Original Article

Comparative Effectiveness of Budesonide-Formoterol Combination and Fluticasone-Salmeterol Combination for Asthma Management: A United States Retrospective Database Analysis

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What is already known about this topic? Results of prior studies have suggested that patients with asthma who initiate budesonide-formoterol combination therapy may have a lower asthma exacerbation rate compared with those who initiate the fluticasone-salmeterol combination, a possible explanation for lower fills of additional asthma controller medication and lower short-acting β_2-adrenergic-agonist prescription claims.

What does this article add to our knowledge? This study adds a US perspective to the data of real-world comparative effectiveness for 2 of the most commonly used inhaled corticosteroid–long-acting β_2-adrenergic agonist medications (budesonide-formoterol combination therapy and fluticasone-salmeterol combination therapy) for the treatment of moderate-to-severe persistent asthma.

How does this study impact current management guidelines? Asthma management imposes heavy demands on available health care resources. This study provides patients, providers, and payers with real-world comparative effectiveness data on 2 of the commonly prescribed asthma therapies.

BACKGROUND: Comparative effectiveness of the budesonide–formoterol fumarate dihydrate combination (BFC) and the fluticasone propionate–salmeterol combination (FSC) therapy on asthma exacerbation has not been assessed in real-world settings in the United States.

OBJECTIVE: To compare exacerbation rates and health care utilization for patients with asthma who initiate BFC versus FSC therapy.

METHODS: This retrospective cohort comparative effectiveness study queried medical and pharmacy data for patients with asthma from a large managed care data repository that covers major US population centers. The patients were 12 to 64 years old, with ≥12 months of pre- and postindex enrollment and ≥1 pharmacy claim(s) for BFC or FSC initiated during June 1, 2007, and September 30, 2010; the first prescription fill date was defined as the index date. Patients with other respiratory diseases and/or cancer were excluded. Exacerbation was defined as asthma-related hospitalization, emergency department visit, and/or oral corticosteroid prescription fill. Cohorts were matched by using propensity scores.

RESULTS: A total of 3043 patients per cohort were matched and balanced. During the 12 months following the initiation the BFC cohort had lower adjusted exacerbations per person year versus the FSC cohort (0.85 vs 0.93; RR 0.92, 95% CI [0.85-0.99]), lower oral corticosteroid fill rates, and fewer asthma-related emergency department visits but comparable asthma-related hospitalization.

CONCLUSIONS: Asthma exacerbation was lower for BFC versus FSC initiators due to lower rates of oral corticosteroid use and asthma-related emergency department visits, which indicate better treatment effectiveness of those patients initiated with BFC compared with FSC. **(J Allergy Clin Immunol Pract 2014;2:719-26)**

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Abbreviations used
BFC- Budesonide–formoterol fumarate dihydrate combination
DCI- Deyo-Charlson index
ED- Emergency department
FSC- Fluticasone propionate–salmeterol combination
GERD- Gastroesophageal reflux disease
ICS- Inhaled corticosteroid
LABA- Long-acting β_2-adrenergic agonist
LTRA- Leukotriene receptor antagonist
OCS- Oral corticosteroid
OR- Odds ratio
PDC- Proportion of days covered
RR- Rate ratio
SABA- Short-acting β_2-adrenergic-agonist

Key words: *Asthma; Comparative effectiveness; Retrospective cohort study; Inhaled corticosteroids; Long-acting β_2-adrenergic agonist; short-acting β_2-adrenergic-agonists; Budesonide-formoterol combination; Fluticasone-salmeterol combination*

Asthma, a common respiratory condition that results from inflammation in both large and small airways,[1,2] directly impacts an estimated 24.6 million people in the United States.[3] Total health care costs directly attributable to asthma care in the United States were estimated at $37.2 billion (in 2007).[4] Medical Expenditure Panel Survey data for 2002 to 2007 showed that asthma imposed an incremental society-wide cost of $56 billion (adjusted to 2009 US$).[5] Treatment goals include achieving adequate control and reducing the risk of exacerbations and serious impairment.[6] Long-term controller medications, such as inhaled corticosteroids (ICS), are recommended by the current Expert Panel Report-3 for patients with persistent asthma.[7] For patients ages ≥12 years, the guidelines for the diagnosis and management of asthma indicate that the addition of a long-acting β_2-adrenergic agonist (LABA) be given equal weight to the option of increasing the ICS alone for patients inadequately controlled on ICS alone and for those patients with high levels of impairment and elevated risks of asthma exacerbation.[7] Currently, 3 ICS-LABA combination therapies are approved for use in the United States: budesonide–formoterol fumarate dihydrate (BFC),[8] fluticasone propionate–salmeterol combinations (FSC) therapy,[9] and mometasone–formoterol fumarate dihydrate.[10]

Clinical trials that assess BFC and FSC showed mixed results in the United States.[11] Lasserson et al[11] reviewed 5 randomized studies (5537 adults) in the Cochrane Airways Group register that compared fixed-dose FSC and BFC of adults and children diagnosed with asthma. Treatment durations were a minimum of 12 weeks; most of the studies assessed treatment for a 6-month period. Study populations had prior treatment with inhaled steroids (fluticasone/salmeterol or orbudesonide/formoterol) and had moderate or mild airway obstruction. Because of the imprecision of the estimated effects of asthma exacerbations, definitive conclusions about the superiority of either agent remain indeterminate.[11] With the growing recognition of the impact of asthma management on health care resources and costs, payers espouse the urgent need for real-world effectiveness data on asthma therapies beyond clinical efficacy and lung function.[12,13] In particular, data on the effect of controller therapies on avoidable asthma exacerbation and health care resource utilization are important.

Two population-based retrospective studies, in Canada[14] and in Germany,[13] evaluated comparative effectiveness of BFC versus FSC in asthma management. By using a matched cohort design, the Canadian study showed that, compared with patients on FSC, patients who received BFC were significantly less likely to require asthma-related emergency department (ED) visits or hospitalizations and oral corticosteroid (OCS) fills, and required less short-acting β_2-adrenergic-agonists (SABA) per week.[14] The German study demonstrated that patients with chronic asthma who initiated BFC therapy had a greater probability of treatment success with fewer severe asthma exacerbations and fewer OCS prescription fills.[13] However, the device (dry powder inhaler) and a commonly used indication (use for maintenance and reliever therapy) for BFC approved in these countries are not approved in the United States. To our knowledge, no studies to date have compared the 2 agents by using the US device (a pressurized metered dose inhaler) and with the US approved indication. The objective of the current study was to evaluate the real-world effectiveness of the ICS-LABA combination by comparing asthma exacerbation rates and health care resource utilization over a 1-year period after initiation of BFC and FSC with devices and indications approved in the United States.

METHODS

Data source and study design

This retrospective cohort study (NCT01623544) used integrated medical and pharmacy claims data to describe and compare differences in key outcomes among patients with asthma who initiated BFC versus FSC treatments between June 1, 2007, and September 30, 2010. The index date was defined as the date of the first pharmacy claim for either study medication. The patients were assigned to BFC or FSC cohorts based on their first prescription fill. Study data were acquired from the HealthCore Integrated Research Database (HealthCore Inc., Wilmington, Del), a diverse longitudinal administrative claims repository that contains data from commercial health plans in the northeast, midwest, south, and west regions of the United States. Researchers only had access to de-identified patient data, and patient anonymity and confidentiality were safeguarded in compliance with the Health Insurance Portability and Accountability Act. Institutional review board approval was not required for this observational study.

Study population

Patients were considered to have a claims-based asthma diagnosis if they had 1 inpatient visit with a primary diagnosis code for asthma or 1 ED visit with an asthma diagnosis or with 2 or more medical claims (any visit combination) with an asthma diagnosis in the 12 months before the index date. Generic Product Identifier Codes (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) were used to identify patients who received BFC or FSC combination therapy. International Classification of Diseases, Ninth Revision Clinical Modification codes (493.0x, 493.1x, or 493.9x) were used to identify asthma.

Inclusion criteria. Patients were required to be between 12 and 64 years of age on the index date and to have ≥1 BFC or FSC prescription fill during the intake period. A second fill for the same ICS-LABA combination in the 12 months after the index prescription (postindex period) was required for inclusion in the study. For inclusion, patients had to be naive (no

TABLE I. Asthma exacerbation rate during the 12-month postindex period

	Unadjusted rate*		Adjusted rate†				
	BFC (n = 3043)	FSC (n = 3043)	BFC (n = 3043)	FSC (n = 3043)	RR†	95% CI†	*P* value†
Asthma exacerbation rate	0.83	0.89	0.85	0.93	0.92	0.85-0.99	.0255
Sensitivity analysis							
Asthma exacerbation rate excluding the first 30 d after the index‡	0.75	0.79	0.70	0.75	0.93	0.86-1.02	.1189
Number of patients	N = 2785	N = 2785	N = 2785	N = 2785			
Asthma exacerbation rate, excluding patients with an index date between Jun 1, 2007, and Nov 30, 2007§	0.82	0.89	0.87	0.95	0.92	0.84-0.99	.0340

*The unadjusted exacerbation rate is the total number of exacerbations in the study population divided by total person years. Because all persons will contribute exactly 1 y, this rate is simply (no. exacerbations)/(no. patients).

†Adjusted exacerbation rates and the RR are from a negative binomial regression model. Statistical comparisons compared BFC with FSC (reference group), in which RR is rate (BFC)/rate (FSC). Model covariates include age at index (continuous), sex, health plan type, geographic region, index year, index physician specialty, DCI score, asthma-related inpatient hospitalization (yes-no during the preindex period), asthma-related ED visits (yes-no during the preindex period), OCS use (yes-no during the preindex period), and preindex comorbid conditions (allergic rhinitis, gastroesophageal reflux disease, major depressive disorder, obesity, sinusitis, sleep apnea [yes-no for each]).

‡Follow-up for asthma exacerbations started 30 d after the index date to ensure that the patients were allowed adequate exposure to the study medication before attributable outcomes were assessed. All the persons contributed 335 d (1 year minus 30 d, excluded from the start of the postindex period).

§The start of the intake period corresponds with the launch of BFC in the US market. All the patients on BFC with an index date during the first 6 mo of the intake period (Jun 1, 2007 to Nov 30, 2007) and their matches were excluded because of the possibility that patients on BFC during this time were characteristically different than the BFC population as a whole.

prescription claims) to ICS-LABA combination therapy during the preindex period.

Exclusion criteria. Patients diagnosed with chronic obstructive pulmonary disease, other respiratory diseases or inflammatory diseases, and any type of cancer (for International Classification of Diseases, Ninth Revision Clinical Modification codes, see Table E2 in this article's Online Repository at www.jaci-inpractice.org) were excluded. Patients with chronic steroid use (patients with 1 or more prescription fills that totaled a ≥60-day supply of continuous OCS treatment) and patients with a claim for Xolair (omalizumab) during the preindex period also were excluded. Patients with prescription claims for more than 1 type of ICS-LABA combination on the index date or with prescription claims for an ICS-LABA combination therapy that was different from the index therapy during the 12-month postindex period (ie, "switchers") also were excluded.

Outcome measurements

Asthma exacerbation rates. The primary outcome was the rate of asthma exacerbation. An asthma exacerbation was defined as an inpatient hospitalization with a primary diagnosis of asthma, an ED visit with a diagnosis of asthma, or a pharmacy claim for OCS medications. The rate of asthma exacerbation was defined as the total number of asthma exacerbations during the postindex period for all patients in the cohort divided by the total follow-up time in person years.

Health care resource utilization. All-cause and asthma-related health care resource utilization during the 12-month postindex period was compared for patients who initiated BFC and FSC. Inpatient visits, ED visits, outpatient and/or office visits, and all procedures and prescriptions were included in the calculations.

Proportion of days covered. The proportion of days covered with the index medication was calculated for each individual as the total days' supply prescribed during the postindex period, including the index fill, divided by the total follow-up time (365 days).

Statistical analysis

Statistical analysis was performed for each postindex outcome between the propensity-score matched BFC and FSC cohorts. Propensity matching details are provided in Supplement E1 (in this article's Online Repository at www.jaci-inpractice.org). A negative binomial model with a logarithmic link function was used to assess asthma exacerbation rates during the 12-month postindex period. Asthma-related health care utilization was analyzed by using generalized linear models from the negative binomial distribution, with a logarithmic link function. Dichotomous outcomes were analyzed by using logistic regression to obtain odds ratios (OR), and Poisson regression was used to obtain risk ratios. All adjusted models controlled for patient demographics, asthma-related resource use, and comorbid conditions. A full list of covariates is provided in the footnotes to Tables I to III. All statistical analyses were performed by using SAS version 9.2 (SAS Institute Inc, Cary, NC), with a statistical significance level of .05.

Sensitivity analyses

Because prescribing information indicates that it could take 1 to 2 weeks before the maximum benefits of BFC and FSC are observed with patients,[8,10] a sensitivity analysis was conducted by using a second follow-up period, which started 31 days after the index date and continued until the end of the remaining 365 days, as shown in the Supplement E2 (in this article's Online Repository at www.jaci-inpractice.org).

RESULTS

Patient disposition

A total of 508,000 patients had at least 1 prescription for ICS-LABA combination treatment during the intake period.

TABLE II. Components of asthma exacerbation during the 12-month postindex period

	BFC (n = 3043)	FSC (n = 3043)	Adjusted means*		Effect estimate†	95% CI†	*P* value
			BFC	FSC			
Asthma exacerbations ≥1							
No. (%)	1292 (42.5)	1341 (44.1)					
Risk ratio					0.96	0.90-1.02	.2196
OR					0.93	0.84-01.04	.1917
Asthma exacerbations ≥2							
No. (%)	607 (19.9)	639 (21.0)					
Risk ratio					0.95	0.87-1.03	.1959
OR					0.93	0.81-1.05	.2434
Asthma exacerbations, no. exacerbations (mean ± SD)	0.83 ± 1.4	0.89 ± 1.48	0.85	0.93	−0.08	−0.14 to −0.01	.0255
OCS fills ≥1							
No. (%)	1216 (40.0)	1274 (41.9)					
Risk ratio					0.95	0.89-1.02	.1329
OR					0.92	0.82-1.02	.1048
OCS fills ≥2							
No. (%)	560 (18.4)	589 (19.4)					
Risk ratio					0.94	0.86-1.03	.1986
OR					0.93	0.81-1.06	.2635
OCS fills (no.), mean ± SD	0.77 ± 1.36	0.82 ± 1.43	0.73	0.79	−0.07	−0.12 to −0.01	.0299
Asthma-related hospitalization ≥1‡							
No. (%)	45 (1.5)	46 (1.5)					
Risk ratio					0.97	0.85-1.11	.6362
Odds ratio					1.01	0.66-1.56	.9651
Asthma-related hospitalization ≥ 2‡							
No. (%)	5 (0.2)	8 (0.3)					
Asthma hospitalizations (no.), mean ± SD	0.02 ± 0.15	0.02 ± 0.16	0.01	0.01	0.00	0.00-0.00	.6390
LOS, mean ± SD§	5.91 ± 6.5	6.28 ± 5.6	5.4	5.4	0.04	−1.40 to 2.00	.9638
Asthma-related ED visits ≥1							
No. (%)	228 (7.5)	258 (8.5)					
Risk ratio					0.90	0.81-1.00	.0540
OR					0.88	0.73-1.07	.1910
Asthma-related ED visits ≥2							
No. (%)	39 (1.3)	64 (2.1)					
Risk ratio					0.63	0.55-0.72	<.0001
OR					0.61	0.40-0.92	.0180
Asthma-related ED visits (no.), mean ± SD	0.09 ± 0.37	0.12 ± 0.49	0.08	0.10	−0.02	−0.03 to 0.00	.0486
Other asthma-related utilization							
Asthma-related outpatient visits ≥1							
No. (%)	2462 (80.9)	2469 (81.1)					
Risk ratio					1.00	0.97-1.03	.9067
OR					0.99	0.87-1.12	.8400
Asthma-related outpatient visits ≥2							
No. (%)	1844 (60.6)	1855 (61.0)					
Risk ratio					0.99	0.95-1.04	.7854
OR					0.98	0.88-1.09	.7001
Asthma-related outpatient no. visits, mean ± SD	3.49 ± 5.7	3.52 ± 5.8	2.8	2.8	0.00	−0.15 to 0.16	.9666
ICS monotherapy fills ≥1							
No. (%)	277 (9.1)	311 (10.2)					
Risk ratio					0.87	0.79-0.97	.0145
OR					0.86	0.72-1.02	.0874
ICS monotherapy fills ≥2							
No. (%)	148 (4.9)	174 (5.7)					
Risk ratio					0.83	0.74-0.94	.0031
OR					0.82	0.66-1.03	.0932

(continued)

TABLE II. *(Continued)*

	BFC (n = 3043)	FSC (n = 3043)	Adjusted means* BFC	Adjusted means* FSC	Effect estimate†	95% CI†	*P* value
ICS monotherapy fills (no.) mean ± SD	0.23 ± 1.06	0.26 ± 1.07	0.28	0.36	-0.08	−0.13 to −0.01	.0325
SABA fills ≥1							
No. (%)	202 (66.4)	2166 (71.2)					
Risk ratio					0.94	0.90-0.98	.0027
OR					0.80	0.72-0.90	<.0001
SABA fills ≥2							
No. (%)	1328 (43.6)	1404 (46.1)					
Risk ratio					0.95	0.89-1.01	.1019
OR					0.91	0.82-1.00	.0568
SABA fills (no.), mean ± SD	2.09 ± 2.78	2.26 ± 2.89	2.4	2.6	−0.18	−0.32 to −0.03	.0221
PDC for index medication, mean ± SD	0.40 ± 0.23	0.43 ± 0.25	0.46	0.49	−0.03	−0.04 to −0.02	<.0001

LOS, Length of stay; *PDC*, proportion of days covered.

*Adjusted means are calculated from regression models by adjusting for all model covariates: age at index (continuous), sex, health plan type, geographic region, index year, index physician specialty, DCI score, asthma-related inpatient hospitalization (yes-no during the preindex period), asthma-related ED visits (yes-no during the preindex period), OCS use (yes-no during the preindex period), and preindex comorbid conditions (allergic rhinitis, gastroesophageal reflux disease, major depressive disorder, obesity, sinusitis, sleep apnea [yes-no for each]).

†The type of effect estimate depends on the outcome and statistical model: ORs for categorical variables are from logistic regression models; risk ratios for categorical variables are from Poisson regression models; the differences in adjusted means for continuous variables are from negative binomial regression models; comparisons are of compared BFC with FSC (reference group); ie, adjusted mean difference = AdjMean (BFC) −AdjMean (FSC) and OR = Odds (BFC)/Odds (FSC). All statistical tests control for model covariates mentioned above.

‡Asthma-related events include inpatient hospitalizations with a primary diagnosis for asthma and asthma-related ED visits are those patients who have a diagnosis for asthma in any position.

§LOS is calculated with patients who had at least 1 hospitalization.

Inclusion-exclusion criteria resulted in 3122 and 8177 patients in the BFC and FSC groups, respectively. Excluding patients who switched study medication during follow-up resulted in the loss of 2.7% of patients, with similar rates within each group: 2.8% of patients on FSC and 2.5% of patients on BFC. After propensity score matching, there were 3043 patients in each cohort (Figure 1).

Characteristics of matched cohorts at baseline

The cohorts were well balanced, and the standardized difference between groups was less than 10% for any given baseline variable after matching (Supplement E1; Table III in this article's Online Repository at www.jaci-inpractice.org). Patients in the BFC and FSC cohorts had a mean ± SD age of 40 ± 14.8 years, and 63.5% were women. The distribution of comorbid conditions within each cohort is shown in Table III. The mean Deyo-Charlson index (DCI) score was similar for each cohort (0.3). Similar proportions of patients on BFC and those on FSC were seen within each specialty, with allergists/immunologists and pulmonologists making up a combined 40.9% and 40.2%, respectively. Patients treated with BFC and those treated with FSC had similar asthma controller medication use during the 12-month preindex period: ICS (38.1% vs 37.0% with at least 1 fill), LABA (7.4% vs 6.2%), leukotriene receptor antagonist (LTRA) (35.0% vs 34.4%), and theophylline use (1.2% vs 1.4%), respectively.

Asthma exacerbation rates

As shown in Table I, the BFC cohort had a lower unadjusted asthma exacerbation rate compared with the FSC cohort, 0.83 versus 0.89, respectively. Adjusted exacerbation rates during the treatment period were lower for the BFC cohort compared with the FSC cohort (adjusted rate ratio [RR] 0.92 [95% CI, 0.85-0.99]). On evaluation of the components of asthma exacerbation rates, compared with FSC, the BFC cohort had fewer OCS fills (mean number of fills for BFC, 0.73; FSC. 0.79; difference −0.07 [95% CI, −0.12 to −0.01]), and fewer ED visits (mean number of visits for BFC, 0.08; FSC, 0.10; difference −0.02 [95% CI, −0.03 to 0.00]), and comparable asthma-related hospitalization rates (mean number of visits for BFC, 0.01; FSC, 0.01; difference 0.0 [95% CI, 0.00-0.00]), as reported in Table II.

A descriptive, unadjusted analysis of exacerbation rates by index medication dose was performed. The majority, 72%, of patients on BFC initiated on the high dose of 160 μg ICS, and 73.5% of patients on FSC who took the powder formulation initiated on 1 of the higher doses: 250 μg (60.2%) or 500 μg ICS (13.3%). The patients on high-dose BFC had an exacerbation rate of 0.88 events per person year and those who initiated high-dose powder FSC had an exacerbation rate of 0.95 (0.86 for the patients on 250 μg and 1.33 for the patients on 500 μg). Patients on lower-dose BFC (80 μg) and those on FSC (100 μg) had similar exacerbation rates (0.68 vs 0.66, respectively). Furthermore, more patients on FSC were receiving ICS therapy (excluding the ICS-LABA combination) during the postindex period (FSC 10.2% vs BFC 9.1%; OR 0.86 [95% CI, 0.72-1.02]), and a greater proportion of patients filled an SABA prescription (FSC 71.2% vs BFC 66.4%; OR 0.80 [95% CI, 0.72-0.90]) after initiation of ICS-LABA. Additional analyses that modeled the relative risks resulted in risk ratios that were in the same direction as the ORs and statistically significant for both ICS and SABA use, although closer to 1.0, and can be found in Table II.

Sensitivity analyses demonstrated that this difference was similar but no longer significant when exacerbations within the first 30 days were excluded (adjusted RR 0.93 [95% CI, 0.86-1.02]). Results were similar to the primary analysis when excluding patients on BFC who initiated therapy during the first 6 months of the intake period (which corresponds to the initial

TABLE III. Characteristics of propensity score matched cohorts

Matched cohort characteristics	BFC (n = 3043)	FSC (n = 3043)	95% CI	*P* value*
Age (y), mean ± SD	40.1 ± 14.8	39.7 ± 14.8	−0.43 to 1.06	.4023
Men, no. (%)	1108 (36.40)	1115 (36.60)	0.89-1.10	.8522
Health plan type, no. (%)				
HMO	443 (14.60)	439 (14.40)	0.88-1.17	.8842
PPO	2353 (77.30)	2,335 (76.70)	0.92-1.17	.5833
POS	141 (4.60)	158 (5.20)	0.70-1.12	.3134
Geographic region, no. (%)				
Northeast	603 (19.80)	629 (20.70)	0.84-1.08	.4069
Midwest	900 (29.60)	893 (29.40)	0.91-1.13	.8440
South	876 (28.80)	888 (29.20)	0.88-1.10	.7346
West	664 (21.80)	633 (20.80)	0.94-1.20	.3319
DCI comorbidity score, mean ± SD	0.35 ± 0.7	0.33 ± 0.7	−0.02 to 0.06	.2994
Comorbidities, no. (%)				
Allergic rhinitis	1451 (47.70)	1441 (47.40)	0.92-1.12	.7974
Sinusitis	957 (31.50)	940 (30.90)	0.92-1.14	.6380
GERD	406 (13.30)	409 (13.40)	0.86-1.15	.9101
Anxiety	228 (7.50)	255 (8.40)	0.74-1.07	.2004
Major depressive disorder	111 (3.70)	110 (3.60)	0.77-1.32	.9454
Obesity	167 (5.50)	170 (5.60)	0.79-1.22	.8665
Sleep apnea	206 (6.80)	206 (6.80)	0.82-1.22	1
Prescriber specialty, no. (%)				
Allergist/Immunologist	823 (27.10)	802 (26.40)	0.93-1.16	.5429
Pulmonologist	421 (13.80)	419 (13.80)	0.87-1.16	.9408
Pediatrics	135 (4.40)	131 (4.30)	0.81-1.32	.8020
Internal medicine	519 (17.10)	527 (17.30)	0.86-1.12	.7858
Family/general practitioner	731 (24.00)	761 (25.00)	0.84-1.07	.3714

GERD, Gastroesophageal reflux disease; *HMO*, health maintenance organization; *POS*, point of service; *PPO*, preferred provider organization.
*For the overall distribution, and most useful for testing the variable of interest.

approval of BFC in the US market) (adjusted RR 0.92 [95% CI, 0.84-0.99]). Differences in exacerbation rates were notable in the number of OCS fills in the postindex period as well as the number of asthma-related ED visits. The frequency of asthma-related inpatient visits was comparable for the 2 cohorts.

DISCUSSION

This first US comparative effectiveness study of BFC versus FSC combination therapies for asthma in a real-world population found lower rates of asthma exacerbation in the BFC cohort compared with the FSC cohort (adjusted RR 0.92 [95% CI, 0.85- 0.99]). Sensitivity analyses demonstrated similar differences. These findings are consistent with prior studies conducted outside of the US. A Canadian retrospective matched cohort study evaluated the real-world effectiveness of BFC (n = 1449) versus FSC (n = 9381) in patients with asthma, as measured by the need for acute care and ambulatory medical visits.[14] On adjusting for all known confounding variables, the investigators found that patients treated with BFC were significantly less likely to have an ED visit for asthma (RR 0.72 [95% CI, 0.54-0.96]), asthma-related hospitalization (RR 0.50 [95% CI, 0.25-0.99]), or fill an OCS prescription (RR 0.83 [95% CI, 0.72-0.95]), and used less SABA per week (mean difference, −1.1 dose/wk [95% CI, −1.7 to −0.5 dose/wk]) than those treated with FSC. Although our study found no difference in asthma-related inpatient hospitalizations, our observations were consistent with the directionality of the findings by Blais et al.[14]

A German study[15] that used administrative claims data from 2001 to 2005 compared outcomes for the postindex year for patients who received BFC (n = 1456) and those who received FSC (n = 982). Patients in the 2 cohorts had similar baseline characteristics, and asthma exacerbation was defined as ≥1 OCS prescription fill, asthma-related inpatient hospitalization, and/or referral. The patients with chronic asthma who initiated BFC therapy had fewer severe exacerbations (33.4% reduction; $P = .0123$), fewer OCS prescriptions (31.5% reduction; $P = .0082$), and less SABA use (13.3% reduction; $P = .2297$) compared with FSC, after controlling for baseline characteristics. The findings from our study were similar to the trend of reductions in OCS and SABA use, with fewer exacerbations reported in the German study.[15] In essence, the exacerbation rates reported in our study were similar to those in both the German[15] and Canadian[14] studies, although these comparisons are limited because there were slight differences in how these studies defined exacerbation rates.

The magnitude of the estimate of sensitivity analysis excluding exacerbations within the first 30 days of treatment (RR, 0.93) is almost exactly that of the primary outcome (RR, 0.92); however, the exclusion of some exacerbations resulted in a loss of statistical power, which may account for the loss of statistical significance of an already marginally significant result. The objective of this sensitivity analysis was to examine the stability and validity of the finding; given the similar effect estimates, we believe that the primary result is not being overly influenced by exacerbations that occur in the brief period of time before the benefit of either study medication takes effect.

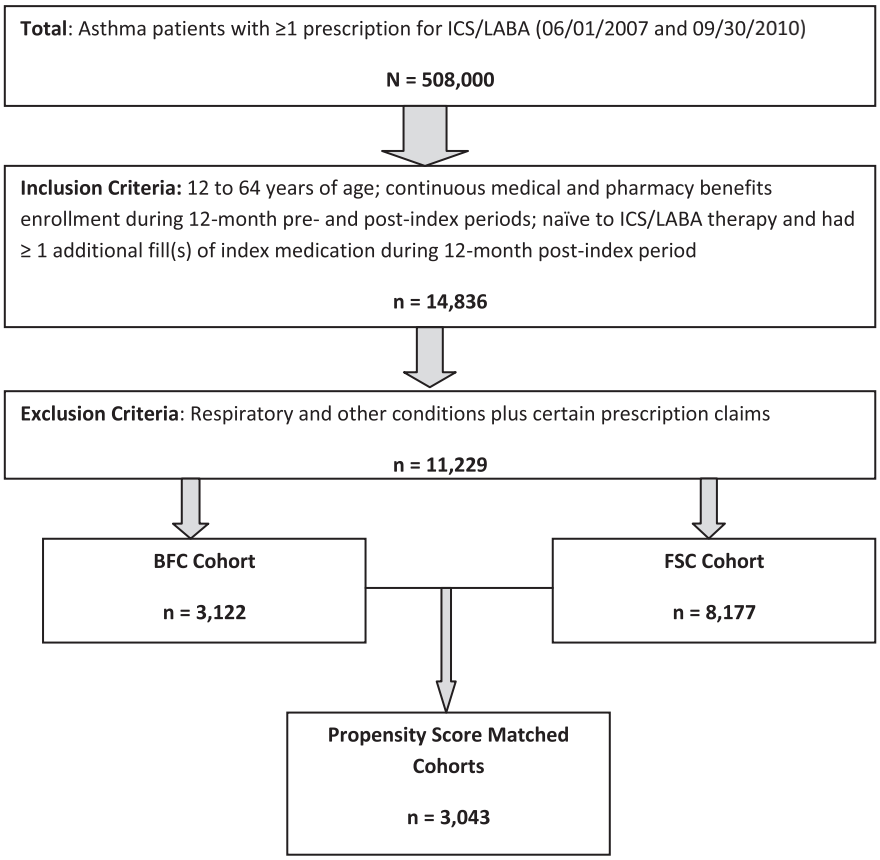

FIGURE 1. Disposition of study population.

The current study results indicated that patients who initiated BFC therapy had a lower asthma exacerbation rate compared with those who initiated FSC. These results are based on matched 1-to-1 patient cohorts that were well balanced on many potential confounding variables and are consistent with findings from previous retrospective observational studies.[14,15] The current study adds the US perspective to the paucity of data of real-world comparative effectiveness for 2 of the most commonly used ICS-LABA medications for the treatment of moderate-to-severe persistent asthma. This type of data facilitates a better understanding of clinical trial results based primarily on responses. The impact of therapy on tangible outcomes important to both patients and health care providers, including the utilization and cost of treatment, can be assessed by using observational data and is increasingly gaining importance for all stakeholders.[12,13]

The current study results should be interpreted within the context of study limitations. To our knowledge, as of now, no studies have compared BFC and FSC among patients by using the US pressurized metered dose inhaler device and the US approved indication. This could limit the extrapolation of the study's findings outside the United States. This study was based on administrative claims data that have inherent limitations, including the absence of clinical indicators of asthma disease severity. Asthma-related utilization was based on having a claim for asthma, which either could overestimate or underestimate the actual utilization for any given patient or population. Our analysis also may be subject to exposure misclassification due to imprecision in the attribution of exacerbations or secondary outcomes to the index medication or other treatments and/or drugs during the follow-up period. The generalization of these results may only be applicable to similar commercially insured patient populations and have limited utility in a population 65 years old and older.

This study demonstrated that patients with asthma who initiated BFC had a lower rate of asthma exacerbations, fewer fills of additional asthma controller medication, and fewer SABA prescription claims. These results must be interpreted within the context of claims database limitations, and future studies in different patient populations may provide additional evidence regarding the real-world effectiveness of these agents. Also, this database analysis can be used to provide evidence for future clinical research. The results of this effectiveness study should be confirmed by a well-designed prospective real-world pragmatic clinical trial.

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APPENDIX. SUPPLEMENT E1. PROPENSITY SCORE MATCHING

Propensity Score Matching

The BFC and FSC cohorts were not randomly assigned to the treatment groups, which may lead to comparisons between cohorts being confounded by selection bias. To ensure comparability and to reduce selection bias, the propensity score matching technique was used to adjust for measured confounders and to create more comparable BFC and FSC cohorts.[E1-E3] The propensity score for each individual was estimated as the probability of receiving BFC therapy (vs FSC), conditional on observed baseline characteristics. Logistic regression was used to calculate the scores. By using estimated propensity scores, a patient in the BFC cohort was matched with a patient in the FSC cohort who had a similar predictive probability when using Greedy nearest neighbor 1:1 matching with no replacement. The cohorts were considered well balanced for a given variable if the standardized difference between cohorts was 10% or less.[E1-E3]

The success of the propensity score model is judged by whether the balance was improved between 2 cohorts with respect to the selected variables. We started with the most comprehensive logistic model and gradually eliminated variables to achieve a final propensity score model. Propensity scores calculated from the final model were used to match 2 cohorts for analysis that provided the best balance of the selected variables between the 2 cohorts, while retaining maximum sample size. The following variables were used in the logistic model to produce propensity scores:

- Dependent variable. Flag for patient indexing BFC (in modeling, the probability that this variable equals 1).
- Independent variables. Sex (flag for female), age (categorically: 12-17, 18-44, 45-64 years old) region (categorically: northeast, midwest, south, west), index year (flags for 2007, 2008, and 2009), prescribing physician type (flags for allergist/immunologist, pulmonologist, pediatrician, internal medicine, family medicine/general practice, and other), previous asthma-related inpatient hospitalization (flag for >0 events), previous asthma-related outpatient visits (flags for 0 visits and 1 visit; and the continuous count), previous OCS use (continuous count of fills), previous ICS use (flag for 0 fills, 1 fill, 2+ fills), previous LTRA use (categorically: 0 fills, 1 fill, 2+ fills), previous LABA use (flags for 0 fill, 1 fill, 2+ fills), previous SABA use (categorically: 0 fills, 1 fill, 2+ fills), allergic rhinitis (flag for previous diagnosis), gastroesophageal reflux disease (flag for previous diagnosis), major depressive disorder (flag for previous diagnosis).
- Interaction terms. Prescribing physician type (categorically) * index year (categorically), region (categorically) * index year (categorically), prescribing physician type (categorically) * region (categorically).

Before the matching algorithm was performed, the 2 cohorts were separated into their own data sets and were sorted by propensity scores (low to high). Sorting was done so that matching can be replicated in the future as long as the data are sorted the same way before initiating the algorithm. The patient with the lowest propensity score in the BFC cohort was selected to find a matching patient in the FSC cohort. By using estimated propensity scores, a patient in the BFC cohort was matched with a patient in the FSC therapy cohort who had a similar predicted probability when using the Greedy nearest neighbor 1:1 matching technique (with no replacement).[E1] First, the algorithm was run to find matches with differences in propensity scores of $<10^{-7}$ and then it was run for the remaining subjects to find matches with differences $<10^{-6}$. This pattern continued up to 10^{-1}, after which no further matches were made. After the first patient in the BFC cohort was either matched or not matched with a patient from the FSC cohort, the patient in the BFC cohort with the next lowest propensity score was selected to find a match and so on. Random numbers were assigned to all the patients on FSC (by using random number generation with a specified seed of 1234567), so that, if 2 or more patients on FSC have the same propensity score and are considered the best match for patient on BFC, the patient with the numerically lowest random number was chosen as the match. The distributions of the propensity scores before and after matching are shown in Figure E1 (in this article's Online Repository at www.jaci-inpractice.org). The distributions were similar before matching, and there were no outliers in either group, which gave all the patients a chance to be matched, while minimizing selection bias.

The balance on key prespecified variables that were unbalanced before propensity score matching are shown in Table E1. Treatment cohorts were considered well balanced for a given variable if the standardized difference between the cohorts was 10% or less. The use of standardized differences for assessing balance in propensity score matching was described in Austin[2] and defined as:

$$d = \frac{(100 * |\bar{x}_{BFC} - \bar{x}_{FSC}|)}{\sqrt{\frac{s^2_{BFC} + s^2_{FSC}}{2}}} \text{ for continuous variables,}$$

and by

$$d = \frac{\left(100 * \left|p_{BFC} - p_{FSC}\right|\right)}{\sqrt{\frac{p_{BFC} * \left(1 - p_{BFC}\right) + p_{FSC} * \left(1 - p_{FSC}\right)}{2}}} \text{ for dichotomous variables.}$$

All the variables were well below the standardized difference threshold of $d = 10.0$, with all but one having values <5.0. Only 79 patients on BFC were not matched. Because FSC had a much larger population to begin with, only those most similar to their FSC counterparts were kept. The patients on FSC who were not matched tended to be those who indexed during 2007 as opposed to later years, were prescribed their medication by a family medicine/general practice or internal medicine physician as opposed to an allergist/immunologist or pulmonologist, and were less likely to have prior asthma medications but were more likely to have a prior ED or inpatient visit.

SUPPLEMENT E2. SENSITIVITY ANALYSIS

Thirty-Day Period

Prescribing information indicates that it could take 1 to 2 weeks before the maximum benefits of BFC and FSC are observed in patients,[E4,E5] and a prior study allowed a 30-day window between treatment initiation and outcomes measurements.[E6] To ensure that patients had adequate exposure to the medications before treatment outcomes were measured, a sensitivity analysis was conducted by using a second follow-up period,

which started 31 days after the index date and continued until the end of remaining 365 days. In addition, because the start of the intake period corresponded with the launch of BFC in the United States, it was possible that the patients who received BFC had different characteristics from the entire BFC population. A second sensitivity analysis excluded patients on BFC and their FSC matches, with index dates between June 1, 2007, and November 30, 2007 (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

SENSITIVITY MEASURES

Exacerbation rate

Both adjusted and unadjusted asthma exacerbations rates, the primary outcome measure, are shown in Table E2.

Switchers

Before excluding the patients who had a fill for a nonindex ICS-LABA during the postindex period (2.7% of all the patients), these patients were examined alongside patients who did not switch ICS-LABA therapy. This analysis also was done before matching the cohorts and the descriptive analysis evaluated both cohorts combined, and did not differentiate between BFC and FSC. Most baseline and preindex tables that were included in the main analysis were replicated for this analysis, along with the primary outcome and asthma-related health care utilization during the postindex period. The primary outcome, including the individual pieces that make up the primary outcome, for switchers (n = 317) and nonswitchers (n = 11,299) are shown in Table E3 (in this article's Online Repository at www.jaci-inpractice.org). Patients who filled a nonindex ICS-LABA had more than twice the number of exacerbations than patients who did not switch (RR 2.13 [95% CI, 1.82-2.49]). The primary result was driven by OCS use (RR 2.09), whereas even bigger differences were seen for inpatient hospitalizations (RR 3.02) and ED visits (RR 2.23). Generic Product Identifier (GPI) codes are provided in Table E4.

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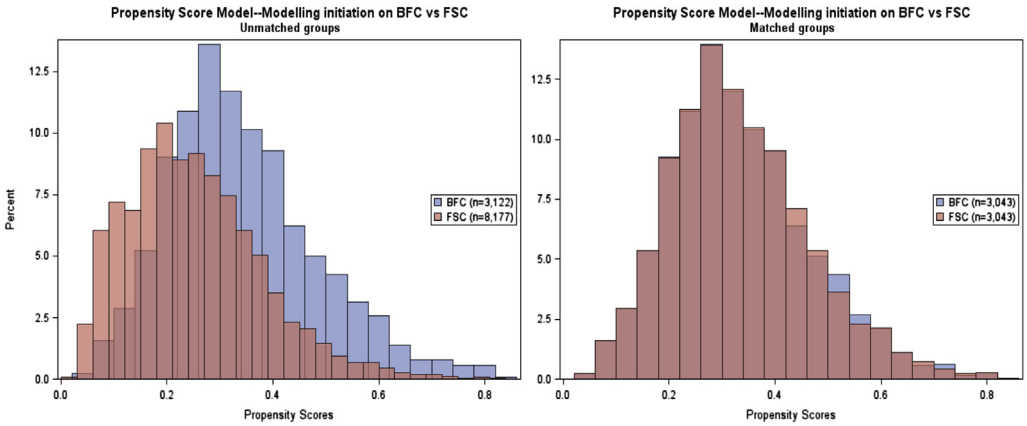

FIGURE E1. Distribution of propensity scores before and after matching.

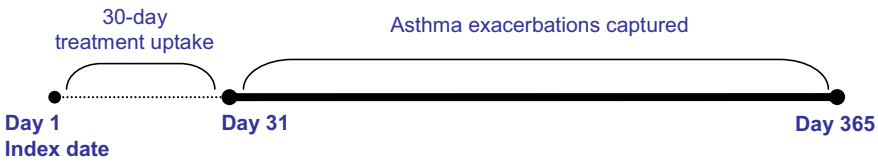

FIGURE E2. The period for sensitivity analysis.

TABLE E1. Characteristics of cohorts before and after propensity score matching

	All BFC, no. (%) (n = 3122)*	All FSC, no. (%) (n = 8177)*	Std diff†	Matched BFC, no. (%) (n = 3043)‡	Matched FSC, no. (%) (n = 3043)‡	Std diff†
Age (for each category)						
12-17 y	378 (12.1)	1137 (13.9)	5.34	374 (12.3)	367 (12.1)	0.70
18-44 y	1385 (44.4)	3484 (42.6)	3.54	1341 (44.1)	1372 (45.1)	2.05
45-64 y	1359 (43.5)	3556 (43.5)	0.08	1328 (43.6)	1304 (42.9)	1.59
Men and boys	1124 (36.0)	2994 (36.6)	1.27	1108 (36.4)	1115 (36.6)	0.48
Prescriber specialty						
Allergist/immunologist	864 (27.7)	1412 (17.3)	25.13	823 (27.0)	802 (26.4)	1.56
Pulmonologist	442 (14.2)	758 (9.3)	15.24	421 (13.8)	419 (13.8)	0.19
Pediatrician	135 (4.3)	521 (6.4)	9.11	135 (4.4)	131 (4.3)	0.64
Internal medicine	521 (16.7)	1705 (20.9)	10.68	519 (17.1)	527 (17.3)	0.70
Family/general practitioner	736 (23.6)	2547 (31.1)	17.05	731 (24.0)	761 (25.0)	2.29
Nonphysician	135 (4.3)	386 (4.7)	1.91	132 (4.3)	138 (4.5)	0.96
Other specialty§	69 (2.2)	306 (3.7)	9.03	69 (2.3)	65 (2.1)	0.90
Unknown‖	220 (7.0)	542 (6.6)	1.66	213 (7.0)	200 (6.6)	1.70
Comorbid conditions						
Allergic rhinitis	1502 (48.1)	3136 (38.4)	19.80	1,451 (47.7)	1441 (47.4)	0.66
Sinusitis	989 (31.7)	2357 (28.8)	6.22	957 (31.4)	940 (30.9)	1.21
GERD	419 (13.4)	920 (11.3)	6.60	406 (13.3)	409 (13.4)	0.29
Major depressive disorder	114 (3.7)	401 (4.9)	6.19	111 (3.6)	110 (3.6)	0.18
Obesity¶	177 (5.7)	454 (5.6)	0.51	167 (5.5)	170 (5.6)	0.43
Sleep apnea	210 (6.7)	487 (6.0)	3.16	206 (6.8)	206 (6.8)	0.00
ICS use						
0 fills	1888 (60.5)	6206 (75.9)	33.57	1,884 (61.9)	1918 (63.0)	2.31
1 fill	380 (12.2)	791 (9.7)	8.02	366 (12.0)	371 (12.2)	0.50
2+ fills	854 (27.4)	1180 (14.4)	32.20	793 (26.1)	754 (24.8)	2.94
LABA use						
0 fills	2846 (91.2)	7938 (97.1)	25.35	2,819 (92.6)	2,856 (93.9)	4.85
1 fill	47 (1.5)	52 (0.6)	8.46	40 (1.3)	36 (1.2)	1.18
2+ fills	229 (7.3)	187 (2.3)	23.76	184 (6.0)	151 (5.0)	4.76
LTRA use						
0 fills	2003 (64.2)	5765 (70.5)	13.56	1,979 (65.0)	1996 (65.6)	1.17
1 fill	257 (8.2)	624 (7.6)	2.22	249 (8.2)	247 (8.1)	0.24
2+ fills	862 (27.6)	1788 (21.9)	13.34	815 (26.8)	800 (26.3)	1.12
SABA use						
0 fills	805 (25.8)	2494 (30.5)	10.50	796 (26.2)	802 (26.4)	0.45
1 fill	760 (24.3)	2026 (24.8)	1.01	737 (24.2)	736 (24.2)	0.08
2+ fills	1557 (49.9)	3657 (44.7)	10.33	1,510 (49.6)	1,505 (49.5)	0.33
OCS use						
0 fills	1473 (47.2)	4147 (50.7)	7.07	1443 (47.4)	1456 (47.8)	0.86
1 fill	846 (27.1)	2197 (26.9)	0.52	830 (27.3)	820 (26.9)	0.74
2+ fills	803 (25.7)	1833 (22.4)	7.73	770 (25.3)	767 (25.2)	0.23
Asthma-related outpatient/office visits						
0	104 (3.3)	604 (7.4)	18.08	104 (3.4)	92 (3.0)	2.23
1	97 (3.1)	463 (5.7)	12.50	97 (3.2)	101 (3.3)	0.74
2+	2921 (93.6)	7110 (87.0)	22.43	2,842 (93.4)	2,850 (93.7)	1.07
Asthma-related ED visits						
0	2662 (85.3)	6528 (79.8)	14.35	2,594 (85.2)	2567 (84.4)	2.47
1+	460 (14.7)	1649 (20.2)	14.35	449 (14.8)	476 (15.6)	2.47
Asthma-related inpatient visits						
0	3017 (96.6)	7778 (95.1)	7.63	2941 (96.6)	2946 (96.8)	0.92
1+	105 (3.4)	399 (4.9)	7.63	102 (3.4)	97 (3.2)	0.92

GERD, Gastroesophageal reflux disease; *LTRA*, Leukotriene receptor antagonist; *std diff*, standardized difference.

*All eligible patients before matching via the propensity score matching algorithm.

†A value ≤ 10 is considered well balanced.; this method is not influenced by sample size, ie, the alternative of using *P* values, which may find clinically irrelevant differences statistically significant solely due to large sample sizes; std diff $= (100 \times |p\_BFC - p\_FSC|)/\sqrt{((p\_BFC \times (1 - p\_BFC) + p\_FSC \times (1 - p\_FSC))/2)}$.

TABLE E2. Asthma exacerbation rate during the 12-month postindex period

	Unadjusted rate*		Adjusted rate†				
	BFC (n = 3043)	FSC (n = 3043)	BFC (n = 3043)	FSC (n = 3043)	RR†	95% CI†	*P* value†
Asthma exacerbation rate, excluding the first 30 d after the index‡	0.75	0.79	0.70	0.75	0.93	0.86-1.02	.1189
Number of patients (excluding patients with an index date between June 1, 2007, and November 30, 2007)	n = 2785	n = 2785					
Asthma exacerbation rate, excluding patients with an index date between Jun 1, 2007, and Nov 30, 2007§	0.82	0.89	0.87	0.95	0.92	0.84-0.99	.0340

*The exacerbation rate is the total no. exacerbations in the study population divided by total person years. Here each person contributed 335 d, ie, approximately 0.9178 y.
†Adjusted exacerbation rates and the RR are from a negative binomial regression model; the statistical comparisons compare BFC with FSC (reference group), in which RR is rate (BFC) − rate (FSC). Model covariates include age at index (continuous), sex, health plan type, geographic region, index year, index physician specialty, DCI score, asthma-related inpatient hospitalization (yes-no during the preindex period), asthma-related ED visits (yes-no during the preindex period), OCS use (yes-no during the preindex period), and preindex comorbid conditions (allergic rhinitis, gastroesophageal reflux disease, major depressive disorder, obesity, sinusitis, sleep apnea [yes-no for each]).
‡Follow-up for asthma exacerbations started 30 d after the index date to ensure that the patients were allowed adequate exposure to the study medication before attributable outcomes were assessed. All the persons contributed 335 d (1 y minus 30 d excluded from the start of the postindex period).
§The start of the intake period corresponds with the launch of BFC in the US market. All the patients on BFC with an index date during the first 6 mo of the intake period (Jun 1, 2007, to Nov 30, 2007), and their matches were excluded because of the possibility that the patients on BFC during this time were characteristically different than the BFC population as a whole.

‡Eligible patients matched via the propensity score matching algorithm; matched patients made up the analytic data set.
§Other specialties include anesthesiology/pain management, cardiology, dermatology, emergency medicine, endocrinology/metabolism, gastroenterology, geriatrics, hematology, infectious disease, nephrology, neurology, nuclear medicine, obstetrics/gynecology, oncology, ophthalmology, otolaryngology, physical medicine/rehabilitation, podiatry, psychiatry, radiology, rheumatology, surgery, urology.
||Physician specialty was not specified in pharmacy claim for index medication, and there was no asthma-related medical claim within 1 mo of the index date.
¶Defined by using the International Classification of Diseases, Ninth Revision Clinical Modification diagnosis codes.

TABLE E3. Asthma exacerbation rate during the 12-month postindex period for "switchers" vs "nonswitchers"*

	Nonswitchers (n = 11,299)†		Switchers (n = 317)†			
	Mean ± SD	Median	Mean ± SD	Median	RR‡	95% CI
Asthma exacerbation rate§	0.87 ± 1.46	0	1.84 ± 2.10	1	2.13	1.82-2.49
Asthma-related inpatient hospitalizations||	0.02 ± 0.17	0	0.06 ± 0.27	0	3.02	1.91-4.77
Asthma-related ED visits	0.11 ± 0.43	0	0.25 ± 0.70	0	2.23	1.59-3.12
OCS fills¶	0.73 ± 1.33	0	1.53 ± 1.85	1	2.09	1.77-2.46

*Switchers are defined as those patients who filled a nonindex ICS-LABA combination at any point during the 12-mo postindex period and were excluded from the study; nonswitchers are defined as those who did not fill a nonindex ICS-LABA combination during the 12-mo postindex period and were included in the study.
†Includes patients before propensity score matching but who met all other inclusion-exclusion criteria up to step 4 of the attrition table.
‡The rate (switchers)/rate (nonswitchers); in this case, the rate is equal to the mean, so the RR is equal to mean (switchers)/mean (nonswitchers).
§The exacerbation rate is the total no. exacerbations in the study population divided by total person years; because all persons contributed exactly 1 y, this rate is simply (no. exacerbations)/(no. patients).
||Those hospitalizations with a primary diagnosis for asthma.
¶Includes only OCS fills that were not within 5 days of an inpatient hospitalization or ED visit.

TABLE E4. Generic product identifier codes

Name of medication	By dose	Generic product identifier code
BFC (Symbicort, Astra Zeneca)	Aerosol 80-4.5 μg	44209902413220
	Aerosol 160-4.5 μg	44209902413240
FSC (Advair, Glaxo Smith Kline)	Aerosol 45-21 μg	44209902703250
	Aerosol 115-21 μg	44209902703260
	Aerosol 230-21 μg	44209902703270
	Powder 100-50 μg/dose	44209902708020, 44209902706320
	Powder 250-50 μg/dose	44209902708030, 44209902706330
	Powder 500-50 μg/dose	44209902708040, 44209902706340