MINI-SENTINEL REGULATORY ASSESSMENT

REPORT OF THE IMPACT OF THE 2010 FDA REGULATORY ACTIONS ON LABA MEDICATION USE

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Mini-Sentinel Regulatory Assessment

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I. INTRODUCTION

Long acting beta$_2$ agonists (LABAs) are sympathomimetic agents that relax airway smooth muscle. [1-3] They differ from short-acting beta$_2$ agonists (SABAs) and their duration of action is longer (12-24 hours vs. 3-6 hours).

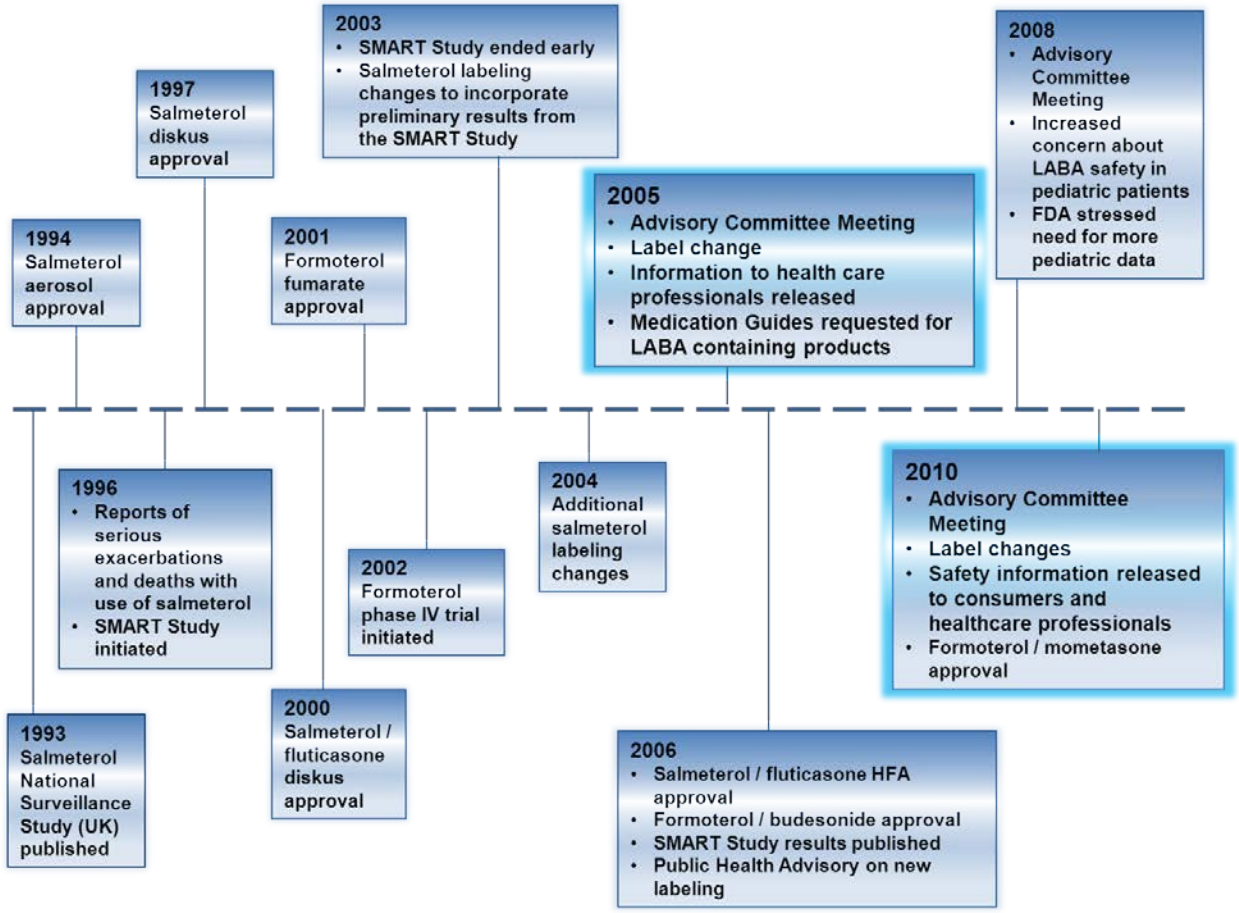
LABA were approved for use as controller medications for asthma management in the United States in the mid-1990s. There are four LABAs available in the United States (US). Of these Salmeterol and formoterol are the only LABA agents approved to treat asthma, and are marketed as single ingredient products or combination products with fluticasone (salmeterol) and mometasone and budesonide (formoterol). Arformoterol and indacaterol do not have an indication to treat asthma. LABAs were initially introduced to the market as monotherapy. However, evidence demonstrating that these agents have no impact on the anti-inflammatory aspects of asthma has led to higher prevalence of their use in combination with inhaled corticosteroids (ICS) and other controller medications.

Safety concerns with LABAs developed soon after they were marketed in the United Kingdom (UK) and the US, resulting in the initiation of the UK's Salmeterol National Surveillance (SNS) Study and the Salmeterol Multicenter Asthma Research Trial (SMART) in the US.[4-6] The SNS Study compared asthma patients randomized to a single-agent LABA or albuterol. There was a small, nonsignificant increase in asthma-related deaths in the LABA study arm. SMART was designed to assess safety among patients naïve to LABAs. Subjects were randomized to a single-agent LABA or placebo. This study was stopped earlier than expected in 2003 because interim results found an increase in serious asthma episodes, asthma-related deaths, and life-threatening events in the salmeterol study arm. Risks of these events were even higher among Blacks who received salmeterol versus placebo.

Because of limitations with the study designs of both SNS and SMART, it was difficult to discern contributors to increased risk among LABA users. In SNS, many patients started the study on LABA monotherapy. Additionally, there were no measures of adherence to asthma medications during the study; therefore there was no way to assess whether subjects stopped using controller medications and continued only on LABA treatment. In addition to gathering insufficient participant demographic characteristics data at baseline, the SMART trial did not measure symptoms and lung function. Like SNS, adherence was not measured and a large number of subjects were treated with LABA monotherapy. Both studies were not powered to assess whether risk was higher among monotherapy users versus subjects using LABAs in conjunction with other controller medications. There were several smaller studies that also supported the notion of increased risk of adverse outcomes among LABA users, particularly when used as monotherapy.[7-9]

In 2003, the United States Food and Drug Administration (FDA) responded to preliminary results of SMART by implementing labeling changes for salmeterol that communicated a small increased risk of life threatening asthma exacerbations and asthma related deaths. Additional salmeterol label changes were implemented in 2004. After the final SMART results became available and new manufacturers reports were submitted to FDA for review,[10] FDA communicated the risk associated with LABAs to the public once again in late 2005. FDA advised health professionals that LABAs should not be prescribed as first line therapy, but only added to regimens that already consisted of an asthma controller medication, such as an ICS.[11,12] Additionally, FDA required manufacturers to update their product labeling to reflect the safety information and requested Medication Guides communicating these risks be given to patients and caregivers at each dispensing.

Figure 1. LABA Regulatory and Safety Timeline



After convening several advisory committee meetings from 2005 to 2010 to obtain input regarding the safety concerns of LABAs and examining data from more than 60,000 people enrolled in 110 clinic trials, FDA concluded there was an increased risk of adverse asthma outcomes associated with LABA agents.[13-16] Their analysis also showed that the risk of adverse asthma outcomes was increased in the pediatric population.[16] In 2010, FDA initiated several regulatory actions. FDA required manufacturers to conduct clinical trials that compared the safety of ICS-LABA combination therapy to ICS monotherapy, to develop Risk Evaluation and Mitigation Strategies (REMS) for LABAs, and to update their product labeling to reflect the risks associated with LABAs.[14] The recommendations for safe use of LABAs for asthma are outlined below:

- The use of LABAs is contraindicated without the use of an asthma controller medication such as inhaled corticosteroid. Single-agent LABAs should only be used in combination with an asthma controller medication and they should not be used alone.
- LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications.

- LABAs should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patients should then be maintained on an asthma controller medication.
- Pediatric and adolescent patients who require a LABA in addition to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA to ensure compliance with both medications.

The regulatory history related to LABA therapy for asthma can be found in Figure 1.

II. METHODS

The objective of this Mini-Sentinel workgroup was to assess the impact of the 2010 FDA regulatory actions on LABA drug utilization patterns.

A protocol that describes the analysis plan has been posted on the Mini-Sentinel website.[17]

A. DATA SOURCE

The Mini-Sentinel program is part of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national system for monitoring the safety of medical products as mandated by the FDA Amendments Act of 2007 and to assess the impact of FDA regulatory action.[18,19] The current assessment included nine Data Partners (DPs) contributing data to the Mini-Sentinel Distributed Database (MSDD), which was comprised of administrative and claims data formatted into a common data model at the time of the assessment.[20] The DPs included in this assessment had data available for the entire study period.

B. ANALYSIS PERIOD

The study period ranged from January 1, 2004 to June 30, 2011; however, medication use was measured between January 1, 2005 and June 30, 2011 to allow for a 12-month baseline period to assess eligibility and to measure cohort characteristics. This study period is one year shorter than was stated in the proposal to allow for the maximum number of DPs that could participate in the project.

C. COHORT

The cohorts formed for each aim differ by the anchor date and key characteristics unique to the question that was explored; however, there were key elements consistent across aims that are presented here. Members were included in an analysis if they met the following criteria within 365 days of their anchor date: 1) continuous health plan enrollment with pharmacy benefits; 2) 65 years of age or younger; and 3) at least two office visits, one emergency department visit, or a hospitalization with a primary ICD-9 code of 493. They were also excluded from the analysis if they had a history of chronic obstructive pulmonary disease (COPD); cystic fibrosis; bronchiectasis; pulmonary hypertension or embolism; bronchopulmonary dysplasia; or congestive heart failure. The codes used to identify these procedures can be found in the proposal.[17]

The definition of asthma differed from the definition in the posted protocol (at least one office visit with a diagnosis code for asthma) because a large number of the members with one outpatient diagnosis code for asthma did not use asthma medications; therefore we could not verify if the person had asthma. We also identified asthma hospitalizations by principal or primary diagnosis codes as opposed

to any hospital diagnoses codes. Asthmatic incidents were defined according to these criteria in the interest of reducing measurement error.

D. STATISTICAL ANALYSIS

All analyses were first done at individual DP sites using the distributed SAS programs developed centrally by the Mini-Sentinel Operations Center (MSOC) programming team. Each program was beta-tested by the MSOC and two DPs prior to full distribution. Summary-level output was transferred to the MSOC, who then analyzed data from all participating DPs to obtain overall estimates ("MS-wide estimates"). None of the analyses required the DPs to transfer individual-level data.

A general description of the overall statistical analysis approach is provided below. Specific statistical analytic information is provided when each aim is reviewed.

1. Pooled Pre- and Post-Policy Comparisons

All pre and post-policy comparisons were based on pooled counts during each policy period and were not based on monthly estimates. There were two pre-policy periods (January 2005 to January 2010, and January 2008 to January 2010) and one post-policy period (February 2010 to June 2011) in aims 1-3. Comparisons were made between each pre-policy period and the post policy period. For aims 4-6 the pre-policy period ran from January 2005 to January 2010 and the post-policy period from February 2010 to June 2011, because there were no earlier policies which addressed length of therapy and step down therapy. We controlled for multiple observations per person using generalized estimating equations[21] because members' data could recur across periods.

2. Interrupted Time Series

To understand when and how medication use patterns may have changed as a result of the FDA regulatory actions, segmented linear regression analysis of an interrupted time series (ITS) design was implemented to assess the change in level (an immediate change in the month following the policy) and change in trend (a change in slope after the policy) of asthma medication use.[22-23] To reflect the beginning and end of FDA regulatory actions in aims 1-3, we examined three policy periods to reflect the major regulatory actions during the project period: 1) January 2005 to November 2005; 2) December 2005 to January 2010; and 3) February 2010 to June 2011. Two policy periods were studied for aims 4-6 as there was only one regulatory action applicable: (1) January 2005 to January 2010; and 2) February 2010 to June 2011.

Prior to estimating the ITS models, the data were adjusted for seasonality on a monthly basis using ARIMA models.[24] To establish the best model fit (i.e. meaning the number of parameters to be included in the model) for the ITS analyses, we conservatively defined the models based on parameter estimates having a p value <0.2. For each parameter, statistical significance was still defined as a p value <0.05. The potential parameters that could be included in a model were the intercept, baseline slope/trend, changes in the trend, and changes in the level. The intercept represents the prevalence of the outcome in January 2005. The baseline trend represents the slope between January 2005 and November 2005 or January 2005 and January 2010 depending on the study aim. Two *change in trend* parameters were estimated for models with three segments (aims 1-3), the first from December 2005 to January 2010 (policy 1 trend change), and the second from February 2010 to June 2011 (policy 2 trend change). The only change in trend calculated for models with two segments (aims 4-6), was from February 2010 to

June 2011. Similarly, there were two *change in level* parameters for the three segment models and one *change in level* parameter for the two segment models, which represent an immediate effect of the policy once implemented.

All models were adjusted for significant autocorrelation terms determined by backstep elimination.[22]

3. Pre-specified Subgroup Analyses

Whenever the sample size allowed, all analyses were stratified by age group (0-4, 5-11, 12-17, 18-44, ≥45-65; or <18, 18-65 years), and sex. We hypothesized that there would be variation by age group because regulatory approval of asthma medication use varies by age and because the 2010 FDA recommendations emphasize pediatric populations. We did not expect differences in outcomes by sex.

The pooled comparisons were stratified by the following age groups: 0-4 years, 5-11 years, 12-17 years, 18-44 years and 45-65 years. Comparisons were made within age groups across policy periods and not between age groups. The two age groups compared in the ITS analyses were <18 years vs. 18-65 years. The data for the adult and pediatric populations were differenced each month. ITS regressions were run on the differenced data to determine if the patterns between children and adults were significantly different.[25]

III. AIM 1 – TO ASSESS TRENDS OF ASTHMA MEDICATION USE IN AN ASTHMA COHORT BEFORE AND AFTER THE 2010 FDA REGULATORY ACTIONS ON LABAS

In this aim, prevalent use of all asthma medications was measured in a cohort of asthma patients. As a result, we were able to assess whether use of asthma medications changed during the analysis period.

A. COHORT

A rolling monthly cohort definition was used to create the cohort. The anchor date for this aim was the 1st of each month, therefore all criteria related to continuous enrollment, age, and asthma diagnoses were identified within 365 days of the 1st of each month.

B. DRUGS OF INTEREST

Day supply was used to measure medication use on a monthly basis. The classes of medications assessed included LABAs (single-agent and fixed-dose combinations), ICSs, leukotriene modifiers (LMs), other asthma controller medications [theophylline, cromolyn, nedocromil, omalizumab] (OCMs), oral corticosteroids (OCSs), SABAs, and other bronchodilators [tiotropium, ipratropium, and ipratropium/albuterol] (OBs). Indacaterol, a LABA approved in 2011, was not included in this analysis because it does not have an indication for asthma. We also assessed the number of members who had no asthma medication supply in any given month. Measuring no medication use was not included in the initial proposal but was considered to be important in understanding low prevalence of medication use and determining the legitimacy of the definition for asthma used in the analyses.

C. OUTCOMES

The outcome for aim 1 is the proportion of eligible members who had a day's supply of any of the asthma medications of interest in a given month (i.e. prevalent medication use).

D. STATISTICAL ANALYSIS

1. Pooled Pre- and Post-Policy Comparisons

Since this analysis was focused on the population, the descriptive statistics were generated by identifying the baseline characteristics of members when they first became eligible to be recruited to the cohort in each of the policy periods. The medication use counts were based on evidence of first use for each medication class. The 'no medication value' estimates take into account no evidence of any medication used during the entire pre- and post-policy periods.

2. Interrupted Time Series

For the ITS analyses, asthma medication use was identified from the monthly cohorts of patients with asthma. Three policy periods were addressed in the ITS analyses.

E. RESULTS

1. Pooled Pre- and Post-Policy Comparisons

There were over 1.5 million individuals who met the inclusion criteria for this aim. Approximately 1.2 million of these individuals were represented in the longer pre-policy period (January 2005 to January 2010). The pre-policy population was 56% female. The mean age was 27.5 (SD=19.5) years, and 59.1% of the population consisted of adults (Table 1). The characteristics of the post-policy population differed only slightly by age (mean 28.5 years (SD=19.7)).

Table 1. Baseline Characteristics of Asthma Patients by Long and Short Pre-Policy and Post-Policy Periods (N= 1,545,077)

	Pre-Policy Periods		Post-Policy Period
	January 2005 – January 2010	**January 2008 – January 2010**	**February 2010 – June 2011**
Variables	(n= 1,274,817)	(n= 757,541)	(n= 650,765)
Sex*			
Female	56.31%	56.63%	56.68%
Male	43.69%	43.37%	43.32%
Age*			
0-4	13.93%	12.21%	11.10%
5-11	16.02%	16.62%	17.43%
12-17	10.99%	11.07%	11.60%
18-45	33.30%	32.53%	31.69%
46-65	25.75%	27.56%	28.18%
Mean Age (±SD), years	27.5±19.5	28.3±19.7	28.5±19.7*^

SD – standard deviation
*p<0.05 for Jan 2005-Jan 2010 vs. Feb 2010-June 2011 comparison
^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

Over the course of the long pre-policy period, the most commonly used asthma medication was SABA (53.24%), followed by ICS (46.22%). Nearly a quarter of members used OCS. Around a fifth of members used LM (21.59%) and LABA containing products (20.20%). Of the LABA users, more members filled fixed-dose ICS-LABAs (18.23%) than single-agent LABAs (2.75%). The other controller medications and bronchodilators were used infrequently among cohort members.

Table 2. Pooled Estimates of Asthma Medication Use Among Asthma Patients by Long and Short Pre-Policy and Post-Policy Periods (N= 1,545,077)

	Pre-Policy Periods		Post-Policy Period
	January 2005 – January 2010	**January 2008 – January 2010**	**February 2010 – June 2011**
Medication Classes	(n= 1,274,817)	(n= 757,541)	(n= 650,765)
Single-agent LABA	2.75%	1.71%	0.98%*^
Fixed-dose ICS-LABA	18.23%	16.39%	15.15%*
Any LABA	20.20%	17.75%	15.96%*^
Leukotriene Modifiers	21.59%	19.30%	17.39%*^
Inhaled Corticosteroids	46.22%	43.30%	42.13%*^
Other Controller Medications	1.60%	1.01%	0.55%*^
SABA	53.24%	49.80%	47.32%*^
Oral Corticosteroids	26.72%	23.43%	21.51%*^
Other Bronchodilators	5.46%	4.22%	3.51%*^
No Medication Use	26.63%	29.43%	31.76%*^

LABA – long-acting beta$_2$ agonists; SABA – short-acting beta$_2$ agonist
*p<0.05 for Jan 2005-Jan 2010 vs. Feb 2010-June 2011 comparison
^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

Overall use of asthma medications declined over time as shown in Table 2 by the increase in proportion of members with asthma who never filled an asthma medication in the post-policy period (26.6% vs. 31.8%, respectively, p<0.01). Drug use in all the drug classes declined. The absolute percentage decline ranged from 1.05 to 5.93% within the drug classes. The smallest absolute change was observed with OCMs, while the largest was seen with SABAs. LABA medication use significantly declined between the pre- and post-policy periods. Single-agent LABA use decreased from 2.75% to 0.98% and fixed-dose ICS-LABA use decreased from 18.23% to 15.15%. Use was already on the decline prior to the 2010 FDA regulatory actions in each drug class; estimates obtained for the shorter pre-policy period (Jan 2008 to Jan 2010) were smaller than those obtained for the longer pre-policy period.

2. Interrupted Time Series

The ITS regression results confirm that the observed changes shown in Table 2 and Figure 2 were significantly related to the regulatory actions. The intercepts of the ITS models provide the prevalence of each medication class at baseline in January 2005 (Table 3). At baseline, the most commonly used controller medication classes at the beginning of the analysis period were ICSs (23.14%), followed by LMs (15.69%). The fixed-dose ICS-LABA medications were used by 12.75% of the asthma population. Only 3% of patients with asthma filled a single-agent LABA. SABAs were the most commonly used non-controller class of medications (22.81%). Approximately 6% of patients had a supply of an OCS. Just over half of all patients had no asthma medication in the beginning of the analysis period.

Prior to the regulatory actions passing in December 2005, there were already declining trends in medication use in fixed-dose ICS-LABAs, single-agent LABAs, OCMs, other bronchodilators, OCSs, and SABAs (Table 3). The absolute cumulative decline in use of fixed-dose ICS-LABA and single-agent LABA

use from baseline to the December 2005 regulatory actions were 0.99 and 0.66 percentage points, respectively. During the same time frame there was an increasing trend in patients not using asthma medications.

With the exception of ICSs, fixed-dose ICS-LABAs, and LMs, very few drug classes were immediately impacted by the December 2005 regulatory actions. There was a 1.10 percentage point immediate decline in fixed-dose ICS-LABA use. ICS and LM use increased immediately after the December 2005 regulatory actions.

Contrary to the trend before December 2005, the change in trend from December 2005 until January 2010 was positive for fixed-dose ICS-LABAs, single-agent LABAs, OCMs, other bronchodilators, OCSs, and SABAs (Table 3). However, for OCMs, single-agent LABAs, and other bronchodilators, the slopes were still declining but not as steeply as the baseline slope because the magnitude of the change in trend was smaller than the baseline slope. The change in trend for fixed-dose ICS-LABAs and SABAs counteracted the baseline slope resulting in what appears to be a flat slope. Figure 3 displays the slopes for the LABA containing products. OCSs had a slightly positive slope because the change in trend was greater than the baseline slope. The opposite relationship was observed with no medication use; the change in slope was negative. However, the effect was smaller than the increasing baseline trend; therefore the slope was still increasing but at a declining rate. The change in trend for LMs was negative, resulting in a declining slope.

The main policy of interest went into effect in February 2010. There was an immediate decline in ICS, LM, and OCM use. There were no immediate effects on LABA containing products (Figure 3).

Compared to the trend from December 2005 until January 2010, the changes in trends from February 2010 until June 2011 were negative for fixed-dose ICS-LABAs, OCSs, and SABAs, resulting in declining slopes. The changes in trends were positive for those on single-agent LABAs, OCMs, and the group with no medication use. While positive, the magnitude of the change in trend was smaller than previous slope changes for single-agent LABAs and OCMs; therefore, the slopes were still declining but not as steeply. The no medication use slope increased as a result of the positive change in trend.

Figure 2. Prevalent of Asthma Medication Use: January 2005 - June 2011

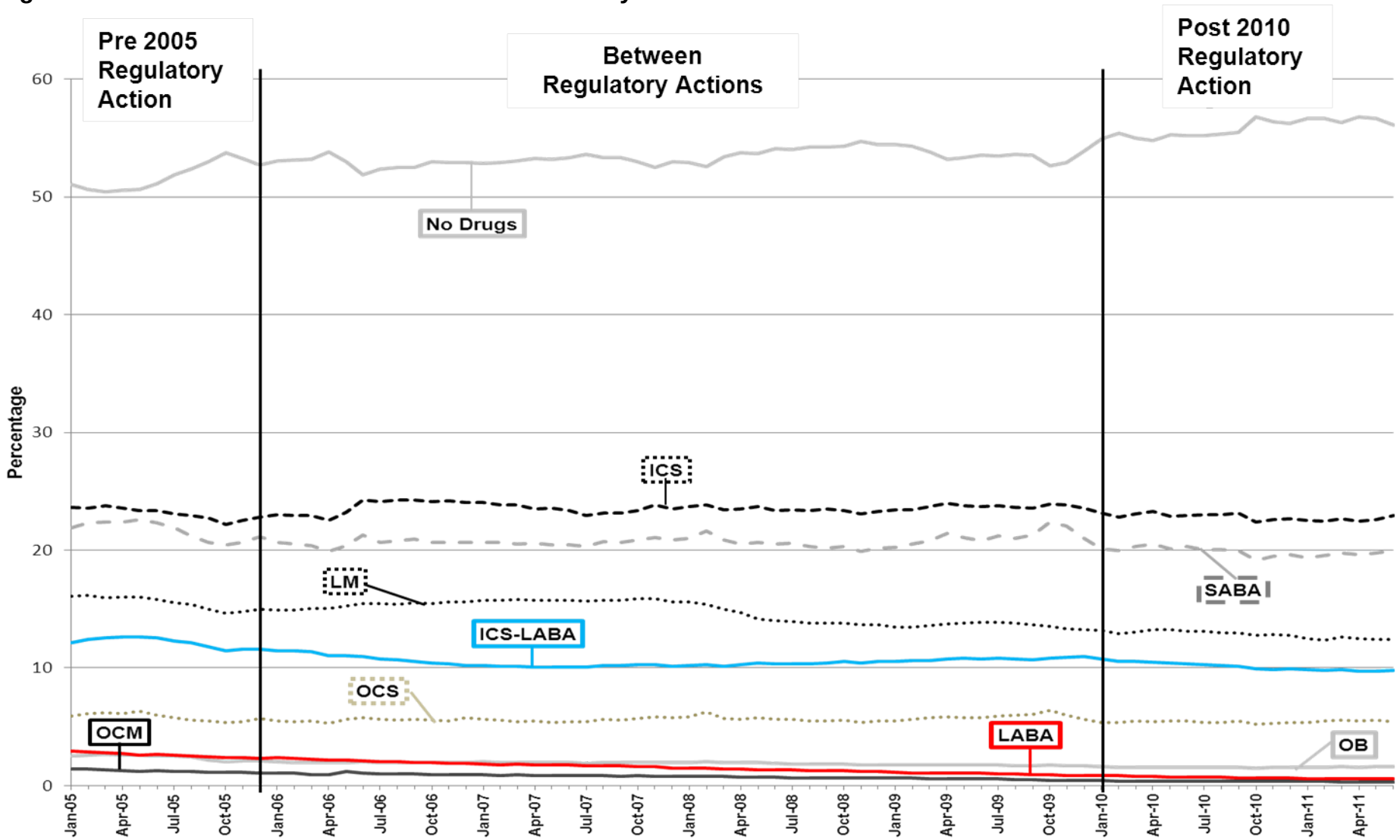
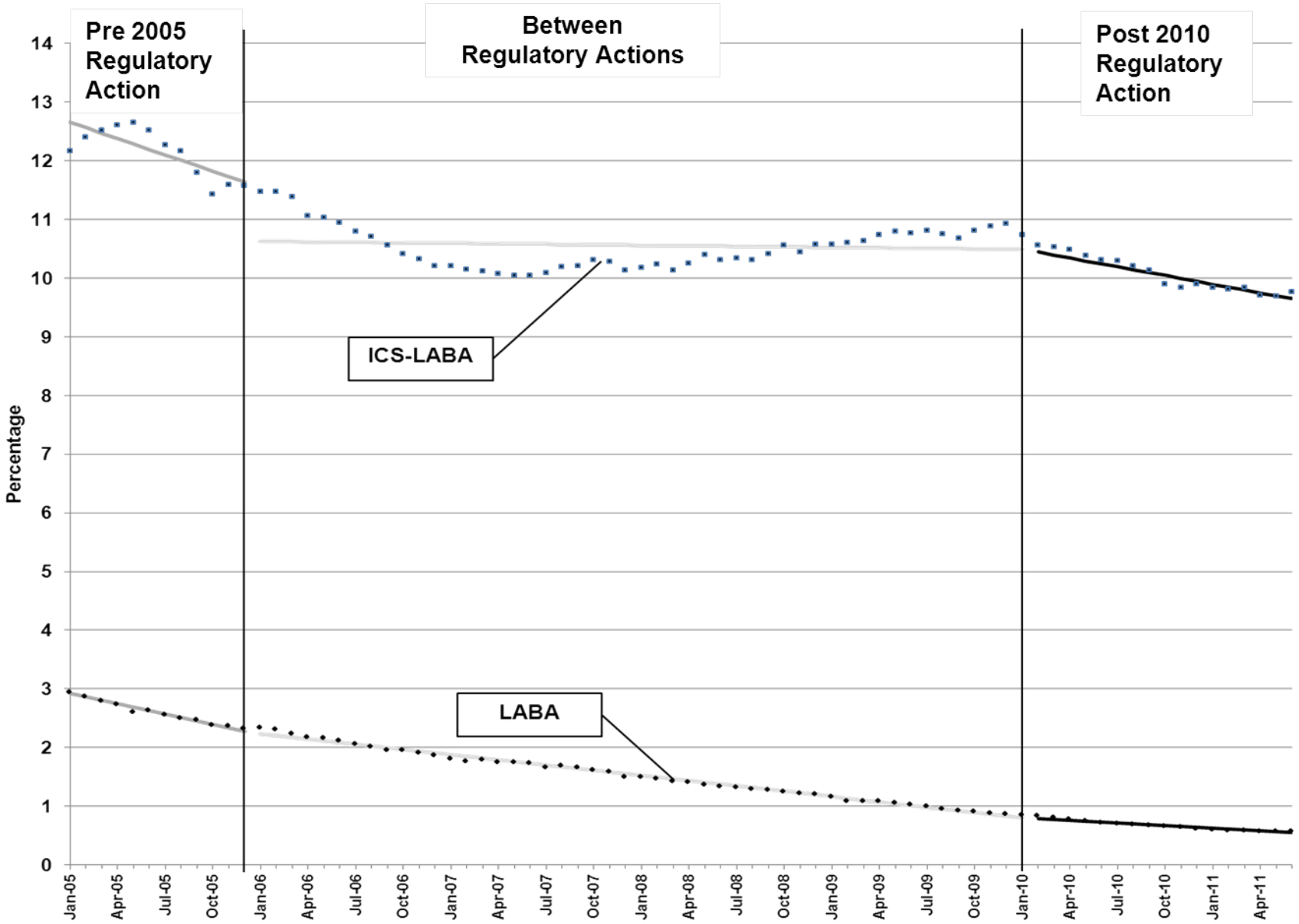


Table 3. Interrupted Time Series Analysis of Prevalent Asthma Medication Use Among Patients with Asthma in Percentage Points

	ICS		Fixed Dose ICS-LABA		Single Agent LABA	
Parameter∞	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
Intercept	23.14**	[22.84, 23.44]	12.75**	[12.31, 13.19]	2.99**	[2.92, 3.05]
Baseline trend			-0.09**	[-0.16, -0.03]	-0.06**	[-0.07, -0.05]
Level change after 2005 policy	0.39*	[0.07, 0.72]	-1.10**	[-1.53, -0.67]	-0.03	[-0.07, 0.00]
Trend change after 2005 policy			0.09**	[0.02, 0.16]	0.03**	[0.02, 0.04]
Level change after 2010 policy	-0.64**	[-0.91, -0.38]				
Trend change after 2010 policy			-0.05**	[-0.07, -0.03]	0.01**	[0.01, 0.02]
	LM		**OCM**		**Other Bronchodilators^**	
Parameter	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
Intercept	15.69**	[15.22, 16.16]	1.40**	[1.36, 1.43]	2.62**	[2.45, 2.79]
Baseline trend			-0.06**	[-0.03, -0.05]	-0.05**	[-0.06, -0.03]
Level change after 2005 policy	0.28*	[0.01, 0.55]				
Trend change after 2005 policy	-0.05**	[-0.06, -0.04]	0.02**	[0.01, 0.02]	0.04**	[0.02, 0.06]
Level change after 2010 policy	-0.27*	[-0.54, -0.00]	-0.06**	[-0.10, -0.02]		
Trend change after 2010 policy			0.01**	[0.01, 0.02]		
	OCS		**SABA**		**No Drug**	
Parameter	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
Intercept	6.12**	[5.85, 6.40]	22.81**	[22.13, 23.49]	50.64**	[49.78, 51.50]
Baseline trend	-0.05**	[-0.08, -0.02]	-0.20**	[-0.27, -0.12]	0.18**	[0.09, 0.27]
Level change after 2005 policy						
Trend change after 2005 policy	0.06**	[0.03, 0.09]	0.20**	[0.12, 0.27]	-0.15**	[-0.25, -0.05]
Level change after 2010 policy						
Trend change after 2010 policy	-0.03**	[-0.05, -0.02]	-0.08**	[-0.12, -0.04]	0.14**	[0.10, 0.18]

CI – Confidence Interval; ICS – Inhales corticosteroid; LM – Leukotriene Modifier ; OCM – Other controller medications (theophylline, nedocromil, cromolyn, omalizumab) ; LABA – Long acting beta agonist ; OCS – Oral Corticosteroids; SABA – short acting Beta-agonist; ^Other bronchodilators - ipratropium, ipratropium/albuterol, titropium; *pvalue<0.05; **pvalue<0.01
∞-Only parameters with pvalues<0.2 were retained in the ITS model

Figure 3. Prevalent Trends of Fixed-dose ICS-LABA and Single-agent LABA Use Among Patients with Asthma: January 2005 - June 2011



3. Pre-specified Subgroup Analyses

a) Pooled Pre- and Post-Policy Comparisons

Because the LABA regulatory recommendations do not differ by sex we only present the age group differences here. The sex-stratified analyses are in the Appendix. The patterns of medication use differed across age groups where adults had the largest contrast in medication use with children <12 years of age (Table 4). Children were more likely to use LM and ICS than adults between 18-44 years, and use of ICS was comparable with adults between the age of 45 and 65 years. Adults were more likely to use fixed-dose ICS-LABAs, single-agent LABAs, and other bronchodilators. Participants not on medication and those on OCSs differed by age group in a non-linear fashion. There was a decline in all medication use across all age groups.

Table 4. Pooled Estimates of Prevalent Asthma Medication Use Among Patients with Asthma by Long and Short Pre-policy and Post-policy Periods and Age Group

	Pre-Policy Periods		Post-Policy Period
Medication Class	**January 2005 – January 2010**	**January 2008 – January 2010**	**February 2010 – June 2011**
Age 0 – 4 years	(N= 177,643)	(N= 92,524)	(N= 72,238)
Single-agent LABA	0.25%	0.12%	0.07%*^
Fixed-dose ICS-LABA	1.95%	1.35%	1.19%*^
Any LABA	2.13%	1.44%	1.24%*
LM	26.23%	22.92%	20.86%*
ICS	54.28%	51.36%	50.44%*^
Other Controller Medications	0.51%	0.20%	0.13%*
SABA	60.57%	56.70%	55.10%*^
OCS	36.26%	32.19%	30.05%*^
Other Bronchodilators	1.94%	1.46%	1.28%*^
No Medication Use	25.12%	27.74%	28.94%*^
Age 5 – 11 years	(N= 204,258)	(N= 125,903)	(N= 113,453)
Single-agent LABA	0.94%	0.42%	0.16%*^
Fixed-dose ICS-LABA	13.33%	9.79%	7.62%*
Any LABA	13.90%	10.07%	7.74%*
LM	30.96%	28.83%	25.48%*^
ICS	52.55%	50.94%	50.79%*^
Other Controller Medications	1.02%	0.51%	0.21%*^
SABA	59.65%	56.57%	53.78%*^
OCS	25.82%	23.06%	21.33%*^
Other Bronchodilators	1.84%	1.42%	1.13%*^
No Medication Use	23.32%	25.70%	28.16%*^
Age 12 – 17 years	(N= 140,041)	(N= 83,894)	(N= 75,458)
Single-agent LABA	1.52%	0.68%	0.28%*^
Fixed-dose ICS-LABA	17.31%	13.97%	11.59%*^
Any LABA	18.31%	14.47%	11.80%*^
LM	21.34%	19.52%	17.62%*^
ICS	41.38%	38.77%	38.46%*^
Other Controller Medications	1.20%	0.65%	0.23%*^
SABA	54.66%	51.15%	48.14%*^
OCS	19.20%	16.79%	15.15%*^
Other Bronchodilators	2.14%	1.52%	1.19%*^
No Medication Use	29.48%	32.70%	35.31%*^
Age 18 – 44 years	(N= 424,575)	(N= 246,422)	(N= 206,239)
Single-agent LABA	2.86%	1.57%	0.81%*^
Fixed-dose ICS-LABA	21.01%	18.56%	16.76%
Any LABA	23.05%	19.80%	17.43%*^

Table 4. Pooled Estimates of Prevalent Asthma Medication Use Among Patients with Asthma by Long and Short Pre-policy and Post-policy Periods and Age Group

	Pre-Policy Periods		Post-Policy Period
Medication Class	**January 2005 – January 2010**	**January 2008 – January 2010**	**February 2010 – June 2011**
LM	16.32%	13.86%	12.20%*^
ICS	39.03%	35.28%	33.76%*^
Other Controller Medications	1.41%	0.83%	0.42%*^
SABA	48.92%	45.48%	42.81%*^
OCS	23.79%	20.80%	19.15%*^
Other Bronchodilators	5.50%	3.87%	3.11%*^
No Medication Use	30.74%	34.28%	37.24%*^
Age 45 – 65 years	(N= 328,300)	(N= 208,798)	(N= 183,377)
Single-agent LABA	5.62%	3.78%	2.33%*^
Fixed-dose ICS-LABA	26.90%	25.43%	24.94%*
Any LABA	31.04%	28.51%	26.92%*^
LM	20.18%	18.27%	16.74%*^
ICS	49.27%	46.43%	44.42%*^
Other Controller Medications	2.98%	2.04%	1.21%*^
SABA	50.29%	47.23%	44.99%*^
OCS	29.11%	25.55%	23.52%*^
Other Bronchodilators	10.96%	8.62%	7.27%*^
No Medication Use	22.98%	25.40%	27.46%*^

LABA - Long-acting beta$_2$ agonist; ICS - Inhaled corticosteroid; SABA - Short-acting beta$_2$ agonists; LM – Leukotriene Modifier ; OCM – Other controller medications (theophylline, nedocromil, cromolyn, omalizumab); OCS – Oral Corticosteroids; Other bronchodilators - ipratropium, ipratropium/albuterol, titropium;
*p<0.05 for Jan 2005-Jan 2010 vs. Feb 2010-June 2011 comparison
^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

b) Interrupted Time Series

There were differences in medication use between pediatric and adult patients. Table 5 shows the ITS regression results by age group. We found the baseline prevalence of these medications was significantly different. Compared to adults, children were less likely to use fixed-dose ICS-LABAs, single-agent LABAs, ICSs, OCMs, other bronchodilators, OCSs, and SABAs but more likely to use LMs (17.88% vs. 15.01%). The largest absolute difference in baseline drug prevalence was in fixed-dose ICS-LABAs, (7.16% vs. 16.10, p<0.01) for pediatric and adults patients, respectively. Pediatric patients were also more likely to have 'no mediation use' at baseline (55.37% vs. 46.36%, p<0.01).

The baseline trends for use of single-agent LABAs, fixed-dose ICS-LABAs, OCMs, other bronchodilators, and SABAs declined in both the pediatric and adult populations, but this decline was more significant among adults for all treatments. There was a declining use of ICSs, LMs, and OCSs in adults only. The baseline trend for no medication use significantly increased in adults only.

Immediate declines in single-agent LABA initiation among adults and fixed-dose ICS-LABA initiation among all populations subsequent to implementation of new regulatory actions in 2005 were noted. Additionally, significant increases in ICS use among children and LM use among adults were observed immediately following these regulatory actions. The change in trends after the 2005 regulatory actions showed increasing use of single-agent LABA and SABA in both pediatric and adult patients with asthma; however difference in the change in trend between children and adults was only significant for single-agent LABAs. In adults there was a positive change in trend for fixed-dose ICS-LABAs, OCMs, other bronchodilator, and OCSs use and a negative change for no medication use. There was a positive change in trend for ICS use in children.

The 2010 regulatory actions had an immediate impact on adult medication use but did not influence pediatric medication use. Adult use of ICSs, OCMs, OCSs, and SABAs declined in February 2010. The

change in trend after the 2010 regulatory actions affected use of single-agent LABAs in both pediatric and adult patients with asthma. The change in trend was positive in both subgroups but the adult change was significantly larger. There was a negative change in trend for fixed-dose ICS-LABA use in all populations and a positive change in trend for OCM use in adults only. In the pediatric population, the trend changes after the 2010 regulatory actions were negative for ICSs, OCSs, and SABAs, but positive for no medication use.

Table 5. Interrupted Time Series Analysis of Prevalent Asthma Medication Use Among Patients with Asthma in Percentage Points by Age Group∞

	Pediatric		Adult	
Medication Class	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
Single-Agent LABA				
Intercept	0.84**	[0.80, 0.88]	4.62**^	[4.49, 4.75]
Baseline trend	-0.02**	[-0.03, -0.02]	-0.09**^	[-0.11, -0.01]
Level change after 2005 policy			-0.07*	[-0.13, -0.01]
Trend change after 2005 policy	0.01**	[0.01, 0.02]	0.05**^	[0.03, 0.06]
Level change after 2010 policy				
Trend change after 2010 policy	0.01**	[0.01, 0.01]	0.02**^	[0.01, 0.03]
Fixed Dose ICS-LABA				
Intercept	7.22**	[7.04, 7.40]	16.77**^	[16.22, 17.32]
Baseline trend	-0.03*	[-0.03, -0.02]	-0.13**^	[-0.21, -0.05]
Level change after 2005 policy	-0.98**	[-1.22, -0.74]	-1.24**^	[-1.78, -0.71]
Trend change after 2005 policy			0.14**^	[0.06, 0.22]
Level change after 2010 policy			0.43	[-0.06, 0.92]
Trend change after 2010 policy			-0.09**^	[-0.14, -0.06]
ICS				
Intercept	21.95**	[21.54, 22.35]	25.04**^	[24.21, 25.87]
Baseline trend			-0.13*^	[-0.23, -0.03]
Level change after 2005 policy	0.54*	[0.01, 1.07]	0.44	[-0.09, 0.96]
Trend change after 2005 policy	0.06**	[0.05, 0.07]	0.10	[-0.01, 0.20]
Level change after 2010 policy			-0.59*	[-1.09, -0.10]
Trend change after 2010 policy	-0.10**	[-0.16, -0.05]		
LM				
Intercept	17.88**	[16.85, 18.91]	15.01**^	[14.37, 15.66]
Baseline trend			-0.12**	[-0.19, -0.05]
Level change after 2005 policy	0.44	[-0.03, 0.91]	0.26*^	[0.04, 0.48]
Trend change after 2005 policy	-0.05**	[-0.08, -0.02]	0.07^	[-0.00, 0.15]
Level change after 2010 policy	-0.36	[-0.83, 0.11]		
Trend change after 2010 policy				
OCM				
Intercept	0.37**	[0.36, 0.39]	2.17**^	[2.13, 2.20]
Baseline trend	-0.00**	[-0.00, -0.00]	-0.04**^	[-0.05, -0.04]
Level change after 2005 policy			-0.03^	[-0.06, 0.01]
Trend change after 2005 policy			0.03**^	[0.02, 0.03]
Level change after 2010 policy			-0.05**	[-0.08, -0.02]
Trend change after 2010 policy			0.01**^	[0.01, 0.01]
Other Bronchodilators				
Intercept	0.59**	[0.54, 0.64]	4.21**	[4.00, 4.41]
Baseline trend	-0.01**	[-0.02, -0.01]	-0.08**^	[-0.11, -0.06]
Level change after 2005 policy				
Trend change after 2005 policy	0.01**	[0.00, 0.01]	0.07**^	[0.04, 0.09]
Level change after 2010 policy			-0.11^	[-0.25, 0.03]
Trend change after 2010 policy			0.01	[-0.00, 0.03]
OCS				
Intercept	5.21**	[4.77, 5.65]	6.93**^	[6.71, 7.16]
Baseline trend	-0.04	[-0.08, 0.01]	-0.08**^	[-0.11, -0.06]
Level change after 2005 policy				

Trend change after 2005 policy	0.04	[-0.01, 0.10]	0.08**	[0.06, 0.11]
Level change after 2010 policy			-0.30**	[-0.43, -0.18]
Trend change after 2010 policy	-0.04**^	[-0.07, -0.02]		
SABA				
Intercept	21.84**	[20.82, 22.85]	23.43**^	[22.88, 23.97]
Baseline trend	-0.15*	[-0.26, -0.04]	-0.19**^	[-0.27, -0.12]
Level change after 2005 policy			-0.46	[-0.96, 0.04]
Trend change after 2005 policy	0.17**	[0.06, 0.29]	0.18**	[0.11, 0.26]
Level change after 2010 policy			-0.54*	[-1.03, -0.04]
Trend change after 2010 policy	-0.11**	[-0.17, -0.05]	-0.04	[-0.08, 0.01]
No Medication Use				
Intercept	55.37**	[53.96, 56.78]	46.36**^	[45.58, 47.13]
Baseline trend	0.12	[-0.06, 0.30]	0.35**^	[0.26, 0.43]
Level change after 2005 policy	-0.65^	[-1.65, 0.35]		
Trend change after 2005 policy	-0.12	[-0.31, 0.07]	-0.29**	[-0.38, -0.20]
Level change after 2010 policy			0.60^	[-0.10, 1.30]
Trend change after 2010 policy	0.15**	[0.06, 0.24]	0.06	[-0.01, 0.13]

OCS – Oral Corticosteroids; SABA – short acting Beta-agonist; Other bronchodilators - ipratropium, ipratropium/albuterol, titropium; ICS – Inhales corticosteroid; LM – Leukotriene Modifier ; OCM – Other controller medications (theophylline, nedocromil, cromolyn, omalizumab); LABA – Long acting beta agonist ;CI – Confidence Interval
*p-value<0.05; **p-value<0.01; ^p-value<0.05 for pediatric vs. adult
∞-Only parameters with pvalues<0.2 were retained in the ITS model

F. DISCUSSION

1. Overall Results

We identified over 1.5 million patients with asthma between January 2005 and June 2011. Their overall use of asthma medications declined during the study period. The 2005 and 2010 FDA LABA regulatory actions contributed to changes in use. However, trends of declining use of all asthma medication classes except ICSs and LMs prior to the 2005 regulatory actions, suggest that other factors also contributed to the decline. One example of these factors could be earlier FDA regulatory actions from 2003 and 2004 which also focused on LABAs (Figure 1).[26]

Once the 2005 FDA regulatory activities were implemented, an expected decline in use was observed for fixed dose ICS-LABAs, but not single-agent LABAs. Since there was a significant increase in LM and ICS use, it appears that some patients switched from LABA-containing products to these alternatives. Another group of patients may have decided to discontinue controller medications altogether, since there was also an immediate increase in the number of patients with no medication use.

After the 2005 regulatory activities went into effect, there was an unexpected lingering impact on the LABA containing products. For fixed-dose ICS-LABAs, the positive change in trend meant use was no longer declining. For single-agent LABAs, the positive change in trend meant use was not declining as rapidly as it was prior to the 2005 regulatory actions. Use of LMs and no medication use were no longer increasing and ICS use remained unchanged between the 2005 and 2010 FDA regulatory actions. The increase in fixed-dose LABA use could have resulted from an increase in public understanding of appropriate use of LABA-containing products following the publication of the Expert Panel Report 3 (EPR-3) guidelines in 2007.[27] The guidelines recommend use of ICSs as first line of treatment in persistent asthma and LABAs to be used with low or medium dose ICSs as an alternative to high dose ICSs.

After the 2010 FDA regulatory actions, the expected immediate decline in LABA containing product use was not observed. However, there were small but immediate reductions in LM, ICS, and OCM use. The effect of the 2010 regulatory actions activities on fixed-dose ICS-LABA use was delayed; the negative change in trend meant use was declining after implementation. Use of single-agent LABAs continued to

decline after implementation but at a slower rate. Patients who had discontinued use of LABA containing products also stopped using controller medications, as evidenced by the increasing number of patients with no medication use between February 2010 and June 2011. There was no evidence of substitution to ICSs or LMs.

Most of the published literature on asthma medication trends did not overlap with our study period, so there were limited opportunities to make direct comparisons. However, the estimates we did find help explain the prevalence and trends of drug use observed in this analysis at baseline. Higashi et al. evaluated yearly prevalence estimates of asthma medication *prescribing* among patients less than 50 years of age with asthma from 1997 to 2009 using the National Ambulatory Care Survey (NACMS) and National Disease and Therapeutic Index (NDTI).[28] This study found asthma medication prescribing changed over time. During the study period, notable prescribing pattern changes included a reduction in SABA prescribing and an increase in ICS, LM and fixed-dose ICS-LABA prescribing. The increase in LM and fixed-dose ICS-LABA prescribing can be attributed to their entry into the market. There were notable declines in single-agent LABA and xanthine prescribing in NAMCS and ICS prescribing in NDTI.

When comparing overlapping time periods, NAMCS and NDTI ICS prescribing ranged from 26-30% and were comparable to prescription fills seen in January 2005 in this analysis (23.14%). Approximately 25% of people were given LM prescriptions, whereas LM fills were lower in our data. Rates of OCM use were similar between the two data sets hovering around 1%. Because the state pharmacy laws require new prescriptions for non-controlled substances on a yearly basis, SABA prescribing rates were probably higher than fill rates observed in our data for this rescue medication. Prescribing of fixed dose ICS-LABAs in NAMCS was higher than fills in our data (19.5% vs. 13%), and prescribing was even higher in NDTI (28%). The declining baseline trend we observed in fixed-dose ICS-LABA fills was mirrored by a large decline in the NDTI data, but not in the NAMCS data. There was no prescribing of single-agent LABAs in 2008 and 2009 in NAMCS and NDTI respectively while these agents were still in use in our population in 2011.

2. Age Group Comparisons

Use of asthma medication differed greatly between adults and children. The differences may be the result of age-related regulatory approvals and ease of use of products (e.g. oral medications vs. inhalers). All medication classes were used less often in children than in adults except LM. Overall, children with asthma used medication less frequently than adults.

Fixed-dose ICS-LABA use changed in children and adults after the 2005 regulatory actions activities, but only among adults after the 2010 regulatory actions. Single-agent LABA use in children and adults changed after both the 2005 and 2010 regulatory actions. After 2005, use of LMs and ICSs increased while single-agent LABA and fixed-dose ICS-LABA use decreased in both age groups, suggesting that a substitution effect may have occurred.

It was difficult to find studies that compared pediatric and adult medication use patterns. Most studies either focus on all age groups or on pediatric populations. Turner et al. studied asthma medication prescribing patterns between 1992 and 2004 using the United Kingdom's General Practice Research Database (GPRD) among children under the age of 12 years.[29] There are starkly different patterns of SABA, ICS and, fixed-dose LABA prescribing compared to fill patterns in the U.S. For instance, in 2004 only 3.3% of children were prescribed an ICS, while 0.35% were prescribed ICS-LABAs (not necessarily fixed-dose).[29] In January 2005, approximately 22% and 13% of all children filled ICSs and fixed-dose ICS-LABAs, respectively. The yearly trends were informative. All asthma medication prescribing declined

between 1998 and 2004. Similarly in our data, the number of children with no medication use was declining before the 2005 regulatory actions were released.

Arellano et al. studied medication use patterns among children with asthma aged 6-18 years in the Pharmetric data from 1995-2008.[30] Children with severe asthma used more medication in all classes than children with less severe asthma. We cannot compare overlapping time frames because Arellano pooled estimates over their entire study period. The pooled estimate of children 6-18 years not using any asthma medications was 37.6%.This estimate was slightly higher than seen in our population where no medication use ranged from 23.3%-29.5% for overlapping ages. Use was comparable among SABAs, OCSs, single-agent LABAs, OCMs, and other bronchodilators, but differed for LMs, ICSs, and fixed dose ICS-LABAs where use was more prevalent.

Korelitz et al. studied prevalent asthma medication use among children with asthma aged 0 to 17 years using data from the Ingenix LabRx Database from 2004-2005.[31] The pooled medication use patterns across age groups were similar to the pooled 2005-2010 estimates in our analysis for OCSs, single-agent LABAs and no medication use, but differed for LMs, SABAs, fixed-dose ICS-LABAs and ICSs.

Wasilevich et al. studied prevalent use of LABA containing products in a Michigan Medicaid population from 2006-2008.[32] Estimates were provided for pediatric and adult populations. The 2006 estimates were comparable to the pooled estimates from 2005-2010. Use of LABA products declined in 2007 and 2008 and the decline was greater in pediatric patients compared to adult patients. The trends were similar to those observed in this analysis.

3. Summary

The impact of the 2010 regulatory actions on use of LABA containing products was smaller than the impact of the 2005 regulatory actions. The limited impact of the February 2010 regulatory actions on use of LABA containing products could be attributed to: 1) already low prevalence rates at the time the regulatory actions were implemented; 2) multiple important regulatory actions prior to 2010; and 3) updated clinical guidelines and the publication of important clinical trials prior to 2010regulatory actions. We did not directly compare changes in LABA use to another asthma medication because the regulatory actions may have impacted all asthma medication use within the U.S. This concern was validated by the data since use of medication classes other than LABAs changed with the implementation of the LABAs regulatory actions

IV. AIM 2 – TO ASSESS TRENDS OF LABA INITIATION IN AN ASTHMA COHORT BEFORE AND AFTER THE 2010 FDA REGULATORY ACTIONS ON LABAS

In this aim, initiation of LABA containing products was measured in a cohort of asthma patients who had no history of using LABA containing products for at least 183 days. As a result, we were able to assess whether initiation of LABA products changed during the analysis period.

A. COHORT

A rolling monthly cohort definition determined the cohort used to measure incident LABA use patterns. The anchor date for this aim was the 1st of each month; therefore, all criteria related to continuous enrollment, age, and asthma diagnoses were identified in the 365 days within the 1st of each month. Members were excluded if they were current LABA users.

B. DRUGS OF INTEREST

Medication initiation was measured on a monthly basis. The drugs of interest included both single-agent and fixed-dose LABAs. Members were considered initiators if they had not been prescribed LABAs for at least 183 days prior to the 1st of each month. Indacaterol was not included in the analysis because it was approved in 2011.

C. OUTCOMES

Outcomes were measured as the proportion of eligible members who initiated LABA containing agents in any given month.

D. STATISTICAL ANALYSIS

1. Pooled Pre- and Post-Policy Comparisons

Descriptive statistics were generated by identifying the baseline characteristics of members only at the 1st time they were eligible for the cohort in each of the follow up periods. The medication use counts are based on the 1st time there was evidence of LABA initiation by the members.

2. Interrupted Time Series

For the ITS analyses, LABA initiation was identified from the monthly pools of health plan members with asthma.

E. RESULTS

1. Pre and Post-Policy Comparisons

There were over 1.4 million individuals who met the inclusion criteria for this aim. Approximately 1.1 million of these individuals were represented in the longer pre-policy period (January 2005 to January 2010). The pre-policy population was 56% female, the mean age was 26.3 (SD=19.4) years, and 56.4% of the population consisted of adults (Table 6). The characteristics of the post-policy population differed only slightly in age (mean 26.9 years (SD=19.5)).

Table 6. Baseline Characteristics of Asthma Patients by Long and Short Pre-Policy and Post-Policy Periods (N= 1,404,228)§

	Pre-Policy Periods		Post-Policy Period
	January 2005 – January 2010	January 2008 – January 2010	February 2010 – January 2010
Variables	(n= 1,147,753)	(n= 673,873)	(n= 577,909)
Sex*			
Female	56.00%	56.30%	56.32%
Male	44.00%	43.70%	43.68%
Age*			
0-4	15.42%	13.67%	12.44%
5-11	16.80%	17.74%	18.76%
12-17	11.37%	11.52%	12.12%
18-45	32.68%	32.02%	31.33%
46-65	23.73%	25.04%	25.35%
Mean Age (±SD), years	26.3±19.4	26.9±19.5	26.9±19.5*^

SD – standard deviation; § Patients all had a 183-day free period of LABA
*p<0.05 for Jan 2005-Jan 2010 vs. Feb 2010-June 2011 comparison; ^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

Very few members of the asthma cohort initiated single-agent LABAs. Initiation of fixed-dose ICS-LABAs was more common. Initiation of LABA containing medications declined over time as shown in Table 7. Initiation of single-agent LABAs declined by more than three quarters, while fixed-dose ICS-LABA initiation fell by half. In all cases, LABA initiation was already declining prior to the 2010 FDA regulatory actions; the estimates for the shorter pre-policy period (Jan 2008 to Jan 2010) are smaller than those of the longer pre-policy period.

Table 7. Pooled Estimates of LABA Initiation Among Asthma Patients by Long and Short Pre-Policy and Post-Policy Periods (N= 1,404,228)§

	Pre-Policy Periods		Post-Policy Period
	January 2005 – January 2010	**January 2008 – January 2010**	**February 2010 – January 2010**
Medication Class	(n= 1,147,753)	(n= 673,873)	(n= 577,909)
Single Agent LABA	0.99%	0.50%	0.23%*^
Fixed Dose ICS-LABA	7.57%	5.98%	4.68%*^
Any LABA	8.48%	6.47%	4.91%*^

LABA – long-acting beta$_2$ agonists; § Patients all had a 183-day free period of LABA
*p<0.05 for Jan 2005-Jan 2010 vs. Feb 2010-June 2011 comparison
^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

2. Interrupted Time Series

The ITS regression results confirm whether changes observed in descriptive statistics and figures were indeed significantly related to the regulatory actions (Table 8 and Figures 4 and 5). The intercepts of the ITS models provide the rate of initiation in January 2005. Fixed-dose ICS-LABAs (1.07%) were initiated more often than single-agent LABAs (0.20%).

Prior to the passage of regulatory actions in December 2005, rates of initiation of fixed-dose ICS-LABAs and single-agent LABAs were already declining (Figures 4 and 5). The cumulative decline in initiation of fixed-dose ICS-LABAs and single-agent LABAs was -0.22 and -0.11 absolute percentage points respectively, during the 11 months prior to the December 2005 regulatory actions.

Only fixed-dose ICS-LABA initiation was immediately impacted by the December 2005 regulatory actions; there was a -0.12 absolute percentage point decline in initiation. The change in trend between December 2005 and January 2010 was positive for both fixed-dose and single-agent LABAs. As a result, the slope for fixed-dose LABAs flattened while the slope for single-agent LABAs continued to decline but less steeply.

The February 2010 regulatory actions did not have an immediate impact on either single-agent or fixed-dose LABA initiation. The change in trend for single-agent LABA use from February 2010 through June 2011 was positive yet minute, resulting in a slope declining less steeply. The change in trend for fixed-dose ICS-LABAs after February 2010 was not significant.

Table 8. Interrupted Time Series Analysis of Initiation of LABA Containing Products Among Patients with Asthma in Percentage Points

	Fixed Dose ICS-LABA		Single Agent LABA	
Parameter∞	**Point Estimate**	**95%CI**	**Point Estimate**	**95%CI**
Intercept	1.07**	[0.99, 1.15]	0.20**	[0.19, 0.22]
Baseline Trend	-0.02**	[-0.03, -0.01]	-0.01**	[-0.01, -0.00]
Level Change after 2005 Policy	-0.12**	[-0.20, -0.05]		
Trend Change after 2005 Policy	0.02**	[0.01, 0.03]	0.00**	[0.00, 0.01]
Level Change after 2010 Policy	-0.07	[-0.14, 0.00]		
Trend Change after 2010 Policy	-0.01	[-0.01, 0.00]	0.00**	[0.00, 0.00]

ICS – Inhaled Corticosteroids; LABA – long-acting beta agonists; CI – Confidence Interval
*p-value<0.05; **p-value<0.01
∞-Only parameters with pvalues<0.2 were retained in the ITS model

Figure 4. Trends of Single-Agent LABA Initiation Among Patients with Asthma: January 2005 - June 2011

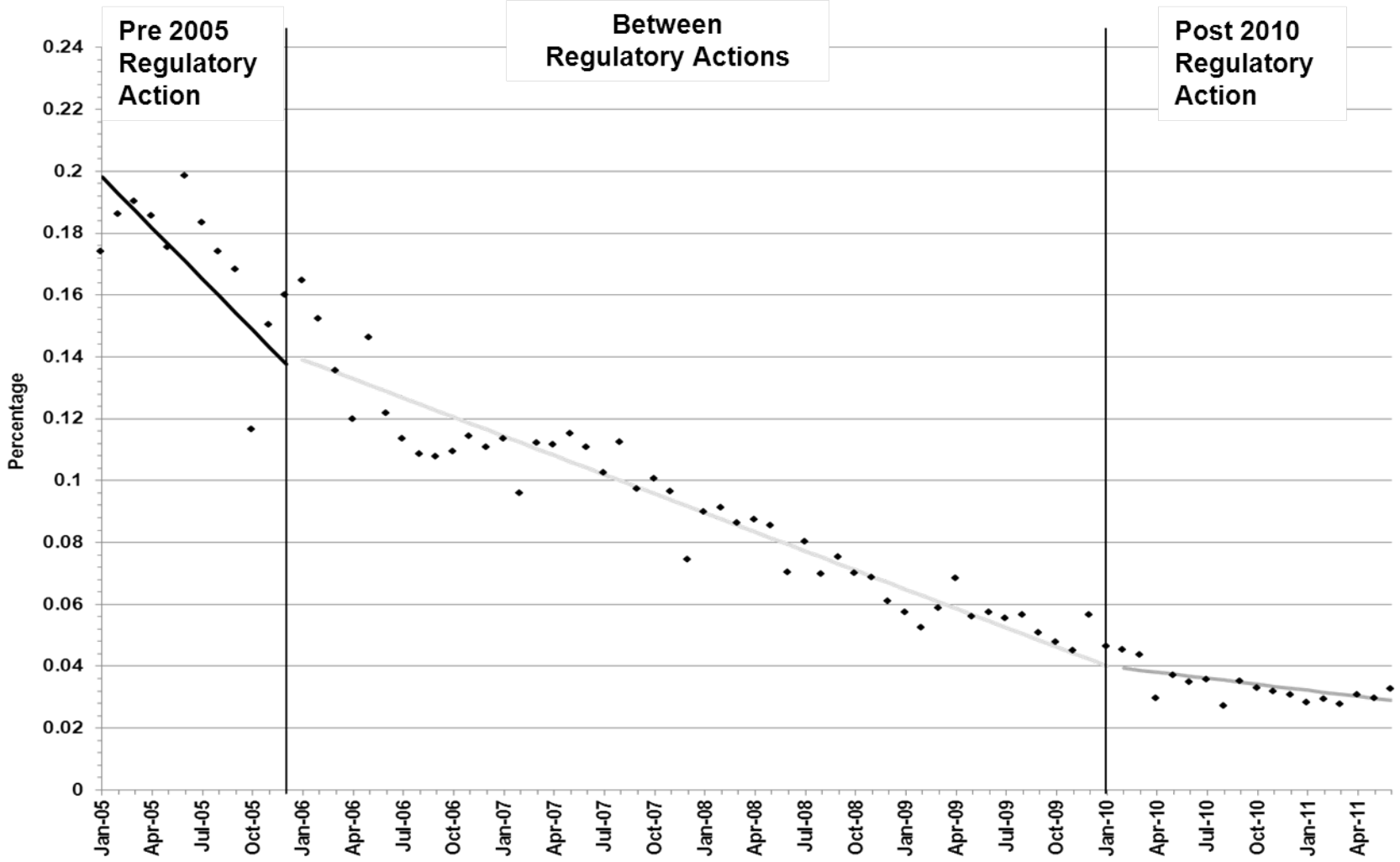
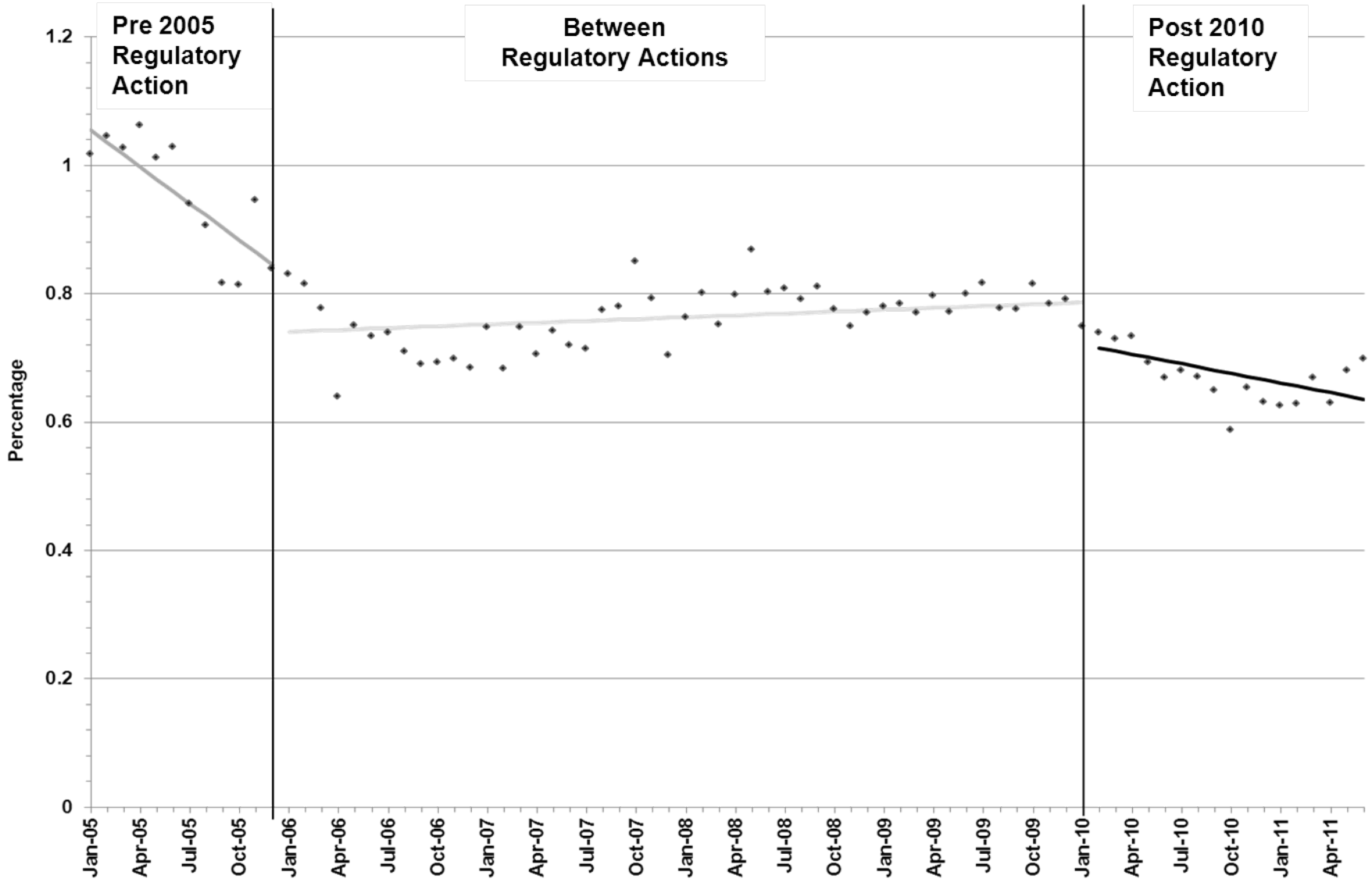


Figure 5. Trends of Fixed-Dose ICS-LABA Initiation Among Patients with Asthma: January 2005 - June 2011



3. Pre-Specified Subgroup Analyses

a) Pooled Pre- and Post-Policy Comparisons

Because the LABA regulatory recommendations do not differ by sex, we only present age group differences. The sex-stratified analyses are in the Appendix. The patterns of LABA initiation differed across age groups (Table 9). Children were less likely than adults to initiate any LABA products. Single-agent LABA initiation declined by more than 75% across all age groups between the long pre-policy period and the post-policy period. Fixed-dose ICS-LABA initiation declined by at least 50% in pediatric patients and by less than 50% among adults during the same time periods.

Table 9. Pooled Estimates of Single-Agent LABA and Fixed-Dose ICS-LABA Initiation Among Patients with Asthma by Long and Short Pre-Policy and Post Policy Periods and Age Group

	Pre-Policy Periods		Post-Policy Period
Medications	**January 2005 – January 2010**	**January 2008 – January 2010**	**February 2010 – June 2011**
Age 0 – 4 years	(N= 176,986)	(N= 92,151)	(N= 71,894)
Single Agent LABA	0.15%	0.07%	0.03%*^
Fixed Dose ICS-LABA	1.42%	0.94%	0.72%*^
Any LABA	1.56%	1.01%	0.75%*^
Age 5 – 11 years	(N= 192,837)	(N= 119,557)	(N= 108,405)
Single Agent LABA	0.39%	0.16%	0.05%*^
Fixed Dose ICS-LABA	6.60%	4.46%	2.97%*^
Any LABA	6.95%	4.61%	3.02%*^
Age 12 – 17 years	(N= 130,500)	(N= 77,646)	(N= 70,040)
Single Agent LABA	0.63%	0.24%	0.08%*^
Fixed Dose ICS-LABA	8.13%	5.99%	4.13%*^
Any LABA	8.68%	6.22%	4.21%*^
Age 18 – 44 years	(N= 375,068)	(N= 215,807)	(N= 181,045)
Single Agent LABA	1.10%	0.52%	0.24%*^
Fixed Dose ICS-LABA	8.63%	6.81%	5.30%*
Any LABA	9.63%	7.32%	5.54%*^
Age 45 – 65 years	(N= 272,362)	(N= 168,712)	(N= 146,525)
Single Agent LABA	1.99%	1.06%	0.53%*^
Fixed Dose ICS-LABA	10.53%	8.76%	7.38%*
Any LABA	12.39%	9.80%	7.91%*^

LABA - Long-acting beta$_2$ agonist; ICS - Inhaled corticosteroid
*p<0.05 for Jan 2005-Jan 2010 vs. Feb 2010-June 2011 comparison
^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

b) Interrupted Time Series

There were differences in the medication initiation patterns between pediatric and adult patients (Table 10). Initiation of single-agent LABAs at baseline was four times greater in adults than in children. Initiation of fixed-dose ICS-LABAs was only two times greater in adults than in children. In both cases this difference was significant. The baseline trend in LABA initiation was negative in adults and children. The adult initiation trend was significantly greater than that of children for both single-agent LABA and fixed-dose ICS-LABA initiation. The 2005 regulatory actions had an immediate negative effect on fixed-dose ICS-LABA initiation in both adults and children, while the effect only occurred in single-agent LABA initiation in children. The difference in level change for fixed-dose ICS-LABAs was significantly greater in adults than in children. The change in trend between December 2005 and January 2010 was significant and positive for all LABA initiation. The slope during this period was flat in both the pediatric and adult populations, because the positive changes in trend had the same magnitude as the initial negative

baseline initiation trends. The change in trend was significantly larger in adults than in children. The only significant level change resulting from the 2010 regulatory actions occurred among fixed-dose ICS-LABA initiation in children; initiation declined. These changes in level did not significantly differ between children and adults. The changes in trend after the 2010 regulatory actions were significantly but small in both children and adult single-agent LABA initiation. Differences in the change in trends were significant different between children and adults for both fixed-dose ICS-LABAs and single-agent LABAs.

Table 10. Interrupted Time Series of Initiation of LABA Containing Products Among Patients with Asthma in Percentage Points by Age Group∞

	Pediatric		Adult	
Medication Class	**Point Estimate**	**95%CI**	**Point Estimate**	**95% CI**
Single Agent LABA				
Intercept	0.08**	[0.07, 0.08]	0.32**^	[0.30, 0.35]
Baseline Trend	-0.00**	[-0.00, -0.00]	-0.01**^	[-0.01, -0.01]
Level Change after 2005 Policy	-0.01*	[-0.01, -0.00]		
Trend Change after 2005 Policy	0.00*	[0.00, 0.00]	0.01**^	[0.00, 0.01]
Level Change after 2010 Policy				
Trend Change after 2010 Policy	0.00**	[0.00, 0.00]	0.00**^	[0.00, 0.00]
Fixed Dose ICS-LABA				
Intercept	0.75**	[0.71, 0.80]	1.42**^	[1.31, 1.52]
Baseline Trend	-0.01**	[-0.02, -0.01]	-0.03**^	[-0.05, -0.02]
Level Change after 2005 Policy	-0.12**	[-0.17, -0.07]	-0.09	[-0.19, 0.00]
Trend Change after 2005 Policy	0.01**	[0.01, 0.02]	0.03**^	[0.02, 0.05]
Level Change after 2010 Policy	-0.05*	[-0.09, -0.01]	-0.07	[-0.16, 0.02]
Trend Change after 2010 Policy	-0.00	[-0.01, 0.00]	-0.01^	[-0.02, 0.00]

ICS – Inhaled Corticosteroids; LABA – long-acting beta agonists; CI – Confidence Interval
*pvalue<0.05; **pvalue<0.01; ^pvalue<0.05 for pediatric vs. adult
∞-Only parameters with pvalues<0.2 were retained in the ITS model

F. DISCUSSION

1. Overall Results

We identified over 1.4 million patients with asthma between January 2005 and June 2011. Initiation of LABA containing products was extremely low at baseline, and declined over the course of the study period. The 2005 and 2010 FDA LABAs regulatory actions affected fixed dose ICS-LABAs and single-agent LABAs differently. Initiation was declining prior to the 2005 regulatory actions for all LABA containing products. Once the 2005 FDA regulatory actions were implemented, an expected decline in use was observed with fixed dose ICS-LABAs, but not single-agent LABAs.

After the 2005 regulatory actions went into effect, there was an unexpected lingering impact on LABA containing products. For fixed-dose ICS-LABAs, the positive change in trend meant initiation was no longer declining. For single-agent LABAs, the positive change in trend meant initiation continued to decline, albeit at a lesser rate. The increase in fixed-dose ICS-LABA initiation could have resulted from compliance with the EPR-3 guidelines.[27] The 2010 FDA regulatory actions did not impact fixed-dose ICS-LABA initiation patterns. For single-agent LABAs, there was a positive change in trend which slowed the pace of declining initiation.

We found no studies examining initiation of LABA-containing products in a general asthma population that consisted of all age groups together for comparison.

2. Age Group Comparisons

Both the 2005 and 2010 regulatory actions had a larger impact on medication initiation among the pediatric population than among the adult population. While the 2010 regulatory actions did have a pediatric focus, factors that were present before the regulatory actions were implemented, including increased awareness of LABA agents not being approved for very young patients, may have contributed changes in initiation patterns.

Current literature on LABA initiation mainly focused on pediatric patients. We found no studies examining initiation of LABA-containing products in an adult asthma population. Arellano et al. studied ICS-LABA initiation in children with asthma aged 6-18 years using Pharmetric data from 1995-2008.[30] The pooled estimate for fixed-dose ICS-LABA initiation was higher for patients with less severe asthma (2.3%) than for those with severe asthma (1.6%). Initiation was higher in our population (~8%). Conversely, Arellano et al. found that initiation of single-agent LABAs was higher in pediatric patients with more severe asthma (1.3%) than less severe asthma (0.5%). The pooled estimates from our analysis were comparable to the less severe asthma population.

Thomas et al. evaluated prescribing trends for pediatric patients with asthma aged 0- 14 years who had never been prescribed controller medications using the UK's GPRD from September 2006 to February 2007.[33] Of all patients who initiated therapy, 5.7% initiated fixed-dose ICS-LABAs and 1.2% initiated single-agent LABAs. The fixed-dose LABA initiation rates are comparable with our population; however, our rate of single-agent LABA initiation was lower.

3. Summary

The impact of the 2010 regulatory actions on LABA initiation was smaller than the impact of the 2005 regulatory actions. The relatively small effect of the regulatory actions on LABA initiation could be due to the already small amount of initiation at the outset of the study period, updated clinical guidelines released prior to the 2010 regulatory actions, and the publication of important clinical trials prior to the 2010 regulatory actions.

V. AIM 3 – TO ASSESS THE UPTAKE OF FIXED-DOSE ICS-LABA COMBINATION PRODUCTS AMONG NEW USERS OF LABAS BEFORE AND AFTER THE 2010 FDA REGULATORY ACTIONS ON LABAS

In this aim, uptake of fixed-dose ICS-LABA products was measured in a cohort of asthma patients who had initiated any LABA product. As a result, we were able to assess whether fixed-dose ICS-LABA product initiation has changed.

A. COHORT

The cohort was created among new LABA users. A LABA index date was assigned the 1st time an individual filled a LABA containing prescription with a 183-day period of no LABA use. The anchor date for this aim was the LABA index date, and all criteria related to continuous enrollment, age, and asthma diagnoses where identified in the 365 days within the LABA index date.

B. COMBINATION PRODUCT USE

The cohort consists of members initiating any LABA product. The combination products of interest include the following fix-dose LABA products: budesonide-formoterol, fluticasone-salmeterol, and mometasone-formoterol.

C. OUTCOMES

Outcome was measured as the proportion of new LABA users who initiated fixed-dose ICS-LABA products.

D. STATISTICAL ANALYSIS

1. Pooled Pre- and Post-Policy Comparisons

In this aim, the descriptive statistics were generated by identifying the baseline characteristics of LABA initiators at the start of each new LABA episode within each policy period. Comorbidity characteristics were measured in addition to demographic characteristics. The fixed-dose ICS-LABA initiation counts were also based on each new LABA episode.

2. Interrupted Time Series

For the ITS analyses, fixed-dose ICS-LABA initiation was grouped by the month of the LABA index date.

E. RESULTS

1. Pooled Pre- and Post-Policy Comparisons

There were 135,601 members who met the inclusion criteria for this aim. These members initiated LABA containing products 159,064 times (episodes). Just over 126,000 of these episodes occurred in the longer pre-policy period (January 2005 to January 2010). Members with a new LABA episode in the longer pre-policy period were 62.5% female, 56.4% adult, and had a mean age of 34.5 (SD=18.0) years (Table 11). Age was significantly different in the post-policy period (mean 36.6 years (SD=17.9)). There were fewer ARIs and cases of allergic rhinitis, but more use of nasal steroids in the post-policy period compared to the pre-policy periods.

Table 11. Baseline Characteristics of LABA Initiators Per New LABA Episode by Long and Short Pre-Policy and Post-Policy Periods (N= 159,064)

	Pre-Policy Periods		Post-Policy Period
	January 2005 – January 2010	**January 2008 – January 2010**	**February 2010 – June 2011**
Variables	(n= 126,198)	(n= 52,215)	(n= 32,866)
Sex			
Female	62.50%	62.87%	63.38%
Male	37.50%	37.13%	36.62%
Age			
0-4	1.15%	1.32%	1.27%
5-11	13.30%	12.17%	10.98%
12-17	12.51%	11.36%	10.66%
18-45	36.73%	36.18%	35.55%
46-65	36.31%	38.97%	41.54%
Mean Age (±SD), years	34.5±18.0	35.6±18.0	36.6±17.9*^
Comorbidities & Utilization			
ARI	51.29%	46.76%	45.34%*^

Table 11. Baseline Characteristics of LABA Initiators Per New LABA Episode by Long and Short Pre-Policy and Post-Policy Periods (N= 159,064)

	Pre-Policy Periods		Post-Policy Period
	January 2005 – January 2010	January 2008 – January 2010	February 2010 – June 2011
Variables	(n= 126,198)	(n= 52,215)	(n= 32,866)
GERD	11.26%	11.26%	12.54%
Allergic Rhinitis	31.98%	29.83%	31.35%*^
Use of nasal steroids	33.05%	33.45%	35.13%*

SD – standard deviation; ARI- acute respiratory infection; GERD – gastrointestinal reflux disease
*p<0.05 for Jan 2005-Jan 2010 vs. Feb 2010-June 2011 comparison
^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

Fixed-dose ICS-LABAs were the agents of choice for the majority of new LABA episodes (88.85%) between January 2005 and January 2010 (Table 12). Initiation of fixed-dose ICS-LABAs increased 7.3% between the pre- and post-policy periods. Initiation was also significantly lower in the shorter pre-policy period (Jan 2008 to Jan 2010) than in the post-policy period.

Table 12. Pooled Estimates of Fixed-dose LABA Initiation Per New LABA Episode by Long and Short Pre-Policy and Post-Policy Periods (N= 159,064)

	Pre-Policy Periods		Post-Policy Period
Medications	January 2005 – January 2010 (n= 126,198)	January 2008 – January 2010 (n= 52,215)	February 2010 – June 2011 (n= 32,866)
Fixed-dose ICS-LABA	88.85%	92.60%	95.34%*^

LABA – long-acting beta$_2$ agonists; ICS – Inhaled Corticosteroids
*p<0.05 for Jan 2005-Jan 2010 vs. Feb 2010-June 2011 comparison
^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

2. Interrupted Time Series

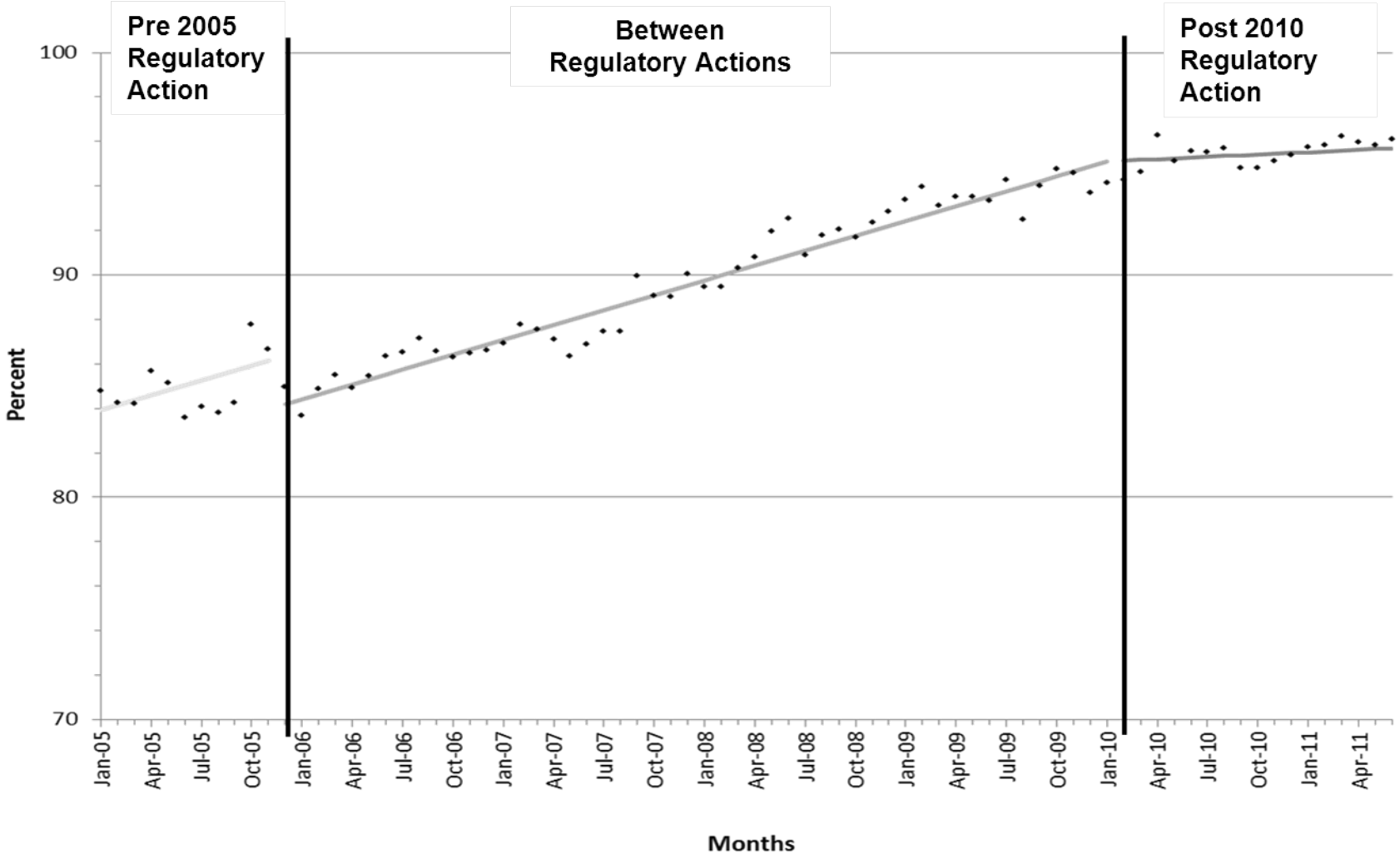
The ITS regression results confirm whether changes observed in descriptive statistics and figures were indeed significantly related to the regulatory actions (Table 13 and Figure 6). The intercepts of the ITS models provide the proportion of new users who start fixed-dose LABAs in January 2005; a majority of new LABA users started a fixed-dose ICS-LABA agent (83.69%). Prior to regulatory actions being passed in December 2005, fixed-dose LABA initiation increased Figure 6). The cumulative increase in new episodes of fixed-dose ICS-LABAs during the 11 months prior to the December 2005 regulatory actions was 2.42 absolute percentage points. Once the 2005 regulatory actions went into effect, there was an immediate drop in fixed-dose LABA initiation. The 2005 regulatory actions did not affect the slope, therefore fixed-dose ICS-LABA initiation increased at the same rate as the baseline trend prior to the regulatory actions. The February 2010 regulatory actions did not have an immediate impact on fixed-dose LABA initiation, however there was a negative change in trend between February 2010 and June 2011. As a result, the slope for fixed-dose ICS-LABA initiation flattened.

Table 13. Interrupted Time Series Analysis of Fixed-Dose ICS-LABA Initiation Among New LABA Episodes in Percentage Points

Parameter∞	Point Estimate	95% CI
Intercept	83.69**	[83.16, 84.22]
Baseline Trend	0.22**	[0.21, 0.24]
Level Change after 2005 Policy	-2.16**	[-2.95, -1.37]
Trend Change after 2005 Policy		
Level Change after 2010 Policy		
Trend Change after 2010 Policy	-0.19**	[-0.25, -0.12]

ICS – Inhales corticosteroid; LABA – Long acting beta agonist; CI – Confidence Interval
*pvalue<0.05; **pvalue<0.01
∞-Only parameters with pvalues<0.2 were retained in the ITS model

Figure 6. Trends of Fixed-Dose ICS-LABA Initiation Among New LABA Episodes: January 2005 - June 2011



3. Pre-specified Subgroup Analyses

c) Pooled Pre- and Post-Policy Comparisons

Because the *regulatory recommendations* governing asthma medications did not differ by sex, we only present the age group differences here. The sex-stratified analyses are in the Appendix. There was variation in fixed-dose ICS-LABA initiation by age group (Table 14). Patients in the youngest and oldest age groups had the lowest prevalence of fixed-dose ICS-LABA initiation in the long pre-policy period; however, initiation of fixed-dose ICS-LABAs increased the most between the long pre-policy period and the post-policy period within these age groups (11% and 10.2%, respectively). During the post-policy period less than 2% of children who initiated LABA products between the ages of 12 to 17 years started single-agent LABAs.

Table 14. Pooled Estimates of Fixed-Dose LABA Initiation Per New LABA Episode by Long and Short Pre-Policy and Post-Policy Periods and Age Group (N= 159,064)

	Pre-Policy Periods		Post-Policy Period
Medication	**January 2005 – January 2010**	**January 2008 – January 2010**	**February 2010 – June 2011**
Age 0 – 4 years	(N= 1,449)	(N= 691)	(N= 419)
Fixed-dose ICS-LABA	85.58%	92.19%	94.99%*
Age 5 – 11 years	(N= 16,783)	(N= 6,354)	(N= 3,608)
Fixed-dose ICS-LABA	94.75%	96.69%	98.14%*^
Age 12 – 17 years	(N= 15,793)	(N=5,934)	(N= 3,504)
Fixed-dose ICS-LABA	93.41%	96.36%	98.23%*^
Age 18 – 44 years	(N= 46,354)	(N= 18,889)	(N= 11,684)
Fixed-dose ICS-LABA	89.31%	93.26%	95.81%*^
Age 45 – 65 years	(N= 45,819)	(N= 20,347)	(N= 13,651)
Fixed-dose ICS-LABA	84.75%	89.63%	93.47%*^

LABA - Long-acting beta$_2$ agonist; ICS - Inhaled corticosteroid
*p<0.05 for Jan 2005-Jan 2010 vs Feb 2010-June 2011 comparison
^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

d) Interrupted Time Series

Children under the age of 18 initiated fixed-dose ICS-LABAs at a much higher rate than adults in January 2005 (Table 15). The positive baseline trend was only significant in the pediatric population. There was an immediate decline in fixed-dose ICS-LABA initiation in adults and pediatric patients once the 2005 regulatory actions were implemented. The changes in level as a result of the 2005 regulatory actions did not significantly differ between children and adults. The change in trend between December 2005 and January 2010 was not significant in either the adult or pediatric populations; however the difference in the changes in trend were significant between them. The 2010 regulatory actions did not have an immediate impact in either population. The negative changes in trend after the 2010 regulatory actions were significant in both children and adult fixed-dose ICS-LABA initiation and the difference in the changes in trend were also significant between the age groups.

Table 15. Interrupted Time Series Analysis of Fixed-Dose ICS-LABA Initiation Among New LABA Episodes in Percentage Points by Age Group

	Pediatric		Adult	
Parameter∞	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
Intercept	90.52**	[89.93, 91.11]	81.33**^	[80.09, 82.58]
Baseline Trend	0.15**	[0.13, 0.16]	0.12	[-0.05, 0.30]
Level Change after 2005 Policy	-1.52**	[-2.41, -0.63]	-1.29*	[-2.47, -0.10]
Trend Change after 2005 Policy			0.13^	[-0.05, 0.31]
Level Change after 2010 Policy				
Trend Change after 2010 Policy	-0.13**	[-0.20, -0.06]	-0.23**^	[-0.30, -0.16]

ICS – Inhaled Corticosteroids; LABA – long-acting beta agonists; CI – Confidence Interval
*pvalue<0.05; **pvalue<0.01; ^pvalue<0.05 for pediatric vs. adult
∞-Only parameters with pvalues<0.2 were retained in the ITS model

F. DISCUSSION

1. Overall Results

We identified 159,054 episodes of LABA initiation between January 2005 and June 2011. The majority of new LABA episodes were for fixed-dose ICS-LABA. Fixed-dose ICS-LABA initiation was increasing prior to the 2005 regulatory actions. Once the 2005 regulatory actions went into effect there was an immediate decline in fixed-dose ICS-LABA initiation which means there was a subsequent increase in single-agent LABA initiation. This observation was not expected and the reason for this decline is unclear. The 2005 regulatory actions did not cause a change in trend; therefore, initiation of fixed-dose ICS-LABAs continued to increase at the same rate it was increasing prior to the 2005 regulatory actions.

We found one study which measured LABA initiation between 2005 and 2009 using IMS Health Plan Claims data. Initiation of fixed-dose ICS-LABA was slightly higher than rates of initiation in this analysis during the same period (96% vs. 89%).[34] The difference in rates may be attributed to differing inclusion criteria. This analysis required two outpatient asthma visits in the absence of either a hospitalization or emergency department visit, while the other study required a single outpatient asthma visit for inclusion.

The 2010 FDA regulatory actions did not immediately impact fixed-dose ICS-LABA initiation patterns, but the increasing rate of fixed-dose ICS-LABA initiation slowed down after the regulatory actions were implemented. The effect was unexpected; however it may demonstrate that fixed-dose ICS-LABA initiation was reaching a plateau.

It appears that fixed-dose ICS-LABA initiation rates level off around 95%. Given that the regulatory actions do not require fixed-dose ICS-LABA use in adults, it is unrealistic to expect 100% initiation with fixed-dose ICS-LABAs. There may always be some people who initiate single-agent LABAs because doing so may allow for more flexibility in dosing the ICS. Additionally, there could be a financial reason. If patients are adding on LABA therapy per clinical guidelines, they may already be on ICS therapy. A patient could continue to use the ICS they have on hand if a single-agent LABA is initiated to avoid wasting the unused supply of an ICS.

2. Age Group Comparisons

The 2010 regulatory actions addressed fixed-dose ICS-LABA initiation in children. However, our data show that the increasing trend in fixed-dose ICS-LABA initiation was occurring prior to the 2005 regulatory actions and was not altered once the 2005 regulatory actions were implemented. Similar patterns were observed in adults however the magnitude differed. Initiation of fixed-dose ICS-LABAs

slowed in both age groups after the 2010 regulatory actions and leveled off around 98% in the pediatric population and around 95% in adults.

A similar decline prior to the 2010 regulatory actions was occurring in the IMS data for both the older pediatric and adult populations.[34]

3. Summary

The 2010 regulatory actions did not impact the proportion of LABA initiators who started fixed-dose ICS LABAs in a meaningful way. All increases observed were occurring prior to either regulatory actions (i.e. 2005 and 2010) and slowed after the 2010 regulatory actions. Maximum rates of fixed-dose ICS-LABAs hover around 95%.

VI. AIM 4 – TO ASSESS APPROPRIATENESS OF LABA INITIATION AMONG NEW USERS OF LABAS BEFORE AND AFTER THE 2010 FDA REGULATORY ACTIONS ON LABAS

This aim focuses on the cohort of health plan members who initiated LABAs during the study period and assesses whether the decision to initiate a LABA was appropriate. A history of controller medication use and evidence of an exacerbation are markers used to measure appropriateness.

A. COHORT

The cohort was created among new LABA users. A LABA index date was assigned the 1st time an individual filled a LABA-containing product following a 183-day period of no LABA use. The anchor date for this aim was the LABA index date, and all the criteria related to continuous enrollment, age, and asthma diagnoses were identified within 365 days of this date.

B. APPROPRIATE USE

Appropriate use was defined by a history of controller medication use and evidence of poor control prior to LABA initiation. Health plan members met the criteria for prior controller medication use if there was evidence of a supply of a controller medication (e.g. ICS or leukotriene inhibitor) within 90 days of the LABA index date. Poor control was established if a health plan member had any of the following events in the 12-month pre-index period: an asthma-related hospitalization or emergency department visit; fills for two or more OCSs with less than a 21-day supply of medication; or ≥6 dispensings of SABAs.

C. OUTCOMES

Two outcomes were studied:

1) The proportion of new LABA users with a history of controller medication use within 90 days of the LABA index date.
2) The proportion of new LABA users with a history of poor control within 365 days of the LABA index date.

D. STATISTICAL ANALYSIS

1. Pooled Pre- and Post-Policy Comparisons

The descriptive statistics were generated by identifying the baseline demographic and comorbidity characteristics of LABA initiators at the start of each new LABA episode within each policy period. The appropriate use counts are based on each new LABA episode.

2. Interrupted Time Series

For the ITS analyses, prior controller medication use and poor control were grouped by the month of the LABA index date.

To reflect the beginning and end of FDA regulatory actions, we examined only two policy periods: 1) January 2005 to January 2010; and 2) February 2010 to June 2011. In the initial protocol,[17] three policy periods were identified: 1) January 2005 to November 2005; 2) December 2005 to January 2010; and 3) February 2010 to June 2011. This change was made because only the 2010 FDA regulatory recommendations address the issue of appropriate use. Prior regulatory actions focused on alerting the public of LABA safety issues. As a result of having two policy periods, the parameters included in the ITS regression models were the intercept, baseline slope/trend, change in the trend, and change in the level. The intercept represents the prevalence of the outcome, appropriate use, in January 2005. The baseline trend represents the slope between January 2005 and January 2010. There is one *change in level* parameter which represents an immediate effect of the policy once implemented in February 2010. Similarly, one *change in trend* parameter was estimated from February 2010 to June 2011.

E. RESULTS

1. Pooled Pre- and Post-Policy Comparisons

The demographic information for the cohort included in this aim is presented in Table 11 of Section V.E.1.

Between January 2005 and January 2010, 47.75% of new LABA episodes were preceded by controller medication use within 90 days of the LABA index date and approximately 50% of new LABA episodes were preceded by a history of poor control in the year prior to initiation. Collectively, 72.64% of LABA initiation was preceded by controller medication and/or poor asthma control. There were no differences in the appropriate use measures before and after the 2010 FDA regulatory recommendations.

Table 16. Pooled Estimates of Measures of Appropriate LABA Initiation Among New LABA Episodes by Long and Short Pre-Policy and Post-Policy Periods (N= 159,064)

	Pre-Policy Periods		Post-Policy Period
	January 2005 – January 2010	**January 2008 – January 2010**	**February 2010 – June 2011**
Appropriate Use	(n= 126,198)	(n= 52,215)	(n= 32,866)
Controller Medications 90 Days Prior to Initiation	47.75%	47.81%	48.74%
Poor Control Prior to Initiation	49.36%	48.57%	49.82%
Any Appropriate Use Prior to Initiation	72.64%	72.03%	72.61%

LABA – long-acting beta$_2$ agonists
*p<0.05 for Jan 2005-Jan 2010 vs. Feb 2010-June 2011 comparison;
^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

2. Interrupted Time Series

The ITS regression results confirm whether changes observed in the descriptive statistics and figures were indeed significantly related to the regulatory activities (Table 17 and Figures 7-9). The intercepts of the ITS models provide the prevalence of the appropriate use measures in January 2005 (Table 17). In the beginning of the analysis period, 47.13% of LABA episodes started after a history of prior controller medication use and 50.59% of LABA episodes started after a history of poor control. A history of previous controller medication use and/or a history of poor control preceded 73.4% of the new LABA episodes.

Prior to the passage of regulatory actions in 2010, the trend of a history of poor control prior to initiating LABA products was on the decline (Figure 8), as was the slope for the overall measure of appropriate use (Figure 9). The cumulative declines in a history of poor control and overall appropriate use from January 2005 to January 2010 were 2.44 and 1.83 absolute percentage points, respectively (Table 17).

Table 17. Interrupted Time Series Analysis of Appropriate LABA Initiation Among New LABA Episodes in Percentage Points

Parameters∞	Point Estimate	95% CI
Controller Medication Use 90 Days Prior to Initiation		
Intercept	47.13**	[45.68, 48.58]
Trend Prior to the 2010 Policy	0.02	[-0.01, 0.05]
2010 Policy Impact		
Trend After the 2010 Policy		
Poor Control Prior to Initiation		
Intercept	50.59**	[50.01, 51.17]
Trend Prior to the 2010 Policy	-0.04**	[-0.05, -0.02]
2010 Policy Impact		
Trend After the 2010 Policy	0.21**	[0.12, 0.30]
Any Appropriate Use Prior to Initiation		
Intercept	73.54**	[72.91, 74.17]
Trend Prior to the 2010 Policy	-0.03**	[-0.04, -0.01]
2010 Policy Impact		
Trend After the 2010 Policy	0.10*	[0.02, 0.19]

LABA – long-acting beta agonists; CI – Confidence Interval
*p-value<0.05; **p-value<0.01
∞-Only parameters with pvalues<0.2 were retained in the ITS model

The 2010 regulatory recommendations had no impact on the proportion of new LABA episodes preceded by controller medication use 90 days prior to initiation (Table 17). These regulatory recommendations also did not have an immediate impact on either the proportion of new LABA episodes preceded by a history of poor control or overall appropriate use, but significantly impacted the change in trend for both outcome measures. The positive changes in trend turned the previously declining slopes into increasing slopes because the magnitudes of the changes in trend were greater than the initial baseline slopes (Figures 15 and 16). As a result, from February 2010 to June 2011 there were 3.57 and 1.70 absolute percentage point increases in new LABA episodes preceded by a history of poor control and overall appropriate use, respectively.

Figure 7. Trends of Controller Medication Use 90 Days Prior to Initiating LABA Products Among New LABA Episodes: January 2005 - June 2011

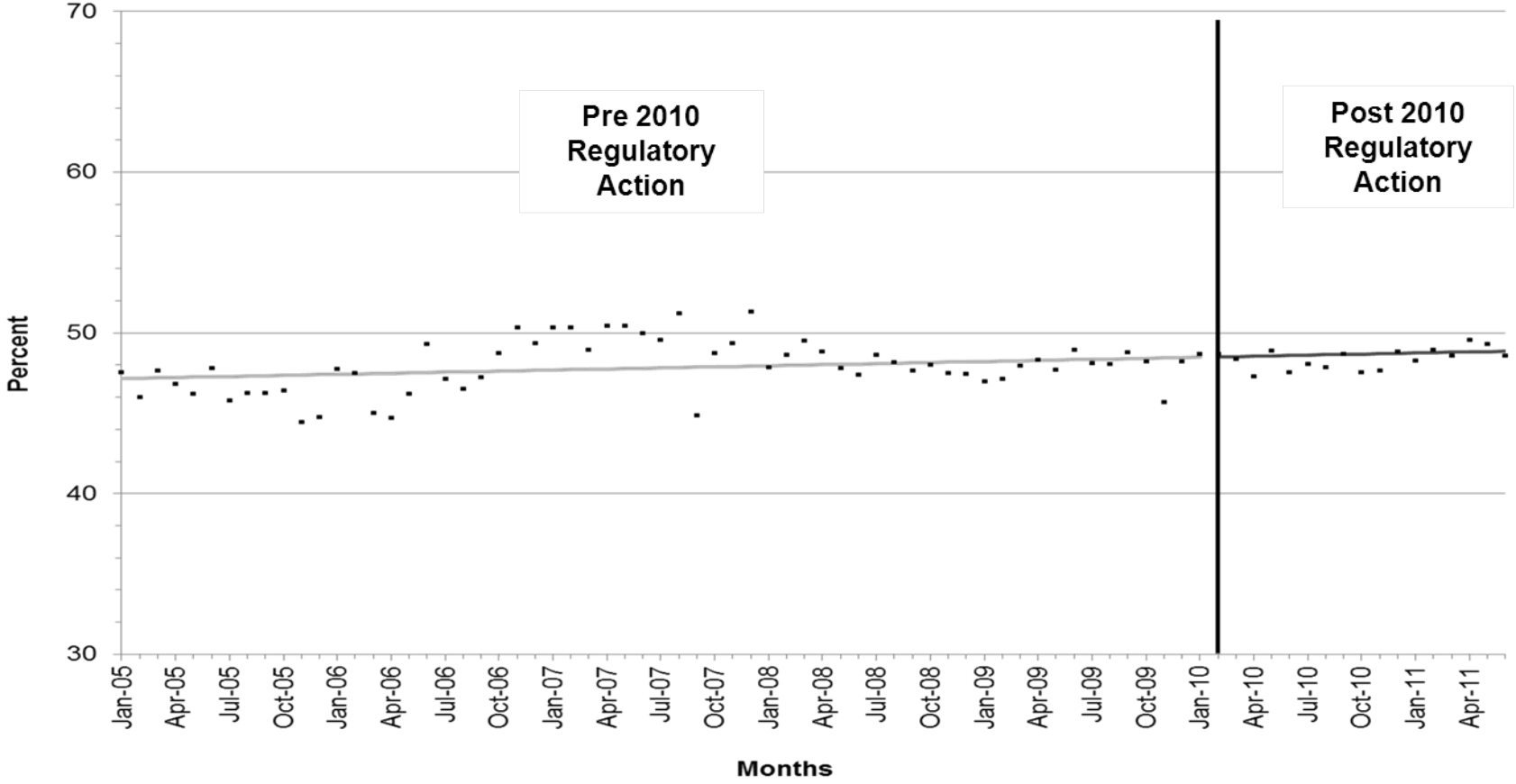


Figure 8. Trends of Poor Asthma Control During the Year Prior to Initiating LABA Products Among New LABA Episodes: January 2005 - June 2011

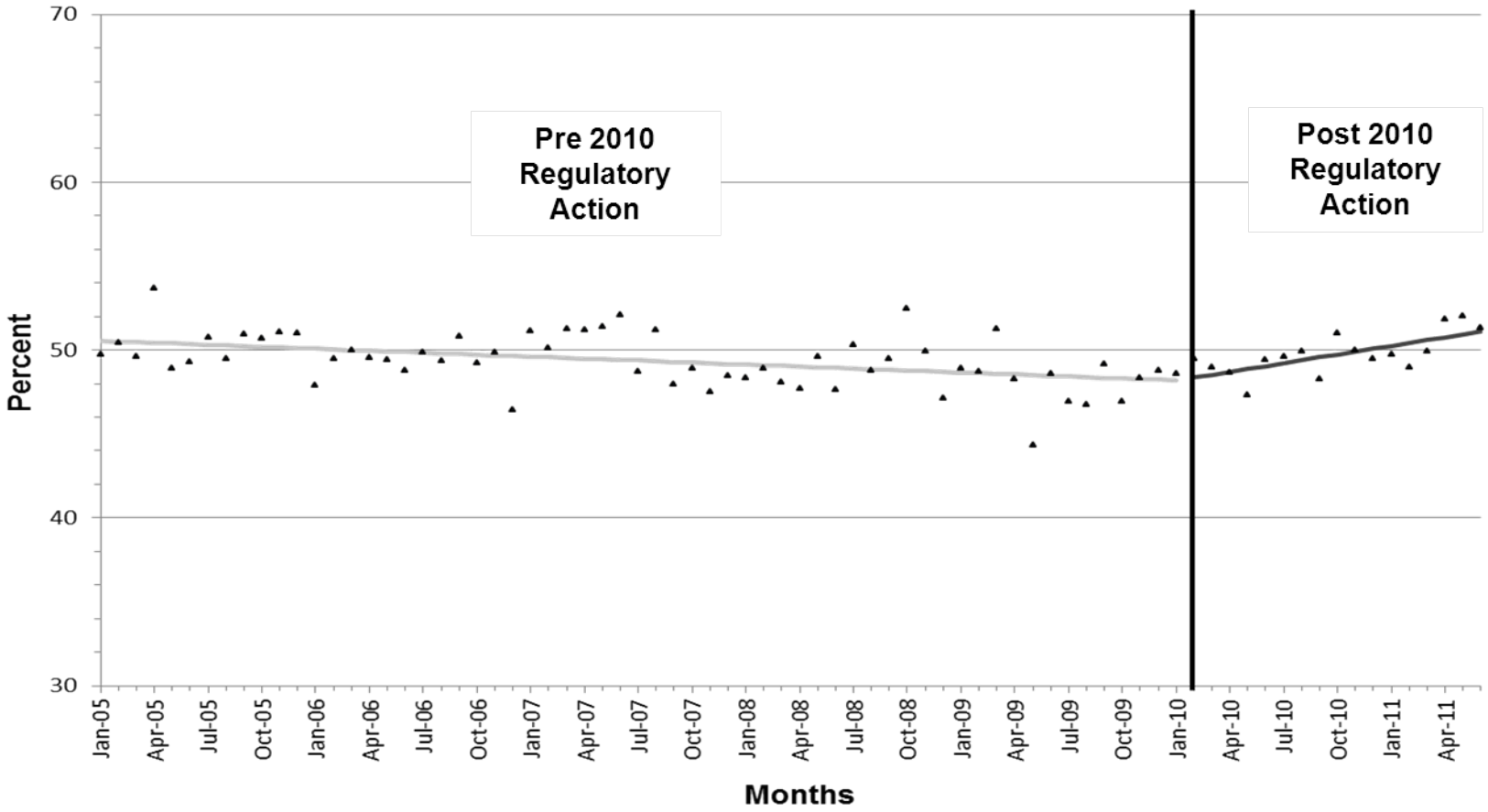
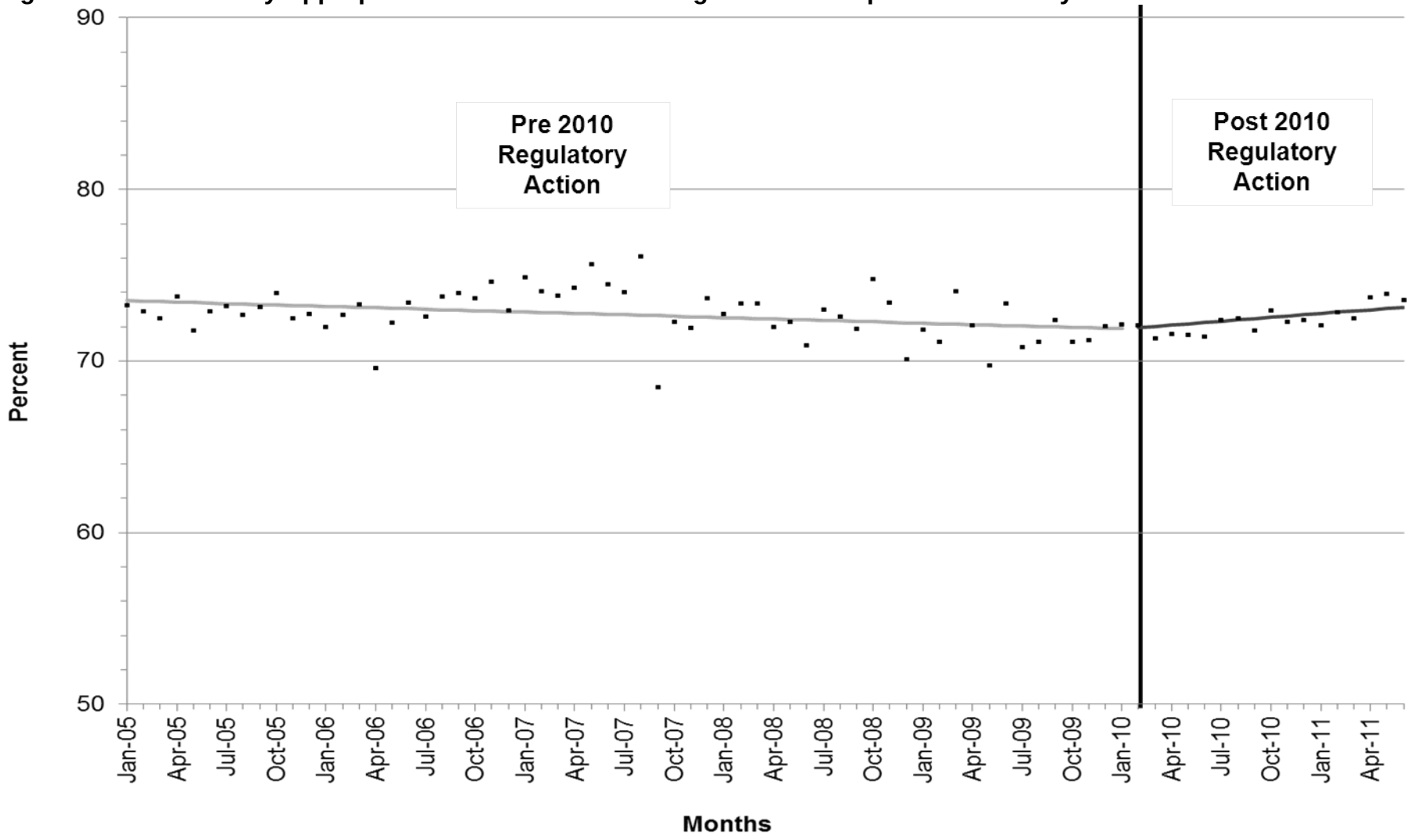


Figure 9. Trends of Any Appropriate LABA Initiation Among New LABA Episodes: January 2005 to June 2011



3. Pre-Specified Subgroup Analyses

e) Pooled Pre- and Post-Policy Comparisons

There was variation in prevalence of appropriate LABA initiation by age group (Table 18). While not tested, the youngest age group appeared to initiate LABAs most appropriately; overall appropriate use was as high as 92.68% in the long pre-policy period. The 2010 FDA regulatory recommendations had no effect on any of the appropriate use measures regardless of the comparisons between both pre-policy periods and the post-policy period.

Because the *regulatory recommendations* governing asthma medications did not differ by sex, we only present the age group differences here. The sex-stratified analyses are in the Appendix.

Table 18. Pooled Estimates of Measures of Appropriate LABA Initiation Among New LABA Episodes by Long and Short Pre-Policy and Post-Policy Periods and Age Group (N= 159,064)

Appropriate Use	Time Periods		
	January 2005 – January 2010	January 2008 – January 2010	February 2010 – June 2011
Age 0 – 4 years	(N= 1,449)	(N= 691)	(N= 419)
Controller Medications Prior to Initiation	79.64%	79.45%	82.10%
Poor Control Prior to Initiation	69.70%	71.78%	76.13%
Any Appropriate Use Prior to Initiation	92.68%	92.62%	93.08%
Age 5 – 11 years	(N= 16,783)	(N= 6,354)	(N= 3,608)
Controller Medications Prior to Initiation	59.47%	62.70%	66.46%
Poor Control Prior to Initiation	50.37%	52.16%	54.07%
Any Appropriate Use Prior to Initiation	77.70%	79.57%	80.60%
Age 12 – 17 years	(N= 15,793)	(N=5,934)	(N= 3,504)
Controller Medications Prior to Initiation	43.3%	44.5%	48.0%
Poor Control Prior to Initiation	45.8%	43.4%	45.0%
Any Appropriate Use Prior to Initiation	68.54%	67.19%	69.38%
Age 18 – 44 years	(N= 46,354)	(N= 18,889)	(N= 11,684)
Controller Medications Prior to Initiation	40.38%	40.34%	41.16%
Poor Control Prior to Initiation	53.48%	51.73%	52.76%
Any Appropriate Use Prior to Initiation	72.10%	71.11%	71.58%
Age 45 – 65 years	(N= 45,819)	(N= 20,347)	(N= 13,651)
Controller Medications Prior to Initiation	51.41%	49.97%	49.70%
Poor Control Prior to Initiation	45.39%	45.24%	46.60%
Any Appropriate Use Prior to Initiation	72.09%	71.24%	71.59%

LABA - Long-acting beta$_2$ agonist

*p<0.05 for Jan 2005-Jan 2010 vs. Feb 2010-June 2011 comparison

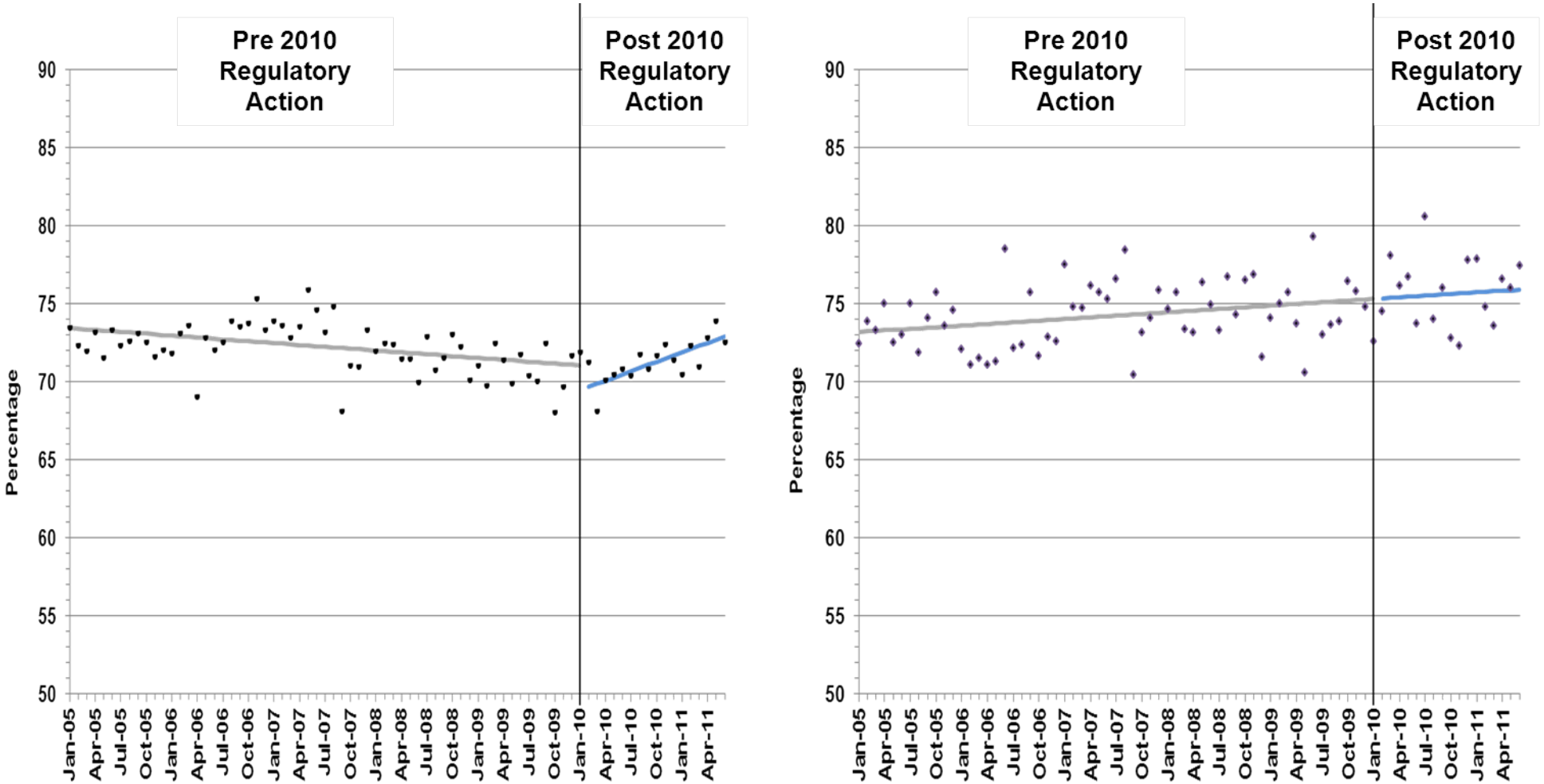
^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

f) Interrupted Time Series

In January 2005, children were more likely to have a history of controller medication use prior to LABA initiation than their adult counterparts (Table 19). The positive baseline trend was only significant in the pediatric population. However, children were less likely than adults to have a history of poor control prior to LABA initiation in January 2005. The negative baseline trend was only significant in the adult population and this parameter was significantly different from the pediatric estimate. While pediatric patients experienced a level change when the 2010 regulatory recommendations went into effect, this parameter was not significantly different from the adult estimate. Lastly, the change in trend for adults after the 2010 regulatory recommendations was positive and significantly different from pediatric estimates.

Figure 10. Trends of Any Appropriate LABA Initiation Among New LABA Episodes: January 2005 to June 2011

A. Adult **B. Pediatric**



The rate of overall appropriate use did not differ by age at baseline; however, baseline trends were significantly different (Table 19). The trend was increasing in children while declining at the same magnitude in adults. While not significant within the stratified model, the 2010 policy impact in adults was significantly different from pediatric estimates. Lastly, the change in trend for adults after the 2010 regulatory recommendations was positive and significantly different from pediatric estimates (Figure 10).

Table 19. Interrupted Time Series Analysis of Appropriate LABA Initiation Among New LABA Episodes in Percentage Points by Age group

	Pediatric		Adult	
Parameters∞	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
Controller Medication Use Prior to Initiation				
Intercept	48.92**^	[47.91, 49.93]	45.89**	[45.00, 46.77]
Trend Prior to the 2010 Policy	0.14**^	[0.11, 0.16]		
2010 Policy Impact				
Trend After the 2010 Policy				
Poor Control Prior to Initiation				
Intercept	49.14**	[48.57, 49.71]	51.18**^	[50.62, 51.74]
Trend Prior to the 2010 Policy			-0.6**^	[-0.07, -0.04]
2010 Policy Impact	1.87**	[0.65, 3.09]		
Trend After the 2010 Policy			0.24**^	[0.15, 0.33]
Appropriate Use				
Intercept	73.17**	[72.41, 73.94]	73.50**	[72.92, 74.08]
Trend Prior to the 2010 Policy	0.04**	[0.02, 0.05]	-0.04**^	[-0.06, -0.02]
2010 Policy Impact			-1.58^	[-3.17, 0.00]]
Trend After the 2010 Policy			0.24**^	[0.10, 0.39]

LABA – long-acting beta agonists; CI – Confidence Interval
*pvalue<0.05; **pvalue<0.01; ^pvalue<0.05 for pediatric vs. adult
∞-Only parameters with pvalues<0.2 were retained in the ITS model

F. DISCUSSION

1. Overall Results

We identified 159,054 episodes of LABA initiation between January 2005 and June 2011. Approximately half of new episodes were preceded by a history of controller medication use within 90 days of the index date. Half were also preceded by a history of poor control within a year if initiation. Rates of prior controller medication use remained unchanged throughout the study period. While initially on the decline, the rate of poor control as a criterion for LABA initiation increased after the 2010 FDA regulatory recommendations. The poor control changes drove the changes seen in the overall appropriate initiation measure.

Prior to the 2010 FDA regulatory recommendations, the EPR-3 guidelines recommended adding LABA to ICS therapy if a patient with persistent asthma was not adequately controlled.[27] The positive slope observed with controller medication use prior to the 2010 may reflect acceptance of the guideline recommendation.

Several studies evaluated appropriate use prior to the 2010 FDA regulatory recommendations. Friedman used Ingenix data from October 1, 2004 to September 30, 2006 to study ICS use prior to initiating fixed-dose ICS-LABAs among asthma patients aged 12 to 62 years.[35] Approximately 31% of patients used ICSs in the pre-index period. Two studies with similar study designs reported use of controller medications at

27.34% and 27.9% in the year prior to initiation.[36,37] The overall appropriate use measures were 37.6% and 39.2%. Ye et al. measured appropriate use in a single health plan between January 1, 2007 and December 31, 2007. The population was limited to patients with asthma between the ages of 12 and 64 years that had a 12-month ICS-LABA free window. Blanchette et al. used the same criteria but used Pharmetric data, which includes multiple health plan data, from July 1, 2007 to June 30, 2008. Both studies measured appropriate use prior to initiation of fixed-dose ICS-LABAs. Controller medication use was only 27.6% between January 1, 2007 and December 31, 2008 in an Oregon Medicaid population.[38] The study based the definition of asthma on HEDIS measures, included recipients between the ages of 5 and 64 years, required a 6-month look back period to assess new LABA use, and included patients with COPD. Lastly, Kaplan et al. used IMS LifeLink data from January 1, 2005 to October 31, 2009 to study controller medication use and poor control prior to LABA initiation in patients with asthma up to the age of 64 year with a 6-month LABA free period.[34] They found 64.1% and 30.6% of single-agent LABA and fixed-dose ICS-LABA initiators used either ICSs or LMs prior to initiation, respectively. Overall appropriate initiation was 45.3%.

Our study differed in that we defined asthma with at least 2 outpatient asthma diagnoses, included children 0-11 years, included initiation of all LABA products, included a LABA free window of 183 days, measured excessive SABA use by dispensing instead of canisters, and we included all controller medications in our definition of prior controller medication use. While we observed higher levels of appropriate use among pediatric patients, they represent a small enough portion of the overall population that their ability to drive up the numbers was minimal. System-related factors (e.g. formulary policies indicating when LABA agents can be prescribed, and clinical guideline compliance) may also play a role. Capturing system-related information was beyond the scope of this project.

2. Age Group Comparisons

Prior controller medication use was greater in children than it was in the adults. There was an increase in prior controller medication use unrelated to the 2010 regulatory recommendations in the pediatric population, while there were no meaningful changes noted in the adult population. Clinicians may be more cautious about prescribing LABAs in the youngest populations since use is off-label. Clinicians may be more inclined to turn to LABAs after controller medications have not adequately controlled their patients' asthma. The increase could also be the result of a diffusion of information associated with the EPR-3 guidelines. The 2010 regulatory recommendations impacted poor control prior to initiation in the adult population only. The overall appropriateness estimates in the pediatric population were driven by the pre-policy trends in controller medication use, while the adult overall appropriateness estimates were driven by the regulatory changes that impacted poor control.

Our analyses focused on all children to capture all LABA initiation, including off-label use while many other studies limited their analyses to ages approved for LABA use (i.e. 12 years and older).[35-37] The rates of appropriate use in children aged 0-11 in the Kaplan et al. evaluation were similar to our rates.[34] The two analyses differ in LABA initiators 12 years and older. In our analysis, rates hover around 70%, whereas appropriate use was less than 50% in the same age groups in the Kaplan's et al. analysis.

3. Summary

The 2010 FDA regulatory recommendations called for appropriate initiation of LABA products which include a history of controller medication use or evidence of poor control prior to LABA initiation. As of June 2011, an impact was observed with a small increase in history of poor control prior to initiation but not with prior controller medication use.

VII. AIM 5 – TO DESCRIBE THE EPISODE OF LABA USE AMONG NEW USERS OF LABAS BEFORE AND AFTER THE 2010 FDA REGULATORY ACTIONS ON LABAS

This aim focuses on the cohort of health plan members who initiated LABAs during the study period and assesses changes in the length of LABA therapy and use of concomitant controller medication before and after the 2010 FDA regulatory recommendations.

A. COHORT

The cohort was created among new LABA users. A LABA index date was assigned the 1st time an individual filled a LABA containing prescription with a 183-day period of no LABA use. The anchor date for this aim was the LABA index date, and all criteria related to continuous enrollment, age, and asthma diagnoses where identified in the 365 days within the LABA index date.

B. LABA FOLLOW-UP TIME

LABA follow-up time ran from the index date until the earliest occurrence of 183 days of follow-up, discontinuation of use, death, disenrollment from the health plan, January 31, 2010 (if a LABA was initiated in the pre-policy period), or June 30, 2011 (if a LABA was initiated in the post-policy period. Discontinuation was defined by a gap in the LABA day supply exceeding 7, 14, 30 and 45 days. Our results showed that very few members remained in the analyses when the gap determining discontinuation was defined as a gap of 7 or 14 days and consequently the statistical models, which will be discussed later in the statistical analysis section, did not converge. Therefore, the meaningful gap definition used throughout the report is 30 days. The discontinuation date is the date at the start of the gap exceeding 30 days.[38]

We censored day supply at January 31, 2010 in the pre-policy period and June 30, 2011 in the post-policy period. Follow-up was censored at the last date of the pre-period for health plan members who initiated in the pre-period, because the regulatory action could have influenced discontinuation behaviors. We chose a maximum follow-up of 183 days to allow more health plan members to have equal follow-up. Any gaps of use between the index date and the end of follow-up that were smaller than 30 days were subtracted from the number of days of the LABA episode.

Health plan members who switched between single-agent LABAs and fixed-dose ICS-LABAs were considered to have continued on therapy. Their medication supply was added to the end of the previous fill's day supply. If both single-agent and fixed-dose LABA products had the same index date, the day supply was based on the medication with the longest day supply; if the day supply was the same, the fixed-dose agent's data were used.

Results based on a 45-day meaningful gap were similar to the 30-day gap results.

C. CONTROLLER MEDICATION FOLLOW-UP TIME

Controller medication follow-up time was measured between the LABA index date and the LABA follow-up end date. The controller medications included ICSs, LMs, and OCMs. If a health plan member switched controller medications within the same class, the day supply of the new medication was added to the end of the day supply of the preceding fill. If a health plan member started a new class of controller medication, follow-up started from the date when the new medication was filled.

D. OUTCOMES

Three outcomes were studied.

1) The total day supply of new LABA episodes.
2) The proportion of controller medication day supply that overlapped with the LABA day supply in a new LABA episode.
3) The percent of new LABA episodes with 100% overlap of controller medication and LABA day supply during a new LABA episode.

E. STATISTICAL ANALYSIS

1. Pooled Pre- and Post-Policy Comparisons

The descriptive statistics were generated to compare outcomes within each of the pre- and post-policy periods.

2. Regression Analyses

Meta-analyses techniques based on random effects models were used to combine the regression model parameters across DPs.[39-41] In addition to an overall model, stratified models based on age, sex and LABA product were also generated. The variable of interest was an indicator of observations occurring after the 2010 FDA regulatory recommendations compared to observations occurring prior to the regulatory recommendations. Covariates included in the models are listed in Table 20. Each covariate was measured in the 12-month pre-index period unless otherwise stated. Since multiple LABA episodes were allowed per person, each regression analysis controlled for multiple observations per person using GEE.

Table 20. Covariates Used in the Multiple Regression Models

Age (reference ≥45 years)
0-4 years
5-11 years
12-17 years
18-44 years
Male (reference female)
Comorbities
GERD
Allergic Rhinitis
Acute Respiratory Infection
Nasal Steroid Use
Time of the year LABA was Initiated
January-March
April-June
July-September
October-December
Appropriate Use
Controller Medication 90 Days Prior to Initiation
Poor Control

GERD – gastrointestinal reflux disease; LABA – long-acting beta agonists

a) Cox Proportional Hazard Models

Unlike the previous analyses, individual-level data were used for multivariate regression analyses. Kaplan-Meier survival curves and extended Cox proportion hazard models were estimated to compare the risk of treatment discontinuation in the post- versus pre-policy cohorts of LABA initiators.[38, 42, 43] We

assessed whether there was an extended number of LABA initiators who discontinued therapy after 30 days by examining the proportional hazard assumption for those who discontinued in 30 days or less versus those who discontinued later. Thus, an extended Cox model was used to model two piecewise hazard ratios comparing two groups if the assumption did not hold.[38, 44] One hazard ratio was for more than 30 days and the other less than or equal to 30 days. The results of the Cox proportional hazard models may be interpreted as X times the risk of treatment discontinuation relative to the pre-policy cohort.

b) Poisson Models

We used individual-level Poisson regression models to analyze the portion of days overlap between LABAs and controller medications. The offset option in Poisson regression allowed us to define the denominator (total number of LABA days for each person). The count of days on controller medications is the numerator. Incidence rate ratios were generated to compare the post-policy cohort to pre-policy cohort. Negative binomial models were explored as an option to correct for overdispersion; however, these models did not consistently converge. The Poisson models did converge. A scale function was used to adjust for overdispersion in the Poisson models.

c) Logistic Regression Models

Individual-level logistic regression models were used to predict the number of LABA initiators with complete controller and LABA medication overlap during a new LABA episode.

F. RESULTS

1. Pooled Pre- and Post-Policy Comparisons

The demographic information for the cohort included in this aim is presented in Table 11 of Section V.E.1.

Between January 2005 and January 2010, the mean day supply of LABA was approximately 55 days (Table 21). Controller medications were almost always used concurrently with LABA agents (0.96 controller days per LABA day), and 88.55% of initiators used a controller medication during the entire time LABA agents were in use. The LABA mean day supply declined in the post-policy period compared to the long pre-policy period. The 2010 regulatory recommendations had no impact on concurrent use of controller medications and LABA agents.

Table 21. Pooled Estimates of Medication Use Patterns Among New LABA Episodes by Long and Short Pre-Policy and Post-Policy Periods (N= 159,064)

	Pre-Policy Periods		Post-Policy Period
Medication Use Patterns	**January 2005 – January 2010** (n= 126,198)	**January 2008 – January 2010** (n= 52,215)	**February 2010 – June 2011** (n= 32,866)
Mean Day supply of LABA After Initiation	55.09 ± 43.05	53.22 ± 41.53	52.89 ± 41.46*
Proportion of Days of LABA and Controller Medication Overlap	0.96±0.16	0.96±0.14	0.97±0.13
Percent of Episodes with 100% Overlap Between LABA and Controller medications	88.55%	88.33%	88.91%

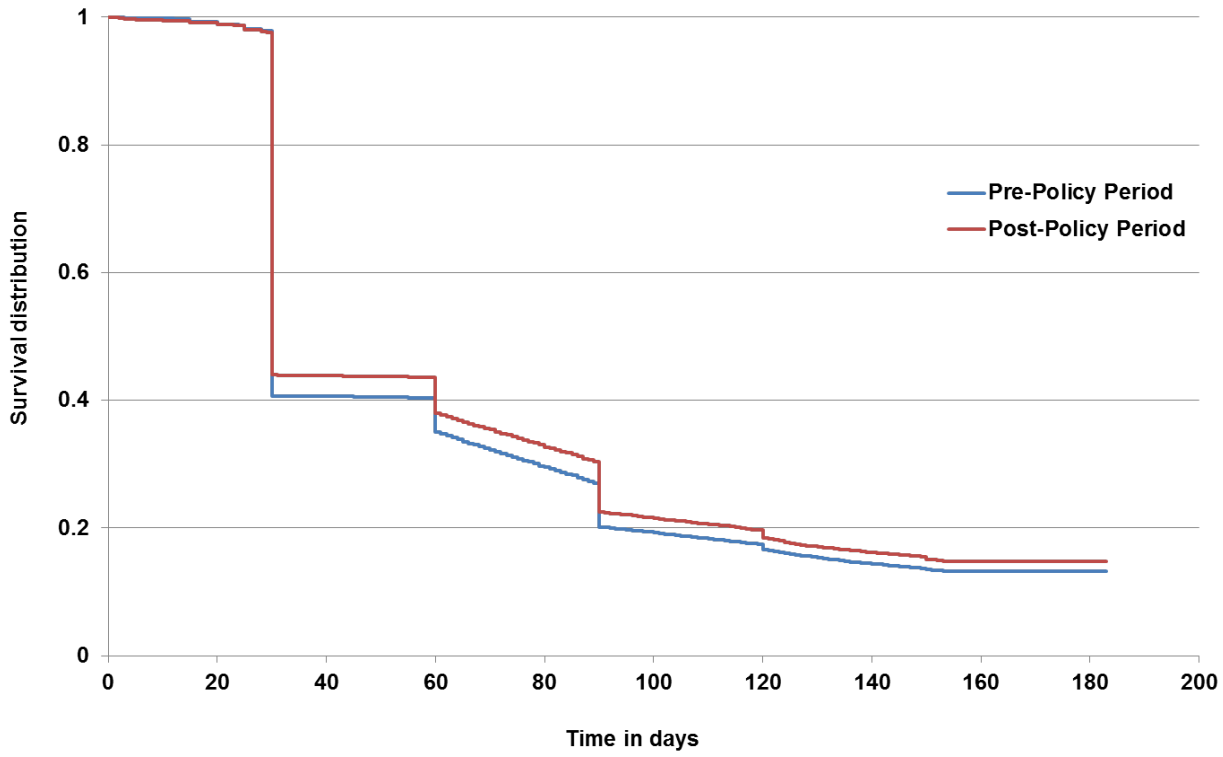
LABA – long-acting beta$_2$ agonists
*p<0.05 for Jan 2005-Jan 2010 vs. Feb 2010-June 2011 comparison;
^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

2. Regression Analyses

a) Cox Regression Models

Over 50% of patients discontinued LABA agents after 30 days of therapy (Figure 11). At the end of 183 days, 13.27% and 14.83% of patients remained on LABA therapy in the pre- and post-policy periods, respectively.

Figure 11. Probability of New LABA Episode Discontinuation



In the extended Cox regression, we found that the hazard ratio for day supply ≤30 days did differ from day supply >30 days (Table 22). Initiators in the post-policy period were 82% less likely to discontinue therapy within 30 days than those who had initiated in the pre-policy period. The 2010 regulatory recommendations did not change the risk of discontinuing LABA therapy greater than 30 days in length. Non-policy-related covariates also significantly impacted the risk of LABA discontinuation. Risk of discontinuation was greater in each age group, with the exception of children between the ages of 0 to 4, than it was in adults aged 45 and older. Risk of discontinuation was lower in males, patients with a history of GERD or allergic rhinitis, patients who initiated LABAs between October and December versus January and March, and patients who initiated LABAs appropriately (i.e. prior controller use and a history of poor control).

Table 22. Extended Cox Regression Model of Risk of LABA Discontinuation Among New LABA Episodes (N=159,064)

Parameter	HR	95% CI
2010 Policy* >30days	0.98	[0.93, 1.03]
2010 Policy* ≤30days	0.18**	[0.07, 0.50]
Single Agent LABA (ref fixed-dose ICS-LABA)	1.05*	[1.00, 1.09]
Male	0.94**	[0.92, 0.97]
Age Group (reference >45)		
Age 0-4	0.99	[0.95, 1.04]
Age 5-11	1.08**	[1.04, 1.12]
Age 12-17	1.21**	[1.17, 1.26]
Age 18-44	1.13**	[1.10, 1.16]
ARI	1.00	[0.98, 1.03]
Allergic Rhinitis	0.96**	[0.93, 0.99]
GERD	0.97**	[0.96, 0.99]
Nasal Steroid Use	1.01	[0.99, 1.03]
Time of Year (reference January-March)		
April-June	0.99	[0.97, 1.02]
July-September	0.99	[0.96, 1.02]
October-December	0.94**	[0.92, 0.96]
Use of Controller Medications 90 days Prior to Initiation	0.71**	[0.67, 0.75]
History of Poor Control Prior to Initiation	0.94**	[0.90, 0.98]

LABA – Long acting beta agonist; CI – Confidence Interval; GERD – gastrointestinal reflux disease; ARI – Acute respiratory infection; HR – Hazard ratio
*pvalue<0.05; **pvalue<0.01

b) Poisson Model

The rate of controller medication and LABA day supply overlap during new episodes of LABAs was not impacted by the 2010 FDA regulatory recommendations (Table 23). Almost all covariates included in the Poisson model had an IRR of approximately one, indicating very little variation in covariates. The only variable with some variation was type of LABA agent initiated. The rate of controller medication overlap with LABA therapy was 21% lower when single-agent LABAs were initiated.

Table 23. Poisson Regression Model Measuring the Rate of LABA and Controller Medications Overlap Among New LABA Episodes (N= 156,064)

Parameter	IRR	95% CI
2010 Policy	0.98	[0.97, 1.00]
Single Agent LABA (ref fixed-dose ICS-LABA)	0.79**	[0.76, 0.82]
Male	0.99**	[0.99, 0.99]
Age Group (reference>45)		
Age 0-4	1.01	[0.98, 1.04]
Age 5-11	1.00	[0.98, 1.01]
Age 12-17	1.01	[1.00, 1.02]
Age 18-44	0.99	[0.98, 1.00]
ARI	0.99**	[0.99, 1.00]
Allergic Rhinitis	1.00	[0.99, 1.00]
GERD	1.00	[1.00, 1.01]
Nasal Steroid Use	1.02	[1.01, 1.04]
Time of Year (reference January-March)		
April-June	1.00	[0.99, 1.00]
July-September	1.00	[0.99, 1.00]
October-December	0.99**	[0.98, 0.99]
Use of Controller Medications within 90 days of initiation	1.00	[0.99, 1.01]
History of Poor Control Prior to Initiation	0.99	[0.99, 1.00]

LABA – Long acting beta agonist; CI – Confidence Interval; GERD – gastrointestinal reflux disease; ARI – Acute respiratory infection; IRR - Incident rate ratio
*pvalue<0.05; **pvalue<0.01

d) Logistic Regression Models

In the logistic regression model predicting the probability of perfect overlap of controller medications during a LABA episode, the odds of perfect overlap declined after the 2010 FDA regulatory recommendations were implemented [OR=0.71 (95% CI: 0.65, 0.77)] (Table 24). Several covariates predicted perfect overlap. The type of LABA agent initiated had the largest impact; the odds of perfect overlap were 92% lower if single-agent LABAs were initiated. Other covariates with lower odds of perfect overlap included a history of an ARI and LABAs initiated between April and June and between October and December compared to LABAs initiated between January and March. The odds of perfect overlap between controller medications and LABAs were 33% higher among nasal steroid users.

Table 24. Logistic Regression Model of 100% Overlap LABA and Controller Medications Among New LABA Episodes (N=156,064)

Parameter	OR	95% CI
2010 Policy	0.71**	[0.65, 0.77]
Single-Agent LABA (ref fixed-dose ICS-LABA)	0.08**	[0.06, 0.10]
Male	0.98	[0.94, 1.02]
Age Group (reference >45)		
Age 0-4	0.76	[0.46, 1.25]
Age 5-11	1.10	[0.91, 1.32]
Age 12-17	1.17	[0.98, 1.40]
Age 18-44	0.99	[0.92, 1.07]
ARI	0.95**	[0.92, 0.99]
Allergic Rhinitis	1.02	[0.97, 1.07]
GERD	1.00	[0.95, 1.06]
Nasal Steroid Use	1.33**	[1.15, 1.54]
Time of Year (reference January-March)		
April-June	0.78**	[0.72, 0.85]
July-September	0.97	[0.90, 1.05]
October-December	0.63**	[0.52, 0.76]
Use of Controller Medications 90 days Prior to initiation	0.88	[0.76, 1.01]
History of Poor Control Prior to Initiation	0.95	[0.90, 1.01]

LABA – Long acting beta agonist; ICS – inhaled corticosteroids; CI – Confidence Interval; GERD – gastrointestinal reflux disease; ARI – Acute respiratory infection
*pvalue<0.05; **pvalue<0.01

3. Pre-Specified Subgroup Analyses

a) Pooled Pre- and Post-Policy Comparisons

There was variation in LABA use patterns by age group (Table 25). The youngest and oldest age groups appeared to remain on therapy the longest and children aged 12 to 17 years appeared to have the shortest duration of LABA use in the long pre-policy period. The 2010 regulatory recommendations had an impact on the length of LABA therapy only. Among children aged 0-4 years, the length of therapy was significantly longer in the post-policy period when compared to the short pre-policy period. The LABA day supply among children aged 5-11 and adults 18-65 declined in the post-policy period. Among the oldest patients, day supply of LABAs was lower in the post-policy period compared with the short pre-policy period.

In the long pre-policy period, the youngest and oldest initiators had the lowest proportion of perfect overlap of LABAs and controller medications. Children between the ages of 5 and 17 years had the highest number of new episodes with perfect overlap. There was no substantial variation in the proportion of days LABAs and controller medications overlapped.

Because the *regulatory recommendations* governing LABAs did not differ by sex, we only present the age group differences here. The sex-stratified analyses are in the Appendix.

Table 25. Pooled Estimates of LABA Medication Use Patters Among New LABA Episodes by Long and Short Pre-Policy and Post-Policy Periods and Age Group (N= 159,064)

Medications Use Patterns	Pre-Policy Periods		Post-Policy Period
	January 2005 – January 2010	January 2008 – January 2010	February 2010 – June 2011
Age 0 – 4 years	(N= 1,449)	(N= 691)	(N= 419)
Mean Day supply of LABA After Initiation	59.31± 47.30	56.66 ± 44.77	63.05 ± 48.99^
Proportion of Days of LABA and Controller Medication Overlap	0.95 ± 0.14	0.97 ± 0.12	0.97 ± 0.09
Proportion of Episodes with 100% Overlap Between LABA and Controller medications	86.68%	85.67%	87.59%
Age 5 – 11 years	(N= 16,783)	(N= 6,354)	(N= 3,608)
Mean Day supply of LABA After Initiation	55.65± 43.19	54.04 ± 44.77	55.21 ± 42.72*
Proportion of Days of LABA and Controller Medication Overlap	0.98 ± 0.11	0.97 ± 0.11	0.98 ± 0.09
Proportion of Episodes with 100% Overlap Between LABA and Controller medications	91.29%	89.77%	89.72%
Age 12 – 17 years	(N= 15,793)	(N=5,934)	(N= 3,504)
Mean Day supply of LABA After Initiation	48.82± 36.68	48.01 ± 35.84	49.72 ± 37.46^
Proportion of Days of LABA and Controller Medication Overlap	0.95 ± 0.14	0.97 ± 0.12	0.97 ± 0.09
Proportion of Episodes with 100% Overlap Between LABA and Controller medications	91.57%	91.59%	91.24%
Age 18 – 44 years	(N= 46,354)	(N= 18,889)	(N= 11,684)
Mean Day supply of LABA After Initiation	51.28± 39.95	49.36 ± 38.45	49.32 ± 37.38*
Proportion of Days of LABA and Controller Medication Overlap	0.96 ± 0.17	0.96 ± 0.15	0.96 ± 0.13
Proportion of Episodes with 100% Overlap Between LABA and Controller medications	88.68%	88.63%	88.48%
Age 45 – 65 years	(N= 45,819)	(N= 20,347)	(N= 13,651)
Mean Day supply of LABA After Initiation	60.78± 47.03	57.96 ± 44.97	55.84 ± 44.72*^
Proportion of Days of LABA and Controller Medication Overlap	0.95 ± 0.18	0.96 ± 0.16	0.96 ± 0.14
Proportion of Episodes with 100% Overlap Between LABA and Controller medications	86.44%	86.73%	88.50%

LABA - Long-acting beta$_2$ agonist; ICS - Inhaled corticosteroid
*p<0.05 for Jan 2005-Jan 2010 vs. Feb 2010-June 2011 comparison;
^p<0.05 for Jan 2008-Jan 2010 vs. Feb 2010-June 2011 comparison

e) Regression Analyses

All comparisons made between pediatric and adult regression models are descriptive.

Based on results of the Kaplan-Meier curves, more pediatric patients remained on therapy for 183 days after the 2010 regulatory recommendations than before the regulatory recommendations (11.68% vs. 15.14%, p<0.05), while approximately 15% of adults remained on therapy for six months regardless of the policy period. In the pediatric model, risk of discontinuation was lower in the post-policy period if use was greater than 30 days (Table 26). The regulatory recommendations did not impact discontinuation in adults. Age was a predictor of discontinuation. Younger children were at a lower risk of discontinuing compared to older children, while older adults had a lower risk of discontinuing therapy compared to younger adults. Acute respiratory infections affected the models differently. The risk of discontinuation was generally lower in pediatric patients. Both a history of GERD and LABA therapy between October and December were associated with lower risk of discontinuation in adults but this

effect was not observed in children. Allergic rhinitis and the appropriate initiation of LABAs had similar magnitudes of association with discontinuation across both subgroups.

Table 26. Extended Cox Regression Model of Risk of LABA Discontinuation Among New LABA Episodes By Age Group (N= 159,064)

	Pediatric		Adult	
Parameter	**HR**	**95% CI**	**HR**	**95% CI**
2010 Policy* ≥30days	0.92**	[0.89, 0.95]	0.99	[0.94, 1.04]
2010 Policy* <30days	0.11	[0.00, 3.64]	0.05	[0.00, 5.69]
Single-Agent LABA	1.04	[0.98, 1.12]	1.05*	[1.00, 1.11]
Male	1.00	[0.98, 1.02]	0.92**	[0.89, 0.95]
Age Group	**(reference Age 12-17)**		**(reference Age >45)**	
Age 0-4	0.86**	[0.80, 0.94]		
Age 5-11	0.91**	[0.89, 0.92]		
Age 18-44			1.13**	[1.10, 1.16]
ARI	0.97*	[0.94, 0.99]	1.02**	[1.01, 1.03]
Allergic Rhinitis	0.95*	[0.91, 0.99]	0.98*	[0.96, 1.00]
GERD	1.13	[1.00, 1.28]	0.97**	[0.96, 0.98]
Nasal Steroid Use	1.00	[0.97, 1.03]	1.01	[0.99, 1.04]
Time of Year (reference January-March)				
April-June	1.02	[0.97, 1.07]	0.98	[0.96, 1.01]
July-September	1.01	[0.97, 1.04]	0.99	[0.95, 1.03]
October-December	0.95	[0.90, 1.00]	0.94**	[0.92, 0.96]
Use of Controller Medications 90 days Prior to initiation	0.73**	[0.69, 0.77]	0.71**	[0.67, 0.76]
History of Poor Control Prior to Initiation	0.90**	[0.86, 0.94]	0.95*	[0.91, 0.99]

LABA – Long acting beta agonist; HR – Hazard Ratio; CI – Confidence Interval; GERD – gastrointestinal reflux disease; ARI – Acute respiratory infection
*pvalue<0.05; **pvalue<0.01

The rate of overlap of controller medication and LABAs in the pediatric population was lower in the post-policy period (3%) [Table 27]. The policy did not significantly impact the rate of overlap in adults. There was little variation in other variables except the type of LABAs initiated. The rate of overlap was lower among single-agent LABA initiators. The magnitude of the effect of initiating single-agent LABAs was similar across children and adults.

Table 27. Poisson Regression Model Measuring the Rate of LABA and Controller Medications Overlap Among New LABA Episodes by Age Group (N= 156,064)

	Pediatric		Adult	
Parameter	IRR	95% CI	IRR	95% CI
2010 Policy	0.97*	[0.95, 1.00]	0.98	[0.97, 1.00]
Single-agent LABA (reference fixed-dose LABA)	0.80**	[0.74, 0.88]	0.78**	[0.74, 0.81]
Male	1.00	[1.00, 1.00]	0.99	[0.98, 1.00]
Age Group	**(reference Age 12-17)**		**(reference Age >45)**	
Age 0-4	1.01	[0.98, 1.03]		
Age 5-11	1.00	[0.98, 1.01]		
Age 18-44			0.99	[0.98, 1.00]
ARI	1.00*	[0.99, 1.00]	0.99**	[0.99, 1.00]
Allergic Rhinitis	1.00	[0.99, 1.01]	1.00	[1.00, 1.00]
GERD	1.01	[0.99, 1.03]	1.00	[1.00, 1.01]
Nasal Steroid Use	1.01	[1.00, 1.02]	1.03	[1.01, 1.04]
Time of Year (reference January-March)				
April-June	1.00	[1.00, 1.01]	1.00	[0.99, 1.00]
July-September	1.00	[1.00, 1.01]	1.00	[0.99, 1.01]
October-December	0.99	[0.98, 1.00]	0.99**	[0.98, 1.00]
Use of Controller Medications 90 days Prior to initiation	0.98**	[0.97, 0.99]	1.01	[1.00, 1.02]
History of Poor Control Prior to Initiation	0.99*	[0.98, 1.00]	1.00	[0.99, 1.00]

LABA – Long acting beta agonist; IRR – Incidence Rate Ratio; CI – Confidence Interval; GERD – gastrointestinal reflux disease; ARI – Acute respiratory infection
*pvalue<0.05; **pvalue<0.01

The odds of perfect overlap of controller medication and LABA use during a new LABA episode were significantly lower after the 2010 FDA regulatory recommendations in both the pediatric and adult models (Table 28). Initiation of single-agent LABAs and initiation of any LABA between October and December as compared to the reference time period, January through March, were also significant in both models and of similar magnitude. Being male and having a history of allergic rhinitis were associated with lower odds of overlap, and nasal steroid use was associated with higher odds of overlap in the adult model only. In the pediatric model, appropriate initiation was associated with lower odds of overlap. Neither of the appropriate use variables were associated with overlap in adults.

Table 28. Logistic Regression Model of 100% Overlap of LABA and Controller Medications Among New LABA Episodes by Age Group (N=156,064)

	Pediatric		Adult	
Parameter	**OR**	**95% CI**	**OR**	**95% CI**
2010 Policy	0.64**	[0.55, 0.74]	0.75**	[0.71, 0.78]
Single-Agent LABA	0.10**	[0.07, 0.15]	0.08**	[0.06, 0.10]
Male	1.07	[0.97, 1.19]	0.95*	[0.91, 0.99]
Age Group	**(reference Age 12-17)**		**(reference Age >45)**	
Age 0-4	0.74	[0.53, 1.05]		
Age 5-11	0.90*	[0.84, 0.98]		
Age 18-44			0.99	[0.92, 1.07]
ARI	0.94	[0.87, 1.02]	0.95*	[0.92, 1.00]
Allergic Rhinitis	1.04	[0.95, 1.12]	1.02	[0.96, 1.07]
GERD	1.06	[0.89, 1.27]	0.99	[0.94, 1.05]
Nasal Steroid Use	1.06	[0.93, 1.21]	1.40**	[1.21, 1.62]
Time of Year (reference January-March)				
April-June	0.89	[0.70, 1.14]	0.75	[0.70, 0.81]
July-September	1.05	[0.93, 1.17]	0.95	[0.88, 1.02]
October-December	0.56**	[0.43, 0.72]	0.65**	[0.53, 0.79]
Use of Controller Medications 90 days Prior to initiation	0.79**	[0.83, 0.86]	0.91	[0.78, 1.06]
Poor Control	0.88**	[0.81, 0.95]	0.97	[0.92, 1.03]

LABA - Long acting beta agonist; OR - Odds Ratio; CI - Confidence Interval; GERD - gastrointestinal reflux disease; ARI - Acute respiratory infection
*pvalue<0.05; **pvalue<0.01

G. DISCUSSION

1. Overall Results

Within our cohort of LABA initiators, the mean duration of therapy was approximately 55 days and declined by approximately 2 days in the post-policy period. Very few initiators maintained therapy past the six-month mark. The lengths of single-agent LABA and fixed-dose ICS-LABA therapy in the pre-period were similar to Kaplan et al.'s estimates of 63 and 53 days, respectively).[34] In our analysis more patients remained on therapy at 90 days (~20% vs. 9-12%). These findings are consistent with other studies that have found asthma medication adherence to be quite low.[46-50]

There were no significant changes in the rate of discontinuing LABA medications between the pre- and post-policy periods. Poor control and concomitant conditions that exacerbate asthma may contribute more to decisions regarding the length of LABA use than regulatory recommendations.

There was little variation in the overlap of controller medications and LABA agents. Overlap varied only by types of LABA products. As was expected, concomitant use was lower when patients used single-agent LABAs. The regulatory recommendations call for 100% overlap between LABAs and controller medications; however, contrary to expectations, fewer LABA initiators used controller medications for the duration of LABA treatment during the post-policy period. As would be expected, initiating single-agent LABAs was a strong contributing factor for less than 100% overlap. As mentioned in earlier discussion sections, there may always be a small subset of patients using single-agent LABAs for the

convenience of stepping up and stepping down therapy. Literature searches yielded no findings pertaining to this topic with which we could compare our results.

We found that the definition for discontinuation of inhalers cannot be as strict as definitions used for oral therapy because of the episodic nature of the asthma. If discontinuation is defined as a 7-day gap in therapy more than 70% of patients would fit this definition within 30 days. Many asthma patients restart therapy after a 7-day gap; therefore, future work in asthma should consider defining discontinuation by a longer gap in therapy such as 30 days.

2. Age Group Comparisons

Pediatric patients were less likely to discontinue use of their LABA agents in the post-policy period compared to the pre-policy period. The regulatory recommendations did not impact the length of use in adults. Discontinuation was associated with appropriate initiation in both populations. The odds of 100% overlap of controller medications and LABA agents were similarly associated with appropriate initiation and initiation of fixed-dose LABAs in adults and children. Further investigation may be needed to understand variation in 100% overlap among children especially.

3. Summary

The 2010 FDA regulatory recommendations had a limited impact on the length of LABA therapy and the extent to which controller medications were used during the entire course of therapy. There are several forces at play that could have limited the effect of the recommendations that LABA medications be used for the shortest time possible. First, we cannot tell whether LABA discontinuation was based on a clinical plan or the patient's own volition. Without information on outcomes or symptoms after initiation, we cannot speak to whether LABAs were discontinued because of a reduction of symptoms. Second, there may have been insufficient time for the 2010 regulatory recommendations to gain traction, especially since the regulatory recommendations focus on clinical decision-making.

VIII. AIM 6 – TO DESCRIBE STEP DOWN THERAPY AFTER LABA DISCONTINUATION BEFORE AND AFTER THE 2010 FDA REGULATORY ACTIONS ON LABAS

This aim focuses on the cohort of health plan members who discontinued LABAs during the study period and assesses the use of controller medication after discontinuation before and after the 2010 FDA regulatory recommendations.

A. COHORT

The cohort was comprised of LABA discontinuers. Discontinuation was defined as a gap in LABA day supply exceeding 30 days. The anchor date for this aim was the LABA discontinuation date defined as the first day of the 30-day gap. All criteria related to continuous enrollment, age, and asthma diagnoses were identified within 365 days of the LABA index date. The last date which a health plan member could be identified as a discontinuer in the pre-policy period was December 31, 2009, and the last date for which they could be considered a post-policy discontinuer was May 31, 2011. The windows for identifying discontinuers in both the pre- and post-policy periods were shortened to allow for the 30-day follow-up period needed to identify controller use after discontinuation. In addition, we avoided studying follow-up time that potentially could have crossed over the policy date.

B. CONTROLLER MEDICATION FOLLOW-UP TIME

Each LABA discontinuer was followed from the date of discontinuation until the earliest occurrence of 30 days of follow-up, death, disenrollment from the health plan, January 31, 2010 if LABAs were discontinued in the pre-policy period, or June 30, 2011 if discontinued in the post-policy period. Any health plan member with evidence of a supply of a controller medication (e.g. ICS or leukotriene modifier) in the follow-up period was considered to have stepped down therapy.

C. OUTCOMES

The proportion of eligible LABA discontinuers who used a controller medication within 30 days of discontinuation.

D. STATISTICAL ANALYSIS

1. Pooled Pre- and Post-Policy Comparisons

Descriptive statistics were generated using monthly discontinuers averages in the pre- and post-policy periods. This change was made because the data on individual discontinuers was not available.

2. Interrupted Time Series

For the ITS analyses, controller medication use after discontinuation was grouped by the month of the LABA discontinuation date.

Two policy periods were evaluated: 1) January 2005 to January 2010; and 2) February 2010 to June 2011.

3. Regression Analyses

Individual-level logistic regression models were used to analyze the proportion of health plan members who discontinued LABAs and used controller medications within 30 days of discontinuing LABA therapy. Covariates included in the models are listed in Table 29. Each covariate was measured in the 12-month pre-discontinuation period unless stated otherwise. In addition to an overall model, stratified models based on age, sex and LABA product were also generated.

Meta-analyses techniques based on random effects models were used to combine the logistic regression model parameters across DPs. Since multiple LABA episodes were allowed per person, each regression analysis controlled for multiple observations per person using GEE.

Table 29. Covariates Used in the Logistic Regression Models

Age at discontinuation(reference ≥45 years)
0-4 years
5-11 years
12-17 years
18-44 years
Male (reference female)
Comorbities
GERD
Allergic Rhinitis
Acute Respiratory Infection
Nasal Steroid Use

Table 29. Covariates Used in the Logistic Regression Models
Time of the year LABA was discontinued
January-March
April-June
July-September
October-December
Asthma History prior to discontinuation
Controller Medication Use within 90 days of discontinuation
Poor Control

GERD – gastrointestinal reflux disease; LABA – long-acting beta agonists

E. RESULTS

1. Pre- and Post-Policy Comparisons

There were 162,731 discontinuation episodes between January 2005 and May 2011. As mentioned above, the descriptive information on the population is based on the monthly characteristics of discontinuers. Comparisons are strictly descriptive and are not based on statistical analysis. In the pre-policy period, 38.46% of discontinuers were male, fixed-dose LABAs were the most commonly discontinued medication, and approximately 60% of patients were on a controller medication other than a LABA containing agent 90 days prior to discontinuation. Notable changes in the post-policy period included an increase in the proportion of patients discontinuing fixed-dose LABAs to patients discontinuing single-agent LABAs, and a decline in patients using controller medications prior to discontinuation.

Table 30. Baseline Characteristics of Monthly LABA Discontinuers (N=162,731)		
Variables	**January 2005 - December 2009**	**February 2010 – May 2011**
Male	38.46%	37.70%
Mean Age, years	35.51	36.92
Type of medication discontinued, fixed-dose ICS-LABA	88.54%	95.54%
Controller medication use 90 days prior to discontinuation	60.40%	55.57%
Poor control in the year prior to discontinuation	45.69%	46.11%

LABA – long-acting beta agonists; ICS- inhaled corticosteroid

Prior to the 2010 regulatory recommendations, 38.24% of patients used controller medications after discontinuing LABA therapy (Table 31). The number of patients using controllers after discontinuing LABAs dropped to 34.57% in the post-policy period.

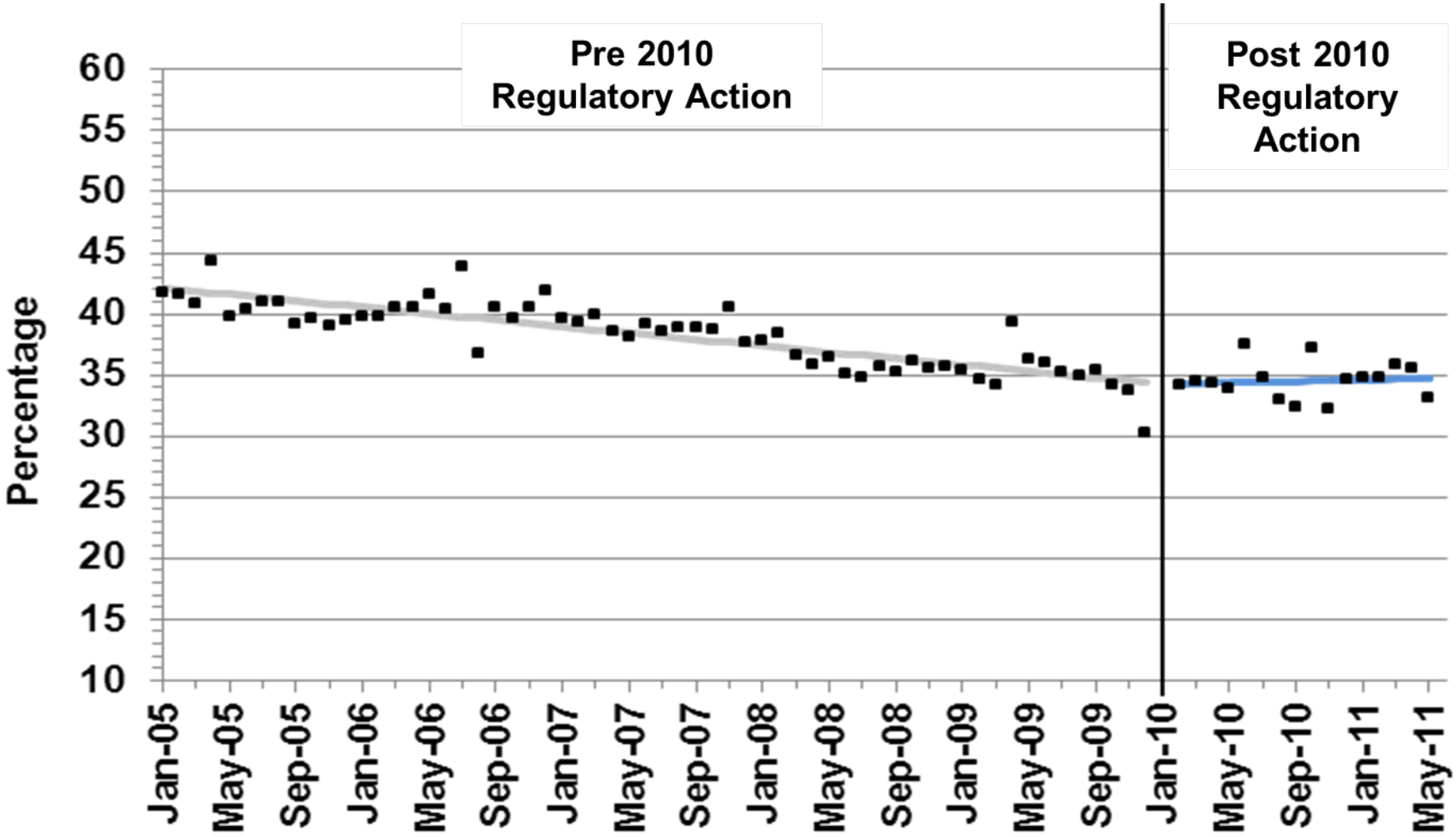
Table 31. Controller Medication Use After Discontinuing LABA Products		
Outcome	**January 2005 - January 2010**	**February 2010 – June 2011**
Controller medication use 30 days after discontinuation	38.24%	34.57%

LABA – long-acting beta agonists

2. Interrupted Time Series

The ITS regression results confirm whether changes observed in descriptive statistics and figures were indeed significantly related to the regulatory recommendations (Table 31 and Figure 12). The intercept of the ITS models indicate the prevalence of the controller use after discontinuation in January 2005 (Table 32).

Figure 12. Trends of Controller Medication Use 30 Days After Discontinuing LABA Among LABA Discontinuers: January 2005 - June 2011



At the beginning of the analysis period, 42.27% of LABA discontinuers used a controller medication within 30 days of discontinuation. Between January 2005 and December 2009 there was a significant decline in controller medication use after discontinuation; the absolute decline was 7.8 percentage points. The 2010 regulatory recommendations did not have an immediate effect on controller use after discontinuation, but did alter the trend in controller use. The change in trend was positive and larger in magnitude than the baseline trend, resulting in a flattening of the slope.

Table 32. Interrupted Time Series Analysis of Controller Medications After LABA Discontinuation in Percentage Points∞

Overall	Point Estimate	95% CI
Intercept	42.27**	[41.51, 43.02]
Trend Prior to the 2010 Policy	-0.13**	[-0.15, -0.11]
2010 Policy Impact		
Change in Trend After the 2010 Policy	0.16**	[0.05, 0.27]

LABA – long-acting beta agonists; CI – Confidence Interval
*pvalue<0.05; **pvalue<0.01
∞-Only parameters with pvalues<0.2 were retained in the ITS model

3. Regression Analyses

In the logistic regression model we found that the odds of using a controller medication after discontinuation were significantly lower in the post-policy period (Table 33). However, there were other covariates that had a stronger effect on controller medication use than the regulatory recommendations. Odds of controller medication use were lower in patients younger than 45 years. The odds asthma controller medication use was positively influenced by comorbid conditions such as ARI, allergic rhinitis and GERD. Patients who used single-agent LABAs had 70% greater odds of using a controller medication after discontinuation than fixed-dose LABA users. The strongest predictor of controller use after discontinuation was use of a controller medication within the 90 days prior to discontinuation [OR:15.99 (12.22, 20.90)].

Table 33. Logistic Regression Model of Predicting Controller Medications After LABA Discontinuation

Parameter	OR	95% CI
2010 Policy	0.93*	[0.87, 0.99]
Single Agent LABA (reference fixed-dose ICS-LABA)	1.70**	[1.50, 1.92]
Male	0.96	[0.91, 1.01]
Age Group (reference >45)		
Age 0-4	1.18	[0.95, 1.45]
Age 5-11	0.87*	[0.76, 1.00]
Age 12-17	0.66**	[0.55, 0.80]
Age 18-44	0.66**	[0.63, 0.71]
ARI	1.06*	[1.01, 1.11]
Allergic Rhinitis	1.16**	[1.13, 1.19]
GERD	1.23**	[1.13, 1.35]
Nasal Steroid Use	1.85**	[1.42, 2.43]
Time of Year (ref January-March)		
April-June	0.98	[0.91, 0.98]
July-September	0.95**	[0.92, 0.98]
October-December	0.98	[0.95, 1.02]
Use of Controller Medications 90 Days Prior to Discontinuation	15.99**	[12.22, 20.90]
History of Poor Control Prior to Initiation	1.14**	[1.11, 1.17]

LABA - Long acting beta agonist; CI - Confidence Interval; GERD - gastrointestinal reflux disease; ARI - Acute respiratory infection; OR - Odds ratio
*pvalue<0.05; **pvalue<0.01

4. Pre-Specified Subgroup Analyses

b) ITS Analyses

In the beginning of the study period, children were significantly less likely to use controller medications after LABA discontinuation compared to adults (40.91% vs. 42.91%) [Table 34 and Figure 13]. Controller medication use after discontinuation was declining prior to the 2010 regulatory recommendations for both adults and children, although to a greater extent for adults. The 2010 regulatory recommendations had an immediate, positive impact on controller use in the pediatric population but not in the adult population. Lastly, there was no change in trend after the 2010 regulatory recommendations in the pediatric population. Despite the immediate increase in controller use, the slope continued to decline at the same rate as prior to the regulatory recommendations. The magnitude of the positive change in trend in the adult population was great enough to reverse the previously declining slope.

Table 34. Interrupted Time Series Analysis of Controller Medications After LABA Discontinuation in Percentage Points by Age Group

	Pediatric		Adult	
Parameter∞	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
Intercept	40.91**	[38.48, 43.33]	42.91**^	[42.29, 43.53]
Trend Prior to the 2010 Policy	-0.08*	[-0.14, -0.02]	-0.16**^	[-0.17, -0.14]
2010 Policy Impact	3.49*	[0.79, 6.20]		
Trend After the 2010 Policy			0.20**	[0.10, 0.31]

LABA – long-acting beta agonists; CI – Confidence Interval
*pvalue<0.05; **pvalue<0.01; ^pvalue<0.05 for pediatric vs. adult
∞-Only parameters with pvalues<0.2 were retained in the ITS model

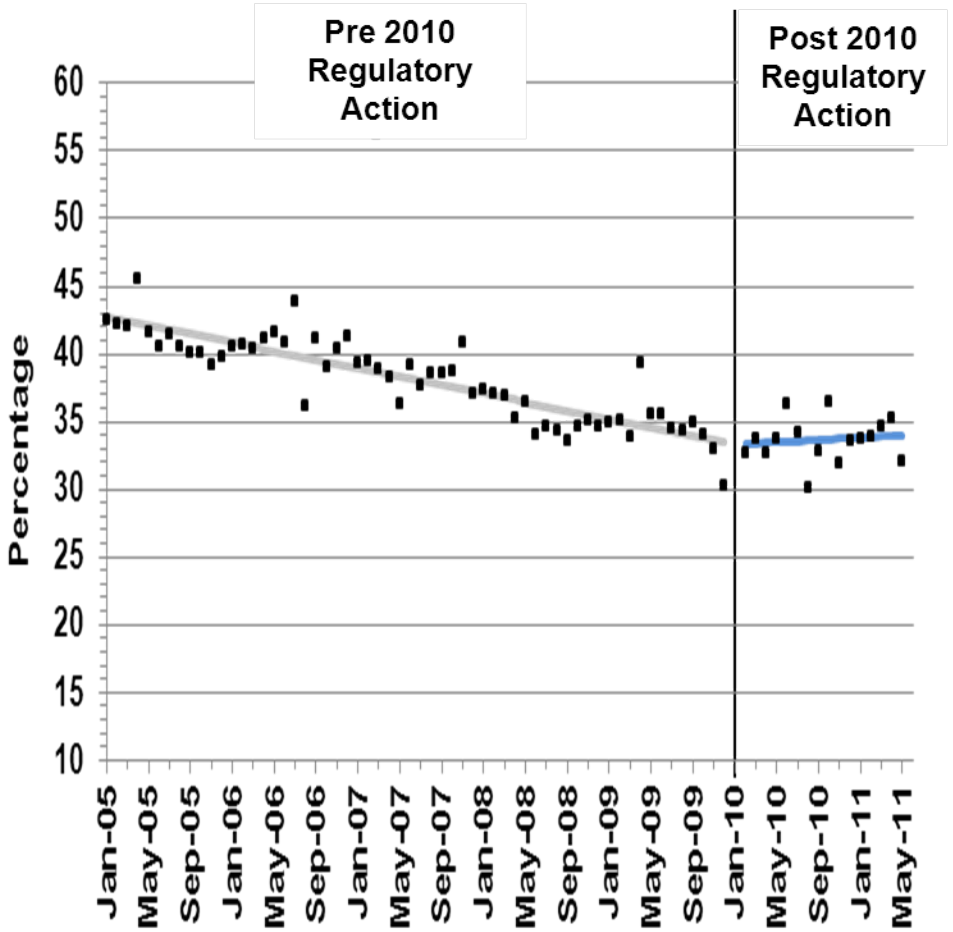
a) Regression Analyses

All comparisons made between pediatric and adult regression models are descriptive and not statistical.

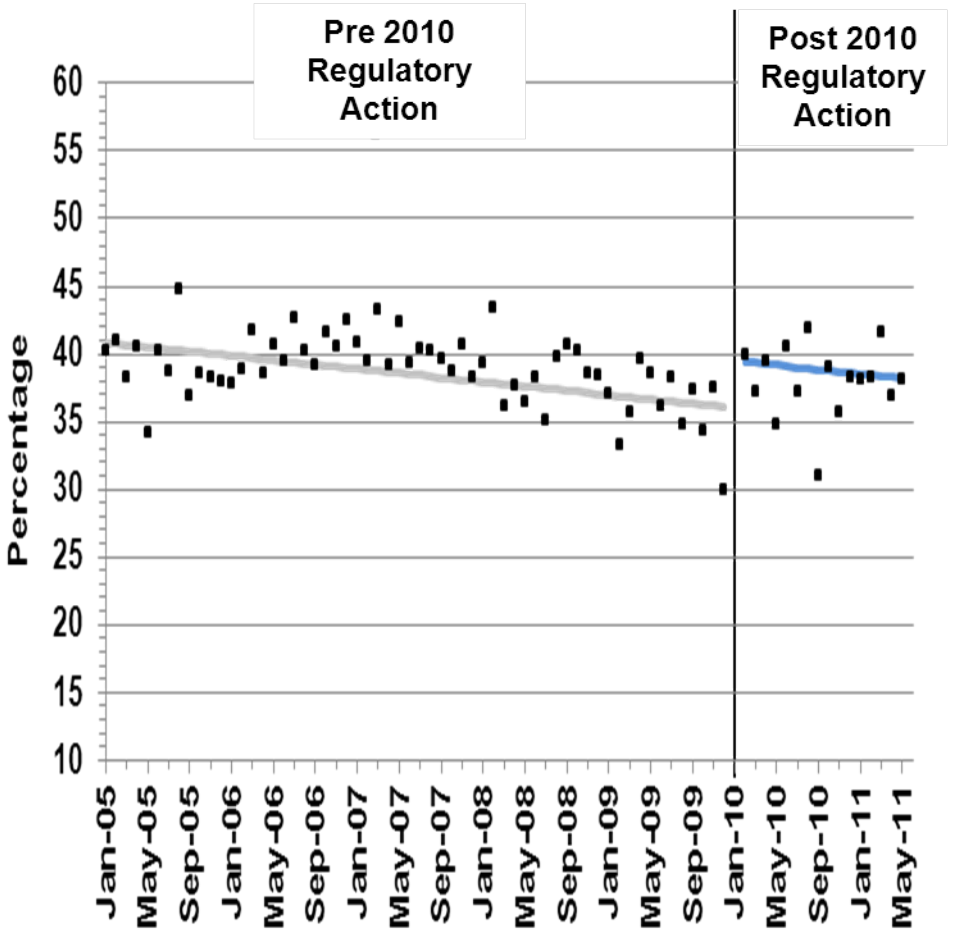
After the 2010 FDA regulatory recommendations, the odds of controller medication use after LABA discontinuation were significantly lower in the adult model only (Table 35). The relationships, which were significant in both models and with similar magnitude, include initiation of single-agent LABAs, history of GERD, use of nasal steroids, controller medication use prior to discontinuation, and poor control prior to discontinuation. In each of these cases, the odds of controller use after discontinuation were greater. Having a history of allergic rhinitis was significantly associated with greater odds of controller medication use after discontinuation in the adult model only. In the pediatric model, ARI was associated with greater odds of controller medication use after LABA discontinuation. The effect of age differed between adults and children; younger children had greater odds of controller medication use than older children, while younger adults were at lower odds of controller medication use compared to older adults.

Figure 13. Trends of Controller Medication Use 30 Days After Discontinuing LABA Among LABA Discontinuers: January 2005 - June 2011

A. Adult



B. Pediatric



Comparisons by sex can be found in the Appendix. Comparisons by LABA product are not available because the models did not converge.

Table 35. Logistic Regression Model of Predicting Controller Medications After LABA Discontinuation by Age Group

	Pediatric		Adult	
Parameter	**OR**	**95% CI**	**OR**	**95% CI**
Policy	1.01	[0.88, 1.16]	0.90*	[0.83, 0.98]
Single Agent LABA	1.85**	[1.43, 2.38]	1.63**	[1.41, 1.88]
Male	1.03	[0.98, 1.08]	0.95	[0.88, 1.03]
Age Group	**(reference 12-17)**		**(reference>45)**	
Age 0-4	1.67**	[1.46, 1.91]		
Age 5-11	1.27**	[1.21, 1.34]		
Age 18-44			0.66**	[0.62, 0.71]
ARI	1.17**	[1.11, 1.24]	1.02	[0.98, 1.08]
Allergic Rhinitis	1.11	[0.99, 1.25]	1.16**	[1.12, 1.20]
GERD	1.25**	[1.11, 1.40]	1.23**	[1.12, 1.35]
Nasal Steroid Use	1.78**	[1.40, 2.26]	1.83**	[1.35, 2.47]
Time of Year (reference January-March)				
April-June	0.98	[0.86, 1.12]	0.99	[0.95, 1.04]
July-September	0.96	[0.89, 1.02]	0.95*	[0.91, 0.99]
October-December	0.98	[0.83, 1.15]	0.98	[0.94, 1.03]
Controller Medication Use 90 Days Prior to Discontinuation	16.77**	[13.30, 21.15]	16.77**	[12.29, 22.87]
Poor Control Prior to Discontinuation	1.09**	[1.03, 1.14]	1.15**	[1.12, 1.19]

LABA – Long acting beta agonist; OR – Odds Ratio; CI – Confidence Interval; GERD – gastrointestinal reflux disease; ARI – Acute respiratory infection
*pvalue<0.05; **pvalue<0.01

F. DISCUSSION

1. Overall Results

We identified 162,731 LABA discontinuation episodes between January 2005 and May 2011. Use of controller medications after LABA discontinuation was declining prior to the 2010 regulatory recommendations. The 2010 FDA regulatory recommendations had no immediate impact on controller medication use. They did, however, precipitate a positive change in trend in use of controller medications within 30 days after LABA discontinuation, negating its previously negative trend. The increase in slope was not large enough to counteract the declining rate of controller medication use prior to the regulatory recommendations. It is difficult to explain why use of controller medications after LABA discontinuation was declining prior to the FDA regulatory recommendations since there are no clinical guidelines that disagree with the practice, and it is unclear whether the decision to discontinue LABAs was the patient's or the clinician's.

The logistic regression results show that the odds of controller medication use after LABA discontinuation were lower in the post-policy period. Other covariates such as use of single-agent LABAs vs. fixed-dose ICS-LABAs and use of controller medications prior to discontinuation were stronger predictors of controller medication use within 30 days after LABA discontinuation. Use of controller medications after discontinuation among patients who were on controller medications prior to discontinuation may reflect LABAs being added to step up therapy and its removal indicating a step down in therapy. As mentioned in other sections of the report, single-agent LABAs may allow for more flexibility in regimens because it may be easily added and removed.

The differing results between the logistic regression and ITS analysis regarding the impact of the 2010 FDA regulatory recommendations are not in conflict. Changes in use after the 2010 regulatory actions were too small to reverse the negative trend prior to the regulatory recommendations. If the logistic regression had been the only tool used to measure the impact of the regulatory recommendations, we would have assumed the regulatory recommendations had the effect of what was expected. Thus, when outcomes can be measured in a discrete period of time, ITS analyses are an important tool for measuring change over time because pooled analyses may hide the true effects of a policy.

2. Age Group Comparisons

Use of controller medication after LABA discontinuation was declining in both pediatric and adult populations prior to the 2010 regulatory recommendations. The declining rate of controller medication use in adults was double the declining rate in children. The 2010 regulatory recommendations had an immediate impact on use of controller medications after discontinuation in the pediatric population; however, after the regulatory recommendations, the declining slope was unchanged. While there was no immediate effect in adults, the slope after the policy was no longer declining and was starting to increase. Despite all the changes, fewer children and adults used controller medications after discontinuing LABAs in June 2011 than in January 2005.

The logistic regression results show that the odds of controller medication use after LABA discontinuation were lower in the post-policy period for adults only. The covariates associated with use of controller medications after LABA discontinuation were very similar among children and adults. The effect of age differed. Younger children had greater odds of using controller medications after LABA discontinuation than older children. The difference may be related to self-administration of medications by children aged 12-17 years and parental administration of medications for younger children. The adult population, between the ages of 18 and 45 had lower odds of using controller medications after LABA discontinuation.

Future research is needed to understand the different patterns seen among pediatric and adult patients.

3. Summary

Less than half of LABA discontinuers use controller medications after LABA discontinuation. The 2010 FDA regulatory recommendations had a limited impact on changing the rate of controller medication use after LABA discontinuation. Other factors may limit the effect of the regulatory recommendations on controller medication use after LABA discontinuation. For instance, we cannot tell whether the decision to discontinue was the clinician's or the patient's. If patients made the decision independently we might not expect to see use of controller medications after the fact. Alternatively for clinicians, stepping down LABAs is not agreed upon in practice because for concerns of exacerbation.[51] Thus when LABAs are discontinued, the whole regimen may be stopped because of a lack of need versus a reduced need for medication to control the patients' asthma. More time may be needed for the 2010 regulatory recommendations to gain traction, especially when recommendations focus on clinical decision-making. Adoption of the recommendations by professional organizations may help change the patterns observed.

IX. LIMITATIONS

The results of this assessment should be interpreted in the context of the following limitations.

- Because US Federal entity implemented the regulatory actions and recommendations evaluated, the entire US asthma population was exposed. Therefore, a concurrent comparator population unaffected by the regulatory actions cannot be identified. In addition, the regulatory actions include implications that affect other controller medications, so a drug comparison was not selected.

- There may be an under-ascertainment of pediatric health plan members even with the more generous definition of asthma. A diagnosis of asthma in children is sometimes not made until the age of 2 or 4 years. Some cohort definitions for pediatric populations have included wheezing to overcome this issue.[33]

- There were no fixed effect year variables in the individual-level regression models, therefore, indicator variables identifying observations in the pre- and post-policy periods would provide an average effect and may not reflect changes happening at intervals within the policy periods.

- We only considered a selected number of confounders for the person level analyses; therefore, residual unmeasured confounding may be an issue.

- There was limited follow-up time to fully assess after the impact of the 2010 FDA regulatory actions and recommendations. It may take more time for practice patterns to change as a result of the FDA recommendations.

- Large population based data systems do not routinely capture information on clinical symptoms and pulmonary function, therefore medication use in relation to asthma severity could not be assessed.

- There was a declining use of medications overall so this could mean the underlying asthma population may be changing with regard to asthma severity.

- We cannot tell if discontinuation decisions were driven by clinicians or patients.

- There was limited follow-up time to fully assess after the impact of the 2010 FDA regulatory actions and recommendations. It may take more time for practice patterns to change as a result of the FDA recommendations.

X. STRENGTHS

This project has several strengths.

- Nine Data Partners contributed data to the analysis. These sites represent geographic regions across the United States and various types of health systems.

- Despite having 9 DPs, only aggregate data was shared. To accomplish this goal, model diagnostics and cohort and outcomes definitions were decided a priori.

- We included the youngest patients using LABA medications in our analyses. Most of the published literature is limited to age groups where medications are approved.

- Methodological techniques such as ITS were used to help uncover trends over time since policy effects may not have been observed if only pooled analyses were conducted.

- We reported asthma population based estimates instead of focusing solely on LABA initiators to help put the use of LABA products in context of the overall asthma armamentarium.

XI. CONCLUSION

In conclusion, this Mini-Sentinel assessment of the impact of FDA regulatory actions on the prescribing and utilization patterns of LABA products found the 2010 regulatory actions that reiterated safety concerns about LABA products impacted the use of LABA agents (i.e. prevalent and incident use). However, the magnitude of the effect may have been limited since there were earlier regulatory activities in 2005 alerting the public about LABA safety, and messages were re-iterated in clinical guidelines. The 2010 regulatory activities that focused on *how* LABA agents should be used had a smaller effect. The 2010 FDA LABA regulatory action went beyond labeling and provided more directed clinical use and prescribing instructions for the safe use of LABAs. Wider adoption and adherence to the regulatory recommendation may increase if updated clinical practice guidelines refer to the 'how to use LABA' regulatory activities. Thus, longer follow-up time may be needed to assess the impact of the regulatory recommendations focused on LABA prescribing decisions.

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XIV. APPENDIX

Table 36. Interrupted Time Series Analysis Results of Prevalent Asthma Medication Use Among Patients with Asthma in Percentage Points by Sex∞

	Male		Female	
Medication Class	**Point Estimate**	**95%CI**	**Point Estimate**	**95%CI**
Single-Agent LABA				
Intercept	2.50**	[2.45, 2.54]	3.39**	[3.31, 3.47]
Baseline Trend	-0.06**	[-0.06, -0.05]	-0.07**	[-0.08, -0.06]
Level Change after 2005 Policy	-0.03	[-0.06, 0.01]	-0.04	[-0.09, 0.00]
Trend Change after 2005 Policy	0.03**	[0.02, 0.04]	0.03**	[0.02, 0.04]
Level Change after 2010 Policy				
Trend Change after 2010 Policy	0.01**	[0.01, 0.01]	0.02**	[0.01, 0.02]
Fixed-Dose ICS-LABA				
Intercept	11.61**	[11.22, 12.01]	13.63**	[13.15, 14.11]
Baseline Trend	-0.05	[-0.11, 0.01]	-0.13**	[-0.20, -0.06]
Level Change after 2005 Policy	-0.97**	[-1.36, -0.59]	-1.19**	[-1.66, -0.72]
Trend Change after 2005 Policy	0.04	[-0.02, 0.10]	0.13**	[0.06, 0.20]
Level Change after 2010 Policy				
Trend Change after 2010 Policy	-0.04**	[-0.059, -0.01]	-0.05**	[-0.08, -0.03]
ICS				
Intercept	23.24**	[22.89, 23.59]	23.07**	[22.82, 23.31]
Baseline Trend			-0.01**	[-0.02, -0.01]
Level Change after 2005 Policy	0.41	[-0.06, 0.87]	0.57**	[0.23, 0.91]
Trend Change after 2005 Policy	0.01**	[0.01, 0.02]		
Level Change after 2010 Policy			-0.69**	[-1.00, -0.39]
Trend Change after 2010 Policy	-0.06*	[-0.11, -0.02]		
LM				
Intercept	16.01**	[15.38, 16.64]	15.87**	[15.42, 16.31]
Baseline Trend			-0.05**	[-0.06, -0.04]
Level Change after 2005 Policy	0.3*	[0.02, 0.69]	0.34*	[0.08, 0.59]
Trend Change after 2005 Policy	-0.05**	[-0.07, -0.04]		
Level Change after 2010 Policy				
Trend Change after 2010 Policy				
OCM				
Intercept	1.03**	[0.99, 1.08]	1.69**	[1.65, 1.73]
Baseline Trend	-0.02**	[-0.03, -0.01]	-0.04**	[-0.04, -0.03]
Level Change after 2005 Policy	0.05*	[0.00, 0.09]		
Trend Change after 2005 Policy	0.01**	[0.01, 0.02]	0.02**	[0.02, 0.03]
Level Change after 2010 Policy	-0.06**	[-0.10, -0.02]	-0.05*	[-0.09, -0.01]
Trend Change after 2010 Policy	0.01	[0.00, 0.01]	0.01**	[0.01, 0.01]
Other Bronchodilators				
Intercept	1.89**	[1.75, 2.03]	3.27**	[3.12, 3.41]
Baseline Trend	-0.03**	[-0.04, -0.01]	-0.07**	[-0.08, -0.05]
Level Change after 2005 Policy	0.05	[-0.02, 0.12]	-0.11	[-0.22, 0.00]
Trend Change after 2005 Policy	0.02**	[0.01, 0.04]	0.06**	[0.04, 0.08]
Level Change after 2010 Policy			-0.12*	[-0.23, -0.01]
Trend Change after 2010 Policy			0.01	[-0.00, 0.02]
OCS				
Intercept	5.68**	[5.39, 5.97]	6.59**	[6.25, 6.93]
Baseline Trend	-0.04**	[-0.07, -0.01]	-0.09**	[-0.14, -0.04]
Level Change after 2005 Policy			0.22	[-0.07, 0.51]
Trend Change after 2005 Policy	0.05**	[0.02, 0.08]	0.09**	[0.05, 0.14]
Level Change after 2010 Policy				
Trend Change after 2010 Policy	-0.03**	[-0.05, -0.02]	-0.30**	[-0.50, -0.11]
SABA				
Intercept	23.08**	[22.32, 23.83]	22.61**	[21.95, 23.27]

Table 36. Interrupted Time Series Analysis Results of Prevalent Asthma Medication Use Among Patients with Asthma in Percentage Points by Sex∞

	Male		Female	
Medication Class	**Point Estimate**	**95%CI**	**Point Estimate**	**95%CI**
Baseline Trend	-0.16**	[-0.24, -0.08]	-0.22**	[-0.29, -0.15]
Level Change after 2005 Policy				
Trend Change after 2005 Policy	0.17**	[0.08, 0.25]	0.22**	[0.15, 0.30]
Level Change after 2010 Policy				
Trend Change after 2010 Policy	-0.09**	[-0.13, -0.05]	-0.08**	[-0.12, -0.04]
No Medication Use				
Intercept	51.54**	[50.51, 52.58]	49.57**	[48.66, 50.49]
Baseline Trend	0.16*	[0.02, 0.30]	0.27**	[0.17, 0.37]
Level Change after 2005 Policy	-0.64	[-1.44, 0.16]		
Trend Change after 2005 Policy	-0.14	[-0.28, 0.01]	-0.24**	[-0.34, -0.13]
Level Change after 2010 Policy			0.56	[-0.21, 1.33]
Trend Change after 2010 Policy	0.13**	[0.07, 0.18]	0.08*	[0.00, 0.16]

OCS – Oral Corticosteroids; SABA – short acting Beta-agonist; ^Other bronchodilators - ipratropium, ipratropium/albuterol, titropium; ICS – Inhales corticosteroid; LM – Leukotriene Modifier ; OCM – Other controller medications (theophylline, nedocromil, cromolyn, omalizumab); LABA – Long acting beta agonist ;CI – Confidence Interval
*pvalue<0.05; **pvalue<0.01
∞-Only parameters with pvalues<0.2 were retained in the ITS model

Table 37. Interrupted Time Series Analysis Results of Initiation of LABA Containing Products Among Patients with Asthma in Percentage Points by Sex∞

	Male		Female	
	Point Estimate	**95% CI**	**Point Estimate**	**95% CI**
Single Agent LABA				
Intercept	0.14**	[0.13, 0.14]	0.26**	[0.24, 0.28]
Baseline Trend	-0.00**	[-0.00, -0.00]	-0.01**	[-0.01, -0.01]
Level Change after 2005 Policy	-0.02**	[-0.03, -0.01]	0.01	[-0.01, 0.03]
Trend Change after 2005 Policy			0.01**	[0.00, 0.01]
Level Change after 2010 Policy				
Trend Change after 2010 Policy	0.00**	[0.00, 0.00]	0.00**	[0.00, 0.00]
Fixed Dose ICS-LABA				
Intercept	0.93**	[0.86, 1.00]	1.20**	[1.11, 1.29]
Baseline Trend	-0.02**	[-0.03, -0.01]	-0.02**	[-0.04, -0.01]
Level Change after 2005 Policy	-0.12**	[-0.18, -0.05]	-0.13**	[-0.21, -0.05]
Trend Change after 2005 Policy	0.02**	[0.01, 0.03]	0.02**	[0.01, 0.04]
Level Change after 2010 Policy	-0.06*	[-0.13, -0.00]	-0.08*	[-0.16, -0.00]
Trend Change after 2010 Policy	-0.01	[-0.01, 0.00]	-0.01	[-0.01, 0.00]

ICS – Inhales corticosteroid;) ; LABA – Long acting beta agonist ;CI – Confidence Interval
*pvalue<0.05; **pvalue<0.01
∞-Only parameters with pvalues<0.2 were retained in the ITS model

Table 38. Interrupted Time Series Analysis Results of Fixed-Dose ICS-LABA Initiation Among New LABA Episodes in Percentage Points by Sex∞

	Male		Female	
	Point Estimate	**95% CI**	**Point Estimate**	**95% CI**
Fixed Dose ICS-LABA				
Intercept	87.46**	[86.85, 88.07]	82.20**^	[81.45, 82.96]
Baseline Trend			0.24**^	[0.23, 0.26]
Level Change after 2005 Policy	-0.95*	[-1.78, -0.12]	-2.46**	[-3.58, -1.34]
Trend Change after 2005 Policy	0.19**	[0.17, 0.21]		
Level Change after 2010 Policy				
Trend Change after 2010 Policy	-0.13**	[-0.16, -0.09]	-0.21**	[-0.30, -0.12]

ICS – Inhaled Corticosteroids; LABA – long-acting beta agonists; CI – Confidence Interval
*pvalue<0.05; **pvalue<0.01; ^pvalue<0.05 for pediatric vs. adult
∞-Only parameters with pvalues<0.2 were retained in the ITS model

Table 39. Interrupted Time Series Analysis of Appropriate LABA Initiation Among New LABA Episodes in Percentage Points by Sex

	Male		Female	
Parameters∞	Point Estimate	95% CI	Point Estimate	95% CI
Controller Medication Use 90 Days Prior to Initiation				
Intercept	46.59**	[45.52, 47.66]	47.37**	[45.95, 48.78]
Trend Prior to the 2010 Policy	0.02**	[0.00, 0.05]	0.02	[-.0.1, 0.05]
2010 Policy Impact			^	
Trend After the 2010 Policy				
Poor Control Prior to Initiation				
Intercept	48.82**	[47.97, 49.66]	51.72**^	[51.00, 52.45]
Trend Prior to the 2010 Policy	-0.03*	[-0.05, -0.00]	-0.5**	[-0.07, -0.03]
2010 Policy Impact				
Trend After the 2010 Policy	0.17**	[0.06, 0.29]	0.24**	[0.13, 0.35]
Appropriate Use				
Intercept	72.01**	[71.36, 72.66]	74.39**^	[73.72, 75.06]
Trend Prior to the 2010 Policy	-0.02**	[-0.04, -0.01]	-0.02*	[-0.04, -0.0]
2010 Policy Impact			-1.43	[-3.19, 0.33]
Trend After the 2010 Policy	0.08	[-0.02, 0.18]	0.19*	[0.03, 0.35]

LABA – long-acting beta agonists; CI – Confidence Interval
*pvalue<0.05; **pvalue<0.01; ^pvalue<0.05 male vs. female
∞-Only parameters with pvalues<0.2 were retained in the ITS model

Table 40. Extended Cox Regression Model of Risk of LABA Discontinuation Among New LABA Episodes By Sex (N= 159,064)

	Male		Female	
Parameter	**HR**	**95% CI**	**HR**	**95% CI**
2010 Policy* ≥30days	0.98	[0.91, 1.06]	0.97	[0.93, 1.02]
2010 Policy* <30days	0.81	[0.03, 19.21]	0.03**	[0.00, 0.23]
Single-Agent LABA	1.03	[0.98, 1.09]	1.06*	[1.00, 1.11]
Age Group (reference ≥45)				
Age 0-4	1.21*	[1.02, 1.44]	0.47*	[0.26, 0.84]
Age 5-11	1.16**	[1.09, 1.22]	1.02	[0.99, 1.06]
Age 12-17	1.29**	[1.22, 1.38]	1.18**	[1.12, 1.25]
Age 18-44	1.15**	[1.10, 1.20]	1.12**	[1.10, 1.14]
ARI	0.99	[0.96, 1.03]	1.01	[0.98, 1.03]
Allergic Rhinitis	0.95*	[0.91, 1.00]	0.97**	[0.95, 0.99]
GERD	0.98	[0.95, 1.00]	0.97**	[0.95, 0.99]
Nasal Steroid Use	1.04	[0.99, 1.09]	1.00	[0.98, 1.01]
Time of Year (ref January-March)				
April-June	1.02	[0.99, 1.04]	0.98	[0.95, 1.01]
July-September	0.99	[0.97, 1.01]	0.99	[0.95, 1.03]
October-December	0.93	[0.91, 0.95]	0.94**	[0.92, 0.97]
Use of Controller Medications within 90 days of initiation	0.69**	[0.64, 0.74]	0.73**	[0.69, 0.77]
History of Poor Control Prior to Initiation	0.92**	[0.87, 0.97]	0.95**	[0.91, 0.99]

LABA – Long acting beta agonist; HR – Hazard Ratio; CI – Confidence Interval; GERD – gastrointestinal reflux disease; ARI – Acute respiratory infection

*pvalue<0.05; **pvalue<0.01

Table 41. Poisson Regression Model Measuring the Rate of LABA and Controller Medications Overlap Among New LABA Episodes by Sex (N= 156,064)

	Male		Female	
Parameter	IRR	95% CI	IRR	95% CI
2010 Policy	0.99	[0.97, 1.00]	0.98*	[0.97, 1.00]
Single-agent LABA (reference fixed-dose LABA)	0.80**	[0.76, 0.85]	0.78**	[0.75, 0.81]
Age Group (reference ≥45)				
Age 0-4	1.02	[0.99, 1.05]	1.01	[0.97, 1.05]
Age 5-11	1.00	[0.98, 1.02]	0.99	[0.98, 1.01]
Age 12-17	1.01**	[1.00, 1.02]	1.00	[0.99, 1.01]
Age 18-44	1.00	[0.99, 1.00]	0.99	[0.98, 1.00]
ARI	1.00	[0.99, 1.00]	0.99**	[0.99, 1.00]
Allergic Rhinitis	1.00	[0.99, 1.00]	1.00	[1.00, 1.00]
GERD	1.00	[1.01, 1.01]	1.00	[1.00, 1.01]
Nasal Steroid Use	1.03**	[1.01, 1.04]	1.02**	[1.01, 1.03]
Time of Year (reference January-March)				
April-June	1.00	[0.99, 1.01]	1.00*	[0.99, 1.00]
July-September	1.00	[0.99, 1.01]	1.00	[0.99, 1.01]
October-December	0.99**	[0.98, 1.00]	0.99*	[0.98, 1.00]
Use of controller medications 90 days prior to initiation	1.00	[0.99, 1.00]	1.01	[0.99, 1.02]
History of poor control prior to initiation	0.99*	[0.98, 1.00]	1.00	[0.99, 1.00]

LABA – Long acting beta agonist; IRR – Incidence Rate Ratio; CI – Confidence Interval; GERD – gastrointestinal reflux disease; ARI – Acute respiratory infection
*pvalue<0.05; **pvalue<0.01

Table 42. Logistic Regression Model of 100% Overlap of LABA and Controller Medications Among New LABA Episodes by Sex (N=156,064)

	Male		Female	
Parameter	OR	95% CI	OR	95% CI
2010 Policy	0.71**	[0.61, 0.82]	0.71**	[0.63, 0.79]
Single-Agent LABA	0.07**	[0.05, 0.10]	0.08**	[0.06, 0.10]
Age Group (reference ≥45)				
Age 0-4	0.66	[0.36, 1.21]	0.95	[0.55, 1.66]
Age 5-11	1.20	[0.99, 1.45]	1.01	[0.82, 1.25]
Age 12-17	1.28**	[1.11, 1.48]	1.16	[0.91, 1.48]
Age 18-44	1.02	[0.95, 1.10]	0.96	[0.87, 1.06]
ARI	0.98	[0.92, 1.04]	0.94**	[0.90, 0.98]
Allergic Rhinitis	0.96	[0.85, 1.09]	1.03	[0.98, 1.09]
GERD	1.01	[0.87, 1.18]	1.01	[0.94, 1.08]
Nasal Steroid Use	1.34	[1.11, 1.63]	1.37**	[1.16, 1.62]
Time of Year (reference January-March)				
April-June	0.83**	[0.75, 0.93]	0.76**	[0.69, 0.85]
July-September	0.92	[0.77, 1.09]	0.97	[0.89, 1.07]
October-December	0.54**	[0.45, 0.64]	0.71*	[0.54, 0.93]
Use of controller medications 90 days prior to initiation	0.86	[0.74, 1.01]	0.88	[0.74, 1.05]
Poor Control	0.91	[0.82, 1.00]	0.96	[0.92, 1.01]

LABA – Long acting beta agonist; OR – Odds Ratio; CI – Confidence Interval; GERD – gastrointestinal reflux disease; ARI – Acute respiratory infection
*pvalue<0.05; **pvalue<0.01

Table 43. Interrupted Time Series Analysis of Controller Medications After LABA Discontinuation in Percentage Points by Sex

	Male		Female	
Parameter∞	**Point Estimate**	**95% CI**	**Point Estimate**	**95% CI**
Intercept	40.42**	[39.53, 41.31]	42.53**^	[42.81, 44.25]
Trend Prior to the 2010 Policy	-0.13**	[-0.15, -0.10]	-0.14**	[-0.16, -0.12]
2010 Policy Impact	1.77*^	[0.39, 3.15]		
Trend After the 2010 Policy			0.15*	[0.04, 0.27]

LABA – long-acting beta agonists; CI – Confidence Interval
*pvalue<0.05; **pvalue<0.01; ^pvalue<0.05 for pediatric vs. adult
∞-Only parameters with pvalues<0.2 were retained in the ITS model

Table 44. Logistic Regression Model of Predicting Controller Medications After LABA Discontinuation by Sex

	Male		Female	
Parameter	**OR**	**95% CI**	**OR**	**95% CI**
2010 Policy	0.96	[0.91, 1.02]	0.93	[0.86, 1.01]
Single-Agent LABA	1.74**	[1.46, 2.06]	1.58**	[1.39, 1.80]
Age Group (reference ≥45)				
Age 0-4	1.15	[0.96, 1.37]	1.00	[0.80, 1.26]
Age 5-11	0.97	[0.80, 1.19]	0.81*	[0.67, 0.99]
Age 12-17	0.73**	[0.59, 0.91]	0.71*	[0.54, 0.94]
Age 18-44	0.67**	[0.58, 0.78]	0.68**	[0.64, 0.72]
ARI	1.12**	[1.08, 1.17]	1.05	[0.99, 1.12]
Allergic Rhinitis	1.12*	[1.02, 1.23]	1.18**	[1.14, 1.23]
GERD	1.25**	[1.13, 1.39]	1.17**	[1.06, 1.29]
Nasal Steroid Use	1.72**	[1.27, 2.33]	1.58**	[1.21, 2.07]
Time of Year (reference January-March)				
April-June	0.95	[0.86, 1.06]	0.97	[0.92, 1.03]
July-September	0.97	[0.92, 1.03]	0.94	[0.89, 0.98]
October-December	0.98	[0.93, 1.04]	0.98	[0.93, 1.02]
Use of controller medications 90 days prior to initiation	21.00**	[16.29, 27.06]	17.66**	[13.53, 23.05]
Poor Control	1.12**	[1.06, 1.19]	1.14**	[1.10, 1.19]

LABA – Long acting beta agonist; OR – Odds Ratio; CI – Confidence Interval; GERD – gastrointestinal reflux disease; ARI – Acute respiratory infection
*pvalue<0.05; **pvalue<0.01

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