Adv Ther (2020) 37:2916–2931
https://doi.org/10.1007/s12325-020-01344-8

ORIGINAL RESEARCH

Persistence and Adherence to ICS/LABA Drugs in UK Patients with Asthma: A Retrospective New-User Cohort Study

Mounika Parimi · Henrik Svedsater · Quratul Ann · Mugdha Gokhale · Christen M. Gray · David Hinds · Mark Nixon · Naomi Boxall

Received: March 11, 2020 / Published online: May 2, 2020

ABSTRACT

Introduction: Asthma is associated with significant economic burden. Inhaled corticosteroid and long-acting beta$_2$-agonist (ICS/LABA) combination therapies are considered mainstays of treatment. We describe real-world use of ICS/LABAs by comparing treatment persistence and adherence among patients with asthma in the United Kingdom initiating fluticasone furoate/vilanterol (FF/VI) versus budesonide/formoterol (BUD/FM) or beclometasone dipropionate/formoterol (BDP/FM).

Methods: A retrospective new-user active comparator database study was conducted in the IQVIA Medical Research Database. Propensity score (PS) matching was performed for FF/VI versus BUD/FM, and FF/VI versus BDP/FM. The primary objective was to compare patient treatment persistence (time to discontinuation), while secondary objectives included assessing adherence (mean proportion of days covered [PDC] with medication in the study period) and the proportions of patients achieving ≥ 50% and ≥ 80% PDC.

Results: New users of FF/VI (N = 966), BUD/FM (N = 5931) and BDP/FM (N = 9607) were identified and PS-matched: FF/VI (n = 945) versus BUD/FM (n = 3272), and FF/VI (n = 902) versus BDP/FM (n = 3465). At 12 months, treatment persistence was 69% (FF/VI), 53% (BUD/FM) and 57% (BDP/FM). The likelihood of treatment discontinuation within 12 months after initiation with FF/VI was 35% lower than with BUD/FM and 31% lower than for BDP/FM (both $p < 0.001$). Mean PDC was higher for FF/VI compared with BUD/FM (77.7 vs 72.4; $p < 0.0001$) and BDP/FM (78.2 vs 71.0; $p < 0.0001$). The odds of achieving ≥ 50% and ≥ 80% PDC were greater for FF/VI than for BUD/FM and BDP/FM.

Conclusions: In this study, patients who initiated FF/VI were less likely to discontinue treatment and showed greater treatment adherence versus patients who initiated BUD/FM or BDP/FM.

Keywords: Adherence; Asthma; Discontinuation; ICS/LABA; New user; Persistence

Digital Features To view digital features for this article go to https://doi.org/10.6084/m9.figshare.12086046.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12325-020-01344-8) contains supplementary material, which is available to authorized users.

M. Parimi · Q. Ann · C. M. Gray · M. Nixon · N. Boxall
Real World Solutions, IQVIA, London, UK

H. Svedsater (✉)
Value Evidence and Outcomes, GlaxoSmithKline Plc., Brentford, Middlesex, UK
e-mail: henrik.x.svedsater@gsk.com

M. Gokhale · D. Hinds
Epidemiology, GlaxoSmithKline Plc., Collegeville, PA, USA

Key Summary Points

Why carry out this study?

Inadequate medication adherence (the extent to which a patient acts in accordance with the interval and dose indicated) and persistence (time from therapy initiation to discontinuation) are widespread issues in asthma treatment that, if properly addressed, could lead to improved symptom control and reduced exacerbations.

Here we compare treatment persistence and adherence among patients using different inhaled corticosteroid/long-acting beta$_2$-agonist (ICS/LABA) combinations in order to evaluate the real-world use of ICS/LABA therapy.

What was learned from the study?

The likelihood of treatment discontinuation in patients treated with fluticasone furoate/vilanterol (FF/VI) within the 12 months following initiation was between 31% and 35% lower than its comparators.

The odds of achieving $\geq$ 50% and $\geq$ 80% in the proportion of days covered (a measure of adherence) were greater for FF/VI than its comparators.

Our findings suggest that the FF/VI is associated with a significantly lower likelihood of discontinuation and a higher adherence to treatment versus other ICS/LABA comparators; improvements could be due to factors such as the simplified (once-a-day) dosing regimen associated with FF/VI and improved asthma control.

INTRODUCTION

Approximately 5.4 million people receive treatment for asthma in the United Kingdom (UK) [1]. Inhaled corticosteroid/long-acting beta$_2$-agonist (ICS/LABA) combination therapies are recommended for patients whose asthma remains uncontrolled with an ICS alone [2]. ICS/LABA therapies have demonstrated effective control of asthma symptoms, including a reduction in severe exacerbations [3]. Various ICS/LABA combinations are available in the UK for the treatment of asthma, including fluticasone furoate/vilanterol (FF/VI), budesonide/formoterol (BUD/FM) and beclometasone dipropionate/formoterol (BDP/FM) [4–6]. Current literature suggests that patients treated with FF/VI may exhibit improved control of asthma symptoms compared with other ICS/LABA combinations [7, 8]. The Salford Lung Study on asthma, an open-label, two-arm, effectiveness randomised controlled trial (RCT), assessed the percentage of responders (patients who achieved an Asthma Control Test score of $\geq$ 20, or an $\geq$ 3-point increase from baseline in Asthma Control Test score at 24 weeks), and found that a higher proportion of patients with uncontrolled asthma achieved better control of their asthma when they were initiated with FF/VI (71%) versus patients continuing usual care (56%) [7, 8]. In another study, patients treated with FF/VI were shown to have a lower risk of treatment discontinuation versus BUD/FM or fluticasone propionate/salmeterol (27% and 30% lower, respectively) [9].

Inadequate medication adherence (the extent to which a patient acts in accordance with the interval and dose indicated) and persistence (time from therapy initiation to discontinuation) [10] is a widespread issue, with an estimated 50% of prescriptions filled for chronic diseases not taken as indicated [11]. Adherence to asthma medication is known to reduce over time, data for which may not be captured in a relatively short-term RCT [12]. A systematic literature review found that good adherence was associated with a lower risk of severe asthma exacerbations, suggesting that improved

adherence to ICS/LABA therapy may improve asthma symptom control [13].

Particular features of a medicine, such as daily dosing schedule (once-daily versus twice-daily administration), duration of action, and ease-of-use of the device may each impact treatment adherence and persistence among patients using asthma maintenance treatments [14–16]. This study described the real-world use of ICS/LABAs by comparing treatment persistence and adherence among patients initiating FF/VI or either BDP/FM or BUD/FM (comparator ICS/LABA combinations, both commonly used in the UK [may be viewed as substitutable]).

METHODS

Study Population

The study population was derived from the IQVIA Medical Research Database (IMRD, including patient data gathered via The Health Improvement Network [THIN; the anonymised UK patient data collection scheme from general practitioners], a Cegedim database [17]). Key inclusion criteria were: ICS/LABA-treated patients for whom the first recorded prescription of FF/VI, BUD/FM or BDP/FM occurred during the study period, with a confirmed asthma diagnosis on or before the index date and at least one subsequent prescription of the same FF/VI, BUD/FM or BDP/FM within 180 days post-index date. See Supplementary Methods for exclusion criteria.

For patients identified as initiating BUD/FM treatment, only those identified in the THIN database as prescribed medication at strengths of 200/6, 100/6 and 400/12 μg (flexible or fixed dose) were included in our analysis, with the aim of generating a cohort representative of SYMBICORT (AstraZeneca) for comparison with FF/VI. Other identifiable BUD/FM medications with differing doses were excluded (a step necessitated as the THIN database does not capture generic/branding medication information) but non-distinguishable generics were included in the specified cohort. Please note that the term "BUD/FM", used hereafter, therefore refers to the specified cohort only. Only one brand of each of FF/VI (RELVAR, GlaxoSmithKline plc.) and BDP/FM (FOSTAIR, Chiesi Ltd) are available in the UK, and so this consideration did not apply to these medications.

Study Design

The primary objective of this study was to compare treatment persistence (time to discontinuation) for patients initiating FF/VI versus patients initiating a comparator ICS/LABA treatment (BUD/FM or BDP/FM, separately). Secondary objectives were to compare adherence to treatment (mean proportion of days covered [PDC]), assess the proportions of patients with $\geq$ 50% and $\geq$ 80% PDC, and describe the annualised number of short-acting bronchodilator (SABD) prescriptions for rescue use per patient.

This retrospective new-user active comparator database study was conducted in the IMRD primary care database (Supplementary Fig. S1). The study period was from January 1, 2013 to January 17, 2018, inclusive. The index date was defined as the date of the first recorded prescription of FF/VI or the comparator ICS/LABA (BUD/FM or BDP/FM) within the study time period. Patients were required to have at least 12 months of data recorded prior to the index date to determine the prescription history (no previous ICS/LABA prescription) and variables to be considered for the propensity score (PS) model. A second prescription of the same index treatment was required within 180 days to better identify patients using ICS/LABAs for long-term maintenance versus short-term treatment. This was termed the index second prescription date.

Patient follow-up started on the index date (date of ICS/LABA initiation) for all analyses, except the discontinuation analyses, where follow-up started on the index second prescription date to avoid potential bias relating to any differences in the time between the index and second prescription when patients were not able to experience the outcome of interest [18]. See Supplementary Methods for additional

follow-up period information for the discontinuation, adherence and SABD rescue use analyses.

For the regression analysis, the risk of discontinuation and the odds of adhering to medication 12 months after the index date were assessed.

A patient was considered to have switched medication from the index treatment if prescription of either of the other two treatments of interest (FF/VI, BUD/FM or BDP/FM) occurred after the index second prescription date. This definition of switching was considered up until 60 days from the date at which the most recent prescription of the original index therapy was due to end.

Persistence was defined as the time to discontinuation (in days) of the index treatment, this being the event of interest. Discontinuation was defined as a gap of 60 days after ICS/LABA prescription or switch to a different ICS/LABA therapy within 60 days after the end of the previous prescription. Adherence was measured as PDC (number of days in period covered by medication divided by the number of days in period, with 100% indicating full or complete adherence). Additionally, two binary outcomes—patients $\geq$ 50% adherent and patients $\geq$ 80% adherent—were created and analysed. Taking $\geq$ 80% of medication as prescribed has been generally considered as acceptable adherence for clinical outcomes, based on findings from a seminal hypertension study [19]; however, as it is now recognised that this cut-off value may vary for different diseases and classes of medication [20], we also analysed a lower adherence cut-point, chosen to allow comparison with previous asthma studies [21–25]. The protocol was approved by local ethics committees. Appropriate consent/approval was obtained to use the dataset; as this study utilized de-identified retrospective claims data compliant with the Health Insurance Portability and Accountability Act (HIPAA), no institutional review board (IRB) approval was required.

Methods

Prior to comparative analyses, PS matching (PSM) methodology was used to create the following cohorts: patients receiving FF/VI were matched at a ratio of 1 to $\leq$ 4 with either patients prescribed BUD/FM or BDP/FM, separately. Greedy nearest-neighbour matching without replacement was used with a caliper of 0.01 standard deviation of the logit. Standardised differences and variance ratios in patient characteristics were used to assess whether appropriate balance between matched groups had been achieved. An absolute standardised difference $\leq$ 0.1 (10%) and a variance ratio of 0–2.0, inclusive, was considered to indicate a close match (good covariate balance) between groups [26]. A comparison of demographic characteristics was conducted between the matched and unmatched cohorts to ensure an unbiased matched population. Prior to persistence and adherence analyses, rules were set regarding multiple prescriptions on the same day, the second prescription and prescriptions lasting more than 365 days. See the Supplementary Methods for additional detail on data cleaning decisions and the considered covariates and confounders.

Analysis

Descriptive statistics were performed for all baseline variables for unmatched and PS-matched cohorts (Supplementary Methods). Kaplan–Meier (KM) curves were used to estimate the time to treatment discontinuation (including switch). Log-rank tests tested observed differences in KM curves between study groups, and Cox proportional-hazard models assessed the association between study groups and persistence at 1 year. Logistic regression analysis was performed to estimate the adherence to treatment (as measured by PDC) over 12 months post-index, whereby censoring criteria included death, exit from the THIN database, end of study time-period and switch to another therapy. In parallel, a chi-square test was performed to compare the

proportion of patients persistent 1 year after index. SABD use was analysed descriptively.

Sensitivity analyses included (1) re-analyses of persistence, with discontinuation defined as a gap of 30 and 90 days; and (2) re-analysis of PDC with censoring criteria, including discontinuation (defined as a gap of 60 days).

RESULTS

PSM

In the IMRD, eligible patients with asthma were identified as new users (ICS/LABA naïve in the past) of FF/VI, BUD/FM or BDP/FM, and PSM was applied as described to generate matched cohorts for analysis. In total, 966 patients initiated treatment with FF/VI, 5931 initiated treatment with BUD/FM, and 9607 initiated treatment with BDP/FM during the study (Fig. 1). A total of 945 FF/VI patients were PS-matched to 3272 BUD/FM new users (Table 1, top), and 902 FF/VI patients were PS-matched to 3465 BDP/FM new users (Table 1, bottom). In both comparisons, PSM resulted in an absolute standardised difference of less than 0.1 for all variables, indicating well-balanced cohorts based on the covariates used for the PSM (Table 1), which included age at baseline, gender, comorbidities, and the number of GP visits or hospitalisations, ICS or SABD prescriptions in the prior year.

Further data cleaning to exclude potential confounders (as detailed in the Supplementary Methods) excluded 8 FF/VI and 40 BUD/FM patients from the FF/VI versus BUD/FM PS-matched cohort, and 8 FF/VI and 32 BDP/FM patients from the FF/VI versus BDP/FM PS-matched cohort (Fig. 1). The number of ICS prescriptions pre-index for FF/VI versus BUD/FM and BDP/FM was found to be similar across treatment groups (Supplementary Tables S1 and S2).

FF/VI Versus BUD/FM

Unadjusted median time to discontinuation of treatment was 99 days for FF/VI, with a median follow-up time of 393 days, and 116.5 days for BUD/FM with 817 days' median follow-up time. FF/VI had notably less follow-up time available

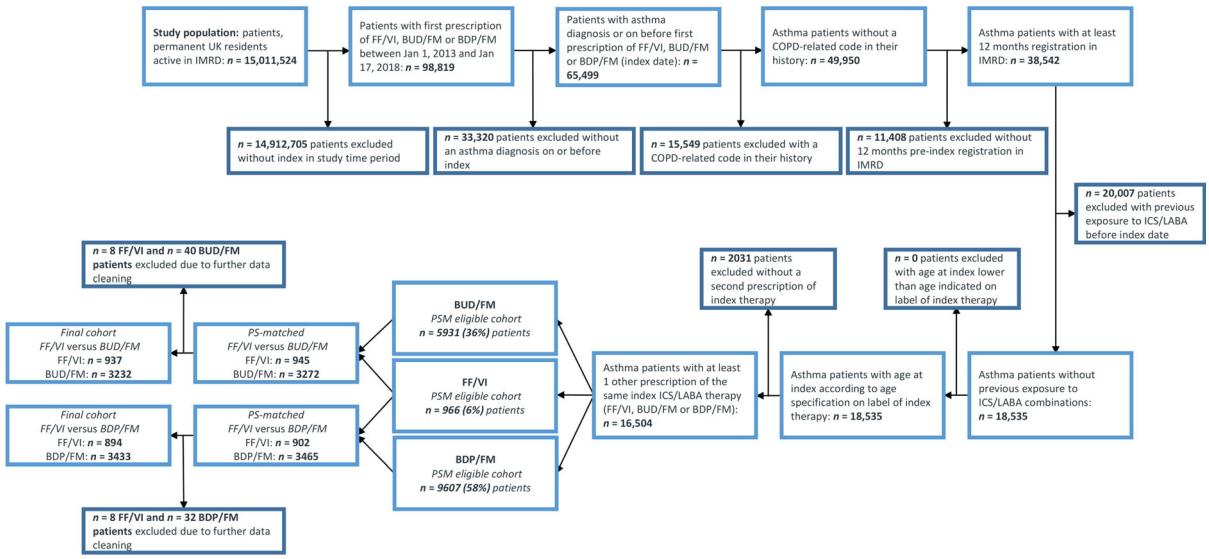

Fig. 1 Patient flow and eligibility diagram (GlaxoSmithKline plc. study 209967). *BDP/FM* beclometasone dipropionate/formoterol, *BUD/FM* budesonide/formoterol, *COPD* chronic obstructive pulmonary disease, *FF/VI* fluticasone furoate/vilanterol, *ICS* inhaled corticosteroid, *IMRD IQVIA* medical research database, *LABA* long-acting beta$_2$-agonist, *PS* propensity score, *PSM* propensity score matching

Table 1 Comparison of demographic characteristics of FF/VI versus BUD/FM or BDP/FM cohorts

Characteristic		Total (N = 4217)	FF/VI (n = 945)	BUD/FM (n = 3272)	Hypothesis test p value	Standardised difference	Variance ratio
FF/VI versus BUD/FM PSM cohorts							
Age at baseline, years	Mean (SD)	48.3 (18.4)	49.1 (18.7)	48.1 (18.4)	0.1259[a]	0.05575	1.0329
	Median (min–max)	49 (12–94)	50 (12–89)	49 (12–94)			
Gender	Male, *n* (%)	1693 (40.15)	388 (41.06)	1305 (39.88)	0.5165[b]	0.02384	1.0093
	Female, *n* (%)	2524 (59.85)	557 (58.94)	1967 (60.12)			
Comorbidities, *n* (%)	Atopic dermatitis	679 (16.10)	153 (16.19)	526 (16.08)		− 0.00308	1.0058
	Allergic rhinitis	984 (23.33)	212 (22.43)	772 (23.59)		0.02701	0.9653
	Diabetes (type I and II)	436 (10.34)	106 (11.22)	330 (10.09)		− 0.03750	1.0982
	Obesity	556 (13.18)	137 (14.50)	419 (12.81)		− 0.05020	1.1101
	Cardiovascular disease	1281 (30.38)	306 (32.38)	975 (29.80)		− 0.05679	1.0467
	Anxiety disorder (acute)	984 (23.33)	224 (23.70)	760 (23.23)		− 0.01131	1.0142
	Depression	1467 (34.79)	344 (36.40)	1123 (34.32)		− 0.04405	1.0270
Exacerbations	Absence, *n* (%)	3750 (88.93)	842 (89.10)	2908 (88.88)	0.8459[b]	0.00724	0.9822
	Presence, *n* (%)	467 (11.07)	103 (10.90)	364 (11.12)			
Number of GP visits	Mean (SD)	8.2 (6.3)	8.4 (6.2)	8.1 (6.3)	0.2116[a]	0.04565	0.9695
	Median (min–max)	7 (0–60)	7 (1–38)	7 (0–60)			
Number of ICS prescriptions	Mean (SD)	3.2 (3.4)	3.2 (3.4)	3.2 (3.4)	0.7184[a]	0.01336	1.0381
	Median (min–max)	2 (0–19)	2 (0–19)	3 (0–19)			
Number of SABD prescriptions	Mean (SD)	4.6 (4.4)	4.9 (4.6)	4.6 (4.4)	0.1015[a]	0.05842	1.0777
	Median (min–max)	3 (0–30)	3 (0–26)	3 (0–30)			
Hospitalisations	Absence, *n* (%)	3065 (72.68)	691 (73.12)	2374 (72.56)	0.7306[b]	0.01264	0.987
	Presence, *n* (%)	1152 (27.32)	254 (26.88)	898 (27.44)			
Characteristic		**Total (N = 4367)**	**FF/VI (n = 902)**	**BDP/FM (n = 3465)**	**Hypothesis test p value**	**Standardised difference**	**Variance ratio**
FF/VI versus BDP/FM PSM cohorts							
Age at baseline, years	Mean (SD)	51.8 (17.37)	51.7 (17.03)	51.8 (17.46)	0.8342[a]	− 0.0079	0.9512
	Median (min–max)	52 (18–96)	52 (18–89)	51 (18–96)			
Gender	Male, *n* (%)	1781 (40.78)	372 (41.24)	1409 (40.66)	0.7531[c]	0.01178	1.0043
	Female, *n* (%)	2586 (59.22)	530 (58.76)	2056 (59.34)			

Table 1 continued

Characteristic		Total (N = 4367)	FF/VI (n = 902)	BDP/FM (n = 3465)	Hypothesis test p value	Standardised difference	Variance ratio
Comorbidities, *n* (%)	Atopic dermatitis	652 (14.93)	131 (14.52)	521 (15.04)		0.01430	0.9717
	Allergic rhinitis	954 (21.85)	198 (21.95)	756 (21.82)		− 0.00310	1.0044
	Diabetes (type I and II)	534 (12.23)	111 (12.31)	423 (12.21)		− 0.00305	1.0069
	Obesity	702 (16.08)	146 (16.19)	556 (16.05)		− 0.00393	1.0070
	Cardiovascular disease	1543 (35.33)	319 (35.37)	1224 (35.32)		− 0.00087	1.0005
	Anxiety disorder (acute)	1118 (25.60)	225 (24.94)	893 (25.77)		0.01895	0.9787
	Depression	1714 (39.25)	357 (39.58)	1357 (39.16)		− 0.00857	1.0037
Exacerbations	Absence, *n* (%)	3886 (88.99)	806 (89.36)	3080 (88.89)	0.6892[c]	0.01533	0.9629
	Presence, *n* (%)	481 (11.01)	96 (10.64)	385 (11.11)			
Number of GP visits	Mean (SD)	8.7 (6.6)	8.7 (6.4)	8.7 (6.6)	0.7963[a]	− 0.0098	0.9194
	Median (min–max)	7 (0–67)	7 (1–38)	7 (0–67)			
Number of ICS prescriptions	Mean (SD)	3.3 (3.1)	3.2 (3.3)	3.3 (3.1)	0.3674[a]	− 0.03211	1.1613
	Median (min–max)	3 (0–16)	2 (0–16)	3 (0–16)			
Number of SABD prescriptions	Mean (SD)	4.9 (4.5)	4.8 (4.5)	4.9 (4.4)	0.7749[a]	− 0.01025	1.0354
	Median (min–max)	3 (0–34)	3 (0–25)	3 (0–34)			
Hospitalisations	Absence, *n* (%)	3242 (74.24)	665 (73.73)	2577 (74.37)	0.6921[c]	− 0.01483	1.0163
	Presence, *n* (%)	1125 (25.76)	237 (26.27)	888 (25.63)			

BDP/FM beclometasone dipropionate/formoterol. *BUD/FM* budesonide/formoterol, *FF/VI* fluticasone furoate/vilanterol, *GP* general practitioner, *ICS* inhaled corticosteroids, *PSM* propensity score matching, *SABD* short-acting bronchodilator, *SD* standard deviation

[a] p values were generated from Students t test

[b] p values were generated from chi-square test. The descriptive breakdown of the unique number of exacerbations (0, 1, 2, > 2 exacerbations) in matched cohorts indicated no difference in spread with respect to this categorisation (chi-square test; $p = 0.3284$)

[c] p values were generated from chi-square test. The descriptive breakdown of the unique number of exacerbations (0, 1, 2, > 2 exacerbations) in matched cohorts indicated no difference in spread with respect to this categorisation (chi-square test; $p = 0.1049$)

than comparators, leading to a lower unadjusted median time to discontinuation. The variation in follow-up times was driven by the different launch dates for these medications and their consequent availability—as FF/VI has been available for a shorter period of time, and numbers for FF/VI are skewed towards the end of the inclusion period (as uptake increased over time), the average follow-up time is shorter. KM-adjusted (for variable follow-up time) median time to discontinuation was not available for FF/VI (as the median time was not reached), but was 427 days for BUD/FM (Table 2), with a significant difference in discontinuation over 12 months (log-rank test: $p < 0.0001$) (Fig. 2). At 12 months, after adjusting for variable

follow-up time, KM analysis showed that the proportion of patients persistent on FF/VI was 69% (324/937; 95% confidence interval [CI] 0.65–0.72) versus 53% (1246/3232; 95% CI 0.51–0.55) of patients prescribed BUD/FM (Fig. 2; Table 2). The likelihood of discontinuing treatment within 12 months after initiation was 35% lower for FF/VI than BUD/FM [Cox proportional-hazards model, index year-adjusted, hazard ratio (HR) 0.65; 95% CI 0.56–0.75; $p < 0.001$] (Table 3).

Mean adherence, measured by PDC, was higher for FF/VI than for BUD/FM (77.7 vs 72.4; $p < 0.0001$) (Table S3). Median (interquartile range) PDC was also higher for FF/VI than for the BUD/FM cohort: 88.2 (61.4–100.0) versus 77.7 (50.7–100.0). After adjusting for the year of index ICS/LABA prescription, the odds of achieving ≥ 50% PDC were higher for patients initiating treatment with FF/VI compared with those on BUD/FM [779/936 (83.2%) vs 2447/3232 (75.7%); odds ratio (OR) 1.35; 95% CI 1.09–1.67; $p = 0.006$]. Similarly, the odds of achieving ≥ 80% PDC were higher for patients initiating FF/VI compared with those on BUD/FM [544/936 (58.1%) vs 1562/3232 (48.3%); OR 1.28; 95% CI 1.08–1.52; $p = 0.004$]. The annualised rate of SABD prescriptions per patient-year was 4.7 for FF/VI and 4.2 for BUD/FM, respectively.

After adjusting for the year of treatment initiation, a Cox regression sensitivity analysis showed that patients who initiated treatment with FF/VI had a 27% lower risk of discontinuing compared with BUD/FM when the definition for discontinuation (or switch) was redefined as a gap of 30 days (HR 0.73; 95% CI 0.64–0.82; $p < 0.001$) and a 38% lower risk of discontinuing compared with BUD/FM (HR 0.62; 95% CI 0.52–0.74; $p < 0.001$) when the definition was set to 90 days.

The logistic regression sensitivity analysis of PDC was conducted whereby discontinuation was included as a censoring criterion. After adjusting for year of treatment initiation and for baseline variables in the PS model, FF/VI had a similar adherence pattern compared with BUD/FM (≥ 50% PDC, OR 1.03; 95% CI 0.72–1.47; $p = 0.880$; ≥ 80% PDC, OR 1.03; 95% CI 0.86–1.23; $p = 0.744$).

FF/VI Versus BDP/FM

For FF/VI, the median time to discontinuation of treatment was 97 days with a median follow-up time of 402 days, and 91 days for BDP/FM with a median follow-up time of 539 days (not adjusted for variable follow-up). As was the case in the previous comparison, the variation in follow-up times was caused by the different

Table 2 Overall time to discontinuation for FF/VI versus BUD/FM (adjusted for variable follow-up time)

	FF/VI (*n* = 937)	**BUD/FM (*n* = 3232)**
Median time to discontinuation, days (95% CI)	NA (904–NA)	427 (397–484)
Interquartile range	236–NA	90–NA
Patients persistent at 3 months, *n*	677	2263
Proportion (95% CI)	0.85 (0.83–0.88)	0.75 (0.73–0.76)
Patients persistent at 6 months, *n*	524	1777
Proportion (95% CI)	0.78 (0.75–0.80)	0.64 (0.62–0.65)
Patients persistent at 12 months, *n*	324	1246
Proportion (95% CI)	0.69 (0.65–0.72)	0.53 (0.51–0.55)

Discontinuation was defined as a gap of 60 days between treatments or a switch of treatment within 60 days. NA represents the numbers that cannot be calculated from the available data

BUD/FM budesonide/formoterol, *CI* confidence interval, *FF/VI* fluticasone furoate/vilanterol, *NA* not available

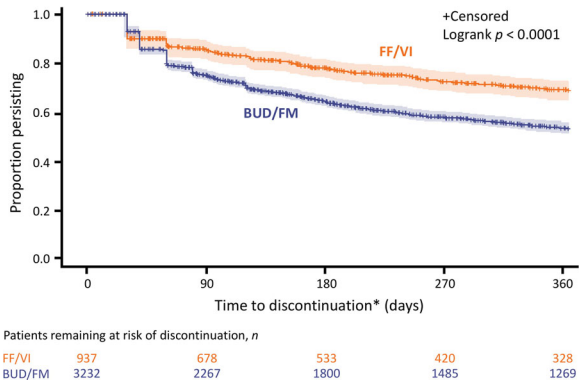

Fig. 2 Kaplan–Meier curve for persistence to FF/VI and BUD/FM (time to discontinuation). *BUD/FM* budesonide/formoterol, *FF/VI* fluticasone furoate/vilanterol. *p value is for analysis at 12 months. Figure adapted from Svedsater H, Parimi M, Ann Q, et al. P230 A retrospective database study of persistence and adherence in patients with asthma in the UK (UK-THIN): fluticasone furoate/vilanterol (FF/VI) versus budesonide/formoterol (BUD/FM) Thorax 2019;74:A215

launch dates for these medications and their consequent availability. When adjusted for variable follow-up time by KM analysis, the median time to discontinuation was not reached for FF/VI, but was 537 days for BDP/FM (Table 4), with a significant difference in discontinuation over 12 months (log-rank test: $p < 0.0001$) (Fig. 3). After adjusting for variable follow-up, KM analysis demonstrated that the proportion of patients persistent on FF/VI at 12 months was 69% (321/894; 95% CI 0.66–0.73) versus 57% (1172/3433; 95% CI 0.55–0.58) of BDP/FM patients (Fig. 3; Table 4). The likelihood of discontinuing treatment within 12 months after initiation was 31% lower for FF/VI than BDP/FM (Cox proportional-hazards model, index year-adjusted, HR 0.69; 95% CI 0.60–0.80; $p < 0.001$) (Table 5).

Mean adherence, measured by PDC, was higher for FF/VI than for BDP/FM (78.2 vs 71.0; $p < 0.0001$) (Table S4). Median (interquartile range) PDC was also higher for FF/VI than for BDP/FM: 89.2 (61.6–100.0) versus 75.9 (50.5–98.0). After adjusting for year of index ICS/LABA prescription, the odds of achieving $\geq$ 50% PDC was greater for FF/VI than for BDP/FM [747/893 (83.7%) vs 2600/3433 (75.7%); OR 1.50; 95% CI 1.23–1.83; $p < 0.001$]. Similarly, the odds of achieving $\geq$ 80% PDC were greater for FF/VI than for BDP/FM [526/893 (58.9%) vs 1571/3433 (45.8%); OR 1.57; 95% CI 1.35–1.83; $p < 0.001$; index year-adjusted]. The annualised rate of SABD prescriptions per patient-year was 4.6 for FF/VI and 4.7 for BDP/FM, respectively.

In the Cox regression sensitivity analysis, after adjustment for year of initiation within the regression model, patients who initiated treatment with FF/VI showed a 32% lower risk of discontinuing compared with BUD/FM when the definition for discontinuation (or switch) was set as a gap of 30 days (HR 0.68; 95% CI 0.60–0.76; $p < 0.001$). For a 90-day definition, patients who initiated FF/VI showed a 27% lower risk of discontinuing (HR 0.73; 95% CI 0.62–0.87; $p < 0.001$).

The logistic regression sensitivity analysis of PDC was conducted whereby discontinuation was included as a censoring criterion. After adjusting for baseline variables in the PS model and for year of initiation within the regression model, FF/VI had an improved adherence pattern compared with BDP/FM ($\geq$ 50% PDC, OR 1.58; 95% CI 1.15–2.19; $p = 0.005$ and $\geq$ 80% PDC, OR 1.38; 95% CI 1.17–1.62; $p < 0.001$).

DISCUSSION

This study indicated that patients who initiated FF/VI were less likely to discontinue treatment (defined as a $\geq$ 60-day gap in prescription or switch to another index therapy in this period) and showed greater adherence to treatment (PDC measurement) compared with patients who initiated BUD/FM or BDP/FM. These results were supported by discontinuation sensitivity analyses (defined as a 30- or 90-day gap). Mean PDC was higher for FF/VI than for both BUD/FM and BDP/FM. Similarly, the odds of achieving $\geq$ 50% and $\geq$ 80% PDC were greater for FF/VI than for both BUD/FM and BDP/FM. The favourable persistence and adherence observed with FF/VI could be due to a number of factors. Firstly, FF/VI is associated with improved asthma control versus other ICS/LABAs and may, therefore, lead to increased

Table 3 Risk of discontinuation for FF/VI versus BUD/FM within 12 months after initiation

	Treatment	*N* total	Discontinued, *n* (%)	Continued, *n* (%)	HR	95% CI	*p* value
PS-matched	FF/VI	937	238 (25.4)	699 (74.6)	0.60	0.52–0.69	< 0.001
	BUD/FM	3232	1384 (42.8)	1848 (57.2)	1.00	Ref.	
	FF/VI	936	238 (25.4)	698 (74.6)	0.65[b]	0.56–0.75	< 0.001
	BUD/FM	3232	1384 (42.8)	1848 (57.2)	1.00	Ref.	
Stratified by low/medium dose[c] adjusted for year of index[a]	FF/VI	709	178 (25.1)	531 (74.9)	0.63	0.53–0.75	< 0.001
	BUD/FM	3131	1342 (42.9)	1789 (57.1)	1.00	Ref.	
Stratified by high dose[c] adjusted for year of index[a]	FF/VI	227	60 (26.4)	167 (73.6)	0.75	0.47–1.21	0.243
	BUD/FM	101	42 (41.6)	59 (58.4)	1.00	Ref.	

Crude numbers show a different proportion of patients adhering to FF/VI compared with BUD/FM, because the Cox proportional-hazards model adjusts for year of initiation when deriving the HR. The proportion of patients in each index year is different for each treatment, impacting the final HR

Note: Covariates used in the PSM (age, gender, comorbidities, exacerbations, number of GP visits, number of ICS prescriptions, number of SABD prescriptions and hospitalisations) were not adjusted for in the models, as PSM showed balanced cohorts. Only year of index (not adjusted for in PSM) was adjusted for in this analysis

BUD/FM budesonide/formoterol, *CI* confidence interval, *FF/VI* fluticasone furoate/vilanterol, *GP* general practitioner, *HR* hazard ratio, *ICS* inhaled corticosteroid, *LABA* long-acting $beta_2$-agonist, *NA* not applicable, *PS* propensity score, *PSM* propensity score matching, *Ref.* Reference, *SABD* short-acting bronchodilator

[a] In 2018, < 6 patients were observed to initiate FF/VI or BUD/FM. Therefore, these patients were excluded from regression models that adjusted for year of index, as including strata with ≤ 5 patients in the regression analysis is not statistically sound

[b] After adjustment for year of index, patients initiating FF/VI had a 35% lower risk of discontinuing treatment compared with BUD/FM within 1 year after initiation

[c] Based on the dose of the ICS component of the ICS/LABA. Low dose: FF/VI 100 µg, BUD/FM 100–400 µg, BDP/FM 100–200 µg. Medium dose: FF/VI NA, BUD/FM > 400–800 µg, BDP/FM > 200–400 µg. High dose: FF/VI 200 µg, BUD/FM 800 µg, BDP/FM 400 µg

patient satisfaction [7]. Secondly, FF/VI is administered once daily via the ELLIPTA inhaler (GlaxoSmithKline plc. group of companies), which has been shown to result in significantly fewer critical errors [14] and is generally preferred to comparator devices [15]. In this study, both comparator ICS/LABAs contained a mix of flexible maintenance and reliever therapy [MART] and fixed dosing regimens. MART may lead to increased adherence (and therefore inflated PDC values) [27] if taken as maintenance plus reliever. Furthermore, ICS/FM combinations are often used only as relief medications in asthma [28], which may bring adherence down; hence, findings in this study may represent a conservative estimate of the PDC difference for FF/VI versus BUD/FM or BDP/FM. It is important that we do not know exactly how many patients are prescribed each regimen and we do not know for sure if and to what extent these effects influence adherence.

Strengths of this study include the IMRD database, which is representative of patients with asthma in the UK whose disease is

Table 4 Overall time to discontinuation for FF/VI versus BDP/FM (adjusted for variable follow-up time)

	FF/VI (n = 894)	BDP/FM (n = 3433)
Median time to discontinuation, days (95% CI)	NA (NA–NA)	537 (485–613)
Interquartile range	243–NA	101–NA
Patients persistent at 3 months, *N*	655	2344
Proportion (95% CI)	0.85 (0.83–0.88)	0.76 (0.75–0.78)
Patients persistent at 6 months, *N*	515	1786
Proportion (95% CI)	0.78 (0.75–0.81)	0.66 (0.64–0.67)
Patients persistent at 12 months, *N*	321	1172
Proportion (95% CI)	0.69 (0.66–0.73)	0.57 (0.55–0.58)

These numbers are not adjusted for variable follow-up time. Discontinuation was defined as a gap of 60 days between treatments or a switch of treatment within 60 days. NA represents the numbers that cannot be calculated from the available data

BDP/FM beclometasone dipropionate/formoterol, *CI* confidence interval, *FF/VI* fluticasone furoate/vilanterol, *NA* not available

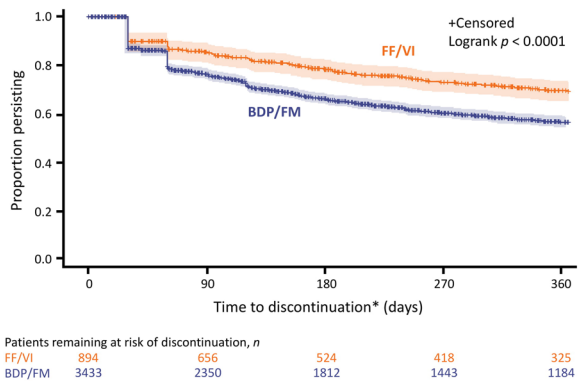

Fig. 3 Kaplan–Meier curve for persistence to FF/VI and BDP/FM (time to discontinuation). *BDP/FM* beclometasone dipropionate/formoterol, *FF/VI* fluticasone furoate/vilanterol. **p* value is for analysis at 12 months. Figure adapted from Svedsater H, Parimi M, Ann Q, et al. P229 A retrospective database study of persistence and adherence in patients with asthma in the UK (UK-THIN): fluticasone furoate/vilanterol (FF/VI) versus beclometasone dipropionate/formoterol (BDP/FM) Thorax 2019;74:A214

predominately managed by their general practitioner [29]; therefore, this study describes real-world findings generalizable to a large population of patients with asthma in the UK. Additionally, the study period provides data relevant to the current asthma treatment landscape in the UK. The use of a new-user active comparator design compared initiators of a therapeutically equivalent drug class and minimised biases due to the inclusion of patients tolerant to prevalent treatments [30]. The large number of patients identified in IMRD (N = 16,504) enabled a matching between FF/VI and comparator ICS/LABAs at a ratio of 1 to > 1, improving the statistical power to detect differences between the matched groups wherever such a difference existed.

Confounding by indication is an important consideration in comparative effectiveness studies resulting from differences in reasons for prescription that may lead to systematic bias in favour of or against FF/VI. PSM seeks to account for potential confounding by indication and the bias caused by unbalanced comparison cohorts. The observed low standardised differences across cohorts support the balance of measured covariates of interest and confirms using PSM for cohort matching and control of potential confounders. Additionally, real-world data from routine clinical practice may provide a more realistic estimate of adherence (based on frequency of prescription) than RCT data, as the

Table 5 Risk of discontinuation for FF/VI versus BDP/FM within 12 months after initiation

	Treatment	*N* total	Discontinued, *n* (%)	Continued, *n* (%)	HR	95% CI	*p* value
PS-matched	FF/VI	894	225 (25.2)	669 (74.8)	0.64	0.55–0.73	< 0.001
	BDP/FM	3434	1302 (37.9)	2132 (62.1)	1.00	Ref.	
Adjusted for year of index[a]	FF/VI	893	225 (25.2)	668 (74.8)	0.69[b]	0.60–0.80	< 0.001
	BDP/FM	3433	1302 (37.9)	2131 (62.1)	1.00	Ref.	
Stratified by low/medium dose[c] adjusted for year of index[a]	FF/VI	672	169 (25.1)	503 (74.9)	0.69	0.58–0.81	< 0.001
	BDP/FM	3301	1258 (38.1)	2043 (61.9)	1.00	Ref.	
Stratified by high dose[c] adjusted for year of index[a]	FF/VI	221	56 (25.3)	165 (74.7)	0.58	0.37–0.91	0.018
	BDP/FM	132	44 (33.3)	88 (66.6)	1.00	Ref.	

Crude numbers show a different proportion of patients adhering to FF/VI compared with BDP/FM, because the Cox proportional-hazards model adjusts for year of initiation when deriving the HR. The proportion of patients in each index year is different for each treatment impacting the final HR

Note: covariates used in the PSM (age, gender, comorbidities, exacerbations, number of GP visits, number of ICS prescriptions, number of SABD prescriptions and hospitalisations) were not adjusted for in the models, as PSM showed balanced cohorts. Only year of index (not adjusted for in PSM) was adjusted for in this analysis

BDP/FM beclometasone dipropionate/formoterol, *CI* confidence interval, *FF/VI* fluticasone furoate/vilanterol, *GP* general practitioner, *HR* hazard ratio, *ICS* inhaled corticosteroid, *LABA* long-acting beta$_2$-agonist, *NA* not applicable, *PS* propensity score, *PSM* propensity score matching, *Ref.* Reference. *SABD* short-acting bronchodilator

[a] In 2018, < 6 patients were observed to initiate FF/VI or BDP/FM. Therefore, these patients were excluded from regression models that adjusted for year of index, as including strata with ≤ 5 patients in the regression analysis is not statistically sound

[b] After adjustment for year of index, patients initiating FF/VI had a 31% lower risk of discontinuing treatment compared with BDP/FM within 1 year after initiation

[c] Based on the dose of the ICS component of the ICS/LABA. Low dose: FF/VI 100 µg, BUD/FM 100–400 µg, BDP/FM 100–200 µg. Medium dose: FF/VI NA, BUD/FM > 400–800 µg, BDP/FM > 200–400 µg. High dose: FF/VI 200 µg, BUD/FM 800 µg, BDP/FM 400 µg

complex behavioural factors involved in patient decision-making are less altered, and longer time frames can capture changes in adherence over time [12].

As well as general limitations in conducting retrospective cohort studies using secondary data collected for patient management purposes, the specific limitations of this study include the lack of spirometry and asthma control measure data (i.e. specific advice given to patients, for example smoking cessation and correct inhaler training) were not available in the structured data used in this analysis. As the data recorded in IMRD is restricted to those input by and for the use of the general practitioner, bias may be introduced when these data are used for research purposes. The utility of findings from research leveraging electronic medical record data is limited by the completeness of these data, which may have been influenced by the longer availability of BUD/FM and BDP/FM (available in the UK from June, 2007, and January, 2008, respectively) [31, 32], compared with FF/VI (available in the UK from January, 2014) [33]. Additionally, patient behaviour is seldom directly captured by electronic databases, thus compliance cannot be directly assessed. Time to discontinuation and PDC are proxies to estimate patient persistence and adherence, respectively, with PDC a

commonly used method endorsed by the Pharmacy Quality Alliance [34]. Exacerbations in the pre-index period were also identified using a proxy, therefore potentially resulting in incomplete capture of data. No matching method can remove the potential for residual confounding due to unmeasured variables. Several severity proxies were used for PSM, as variables directly related to patients' severity of asthma were not recorded in IMRD (e.g. daily dose, exacerbations and healthcare resource use).

Our results are broadly comparable with those of three database studies performed in the USA and Japan [21, 35, 36]. In their retrospective cohort study, Stanford et al. found that patients initiating once-daily FF/VI were more likely to be adherent (measured by PDC) and less likely to discontinue treatment than patients initiating twice-daily BUD/FM; however, persistence was low for both treatments [35]. Averell et al. similarly found that adherence (measured by PDC) was higher and discontinuation less likely for FF/VI compared with BUD/FM and fluticasone propionate/salmeterol (FP/SAL) [9, 21]. Moreover, a Japanese cohort study showed that adherence and PDC were significantly higher with FF/VI than with twice-daily FP/SAL treatment [36]. The results of these previous studies add further weight to the finding that FF/VI is associated with a significantly lower likelihood of discontinuation and a higher adherence to treatment versus ICS/LABA comparators. These studies shared some methodological aspects (non-interventional, retrospective cohort studies) and mostly utilised the IMRD for their data; however, Atsuta et al. used data from the Japan Medical Data Center Claims Database [36].

The driving forces behind changes in adherence status could warrant further study. Of particular interest would be whether these changes can be attributed to patient behaviour or to the medication itself. As many of the patients studied were using multiple drugs for multiple conditions, a future study, which is adequately designed for such an evaluation, could compare patient adherence to these other medications with patient adherence to ICS/LABA. This could provide valuable data for evaluating whether patient adherence status is consistent across medication types.

CONCLUSION

Patients in the UK with asthma initiating FF/VI in our study were more likely to exhibit greater persistence and adherence to treatment than those initiating BUD/FM (200/6, 100/6 and 400/12 μg) or BDP/FM during the same study period.

ACKNOWLEDGEMENTS

The authors thank all individuals who contributed to the IQVIA Medical Research Database and The Health Improvement Network database, which were used for this retrospective study.

Funding. This work was funded by GlaxoSmithKline plc. (study 209967), open access and rapid service publication charges were also funded by GlaxoSmithKline plc. Trade marks are owned by or licensed to their respective owners (the GlaxoSmithKline group of companies, The Health Improvement Network, IQVIA, AstraZeneca UK Ltd or Chiesi Ltd).

Authorship. All authors were involved in the preparation of the manuscript, drafting the work, and/or revising it critically for important intellectual content, and approved the final version for submission for publication. MP, HS, MG, DH, and NB were involved in the conception or design (e.g. protocol development and/or design advice), data analysis, or interpretation. QA and CMG were involved in data analysis or interpretation. MN was involved in the conception or design (e.g. protocol development and/or design advice), acquisition of data (e.g. study investigator), and data analysis/interpretation. These contributions were in keeping with the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship.

Medical Writing, Editorial, and Other Assistance. Editorial support (in the form of editorial suggestions to draft versions of this paper, assembling tables and figures, collating author comments, copyediting, referencing and graphic services) was provided by Roddy Lindsay, MSc, and Kyle Kennedy, MBChB, of Gardiner-Caldwell Communications (Macclesfield, UK), and was funded by GlaxoSmithKline plc.

Prior Presentations. Some aspects of this research were shown at the British Thoracic Society's 2019 Winter Meeting only (Svedsater H, et al. P229 A retrospective database study of persistence and adherence in patients with asthma in the UK [UK-THIN]: fluticasone furoate/vilanterol [FF/VI] versus beclometasone dipropionate/formoterol [BDP/FM]. Thorax 2019;74:A214. https://thorax.bmj.com/content/74/Suppl_2/A214; Svedsater H, et al. P230 A retrospective database study of persistence and adherence in patients with asthma in the UK [UK-THIN]: fluticasone furoate/vilanterol [FF/VI] versus budesonide/formoterol [BUD/FM]. Thorax 2019;74:A215. https://thorax.bmj.com/content/74/Suppl_2/A215).

Disclosures. Mounika Parimi, Quratul Ann, Christen M. Gray, Mark Nixon, and Naomi Boxall report employment and stock/share ownership in IQVIA. Henrik Svedsater and Mugdha Gokhale report employment and stock/share ownership in GlaxoSmithKline plc. David Hinds was an employee of and stock/shareholder in GlaxoSmithKline plc. at the time of the study, and is currently an employee of BioMarin Pharmaceutical Inc.

Compliance with Ethics Guidelines. The protocol was approved by local ethics committees. Appropriate consent/approval was obtained to use the dataset; as this study utilized de-identified retrospective claims data compliant with the Health Insurance Portability and Accountability Act (HIPAA), no institutional review board (IRB) approval was required.

Data Availability. This study uses medical record data from IQVIA Medical Research Database. Data are available from IQVIA Ltd for researchers who meet the criteria for access to confidential data. If access to the data in this study is required, please contact Mounika Parimi (Mounika.Parimi@iqvia.com).

REFERENCES

1. British Lung Foundation. Asthma statistics, 2018. https://statistics.blf.org.uk/asthma. Accessed 11 Mar 2020.
2. 2019 Pocket Guide for Asthma Management and Prevention. https://ginasthma.org/pocket-guide-for-asthma-management-and-prevention/. Accessed 11 Mar 2020.
3. Miller-Larsson A, Selroos O. Advances in asthma and COPD treatment: combination therapy with inhaled corticosteroids and long-acting beta 2-agonists. Curr Pharm Des. 2006;12:3261–79.
4. Electronic Medicines Compendium. Fostair 100/6 inhalation solution. August 2018. https://www.medicines.org.uk/emc/product/6318/smpc. Accessed 11 Mar 2020.
5. AstraZeneca Canada SYMBICORT® TURBUHALER product monograph. August 2018. https://www.astrazeneca.ca/content/dam/az-ca/downloads/productinformation/symbicort-turbuhaler-product-monograph-en.pdf. Accessed 11 Mar 2020.

6. European Medicines Agency. Relvar Ellipta product monograph. August 2018. https://www.ema.europa.eu/en/documents/product-information/relvar-ellipta-epar-product-information_en.pdf. Accessed 11 Mar 2020.

7. Woodcock A, Vestbo J, Bakerly ND, et al. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial. Lancet. 2017;390:2247–55.

8. Jacques L, Bakerly ND, New JP, Svedsater H, Lay-Flurrie J, Leather DA. Effectiveness of fluticasone furoate/vilanterol versus fluticasone propionate/salmeterol on asthma control in the Salford Lung Study. J Asthma. 2019;56:748–57.

9. Averell CS, Stanford R, Laliberte F, Wu J, Germain G, Duh M. Adherence with once-daily fluticasone furoate/vilanterol compared to twice-daily budesonide/formoterol or fluticasone propionate/salmeterol in asthma. Ann Allergy Asthma Immunol. 2018;121:S39.

10. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. Value Health. 2008;11:44–7.

11. Brown MT, Bussell JK. Medication adherence: WHO cares? Mayo Clin Proc. 2011;86:304–14.

12. Price D, Brusselle G, Roche N, Freeman D, Chisholm A. Real-world research and its importance in respiratory medicine. Breathe. 2015;11:26–38.

13. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MC, Verhamme KM. Medication adherence and the risk of severe asthma exacerbations: a systematic review. Eur Respir J. 2015;45:396–407.

14. van der Palen J, Thomas M, Chrystyn H, et al. A randomised open-label cross-over study of inhaler errors, preference and time to achieve correct inhaler use in patients with COPD or asthma: comparison of ELLIPTA with other inhaler devices. NPJ Prim Care Respir Med. 2016;26:16079.

15. Svedsater H, Jacques L, Goldfrad C, Bleecker ER. Ease of use of the ELLIPTA dry powder inhaler: data from three randomised controlled trials in patients with asthma. NPJ Prim Care Respir Med. 2014;24:14019.

16. Murphy KR, Bender BG. Treatment of moderate to severe asthma: patient perspectives on combination inhaler therapy and implications for adherence. J Asthma Allergy. 2009;2(63–72):17.

17. The Health Improvement Network (THIN). https://www.visionhealth.co.uk/portfolio-items/the-health-improvement-network-thin/. Accessed 11 Mar 2020

18. Suissa S. Immortal time bias in pharmacoepidemiology. Am J Epidemiol. 2007;167:492–9.

19. Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD, Mukherjee J. Can simple clinical measurements detect patient noncompliance? Hypertension. 1980;2(6):757–64.

20. Baumgartner PC, Haynes RB, Arnet I, et al. A systematic review of medication adherence thresholds dependent of clinical outcomes. Front Pharmacol. 2018;9:1290.

21. Averell CM, Stanford RH, Laliberte F, Wu JW, Germain G, Duh MS. Medication adherence in patients with asthma using once-daily versus twice-daily ICS/LABAs. J Asthma. 2019;1:1–10. https://doi.org/10.1080/02770903.2019.1663429.

22. Wu AC, Butler MG, Li L, et al. Primary adherence to controller medications for asthma is poor. Ann Am Thorac Soc. 2015;12:161–6. https://doi.org/10.1513/AnnalsATS.201410-459OC.

23. Makhinova T, Barner JC, Richards KM, Rascati KL. Asthma controller medication adherence, risk of exacerbation, and use of rescue agents among texas medicaid patients with persistent asthma. J Manag Care Spec Pharm. 2015;21:1124–32. https://doi.org/10.18553/jmcp.2015.21.12.1124.

24. Boutopoulou B, Koumpagioti D, Matziou V, Priftis KN, Douros K. Interventions on adherence to treatment in children with severe asthma: a systematic review. Front Pediatr. 2018;6:232.

25. Stanford RH, Averell C, Parker ED, Blauer-Peterson C, Reinsch TK, Buikema AR. Assessment of adherence and asthma medication ratio (AMR) for a once-daily and twice-daily inhaled corticosteroid/long acting beta agonist (ICS/LABA) for asthma. J Allergy Clin Immunol Pract. 2019;7(14–1496):e7. https://doi.org/10.1016/j.jaip.2018.12.021.

26. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009;28:3083–107.

27. Sovani MP, Whale CI, Oborne J, et al. Poor adherence with inhaled corticosteroids for asthma: can using a single inhaler containing budesonide and formoterol help? Br J Gen Pract. 2008;58:37–433.

28. Berger WE. The use of inhaled formoterol in the treatment of asthma. Ann Allergy Asthma Immunol. 2006;97(1):24–33.

29. THIN-HES Privacy Notice. https://www.iqvia.com/locations/united-kingdom/information-for-members-of-the-public/thin-hes-data. Accessed 01 Apr 2020.

30. Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep. 2015;2:221–8.

31. AstraZeneca launches Symbicort SMART in UK. https://www.thepharmaletter.com/article/astrazeneca-launches-symbicort-smart-in-uk. Accessed 02 April 2020.

32. Fostair launched in UK as cheaper than GSK/AZ asthma MDIs. https://www.thepharmaletter.com/article/fostair-launched-in-uk-as-cheaper-than-gsk-az-asthma-mdis. Accessed 02 April 2020.

33. Asthma: fluticasone furoate/vilanterol (Relvar Ellipta) combination inhaler. https://www.nice.org.uk/advice/esnm34/chapter/product-overview. Accessed 02 Apr 2020.

34. Pharmacy Quality Alliance. Adherence: PQA adherence measures. https://www.pqaalliance.org/adherence-measures. Accessed 11 Mar 2020.

35. Stanford RH, Averell C, Parker ED, Blauer-Peterson C, Reinsch TK, Buikema AR. Assessment of adherence and asthma medication ratio for a once-daily and twice-daily inhaled corticosteroid/long-acting beta-agonist for asthma. J Allergy Clin Immunol Pract. 2019;7(1488–96):e7.

36. Atsuta R, TakaiIsao J, Mukai I, Kobayashi A, Ishii T, Svedsater H. Patients with asthma prescribed once-daily fluticasone furoate/vilanterol or twice-daily fluticasone propionate/salmeterol as maintenance treatment: analysis from a claims database. Pulm Ther. 2018;4:135–47.