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Patient-reported outcomes with initiation of fluticasone furoate/vilanterol versus continuing usual care in the Asthma Salford Lung Study

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Abbreviations:

ACT, Asthma Control Test; ANCOVA, analysis of covariance; AQLQ (S), Standardized Asthma Quality of Life Questionnaire; CI, confidence interval; EQ-5D-3L, EuroQol 5-Dimensions 3-Levels Questionnaire; EQ VAS, EuroQol visual analogue scale; FF/VI, fluticasone furoate/vilanterol; HR-QoL; health-related quality of life; ICS, inhaled corticosteroid; ITT, intention-to-treat; LABA, long-acting beta$_2$-agonist; LS, least squares; MID, minimally important difference; OR, odds ratio; PC, partially controlled; PEA, primary effectiveness analysis; PRO, patient-reported outcome; QoL, quality of life; RCT, randomized controlled trial; SD, standard deviation; SE, standard error; SLS, Salford Lung Study; UC, usual care; UnC, uncontrolled; WC, well controlled; WPAI, Work Productivity and Activity Impairment

Keywords:

Patient-reported outcomes

Health-related quality of life

Work and activity impairment

Asthma

Real-world

Fluticasone furoate/vilanterol

ABSTRACT

Background: The Asthma Salford Lung Study demonstrated the effectiveness and safety of initiating once-daily inhaled fluticasone furoate/vilanterol (FF/VI) *versus* continuing usual care (UC) in asthma patients in UK primary care [1]. Here, we report a detailed analysis of patient-reported outcome (PRO) endpoints.

Methods: Adults with symptomatic asthma maintained on inhaled corticosteroids (ICS) ± long-acting beta$_2$-agonists (LABA) were randomized 1:1 to initiate FF/VI (100[200]/25 µg) or continue UC. PROs were measured using the Asthma Control Test (ACT), Standardised Asthma Quality of Life Questionnaire (AQLQ [S]), Work Productivity and Activity Impairment: asthma questionnaire, and EQ-5D-3L questionnaire, at timepoints across the 12-month study period.

Results: The individual components of ACT response (total score ≥20 or improvement from baseline ≥3) both contributed to the composite primary effectiveness endpoint at Week 24, with odds ratios favoring FF/VI over UC in both cases. Patients initiating FF/VI *versus* continuing UC were more likely to maintain/improve asthma control, regardless of baseline control status. The odds of patients being responders on AQLQ (S) total score and on individual AQLQ domains at Week 52 were significantly higher for FF/VI *versus* UC (all $p < .001$). FF/VI was associated with significantly greater reductions in overall work and activity impairment due to asthma (both $p < .001$), and a significantly greater change from baseline in EQ visual analogue scale score ($p = .007$), *versus* UC at Week 52. PRO findings were consistent across baseline ICS and ICS/LABA subsets.

Conclusions: Initiation of FF/VI *versus* continuing UC was associated with consistent improvements in PROs.

Introduction

Asthma is one of the most common chronic respiratory diseases, affecting more than 300 million people worldwide [2] and approximately 5.4 million in the UK [3]. The clinical symptoms and airway obstruction that characterize asthma fluctuate widely over time and range from mild to profoundly disabling [4]. Acute exacerbations of asthma impose considerable morbidity on patients and constitute a major burden on healthcare resources [4]. Their unpredictable nature can impact patients' psychological well-being, particularly in causing feelings of anxiety and loss of control, and worsen patients' quality of life (QoL) [5–8].

The main goal of asthma treatment is to achieve asthma control and minimize the risk of exacerbations and side effects [4]; consequently, the main clinical focus tends to be on symptoms management. However, patients are often more concerned with how their symptoms make them feel and the impact that symptoms have on their everyday lives [8]. Therefore, as well as improving objective clinical outcomes, therapeutic interventions for asthma should also aim to improve patients' health-related-QoL (HR-QoL) [9].

In recent years, health care has moved towards a patient-centric approach, which considers patients' perspectives regarding the impact of disease and its treatment. Patient-reported outcomes (PROs) are now widely used in clinical practice, and in clinical trials, to capture patients' subjective perceptions of changes in health status (symptoms or function) and HR-QoL that occur as a result of treatment intervention [10–12]. PROs are measures of health status directly elicited from patients, without external interpretation, and usually take the form of short, self-completed questionnaires. Numerous PRO instruments have been developed for use in patients with asthma, but not all are validated [12]. Including PRO endpoints in asthma clinical trials can complement more traditional efficacy endpoints, such as lung function, and provide a more comprehensive picture of the response to treatment. However, a review of recently published asthma clinical trials found that fewer than 10% had included PRO evaluations and none had been conducted in a real-world setting [13].

Effectiveness studies are often favored over traditional double-blind, randomized controlled trials (RCTs) for conducting comprehensive PRO assessments to determine the real-world impact of treatment, because they more closely reflect routine clinical care [11]. The Salford Lung Study in asthma (SLS asthma), a 12-month, open-label RCT conducted in UK primary care, compared the effectiveness and safety of initiating fluticasone furoate/vilanterol (FF/VI) *versus* continuing usual care (UC) in patients with symptomatic asthma. The trial incorporated a number of PRO effectiveness endpoints and topline PRO data have been published previously [1]. Here, we expand on the primary analysis of SLS asthma, reporting additional PRO findings from the study to provide a comprehensive picture of the impact of initiating FF/VI *versus* continuing UC in the overall patient population, and in patient subsets defined by asthma maintenance therapy at baseline. In particular, we aim to provide new, more detailed information on the impact of treatment on the components (i.e. domains/individual items) of the various PROs included in the study and on the likelihood of patients maintaining or improving asthma control during the study period.

Methods

Study design and patients

The SLS asthma study design has been described previously [1]. Briefly, this prospective, 12-month, open-label, RCT was conducted across 74 general practice clinics in Salford and South Manchester, UK, between November 2012 and December 2016. Adults aged ≥ 18 years, with a general practitioner's (GP's) diagnosis of symptomatic asthma, who were receiving regular maintenance inhaler therapy with an inhaled corticosteroid (ICS) alone or in combination with a long-acting beta$_2$-agonist (LABA), were included. Exclusion criteria were minimal. Patients were randomized 1:1 to initiate once-daily inhaled FF/VI (100 µg/25 µg or 200 µg/25 µg) or to continue with their UC, with stratification according to baseline Asthma Control Test (ACT) score (≤ 15, 16–19 or ≥ 20) and baseline intended asthma maintenance therapy (ICS or ICS/LABA); follow up was for 12 months.

The SLS asthma study was designed to mimic routine clinical practice, with minimal disruption to patients' everyday lives, and treatment modifications were permitted at GPs' discretion throughout the study in both treatment groups. There were few protocol-mandated clinic visits (screening, randomization and 12 months/early withdrawal visit only) and data were collected continuously and remotely via patients' electronic health records using an integrated primary and secondary care-linked database system.

All patients provided written informed consent. The study was conducted in accordance with the International Conference on Harmonisation, Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki, 2008. The study was approved by the National Research Ethics Service Committee North West, Greater Manchester South (approval number: 12/NW/0455).

PRO questionnaires

Asthma Control Test

The ACT is a validated, self-administered questionnaire, including for use over the telephone [14]. It comprises 5 questions that assess asthma control during the past 4 weeks on a 5-point categorical scale with the total score calculated as the sum of the scores from all 5 questions (range 5–25) [15]. Questions evaluate the effect of asthma on daily functioning, frequency of shortness of breath, frequency of asthma symptoms leading to night-time awakenings, frequency of rescue medication use, and overall self-assessment of asthma control. A higher total ACT score indicates better asthma control: 'well controlled', ≥ 20 points; 'partially controlled', 16–19 points; 'uncontrolled', ≤ 15 points. The minimally important difference (MID) for ACT is 3 points [16]. The ACT was completed at baseline (randomization) and at Weeks 12, 24, 40, and 52/early withdrawal visit. Patients completed the questionnaire electronically at baseline and the Week 52/early withdrawal visit (as these were the protocol-mandated study visits), and over the telephone at Weeks 12, 24, 40 (questionnaire conducted remotely so as to preserve the real-world nature of the trial).

Standardised Asthma Quality of Life Questionnaire

The Standardised Asthma Quality of Life Questionnaire (AQLQ [S]), a modified version of the original AQLQ, is a validated, disease-specific, self-administered questionnaire [17, 18] designed to evaluate the impact of asthma treatment on patients' QoL over the past 2 weeks. The AQLQ (S) comprises 32 items in 4 domains (activity limitation [11 items], symptoms [12 items], emotional function [5 items], environmental stimuli [4 items]) that are each rated on a 7-point scale, where 1 = total impairment and 7 = no impairment. The AQLQ (S) total score is calculated as the mean of all 32 items in the questionnaire and each individual domain score is calculated as the mean of the items within that domain. Therefore, the total and domain scores are also each defined on a range from 1–7 with higher scores indicating better QoL. The MID for overall or domain-specific QoL is 0.5 points [19]. The AQLQ (S) was completed at baseline, at Week 24, and at the Week 52/early withdrawal visit; electronically at baseline and Week 52/early withdrawal visit, and by telephone at Week 24.

Work Productivity and Activity Impairment: asthma

The Work Productivity and Activity Impairment (WPAI): asthma questionnaire is a validated, self-administered, 6-item questionnaire [20, 21] designed to quantitatively assess patients' overall work impairment and overall activity impairment due to asthma during the past 7 days. Four types of asthma-derived scores are calculated: absenteeism (work time missed); presenteeism (impairment at work/reduced on-the-job effectiveness); work productivity loss (overall work impairment/absenteeism plus presenteeism) and activity impairment. The WPAI: asthma questionnaire was completed electronically at baseline and at the Week 52/early withdrawal visit.

EuroQol 5-Dimensions 3-Levels questionnaire

The EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L) is a standardized,

self-administered instrument used to provide a simple, generic measure of patients' health status "today" [22]. The questionnaire comprises 2 parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system covers 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each measured on a 3-point Likert scale (1 = no problems, 2 = some problems, and 3 = extreme problems). Based on patients' selection of levels that reflect their "own health state today" for each of the 5 dimensions, 1 of 243 distinct health states can be assigned and a single utility score calculated, ranging from 0–1. A higher utility score is indicative of better QoL. For the EQ VAS, patients rate their current health status by selecting a score on a continuous vertical visual scale ranging from 0 = worst imaginable health state to 100 = best imaginable health state. The EQ-5D-3L questionnaire was completed electronically at baseline and at the Week 52/early withdrawal visit.

Study endpoints

Pre-planned PRO endpoints included: the percentage of ACT responders at Week 24 (responders defined as patients who achieved an ACT total score of ≥ 20 and/or an improvement from baseline of ≥ 3; composite primary effectiveness endpoint); the relative contributions of the individual components of ACT total score ≥ 20 or improvement from baseline ≥ 3 to the composite primary effectiveness endpoint at Week 24; mean change from baseline in ACT score at Week 24; transitional probability of patients' ACT control status in any visit (Weeks 12, 24, 40, and 52) according to control status at the previous visit, and probability of control status in a recorded visit according to control status at the previous visit; mean change from baseline in AQLQ (S) total score and domain scores at Week 52; percentage of AQLQ (S) responders (defined as patients with an increase from baseline of ≥ 0.5 points at Week 52) for total score and the environmental stimuli domain; mean change from baseline in WPAI: asthma-derived scores at Week 52; and EQ-5D-3L health status at Week 52.

Post-hoc analyses were conducted for the percentage of AQLQ (S) responders

(patients with an increase from baseline of ≥ 0.5 points at Week 52) for the symptoms, activity limitation, and emotional function domains.

Statistical analyses

Analysis populations

All analyses were conducted according to the intention-to-treat (ITT) principle. The overall study population included all randomized patients who received at least 1 prescription of study medication (FF/VI or UC). The primary effectiveness analysis (PEA) population included all patients in the overall study population with a baseline ACT score of < 20. Subsets of the overall and PEA populations defined by baseline intended asthma maintenance therapy (ICS or ICS/LABA) were also analyzed; these included patients whose asthma maintenance therapy at baseline per randomization stratification and whose pre-randomization prescription was either ICS alone or ICS/LABA (fixed dose combination or in separate inhalers).

PRO analyses

The percentage of ACT responders based on the composite primary endpoint at Week 24 was analyzed in the overall PEA population and corresponding ICS and ICS/LABA subsets. A supporting analysis in the overall study population was also conducted. The percentage of patients achieving either the threshold of ≥ 20 points for 'well controlled' asthma or achieving the MID for ACT of ≥ 3 points at Week 24 were determined separately for each population. Statistical analyses were conducted using logistic regression.

ACT transitional probabilities were analyzed in the overall study population and corresponding ICS and ICS/LABA subsets. A PEA sensitivity analysis was also conducted. Using a Markov chain method, the probabilities of patients transitioning from one state of asthma control to another based on ACT score at a given time point were determined for the FF/VI and UC treatment groups (e.g., the probability of patients transitioning from an uncontrolled state to a partially controlled state or a well-controlled state, etc). Probabilities

were calculated using an ordinal logistic regression model [23]; summary statistics were descriptive only.

AQLQ (S) responder analyses at Week 52 were performed in the overall study population and corresponding ICS and ICS/LABA subsets using logistic regression. Mean change from baseline in WPAI: asthma-derived scores at Week 52 were analyzed in the overall study population and corresponding ICS and ICS/LABA subsets. Statistical analyses were performed using analysis of covariance (ANCOVA). EQ-5D-3L analyses were performed in the overall study population and corresponding ICS and ICS/LABA subsets. The percentage of responders (patients self-scoring 1 = no problems) for each of the 5 descriptive domains was calculated for FF/VI and UC and between-group differences were analyzed using logistic regression. Least squares (LS) mean change from baseline to Week 52 in EQ-5D-3L utility and EQ VAS scores were also calculated, and between-group differences were determined using ANCOVA.

Results

Patients

In total, 4233 patients (2114 FF/VI; 2119 UC) were included in the overall study population. Patient demographics and baseline characteristics have been reported previously; these were well matched between the treatment groups [1]. Briefly, patients had a mean (standard deviation [SD]) age of 50 (16) years and 59% were female. Mean (SD) body mass index was 30 (7) kg/m^2 and 53% were current or former smokers. Most patients (87%) had been diagnosed with asthma at least 5 years previously; 90% experienced daytime symptoms at least twice weekly and 36% had experienced at least 1 exacerbation in the year before randomization. In total, 3026 (71%) patients in the overall study population had a baseline ACT score < 20 and were included in the PEA population (1512 FF/VI; 1514 UC).

ACT – Individual questions

A summary of patients' responses to the five individual questions of the ACT by treatment group at Week 24 is provided in **Supplementary Table 1** (overall study population and corresponding ICS and ICS/LABA subsets, plus PEA population). Findings were consistent across the individual ACT questions for the different populations analysed.

ACT composite analysis

Analysis of the percentage of patients who achieved either an ACT total score ≥ 20 or an improvement from baseline of ≥ 3 points at Week 24 demonstrated that both individual measures contributed to the composite primary effectiveness endpoint in SLS asthma. Odds ratios (ORs) favored FF/VI over UC in both cases (PEA population, ACT total score ≥ 20: OR 1.98 [95% confidence interval (CI): 1.69–2.33]; improvement from baseline ≥ 3 points: OR 2.05 [95% CI: 1.75–2.40]) consistent with the primary analysis [1]. Similar results were observed for the ICS and ICS/LABA subsets of the PEA population **(Table 1).** Findings were also consistent in the overall study population (data not shown).

Table 1

Contribution of ACT total score ≥ 20 and improvement from baseline ≥ 3 to the composite primary effectiveness endpoint in SLS asthma (Week 24 data; PEA population).

Patients, n/N (%)[a]	Overall PEA population			ICS subset			ICS/LABA subset		
	FF/VI n = 1512	UC n = 1514	Adjusted OR (95% CI)[b]	FF/VI n = 484	UC n = 492	Adjusted OR (95% CI)[c]	FF/VI n = 997	UC n = 989	Adjusted OR (95% CI)[c]
ACT total score ≥ 20 and/or improvement from baseline ≥ 3 (composite endpoint)	977/1373 (71)	784/1399 (56)	2.00 (1.70–2.34)	324/440 (74)	259/454 (57)	2.13 (1.60–2.83)	637/908 (70)	511/916 (56)	1.95 (1.60–2.38)
ACT total score ≥ 20	704/1373 (51)	501/1399 (36)	1.98 (1.69–2.33)	257/440 (58)	183/454 (40)	2.34 (1.77–3.11)	432/908 (48)	308/916 (34)	1.84 (1.51–2.24)
Improvement from baseline ≥ 3	927/1373 (68)	724/1399 (52)	2.05 (1.75–2.40)	304/440 (69)	234/454 (52)	2.15 (1.62–2.84)	607/908 (67)	476/916 (52)	2.01 (1.66–2.45)

[a]Percentages based on a denominator of the number of patients evaluable for ACT.

[b]ORs and 95% CIs for the difference between FF/VI and UC were determined using a logistic regression model adjusted for randomized treatment, baseline ACT total score, baseline ACT total score squared (composite endpoint only), asthma maintenance therapy at baseline per randomization stratification, age, and gender.

[c]For analysis of the ICS and ICS/LABA subsets of the PEA population, the statistical models did not include the asthma maintenance therapy at baseline per randomization stratification variable.

Abbreviations: ACT, Asthma Control Test; CI, confidence interval; FF/VI, fluticasone furoate/vilanterol; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; OR, odds ratio; PEA, primary effectiveness analysis; SLS, Salford Lung Study; UC, usual care.

ACT transitional probabilities

A higher proportion of patients initiating FF/VI *versus* continuing UC maintained or improved their asthma control during the study, regardless of control status at baseline **(Fig. 1, A).** Similar findings were observed in the ICS and ICS/LABA subsets **(Fig. 1, B, C).** Conversely, patients continuing on UC were more likely to have worsening of asthma control **(Supplementary Fig. 1)** or to remain uncontrolled or partially controlled **(Supplementary Fig. 2).** Results were consistent in the PEA population (data not shown).

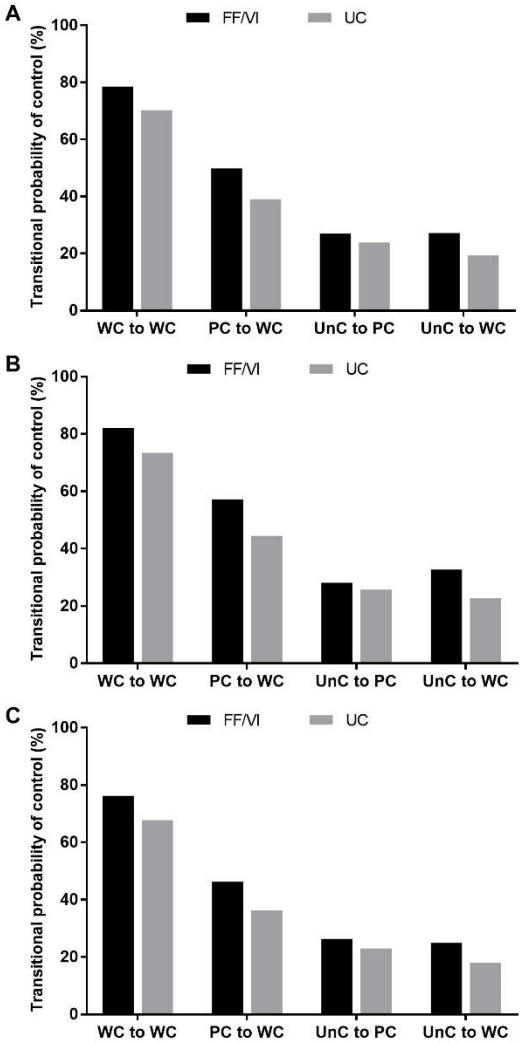

Fig. 1. Transitional probabilities of maintaining or improving asthma control based on ACT scores measured across the 12-month study period.[a,b] (A) Overall study population, (B) ICS subset, (C) ICS/LABA subset. [a]Transitional probability of control status in any visit according to control status at the previous visit. [b]Probabilities

were calculated using an ordinal logistic regression model adjusted for randomized treatment and previous control status. (A) Overall study population: data based on n = 2052 patients in the FF/VI group and n = 2076 in the UC group contributing to at least 1 transition. (B) ICS subset: data based on n = 724 patients in the FF/VI group and n = 743 in the UC group contributing to at least 1 transition. (C) ICS/LABA subset: data based on n = 1290 patients in the FF/VI group and n = 1296 in the UC group contributing to at least 1 transition. Abbreviations: FF/VI, fluticasone furoate/vilanterol; PC, partially controlled; UC, usual care; UnC, uncontrolled; WC, well controlled.

Many patients showed improved asthma control early on in the trial, with the most prominent effect seen during the baseline to 12 weeks interval followed by a trend of stabilization thereafter (**Supplementary Table 2**; overall study population). Similar findings were observed in the ICS and ICS/LABA subsets of the overall study population **(Supplementary Tables 3 and 4)** and in the PEA population (data not shown).

AQLQ (S) analyses

At baseline, mean total AQLQ (S) scores were 5.01 in the FF/VI group and 5.00 in the UC group (overall study population). At Week 52, mean scores had increased by 0.70 and 0.42 points in the FF/VI and UC groups, respectively. At Week 52, 55% of patients initiated on FF/VI and 43% continuing on UC were classified as responders based on change from baseline ≥ 0.5 in AQLQ (S) total score (OR: 1.79 [95% CI: 1.55–2.06], $p < .001$) [1]. Similar findings with respect to the proportions of AQLQ (S) responders by treatment group were observed across all 4 individual AQLQ (S) domains, with ORs favoring FF/VI over UC in the overall study population and in the ICS and ICS/LABA subsets (OR range: 1.51–1.92; all $p < .001$; **Fig. 2).**

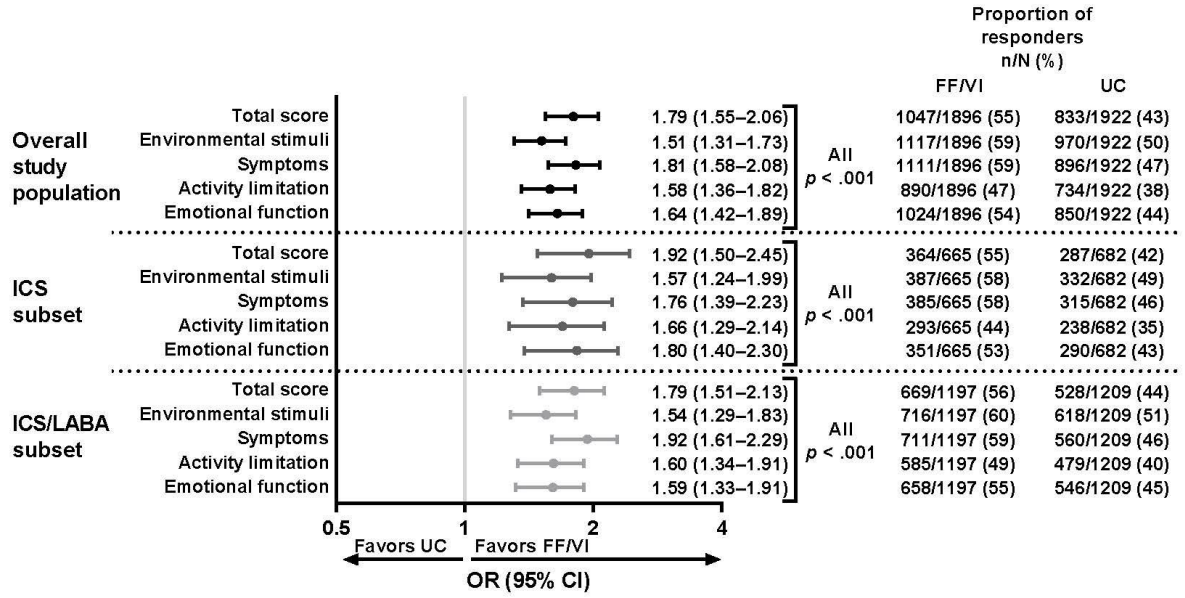

Fig. 2. Statistical analysis of AQLQ (S) responders by individual domains with FF/VI *versus* UC (Week 52 data) [a].
[a]Logistic regression model adjusted for randomized treatment, baseline AQLQ (S) score, asthma maintenance therapy at baseline per randomization stratification, ACT total score at baseline per randomization stratification, age, and gender. For analysis of the ICS and ICS/LABA subsets of the overall study population, the statistical models did not include the asthma maintenance therapy at baseline per randomization stratification variable.
Abbreviations: AQLQ (S), Standardized Asthma Quality of Life Questionnaire; CI, confidence interval; FF/VI, fluticasone furoate/vilanterol; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; OR, odds ratio; UC, usual care.

WPAI: asthma-derived scores

In the overall study population, mean baseline WPAI scores for FF/VI and UC, respectively, were 1.9% and 2.9% for work time missed, 15.4% and 16.1% for impairment while working, 15.8% and 16.8% for overall work impairment, and 28.1% and 28.4% for activity impairment. Initiating FF/VI was associated with statistically significantly greater reductions in impairment while working (difference -2.8% [95% CI: -4.3 to -1.3], $p < .001$), overall work impairment (difference -2.8% [95% CI: -4.4 to -1.1], $p < .001$), and activity impairment (difference -4.5% [95% CI: -5.9 to -3.2], $p < .001$) due to asthma, but not for work time missed due to asthma (difference -0.6% [95% CI: -1.7 to 0.4], $p = .223$), compared with continuing UC at Week 52. Similar results were observed in the ICS and ICS/LABA subsets **(Table 2).**

Table 2.

Statistical analysis of change from baseline in WPAI: asthma-derived scores (Week 52 data).[a]

	Overall study population			ICS subset			ICS/LABA subset		
	LS mean change from baseline (SE), %		Difference FF/VI *versus* UC, % (95% CI)[b] p-value	LS mean change from baseline (SE), %		Difference FF/VI *versus* UC, % (95% CI)[c] p-value	LS mean change from baseline (SE), %		Difference FF/VI *versus* UC, % (95% CI)[c] p-value
	FF/VI (n = 2114)	UC (n = 2119)		FF/VI (n = 750)	UC (n = 755)		FF/VI (n = 1325)	UC (n = 1325)	
Percent work time missed due to asthma	n = 833 -0.3 (0.38)	n = 835 0.3 (0.37)	-0.6 (-1.7 to 0.4) *p* = .223	n = 311 -0.0 (0.62)	n = 338 0.4 (0.59)	-0.4 (-2.0 to 1.3) *p* = .650	n = 508 -0.6 (0.45)	n = 484 -0.1 (0.47)	-0.5 (-1.8 to 0.8) *p* = .440
Percent impairment while working due to asthma	n = 823 -6.9 (0.56)	n = 822 -4.1 (0.55)	-2.8 (-4.3 to -1.3) *p* < .001	n = 305 -5.7 (0.81)	n = 335 -2.9 (0.77)	-2.8 (-5.0 to -0.6) *p* = .011	n = 503 -7.4 (0.75)	n = 476 -4.5 (0.78)	-2.9 (-5.0 to -0.8) *p* = .007
Percent overall work impairment due to asthma	n = 822 -6.7 (0.60)	n = 823 -4.0 (0.59)	-2.8 (-4.4 to -1.1) *p* < .001	n = 305 -5.6 (0.88)	n = 335 -2.8 (0.84)	-2.9 (-5.2 to -0.5) *p* = .018	n = 503 -7.1 (0.80)	n = 476 -4.4 (0.83)	-2.7 (-5.0 to -0.4) *p* = .019
Percent activity impairment due to asthma	n = 1982 -10.4 (0.50)	n = 1987 -5.9 (0.50)	-4.5 (-5.9 to -3.2) *p* < .001	n = 696 -8.5 (0.77)	n = 710 -4.1 (0.76)	-4.4 (-6.5 to -2.3) *p* < .001	n = 1250 -10.8 (0.65)	n = 1243 -6.0 (0.66)	-4.8 (-6.6 to -3.0) *p* < .001

[a]Data based on last available on-treatment measurement (Week 52 or early withdrawal visit).

[b]Between-group differences (FF/VI *versus* UC), 95% CIs, and associated p-values were calculated using an ANCOVA model adjusted for randomized treatment, asthma maintenance therapy at baseline per randomization stratification, ACT total score at baseline per randomization stratification, gender, age, and baseline WPAI score.

[c]For analysis of the ICS and ICS/LABA subsets of the overall study population, the statistical models did not include the asthma maintenance therapy at baseline per randomization stratification variable.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; FF/VI, fluticasone furoate/vilanterol; ICS, inhaled corticosteroid; LABA, long-acting beta$_2$-agonist; LS, least squares; SE, standard error; UC, usual care; WPAI, work productivity and activity impairment.

EQ-5D-3L health status

At baseline, the proportions of responders for each of the 5 EQ-5D-3L descriptive dimensions appeared similar between the FF/VI and UC groups in the overall study population (**Table 3**). The odds of patients being responders at Week 52 were statistically significantly higher with FF/VI *versus* UC for the mobility ($p < .001$), usual activities ($p = .027$), and pain/discomfort ($p = .043$) dimensions, but not for the self-care ($p = .409$) and anxiety/depression ($p = .180$) dimensions **(Table 3).** Corresponding data for the ICS and ICS/LABA subsets of the overall study population are summarized in **Supplementary Tables 5 and 6**.

Table 3

Statistical analysis of the proportion of responders[a] on individual EQ-5D-3L descriptive dimensions (Week 52 data[b]; overall study population).

	Baseline		Week 52		
	Patients, n/N (%)		Patients, n/N (%)		Adjusted OR (95% CI)[c]
EQ-5D-3L dimension	FF/VI n = 2114	UC n = 2119	FF/VI n = 2114	UC n = 2119	p-value
Mobility	1429/2113 (68)	1416/2119 (67)	1417/1984 (71)	1330/1988 (67)	1.35 (1.15–1.60) $p < .001$
Self-care	1882/2113 (89)	1882/2119 (89)	1747/1984 (88)	1757/1988 (88)	0.90 (0.71–1.15) $p = .409$
Usual activities	1394/2113 (66)	1354/2119 (64)	1416/1984 (71)	1352/1988 (68)	1.20 (1.02–1.40) $p = .027$
Pain / discomfort	1120/2113 (53)	1190/2119 (56)	1152/1984 (58)	1113/1988 (56)	1.16 (1.01–1.34) $p = .043$
Anxiety / depression	1443/2113 (68)	1445/2119 (68)	1396/1984 (70)	1360/1988 (68)	1.11 (0.95–1.30)

					p = .180

[a]Responders were defined as patients who self-scored 1 = no problems for a given dimension.

[b]Data based on last available on-treatment measurement (Week 52 or early withdrawal visit).

[c]ORs, 95% CIs, and p-values were calculated using a logistic regression model adjusted for randomized treatment, asthma maintenance therapy at baseline per randomization stratification, ACT total score at baseline per randomization stratification, gender, age, and the relevant baseline EQ-5D-3L domain score.

Abbreviations: CI, confidence interval; EQ-5D-3L, EuroQol 5-Dimensions 3-Levels Questionnaire; FF/VI, fluticasone furoate/vilanterol; OR, odds ratio; UC, usual care.

In the overall study population, the LS mean change in EQ-5D-3L utility score from baseline to Week 52 was 0.0170 for FF/VI and 0.0051 for UC; the between-group difference was not statistically significant (difference: 0.0119 [95% CI: -0.0017 to 0.0254]; *p* = .086) (**Table 4**). The LS mean change from baseline to Week 52 in EQ VAS score was 3.0 for FF/VI and 1.4 for UC, with a statistically significant difference between the groups (difference 1.6 [95% CI: 0.4–2.7]; *p* = .007). A similar treatment effect with FF/VI *versus* UC was also observed in the ICS and ICS/LABA subsets **(Table 4).**

Table 4

Statistical analysis of change from baseline in EQ-5D-3L utility and VAS scores (Week 52 data[a]).

	Overall study population			ICS subset			ICS/LABA subset		
	LS mean change from baseline (SE)		Difference FF/VI *versus* UC (95% CI)[b] p-value	LS mean change from baseline (SE)		Difference FF/VI *versus* UC (95% CI)[c] p-value	LS mean change from baseline (SE)		Difference FF/VI *versus* UC (95% CI)[c] p-value
	FF/VI (n = 2114)	UC (n = 2119)		FF/VI (n = 750)	UC (n =755)		FF/VI (n = 1325)	UC (n = 1325)	
EQ-5D-3L utility score	n = 1984 0.0170 (0.00504)	n = 1988 0.0051 (0.00502)	0.0119 (-0.0017 to 0.0254) *p* = .086	n = 696 0.0124 (0.00768)	n = 711 -0.0027 (0.00756)	0.0151 (-0.0060 to 0.0361) *p* = .161	n = 1252 0.0193 (0.00655)	n = 1243 0.0075 (0.00657)	0.0118 (-0.0058 to 0.0295) *p* = .189
EQ VAS score	n = 1984 3.0 (0.43)	n = 1988 1.4 (0.43)	1.6 (0.4 to 2.7) *p* = .007	n = 696 1.3 (0.70)	n = 711 -0.4 (0.69)	1.7 (-0.2 to 3.6) *p* = .083	n = 1252 4.0 (0.54)	n = 1243 2.3 (0.55)	1.7 (0.2 to 3.2) *p* = .024

[a]Data based on last available on-treatment measurement (Week 52 or early withdrawal visit).

[b]Between-group differences (FF/VI *versus* UC), 95% CIs, and p-values were calculated using an ANCOVA model adjusted for randomized treatment, asthma maintenance therapy at baseline per randomization stratification, ACT total score at baseline per randomization stratification, gender, age, and baseline EQ-5D-3L utility/VAS score (as appropriate).

[c]For analysis of the ICS and ICS/LABA subsets of the overall study population, the statistical models did not include the asthma maintenance therapy at baseline per randomization stratification variable.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; EQ-5D-3L, EuroQol 5-Dimensions 3-Levels Questionnaire; EQ VAS, EuroQol visual analogue scale; FF/VI, fluticasone furoate/vilanterol; LS, least squares; SE, standard error; UC, usual care.

Discussion

In this detailed analysis of prospectively collected PRO data from the SLS asthma study, we aimed to provide a fuller picture of the impact of initiating FF/VI *versus* continuing UC on asthma patients' HR-QoL, and also to explore the impact of patients' baseline asthma maintenance therapy (ICS or ICS/LABA) on PRO findings. The present work expands on the primary results of the SLS asthma study [1], demonstrating that the observed improvement in asthma control (as measured by ACT) with initiation of FF/VI *versus* continuing UC translates into patient-perceived benefits in HR-QoL (as measured by the AQLQ [S], work-relevant WPAI: asthma, and EQ-5D-3L instruments).

Analysis of the individual components of ACT total score ≥ 20 or improvement from baseline ≥ 3 demonstrated that both measures contributed to the composite primary effectiveness endpoint used in SLS asthma, with ORs favoring FF/VI *versus* UC in both cases. This suggests that the benefit of initiating FF/VI *versus* continuing UC on asthma control holds true both for patients achieving the threshold of ≥ 20 points for 'well controlled' asthma and for those achieving a change from baseline equating to the MID for ACT of ≥ 3 points. The benefit of FF/VI *versus* UC was also observed across different 'states' of asthma control based on ACT scores. Results from the Markov transitional probability modeling suggest that patients initiated on FF/VI were more likely to maintain or improve asthma control during the 12-month study period compared with patients who continued on UC, irrespective of their asthma control status at baseline. Many patients showed improved asthma control early on in the trial, with the most prominent effect seen during the baseline to 12 weeks interval and a trend of stabilization thereafter. Although this effect was observed in both treatment groups, it is important to note that the treatment effect of FF/VI *versus* UC persisted throughout the 12-month study duration.

The observed benefit of FF/VI *versus* UC at Week 52 for total AQLQ (S) score and across all 4 individual AQLQ (S) domains suggests an all-round more favorable impact of

initiating FF/VI *versus* continuing UC on patients' HR-QoL. To note, there is some overlap in the concepts captured by the domains of AQLQ and in the questions comprising the ACT, supporting the consistency of our findings across different questionnaires/endpoints used in this study. The benefit of FF/VI over UC on PROs was also demonstrated for WPAI: asthma-derived scores at Week 52, indicating a lesser impact of initiating FF/VI *versus* continuing UC on patients' ability to work and carry out regular daily activities. While there is no reported MID for the WPAI: asthma questionnaire, our results for the magnitude of change from baseline to Week 52 in WPAI scores should be interpreted in the context of patients' baseline impairment scores.

In addition to the asthma-specific PRO tools used in the SLS asthma study, patients' perceptions of generic health status were also recorded using EQ-5D-3L. At Week 52, the odds of patients being EQ-5D-3L responders were statistically significantly higher with initiating FF/VI *versus* continuing UC for 3 of the 5 descriptive domains (mobility, usual activities, and pain/discomfort); however, this did not translate into a significantly greater change from baseline to Week 52 in overall EQ-5D-3L utility scores with FF/VI *versus* UC. In contrast, patients initiating FF/VI had a statistically significantly greater improvement from baseline to Week 52 in EQ VAS score.

The results for all evaluated PRO endpoints in the overall/PEA populations were consistent across the ICS and ICS/LABA subsets, supporting the benefit of FF/VI over UC regardless of patients' baseline maintenance therapy. As baseline therapy is likely indicative of baseline asthma severity/degree of asthma control (with addition of LABA to ICS recommended as an option for patients whose asthma is uncontrolled on ICS alone [4]), the consistency of findings in these subsets suggests that the patient-perceived benefits of initiating FF/VI *versus* continuing UC may be relevant across different severities of disease, and also suggest that the results were not mediated by a step-up in treatment from ICS to ICS/LABA as part of the study design.

Although the SLS asthma study demonstrated improved asthma control (based on ACT) with initiation of FF/VI *versus* continuing UC, there was no observed between-group difference in asthma exacerbation rates in the overall SLS population [1]. It could be hypothesized, therefore, that the observed effects of FF/VI *versus* UC on PROs in the present study are not due to a reduction in exacerbations but instead due to an "everyday" effect on asthma control. In support of this, the PRO questionnaires utilized in this study recorded a range of outcomes (including asthma symptoms, impairment of function/activities of daily living, ability to work, and overall health status) and we observed a consistent treatment effect with FF/VI *versus* UC across the different domains/items of the various questionnaires. It was not possible, however, to pinpoint individual elements that may have been responsible for the observed results or that were predictive of positive outcomes; this may be of interest to explore in future studies.

While our findings provide support for improved PROs with initiating FF/VI *versus* continuing UC, limitations of the reported analyses should also be considered including the open-label design of the trial and the potential for bias, as well as the post-hoc nature of a subset of the AQLQ (S) analyses.

Although efficacy data from double-blind RCTs are typically used to inform clinical practice guidelines [24], patients enrolled in these studies tend to be highly selected and closely monitored, and therefore such trials are of limited relevance to patients seen in everyday clinical practice [25, 26]. There is now increasing interest in conducting prospective real-world studies to assess the comparative effectiveness of treatment interventions [27] and an increasing recognition of the value provided by PROs in guiding treatment decisions and informing health policy [12]. Our findings from SLS asthma add to the currently limited body of literature around the use of PROs in asthma clinical trials and on how asthma control is associated with patient-experienced benefits. Our findings may also have relevance for the everyday clinical management of patients with asthma. The very limited inclusion/exclusion criteria and minimal impact of trial procedures on patients' everyday

lives/routine clinical care in SLS asthma lend support to the applicability of our findings to a broad population of patients with symptomatic asthma. Furthermore, the use of disease-specific PRO instruments with validated MIDs in the study design allowed us to measure changes that are clinically meaningful to patients. Our results also underscore the importance validating findings from highly controlled asthma efficacy RCTs in real-world effectiveness studies [28].

Conclusions

Overall, our findings suggest that initiating treatment with once-daily inhaled FF/VI provides not only better asthma control compared with continuing UC in patients with symptomatic asthma, but also results in consistent improvements in HR-QoL as perceived by patients, which are highly relevant factors for guiding asthma treatment. Furthermore, the observed effects of initiating FF/VI *versus* continuing UC on asthma control were shown to be consistent regardless of patients' initial asthma control status.

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Conflicts of interest

HS, LJ, JL-F, DAL, and SC are employed by and hold stocks/shares in GSK. RJ reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GSK, Novartis, and Pfizer. JV reports honoraria for consulting/presenting with AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, and Novartis. AW reports speaker fees and expenses from GSK, advisory board and expenses from Chiesi, and is a chairman/shareholder of Reacta Biotech.

Supplementary information

Supplementary Table 1

Summary of patients' responses to individual questions of the ACT questionnaire by treatment group (Week 24 data).

Patients, n (%)		Overall study population		PEA population		ICS subset[a,b]		ICS/LABA subset[a,c]	
		FF/VI N = 2114	UC N = 2119	FF/VI N = 1512	UC N = 1514	FF/VI N = 750	UC N = 755	FF/VI N = 1325	UC N = 1325
Q1. Getting as much done at work, school, or home	***Evaluable, n***	*1936*	*1957*	*1373*	*1399*	*689*	*699*	*1214*	*1223*
	1. All of the time	21 (1)	36 (2)	18 (1)	34 (2)	7 (1)	10 (1)	14 (1)	25 (2)
	2. Most of the time	97 (5)	133 (7)	90 (7)	126 (9)	23 (3)	42 (6)	72 (6)	89 (7)
	3. Some of the time	292 (15)	383 (20)	256 (19)	337 (24)	84 (12)	110 (16)	203 (17)	265 (22)
	4. A little of the time	391 (20)	485 (25)	310 (23)	371 (27)	134 (19)	174 (25)	256 (21)	299 (24)
	5. None of the time	1135 (59)	920 (47)	699 (51)	531 (38)	441 (64)	363 (52)	669 (55)	545 (45)
Q2. Shortness of breath	***Evaluable, n***	*1936*	*1957*	*1373*	*1399*	*689*	*699*	*1214*	*1223*
	1. More than once a day	224 (12)	332 (17)	193 (14)	301 (22)	71 (10)	83 (12)	150 (12)	243 (20)
	2. Once a day	161 (8)	204 (10)	144 (10)	161 (12)	43 (6)	66 (9)	115 (9)	135 (11)
	3. 3 to 6 times a week	188 (10)	256 (13)	159 (12)	200 (14)	58 (8)	91 (13)	127 (10)	161 (13)
	4. Once or twice a week	767 (40)	801 (41)	538 (39)	548 (39)	263 (38)	304 (43)	493 (41)	479 (39)
	5. Not at all	596 (31)	364 (19)	339 (25)	189 (14)	254 (37)	155 (22)	329 (27)	205 (17)
	Evaluable, n	*1936*	*1957*	*1373*	*1399*	*689*	*699*	*1214*	*1223*

Q3. Asthma symptoms woken up at night or earlier than usual	**1. 4 or more nights a week**	144 (7)	206 (11)	130 (9)	186 (13)	46 (7)	62 (9)	95 (8)	141 (12)
	2. 2 to 3 nights a week	182 (9)	253 (13)	162 (12)	211 (15)	59 (9)	78 (11)	120 (10)	170 (14)
	3. Once a week	90 (5)	117 (6)	80 (6)	103 (7)	17 (2)	41 (6)	72 (6)	74 (6)
	4. Once or twice	340 (18)	397 (20)	266 (19)	310 (22)	131 (19)	133 (19)	204 (17)	255 (21)
	5. Not at all	1180 (61)	984 (50)	735 (54)	589 (42)	436 (63)	385 (55)	723 (60)	583 (48)
Q4. Used rescue inhaler or nebulizer medication	***Evaluable, n***	*1936*	*1957*	*1373*	*1399*	*689*	*699*	*1214*	*1223*
	1. 3 or more times per day	165 (9)	301 (15)	148 (11)	264 (19)	43 (6)	87 (12)	117 (10)	208 (17)
	2. 1 or 2 times per day	380 (20)	553 (28)	318 (23)	442 (32)	102 (15)	189 (27)	272 (22)	353 (29)
	3. 2 or 3 times a week	413 (21)	449 (23)	305 (22)	321 (23)	145 (21)	167 (24)	263 (22)	272 (22)
	4. Once a week or less	532 (27)	413 (21)	353 (26)	243 (17)	210 (30)	167 (24)	312 (26)	242 (20)
	5. Not at all	446 (23)	241 (12)	249 (18)	129 (9)	189 (27)	89 (13)	250 (21)	148 (12)
Q5. Asthma control	***Evaluable, n***	*1936*	*1957*	*1373*	*1399*	*689*	*699*	*1214*	*1223*
	1. Not controlled at all	24 (1)	33 (2)	21 (2)	30 (2)	8 (1)	9 (1)	16 (1)	24 (2)
	2. Poorly controlled	87 (4)	113 (6)	76 (6)	106 (8)	25 (4)	26 (4)	60 (5)	84 (7)
	3. Somewhat controlled	331 (17)	498 (25)	287 (21)	421 (30)	96 (14)	149 (21)	230 (19)	336 (27)
	4. Well controlled	893 (46)	870 (44)	647 (47)	613 (44)	309 (45)	323 (46)	567 (47)	535 (44)
	5. Completely controlled	601 (31)	443 (23)	342 (25)	229 (16)	251 (36)	192 (27)	341 (28)	244 (20)

[a]ICS and ICS/LABA subsets of the overall study population; [b]Patients whose asthma maintenance therapy at baseline per randomization stratification was ICS alone and pre-randomization prescription was ICS alone; [c]Patients whose asthma maintenance therapy at baseline per randomization stratification was ICS/LABA and pre-randomization prescription was ICS/LABA.

Supplementary Table 2

Transitional probability of asthma control status (based on ACT scores) in a recorded visit according to control status in the previous visit (overall study population; FF/VI n = 2114; UC n = 2119).[a,b]

Transitional probability, %	Baseline to Week 12		Week 12 to Week 24		Week 24 to Week 40		Week 40 to Week 52	
	FF/VI	UC	FF/VI	UC	FF/VI	UC	FF/VI	UC
WC to WC	n = 572 86.7	n = 583 80.9	n = 1163 77.2	n = 883 68.8	n = 1102 76.3	n = 857 67.7	n = 1063 77.2	n = 841 68.8
WC to PC	n = 572 9.3	n = 583 13.0	n = 1163 15.4	n = 883 20.2	n = 1102 15.9	n = 857 20.8	n = 1063 15.4	n = 841 20.2
WC to UnC	n = 572 4.0	n = 583 6.0	n = 1163 7.5	n = 883 11.0	n = 1102 7.8	n = 857 11.5	n = 1063 7.5	n = 841 11.0
PC to WC	n = 625 60.8	n = 631 50.3	n = 377 44.6	n = 507 34.4	n = 362 43.4	n = 464 33.3	n = 385 44.6	n = 458 34.4
PC to PC	n = 625 26.0	n = 631 30.8	n = 377 32.7	n = 507 34.5	n = 362 33.0	n = 464 34.5	n = 385 32.7	n = 458 34.5
PC to UnC	n = 625 13.2	n = 631 19.0	n = 377 22.7	n = 507 31.1	n = 362 23.6	n = 464 32.2	n = 385 22.7	n = 458 31.1
UnC to WC	n = 812 35.4	n = 818 26.3	n = 346 22.1	n = 525 15.6	n = 363 21.3	n = 543 15.0	n = 390 22.2	n = 571 15.6
UnC to PC	n = 812 28.8	n = 818 27.6	n = 346 26.1	n = 525 22.1	n = 363 25.7	n = 543 21.6	n = 390 26.1	n = 571 22.1
UnC to UnC	n = 812 35.8	n = 818 46.1	n = 346 51.8	n = 525 62.2	n = 363 53.0	n = 543 63.4	n = 390 51.8	n = 571 62.2

Individual patient numbers refer to patients with the specific control status at the index visit who had a recorded ACT total score in the following visit.

[a]Asthma control status based on ACT scores.

[b]Probabilities were calculated using an ordinal logistic regression model adjusted for randomized treatment and previous control status.

Abbreviations: ACT, Asthma Control Test; FF/VI, fluticasone furoate/vilanterol; PC, partially controlled; UC, usual care; UnC, uncontrolled; WC, well controlled.

Supplementary Table 3

Transitional probability of asthma control status (based on ACT scores) in a recorded visit according to control status in the previous visit (ICS subset of overall study population; FF/VI n = 750; UC n = 755).[a,b]

Transitional probability, %	Baseline to Week 12		Week 12 to Week 24		Week 24 to Week 40		Week 40 to Week 52	
	FF/VI	UC	FF/VI	UC	FF/VI	UC	FF/VI	UC
WC to WC	n = 255 88.3	n = 255 82.1	n = 476 80.0	n = 361 71.0	n = 433 80.4	n = 352 71.6	n = 432 81.2	n = 347 72.5
WC to PC	n = 255 8.3	n = 255 12.4	n = 476 13.7	n = 361 19.2	n = 433 13.5	n = 352 18.9	n = 432 13.0	n = 347 18.3
WC to UnC	n = 255 3.4	n = 255 5.5	n = 476 6.2	n = 361 9.8	n = 433 6.1	n = 352 9.6	n = 432 5.8	n = 347 9.1
PC to WC	n = 239 65.8	n = 247 54.1	n = 103 50.7	n = 176 38.6	n = 105 51.3	n = 160 39.2	n = 118 52.6	n = 157 40.4
PC to PC	n = 239 23.5	n = 247 29.6	n = 103 31.1	n = 176 34.7	n = 105 30.8	n = 160 34.5	n = 118 30.3	n = 157 34.3
PC to UnC	n = 239 10.6	n = 247 16.3	n = 103 18.3	n = 176 26.7	n = 105 17.9	n = 160 26.2	n = 118 17.2	n = 157 25.3
UnC to WC	n = 217 40.7	n = 223 29.6	n = 95 26.8	n = 146 18.3	n = 105 27.3	n = 150 18.7	n = 86 28.3	n = 161 19.5
UnC to PC	n = 217 28.5	n = 223 28.3	n = 95 27.7	n = 146 24.0	n = 105 27.8	n = 150 24.3	n = 86 28.1	n = 161 24.7
UnC to UnC	n = 217 30.8	n = 223 42.1	n = 95 45.5	n = 146 57.7	n = 105 44.8	n = 150 57.0	n = 86 43.6	n = 161 55.9

Individual patient numbers refer to patients with the specific control status at the index visit who had a recorded ACT total score in the following visit.

[a]Control status based on ACT scores.

[b]Probabilities were calculated using an ordinal logistic regression model adjusted for randomized treatment and previous control status.

Abbreviations: ACT, Asthma Control Test; FF/VI, fluticasone furoate/vilanterol; ICS, inhaled corticosteroid; PC, partially controlled; UC, usual care; UnC, uncontrolled; WC, well controlled.

Supplementary Table 4

Transitional probability of asthma control status (based on ACT scores) in a recorded visit according to control status in the previous visit (ICS/LABA subset of overall study population; FF/VI n = 1325; UC n = 1325).[a,b]

Transitional probability, %	Baseline to Week 12		Week 12 to Week 24		Week 24 to Week 40		Week 40 to Week 52	
	FF/VI	UC	FF/VI	UC	FF/VI	UC	FF/VI	UC
WC to WC	n = 309 85.3	n = 322 79.4	n = 665 75.3	n = 506 66.9	n = 648 73.2	n = 493 64.4	n = 608 74.7	n = 477 66.2
WC to PC	n = 309 10.2	n = 322 14.0	n = 665 16.5	n = 506 21.2	n = 648 17.7	n = 493 22.4	n = 608 16.8	n = 477 21.6
WC to UnC	n = 309 4.5	n = 322 6.6	n = 665 8.3	n = 506 11.9	n = 648 9.1	n = 493 13.1	n = 608 8.5	n = 477 12.3
PC to WC	n = 369 58.0	n = 373 47.8	n = 270 41.9	n = 319 32.4	n = 253 39.3	n = 291 30.1	n = 261 41.2	n = 293 31.7
PC to PC	n = 369 27.4	n = 373 31.6	n = 270 33.4	n = 319 34.5	n = 253 33.9	n = 291 34.4	n = 261 33.5	n = 293 34.5
PC to UnC	n = 369 14.7	n = 373 20.5	n = 270 24.7	n = 319 33.1	n = 253 26.8	n = 291 35.5	n = 261 25.3	n = 293 33.8
UnC to WC	n = 583 33.0	n = 575 24.7	n = 245 20.5	n = 372 14.6	n = 251 18.8	n = 385 13.3	n = 300 20.0	n = 405 14.2
UnC to PC	n = 583 28.9	n = 575 27.2	n = 245 25.4	n = 372 21.4	n = 251 24.5	n = 385 20.3	n = 300 25.2	n = 405 21.1
UnC to UnC	n = 583 38.1	n = 575 48.1	n = 245 54.1	n = 372 64.0	n = 251 56.8	n = 385 66.4	n = 300 54.9	n = 405 64.7

Individual patient numbers refer to patients with the specific control status at the index visit who had a recorded ACT total score in the following visit.

[a]Control status based on ACT scores.

[b]Probabilities were calculated using an ordinal logistic regression model adjusted for randomized treatment and previous control status.

Abbreviations: ACT, Asthma Control Test; FF/VI, fluticasone furoate/vilanterol; ICS/LABA; inhaled corticosteroid/long-acting beta$_2$ agonist combination; PC, partially controlled; UC, usual care; UnC, uncontrolled; WC, well controlled.

Supplementary Table 5

Statistical analysis of the proportion of responders[a] on individual EQ-5D-3L descriptive dimensions (Week 52 data[b]; ICS subset of overall study population).

EQ-5D-3L dimension	Baseline		Week 52[b]		
	Patients, n/N (%)		Patients, n/N (%)		Adjusted OR (95% CI)[c]
	FF/VI n = 750	UC n = 755	FF/VI n = 750	UC n = 755	p-value
Mobility	545/749 (73)	571/755 (76)	525/696 (75)	515/711 (72)	1.46 (1.08 –1.96) *p* = .013
Self-care	678/749 (91)	696/755 (92)	632/696 (91)	659/711 (93)	0.77 (0.48 –1.23) *p* = .273
Usual activities	531/749 (71)	538/755 (71)	526/696 (76)	537/711 (76)	1.06 (0.79 –1.41) *p* = .697
Pain / discomfort	428/749 (57)	478/755 (63)	418/696 (60)	436/711 (61)	1.09 (0.85 –1.39) *p* = .509
Anxiety / depression	534/749 (71)	535/755 (71)	521/696 (75)	510/711 (72)	1.23 (0.93 –1.63) *p* = .140

[a]Responders were defined as patients who self-scored 1 = no problems for a given dimension.

[b]Data based on last available on-treatment measurement (Week 52 or early withdrawal visit).

[c]ORs, 95% CIs, and p-values were calculated using a logistic regression model adjusted for randomized treatment, ACT total score at baseline per randomization stratification, gender, age, and the relevant baseline EQ-5D-3L domain score.

Abbreviations: CI, confidence interval; EQ-5D-3L, EuroQol 5-Dimensions 3-Levels Questionnaire; FF/VI, fluticasone furoate/vilanterol; OR, odds ratio; UC, usual care.

Supplementary Table 6

Statistical analysis of the proportion of responders[a] on individual EQ-5D-3L descriptive dimensions (Week 52 data[b]; ICS/LABA subset of overall study population).

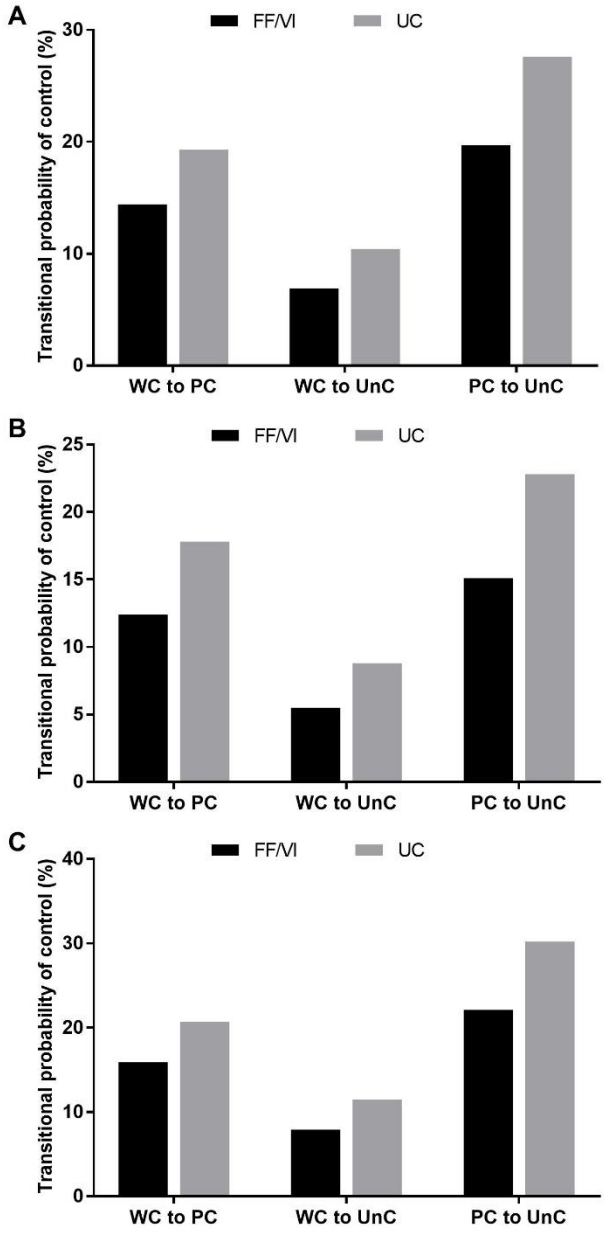
EQ-5D-3L dimension	Baseline		Week 52[b]		
	Patients, n/N (%)		Patients, n/N (%)		Adjusted OR (95% CI)[c] p-value
	FF/VI n = 1325	UC n = 1325	FF/VI n = 1325	UC n = 1325	
Mobility	861/1325 (65)	815/1325 (62)	868/1252 (69)	790/1243 (64)	1.32 (1.08 –1.63) *p* = .008
Self-care	1167/1325 (88)	1147/1325 (87)	1085/1252 (87)	1067/1243 (86)	0.98 (0.74 –1.31) *p* = .913
Usual activities	836/1325 (63)	792/1325 (60)	868/1252 (69)	791/1243 (64)	1.31 (1.08 –1.59) *p* = .006
Pain / discomfort	668/1325 (50)	687/1325 (52)	713/1252 (57)	655/1243 (53)	1.22 (1.02–1.46) *p* = .029
Anxiety / depression	880/1325 (66)	877/1325 (66)	849/1252 (68)	820/1243 (66)	1.09 (0.90 –1.33) *p* = .366

[a]Responders were defined as patients who self-scored 1 = no problems for a given dimension.

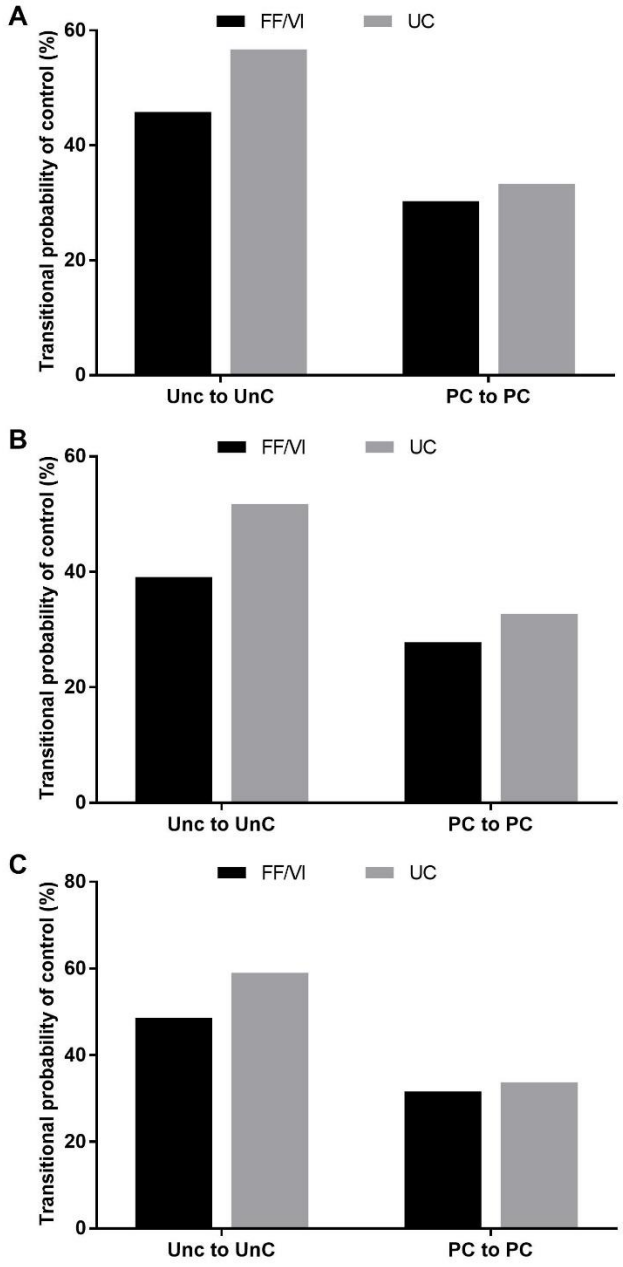
[b]Data based on last available on-treatment measurement (Week 52 or early withdrawal visit).

[c]ORs, 95% CIs, and p-values were calculated using a logistic regression model adjusted for randomized treatment, ACT total score at baseline per randomization stratification, gender, age, and the relevant baseline EQ-5D-3L domain score.

Abbreviations: CI, confidence interval; EQ-5D-3L, EuroQol 5-Dimensions 3-Levels questionnaire; FF/VI, fluticasone furoate/vilanterol; OR, odds ratio; UC, usual care.



Supplementary Fig. 1. Transitional probabilities of worsening asthma control based on ACT scores measured across the 12-month study period.[a,b] (A) Overall study population, (B) ICS subset, (C) ICS/LABA subset. [a]Transitional probability of control status in any visit according to control status in the previous visit. [b]Probabilities were calculated using an ordinal logistic regression model adjusted for randomized treatment and previous control status. (A) Overall study population: data based on n = 2052 patients in the FF/VI group and n = 2076 in the UC group contributing to at least 1 transition. (B) ICS subset: data based on n = 724 patients in the FF/VI group and n = 743 in the UC group contributing to at least 1 transition. (C) ICS/LABA subset: data based on n = 1290 patients in the FF/VI group and n = 1296 in the UC group contributing to at least 1 transition. Abbreviations: FF/VI, fluticasone furoate/vilanterol; PC, partially controlled; UC, usual care; UnC, uncontrolled; WC, well controlled.



Supplementary Fig. 2. Transitional probabilities of remaining uncontrolled or partially controlled based on ACT scores measured across the 12-month study period.[a, b] (A) Overall study population, (B) ICS subset, (C) ICS/LABA subset. [a]Transitional probability of control status in any visit according to control status in the previous visit. [b]Probabilities were calculated using an ordinal logistic regression model adjusted for randomized treatment and previous control status. (A) Overall study population: data based on n = 2052 patients in the FF/VI group and n = 2076 in the UC group contributing to at least 1 transition. (B) ICS subset: data based on n = 724 patients in the FF/VI group and n = 743 in the UC group contributing to at least 1 transition. (c) ICS/LABA subset: data based on n = 1290 patients in the FF/VI group and n = 1296 in the UC group contributing to at least 1 transition. Abbreviations: FF/VI, fluticasone furoate/vilanterol; PC, partially controlled; UC, usual care; UnC, uncontrolled.