

<b>GSK Medicine:</b> fluticasone propionate/salmeterol combination (FSC); fluticasone propionate (FP)
<b>Study No.:</b> ADA109315
<b>Title:</b> A Retrospective Study of Healthcare Utilization and Costs of Step-Down Therapy in Asthma Patients Receiving Fluticasone Propionate/Salmeterol Combination
<b>Rationale:</b> Clinical guidelines recommend add-on therapy with long-acting $\beta_2$ -agonists (LABA) in patients with mild-to-moderate persistent asthma whose disease is not adequately controlled with inhaled corticosteroids (ICS) alone. For those achieving control with add-on therapy, careful reduction in ICS dose followed by withdrawal of LABA is recommended.
<b>Objectives:</b> To compare healthcare utilization and costs in asthma patients receiving FSC who step down the dose of FSC versus those who step down to FP only.
<b>Indication:</b> asthma
<b>Study Investigators/Centers:</b> Analysis conducted by Policy Analysis Inc (PAI), Brookline, MA
<b>Research Methods</b>
<b>Data Source:</b> Data for this study were obtained from the combined databases of i3 InVision Data Mart and the Ingenix Impact National Managed Care Databases (IMPACT). The i3 InVision Data Mart, is a comprehensive, de-identified U.S. healthcare claims database that contains aggregated healthcare claims of the covered managed care lives that is geographically diverse, and includes data for members in all 50 states. It contains inpatient, outpatient and pharmacy claims, lab results and enrollment information on over 30 million lives. The IMPACT database compiles claims data submitted by healthcare providers and pharmacies from 46 different healthcare plans serving members across nine census regions. Overall, the IMPACT database includes data on 93 million lives. The study data spanned the period from January 1, 2000 (seven months prior to the US introduction of FSC) through June 2007 (the latest date for which claims data are available) (study period).
<b>Study Design:</b> This was a retrospective cohort study using health insurance claims data to compare healthcare utilization and costs in asthma patients receiving FSC who step down the dose of FSC versus step down to FP only. Patients who met inclusion criteria who stepped down the dose of FSC were matched to those who stepped down to FP only using propensity score matching to control for potential differences in baseline demographic and clinical characteristics. Matched patients were then compared with respect to measures of asthma-related healthcare resource utilization and costs after step-down.
<b>Study Population:</b> Study subjects included patients with one or more medical claims with a diagnosis (primary or secondary) of asthma (ICD-9-CM 493.xx) during the study period and two or more outpatient pharmacy claims for FSC during the study period. Patients with any medical claims during the study period with a diagnosis of chronic obstructive pulmonary disease (COPD) (ICD-9-CM CD-9-CM 491, 492, 494, or 496) or respiratory tract cancer (ICD-9-CM 160-164, or 231), or pharmacy claims for ipratropium or tiotropium, were excluded. Remaining patients constituted the base sample.
For all patients in the base sample, pharmacy claims for FSC and FP (beginning with the first claim for FSC) were arrayed in chronological order. These claims were then scanned to identify patients who experienced one of the four qualifying changes in therapy within 365 days of the first claim for FSC: (1) FSC 500/50 followed by FSC 250/50 mcg, (2) FSC 500/50 mcg followed by FP 220 mcg, (3) FSC 250/50 mcg followed by FSC 100 mcg, or (4) FSC 250/50 mcg followed by FP 110 mcg. Patients were classified as FSC patients if the first qualifying change was from FSC 500/50 mcg to FSC 250/50 mcg or from FSC 250/50 mcg to FSC 100/50 mcg. Because FSC is administered as one inhalation twice daily, whereas FP is administered as two inhalations twice daily, the daily dosage for a prescription for FP 220 mcg is approximately equivalent to that for a prescription for FSC 500/50 mcg, and the daily dosage for a prescription for FP 110 mcg is approximately equivalent to that for FSC 250/50 mcg. Patients were therefore assumed to have stepped down to FP (FP patients) if the first qualifying change was from FSC 500/50 mcg to FP

220 mcg or from FSC 250/50 mcg to FP 110 mcg. Patients who were not classified as FSC or FP patients were dropped from the analysis sample.

For patients in the FSC and FP groups, the date of the first qualifying switch was designated the "index date." The 12-month (365-day) period prior to the index date was designated the "pre-index period." The period beginning with the index date and ending with the last date for which complete claims data were available was designated the "follow-up period" (in the dataset follow-up may be truncated by health-plan disenrollment or end of the study period).

Patients were excluded if they met any of the following criteria: (1) less than 12 months of continuous enrollment during pre-index period; (2) less than three months of continuous enrollment during the follow-up period; (3) less than two prescriptions for FSC during pre-index period; (4) one or more prescription for leukotriene receptor antagonist, inhaled mast-cell stabilizer, methylxanthine, IgE blocker or non-study ICS or LABA between FSC therapy initiation during the three months beginning with the index date; (5) age less than 12 years or greater than 64 years at the index date; or (6) index date prior to January 1, 2001; (7) missing or invalid data for demographic or plan characteristics, or missing or invalid data on claims required to calculate pre-index characteristics or study outcomes (e.g., FSC/FP days supply, payments information on asthma-related claims).

**Study Exposures, Outcomes:** For each patient, several measures of the utilization of asthma-related healthcare services during the follow-up period were assessed, including numbers of pharmacy claims for Short Acting Beta Agonists (SABAs), receipt of systemic corticosteroids SCS (yes/no), numbers of asthma-related physicians' office visits, and Emergency Department (ED) visits (yes/no). Two composite outcomes measures were also assessed: 1) ED visits or hospitalizations and 2) ED visits, hospitalizations, or receipt of SCS. Inpatient medical claims were considered asthma-related if a diagnosis of asthma was in the primary position on the claim. Outpatient claims were considered asthma-related if there was any diagnosis of asthma on the claims. Amount of albuterol used was considered a proxy for asthma control. Several measures of the costs of asthma-related healthcare during the follow-up period also were assessed, including the costs of asthma-related medications, the costs of ED visits and hospitalizations, the costs of other services, total costs, and total costs excluding FSC and FP. Study medications, SABAs, SCSs, and controller medications were considered asthma-related. Adherence to ICS therapy during follow-up was measured in terms of medication possession ratio (MPR) and the refill rate.

**Data Analysis Methods:** Patients in the FSC group were matched to those in the FP group using propensity score matching. Propensity scores were calculated for all members by estimating a logistic regression model with treatment group (FP vs. FSC) as the dependent variable, and pre-treatment characteristics as independent variables (FP was used as the reference category, as it was the smallest cohort). Propensity scores for each subject were defined as the predicted probability (range: 0 - 1) of being in the FP group, conditional on the observed values of the other characteristics. Matched pairs of FP and FSC patients were identified using nearest neighbor matching.

To assess the quality of propensity-score matching, the pre-index characteristics of matched samples were compared using McNemar test or Bowker test for categorical variables, and paired t-test for continuous variables. Also, the distribution of propensity scores across groups were arrayed and compared graphically (i.e., via histogram) to assess the degree of overlap of the propensity score distributions.

Outcome measures were compared using McNemar or Bowker tests for categorical variables, and paired t-tests for continuous variables. Odds ratios for binary outcomes, rate ratios for count

outcomes, and cost ratios for cost outcomes were calculated using Generalized Linear Model (GLM) regression. For binary outcomes, a logit link and binomial error term distribution were employed. For counts, a log link and a negative binomial distribution were employed. For costs, log link and gamma distributions were employed. A p-value of 0.05 was used in all tests of statistical significance.

**Limitations:** Treatment was not randomly assigned, so it is possible that differences between cohorts in study outcomes may be due to differences in patient characteristics that were not controlled by propensity score matching (i.e., “selection bias” or “residual confounding”). In addition, because our study relied on health-insurance claims, we lacked information in patient records on clinical parameters that may define asthma phenotypes that may be independently predictive of outcomes (e.g., frequency and severity of symptoms). The total number of subjects who stepped down to a lower dose of FSC (n=3881) was substantially larger than the number who stepped down to FP only (n=469). Accordingly, while most of the patients in the FP only group were included in the matched sample, only 11% of those in the FSC groups were analyzed, therefore, the findings of this analysis may not be generalizable to all patients stepping down from FSC. However, since the matched analysis retained a large percent of the FP only group, this study allowed for a valid comparison of step down to same dose ICS without LABA to similar patients that step down to lower dose FSC.

**Study Results:** Patient characteristics are shown in table 1. A total of 370,170 patients met criteria for inclusion in the base sample. Of these, 30,799 had one or more qualifying therapy change within 12-months after initiation of FSC. A total of 4350 subjects met all inclusion criteria, including 3881 (89%) patients who stepped down to a lower dose of FSC and 469 (11%) who stepped down to FP only at the same dose. The largest sources of attrition (sources are not mutually exclusive) were less than 12 months of continuous health-plan enrollment pre-index (44%), less than two prescriptions for FSC during the pre-index period, and one or more prescription for leukotriene receptor antagonist, inhaled mast-cell stabilizer, methylxanthine, IgE blocker or non-study ICS or LABA between FSC therapy initiation during the three months period starting with the index date (45%). After matching, there were 447 pairs of stepped down FSC and FP patients, which were well matched on all baseline characteristics. Mean follow-up among matched patients was 10.8 months for both groups.

FSC patients had 30% fewer prescriptions for short acting beta agonists, a 26% lower risk of receiving systemic corticosteroids, and a 48% lower risk of asthma-related hospitalization or emergency department visit during follow-up (table 3)

**Table 1: Baseline (12 month pre-index) demographics**

Demographics/Baseline Characteristics	Study Group	Comparison Group
Total (N)	FP (447)	FSC (447)
FSC therapy prior to step-down, No. (%)		
FSC 250/50	369 (83)	365 (82)
FSC 100/50	78 (17)	82 (18)
Age, y, Mean (SD)	37.9 (14.8)	37.5 (15.5)
Males, No. (%)	186 (42)	200 (45)
Charlson Index, Mean (SD)	1.1 (0.9)	1.0 (0.7)

Asthma related Medical usage		
ED visits, No. (%)	44 (10)	49 (11)
Hospitalizations, No. (%)	2 (0)	4 (1)
SABA Rx's, No. Mean (SD)	2.7 (3.3)	2.8 (3.5)
SCS Rx's, No. Mean (SD)	0.7 (1.1)	0.7 (1.1)
Physician office visits, No. Mean (SD)	2.5 (3.3)	2.5 (2.4)
FSC MPR, Mean (SD)	61 (28)	61 (27)
Duration of follow-up, Mean (SD)	327.3 (71.9)	328.5 (73.4)
Propensity score, Mean (SD)	0.16 (0.09)	0.16 (0.09)

<b>Table 2: Asthma related utilization and costs during follow-up</b>			
<b>Primary and Secondary Outcome(s)</b>	<b>Study Group</b>	<b>Comparison Group</b>	<b>Evaluation of Study Outcome</b>
	<b>FP (N=447)</b>	<b>FSC (N=447)</b>	<b>p-value</b>
<b>Outcome measure</b>			
SABA prescriptions	2.48 (3.20)	1.72 (2.84)	<.001
SABA prescriptions, No. (%)	327 (73)	262 (59)	<.001
SCS claims, No. (%)	143 (32)	106 (24)	.006
Hospitalizations, No. (%)	3 (0.7)	0 (0.0)	--
ED visits, No. (%)	30 (6.7)	17 (3.8)	.037
ED visits or hospitalizations, No. (%)	33 (7.4)	17 (3.8)	.014
ED visits, hospitalizations, or SCS, No. (%)	158 (35)	111 (25)	<.001
<b>Costs, \$</b>			
ED visits and hospitalizations	81 (606)	25 (164)	.062
Outpatient pharmacy	856 (736)	951 (634)	.041
Other	573 (1,495)	451 (1,308)	.153
Total	1,429 (1,751)	1,402 (1,535)	.791
Total excluding FSC/FP	712 (1,564)	532 (1,326)	.040
FSC/FP	716 (647)	870 (595)	<.001
<b>ICS adherence</b>			
Refill rate	4.6 (3.4)	5.3 (3.5)	.005
ICS MPR	46.0 (30.5)	53.5 (29.7)	<.001

<b>Table 3: Risk of an asthma related event FSC vs FP</b>
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	Odds or Rate, Ratio (95%CI)
<b>Outcome measure</b>	
SABA prescriptions	0.70 (0.58-0.84)
SABA prescriptions, No. (%)	0.52 (0.39-0.69)
SCS claims, No. (%)	0.66 (0.49-0.88)
Hospitalizations, No. (%)	--
ED visits, No. (%)	0.50 (0.25-0.96)
ED visits or hospitalizations, No. (%)	0.45 (0.23-0.84)
ED visits, hospitalizations, or SCS, No. (%)	0.60 (0.44-0.80)

**Conclusion:**

This retrospective observational study using 2 large manage care databases suggests that asthma patients stepping down to a lower dose of FSC were associated with better control of asthma symptoms (as measured by albuterol use), better adherence to controller medication (as measured by MPR and refill rates), and decreased risk of severe exacerbations (asthma related ED, hospitalization or SCS use) compared to stepping down to FP only.