MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA 21254	**TRADE NAME:**	Advair HFA
APPLICANT/SPONSOR:	GlaxoSmithKline	**USAN NAME:**	Fluticasone/salmeterol
MEDICAL OFFICER:	Robert Lim, MD		
TEAM LEADER:	Anthony Durmowicz, MD	**CATEGORY:**	ICS/LABA
DUE DATE:	6/24/11	**ROUTE:**	inhaled

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
1/23/2009		PMC studies SD 160	PMC fulfilled

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY:

This is a medical officer review of two post marketing commitment studies for the GlaxoSmithKline (GSK) product Advair HFA metered dose inhaler (MDI), a fixed dose combination of fluticasone propionate (FP) and salmeterol xinafoate (SAL) in children 4-11 years of age. Advair HFA comes in three dosage strengths (ex-actuator): 1) 45 mcg FP and 21 mcg SAL (45/21), 2) 115/21, and 3) 230/21. In June 2006, the lowest dosage form of this product (45/21) was approved for the long term treatment of asthma in patients 12 years old and older. Of note, a dry powder formulation of Advair containing 100 mcg FP and 50 mcg SAL (Advair Diskus) was approved for use in children 4 years of age and above on 4/21/04. Prior to approval of the Advair HFA product for children 12 years of age and above and adults, GSK met with the Division to discuss (b) (4) Advair HFA for the 4-11 year old population. GSK agreed to perform 2 pediatric studies as post-marketing commitments which would fulfill their PREA requirement. The goals of these PMC studies were 1) to evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of Advair HFA 45/21 (Advair 45/21) in this age group, and 2) to evaluate for safety and tolerability of Advair 45/21 in this age group. The completed study reports were submitted on 1/23/2009 for review by the FDA. Study SAS105919 addressed the PK/PD of Advair 45/21 in the 4-11 year old population. Subjects received 2 of 3 treatments regimens. The regimens were Advair 45/21 with spacer, without spacer, and Advair Diskus (100/50 mcg). PD results demonstrated a slight, clinically insignificant, decrease in serum cortisol levels in all Advair groups consistent with the known effects of inhaled corticosteroids such as fluticasone propionate in both children and adults. PK data indicated fluticasone exposure was low and similar for all treatments and the fluticasone exposure was less in the HFA groups as compared to the Diskus group. The PK parameters for salmeterol were also similar for all treatments. The second PMC, Study SFA106484, assessed the safety and tolerability of Advair 45/21 in mild asthmatics. Treatment arms were Advair 45/21 and fluticasone, 44 mcg/actuation, alone. The study was complicated by what appears to have been ECG readings by a central cardiology service that did not account for inherent differences between pediatric and adult ECGs. This was manifest by a high number of screening failures due to ECG abnormalities in children prior to any study drug administration and a relatively high number of ECG abnormalities noted in children who received fluticasone only during the study, a drug which does not cause ECG changes. As a result of the high number of ECG abnormalities reported by the central cardiology service, the ECGs were evaluated by a pediatric cardiologist who was blinded to study treatments and previous interpretation. All children's ECGs, but one, were determined to be either normal or any changes were clinically insignificant. Given these findings by a pediatric cardiologist and no other safety signals identified, the safety/tolerability profile of Advair 45/21 was similar to fluticasone alone.

These study results and subsequent labeling changes were discussed at the PeRC meeting on 6/8/11. The PeRC agreed with DPARP's assessment that these studies fulfilled GSK's PREA required post-marketing commitment. DPARP has agreed with GSK submitted label changes which reflect the results of the PK/PD study (12.2, 12.3). GSK did not submit label changes that reflected results of the safety study. DPARP has suggested additional text for section 6.1 of the label.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION : PMC Fulfilled

IND/NEW STUDIES:	____ SAFE TO PROCEED	____ CLINICAL HOLD		
NDA/SUPPLEMENTS:	____ FILEABLE	____ NOT FILEABLE		
	APPROVAL	APPROVABLE	NOT APPROVABLE	

1. General Information:

This is a medical officer review of two post marketing commitment studies for the GlaxoSmithKline (GSK) product Advair HFA MDI, a fixed ex-actuator dose combination of fluticasone propionate 45 mcg and salmeterol xinafoate 21 mcg (Advair 45/21) in children 4-11 years of age. In June 2006, this product was approved for the long term treatment of asthma in patients 12 years old and older. Shortly prior to approval, GSK met with the division to discuss (b) (4) Advair 45/21 for the 4-11 year old population. During that meeting (2/22/2006), GSK agreed to perform 2 pediatric studies as a post-marketing commitment which would fulfill their PREA requirement. The goals of these PMC studies were 1) to evaluate pharmacokinetic and pharmacodynamics parameters of Advair 45/21 in this age group, and 2) to evaluate for safety and tolerability in this age group. The PK/PD study was required to consist of at least twenty 4-11 year olds with at least 1/3 in the 4-7 year old age range. The safety study was required to include at least 150-200 patients in the Advair group, be of 12 weeks duration, and preferably recruit the majority of patients from the U.S. The completed study reports were submitted on 1/23/2009 for review by the FDA. Following are reviews of the 2 PMC studies followed by proposed additions to the pediatric use section of Advair 45/21 label.

2. Pediatric PMC Study #1 (SAS105519)

2.1. Title

A repeat-dose, open-label, randomized, incomplete block design 6 week study in 31 pediatric subjects with asthma, ages 4-11 years to compare systemic exposure and pharmacodynamics of fluticasone (FP) and salmeterol xinafoate (SAL) following 2 inhalations of Advair 45/21, Advair 45/21 mcg (2 inhalations) with the Aerochamber Plus Spacer device and Advair Diskus, 100 mcg FP/50 mcg SAL, one actuation (Advair Diskus 100/50), twice daily.

2.2. Primary Objectives

To assess the pharmacodynamics (PD) of FP as measured by serum cortisol levels following administration of 2 inhalations of Advair 45/21, 2 inhalations of Advair 45/21 using an Aerochamber Plus Spacer, and 1 actuation of Advair Diskus 100/50.

2.3. Secondary Objectives

- To assess the systemic exposure of FP and SAL following administration of 2 inhalations of Advair 45/21, 2 inhalations of Advair 45/21 using an Aerochamber Plus Spacer, and Advair Diskus 100/50
- To assess the effect of 2 inhalations of Advair 45/21, 2 inhalations of Advair 45/21 using an Aerochamber Plus Spacer, and Advair Diskus 100/50 on heart rate, blood pressure, and electrocardiogram (ECG) measurements
- To evaluate the safety of 2 inhalations of Advair 45/21, 2 inhalations of Advair 45/21 using an Aerochamber Plus Spacer, and Advair Diskus 100/50 as assessed by adverse events (AEs)

2.4. Endpoints

2.4.1. Primary:

Serum cortisol weighted mean (0-12hr) and minimum measured concentration (0-12hr) [C_{min}].

2.4.2. Secondary:

1. FP and SAL C_{max}, AUC_{last}, and t_{max}

2. Heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), QTc(B), and QTc(F) weighted mean (0-9hr) and maximum (or minimum for DBP).

3. Adverse Events

2.5. Study Design

This was a repeat dose, open-label, randomized, incomplete block design 6 week study comparing systemic exposure and pharmacodynamics of Advair 45/21, Advair Diskus 100/50, and Advair 45/21 with a spacer. It was planned to recruit approximately 30 subjects for this study to ensure that at least 24 would be complete the study (both treatment periods). Following screening and baseline assessment, subjects were randomized into one of six possible treatment sequences (AB, BA, AC, CA, BC, or CB) with the treatment regimens summarized in table 1 below. Total treatment period for each subject that completed the study was 42 days (21 days on each regimen).

Table 1. Treatment Regimens

Treatment Regimen	Description
A	2 inhalations of Advair 45/21 BID x 21 days
B	1 inhalations Advair Diskus 100/50 BID x 21days
C	2 inhalations of Advair 45/21 with spacer BID x 21 days

Except for the day 21 dose, all doses were given on an outpatient basis. Between treatment regimens, there was no washout period. Parents were called on days 3, 7, and 14 after the first dose of each dosing period. These calls were to answer any questions and determine if there were any AE's. Parents were encouraged to call if any issues arose. During the study, daily peak expiratory flows (PEF's) and dairies were maintained. On day 21, PK and PD samples were obtained.

Key inclusion criteria

1) Males and females (pre-menarchal) 4-11 years old with mild asthma (PEF's >70% predicted).
2) No other serious medical conditions
3) Ability to use MDI, spacer, and DPI

Key exclusion criteria

1) Subjects who were on LABA and/or asthma was not controlled with intermittent non-steroidal asthma medications
2) Use of corticosteroids (PO/IV within 10 weeks prior, nasal within 2 weeks prior, inhaled within 6 weeks prior, topical anytime during the study)

2.6. Study Results

2.6.1. **Disposition**

This study enrolled a total of 31 subjects. Three subjects withdrew from the study; one subject withdrew on day 21 of the second treatment period due to problems with the IV catheter, and two withdrew at the end of the first treatment period. For these two subjects, the day 21 procedures were not completed. Reason for withdrawal was not specified by the sponsor. There were no protocol deviations in the eligibility criteria. There were some other protocol deviations which were considered minor (per sponsor), and did not affect safety nor data interpretation. The sponsor did not specify these deviations. The majority of patients enrolled were male and of White/Caucasian/European Heritage (77% and 81%, respectively). Age range was from 4-11 years old, with 48% of subjects ≤ 7 years of age.

2.6.2. **Safety Evaluation**

31 subjects received at least one dose of study medication and 28 completed the study. Twenty one subjects received Advair 45/21 (21.6 days mean exposure), 20 received Advair Diskus (22.2 days), and 19 received Advair 45/21 with spacer (21.4 days).

- Deaths, Serious Adverse Events, Discontinuations due to Adverse Events

No deaths, SAE's, or discontinuations due to AEs were reported.

- Adverse Events

During treatment, adverse events occurred in 13 (62%) subjects receiving Advair 45/21, 14 (70%) subjects receiving Advair Diskus 100/50, and 9 (47%) of those receiving Advair 45/21 with spacer. The most frequent AE's reported were in the respiratory, thoracic, and mediastinal system organ class. Most AE's were mild to moderate in nature, however severe cough was reported in 4 subjects who received Advair 45/21. These results are summarized in table 2:

Table 2. AE's reported during treatment for respiratory, thoracic, mediastinal disorders system organ class (MedDRA).

	Advair 45/21	Advair Diskus 100/50	Advair 45/21 with spacer
Number of subjects exposed	21	20	19
Number of subjects with any AE n(%)	13 (82)	14 (71)	9 (47)
Number of subjects with AE's in Respiratory, thoracic, and mediastinal disorders SOC n(%)	11 (52)	7 (35)	5 (26)
Cough	9 (43)	5 (25)	3 (16)
Rhinorrhea	4 (19)	5 (25)	3 (16)
Nasal Congestion	5 (24)	2 (10)	1 (5)
Wheezing	2 (10)	2 (10)	1 (5)
Dyspnea	1 (5)	1 (5)	0
Asthma	1 (5)	0	0
Pharyngolaryngeal pain	1 (5)	0	0

In addition to the above AE's, others that occurred in greater than one subject were upper respiratory infection (1 for Advair 45/21 and 4 for Advair Diskus 100/50), gastroenteritis (2 each for Advair 45/21 and Advair Diskus 100/50), and pyrexia (2 each for Advair 45/21 and Advair Diskus 100/50).

- Vital Signs/ECG's

Following administration of study medication, for heart rate, there were adjusted mean increases in the weighted mean change from baseline of 4.1 bpm, 3.2 bpm, and 5.8 bpm in the Advair 45/21, Advair 45/21 with spacer, and Advair Diskus 100/50 treatment groups, respectively. For systolic/diastolic blood pressures and ECG parameters, there were only minimal changes from baseline when comparing pre and post dose values. Overall, heart rate/blood pressure differences and ECG changes were not clinically significant.

Reviewer Comment:

The AE of cough was most notable in subjects who received Advair 45/21 without spacer. Those who used a spacer, or those administered Advair Diskus 100/50 had minimal cough. As usage of spacers with metered dose inhalers is recommended in pediatric populations, this AE may not be of significance when real world usage is taken into account.

2.6.3. Pharmacodynamic/Pharmacokinetic Evaluation

The primary objective of this study was to assess the pharmacodynamics/pharmacokinetic of Advair 45/21 in the 4-11 year old population. The primary pharmacodynamic assessment measured was serum cortisol levels at baseline compared to after each treatment regimen. Pharmacodynamic results demonstrated that there was a decrease in serum cortisol from baseline in all treatment groups (14%, 22%, and 13% for Advair 45/21, Advair 45/21 with spacer, and Advair Diskus 100/50, respectively). The ratio of adjusted geometric mean values for serum cortisol weighted mean at baseline compared to at 21 days were 0.86, 0.78, and 0.87 for Advair 45/21, Advair 45/21 with spacer, and Advair Diskus 100/50, respectively. These results demonstrated minor and similar reductions in serum cortisol across all treatment groups.

Fluticasone (FP) and Salmeterol (SAL) plasma pharmacokinetic results are summarized below in table 3. With regard to FP, Advair 45/21 with spacer had similar AUC_{last} and C_{max} compared to Advair Diskus 100/50. These values were the lowest for Advair 45/21 without use of a spacer. With regard to SAL, the $AUC_{last,}$ $C_{max,}$ and t_{max} values were similar between groups.

Table 3. FP/SAL Pharmacokinetic Parameters

Parameter	Geometric Mean (95% CI)		
	Advair 45/21 (n=18)	Advair Diskus 100/50 (n=20)	Advair 45/21 with spacer (n=19)
FP AUC_{last}	24.1 (9.6, 60.2)	137.6 (69.3, 273.2)	107.4 (45.7, 252.2)
FP C_{max}	15.7 (8.5, 29)	54.4 (33.1, 89.4)	35 (20.4, 60.3)
FP t_{max}	0.74 (.47, 2.02)	0.5 (0.00, 1.00)	0.98 (0.00, 8.17)
SAL AUC_{last}	125.7 (70.3, 224.6)	110.1 (55.4, 219)	103.4 (53.6, 199.6)
SAL C_{max}	73.9 (52, 105.1)	96.5 (60.4, 154.2)	121.2 (77.5, 189.6)
SAL t_{max}	0.2 (0.03, 2.02)	0.175 (0.13, 1.97)	0.17 (0.08, 0.22)

Reviewer Comment:

The effect of all treatment groups on systemic cortisol levels is similar. The systemic exposure to FP is lower in both Advair 45/21 groups versus the Advair Diskus 100/50 group. This is consistent with adult data. The increase in systemic FP exposure in the Advair 45/21 with spacer group as compare to the without spacer group probably indicates that use of the spacer increases lung deposition of FP or that more of the FP is swallowed when used without the spacer. As stated earlier, in clinical pediatric practice, spacer use is standard, thus, the results from the Advair 45/21 with spacer group may be more indicative of FP systemic exposure in a real world setting.

2.7. Conclusion

No significant safety signal was detected in this small study of 31 patients treated for up to 42 days with Advair 45/21 and/or Advair Diskus 100/50. No SAE's or deaths were reported. The other AE's seen in this study are commonly observed in asthmatic children 4-11 years in age. PD data indicate a mild corticosteroid effect consistent across different Advair presentations, however, there were no significant differences in the weighted means for serum cortisol across groups. PK data indicate fluticasone exposure was low and similar for all treatments and the FP exposure was less in both Advair 45/21 groups as compared to the Advair Diskus 100/50 group. The PK parameters for salmeterol were also similar for all treatments.

3. Pediatric PMC Study #2 (SFA 106484)

3.1. Title

A randomized, double-blind, double-dummy, parallel group study evaluating the safety of fluticasone propionate/salmeterol HFA 2 inhalations of 45/21mcg twice daily compared with fluticasone propionate HFA 2 inhalations of 44mcg twice daily in 350 subjects 4-11 years of age with persistent asthma.

3.2. Primary Objectives

The primary objective of this study was to evaluate the safety of 2 inhalations of fluticasone propionate/salmeterol HFA 45/21mcg twice daily compared with 2 inhalations of fluticasone propionate HFA 44 mcg twice daily in subjects 4-11 years of age with persistent asthma.

3.3. Study Design

This was a 12 week, international, multi-center, randomized, double-blind, double dummy, parallel-group study that was conducted on an outpatient basis. There were 2 treatment arms:

1) Advair (45 mcg fluticasone propionate and 21 mcg salmeterol xinafoate) HFA (Advair 45/21), 2 inhalations twice daily and placebo inhaler matching the fluticasone propionate 44mcg HFA inhaler (FP), also 2 actuations twice daily.

2) FP 2 inhalations twice daily and a placebo HFA inhaler matching the Advair 45/21inhaler twice daily.

One hundred and fifty subjects were planned to be enrolled in each treatment arm, with a target of 10-15% at 4-5 years of age. A target of 20-25% of the subjects was to be enrolled from U.S. sites.

This study was comprised of a 2 week run-in period, 12 weeks of treatment, and a 5 day follow-up visit after completion of treatment. The 2 week run-in period began at the 1st visit. During the run-in period subjects were on placebo HFA inhaler alone. At visit 1, subjects who met the inclusion/exclusion criteria were randomized to one of the two treatment groups. If the subjects were screened out, they were allowed to return on visit 1a for re-screening. Once randomized (visit 2), the subjects received study drugs, and returned to clinic for 5 study visits (1 week, 2 weeks, 4 weeks, and 12 weeks). To be randomized, subjects were required to have had a symptom score indicating asthma related symptoms or albuterol use on 2 or more days in the past 7 days. Safety parameters assessed include: AE, SAE, lab evaluations (CBC/chemistries), 24 hour urinary cortisol and creatinine excretion, blood pressure, ECG, oropharyngeal exam and asthma exacerbation detection and documentation. The visit schedule is summarized in the Table 4 below:

Table 4. Study Visits

Visit	1	1A	2	3	4	5	6	T/C	7	Disc	F/U
Week of Study				1	2	4	8	10	12		
Number of Days from Visit 2	-14±2	-14±2	0	7±2	14±3	28±3	56±3	70±3	84±3		5±2[1]
Informed consent	X[2]										
Medical history	X	X									
Physical exam	X	X							X	X	
Concomitant medication/medical conditions assessment	X	X	X	X	X	X	X		X	X	
Blood pressure	X	X							X	X	
Adverse event assessment	X[3]	X	X	X	X	X	X	X	X	X	X
Oropharyngeal exam	X	X	X	X	X	X	X		X	X	
Rhythm strip and 12-lead ECG	X[4]	X[4]							X[6]	X	
Clinic FEV_1 (6-11 years)	X[5]	X[5]	X[6]						X	X	
Clinic AM PEF (4 & 5 years)	X[5]	X[5]	X[6]								
Clinical laboratory tests	X	X							X	X	
24-hour urine collection			X[7]						X[7]		
Assess the subject's ability to use an MDI	X	X									
Dispense run-in placebo	X										
Train subjects on how to administer medications	X		X								
Collect/review diary data			X	X	X	X	X		X	X	
Collect run-in placebo			X								
Administer Childhood Asthma Control Test			X[8]								
Dispense study drug (double-blind)			X[9]			X	X				
Collect study drugs						X	X		X	X	
Dispense study-issued albuterol monthly (and as needed)	X	X	X	X	X	X	X				
Reminder of 24-hr urine collection								X			
Pharmacogenetics									X	X	
Urine pregnancy test										X[10]	

1. Follow-up telephone call 5 ± 2 days from Visit 7 or Discontinuation Visit
2. Consent must be signed prior to the withholding of any medication (including baseline ICS/short-acting $beta_2$-agonist at Visit 1)
3. Study related AEs at Visit 1
4. ECG performed prior to administration of albuterol at Visit 1 (if reversibility performed) and prior to double-blind medication at Week 12 and after withholding albuterol for four hours at Week 12
5. Calculate Visit 1 percent predicted and reversibility assessment (if reversibility required)
6. Calculate Visit 2 percent predicted
7. Complete during the 7 days prior to Visit 2 and during the 7 days prior to Visit 7
8. Childhood ACT was administered only to subjects who are eligible for double-blind treatment
9. Administer the first dose of double-blind treatment in the clinic after the subject has meet the randomization criteria
10. Performed on female subjects who are discontinued due to menses

*Source: Sponsor Table 2

Key Inclusion Criteria

1) 4-11 year old male or pre-menarchal female.
2) A diagnosis of asthma that required physician prescribed pharmacotherapy for at least 2 months prior to visit 1. Subjects 6-11 years of age must demonstrate baseline morning pre-albuterol FEV-1 ≥60% of predicted value. 4-5 years must demonstrate in clinic morning PEF ≥60% of predicted.
3) Subjects must either demonstrate reversibility of ≥12% in FEV-1 (6-11year olds) or PEF (4-5 year olds) on visit 1, or have a documented history of reversibility.
4) Subjects must be on a stable dose of inhaled corticosteroid for at least 1 month prior to visit 1.
5) Subjects must be able to replace their short acting beta-agonist with study issued albuterol.
6) Subjects (6-11 year olds) must be able to adequately perform spirometry.

Key Exclusion Criteria

1) Subject must not have life-threatening asthma, defined as a h/o significant asthma episode(s) requiring intubation, associated with hypercapnia, respiratory arrest or

hypoxic seizures, or asthma-related syncopal event. Subject cannot have been hospitalized more than twice in the past year.

2) Usage of beta-adrenergic receptor blocking agents, MAO inhibitors, TCA's, ritonavir, ketoconazole, immunosuppressive medications
3) Usage of specific asthma medications for specific durations prior to study as per table 5 below. These medications must also not be taken during study.
4) Any corticosteroid medication other than study drug, intranasal corticosteroids, and low potency hydrocortisone cream.
5) Significant uncontrolled disease or clinical significant lab abnormalities.
6) Clinically significant abnormal ECG or a QTc>449msec at visit 1.

Table 5. Prohibited Asthma Medications

Medication	Excluded time
Oral short-acting beta-agonists	12 hours
Nebulized short-acting $beta_2$-agonists[a]	6 hours
Inhaled anticholinergics	24 hours
Theophylline	
Short-acting forms of theophylline	12 hours
Twice-daily forms of theophylline	24 hours
Once-a-day controlled-release forms of theophylline	36 hours
Any leukotriene modifier[b]	14 days
Nedocromil	14 days
Cromolyn	14 days
Any inhaled long-acting $beta_2$-agonists alone, or in combination with an inhaled corticosteroid	28 days
Oral corticosteroids[c]	28 days
Parenteral corticosteroids	28 days

a. Nebulized albuterol may be used for reversibility at Visit 1
b. Leukotriene modifiers for any reason are excluded 2 weeks prior to and during the study (e.g. montelukast for rhinitis)
c. Any subject receiving daily oral corticosteroid treatment for 2 months or longer must have discontinued this medication at least 6 months prior to Visit 1.

*Source: Sponsor Package (section 5.3.2)

3.4. Study Summary

3.4.1. **Disposition**

A total of 429 subjects were screened for this study, of which 79 (18%) were excluded leaving 350 subjects who were randomized for double-blind treatment. The most common reason for exclusion was lack of reversibility (20 subjects, 5% of screened population) and clinically significant abnormal ECG findings (16 subjects, 4% of screened population) during the screening visit (visit 1). Of those that failed screening for other reasons, 17 also had ECG findings that would have excluded them from the study meaning that 33 subjects (7.7% of screened population) had ECG's findings that did or would have excluded them from the study. The most common ECG abnormality that led to failure at screening was QTc prolongation. In addition to initial screening failures noted above, 13 individuals were excluded at the randomization visit (visit 2) due a lack of asthma symptoms (to be

randomized, subjects were required to have had a symptom score indicating asthma related symptoms or albuterol use on 2 or more days in the past 7 days).

Of the 350 subjects randomized, 11 from the Advair 45/21 group and 14 from the FP group withdrew. The most common reason was protocol deviations (similar frequency between groups). Two subjects from the Advair 45/21 group withdrew due to AE's (both for cough), as compared to 1 in the FP group (headache). The demographics of the study population are summarized in Table 6 below.

Table 6. Study Population Demographics

Demographic Characteristic	Advair 45/21 N=173	FP N=177
Gender, n (%)		
Male	107 (62)	106 (60)
Female	66 (38)	71 (40)
Age		
Mean (years)	7.7	7.6
4-5 years, n (%)	36 (21)	41 (23)
6-11 years, n (%)	137 (79)	136 (77)
Ethnic origin, n (%)		
Hispanic or Latino	70 (40)	73 (41)
Not Hispanic or Latino	103 (60)	104 (59)
Race, n (%)		
White	116 (67)	114 (64)
Black	7 (4)	8 (5)
Other	50 (29)	55 (31)
Height, cm		
Mean (sd)	129.0 (14.33)	128.2 (13.47)
Weight , kg		
Mean (sd)	31.3 (11.70)	29.8 (9.76)
Spacer Use, n (%)		
Yes	135 (78)	137 (77)
4-5 years	33 (24)	39 (28)
6-11 years	102 (76)	98 (72)

The demographics, previous ICS use, screening and baseline pulmonary function (FEV-1 and PEF) were similar between treatment groups. Overall compliance for the Advair 45/21 and FP groups were similar (>95%). The mean exposure for the Advair 45/21 treatment arm was 80.9 days (SD 15.38), and 80.2 days (SD 16.41) in the FP treatment arm.

3.4.2. **Safety Evaluation**

- Serious Adverse Events/Deaths

No deaths occurred during this study. One subject who failed Screening reported an asthma exacerbation during the run in period while on placebo. One subject in the Advair 45/21

group reported a head injury during the double-blind treatment period. This subject remained in the study.

- Adverse Events

The most common (>3%) adverse events in the intent to treat (ITT) population during the double blind period are summarized in the table below.

Table 7. Common Adverse Events (>3%) in the ITT Population

SOC Adverse Event	Advair 45/21 N=173 n (%)	FP N=177 n (%)
Number (%) of subjects with any adverse event	98 (57)	103 (58)
Infections and infestations		
Nasopharyngitis	16 (9)	21 (12)
Upper respiratory tract infection	11 (6)	13 (7)
Pharyngitis	4 (2)	12 (7)
Rhinitis	8 (5)	6 (3)
Sinusitis	5 (3)	4 (2)
Nervous system disorders		
Headache	26 (15)	25 (14)
Respiratory, thoracic and mediastinal disorders		
Cough	9 (5)	7 (4)
Pharyngolaryngeal pain	6 (3)	2 (1)
General disorders and administrative site conditions		
Pyrexia	8 (5)	16 (9)
Gastrointestinal disorders		
Vomiting	3 (2)	5 (3)

Between treatment arms, there were no clinically significant differences in AE's. In subgroup analysis, for age (4-5 year old vs. 6-11 year old), gender, race (White, Black, and Other), and ethnicity (Hispanics/Latinos and Non-Hispanics/Latinos) there were some, though minimal differences in AE's. However, the overall numbers in the subgroups were small.

In addition to reporting the most common AE's, the sponsor also specifically reported "pharmacologically predictable AE's." These included headache, pharyngolaryngeal discomfort or pain, dysphonia, oral or oropharyngeal candidiasis, cardiac arrhythmia, and premature atrial contraction. These frequencies were generally similar between groups, however only the Advair 45/21 group reported cardiac arrhythmia (1 subject) and premature atrial contraction (1 subject).

- ECG's:

ECG's were performed at baseline and 12 weeks. They were read by central cardiologists at (b) (4), an ECG interpretation service. Abnormal was defined as PR interval > 180ms, Bradycardia <55bpm, Tachycardia >134bpm, QTc >449ms and QRS >89ms. At baseline, both treatment arms had a similar number of normal and abnormal ECG's. Many of those with abnormal ECG's, as assessed by the central cardiology service, were allowed to continue because they were not considered clinically significant by the investigators. During the post-randomization phase, not all abnormal ECG's, as assessed by the central cardiology service, were reported as AE's if investigators did not believe them to be clinically significant.

The majority of AE's related to ECG's abnormalities, based on the readings by the central cardiology service, were related to the QT interval or intraventricular conduction defects. The total cardiovascular AE's during the double blind treatment period, all related to non-symptomatic ECG findings, are summarized in the table below.

Table 8. Cardiac Adverse Events Reported during double blind treatment

Adverse Event During treatment	**Advair 45/21 N=173 (%)**	**FP N=177 (%)**
Investigations		
ECG change	3 (2)	2 (1)
ECG QTc prolonged	2 (1)	1 (<1)
ECG abnormal	1 (<1)	1 (<1)
ECG borderline QTc prolonged	1 (1)	0
Cardiac disorders		
Defect intraventricular conduction	4 (2)	3 (2)
Conduction disorder	0	0
Cardiac Arrhythmia	1 (<1)	0
Premature Atrial contraction	1 (<1)	0

Overall, there appeared to be more subjects with cardiovascular AE's in the Advair 45/21 arm versus the FP arm (13 subjects versus 7). Cardiac arrhythmia and premature atrial contractions were present in only the Advair 45/21 group. In addition there were also more subjects in the Advair 45/21 group who had either a borderline prolonged or prolonged QTc versus the FP group (3 subjects versus 1). Overall, this imbalance is relatively minor.

In addition to the above stated cardiovascular AE's, the sponsor also reported ECG changes at 12 weeks that were considered "Significant change: Unfavorable" as compared to baseline. There was not a significant difference in frequency or number of ECG abnormalities between treatment groups. When ECG's were taken at week 12 and compared to baseline for the Advair 45/21 and FP groups, 15% (24 subjects) and 11% (18 subjects), respectively were determined to be clinically significant and unfavorable. Of these, 22 and 18 were reported as AE's in the Advair 45/21 and FP groups respectively. In examining these specific cases, the most common reason for abnormality was prolongation of the corrected QT interval [Bazett (B), or Fridericia (F)]. For almost all cases, the QTc(B) was prolonged (>449ms), however, the QTc(F) was normal (<449ms). The total number of ECG related AE's is greater than that summarized in Table 8, as the AE's mentioned immediately above also included AE's that occurred outside of the double-blind treatment period.

Due to the high rate of ECG abnormalities seen during the screening process and the post-randomization period for all subjects regardless of treatment (placebo, Advair 45/21, or FP alone), 2 subject subsets had their ECG's read *post-hoc* by an independent pediatric cardiologist blinded to treatment and the central cardiologists' findings. The first subset included those who were excluded from the study due to ECG findings (16 subjects) or were excluded for another reason, but also had ECG findings which would have excluded them from the study (17 subjects). Of these 33 subjects (7.7% of the screening population), 26 were read as normal, 6 were read as abnormal, but not clinically significant, and 1 subject was read as abnormal and clinically significant.

The second subset in the *post-hoc* ECG analysis included subjects from the ITT population who had normal ECG's at baseline, but then had "Significant change: Unfavorable" at a post-randomization ECG. A total of 116 ECG's from 43 subjects were read by an independent cardiologist. Of the 116 ECG's read, 102 had completely normal morphology, and the 14 with abnormal morphology were not deemed clinically significant. The abnormal morphology included sinus tachycardia, right ventricular hypertrophy, left axis deviation, and right axis deviation.

Reviewer Comment:

The high percentage of abnormal ECG findings (7.7% of those screened) in the screened population raises a question as to the reliability of the central cardiology service reading of pediatric ECG's. Due to this concern, and due to high rate of ECG abnormalities seen in the post-randomization period, the sponsor performed a post-hoc analysis on subjects that failed screening and a subset of the ITT population. The post-hoc analysis was performed by an independent pediatric cardiologist blinded to treatment and previous findings. The results of that analysis were that a majority of the abnormal findings for both analyzed groups (screening failure and subset of ITT) were within normal limits, or not clinically significant. In addition, in the original analysis, the majority of the ECG abnormalities were related to QT prolongation. It was primarily the QTc(B) that was prolonged, and the QTc(F) was never prolonged (>449ms). The sponsor argues that the QTc(B) correction is known to be susceptible to over-estimation of the QT interval, especially when heart rates are high (short RR intervals). This is a valid argument, and usage of the QTc(F) correction as opposed to the QTc(B) may be more appropriate in the pediatric population as children's heart rates tend to be more rapid. It should also be noted that in the pediatric clinical setting, it is not uncommon to have an adult cardiologist read a pediatric ECG as abnormal, when a pediatric cardiologist would have deemed it normal, or not clinically significant. Given the relatively even distribution of cardiac AE's between treatment arms (as interpreted by the central cardiology service), the known issues with QT interval overestimation using the Bazett correction, the pediatric cardiologist's post-hoc reading of the ECG's, and clinical experience; it unlikely that there is a new cardiovascular safety signal identified in this study.

Laboratory Evaluation:

Hematology, chemistry, and electrolytes were assessed at baseline and at the end of treatment. There were no significant differences between the 2 treatment groups at either time point. Although several subjects did have elevations in serum potassium (Advair 45/2, 3 subjects; FP, 6 subjects), these numbers were similar between groups.

24 hour urine cortisol:

Urine cortisol was measured in a subset of subjects. This subset consisted as all subjects in the ITT population except those who had one or more of the following:

1) Urine volume <300mL (4-5 year olds) or <400mL (6-11 year olds) and 24 hour creatinine excretion below the lower limit of the threshold range.
2) Collection of urine outside of the specified time intervals.
3) Start of post-baseline urine collection time more than one day after the double blind treatment stop date.
4) Use of any corticosteroid in deviation of the protocol.
5) Use of inhaled steroid other than the double blind treatment.

The geometric mean of the urinary cortisol levels was similar at baseline and at 12 weeks between both treatment arms. The geometric mean ratio for urinary cortisol excretion (week 12/baseline), was also similar between treatment arms (0.77 for Advair 45/21 and 0.75 for FP). Mean change from baseline for the Advair 45/21 was -7.12 and -24.09 for the FP group. *Post-hoc* analysis was also performed after excluding subjects with baseline urinary cortisol values of >200nmol/24 hours. All subjects excluded (4) were in the FP group. In this analysis, the ratios remained similar, however, the mean change from baseline for the FP was -8.36 (versus -24.09). Overall, subjects in both the Advair 45/21 and FP treatment arms had some decrease in the 24 hour urinary cortisol at the end of treatment as compared to baseline.

Reviewer comment:

The overall effect of Advair 45/21 and FP on urine cortisol while minimal was present and is consistent with the effects of fluticasone in other studies and for inhaled corticosteroids in general. However, the decrease seen at week 12 is of little clinical significance does not likely represent a clinically significant alteration in the HPA axis. Post-hoc removal of subjects from analysis can be problematic, however in this case is likely acceptable. Given that removal of 4 of 144 subjects receiving FP affected the urinary cortisol mean change from baseline so significantly (from -24.09 to -7.12), those subject were likely true outliers. In addition, median change in urinary cortisol from baseline for the FP group was -6.95, compared to a mean of -24.09. This would imply that there were outliers.

Blood Pressure and Heart Rate:

There were no significant differences in blood pressure and heart rate between treatment arms.

Asthma Exacerbations:

One subject in the Advair 45/21 group had an asthma exacerbation (mild) and withdrew from the study. Three subjects in the FP group had asthma exacerbations (2 mild, 1 severe), and 2 withdrew from the study.

Other Measures:

Baseline pre-dose FEV-1's were similar between both treatment groups. At 12 weeks, subjects in the Advair 45/21 group demonstrated greater mean improvement in FEV-1 from baseline as compared to the FP group (0.23 L versus 0.17 L). The Advair 45/21 group also demonstrated a greater improvement from baseline in PEF compared to the FP group (25.3

L/min versus 23.3 L/min). While there was a nominal differences which favored the Advair 45/21 group versus the FP group, statistical analysis was not performed.

3.5. Conclusion

Based on the results of this safety study, Advair 45/21 appears to have a similar safety profile compared to fluticasone alone, and there do not appear to be any new safety signals. This is not surprising given the PK/PD data in the study SAS 105519. From a cardiac safety standpoint, the study was complicated by what appears to have been ECG readings by a central cardiology service that did not account for inherent differences between pediatric and adult ECGs. This was manifest by the high number of screening failures due to ECG abnormalities in children prior to any study drug administration and a relatively high number of ECG abnormalities noted in children who received fluticasone only during the study, a drug which does not cause ECG changes. As a result of the high number of ECG abnormalities reported by the central cardiology service, two ECG subsets were evaluated *post-hoc* by an independent pediatric cardiologist who was blinded to study treatments and the previous interpretation. All children's ECG's except one were determined to be either normal or any changes were clinically insignificant. Given these findings by a pediatric cardiologist and no other safety signals identified, the overall results of the study indicated that the safety/tolerability profile of Advair 45/21 was similar to fluticasone alone.

4. Recommended Regulatory Action

These two studies have fulfilled GSK's post-marketing commitment.

5. Label Changes

The following additional language incorporating the results of the 2 PMC studies is recommended to be added to the pediatric section (section 8.4) of the Advair HFA label. The Applicant, GSK has already included PK and PD information from Study 1 in the appropriate sections of the Advair HFA labeling supplement dated January 31, 2011.

In a 12-week study, the safety of Advair HFA 45/21 given as 2 inhalations twice daily was compared with that of fluticasone propionate 44 mcg HFA (Flovent HFA) 2 inhalations twice daily in 350 subjects 4-11 years of age with persistent asthma currently being treated with inhaled corticosteroids. No new safety concerns were observed in children 5-11 years of age treated for 12 weeks with Advair 45/21 compared (b) (4) adults and adolescents 12 years (b) (4) and older. Common adverse reactions (≥3%) seen in children 5-11 years (b) (4) treated with Advair HFA 45/21 but not reported in the adult and adolescent (b) (4) clinical trials include: pyrexia, cough, pharyngolaryngeal pain, rhinitis, and sinusitis *[see Adverse Reactions (6.1)]*. The study was not (b) (4)

The pharmacokinetics and pharmacodynamic effect on serum cortisol of 21 days of treatment with Advair HFA 45/21 (2 inhalations twice daily with or without a spacer) or Advair Diskus 100/50 (1 inhalation twice daily) was evaluated in a study of 31 children aged 4 to 11 years with mild asthma. Systemic exposure to salmeterol xinafoate was similar for Advair HFA, Advair HFA delivered with a spacer, and Advair Diskus while the systemic exposure to fluticasone propionate was lower with Advair HFA compared (b) (4) with Advair HFA delivered with a spacer or Advair Diskus. There were reductions in serum cortisol from baseline in all treatment groups (14%, 22%, and 13% for Advair HFA, Advair HFA delivered with a spacer, and Advair Diskus, respectively) *[see Clinical Pharmacology (12.2, 12.3)]*.

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/s/

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06/27/2011

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Agree - PMCs fulfilled