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ARTICLE



Medication adherence in patients with asthma using once-daily versus twice-daily ICS/LABAs

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ABSTRACT

Objective: This real-world observational study compared medication adherence and persistence among patients with asthma receiving the once-daily inhaled corticosteroid/long-acting β_2 -agonist (ICS/LABA) fluticasone furoate/vilanterol (FF/VI) versus the twice-daily ICS/LABAs budesonide/formoterol (B/F) and fluticasone propionate/salmeterol (FP/SAL).

Methods: This retrospective cohort study conducted using IQVIATM Health Plan Claims Data included patients with asthma ≥ 18 years of age initiating ICS/LABA therapy with FF/VI, B/F, or FP/SAL between January 1, 2014 and June 30, 2016 (index date). Patients had ≥ 12 months and ≥ 3 months of continuous eligibility pre- and post-index date, respectively. Patients receiving FF/VI were separately matched 1:1 with patients receiving B/F or FP/SAL using propensity score matching (PSM) and multivariable regression to balance baseline covariates between cohorts. The primary endpoint was medication adherence, measured by proportion of days covered (PDC). Secondary endpoints included proportion of patients achieving PDC ≥ 0.5 and PDC ≥ 0.8 and persistence with index medication, measured by time to discontinuation (>45 -day gap in therapy).

Results: After PSM, 3,764 and 3,339 patients receiving FF/VI were matched with patients receiving B/F or FP/SAL, respectively. Mean PDC was significantly higher for FF/VI versus B/F (0.453 vs 0.345; adjusted $p < 0.001$) and FP/SAL (0.446 vs 0.341; adjusted $p < 0.001$). The proportion of patients achieving PDC ≥ 0.5 or PDC ≥ 0.8 , and treatment persistence were significantly higher for FF/VI versus B/F and FP/SAL (all $p < 0.001$).

Conclusions: In this real-world study, patients initiating FF/VI had better adherence and lower risk of discontinuing treatment versus B/F or FP/SAL, suggesting that once-daily ICS/LABA treatment might improve adherence and persistence compared with twice-daily alternatives.

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Introduction

Guidelines developed by the Global Initiative for Asthma (GINA) and the US National Heart, Lung and Blood Institute (NHLBI) recommend inhaled corticosteroids (ICS) for long-term treatment of patients with persistent asthma (1,2). In patients whose symptoms are not controlled by ICS alone, guidelines recommend the addition of a long-acting β_2 -agonist (LABA) to the treatment regimen (1,2). ICS/LABA fixed-dose combination (FDC) therapies combine these controller medications into a single inhaler, which can lead to improved asthma control compared with ICS and LABA treatments administered with separate inhalers (3). Several ICS/LABA FDCs are available for patients with asthma, including

twice-daily budesonide/formoterol (B/F) and fluticasone propionate/salmeterol (FP/SAL), and once-daily fluticasone furoate/vilanterol (FF/VI) (4–6). In the USA, FF/VI is administered via a dry powder inhaler (DPI) (4), B/F is administered via a pressurized metered dose inhaler (pMDI) (5), and FP/SAL is available as both a DPI and a pMDI (6,7).

Treatment guidelines highlight the importance of adherence to medication in achieving asthma control (1,2). However, adherence to long-term controller medications among patients with asthma is often low in the real-world setting (8–10). Uncontrolled asthma is often associated with poor medication adherence or suboptimal therapy resulting in an increased risk of exacerbations and higher associated

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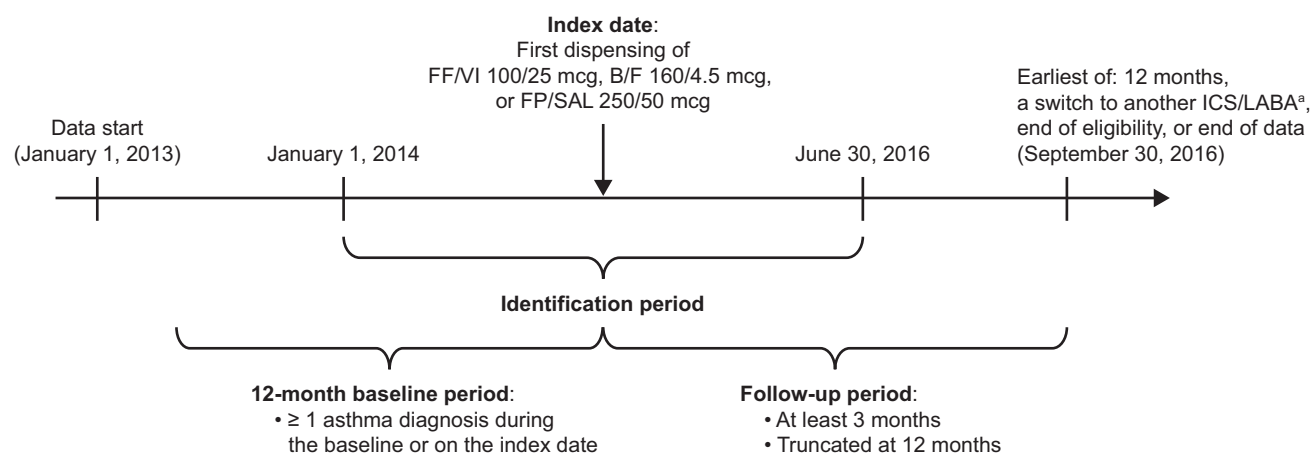


Figure 1. Study design. ^aIncluded patients who switched to another ICS/LABA FDC or to a different dose of the index ICS/LABA. B/F, budesonide/formoterol; FF/VI, fluticasone furoate/vilanterol; FDC, fixed-dose combination; FP/SAL, fluticasone propionate; ICS/LABA, inhaled corticosteroid/long-acting β_2 -agonist.

medical costs (9,11–14). Adherence to medication can be influenced by aspects of the treatment regimen, such as the number of individually administered agents, dosing frequency, and ease of administration (15,16). Previous studies have shown significant improvements in adherence to treatment with once-daily compared with twice-daily controller medications (17–23). Furthermore, a recent study reported greater adherence and a lower risk of discontinuation in patients initiating FF/VI compared with patients initiating B/F (24).

However, real-world data on treatment patterns and adherence with ICS/LABAs is currently limited. This study aimed to evaluate real-world adherence, as measured by proportion of days covered (PDC), and persistence among patients who initiated treatment with FF/VI compared with those who initiated B/F or FP/SAL.

Methods

Study design and patient selection

This was a retrospective cohort study using medical and pharmacy claims data and enrollment information from IQVIATM Health Plan Claims Data between January 1, 2013 and September 30, 2016 (Figure 1).

Patients were included in the study population if they had ≥ 1 prescription fill for FF/VI (100/25 mcg), B/F (160/4.5 mcg), or FP/SAL (250/50 mcg) during the patient identification period (January 1, 2014 to June 30, 2016). Of note, only the DPI form of FP/SAL was used in this study. The baseline period was defined as the 12-month period prior to the date of first dispensing of FF/VI, B/F, or FP/SAL (index date), and the follow-up period was defined as the period from the index date to the earliest of 12 months, switch to another ICS/LABA, health plan disenrollment, or the end of

data availability (September 30, 2016). Patients were included if they had ≥ 12 months of continuous eligibility before the index date, ≥ 3 months of continuous eligibility after the index date, ≥ 1 diagnosis of asthma during the baseline period or on the index date, and age of ≥ 18 years as of the index date. Patients were excluded if they had ≥ 1 diagnosis of chronic obstructive pulmonary disease or cystic fibrosis during the baseline period, on the index date, or during the follow-up period, a diagnosis of acute respiratory failure during the baseline period or on the index date, or ≥ 1 prescription fill for any ICS/LABA (including the index medication) within the 12-month baseline period prior to the index prescription fill. The presence of specific conditions was identified using diagnosis codes from the International Classification of Disease, 9th/10th Edition, Clinical Modification (Supplementary Table S1 in supplementary material). This study utilized de-identified retrospective claims data compliant with the Health Insurance Portability and Accountability Act (HIPAA), and no institutional review board (IRB) approval was required.

Endpoints

The primary endpoint was treatment adherence, measured by mean PDC in the follow-up period. To calculate PDC, the number of days the index medication was available (based on filled prescriptions) was divided by the total number of days of follow-up in the post-index period for each patient.

Secondary endpoints were treatment adherence, based on the proportion of patients who achieved $\text{PDC} \geq 0.5$ and $\text{PDC} \geq 0.8$ for the index medication during the follow-up period (including the index date), and persistence, as measured by time to index

medication discontinuation. Medication discontinuation was defined as a gap in therapy of >45 days from the run-out date of the ICS/LABA pharmacy fill and the next fill, or between the end of the days of supply of the last dispensing and the end of follow-up, whichever occurred first.

Statistical analysis

Propensity score matching (PSM) was used to control for differences in baseline characteristics between treatment cohorts. Patients initiating FF/VI were separately matched 1:1 with patients initiating B/F and 1:1 with patients initiating FP/SAL using multivariable propensity score (PS) with a greedy matching algorithm and caliper widths of 0.01. The PS is the conditional probability of being treated with FF/VI based on observable baseline demographics and socioeconomic and clinical characteristics. PS was generated using probability estimates from a logistic regression model in which treatment with FF/VI was the binary (yes/no) dependent variable and patient characteristics were used as predictors of being treated with FF/VI. PS was used to match the FF/VI cohort with the B/F cohort, and separately with the FP/SAL cohort. After PSM, the distribution of patient characteristics of the post-matched cohorts was evaluated. Exact 1:1 matching was conducted on the factors that remained unbalanced between cohorts, including prescribing physician specialty, specifically respiratory specialists, and index medication costs.

Inverse probability of treatment weighting (IPTW), an alternative method of correcting for differences in baseline characteristics between cohorts, was conducted as a sensitivity analysis. Unlike PSM, IPTW allows all patients to be retained for analysis. Each patient was attributed a weight, calculated as $1/PS$ for the FF/VI cohort and $1/(1-PS)$ for the B/F and FP/SAL cohorts. Weights were normalized by the mean weight.

Demographics and clinical characteristics were assessed during the 12-month baseline period and analyzed descriptively. Bivariate comparisons in the pre- and post-matched cohorts were based on p values and standardized differences. For bivariate comparisons of baseline characteristics between the pre-matched cohorts, significance was tested using the Wilcoxon rank-sum test for unpaired continuous variables and the chi-square test for unpaired dichotomous variables; whereas the Wilcoxon sign-rank test for paired continuous variables and McNemar's test for paired dichotomous variables were used for comparisons of the post-matched cohorts. For the IPTW sensitivity analyses, significance was evaluated using

t -tests for continuous variables and chi-square tests for dichotomous variables.

In the primary analysis, mean PDC and the proportion of patients achieving PDC by cutoff were compared in the post-matched cohorts. Multivariable regression models were used for post-match adjustment of covariates with residual imbalance, defined as $p \leq 0.05$ following PSM or standardized difference $\geq 10\%$ following inverse probability of treatment weighting (IPTW). Specifically, generalized linear regression was used for mean PDC and logistic regression was used for PDC ≥ 0.5 and PDC ≥ 0.8 endpoints.

To evaluate persistence with index therapy, Kaplan–Meier survival analysis was used to calculate the cumulative incidence of index medication discontinuation. Cox proportional hazards regression was used to analyze time-to-treatment discontinuation.

As an additional sensitivity analysis, a pre-specified subgroup analysis evaluated medication adherence and persistence among patients with at least 12 months of follow-up. For this analysis, additional residual imbalances in baseline characteristics were accounted for in the multivariable models since the baseline characteristics of this subgroup of patients differ from those of the overall study population.

Results

Study population

In total, 3,973 patients receiving treatment with FF/VI, 29,661 patients receiving B/F, and 26,745 patients receiving FP/SAL met the study criteria (Figure 2). After PSM, 3,764 and 3,339 patients initiating FF/VI were matched to 3,764 patients receiving B/F and 3,339 patients receiving FP/SAL, respectively.

After matching, the mean post-index follow-up time was similar for the FF/VI and B/F cohorts (257.1 vs 260.3 days; $p = 0.125$) and for the FF/VI and FP/SAL cohorts (258.1 vs 259.8 days; $p = 0.434$). Selected post-match baseline demographics and clinical characteristics that may be related to adherence are described in Table 1. All pre- and post-match baseline demographics and clinical characteristics are described in Supplementary Tables S2 and S3 in supplementary material.

Treatment adherence

Mean PDC was significantly higher among FF/VI initiators compared with either B/F or FP/SAL initiators (Figure 3A). For FF/VI versus B/F, the mean (standard deviation [SD]) PDC was 0.453 (0.300) in the

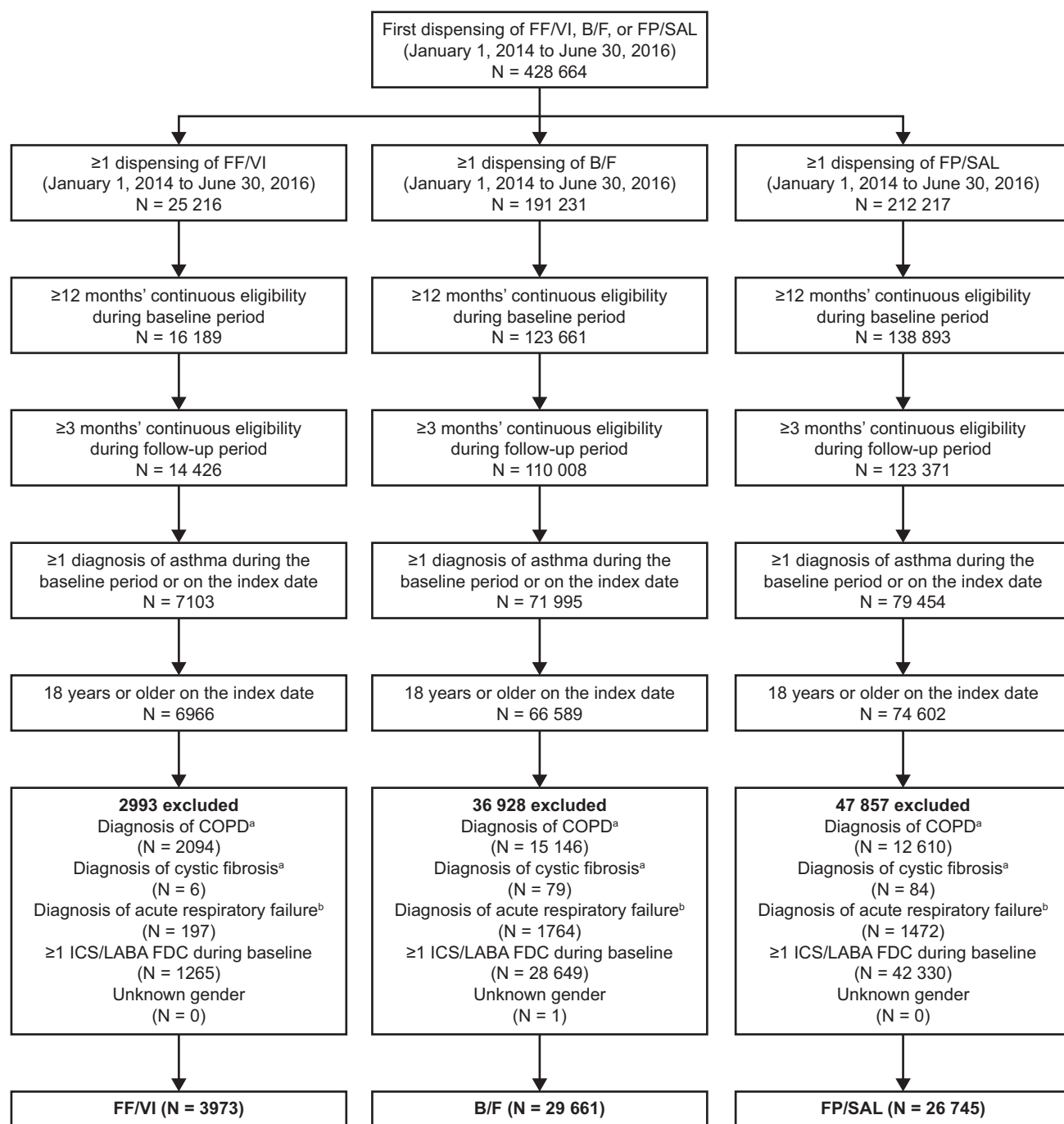


Figure 2. Study population selection. ^aDuring the baseline or follow-up period. ^bDuring the baseline period or on the index date. B/F, budesonide/formoterol; COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; FF/VI, fluticasone furoate/vilanterol; FP/SAL, fluticasone propionate; ICS/LABA, inhaled corticosteroid/long-acting β_2 -agonist.

FF/VI cohort and 0.345 (0.252) in the B/F cohort ($p < 0.001$), and the adjusted mean difference in PDC was 0.11 (95% CI: 0.10–0.12; $p < 0.001$). For FF/VI versus FP/SAL, the mean PDC (SD) was 0.446 (0.300) in the FF/VI cohort and 0.341 (0.257) in the FP/SAL cohort, with the adjusted mean difference in PDC as 0.10 (95% CI: 0.09–0.12; $p < 0.001$).

A greater proportion of FF/VI initiators achieved $PDC \geq 0.5$ and $PDC \geq 0.8$ compared with B/F

initiators (40.5% vs 24.1%; $p < 0.001$ and 20.5% vs 8.4%; $p < 0.001$, respectively) and FP/SAL initiators (39.4% vs 23.4%; $p < 0.001$ and 20.0% vs 9.1%; $p < 0.001$, respectively). The adjusted odds of FF/VI initiators achieving $PDC \geq 0.5$ and $PDC \geq 0.8$ were 2.14 times higher (95% CI: 1.95–2.36) and 2.84 times higher (95% CI: 2.46–3.26), respectively, compared with B/F initiators (Figure 3B). For FF/VI initiators versus FP/SAL initiators, the adjusted odds of

Table 1. Selected post-match baseline characteristics.

Characteristic	FF/VI versus B/F				FF/VI versus FP/SAL			
	FF/VI (N = 3764)	B/F (N = 3764)	Std diff (%)	p-value	FF/VI (N = 3,339)	FP/SAL (N = 3,339)	Std diff (%)	p-value
Age, years, mean (SD)	46.6 (13.4)	46.7 (13.3)	−1.0	0.686	46.4 (13.6)	46.4 (13.7)	−0.1	0.916
Female, n (%)	2,346 (62.3)	2,340 (62.2)	0.3	0.887	2,091 (62.6)	2,105 (63.0)	−0.9	0.721
Respiratory medication use								
AMRa, mean (SD)	0.33 (0.38)	0.35 (0.39)	−5.7	0.189	0.31 (0.38)	0.32 (0.38)	−2.0	0.178
≥1 ICS, n (%)	599 (15.9)	582 (15.5)	1.2	0.586	489 (14.6)	498 (14.9)	−0.8	0.758
≥1 OCS, n (%)	1,942 (51.6)	1,968 (52.3)	−1.4	0.548	1,666 (49.9)	1,686 (50.5)	−1.2	0.625
Number of SABA canisters ^b per patient, mean (SD)	2.1 (3.4)	2.0 (3.3)	2.4	0.233	2.1 (3.4)	2.1 (3.4)	−0.3	0.913
Overall exacerbations^c								
Number of exacerbations per patient, mean (SD)	0.24 (0.55)	0.24 (0.55)	0.1	0.907	0.22 (0.53)	0.24 (0.52)	−2.3	0.286
≥1 exacerbation, n (%)	731 (19.4)	734 (19.5)	−0.2	0.931	609 (18.2)	660 (19.8)	−3.9	0.109
Asthma-related healthcare resource utilization, n (%)								
≥1 ED visit	180 (4.8)	187 (5.0)	−0.9	0.706	163 (4.9)	196 (5.9)	−4.4	0.075
≥1 IP visit	38 (1.0)	30 (0.8)	2.2	0.332	37 (1.1)	34 (1.0)	0.9	0.718
Asthma-related healthcare costs^d, \$, mean (SD)								
Total cost	940 (4,603)	953 (5,207)	−0.3	0.595	895 (4,621)	1,024 (6,252)	−2.4	0.956
Medical costs	366 (2,834)	281 (1,549)	3.7	0.729	349 (2,819)	347 (2,323)	0.1	0.315
Pharmacy costs	574 (3,184)	672 (4,969)	−2.3	0.536	546 (3,168)	677 (5,789)	−2.8	0.903
Patient-paid cost of index medication fill	44 (51)	43 (44)	2.9	0.057	45 (51)	43 (42)	3.5	0.389
Post-index follow-up time, days, mean (SD)	257.1 (94.9)	260.3 (94.1)	−3.4	0.125	258.1 (95.6)	259.8 (94.7)	−1.8	0.434

^aBaseline AMR was calculated as the total number of controller medication units dispensed in the baseline period (including ICS, LTRA, methylxanthines, and mast cell stabilizers) divided by the total number of controller medication plus rescue medication (SABA) units dispensed in the baseline period.

^bOne canister of SABA medication was defined as the quantity of the dispensing decided by the package quantity and further divided by 100 if the units were in mg.

^cOverall asthma exacerbation was defined as having a moderate or severe exacerbation. Moderate asthma exacerbation was defined as an asthma-related ED visit or physician office visit or urgent care visit with an SCS/OCS prescription administration within ± 5 days. Severe asthma exacerbation was defined as an asthma-related hospitalization or asthma-related ED visit that results in a hospitalization within ± 1 day. Patients with two or more exacerbations within 14 days of each other were considered as one exacerbation and classified according to the highest severity of the contributing events.

^dCosts were adjusted based on the 2016 Consumer Price Index.

AMR, asthma medication ratio; B/F, budesonide/formoterol; ED, emergency department; FF/VI, fluticasone furoate/vilanterol; FP/SAL, fluticasone propionate/salmeterol; ICS, inhaled corticosteroid; IP, inpatient; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SABA, short-acting β_2 -agonist; SCS, systemic corticosteroid; SD, standard deviation; Std diff, standardized difference.

achieving $\text{PDC} \geq 0.5$ and $\text{PDC} \geq 0.8$ were 2.11 times higher (95% CI: 1.90–2.35) and 2.49 times higher (95% CI: 2.16–2.88), respectively (Figure 3C).

Treatment persistence

Kaplan–Meier curves of persistence to FF/VI versus B/F and to FF/VI versus FP/SAL are shown in Figure 4, panels A and B, respectively. Treatment persistence was significantly better with FF/VI versus B/F ($p < 0.001$) and with FF/VI versus FP/SAL ($p < 0.001$). The adjusted risk of discontinuation was 30% lower (adjusted HR = 0.70; 95% CI: 0.66–0.74) and 27% lower (adjusted HR = 0.73; 95% CI: 0.68–0.77) among patients receiving FF/VI compared with patients receiving B/F and FP/SAL, respectively.

Sensitivity analyses

In a pre-specified subgroup analysis of patients with 12 months of follow-up, mean PDC at 12 months and

the odds of achieving $\text{PDC} \geq 0.5$ and $\text{PDC} \geq 0.8$ were significantly higher among FF/VI initiators compared with B/F and FP/SAL initiators, and the risk of discontinuation was significantly lower (all $p < 0.001$; Table S4 in [supplementary material](#)).

The sensitivity analysis of adherence using IPTW is shown in Table S5 in [supplementary material](#). When IPTW was used as an alternative method, outcomes were consistent and similar to what was observed for the PSM analyses for all endpoints (all $p < 0.001$).

Discussion

This retrospective observational study used data from a large US claims database to evaluate treatment adherence and persistence among patients with asthma receiving once-daily FF/VI, twice-daily B/F, or twice daily FP/SAL in the real-world setting. Compared with B/F or FP/SAL initiators, patients initiating FF/VI had significantly better adherence and persistence to their medication.

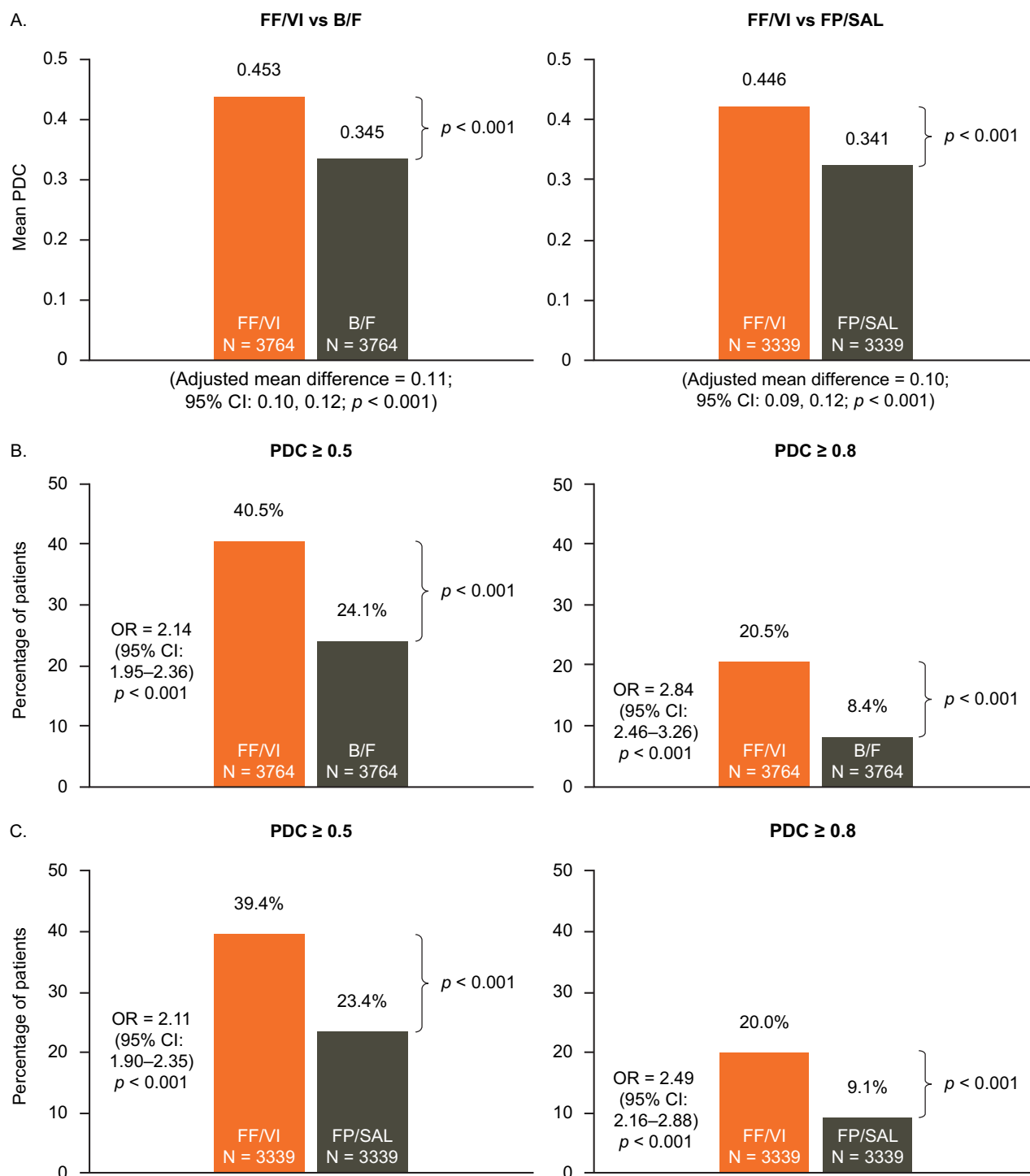


Figure 3. Mean PDC (A) and proportion of patients achieving PDC ≥ 0.5 and PDC ≥ 0.8 with FF/VI versus B/F (B) and FF/VI versus FP/SAL (C). Mean PDC and OR were calculated using generalized linear regression and logistic regression models, respectively, including the following baseline covariates: (A) FF/VI versus B/F: region, insurance product type, log of all-cause medical cost, log of all-cause medical cost paid by patient, log of all-cause outpatient costs, number of all-cause outpatient visits, and baseline LAMA/LABA use (yes/no); (B) FF/VI versus FP/SAL: insurance product type, log of all-cause total cost, log of all-cause medical cost, log of all-cause ED visit cost, log of all-cause outpatient costs, log of all-cause medical cost paid by patient, number of all-cause ED visits, number of all-cause outpatient visits, and baseline rescue medication use (yes/no). B/F, budesonide/formoterol; CI, confidence interval; ED, emergency department; FF/VI, fluticasone furoate/vilanterol; FP/SAL, fluticasone propionate; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; OR, odds ratio; PDC, proportion of days covered.

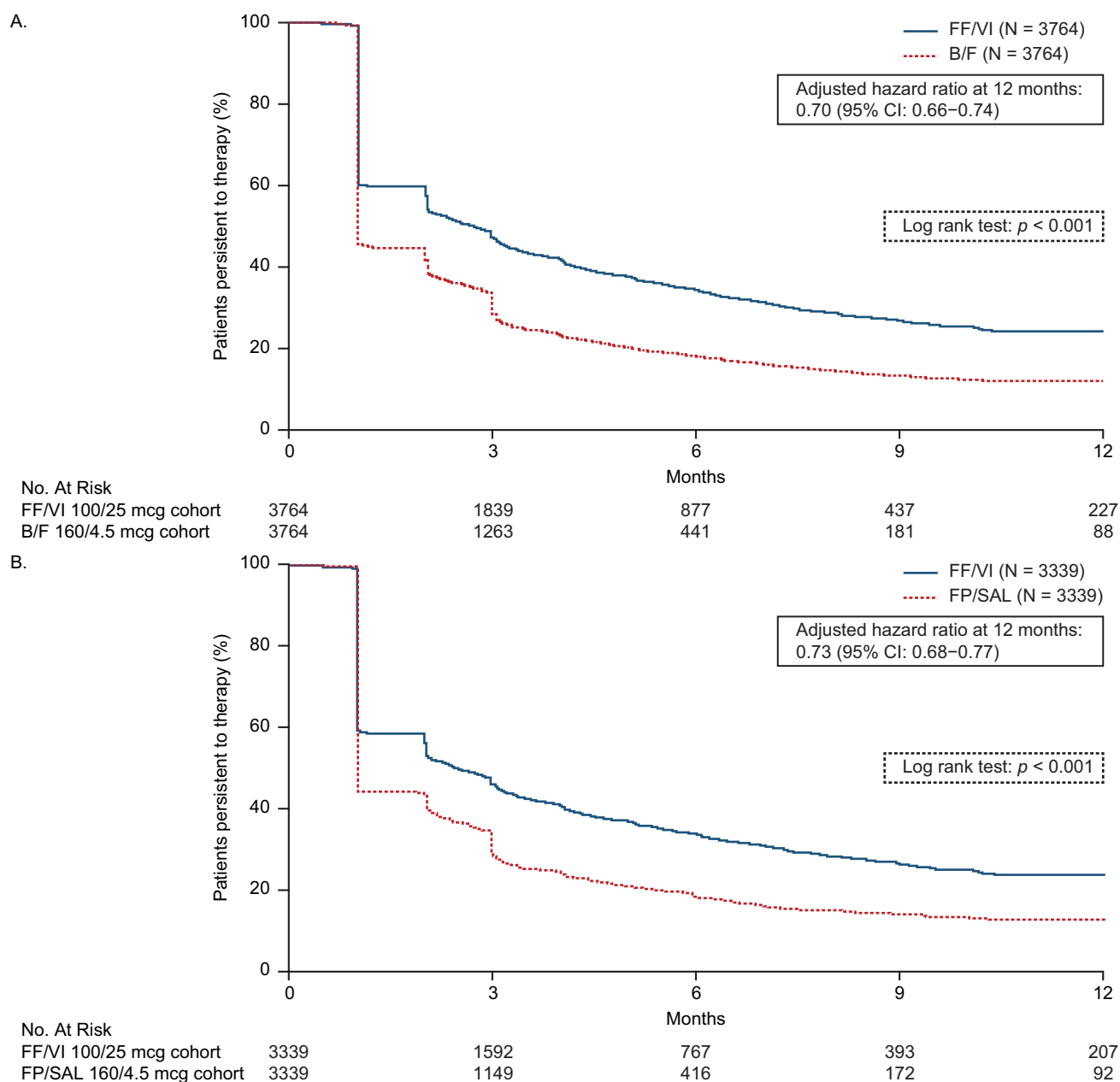


Figure 4. Kaplan–Meier analysis of persistence to (A) FF/VI versus B/F and (B) FF/VI versus FP/SAL. Treatment discontinuation was defined as a gap in therapy of >45 days from the run-out date of the ICS/LABA pharmacy fill and the next fill, or between the end of the days of supply of the last dispensing and the end of follow-up, whichever occurred first. Hazard ratios were calculated using a Cox proportional hazards model adjusted for baseline covariates including: (A) FF/VI versus B/F: region, insurance product type, log of all-cause medical cost, log of all-cause medical cost paid by patient, log of all-cause outpatient costs, number of all-cause outpatient visits, and baseline LAMA/LABA use (yes/no); (B) FF/VI versus FP/SAL: insurance product type, log of all-cause total cost, log of all-cause medical cost, log of all-cause ED cost, log of all-cause outpatient costs, log of all-cause medical cost paid by patient, number of all-cause ED visits, number of all-cause outpatient visits, and baseline rescue medication use (yes/no). B/F, budesonide/formoterol; ED, emergency department; FF/VI, fluticasone furoate/vilanterol; FP/SAL, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist.

The findings in a subgroup of patients with at least 12 months of follow-up and in cohorts balanced using IPTW, an alternative method to correct for confounding differences in baseline characteristics, were consistent with the primary PSM analyses. These findings are based on a data source representing patient

populations from multiple health plans and providers across the USA, and support recent studies that showed significantly higher mean PDC, greater odds of achieving $PDC \geq 0.5$ or $PDC \geq 0.8$, and lower risk of discontinuation among FF/VI initiators compared with B/F initiators (24) or FP/SAL initiators (25).

Previous studies have shown that adherence and persistence to controller medication among patients with asthma is suboptimal (8–10,15,16,20). While adherence in the present study was better among patients receiving FF/VI, low adherence to controller medications was observed across all cohorts. The range of mean PDC values across the cohorts was 0.34–0.45, which is consistent with the range of approximately 0.30–0.70 reported by previous studies of adherence to controller medications in patients with asthma (8–10,24). Additionally, a high proportion of patients in this study discontinued the index medication within 12 months, which is also consistent with earlier studies of persistence with controller medications (26). Better adherence is associated with improved outcomes in patients with asthma, including a lower risk of exacerbations, reduced rescue medication use, and fewer asthma-related hospitalizations and emergency department visits (11,13,14,16,20,21,27–30). There is therefore an unmet need for treatment regimens promoting improved adherence and outcomes among patients with asthma.

The present study was the first head-to-head investigation of adherence to ICS/LABA FDCs administered via DPIs in patients with asthma in the USA, supporting the findings of a previous US-based study that compared adherence to FF/VI administered via a DPI and B/F via a pMDI in patients with asthma (24). Patients receiving FF/VI demonstrated significantly higher mean PDC and probability of achieving a clinically significant level of adherence, as well as lower risk of discontinuation compared with those receiving B/F or FP/SAL. Adherence can be influenced by multiple factors, including patient understanding of the disease and treatments, as well as complexity of the medication regimen with respect to the number of agents, dosing frequency and ease of inhaler use (1,15,16,31,32). The importance of dosing frequency in medication adherence in the real-world setting has been highlighted by previous studies demonstrating better adherence with once-daily versus twice-daily inhalers in patients receiving ICS monotherapy (17–19,21–23) and more recently with other controller medications (20). The findings of the current study corroborate previous findings and provides additional evidence of the association of once-daily FF/VI with better adherence and persistence compared with twice-daily ICS/LABAs, specifically B/F and FP/SAL.

There are several general limitations associated with assumptions inherent in claims-based observational studies that should be considered in interpretation of the results of the present study. Firstly, this analysis used indirect measures of adherence and persistence, which were based on medical and pharmacy

claims data and therefore not prospectively measured. Secondly, adherence was calculated using dispensing data; however, the presence of a claim for a filled prescription does not confirm that a patient used their medication, and medications obtained as samples or during inpatient visits are not captured. Thirdly, dosing frequency was not evaluated in this analysis, and as such it is assumed that dosing frequency for each product was in accordance with the relevant prescribing information. Finally, while PS methods and statistical modeling were used to balance cohorts on observed variables, as this was a non-randomized study, residual confounding could arise from variables not captured in matching, weighting or adjustment models, such as lung function, symptom severity, or smoking history. In addition, this study was not designed to assess the effects of increased adherence on outcomes such as exacerbations or oral corticosteroid use, and data on these outcomes in the follow-up period were not collected. Future studies are warranted to evaluate the relationship between adherence and outcomes. Despite these possible limitations, claims data are a valuable tool for assessing real-world treatment patterns, as they provide access to a large and diverse sample of patients initiated on different ICS/LABA treatments for asthma with a wide geographic distribution across the USA.

Conclusions

This retrospective study using a large US claims database found that patients initiating once-daily FF/VI had better adherence (as measured by PDC) and lower risk of discontinuing therapy compared with twice-daily B/F or FP/SAL in the real world. These findings suggest that once-daily ICS/LABA therapy could improve adherence and persistence relative to a twice-daily alternative.

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Author contributions

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, take responsibility for the integrity of the work as a whole, contributed to the writing and reviewing of the manuscript, and have given final approval for the version to be published. All authors had full access to all of the data and take complete responsibility for the integrity of the data and accuracy of the data analysis. CA and RHS contributed to conception and design of the study and data analysis and interpretation. FL, JWW, GG, and MSD contributed to conception and design of the study, acquisition of data, and data analysis and interpretation.

Conflicts of interest

RHS and CMA are employees of GSK and hold stocks/shares in GSK. FL, JWW, GG, and MSD are employees of Analysis Group, Inc., a consulting company that has received research funds from GSK. to conduct this study.

Data sharing

To request access to patient-level data and documents for this study, please submit an enquiry via www.clinicalstudy-datarequest.com. Data included in this manuscript are derived from a database owned by IQVIATM and contain proprietary elements, and therefore data cannot be broadly disclosed or made publicly available at this time. The disclosure of this data to third-party clients assumes certain data security and privacy protocols are in place and that the third-party client has executed IQVIA's standard license agreement, which includes restrictive covenants governing the use of the data.

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Supplementary Table S1 Diagnosis codes used to identify specific conditions

Condition	ICD-9-CM codes	ICD-10-CM codes
Asthma	493.xx	J45.3, J45.4, J45.5, J45.9
COPD	491.x, 492.x, 496.x	J41–J44
Cystic fibrosis	277.0	E84.0–E84.9
Acute respiratory failure	518.81	J96.0, J96.2

COPD, chronic obstructive pulmonary disease; ICD-9-CM, International Classification of Disease, 9th Edition, Clinical Modification; ICD-10-CM, International Classification of Disease, 10th Edition, Clinical Modification

Supplementary Table S2 Baseline demographics, healthcare resource utilization, healthcare costs, clinical characteristics, and respiratory medication use in the pre- and post-matched FF/VI versus B/F cohorts

Characteristics ^a	Pre-matched cohorts (FF/VI vs B/F)				Post-matched cohorts (FF/VI vs B/F)			
	FF/VI N=3973	B/F N=29 661	Std Diff (%)	p-value	FF/VI N=3764	B/F N=3764	Std Diff (%)	p-value
Age, years, mean ± SD [median]	46.5±13.5 [48]	46.1±13.4 [48]	3.5	0.039	46.6±13.4 [48]	46.7±13.3 [48]	-1.0	0.686
Age, years, n (%)								
18–29	558 (14.0)	4196 (14.1)	-0.3	0.863	521 (13.8)	508 (13.5)	1.0	0.666
30–39	598 (15.1)	4915 (16.6)	-4.2	0.015	574 (15.2)	573 (15.2)	0.1	0.974
40–49	964 (24.3)	7273 (24.5)	-0.6	0.724	917 (24.4)	932 (24.8)	-0.9	0.690
50–59	1155 (29.1)	8152 (27.5)	3.5	0.036	1089 (28.9)	1076 (28.6)	0.8	0.744
60–64	478 (12.0)	3537 (11.9)	0.3	0.846	456 (12.1)	468 (12.4)	-1.0	0.674
65+	220 (5.5)	1588 (5.4)	0.8	0.630	207 (5.5)	207 (5.5)	0.0	1.000
Female, n (%)	2467 (62.1)	19 035 (64.2)	-4.3	0.010	2346 (62.3)	2340 (62.2)	0.3	0.887
Region, n (%)								
Midwest	894 (22.5)	6963 (23.5)	-2.3	0.173	862 (22.9)	884 (23.5)	-1.4	0.543
South	2142 (53.9)	10 229 (34.5)	39.9	<0.001	1969 (52.3)	2017 (53.6)	-2.6	0.225
West	356 (9.0)	3382 (11.4)	-8.1	<0.001	352 (9.4)	361 (9.6)	-0.8	0.721
Northeast	570 (14.3)	8275 (27.9)	-33.7	<0.001	570 (15.1)	499 (13.3)	5.4	0.014
Unknown	11 (0.3)	812 (2.7)	-20.3	<0.001	11 (0.3)	3 (0.1)	4.9	0.033
Insurance product type, n (%)								
PPO	3567 (89.8)	23 998 (80.9)	25.3	<0.001	3367 (89.5)	3402 (90.4)	-3.1	0.174
HMO	216 (5.4)	3838 (12.9)	-26.2	<0.001	214 (5.7)	177 (4.7)	4.4	0.048
Indemnity/Traditional	50 (1.3)	432 (1.5)	-1.7	0.324	49 (1.3)	56 (1.5)	-1.6	0.486
POS	118 (3.0)	1068 (3.6)	-3.5	0.043	112 (3.0)	110 (2.9)	0.3	0.892
CDHC	4 (0.1)	84 (0.3)	-4.2	0.034	4 (0.1)	4 (0.1)	0.0	1.000
Unknown	18 (0.5)	241 (0.8)	-4.5	0.015	18 (0.5)	15 (0.4)	1.2	0.602
Physician specialty at index date, n (%)								
Primary care	1852 (46.6)	13 592 (45.8)	1.6	0.348	1789 (47.5)	1814 (48.2)	-1.3	0.480
Respiratory specialist ^b	1059 (26.7)	4776 (16.1)	26.0	<0.001	921 (24.5)	921 (24.5)	0.0	N/A

Characteristics ^a	Pre-matched cohorts (FF/VI vs B/F)				Post-matched cohorts (FF/VI vs B/F)			
	FF/VI N=3973	B/F N=29 661	Std Diff (%)	p-value	FF/VI N=3764	B/F N=3764	Std Diff (%)	p-value
Year/quarter of index date, n (%)								
2014	274 (6.9)	12 795 (43.1)	-92.1	<0.001	274 (7.3)	286 (7.6)	-1.2	0.427
Q1	33 (0.8)	3362 (11.3)	-45.0	<0.001	33 (0.9)	30 (0.8)	0.9	0.680
Q2	63 (1.6)	3273 (11.0)	-39.6	<0.001	63 (1.7)	67 (1.8)	-0.8	0.703
Q3	73 (1.8)	2772 (9.3)	-33.1	<0.001	73 (1.9)	80 (2.1)	-1.3	0.531
Q4	105 (2.6)	3388 (11.4)	-34.9	<0.001	105 (2.8)	109 (2.9)	-0.6	0.768
2015	2013 (50.7)	12 008 (40.5)	20.6	<0.001	1943 (51.6)	1948 (51.8)	-0.3	0.900
Q1	224 (5.6)	3556 (12.0)	-22.5	<0.001	224 (6.0)	261 (6.9)	-4.0	0.058
Q2	399 (10.0)	3409 (11.5)	-4.7	0.007	398 (10.6)	395 (10.5)	0.3	0.904
Q3	621 (15.6)	2404 (8.1)	23.4	<0.001	594 (15.8)	579 (15.4)	1.1	0.626
Q4	769 (19.4)	2639 (8.9)	30.4	<0.001	727 (19.3)	713 (18.9)	0.9	0.667
2016	1686 (42.4)	4858 (16.4)	59.7	<0.001	1547 (41.1)	1530 (40.6)	0.9	0.651
Q1	851 (21.4)	2676 (9.0)	35.0	<0.001	796 (21.1)	815 (21.7)	-1.2	0.576
Q2	835 (21.0)	2182 (7.4)	39.9	<0.001	751 (20.0)	715 (19.0)	2.4	0.258
Asthma-related baseline healthcare resource utilization^c								
Number of patients with at least one IP visit, n (%)	39 (1.0)	464 (1.6)	-5.2	0.004	38 (1.0)	30 (0.8)	2.2	0.332
IP visits, mean ± SD [median]	0.01±0.11 [0]	0.02±0.13 [0]	-5.0	0.004	0.01±0.11 [0]	0.01±0.09 [0]	2.7	0.247
Number of patients with at least one ED visit, n (%)	186 (4.7)	1791 (6.0)	-6.0	<0.001	180 (4.8)	187 (5.0)	-0.9	0.706
ED visits, mean ± SD [median]	0.1±0.3 [0]	0.1±0.4 [0]	-4.8	<0.001	0.1±0.3 [0]	0.1±0.3 [0]	0.1	0.814
Number of patients with at least one OP visit, n (%)	2483 (62.5)	15 804 (53.3)	18.7	<0.001	2307 (61.3)	2323 (61.7)	-0.9	0.698
OP visits, mean ± SD [median]	1.3±4.6 [1]	1.1±2.2 [1]	5.7	<0.001	1.3±2.3 [1]	1.2±2.1 [1]	0.8	0.709
Number of patients with at least one OP-related event	795 (20.0)	9747 (32.9)	-29.5	<0.001	787 (20.9)	774 (20.6)	0.9	0.693
Asthma-related baseline healthcare cost, US\$ 2016, mean ± SD^c								
Total healthcare cost	940±4510	978±4662	-0.8	0.002	940±4603	953±5207	-0.3	0.595
Medical costs	368±2784	348 ± 2150	0.8	<0.001	366 ± 2834	281 ± 1549	3.7	0.729

Characteristics ^a	Pre-matched cohorts (FF/VI vs B/F)				Post-matched cohorts (FF/VI vs B/F)			
	FF/VI N=3973	B/F N=29 661	Std Diff (%)	p-value	FF/VI N=3764	B/F N=3764	Std Diff (%)	p-value
IP visit costs	45±652	82 ± 1080	-4.2	0.002	45 ± 657	29 ± 435	2.9	0.312
ED visit costs	26±176	37 ± 288	-4.5	<0.001	27 ± 180	27 ± 281	0.0	0.638
OP visit costs	297±2680	229 ± 1755	3.0	<0.001	294 ± 2730	225 ± 1432	3.2	0.915
Pharmacy costs	572±3113	630 ± 4081	-1.6	0.103	574 ± 3184	672 ± 4969	-2.3	0.536
Total costs paid by patients								
Medical costs	229±2060	223±2467	0.3	<0.001	224±2042	192±1508	1.7	0.322
Pharmacy costs	250±340	238±451	2.9	<0.001	248 ± 338	265±614	-3.4	0.443
Index medication cost ^b	45±51	36±38	20.3	<0.001	44±51	43±44	2.9	0.057
All-cause baseline healthcare cost, US\$ 2016, mean ± SD^c								
Total healthcare cost	9200±22 712	9097±32 768	0.4	0.928	9291±23 189	11 179±71 780	-3.5	0.105
Medical costs	6968±20 275	7053±30 787	-0.3	0.324	7049±20 719	8689±69 272	-3.2	0.033
IP visit costs	1662±11 311	1788±13 877	-1.0	0.043	1704±11 563	2404±27 661	-3.3	0.173
ED visit costs	273±840	293±1067	-2.1	0.138	280±856	282±920	-0.3	0.839
OP visit costs	5033±14 926	4971±20 509	0.3	0.964	5066±15 243	6004±43 595	-2.9	0.024
Pharmacy costs	2232±6917	2043±7619	2.6	<0.001	2243±6980	2489±11 404	-2.6	0.739
Total costs paid by patients								
Medical costs	3305±11 824	2752±10 168	5.0	<0.001	3311±11 762	3462±10 937	-1.3	0.005
Pharmacy costs	367±499	331±480	7.2	<0.001	365±500	378±562	-2.6	0.405
All-cause baseline healthcare resource utilization^c								
Number of patients with at least one IP visit, n (%)	275 (6.9)	2,346 (7.9)	-3.8	0.029	263 (7.0)	299 (7.9)	-3.6	0.114
IP visits, mean ± SD [median]	0.08±0.33 [0]	0.10±0.38 [0]	-4.3	0.032	0.08±0.33 [0]	0.10±0.38 [0]	-3.7	0.169
Number of patients with at least one ED visit, n (%)	1207 (30.4)	9157 (30.9)	-1.1	0.528	1155 (30.7)	1155 (30.7)	0.0	1.000
ED visits, mean ± SD [median]	0.5±1.1 [0]	0.6±1.3 [0]	-2.8	0.345	0.5±1.1 [0]	0.5±1.1 [0]	-1.1	0.373
Number of patients with at least one OP visit, n (%)	3951 (99.4)	29 159 (98.3)	10.8	<0.001	3743 (99.4)	3730 (99.1)	4.1	0.080
OP visits, mean ± SD [median]	16.2±16.4 [11]	15.8±16.8 [11]	2.3	<0.001	16.0±16.0 [11]	16.9±17.3	-5.2	0.023

Characteristics ^a	Pre-matched cohorts (FF/VI vs B/F)				Post-matched cohorts (FF/VI vs B/F)			
	FF/VI N=3973	B/F N=29 661	Std Diff (%)	p-value	FF/VI N=3764	B/F N=3764	Std Diff (%)	p-value
						[12]		
Comorbidities								
Quan-Charlson comorbidity index, mean ± SD [median] ^d	1.52±1.21 [1]	1.50±1.18 [1]	1.3	0.698	1.52±1.21 [1]	1.51±1.18 [1]	0.7	0.773
1–2	3461 (87.1)	26 062 (87.9)	-2.3	0.173	3283 (87.2)	3305 (87.8)	-1.8	0.450
3–4	369 (9.3)	2598 (8.8)	1.8	0.270	346 (9.2)	326 (8.7)	1.9	0.423
5+	143 (3.6)	1001 (3.4)	1.2	0.464	135 (3.6)	133 (3.5)	0.3	0.902
AHRQ comorbidities, n (%) ^d								
Other lower respiratory disease	2311 (58.2)	15 623 (52.7)	11.1	<0.001	2164 (57.5)	2141 (56.9)	1.2	0.584
Dyslipidemia	1308 (32.9)	9353 (31.5)	3.0	0.077	1230 (32.7)	1261 (33.5)	-1.8	0.448
Diabetes mellitus, without complications	712 (17.9)	5132 (17.3)	1.6	0.334	673 (17.9)	667 (17.7)	0.4	0.857
Substance-related disorders	144 (3.6)	784 (2.6)	5.6	<0.001	136 (3.6)	125 (3.3)	1.6	0.489
Developmental disorder and ADHD	142 (3.6)	1039 (3.5)	0.4	0.819	133 (3.5)	133 (3.5)	0.0	1.000
Asthma exacerbations ^e								
Baseline period ^c								
Overall exacerbations								
Total count, n, mean ± SD [median]	0.23±0.54 [0]	0.25±0.58 [0]	-3.1	0.205	0.24±0.55 [0]	0.24±0.55 [0]	0.1	0.907
≥ 1 exacerbation, n (%)	755 (19.0)	5867 (19.8)	-2.0	0.247	731 (19.4)	734 (19.5)	-0.2	0.931
Moderate exacerbations								
Total count, n, mean ± SD [median]	0.22±0.53 [0]	0.23±0.56 [0]	-2.2	0.413	0.23±0.54 [0]	0.23±0.54 [0]	-0.3	0.905
≥ 1 exacerbation, n (%)	715 (18.0)	5403 (18.2)	-0.6	0.736	693 (18.4)	704 (18.7)	-0.8	0.744
Severe exacerbations								
Total count, n, mean ± SD [median]	0.01±0.11 [0]	0.02±0.13 [0]	-4.4	0.007	0.01±0.11 [0]	0.01±0.09 [0]	2.7	0.247
≥ 1 exacerbation, n (%)	40 (1.0)	464 (1.6)	-5.0	0.007	38 (1.0)	30 (0.8)	2.2	0.332
Exacerbation on the index date, n (%)								

Characteristics ^a	Pre-matched cohorts (FF/VI vs B/F)				Post-matched cohorts (FF/VI vs B/F)			
	FF/VI N=3973	B/F N=29 661	Std Diff (%)	p-value	FF/VI N=3764	B/F N=3764	Std Diff (%)	p-value
Overall exacerbations	170 (4.3)	3282 (11.1)	-25.7	<0.001	168 (4.5)	184 (4.9)	-2.0	0.373
Moderate exacerbations	165 (4.2)	3174 (10.7)	-25.2	<0.001	164 (4.4)	176 (4.7)	-1.5	0.496
Severe exacerbations	5 (0.1)	108 (0.4)	-4.8	0.015	4 (0.1)	8 (0.2)	-2.7	0.248
Asthma-related ED exacerbation event	2 (0.1)	94 (0.3)	-6.2	0.003	2 (0.1)	3 (0.1)	-1.0	0.655
Asthma-related IP exacerbation event	5 (0.1)	108 (0.4)	-4.8	0.015	4 (0.1)	8 (0.2)	-2.7	0.248
Asthma-related OP exacerbation event	163 (4.1)	3080 (10.4)	-24.4	<0.001	162 (4.3)	173 (4.6)	-1.4	0.529
Baseline medication use^c								
AMR, mean ± SD [median]^d	0.33±0.38 [0]	0.30±0.37 [0]	9.3	<0.001	0.33±0.38 [0]	0.35±0.39 [0]	-5.7	0.189
Baseline respiratory medication, mean ± SD [median]								
Count of unique medication use during baseline	6.8±6.3 [5]	6.1±6.1 [4]	11.8	<0.001	6.8±6.2 [5]	6.9±6.3 [5]	-1.2	0.711
Count of unique medication use on the index date	1.4±0.7 [1]	1.8±0.9 [2]	-44.7	<0.001	1.4±0.8 [1]	1.4±0.7 [1]	-1.4	0.452
Controller medications, n (%)								
Any use	1614 (40.6)	10 579 (35.7)	10.2	<0.001	1510 (40.1)	1535 (40.8)	-1.4	0.555
Leukotriene modifiers	1202 (30.3)	7396 (24.9)	11.9	<0.001	1119 (29.7)	1178 (31.3)	-3.4	0.139
ICS	632 (15.9)	4680 (15.8)	0.4	0.834	599 (15.9)	582 (15.5)	1.2	0.586
LAMA	53 (1.3)	276 (0.9)	3.8	0.015	50 (1.3)	48 (1.3)	0.5	0.837
Count of LAMA dispensings, mean ± SD [median]	0.04±0.47 [0]	0.02±0.37 [0]	3.6	0.015	0.04±0.48 [0]	0.03±0.38 [0]	2.6	0.349
LAMA use on index date	22 (0.6)	177 (0.6)	-0.6	0.740	22 (0.6)	13 (0.3)	3.5	0.128
LABA	36 (0.9)	170 (0.6)	3.9	0.012	31 (0.8)	25 (0.7)	1.9	0.423
Methylxanthines	19 (0.5)	124 (0.4)	0.9	0.584	18 (0.5)	18 (0.5)	0.0	1.000
LAMA/LABA	10 (0.3)	8 (0.0)	6.0	<0.001	7 (0.2)	1 (0.0)	4.9	0.034
Biologics (Anti-IgE and IL-5)	3 (0.1)	43 (0.1)	-2.1	0.266	3 (0.1)	1 (0.0)	2.3	0.317
Mast cell stabilizers	3 (0.1)	17 (0.1)	0.7	0.659	3 (0.1)	3 (0.1)	0.0	1.000

Characteristics ^a	Pre-matched cohorts (FF/VI vs B/F)				Post-matched cohorts (FF/VI vs B/F)			
	FF/VI N=3973	B/F N=29 661	Std Diff (%)	p-value	FF/VI N=3764	B/F N=3764	Std Diff (%)	p-value
Rescue medications, n (%)								
Any use	3579 (90.1)	25 457 (85.8)	13.1	<0.001	3385 (89.9)	3336 (88.6)	4.2	0.064
OCS	2050 (51.6)	14 329 (48.3)	6.6	<0.001	1942 (51.6)	1968 (52.3)	-1.4	0.548
Antibiotic	2838 (71.4)	19 963 (67.3)	9.0	<0.001	2687 (71.4)	2654 (70.5)	1.9	0.401
SABA use	2617 (65.9)	17 970 (60.6)	11.0	<0.001	2464 (65.5)	2426 (64.5)	2.1	0.355
Number of canisters per patient, mean ± SD [median] ^f	2.1±3.4 [1]	1.9±3.2 [1]	6.1	<0.001	2.1±3.4 [1]	2.0±3.3 [1]	2.4	0.233
>6 canisters	329 (8.3)	2113 (7.1)	4.3	0.008	312 (8.3)	293 (7.8)	1.9	0.417
SABA use on index date	618 (15.6)	8808 (29.7)	-34.3	<0.001	614 (16.3)	616 (16.4)	-0.1	0.947
SAMA use	34 (0.9)	287 (1.0)	-1.2	0.496	33 (0.9)	31 (0.8)	0.6	0.803
Number of canisters per patient, mean ± SD [median] ^f	0.9±22.5 [0]	0.7±13.8 [0]	1.4	0.499	1.0±23.1 [0]	0.6±13.0 [0]	1.9	0.748
SAMA/SABA use	171 (4.3)	958 (3.2)	5.6	<0.001	159 (4.2)	174 (4.6)	-1.9	0.402
Number of canisters per patient, mean ± SD [median] ^f	0.1±0.7 [0]	0.1±0.7 [0]	2.5	<0.001	0.1±0.6 [0]	0.1±0.7 [0]	-0.3	0.976

^aCovariates shaded in grey were used in PSM. ^bExact matching was conducted on this variable. ^cEvaluated during the baseline period. ^dEvaluated during the baseline period and on the index date. ^eOverall asthma exacerbation was defined as having a moderate or severe exacerbation. Moderate exacerbations were defined as an asthma-related ED visit or physician office visit or urgent care visit with a SCS/OCS prescription administration within ±5 days. Severe asthma exacerbation was defined as an asthma-related hospitalization or asthma-related ED visit resulting in hospitalization within 1 day. Patients with two or more exacerbations within 14 days of each other were considered as having one exacerbation, which was classified according to the highest severity of the contributing events. ^fOne canister of SABA, SAMA, or SABA/SAMA medication was defined as the quantity of the dispensing divided by the package quantity and further divided by 100 if units were in mg.

ADHD, attention deficit hyperactivity disorder; AHRQ, Agency for Healthcare Research and Quality; AMR, asthma medication ratio; B/F, budesonide/formoterol; CDHC, consumer directed health care; ED, emergency department; FF/VI, fluticasone furoate/vilanterol; HMO, health maintenance

organization; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL-5, interleukin-5; IP, inpatient; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; N/A, not available; OCS, oral corticosteroid; OP, outpatient; POS, point of service; PPO, preferred provider organization; PSM, propensity score matching; SABA, short-acting β_2 -agonist; SAMA, short-acting muscarinic antagonist; SCS, systemic corticosteroid; SD, standard deviation; Std Diff, standardized difference

Supplementary Table S3 Baseline demographics, healthcare resource utilization, healthcare costs, clinical characteristics, and respiratory medication use in the pre- and post-matched FF/VI vs FP/SAL cohorts

Characteristics ^a	Pre-matched cohorts (FF/VI vs FP/SAL)				Post-matched cohorts (FF/VI vs FP/SAL)			
	FF/VI N=3973	FP/SAL N=26 745	Std Diff (%)	p-value	FF/VI N=3339	FP/SAL N=3339	Std Diff (%)	p-value
Age, years, mean ± SD [median]	46.5±13.5 [48]	45.5±14.0 [47]	7.6	<0.001	46.4±13.6 [48]	46.4±13.7 [48]	-0.1	0.916
Age, years, n (%)								
18–29	558 (14.0)	4435 (16.6)	-7.1	<0.001	479 (14.3)	489 (14.6)	-0.9	0.725
30–39	598 (15.1)	4344 (16.2)	-3.3	0.057	514 (15.4)	510 (15.3)	0.3	0.893
40–49	964 (24.3)	6342 (23.7)	1.3	0.447	805 (24.1)	776 (23.2)	2.0	0.406
50–59	1155 (29.1)	6954 (26.0)	6.9	<0.001	949 (28.4)	972 (29.1)	-1.5	0.532
60–64	478 (12.0)	3045 (11.4)	2.0	0.233	406 (12.2)	409 (12.2)	-0.3	0.911
65+	220 (5.5)	1625 (6.1)	-2.3	0.183	186 (5.6)	183 (5.5)	0.4	0.872
Female, n (%)	2467 (62.1)	17 033 (63.7)	-3.3	0.052	2091 (62.6)	2105 (63.0)	-0.9	0.721
Region, n (%)								
Midwest	894 (22.5)	8331 (31.1)	-19.6	<0.001	814 (24.4)	847 (25.4)	-2.3	0.331
South	2142 (53.9)	9336 (34.9)	39.0	<0.001	1667 (49.9)	1630 (48.8)	2.2	0.324
West	356 (9.0)	3622 (13.5)	-14.5	<0.001	339 (10.2)	352 (10.5)	-1.3	0.593
Northeast	570 (14.3)	4953 (18.5)	-11.3	<0.001	508 (15.2)	499 (14.9)	0.8	0.757
Unknown	11 (0.3)	501 (1.9)	-15.5	<0.001	11 (0.3)	11 (0.3)	0.0	1.000
Insurance product type, n (%)								
PPO	3567 (89.8)	21 829 (81.6)	23.5	<0.001	2966 (88.8)	3007 (90.1)	-4.0	0.100
HMO	216 (5.4)	2727 (10.2)	-17.8	<0.001	199 (6.0)	162 (4.9)	4.9	0.044
Indemnity/Traditional	50 (1.3)	507 (1.9)	-5.1	0.005	43 (1.3)	42 (1.3)	0.3	0.913
POS	118 (3.0)	1405 (5.3)	-11.5	<0.001	109 (3.3)	106 (3.2)	0.5	0.835
CDHC	4 (0.1)	99 (0.4)	-5.6	0.006	4 (0.1)	7 (0.2)	-2.2	0.366
Unknown	18 (0.5)	178 (0.7)	-2.8	0.117	18 (0.5)	15 (0.4)	1.3	0.602
Physician specialty at index date, n (%)								
Primary care	1852 (46.6)	14 650 (54.8)	-16.4	<0.001	1726 (51.7)	1739 (52.1)	-0.8	0.715
Respiratory specialist ^b	1059 (26.7)	2357 (8.8)	48.0	<0.001	598 (17.9)	598 (17.9)	0.0	N/A
Year/quarter of index date, n (%)								
2014	274 (6.9)	13 029 (48.7)	-105.5	<0.001	271 (8.1)	276 (8.3)	-0.5	0.746

Characteristics ^a	Pre-matched cohorts (FF/VI vs FP/SAL)				Post-matched cohorts (FF/VI vs FP/SAL)			
	FF/VI N=3973	FP/SAL N=26 745	Std Diff (%)	p-value	FF/VI N=3339	FP/SAL N=3339	Std Diff (%)	p-value
Q1	33 (0.8)	3787 (14.2)	-52.3	<0.001	33 (1.0)	20 (0.6)	4.4	0.053
Q2	63 (1.6)	3301 (12.3)	-43.2	<0.001	62 (1.9)	61 (1.8)	0.2	0.920
Q3	73 (1.8)	2699 (10.1)	-35.4	<0.001	73 (2.2)	68 (2.0)	1.0	0.647
Q4	105 (2.6)	3242 (12.1)	-36.9	<0.001	103 (3.1)	127 (3.8)	-3.9	0.080
2015	2013 (50.7)	10 088 (37.7)	26.3	<0.001	1755 (52.6)	1747 (52.3)	0.5	0.829
Q1	224 (5.6)	3144 (11.8)	-21.8	<0.001	220 (6.6)	225 (6.7)	-0.6	0.788
Q2	399 (10.0)	2715 (10.2)	-0.4	0.832	372 (11.1)	357 (10.7)	1.4	0.539
Q3	621 (15.6)	2042 (7.6)	25.1	<0.001	520 (15.6)	518 (15.5)	0.2	0.946
Q4	769 (19.4)	2187 (8.2)	32.9	<0.001	643 (19.3)	647 (19.4)	-0.3	0.898
2016	1686 (42.4)	3628 (13.6)	67.9	<0.001	1313 (39.3)	1316 (39.4)	-0.2	0.930
Q1	851 (21.4)	2049 (7.7)	39.8	<0.001	666 (19.9)	690 (20.7)	-1.8	0.453
Q2	835 (21.0)	1579 (5.9)	45.4	<0.001	647 (19.4)	626 (18.7)	1.6	0.486
Asthma-related baseline healthcare resource utilization^c								
Number of patients with at least one IP visit, n (%)	39 (1.0)	436 (1.6)	-5.7	0.002	37 (1.1)	34 (1.0)	0.9	0.718
IP visits, mean ± SD [median]	0.01±0.11 [0]	0.02±0.14 [0]	-5.5	0.002	0.01±0.11 [0]	0.01±0.10 [0]	1.1	0.652
Number of patients with at least one ED visit, n (%)	186 (4.7)	1514 (5.7)	-4.4	0.012	163 (4.9)	196 (5.9)	-4.4	0.075
ED visits, mean ± SD [median]	0.1±0.3 [0]	0.1±0.4 [0]	-4.0	0.011	0.1±0.3 [0]	0.1±0.3 [0]	-1.4	0.292
Number of patients with at least one OP visit, n (%)	2483 (62.5)	11 939 (44.6)	36.4	<0.001	1960 (58.7)	1968 (58.9)	-0.5	0.838
OP visits, mean ± SD [median]	1.3±4.6 [1]	0.8±1.8 [0]	15.1	<0.001	1.2±2.2 [1]	1.1±2.3 [1]	1.4	0.228
Number of patients with at least one OP-related event	795 (20.0)	8249 (30.8)	-25.1	<0.001	714 (21.4)	731 (21.9)	-1.2	0.601
Asthma-related baseline healthcare cost, US\$ 2016, mean ± SD^c								
Total healthcare cost	940±4510	827±4588	2.5	<0.001	895±4621	1024±6252	-2.4	0.956
Medical costs	368±2784	264±1761	4.5	<0.001	349±2819	347±2323	0.1	0.315
IP visit costs	45±652	81±1088	-4.1	0.002	49±690	55±883	-0.8	0.720
ED visit costs	26±176	33±230	-3.6	0.006	27±182	35±244	-3.5	0.202

Characteristics ^a	Pre-matched cohorts (FF/VI vs FP/SAL)				Post-matched cohorts (FF/VI vs FP/SAL)			
	FF/VI N=3973	FP/SAL N=26 745	Std Diff (%)	p-value	FF/VI N=3339	FP/SAL N=3339	Std Diff (%)	p-value
OP visit costs	297±2680	149±1311	7.0	<0.001	272±2707	257±2122	0.6	0.264
Pharmacy costs	572±3113	563±4219	0.2	<0.001	546±3168	677±5789	-2.8	0.903
Total costs paid by patients								
Medical costs	229 ± 2060	173±1870	2.8	<0.001	233±2157	182±1645	2.7	0.622
Pharmacy costs	250±340	224±904	3.7	<0.001	240±330	250±462	-2.6	0.975
Index medication cost ^b	45±51	41±45	8.1	0.007	45±51	43±42	3.5	0.389
All-cause baseline healthcare cost, US\$ 2016, mean ± SD^c								
Total healthcare cost	9200±22,712	8719±22 157	2.1	<0.001	9155±23 443	10 275±28 826	-4.3	0.048
Medical costs	6968±20 275	6863±19 920	0.5	0.006	6978±21 205	8032±24 863	-4.6	0.020
IP visit costs	1662±11 311	2031±12 472	-3.1	0.001	1741±11 909	2398±16 371	-4.6	0.095
ED visit costs	273±840	287±999	-1.5	0.084	279±872	346±1293	-6.0	0.040
OP visit costs	5033±14 926	4545±12 774	3.5	<0.001	4958±15 509	5288±13 326	-2.3	0.009
Pharmacy costs	2232±6917	1857±6314	5.7	<0.001	2177±6841	2243±8009	-0.9	0.329
Total costs paid by patients								
Medical costs	3305±11 824	2567±9208	7.0	<0.001	3176±11 867	3082±10 760	0.8	0.031
Pharmacy costs	367±499	315±478	10.5	<0.001	360±501	357±537	0.5	0.477
All-cause baseline healthcare resource utilization^c								
Number of patients with at least one IP visit, n (%)	275 (6.9)	2274 (8.5)	-5.9	<0.001	234 (7.0)	270 (8.1)	-4.1	0.092
IP visits, mean ± SD [median]	0.08±0.33 [0]	0.10±0.41 [0]	-6.1	<0.001	0.08±0.33 [0]	0.11±0.48 [0]	-5.8	0.080
Number of patients with at least one ED visit, n (%)	1207 (30.4)	8348 (31.2)	-1.8	0.290	1005 (30.1)	1101 (33.0)	-6.2	0.011
ED visits, mean ± SD [median]	0.5±1.1 [0]	0.6±1.4 [0]	-4.9	0.130	0.5±1.1 [0]	0.6±1.3 [0]	-6.7	0.004
Number of patients with at least one OP visit, n (%)	3951 (99.4)	26 088 (97.5)	15.7	<0.001	3319 (99.4)	3303 (98.9)	5.3	0.024
OP visits, mean ± SD [median]	16.2±16.4 [11]	14.7±16.2 [10]	8.8	<0.001	15.6±15.8 [11]	16.3±18.6 [11]	-4.1	0.232
Comorbidities								
Quan-Charlson comorbidity index, mean ± SD [median]^d	1.52±1.21 [1]	1.46±1.11 [1]	5.0	0.018	1.52±1.22 [1]	1.53±1.22 [1]	-1.2	0.572
1-2	3461 (87.1)	23 777 (88.9)	-5.5	<0.001	2917 (87.4)	2917 (87.4)	0.0	1.000

Characteristics ^a	Pre-matched cohorts (FF/VI vs FP/SAL)				Post-matched cohorts (FF/VI vs FP/SAL)			
	FF/VI N=3973	FP/SAL N=26 745	Std Diff (%)	p-value	FF/VI N=3339	FP/SAL N=3339	Std Diff (%)	p-value
Count of unique medication use during baseline, mean ± SD [median]	6.8±6.3 [5]	5.2±5.5 [4]	27.5	<0.001	6.5±6.1 [5]	6.6±6.2 [5]	-0.5	0.909
Count of unique medication use on the index date, mean ± SD [median]	1.4±0.7 [1]	1.8±0.9 [2]	-48.9	<0.001	1.5±0.8 [1]	1.5±0.7 [1]	-1.0	0.592
Controller medications, n (%)								
Any use	1614 (40.6)	7426 (27.8)	27.4	<0.001	1263 (37.8)	1285 (38.5)	-1.4	0.578
Leukotriene modifiers	1202 (30.3)	5365 (20.1)	23.7	<0.001	928 (27.8)	952 (28.5)	-1.6	0.510
ICS	632 (15.9)	2845 (10.6)	15.6	<0.001	489 (14.6)	498 (14.9)	-0.8	0.758
LAMA	53 (1.3)	102 (0.4)	10.3	<0.001	31 (0.9)	25 (0.7)	2.0	0.414
Count of LAMA dispensings, mean ± SD [median]	0.04±0.47 [0]	0.01±0.22 [0]	8.1	<0.001	0.04±0.48 [0]	0.01±0.24 [0]	5.3	0.062
LAMA use on index date	22 (0.6)	79 (0.3)	4.0	0.008	17 (0.5)	10 (0.3)	3.3	0.178
LABA	36 (0.9)	71 (0.3)	8.4	<0.001	23 (0.7)	21 (0.6)	0.7	0.763
Methylxanthines	19 (0.5)	77 (0.3)	3.1	0.045	13 (0.4)	16 (0.5)	-1.4	0.577
LAMA/LABA	10 (0.3)	5 (0.0)	6.3	<0.001	5 (0.1)	1 (0.0)	4.0	0.102
Biologics (Anti-IgE and IL-5)	3 (0.1)	17 (0.1)	0.5	0.783	2 (0.1)	4 (0.1)	-2.0	0.414
Mast cell stabilizers	3 (0.1)	4 (0.0)	2.8	0.018	2 (0.1)	0 (0.0)	3.5	0.510
Rescue medications, n (%)								
Any use	3579 (90.1)	21 975 (82.2)	23.1	<0.001	2985 (89.4)	2932 (87.8)	5.0	0.041
OCS	2050 (51.6)	11 211 (41.9)	19.5	<0.001	1666 (49.9)	1686 (50.5)	-1.2	0.625
Antibiotic	2838 (71.4)	16 849 (63.0)	18.0	<0.001	2346 (70.3)	2289 (68.6)	3.7	0.122
SABA use	2617 (65.9)	15 228 (56.9)	18.4	<0.001	2169 (65.0)	2153 (64.5)	1.0	0.677
Number of canisters per patient, mean ± SD [median] ^f	2.1±3.4 [1]	1.8±3.2 [1]	9.1	<0.001	2.1±3.4 [1]	2.1±3.4 [1]	-0.3	0.913
>6 canisters	329 (8.3)	1839 (6.9)	5.3	0.001	279 (8.4)	296 (8.9)	-1.8	0.461
SABA use on index date	618 (15.6)	9346 (34.9)	-45.8	<0.001	584 (17.5)	569 (17.0)	1.2	0.604
SAMA use	34 (0.9)	182 (0.7)	2.0	0.217	27 (0.8)	29 (0.9)	-0.7	0.789
Number of canisters per patient, mean ± SD [median] ^f	0.9±22.5 [0]	0.3±11.1 [0]	3.3	0.214	0.9±23.7 [0]	0.5±6.9 [0]	2.4	0.732

Characteristics ^a	Pre-matched cohorts (FF/VI vs FP/SAL)				Post-matched cohorts (FF/VI vs FP/SAL)			
	FF/VI N=3973	FP/SAL N=26 745	Std Diff (%)	p-value	FF/VI N=3339	FP/SAL N=3339	Std Diff (%)	p-value
SAMA/SABA use	171 (4.3)	664 (2.5)	10.1	<0.001	125 (3.7)	128 (3.8)	-0.5	0.844
Number of canisters per patient, mean ± SD [median] ^f	0.1±0.7 [0]	0.1±0.7 [0]	4.2	<0.001	0.1±0.6 [0]	0.1±0.7 [0]	0.5	0.550

^aCovariates shaded in grey were used in PSM. ^bExact matching was conducted on this variable. ^cEvaluated during the baseline period. ^dEvaluated during the baseline period and on the index date. ^eOverall asthma exacerbation was defined as having a moderate or severe exacerbation. Moderate exacerbations were defined as an asthma-related ED visit or physician office visit or urgent care visit with a SCS/OCS prescription administration within ±5 days. Severe asthma exacerbation was defined as an asthma-related hospitalization or asthma-related ED visit resulting in hospitalization within 1 day. Patients with two or more exacerbations within 14 days of each other were considered as having one exacerbation, which was classified according to the highest severity of the contributing events. ^fOne canister of SABA, SAMA, or SABA/SAMA medication was defined as the quantity of the dispensing divided by the package quantity and further divided by 100 if units were in mg.

ADHD, attention deficit hyperactivity disorder; AHRQ, Agency for Healthcare Research and Quality; AMR, asthma medication ratio; CDHC, consumer directed health care; ED, emergency department; FF/VI, fluticasone furoate/vilanterol; FP/SAL, fluticasone propionate/salmeterol; HMO, health maintenance organization; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL-5, interleukin-5; IP, inpatient; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; N/A, not available; OCS, oral corticosteroid; OP, outpatient; POS, point of service; PPO, preferred provider organization; SABA, short-acting β_2 -agonist; SAMA, short-acting muscarinic antagonist; SCS, systemic corticosteroid; SD, standard deviation; Std Diff, standardized difference

Supplementary Table S4 Sensitivity analysis of adherence in a subgroup of patients with 12 months of follow-up

Outcomes	FF/VI (N=1082)	B/F (N=1117)	Adjusted difference ^a (95% CI)	Adjusted OR ^a (95% CI)	Adjusted HR ^a (95% CI)	<i>p</i> -value
PDC at 12 months, mean (SD)	0.400 (0.309)	0.276 (0.234)	0.12 (0.10–0.15)	-	-	<0.001
PDC≥0.5, n (%)	356 (32.9)	168 (15.0)	-	2.75 (2.24–3.39)	-	<0.001
PDC≥0.8, n (%)	199 (18.4)	64 (5.7)	-	3.67 (2.73–4.94)	-	<0.001
Risk of treatment discontinuation ^c	-	-	-	-	0.72 (0.62–0.85)	<0.001
Outcomes	FF/VI (N=996)	FP/SAL (N=995)	Adjusted difference ^b (95% CI)	Adjusted OR ^b (95% CI)	Adjusted HR ^b (95% CI)	<i>p</i> -value
PDC at 12 months, mean (SD)	0.396 (0.310)	0.284 (0.242)	0.11 (0.09–0.13)	-	-	<0.001
PDC≥0.5, n (%)	322 (32.3)	160 (16.1)	-	2.47 (1.99–3.06)	-	<0.001
PDC≥0.8, n (%)	182 (18.3)	57 (5.7)	-	3.69 (2.70–5.04)	-	<0.001
Risk of treatment discontinuation ^c	-	-	-	-	0.76 (0.64–0.90)	<0.001

Generalized linear, logistic regression, and Cox proportional hazard models were used for mean PDC, PDC by cut-off and risk of discontinuation, respectively. ^aIn the FF/VI versus B/F analysis, models were adjusted for the following covariates: log all-cause pharmacy costs, other lower respiratory diseases, and baseline rescue medication use (yes/no). ^bIn the FF/VI versus FP/SAL analysis, models were adjusted for the following covariates: substance-related disorders and overall asthma exacerbations on index date. ^cTreatment discontinuation was defined as a gap in therapy of >45 days from the run-out date of the ICS/LABA pharmacy fill and the next fill, or between the end of the days of supply of the last dispensing and the end of follow-up, whichever occurred first.

B/F, budesonide/formoterol; CI, confidence interval; FF/VI, fluticasone furoate/vilanterol; FP/SAL, fluticasone propionate/salmeterol; HR, hazard ratio; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; OR, odds ratio; PDC, proportion of days covered; SD, standard deviation

Supplementary Table S5 Sensitivity analysis of adherence using IPTW

	FF/VI (N=3973)	B/F (N=29 661)	Std Diff (%)	Adjusted difference^a (95% CI)	Adjusted OR^a (95% CI)	Adjusted HR^a (95% CI)	p-value
Weighted observation period, days, mean (SD)	293.9 (92.4)	296.1 (90.8)	-2.4	-	-	-	-
PDC, mean (SD)	0.377 (0.301)	0.304 (0.243)	-	0.07 (0.07–0.08)	-	-	<0.001
PDC≥0.5, n (%)	1240 (31.2)	5731 (19.3)	-	-	1.91 (1.78–2.06)	-	<0.001
PDC≥0.8, n (%)	639 (16.1)	1955 (6.6)	-	-	2.75 (2.50–3.03)	-	<0.001
Risk of treatment discontinuation ^c	-	-	-	-	-	0.76 (0.73–0.79)	<0.001
	FF/VI (N=3973)	FP/SAL (N=26 745)	Std Diff (%)	Adjusted difference^b (95% CI)	Adjusted OR^b (95% CI)	Adjusted HR^b (95% CI)	p-value
Observation period, days, mean (SD)	298.3 (90.8)	298.8 (90.1)	-0.6	-	-	-	-
PDC, mean (SD)	0.356 (0.294)	0.295 (0.242)	-	0.06 (0.05–0.07)	-	-	<0.001
PDC≥0.5, n (%)	1124 (28.3)	4883 (18.3)	-	-	1.78 (1.65–1.92)	-	<0.001
PDC≥0.8, n (%)	579 (14.6)	1749 (6.5)	-	-	2.47 (2.23–2.73)	-	<0.001
Risk of treatment discontinuation ^c	-	-	-	-	-	0.82 (0.79–0.85)	<0.001

Generalized linear, logistic regression, and Cox proportional hazards models were used for mean PDC, PDC by cut-off and risk of discontinuation, respectively. ^aIn the FF/VI versus B/F analysis, models were adjusted for the following covariates: insurance product type, number of asthma-related outpatient visits, log of asthma-related medical costs, log of asthma-related outpatient costs, and log of index medication costs paid by patient. ^bIn the FF/VI versus FP/SAL analysis, models were adjusted for the following covariates: region, insurance product type, asthma-related outpatient exacerbation event

on the index date (yes/no), and any baseline rescue medication use (yes/no). ^cTreatment discontinuation was defined as a gap in therapy of >45 days from the run-out date of the ICS/LABA pharmacy fill and the next fill, or between the end of the days of supply of the last dispensing and the end of follow-up, whichever occurred first.

B/F, budesonide/formoterol; CI, confidence interval; FF/VI, fluticasone furoate/vilanterol; FP/SAL, fluticasone propionate/salmeterol; HR, hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; OR, odds ratio; PDC, proportion of days covered; SD, standard deviation; Std diff, standardized difference

Supplementary Table S1 Diagnosis codes used to identify specific conditions

Condition	ICD-9-CM codes	ICD-10-CM codes
Asthma	493.xx	J45.3, J45.4, J45.5, J45.9
COPD	491.x, 492.x, 496.x	J41–J44
Cystic fibrosis	277.0	E84.0–E84.9
Acute respiratory failure	518.81	J96.0, J96.2

COPD, chronic obstructive pulmonary disease; ICD-9-CM, International Classification of Disease, 9th Edition, Clinical Modification; ICD-10-CM, International Classification of Disease, 10th Edition, Clinical Modification

Supplementary Table S2 Baseline demographics, healthcare resource utilization, healthcare costs, clinical characteristics, and respiratory medication use [in the pre- and post-matched](#) FF/VI versus B/F [cohorts](#)

Characteristics ^a	Pre-matched cohorts (FF/VI vs B/F)				Post-matched cohorts (FF/VI vs B/F)			
	FF/VI N=3973	B/F N=29 661	Std Diff (%)	p-value	FF/VI N=3764	B/F N=3764	Std Diff (%)	p-value
Age, years, mean ± SD [median]	46.5±13.5 [48]	46.1±13.4 [48]	3.5	0.039	46.6±13.4 [48]	46.7±13.3 [48]	-1.0	0.686
Age, years, n (%)								
18–29	558 (14.0)	4196 (14.1)	-0.3	0.863	521 (13.8)	508 (13.5)	1.0	0.666
30–39	598 (15.1)	4915 (16.6)	-4.2	0.015	574 (15.2)	573 (15.2)	0.1	0.974
40–49	964 (24.3)	7273 (24.5)	-0.6	0.724	917 (24.4)	932 (24.8)	-0.9	0.690
50–59	1155 (29.1)	8152 (27.5)	3.5	0.036	1089 (28.9)	1076 (28.6)	0.8	0.744
60–64	478 (12.0)	3537 (11.9)	0.3	0.846	456 (12.1)	468 (12.4)	-1.0	0.674
65+	220 (5.5)	1588 (5.4)	0.8	0.630	207 (5.5)	207 (5.5)	0.0	1.000
Female, n (%)	2467 (62.1)	19 035 (64.2)	-4.3	0.010	2346 (62.3)	2340 (62.2)	0.3	0.887
Region, n (%)								
Midwest	894 (22.5)	6963 (23.5)	-2.3	0.173	862 (22.9)	884 (23.5)	-1.4	0.543
South	2142 (53.9)	10 229 (34.5)	39.9	<0.001	1969 (52.3)	2017 (53.6)	-2.6	0.225
West	356 (9.0)	3382 (11.4)	-8.1	<0.001	352 (9.4)	361 (9.6)	-0.8	0.721
Northeast	570 (14.3)	8275 (27.9)	-33.7	<0.001	570 (15.1)	499 (13.3)	5.4	0.014
Unknown	11 (0.3)	812 (2.7)	-20.3	<0.001	11 (0.3)	3 (0.1)	4.9	0.033
Insurance product type, n (%)								
PPO	3567 (89.8)	23 998 (80.9)	25.3	<0.001	3367 (89.5)	3402 (90.4)	-3.1	0.174
HMO	216 (5.4)	3838 (12.9)	-26.2	<0.001	214 (5.7)	177 (4.7)	4.4	0.048
Indemnity/Traditional	50 (1.3)	432 (1.5)	-1.7	0.324	49 (1.3)	56 (1.5)	-1.6	0.486
POS	118 (3.0)	1068 (3.6)	-3.5	0.043	112 (3.0)	110 (2.9)	0.3	0.892
CDHC	4 (0.1)	84 (0.3)	-4.2	0.034	4 (0.1)	4 (0.1)	0.0	1.000
Unknown	18 (0.5)	241 (0.8)	-4.5	0.015	18 (0.5)	15 (0.4)	1.2	0.602
Physician specialty at index date, n (%)								
Primary care	1852 (46.6)	13 592 (45.8)	1.6	0.348	1789 (47.5)	1814 (48.2)	-1.3	0.480
Respiratory specialist ^b	1059 (26.7)	4776 (16.1)	26.0	<0.001	921 (24.5)	921 (24.5)	0.0	N/A

Characteristics ^a	Pre-matched cohorts (FF/VI vs B/F)				Post-matched cohorts (FF/VI vs B/F)			
	FF/VI N=3973	B/F N=29 661	Std Diff (%)	p-value	FF/VI N=3764	B/F N=3764	Std Diff (%)	p-value
Year/quarter of index date, n (%)								
2014	274 (6.9)	12 795 (43.1)	-92.1	<0.001	274 (7.3)	286 (7.6)	-1.2	0.427
Q1	33 (0.8)	3362 (11.3)	-45.0	<0.001	33 (0.9)	30 (0.8)	0.9	0.680
Q2	63 (1.6)	3273 (11.0)	-39.6	<0.001	63 (1.7)	67 (1.8)	-0.8	0.703
Q3	73 (1.8)	2772 (9.3)	-33.1	<0.001	73 (1.9)	80 (2.1)	-1.3	0.531
Q4	105 (2.6)	3388 (11.4)	-34.9	<0.001	105 (2.8)	109 (2.9)	-0.6	0.768
2015	2013 (50.7)	12 008 (40.5)	20.6	<0.001	1943 (51.6)	1948 (51.8)	-0.3	0.900
Q1	224 (5.6)	3556 (12.0)	-22.5	<0.001	224 (6.0)	261 (6.9)	-4.0	0.058
Q2	399 (10.0)	3409 (11.5)	-4.7	0.007	398 (10.6)	395 (10.5)	0.3	0.904
Q3	621 (15.6)	2404 (8.1)	23.4	<0.001	594 (15.8)	579 (15.4)	1.1	0.626
Q4	769 (19.4)	2639 (8.9)	30.4	<0.001	727 (19.3)	713 (18.9)	0.9	0.667
2016	1686 (42.4)	4858 (16.4)	59.7	<0.001	1547 (41.1)	1530 (40.6)	0.9	0.651
Q1	851 (21.4)	2676 (9.0)	35.0	<0.001	796 (21.1)	815 (21.7)	-1.2	0.576
Q2	835 (21.0)	2182 (7.4)	39.9	<0.001	751 (20.0)	715 (19.0)	2.4	0.258
Asthma-related baseline healthcare resource utilization^c								
Number of patients with at least one IP visit, n (%)	39 (1.0)	464 (1.6)	-5.2	0.004	38 (1.0)	30 (0.8)	2.2	0.332
IP visits, mean ± SD [median]	0.01±0.11 [0]	0.02±0.13 [0]	-5.0	0.004	0.01±0.11 [0]	0.01±0.09 [0]	2.7	0.247
Number of patients with at least one ED visit, n (%)	186 (4.7)	1791 (6.0)	-6.0	<0.001	180 (4.8)	187 (5.0)	-0.9	0.706
ED visits, mean ± SD [median]	0.1±0.3 [0]	0.1±0.4 [0]	-4.8	<0.001	0.1±0.3 [0]	0.1±0.3 [0]	0.1	0.814
Number of patients with at least one OP visit, n (%)	2483 (62.5)	15 804 (53.3)	18.7	<0.001	2307 (61.3)	2323 (61.7)	-0.9	0.698
OP visits, mean ± SD [median]	1.3±4.6 [1]	1.1±2.2 [1]	5.7	<0.001	1.3±2.3 [1]	1.2±2.1 [1]	0.8	0.709
Number of patients with at least one OP-related event	795 (20.0)	9747 (32.9)	-29.5	<0.001	787 (20.9)	774 (20.6)	0.9	0.693
Asthma-related baseline healthcare cost, US\$ 2016, mean ± SD^c								
Total healthcare cost	940±4510	978±4662	-0.8	0.002	940±4603	953±5207	-0.3	0.595
Medical costs	368±2784	348 ± 2150	0.8	<0.001	366 ± 2834	281 ± 1549	3.7	0.729

Characteristics ^a	Pre-matched cohorts (FF/VI vs B/F)				Post-matched cohorts (FF/VI vs B/F)			
	FF/VI N=3973	B/F N=29 661	Std Diff (%)	p-value	FF/VI N=3764	B/F N=3764	Std Diff (%)	p-value
IP visit costs	45±652	82 ± 1080	-4.2	0.002	45 ± 657	29 ± 435	2.9	0.312
ED visit costs	26±176	37 ± 288	-4.5	<0.001	27 ± 180	27 ± 281	0.0	0.638
OP visit costs	297±2680	229 ± 1755	3.0	<0.001	294 ± 2730	225 ± 1432	3.2	0.915
Pharmacy costs	572±3113	630 ± 4081	-1.6	0.103	574 ± 3184	672 ± 4969	-2.3	0.536
Total costs paid by patients								
Medical costs	229±2060	223±2467	0.3	<0.001	224±2042	192±1508	1.7	0.322
Pharmacy costs	250±340	238±451	2.9	<0.001	248 ± 338	265±614	-3.4	0.443
Index medication cost ^b	45±51	36±38	20.3	<0.001	44±51	43±44	2.9	0.057
All-cause baseline healthcare cost, US\$ 2016, mean ± SD^c								
Total healthcare cost	9200±22 712	9097±32 768	0.4	0.928	9291±23 189	11 179±71 780	-3.5	0.105
Medical costs	6968±20 275	7053±30 787	-0.3	0.324	7049±20 719	8689±69 272	-3.2	0.033
IP visit costs	1662±11 311	1788±13 877	-1.0	0.043	1704±11 563	2404±27 661	-3.3	0.173
ED visit costs	273±840	293±1067	-2.1	0.138	280±856	282±920	-0.3	0.839
OP visit costs	5033±14 926	4971±20 509	0.3	0.964	5066±15 243	6004±43 595	-2.9	0.024
Pharmacy costs	2232±6917	2043±7619	2.6	<0.001	2243±6980	2489±11 404	-2.6	0.739
Total costs paid by patients								
Medical costs	3305±11 824	2752±10 168	5.0	<0.001	3311±11 762	3462±10 937	-1.3	0.005
Pharmacy costs	367±499	331±480	7.2	<0.001	365±500	378±562	-2.6	0.405
All-cause baseline healthcare resource utilization^c								
Number of patients with at least one IP visit, n (%)	275 (6.9)	2,346 (7.9)	-3.8	0.029	263 (7.0)	299 (7.9)	-3.6	0.114
IP visits, mean ± SD [median]	0.08±0.33 [0]	0.10±0.38 [0]	-4.3	0.032	0.08±0.33 [0]	0.10±0.38 [0]	-3.7	0.169
Number of patients with at least one ED visit, n (%)	1207 (30.4)	9157 (30.9)	-1.1	0.528	1155 (30.7)	1155 (30.7)	0.0	1.000
ED visits, mean ± SD [median]	0.5±1.1 [0]	0.6±1.3 [0]	-2.8	0.345	0.5±1.1 [0]	0.5±1.1 [0]	-1.1	0.373
Number of patients with at least one OP visit, n (%)	3951 (99.4)	29 159 (98.3)	10.8	<0.001	3743 (99.4)	3730 (99.1)	4.1	0.080
OP visits, mean ± SD [median]	16.2±16.4 [11]	15.8±16.8 [11]	2.3	<0.001	16.0±16.0 [11]	16.9±17.3	-5.2	0.023

Characteristics ^a	Pre-matched cohorts (FF/VI vs B/F)				Post-matched cohorts (FF/VI vs B/F)			
	FF/VI N=3973	B/F N=29 661	Std Diff (%)	p-value	FF/VI N=3764	B/F N=3764	Std Diff (%)	p-value
						[12]		
Comorbidities								
Quan-Charlson comorbidity index, mean ± SD [median]^d	1.52±1.21 [1]	1.50±1.18 [1]	1.3	0.698	1.52±1.21 [1]	1.51±1.18 [1]	0.7	0.773
1–2	3461 (87.1)	26 062 (87.9)	-2.3	0.173	3283 (87.2)	3305 (87.8)	-1.8	0.450
3–4	369 (9.3)	2598 (8.8)	1.8	0.270	346 (9.2)	326 (8.7)	1.9	0.423
5+	143 (3.6)	1001 (3.4)	1.2	0.464	135 (3.6)	133 (3.5)	0.3	0.902
AHRQ comorbidities, n (%)^d								
Other lower respiratory disease	2311 (58.2)	15 623 (52.7)	11.1	<0.001	2164 (57.5)	2141 (56.9)	1.2	0.584
Dyslipidemia	1308 (32.9)	9353 (31.5)	3.0	0.077	1230 (32.7)	1261 (33.5)	-1.8	0.448
Diabetes mellitus, without complications	712 (17.9)	5132 (17.3)	1.6	0.334	673 (17.9)	667 (17.7)	0.4	0.857
Substance-related disorders	144 (3.6)	784 (2.6)	5.6	<0.001	136 (3.6)	125 (3.3)	1.6	0.489
Developmental disorder and ADHD	142 (3.6)	1039 (3.5)	0.4	0.819	133 (3.5)	133 (3.5)	0.0	1.000
Asthma exacerbations^e								
Baseline period^c								
Overall exacerbations								
Total count, n, mean ± SD [median]	0.23±0.54 [0]	0.25±0.58 [0]	-3.1	0.205	0.24±0.55 [0]	0.24±0.55 [0]	0.1	0.907
≥ 1 exacerbation, n (%)	755 (19.0)	5867 (19.8)	-2.0	0.247	731 (19.4)	734 (19.5)	-0.2	0.931
Moderate exacerbations								
Total count, n, mean ± SD [median]	0.22±0.53 [0]	0.23±0.56 [0]	-2.2	0.413	0.23±0.54 [0]	0.23±0.54 [0]	-0.3	0.905
≥ 1 exacerbation, n (%)	715 (18.0)	5403 (18.2)	-0.6	0.736	693 (18.4)	704 (18.7)	-0.8	0.744
Severe exacerbations								
Total count, n, mean ± SD [median]	0.01±0.11 [0]	0.02±0.13 [0]	-4.4	0.007	0.01±0.11 [0]	0.01±0.09 [0]	2.7	0.247
≥ 1 exacerbation, n (%)	40 (1.0)	464 (1.6)	-5.0	0.007	38 (1.0)	30 (0.8)	2.2	0.332
Exacerbation on the index date, n (%)								

Characteristics ^a	Pre-matched cohorts (FF/VI vs B/F)				Post-matched cohorts (FF/VI vs B/F)			
	FF/VI N=3973	B/F N=29 661	Std Diff (%)	p-value	FF/VI N=3764	B/F N=3764	Std Diff (%)	p-value
Overall exacerbations	170 (4.3)	3282 (11.1)	-25.7	<0.001	168 (4.5)	184 (4.9)	-2.0	0.373
Moderate exacerbations	165 (4.2)	3174 (10.7)	-25.2	<0.001	164 (4.4)	176 (4.7)	-1.5	0.496
Severe exacerbations	5 (0.1)	108 (0.4)	-4.8	0.015	4 (0.1)	8 (0.2)	-2.7	0.248
Asthma-related ED exacerbation event	2 (0.1)	94 (0.3)	-6.2	0.003	2 (0.1)	3 (0.1)	-1.0	0.655
Asthma-related IP exacerbation event	5 (0.1)	108 (0.4)	-4.8	0.015	4 (0.1)	8 (0.2)	-2.7	0.248
Asthma-related OP exacerbation event	163 (4.1)	3080 (10.4)	-24.4	<0.001	162 (4.3)	173 (4.6)	-1.4	0.529
Baseline medication use^c								
AMR, mean ± SD [median]^d	0.33±0.38 [0]	0.30±0.37 [0]	9.3	<0.001	0.33±0.38 [0]	0.35±0.39 [0]	-5.7	0.189
Baseline respiratory medication, mean ± SD [median]								
Count of unique medication use during baseline	6.8±6.3 [5]	6.1±6.1 [4]	11.8	<0.001	6.8±6.2 [5]	6.9±6.3 [5]	-1.2	0.711
Count of unique medication use on the index date	1.4±0.7 [1]	1.8±0.9 [2]	-44.7	<0.001	1.4±0.8 [1]	1.4±0.7 [1]	-1.4	0.452
Controller medications, n (%)								
Any use	1614 (40.6)	10 579 (35.7)	10.2	<0.001	1510 (40.1)	1535 (40.8)	-1.4	0.555
Leukotriene modifiers	1202 (30.3)	7396 (24.9)	11.9	<0.001	1119 (29.7)	1178 (31.3)	-3.4	0.139
ICS	632 (15.9)	4680 (15.8)	0.4	0.834	599 (15.9)	582 (15.5)	1.2	0.586
LAMA	53 (1.3)	276 (0.9)	3.8	0.015	50 (1.3)	48 (1.3)	0.5	0.837
Count of LAMA dispensings, mean ± SD [median]	0.04±0.47 [0]	0.02±0.37 [0]	3.6	0.015	0.04±0.48 [0]	0.03±0.38 [0]	2.6	0.349
LAMA use on index date	22 (0.6)	177 (0.6)	-0.6	0.740	22 (0.6)	13 (0.3)	3.5	0.128
LABA	36 (0.9)	170 (0.6)	3.9	0.012	31 (0.8)	25 (0.7)	1.9	0.423
Methylxanthines	19 (0.5)	124 (0.4)	0.9	0.584	18 (0.5)	18 (0.5)	0.0	1.000
LAMA/LABA	10 (0.3)	8 (0.0)	6.0	<0.001	7 (0.2)	1 (0.0)	4.9	0.034
Biologics (Anti-IgE and IL-5)	3 (0.1)	43 (0.1)	-2.1	0.266	3 (0.1)	1 (0.0)	2.3	0.317
Mast cell stabilizers	3 (0.1)	17 (0.1)	0.7	0.659	3 (0.1)	3 (0.1)	0.0	1.000

Characteristics ^a	Pre-matched cohorts (FF/VI vs B/F)				Post-matched cohorts (FF/VI vs B/F)			
	FF/VI N=3973	B/F N=29 661	Std Diff (%)	p-value	FF/VI N=3764	B/F N=3764	Std Diff (%)	p-value
Rescue medications, n (%)								
Any use	3579 (90.1)	25 457 (85.8)	13.1	<0.001	3385 (89.9)	3336 (88.6)	4.2	0.064
OCS	2050 (51.6)	14 329 (48.3)	6.6	<0.001	1942 (51.6)	1968 (52.3)	-1.4	0.548
Antibiotic	2838 (71.4)	19 963 (67.3)	9.0	<0.001	2687 (71.4)	2654 (70.5)	1.9	0.401
SABA use	2617 (65.9)	17 970 (60.6)	11.0	<0.001	2464 (65.5)	2426 (64.5)	2.1	0.355
Number of canisters per patient, mean ± SD [median] ^f	2.1±3.4 [1]	1.9±3.2 [1]	6.1	<0.001	2.1±3.4 [1]	2.0±3.3 [1]	2.4	0.233
>6 canisters	329 (8.3)	2113 (7.1)	4.3	0.008	312 (8.3)	293 (7.8)	1.9	0.417
SABA use on index date	618 (15.6)	8808 (29.7)	-34.3	<0.001	614 (16.3)	616 (16.4)	-0.1	0.947
SAMA use	34 (0.9)	287 (1.0)	-1.2	0.496	33 (0.9)	31 (0.8)	0.6	0.803
Number of canisters per patient, mean ± SD [median] ^f	0.9±22.5 [0]	0.7±13.8 [0]	1.4	0.499	1.0±23.1 [0]	0.6±13.0 [0]	1.9	0.748
SAMA/SABA use	171 (4.3)	958 (3.2)	5.6	<0.001	159 (4.2)	174 (4.6)	-1.9	0.402
Number of canisters per patient, mean ± SD [median] ^f	0.1±0.7 [0]	0.1±0.7 [0]	2.5	<0.001	0.1±0.6 [0]	0.1±0.7 [0]	-0.3	0.976

^aCovariates shaded in grey were used in PSM. ^bExact matching was conducted on this variable. ^cEvaluated during the baseline period. ^dEvaluated during the baseline period and on the index date. ^eOverall asthma exacerbation was defined as having a moderate or severe exacerbation. Moderate exacerbations were defined as an asthma-related ED visit or physician office visit or urgent care visit with a SCS/OCS prescription administration within ±5 days. Severe asthma exacerbation was defined as an asthma-related hospitalization or asthma-related ED visit resulting in hospitalization within 1 day. Patients with two or more exacerbations within 14 days of each other were considered as having one exacerbation, which was classified according to the highest severity of the contributing events. ^fOne canister of SABA, SAMA, or SABA/SAMA medication was defined as the quantity of the dispensing divided by the package quantity and further divided by 100 if units were in mg.

ADHD, attention deficit hyperactivity disorder; AHRQ, Agency for Healthcare Research and Quality; AMR, asthma medication ratio; B/F, budesonide/formoterol; CDHC, consumer directed health care; ED, emergency department; FF/VI, fluticasone furoate/vilanterol; HMO, health maintenance

organization; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL-5, interleukin-5; IP, inpatient; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic antagonist; N/A, not available; OCS, oral corticosteroid; OP, outpatient; POS, point of service; PPO, preferred provider organization; PSM, propensity score matching; SABA, short-acting β_2 -agonist; SAMA, short-acting muscarinic antagonist; SCS, systemic corticosteroid; SD, standard deviation; Std Diff, standardized difference

Supplementary Table S3 Baseline demographics, healthcare resource utilization, healthcare costs, clinical characteristics, and respiratory medication use [in the pre- and post-matched](#) FF/VI vs FP/SAL [cohorts](#)

Characteristics ^a	Pre-matched cohorts (FF/VI vs FP/SAL)				Post-matched cohorts (FF/VI vs FP/SAL)			
	FF/VI N=3973	FP/SAL N=26 745	Std Diff (%)	p-value	FF/VI N=3339	FP/SAL N=3339	Std Diff (%)	p-value
Age, years, mean ± SD [median]	46.5±13.5 [48]	45.5±14.0 [47]	7.6	<0.001	46.4±13.6 [48]	46.4±13.7 [48]	-0.1	0.916
Age, years, n (%)								
18–29	558 (14.0)	4435 (16.6)	-7.1	<0.001	479 (14.3)	489 (14.6)	-0.9	0.725
30–39	598 (15.1)	4344 (16.2)	-3.3	0.057	514 (15.4)	510 (15.3)	0.3	0.893
40–49	964 (24.3)	6342 (23.7)	1.3	0.447	805 (24.1)	776 (23.2)	2.0	0.406
50–59	1155 (29.1)	6954 (26.0)	6.9	<0.001	949 (28.4)	972 (29.1)	-1.5	0.532
60–64	478 (12.0)	3045 (11.4)	2.0	0.233	406 (12.2)	409 (12.2)	-0.3	0.911
65+	220 (5.5)	1625 (6.1)	-2.3	0.183	186 (5.6)	183 (5.5)	0.4	0.872
Female, n (%)	2467 (62.1)	17 033 (63.7)	-3.3	0.052	2091 (62.6)	2105 (63.0)	-0.9	0.721
Region, n (%)								
Midwest	894 (22.5)	8331 (31.1)	-19.6	<0.001	814 (24.4)	847 (25.4)	-2.3	0.331
South	2142 (53.9)	9336 (34.9)	39.0	<0.001	1667 (49.9)	1630 (48.8)	2.2	0.324
West	356 (9.0)	3622 (13.5)	-14.5	<0.001	339 (10.2)	352 (10.5)	-1.3	0.593
Northeast	570 (14.3)	4953 (18.5)	-11.3	<0.001	508 (15.2)	499 (14.9)	0.8	0.757
Unknown	11 (0.3)	501 (1.9)	-15.5	<0.001	11 (0.3)	11 (0.3)	0.0	1.000
Insurance product type, n (%)								
PPO	3567 (89.8)	21 829 (81.6)	23.5	<0.001	2966 (88.8)	3007 (90.1)	-4.0	0.100
HMO	216 (5.4)	2727 (10.2)	-17.8	<0.001	199 (6.0)	162 (4.9)	4.9	0.044
Indemnity/Traditional	50 (1.3)	507 (1.9)	-5.1	0.005	43 (1.3)	42 (1.3)	0.3	0.913
POS	118 (3.0)	1405 (5.3)	-11.5	<0.001	109 (3.3)	106 (3.2)	0.5	0.835
CDHC	4 (0.1)	99 (0.4)	-5.6	0.006	4 (0.1)	7 (0.2)	-2.2	0.366
Unknown	18 (0.5)	178 (0.7)	-2.8	0.117	18 (0.5)	15 (0.4)	1.3	0.602
Physician specialty at index date, n (%)								
Primary care	1852 (46.6)	14 650 (54.8)	-16.4	<0.001	1726 (51.7)	1739 (52.1)	-0.8	0.715
Respiratory specialist ^b	1059 (26.7)	2357 (8.8)	48.0	<0.001	598 (17.9)	598 (17.9)	0.0	N/A
Year/quarter of index date, n (%)								
2014	274 (6.9)	13 029 (48.7)	-105.5	<0.001	271 (8.1)	276 (8.3)	-0.5	0.746

Characteristics ^a	Pre-matched cohorts (FF/VI vs FP/SAL)				Post-matched cohorts (FF/VI vs FP/SAL)			
	FF/VI N=3973	FP/SAL N=26 745	Std Diff (%)	p-value	FF/VI N=3339	FP/SAL N=3339	Std Diff (%)	p-value
Q1	33 (0.8)	3787 (14.2)	-52.3	<0.001	33 (1.0)	20 (0.6)	4.4	0.053
Q2	63 (1.6)	3301 (12.3)	-43.2	<0.001	62 (1.9)	61 (1.8)	0.2	0.920
Q3	73 (1.8)	2699 (10.1)	-35.4	<0.001	73 (2.2)	68 (2.0)	1.0	0.647
Q4	105 (2.6)	3242 (12.1)	-36.9	<0.001	103 (3.1)	127 (3.8)	-3.9	0.080
2015	2013 (50.7)	10 088 (37.7)	26.3	<0.001	1755 (52.6)	1747 (52.3)	0.5	0.829
Q1	224 (5.6)	3144 (11.8)	-21.8	<0.001	220 (6.6)	225 (6.7)	-0.6	0.788
Q2	399 (10.0)	2715 (10.2)	-0.4	0.832	372 (11.1)	357 (10.7)	1.4	0.539
Q3	621 (15.6)	2042 (7.6)	25.1	<0.001	520 (15.6)	518 (15.5)	0.2	0.946
Q4	769 (19.4)	2187 (8.2)	32.9	<0.001	643 (19.3)	647 (19.4)	-0.3	0.898
2016	1686 (42.4)	3628 (13.6)	67.9	<0.001	1313 (39.3)	1316 (39.4)	-0.2	0.930
Q1	851 (21.4)	2049 (7.7)	39.8	<0.001	666 (19.9)	690 (20.7)	-1.8	0.453
Q2	835 (21.0)	1579 (5.9)	45.4	<0.001	647 (19.4)	626 (18.7)	1.6	0.486
Asthma-related baseline healthcare resource utilization^c								
Number of patients with at least one IP visit, n (%)	39 (1.0)	436 (1.6)	-5.7	0.002	37 (1.1)	34 (1.0)	0.9	0.718
IP visits, mean ± SD [median]	0.01±0.11 [0]	0.02±0.14 [0]	-5.5	0.002	0.01±0.11 [0]	0.01±0.10 [0]	1.1	0.652
Number of patients with at least one ED visit, n (%)	186 (4.7)	1514 (5.7)	-4.4	0.012	163 (4.9)	196 (5.9)	-4.4	0.075
ED visits, mean ± SD [median]	0.1±0.3 [0]	0.1±0.4 [0]	-4.0	0.011	0.1±0.3 [0]	0.1±0.3 [0]	-1.4	0.292
Number of patients with at least one OP visit, n (%)	2483 (62.5)	11 939 (44.6)	36.4	<0.001	1960 (58.7)	1968 (58.9)	-0.5	0.838
OP visits, mean ± SD [median]	1.3±4.6 [1]	0.8±1.8 [0]	15.1	<0.001	1.2±2.2 [1]	1.1±2.3 [1]	1.4	0.228
Number of patients with at least one OP-related event	795 (20.0)	8249 (30.8)	-25.1	<0.001	714 (21.4)	731 (21.9)	-1.2	0.601
Asthma-related baseline healthcare cost, US\$ 2016, mean ± SD^c								
Total healthcare cost	940±4510	827±4588	2.5	<0.001	895±4621	1024±6252	-2.4	0.956
Medical costs	368±2784	264±1761	4.5	<0.001	349±2819	347±2323	0.1	0.315
IP visit costs	45±652	81±1088	-4.1	0.002	49±690	55±883	-0.8	0.720
ED visit costs	26±176	33±230	-3.6	0.006	27±182	35±244	-3.5	0.202

Characteristics ^a	Pre-matched cohorts (FF/VI vs FP/SAL)				Post-matched cohorts (FF/VI vs FP/SAL)			
	FF/VI N=3973	FP/SAL N=26 745	Std Diff (%)	p-value	FF/VI N=3339	FP/SAL N=3339	Std Diff (%)	p-value
OP visit costs	297±2680	149±1311	7.0	<0.001	272±2707	257±2122	0.6	0.264
Pharmacy costs	572±3113	563±4219	0.2	<0.001	546±3168	677±5789	-2.8	0.903
Total costs paid by patients								
Medical costs	229 ± 2060	173±1870	2.8	<0.001	233±2157	182±1645	2.7	0.622
Pharmacy costs	250±340	224±904	3.7	<0.001	240±330	250±462	-2.6	0.975
Index medication cost ^b	45±51	41±45	8.1	0.007	45±51	43±42	3.5	0.389
All-cause baseline healthcare cost, US\$ 2016, mean ± SD^c								
Total healthcare cost	9200±22,712	8719±22 157	2.1	<0.001	9155±23 443	10 275±28 826	-4.3	0.048
Medical costs	6968±20 275	6863±19 920	0.5	0.006	6978±21 205	8032±24 863	-4.6	0.020
IP visit costs	1662±11 311	2031±12 472	-3.1	0.001	1741±11 909	2398±16 371	-4.6	0.095
ED visit costs	273±840	287±999	-1.5	0.084	279±872	346±1293	-6.0	0.040
OP visit costs	5033±14 926	4545±12 774	3.5	<0.001	4958±15 509	5288±13 326	-2.3	0.009
Pharmacy costs	2232±6917	1857±6314	5.7	<0.001	2177±6841	2243±8009	-0.9	0.329
Total costs paid by patients								
Medical costs	3305±11 824	2567±9208	7.0	<0.001	3176±11 867	3082±10 760	0.8	0.031
Pharmacy costs	367±499	315±478	10.5	<0.001	360±501	357±537	0.5	0.477
All-cause baseline healthcare resource utilization^c								
Number of patients with at least one IP visit, n (%)	275 (6.9)	2274 (8.5)	-5.9	<0.001	234 (7.0)	270 (8.1)	-4.1	0.092
IP visits, mean ± SD [median]	0.08±0.33 [0]	0.10±0.41 [0]	-6.1	<0.001	0.08±0.33 [0]	0.11±0.48 [0]	-5.8	0.080
Number of patients with at least one ED visit, n (%)	1207 (30.4)	8348 (31.2)	-1.8	0.290	1005 (30.1)	1101 (33.0)	-6.2	0.011
ED visits, mean ± SD [median]	0.5±1.1 [0]	0.6±1.4 [0]	-4.9	0.130	0.5±1.1 [0]	0.6±1.3 [0]	-6.7	0.004
Number of patients with at least one OP visit, n (%)	3951 (99.4)	26 088 (97.5)	15.7	<0.001	3319 (99.4)	3303 (98.9)	5.3	0.024
OP visits, mean ± SD [median]	16.2±16.4 [11]	14.7±16.2 [10]	8.8	<0.001	15.6±15.8 [11]	16.3±18.6 [11]	-4.1	0.232
Comorbidities								
Quan-Charlson comorbidity index, mean ± SD [median]^d	1.52±1.21 [1]	1.46±1.11 [1]	5.0	0.018	1.52±1.22 [1]	1.53±1.22 [1]	-1.2	0.572
1-2	3461 (87.1)	23 777 (88.9)	-5.5	<0.001	2917 (87.4)	2917 (87.4)	0.0	1.000

Characteristics ^a	Pre-matched cohorts (FF/VI vs FP/SAL)				Post-matched cohorts (FF/VI vs FP/SAL)			
	FF/VI N=3973	FP/SAL N=26 745	Std Diff (%)	p-value	FF/VI N=3339	FP/SAL N=3339	Std Diff (%)	p-value
Count of unique medication use during baseline, mean ± SD [median]	6.8±6.3 [5]	5.2±5.5 [4]	27.5	<0.001	6.5±6.1 [5]	6.6±6.2 [5]	-0.5	0.909
Count of unique medication use on the index date, mean ± SD [median]	1.4±0.7 [1]	1.8±0.9 [2]	-48.9	<0.001	1.5±0.8 [1]	1.5±0.7 [1]	-1.0	0.592
Controller medications, n (%)								
Any use	1614 (40.6)	7426 (27.8)	27.4	<0.001	1263 (37.8)	1285 (38.5)	-1.4	0.578
Leukotriene modifiers	1202 (30.3)	5365 (20.1)	23.7	<0.001	928 (27.8)	952 (28.5)	-1.6	0.510
ICS	632 (15.9)	2845 (10.6)	15.6	<0.001	489 (14.6)	498 (14.9)	-0.8	0.758
LAMA	53 (1.3)	102 (0.4)	10.3	<0.001	31 (0.9)	25 (0.7)	2.0	0.414
Count of LAMA dispensings, mean ± SD [median]	0.04±0.47 [0]	0.01±0.22 [0]	8.1	<0.001	0.04±0.48 [0]	0.01±0.24 [0]	5.3	0.062
LAMA use on index date	22 (0.6)	79 (0.3)	4.0	0.008	17 (0.5)	10 (0.3)	3.3	0.178
LABA	36 (0.9)	71 (0.3)	8.4	<0.001	23 (0.7)	21 (0.6)	0.7	0.763
Methylxanthines	19 (0.5)	77 (0.3)	3.1	0.045	13 (0.4)	16 (0.5)	-1.4	0.577
LAMA/LABA	10 (0.3)	5 (0.0)	6.3	<0.001	5 (0.1)	1 (0.0)	4.0	0.102
Biologics (Anti-IgE and IL-5)	3 (0.1)	17 (0.1)	0.5	0.783	2 (0.1)	4 (0.1)	-2.0	0.414
Mast cell stabilizers	3 (0.1)	4 (0.0)	2.8	0.018	2 (0.1)	0 (0.0)	3.5	0.510
Rescue medications, n (%)								
Any use	3579 (90.1)	21 975 (82.2)	23.1	<0.001	2985 (89.4)	2932 (87.8)	5.0	0.041
OCS	2050 (51.6)	11 211 (41.9)	19.5	<0.001	1666 (49.9)	1686 (50.5)	-1.2	0.625
Antibiotic	2838 (71.4)	16 849 (63.0)	18.0	<0.001	2346 (70.3)	2289 (68.6)	3.7	0.122
SABA use	2617 (65.9)	15 228 (56.9)	18.4	<0.001	2169 (65.0)	2153 (64.5)	1.0	0.677
Number of canisters per patient, mean ± SD [median] ^f	2.1±3.4 [1]	1.8±3.2 [1]	9.1	<0.001	2.1±3.4 [1]	2.1±3.4 [1]	-0.3	0.913
>6 canisters	329 (8.3)	1839 (6.9)	5.3	0.001	279 (8.4)	296 (8.9)	-1.8	0.461
SABA use on index date	618 (15.6)	9346 (34.9)	-45.8	<0.001	584 (17.5)	569 (17.0)	1.2	0.604
SAMA use	34 (0.9)	182 (0.7)	2.0	0.217	27 (0.8)	29 (0.9)	-0.7	0.789
Number of canisters per patient, mean ± SD [median] ^f	0.9±22.5 [0]	0.3±11.1 [0]	3.3	0.214	0.9±23.7 [0]	0.5±6.9 [0]	2.4	0.732

Characteristics ^a	Pre-matched cohorts (FF/VI vs FP/SAL)				Post-matched cohorts (FF/VI vs FP/SAL)			
	FF/VI N=3973	FP/SAL N=26 745	Std Diff (%)	p-value	FF/VI N=3339	FP/SAL N=3339	Std Diff (%)	p-value
SAMA/SABA use	171 (4.3)	664 (2.5)	10.1	<0.001	125 (3.7)	128 (3.8)	-0.5	0.844
Number of canisters per patient, mean ± SD [median] ^f	0.1±0.7 [0]	0.1±0.7 [0]	4.2	<0.001	0.1±0.6 [0]	0.1±0.7 [0]	0.5	0.550

^aCovariates shaded in grey were used in PSM. ^bExact matching was conducted on this variable. ^cEvaluated during the baseline period. ^dEvaluated during the baseline period and on the index date. ^eOverall asthma exacerbation was defined as having a moderate or severe exacerbation. Moderate exacerbations were defined as an asthma-related ED visit or physician office visit or urgent care visit with a SCS/OCS prescription administration within ±5 days. Severe asthma exacerbation was defined as an asthma-related hospitalization or asthma-related ED visit resulting in hospitalization within 1 day. Patients with two or more exacerbations within 14 days of each other were considered as having one exacerbation, which was classified according to the highest severity of the contributing events. ^fOne canister of SABA, SAMA, or SABA/SAMA medication was defined as the quantity of the dispensing divided by the package quantity and further divided by 100 if units were in mg.

ADHD, attention deficit hyperactivity disorder; AHRQ, Agency for Healthcare Research and Quality; AMR, asthma medication ratio; CDHC, consumer directed health care; ED, emergency department; FF/VI, fluticasone furoate/vilanterol; FP/SAL, fluticasone propionate/salmeterol; HMO, health maintenance organization; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL-5, interleukin-5; IP, inpatient; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic antagonist; N/A, not available; OCS, oral corticosteroid; OP, outpatient; POS, point of service; PPO, preferred provider organization; SABA, short-acting β₂-agonist; SAMA, short-acting muscarinic antagonist; SCS, systemic corticosteroid; SD, standard deviation; Std Diff, standardized difference

Supplementary Table S4 Sensitivity analysis of adherence in a subgroup of patients with 12 months of follow-up

Outcomes	FF/VI (N=1082)	B/F (N=1117)	Adjusted difference ^a (95% CI)	Adjusted OR ^a (95% CI)	Adjusted HR ^a (95% CI)	<i>p</i> -value
PDC at 12 months, mean (SD)	0.400 (0.309)	0.276 (0.234)	0.12 (0.10–0.15)	-	-	<0.001
PDC≥0.5, n (%)	356 (32.9)	168 (15.0)	-	2.75 (2.24–3.39)	-	<0.001
PDC≥0.8, n (%)	199 (18.4)	64 (5.7)	-	3.67 (2.73–4.94)	-	<0.001
Risk of treatment discontinuation ^c	-	-	-	-	0.72 (0.62–0.85)	<0.001
Outcomes	FF/VI (N=996)	FP/SAL (N=995)	Adjusted difference ^b (95% CI)	Adjusted OR ^b (95% CI)	Adjusted HR ^b (95% CI)	<i>p</i> -value
PDC at 12 months, mean (SD)	0.396 (0.310)	0.284 (0.242)	0.11 (0.09–0.13)	-	-	<0.001
PDC≥0.5, n (%)	322 (32.3)	160 (16.1)	-	2.47 (1.99–3.06)	-	<0.001
PDC≥0.8, n (%)	182 (18.3)	57 (5.7)	-	3.69 (2.70–5.04)	-	<0.001
Risk of treatment discontinuation ^c	-	-	-	-	0.76 (0.64–0.90)	<0.001

Generalized linear, logistic regression, and Cox proportional hazard models were used for mean PDC, PDC by cut-off and risk of discontinuation, respectively. ^aIn the FF/VI versus B/F analysis, models were adjusted for the following covariates: log all-cause pharmacy costs, other lower respiratory diseases, and baseline rescue medication use (yes/no). ^bIn the FF/VI versus FP/SAL analysis, models were adjusted for the following covariates: substance-related disorders and overall asthma exacerbations on index date. ^cTreatment discontinuation was defined as a gap in therapy of >45 days from the run-out date of the ICS/LABA pharmacy fill and the next fill, or between the end of the days of supply of the last dispensing and the end of follow-up, whichever occurred first.

B/F, budesonide/formoterol; CI, confidence interval; FF/VI, fluticasone furoate/vilanterol; FP/SAL, fluticasone propionate/salmeterol; HR, hazard ratio; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; OR, odds ratio; PDC, proportion of days covered; SD, standard deviation

Supplementary Table S5 Sensitivity analysis of adherence using IPTW

	FF/VI (N=3973)	B/F (N=29 661)	Std Diff (%)	Adjusted difference^a (95% CI)	Adjusted OR^a (95% CI)	Adjusted HR^a (95% CI)	p-value
Weighted observation period, days, mean (SD)	293.9 (92.4)	296.1 (90.8)	-2.4	-	-	-	-
PDC, mean (SD)	0.377 (0.301)	0.304 (0.243)	-	0.07 (0.07–0.08)	-	-	<0.001
PDC≥0.5, n (%)	1240 (31.2)	5731 (19.3)	-	-	1.91 (1.78–2.06)	-	<0.001
PDC≥0.8, n (%)	639 (16.1)	1955 (6.6)	-	-	2.75 (2.50–3.03)	-	<0.001
Risk of treatment discontinuation ^c	-	-	-	-	-	0.76 (0.73–0.79)	<0.001
	FF/VI (N=3973)	FP/SAL (N=26 745)	Std Diff (%)	Adjusted difference^b (95% CI)	Adjusted OR^b (95% CI)	Adjusted HR^b (95% CI)	p-value
Observation period, days, mean (SD)	298.3 (90.8)	298.8 (90.1)	-0.6	-	-	-	-
PDC, mean (SD)	0.356 (0.294)	0.295 (0.242)	-	0.06 (0.05–0.07)	-	-	<0.001
PDC≥0.5, n (%)	1124 (28.3)	4883 (18.3)	-	-	1.78 (1.65–1.92)	-	<0.001
PDC≥0.8, n (%)	579 (14.6)	1749 (6.5)	-	-	2.47 (2.23–2.73)	-	<0.001
Risk of treatment discontinuation ^c	-	-	-	-	-	0.82 (0.79–0.85)	<0.001

Generalized linear, logistic regression, and Cox proportional hazards models were used for mean PDC, PDC by cut-off and risk of discontinuation, respectively. ^aIn the FF/VI versus B/F analysis, models were adjusted for the following covariates: insurance product type, number of asthma-related outpatient visits, log of asthma-related medical costs, log of asthma-related outpatient costs, and log of index medication costs paid by patient. ^bIn the FF/VI versus FP/SAL analysis, models were adjusted for the following covariates: region, insurance product type, asthma-related outpatient exacerbation event

on the index date (yes/no), and any baseline rescue medication use (yes/no). ^cTreatment discontinuation was defined as a gap in therapy of >45 days from the run-out date of the ICS/LABA pharmacy fill and the next fill, or between the end of the days of supply of the last dispensing and the end of follow-up, whichever occurred first.

B/F, budesonide/formoterol; CI, confidence interval; FF/VI, fluticasone furoate/vilanterol; FP/SAL, fluticasone propionate/salmeterol; HR, hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; OR, odds ratio; PDC, proportion of days covered; SD, standard deviation; Std diff, standardized difference