorders | 1 (0.2) | 0 | 1 (0.1) |
| General disorders and administration site conditions | 0 | 1 (0.2) | 1 (0.1) |
| Injury, poisoning, and procedural complications | 0 | 1 (0.2) | 1 (0.1) |
| Vascular disorders | 0 | 1 (0.2) | 1 (0.1) |
| Any trial intervention/treatment-related serious TEAE | 1 (0.2) | 0 | 1 (0.1) |
| Infections and infestations | 1 (0.2) | 0 | 1 (0.1) |
| Any cardiovascular event | 4 (0.6) | 0 | 4 (0.3) |
| TEAEs leading to trial intervention withdrawal/interruption | 15 (2.4) | 4 (0.7) | 19 (1.5) |
| TEAEs leading to death | 0 | 1 (0.2) | 1 (0.1) |

**Notes**: [a]Defined as any AE (trial intervention/treatment-related AEs and all serious AEs) with onset dates on or after the start of the trial intervention and up to 7 days after the last dose of trial intervention; [b]including trial intervention/treatment-related AEs and trial intervention/treatment-related serious AEs.

**Abbreviations**: AE, adverse event; FF, fluticasone furoate; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; SAF-Modified-1, modified safety analysis set 1; TEAE, treatment-emergent adverse event; UMEC, umeclidinium; VI, vilanterol.

The current treatment landscape includes 4 SITT formulations, which have been shown in pivotal Phase 3 RCTs to significantly improve lung function versus ICS/LABA, albeit in populations with uncontrolled moderate-to-severe asthma, impaired lung function, and generally with a history of exacerbations.[9–12] In contrast, although patients in PERFORM had uncontrolled asthma, over 80% had no severe exacerbations in the prior year and baseline mean $FEV_1$% predicted was 85.74%. Treatment with FF/UMEC/VI and ICS/LABA resulted in 178 mL and 110 mL improvements from baseline in $FEV_1$ at Week 24, respectively, which are broadly in line with previous findings.[9–12] Notably, initiating FF/UMEC/VI led to a statistically significant 68 mL improvement in trough $FEV_1$ at Week 24 compared with usual care ICS/LABA, consistent with results from explanatory Phase 3 RCTs.[9–12] These findings provide an aspirational treatment goal for physicians and patients alike, indicating that improvements in lung function are still achievable even for patients with minimal lung function impairment. Moreover, a recent study using computed tomography and magnetic resonance imaging found that in patients with uncontrolled asthma previously treated with ICS/LABA, switching to FF/UMEC/VI led to improved lung function and structural changes consistent with reversal of airway remodeling,[28] highlighting the clinical benefits of stepping up treatment to FF/UMEC/VI SITT.

In real-world asthma populations, average exacerbation rates are 0.11–0.16 per patient per year,[29] whereas approximately 80% of patients experience weekly symptoms.[30,31] This highlights a considerable unmet need in a population not represented in Phase 3 RCTs of SITT, which typically enroll uncontrolled patients with a history of exacerbations. PERFORM was designed with this mind and was powered to assess asthma control using the ACQ-7 as a key secondary endpoint. Disease burden in PERFORM was primarily impacted by asthma symptoms, with a mean ACQ-7 score of 2.46 at baseline (ACQ-7 score ≥1.5 indicates not well-controlled asthma[32]). At Week 24, patients had significantly greater odds of achieving a ≥0.5-point improvement from baseline with FF/UMEC/VI versus ICS/LABA (OR [95% CI]: 1.47 [1.13, 1.92], $P$=0.004). These improvements in symptom control with FF/UMEC/VI versus ICS/LABA may also reflect the improved lung function with FF/UMEC/VI versus ICS/LABA, potentially resulting in a reduction in respiratory symptoms.[33] Of note, the ACQ-7 includes lung function, rescue medication and symptom control items, whereas the shorter ACQ-6 omits the lung function item, and the ACQ-5 includes only symptom control items.[27] It is therefore notable that the improved treatment effect with FF/UMEC/VI versus ICS/LABA was generally consistent across the ACQ-7 (OR: 1.47), ACQ-6 (OR: 1.26), and ACQ-5 (OR: 1.33) responder analyses, highlighting the robustness of our findings.

GINA recommends a stepwise approach to asthma treatment, where patients are first escalated through increasing ICS/LABA doses to achieve symptom control.[1] Escalation to ICS/LAMA/LABA triple therapy is recommended for patients already uncontrolled and at risk of exacerbations,[1] based on evidence from pivotal Phase 3 RCTs showing inconsistent effects on exacerbations and symptom control versus ICS/LABA.[9–12] These RCTs recruited highly selective populations, including exacerbating patients with moderate-to-severe disease and compromised lung function.[9–11] However, real-world burden is likely to differ.[34,35] Indeed, most patients have mild or moderate asthma with uncompromised lung function and reduced risk of exacerbations,[29,36,37] yet almost 80% of this population are not controlled,[37] and up to 76% are estimated to be undertreated,[38] further risking daily symptoms.[39,40] By omitting strict eligibility criteria, PERFORM enrolled a population with uncontrolled asthma, infrequent exacerbations and minimal lung function impairment, reflecting real-world patients who would otherwise be excluded from prior SITT Phase 3 RCTs. These patients represent an unmet need in current asthma treatment guidelines; patients were either uncontrolled despite existing ICS/LABA maintenance therapy or had high symptom burden but no prior asthma maintenance therapy. The Week 24 results from PERFORM provide the first pragmatic RCT data showing statistically significant improvements in symptom control with FF/UMEC/VI SITT versus usual care ICS/LABA in this population, and longer-term and stratified data are needed before guideline implications can be drawn.

Clinical remission is recognized by GINA as an ambitious, long-term asthma treatment goal,[1] and the concept of clinical remission is considered appealing and achievable by patients.[41,42] Clinical remission aims for patients to live free from the burden of asthma, including no exacerbations, not requiring OCS, with controlled symptoms and stabilized or optimized lung function, and must be assessed for at least 1 year.[1,43,44] A recent post hoc analysis of the CAPTAIN trial showed that over 30% of patients treated with FF/UMEC/VI (100/62.5/25: 31%; 200/62.5/25: 36%) met a composite endpoint at 24 weeks comprising the same 4 components (no systemic corticosteroid use, no severe exacerbations, asthma control [ACQ-5 total score <1.50], and optimized lung function [CFB in trough $FEV_1$ ≥100 mL]);[45] this is generally consistent with the 33.9% of patients who met the exploratory composite endpoint with FF/UMEC/VI at Week 24 in PERFORM. In the CAPTAIN post hoc

analysis, a similar proportion of patients also achieved the composite endpoint at 52 weeks with FF/UMEC/VI (100/62.5/25: 30%; 200/62.5/25: 38%).[45] While PERFORM includes a prespecified composite endpoint for clinical remission at 52 weeks, which will be available following the Week 52 final analysis,[25] results for the exploratory Week 24 composite endpoint may provide an indication of the attainability of key clinical outcomes in a different patient population and trial setting.

The safety profile of FF/UMEC/VI was consistent with its known pharmacology,[10,46–48] with no new safety signals identified over 24 weeks. Rates of TEAEs were low, albeit with slightly higher rates in the FF/UMEC/VI arm (7.0%) than the ICS/LABA arm (3.5%), and a total of 4 CV events were reported with FF/UMEC/VI, and none with ICS/LABA. Although CV safety data for LAMA in asthma are limited, explanatory Phase 3 RCTs in COPD report no increased CV risk with the addition of LAMA to ICS/LABA.[46–51] As a pragmatic, open-label trial, PERFORM included a broad asthma population reflecting routine practice, not restricted by smoking history, treatment history or comorbidities, which may influence AEs in this population.

PERFORM is the first pragmatic, open-label RCT to evaluate the effectiveness and safety of FF/UMEC/VI SITT versus usual care ICS/LABA in patients with uncontrolled asthma, without a history of frequent exacerbations. The trial has a number of strengths. PERFORM was designed to reflect treatment conditions in routine clinical practice, with findings that are generalizable to real-world patients. The trial included a broad asthma population, not restricted by the rigid eligibility criteria of explanatory Phase 3 RCTs, such as treatment history, smoking status, comorbidities or exacerbations. Physicians prescribed trial interventions based on local approval labels and availability, allowing effectiveness to be assessed according to usual practice across different healthcare providers and countries. Patients accessed trial intervention via community pharmacy and collected refills as needed, including MART if recommended by the treating physician, thereby avoiding the strict monitoring associated with explanatory Phase 3 RCTs and mirroring real-world treatment use.

Nonetheless, there are limitations that should be considered. PERFORM was an open-label trial, therefore, clinical practice staff and patients were not blinded to the prescribed intervention. However, trial team personnel involved in data review and preparations for statistical analyses used blinded data to ensure the integrity of the data and analysis plan. Whereas all patients randomized to FF/UMEC/VI newly initiated SITT, 63.4% of patients randomized to ICS/LABA continued treatment despite having uncontrolled asthma. This may lead to expectation bias, particularly with patient-reported outcomes (PROs), although this was mitigated by the 6-month period between site visits and PROs only requiring recall from the past week. Notably, for patients randomized to ICS/LABA, treatment choice was at the treating physician's discretion, and patients could change ICS/LABA formulation or increase ICS dose, mirroring routine practice. Furthermore, PERFORM evaluated FF/UMEC/VI ELLIPTA versus heterogeneous non-ELLIPTA ICS/LABA combinations. As adherence measures were not included in PERFORM to encourage usual patient behavior, this approach risks conflating the pharmacologic effect of adding a LAMA to ICS/LABA with the behavioral effect of single-inhaler once-daily dosing. However, this reflects decision-making in routine practice, where the mechanism of delivery is an integral component of therapy choice, and holistic real-world effectiveness is defined by the combined effects of therapeutic agent, dosing strategy and inhaler device. Lastly, while patient recall of serious AEs is unlikely to be affected, the 6-month interval between trial visits may have reduced the frequency of reporting, or impacted recollection of non-serious TEAEs.

## Conclusion

Once-daily FF/UMEC/VI significantly improved lung function and asthma control at Week 24 compared with usual care ICS/LABA in patients with high symptom burden, minimal lung function impairment and infrequent exacerbations. PERFORM is the first pragmatic RCT to demonstrate the effectiveness of FF/UMEC/VI in this patient population and provides further evidence to inform for optimized use of FF/UMEC/VI in patients with uncontrolled asthma.

## Trial Oversight

PERFORM was sponsored by GSK (219912; NCT06372496) and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guideline for Good Clinical Practice, as well as applicable local regulations. Trial documents and protocol amendments received approval by relevant local Institutional Review Boards and/or Independent Ethics Committees. All patients provided written, informed consent.

## Abbreviations

ACQ-5/-6/-7, Asthma Control Questionnaire-5/-6/-7; ACT, Asthma Control Test; AE, adverse event; CFB, change from baseline; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; FAS, full analysis set; FAS-Modified-1, modified full analysis set 1; FAS-Modified-2, modified full analysis set 2; $FEV_1$, forced expiratory volume in 1 second; FF, fluticasone furoate; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonist; LAMA, long-acting muscarinic antagonist; LS, least squares; MART, maintenance and reliever therapy; MCID, minimum clinically important difference; OCS, oral corticosteroid; OR, odds ratio; RCT, randomized controlled trial; SAE, serious adverse event; SAF, safety analysis set; SAF-Modified-1, modified safety analysis set; SD, standard deviation; SITT, single-inhaler triple therapy; TEAE, treatment-emergent adverse event; UMEC, umeclidinium; VI, vilanterol.

## Data Sharing Statement

Anonymized subject level data and trial documents will be made available to researchers a maximum of 18 months following trial completion, following approval of proposed use. Please refer to GSK weblink to access GSK's data sharing policies and as applicable seek anonymized subject level data via the link https://www.gsk-studyregister.com/en/.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, trial design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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