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APPLICATION NUMBER:

NDA 21-254

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-254
Submission Code	s_000
Letter Date	December 7, 2005
Stamp Date	December 7. 2005
PDUFA Goal Date	June 7, 2006
Reviewer Name	Carol H. Bosken, MD
Review Completion Date	April , 2006
Established Name	Fluticasone propionate /salmeterol
Trade Name	Advair HFA
Therapeutic Class	Corticosteroid
Applicant	GlaxoSmithKline
Priority Designation	S
Formulation	HFA Aerosol
Dosing Regimen	90/42, 230/42, 460/42 BID
Indication	Asthma
Intended Population	≥ 12 years of age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This application to support the use of Advair HFA in the maintenance treatment of asthma in subjects ≥ 12 years of age is approvable as assessed in the original review.

1.2 Recommendation on Postmarketing Actions

No specific postmarketing or risk management activity is required. However, due to the findings of the SMART study with Advair Diskus, the Advair HFA label will carry the same black box warnings and will be dispensed with a medication guide

1.3 Summary of Clinical Findings

The data submitted with this application consist of a safety update. The safety results obtained in two completed pharmacology studies and three completed clinical efficacy studies in which Advair HFA was administered were summarized in detail. Death and serious adverse events were summarized from two ongoing pharmacology studies and three non-US local (regional) studies. In addition, safety results from 48 studies testing the effects of Advair Diskus were summarized. A review of the postmarketing results from the GSK safety database are also included.

The incidence of serious adverse events was low in all of the populations reported and very few were likely to have been related to treatment with Advair.

1.3.3 Safety

No new safety signal was identified in this application. In general the adverse event rate was low and the distribution of events was similar to that seen in previous reviews. There were no deaths in the Advair HFA trials. Thirteen deaths were recorded for all of the Advair Diskus trials: no one diagnosis was made in more than three subjects and all of the diagnoses were common diseases. Serious adverse events were distributed evenly across treatment groups with the majority affecting the respiratory tract and/or non-respiratory infections. Oropharyngitis, non-specific or associated with candida infection was rare and no adrenal insufficiency was reported. In one study urinary cortisol was reported and the difference between Advair and placebo was very small.

1.3.4 Dosing Regimen and Administration

The doses will include 90/42 (2 puffs of 45/21), 230/42 (2 puffs of 115/21), and 460/42 (2 puffs of 230/21) mcg (ex-actuator) BID with steroid naïve patients starting with the —— and patients on maintenance corticosteroids starting with —— These doses

differ slightly from those described in the original label (44/21, 110/21 and 220/21 mcg). The change was recommended in prior CMC reviews because the original doses in the label did not correspond to the results obtained from empirical testing of the devices.

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2 INTRODUCTION AND BACKGROUND

This NDA was first submitted for review in December of 2000. It received an approvable rating due to CMC and biopharm issues, and a complete response was submitted on April 15, 2002. Two safety updates and revised labeling were reviewed at that time. There remained significant CMC issues and the application again received an approvable action. One of the CMC issues was the failure to document that the doses delivered at the actuator were 44, 110, and 220 mcg of fluticasone as stated in the label. The Applicant was instructed to adjust the label to fit the empirical data. From the clinical point of view there were no issues that would prevent approval, and only minor comments on labeling were sent to the sponsor. This submission is the second complete response. It contains a response to the CMC comments, a revised label and a safety update.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC

Stability issues which were a large part of the deficiencies of the last application have been resolved. [redacted] of data have been submitted and this is considered to be acceptable to grant a 12 month expiry. There was persistent non-proportionality of the in vitro measured fine particle mass (by cascade impaction or CI). However, the deviation from proportionality was not thought to be significant enough to be clinically meaningful

Taken from the safety update: Study CCI18781 measured the protein binding of fluticasone propionate in human plasma. At a nominal concentration of 5 – 100 mg/mL the protein binding was >99% and was not concentration dependent.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Source of Clinical Studies

This review is taken entirely from the Safety Update (February 2004 through May 31, 2005) and revised label that was submitted with the complete response. This includes summaries of study reports from studies completed since the last safety update and summaries of safety data from studies that are ongoing. No new data was reviewed. Comments on data quality and financial disclosures are not included in the submission.

4.2 Tables of Clinical Studies

Table 1. Studies Included in Safety Update for the use of Advair-HFA to Treat Asthma.

Study	Design	Dose Advair/Seretide	Duration (Days)	N	Age (yrs)	Outcome/objective
SAS10007	R,DB,PC,Cross	220/42 BID	28	18	19-47	PK
SAS10017	R,Open,Cross	110/21 SD	1	32	20-49	PK
SAS101877	R, Open, Cross	250/50	1	19	18-59	PK-Compare Devices
SAS104449	R, Open, Cross	220/42	1	20	18-55	PK
SAS30023	R,DB,PC,PG	88/42 QD	84	464	12-73	S & E
SAS30033	Open	220/42 BID	40	237	13-86	Tolerability
SAM30013	R,DB,PC	88/42 BID	126	237	12-86	
SAM30022	R,DB,PC	88/42 BID	84	68	13-79	
SAM40120	R,DB,PC	88/42 BID	84	18	≥ 30	

5 CLINICAL PHARMACOLOGY

Study SAS10007 was a 16-week randomized, multiple-dose double-blind, placebo-controlled 4-way crossover study in adult subjects with asthma. Treatment consisted of a single dose of Advair Diskus 250/50 mcg, Advair HFA 220/42, FP HFA 220 mcg, or placebo.

In study SAS101877 the systemic exposure to salmeterol and fluticasone was measured after administration of the drugs with three different devices. The study was an open-label 5-way crossover study conducted in the U.K in 19 otherwise healthy asthmatics 18 to 65 years of age. They received one of the following treatments in random order:

- 2 inhalations of Seretide 250 mcg HFA MDI without spacer
- 2 inhalations of Seretide 250 mcg HFA MDI with — spacer
- 2 inhalations of Seretide 250 mcg HFA MDI with — spacer
- 2 inhalations of Seretide 250 mcg HFA MDI with — spacer
- 1 inhalation of Seretide 500 mcg Diskus

The inhalations were given at 30 second intervals. On the study day blood was sampled for fluticasone for 12 hours after the dose and for salmeterol for 2 hours. There was a 5-day washout between treatments. The subjects had stable asthma with an FEV1 ≥ 80% on a stable

medical regimen. They could be treated with up to 800 mcg budesonide or equivalent daily but they could not have been taking fluticasone.

There was a large variation in the exposure to both fluticasone and salmeterol depending upon the method of administration. Exposure to fluticasone was after inhalation from the — was more than three times higher than after exposure to with the — spacer. Exposure to salmeterol was also highest when delivered with the — However, the lowest exposure was from the Diskus with the — the second lowest (Table 2) .

Table 2. PK Parameters After Inhalation of Seretide Using Various Spacers

	geometric mean (min-max)		
Dosing type	AUC_{0-t} (pg.h/mL)	C_{max} (pg/mL)	t_{max} (h)
	FP		
MDI + —	714.27 (107.9 - 2382.3)	148.6 (42.6 - 404.0)	0.75 (0.48 – 2.00)
MDI + —	513.75 (126.1 - 1349.5)	115.7 (60.3 - 244.0)	1.00 (0.17 – 2.00)
MDI + —	288.65 (14.7 - 783.1)	57.7 (9.2 - 146.0)	1.00 (0.50 – 4.00)
MDI	360.35 (102.4 - 1104.9)	90.8 (49.4 - 211.0)	0.75 (0.50 – 1.50)
DISKUS	395.98 (196.5 - 835.9)	78.3 (44.2-161.0)	0.78 (0.50 – 2.00)
	SALM		
MDI + —	91.62 (18.38 – 268.55)	158.8 (29.7 – 727.0)	0.20 (0.08 – 0.75)
MDI + —	62.79 (1.19 – 162.15)	117.1 (28.6 – 400.0)	0.24 (0.08 – 0.77)
MDI + —	17.78 (4.69 – 94.84)	87.8 (40.4 – 161.0)	0.10 (0.05 – 0.18)
MDI	56.36 (9.94 – 141.94)	72.8 (28.7 – 250.0)	0.32 (0.08 – 1.00)
DISKUS	14.79 (1.11 – 108.35)	81.9 (26.7 – 276.0)	0.19 (0.08 – 1.00)

The blood levels of fluticasone are shown graphically in figure 1.

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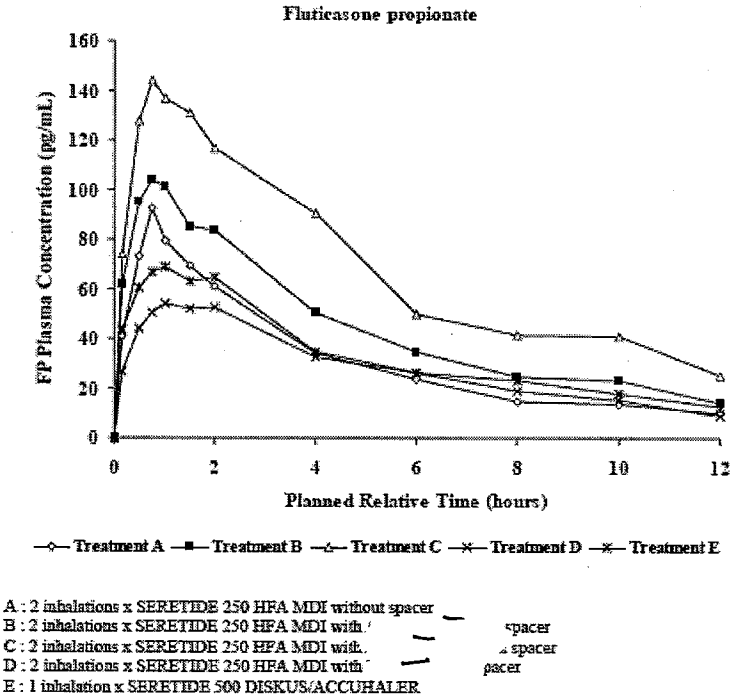
Figure 1. Blood levels of fluticasone after inhalation of Advair 500 mcg through various spacers



6 INTEGRATED REVIEW OF EFFICACY

The only efficacy data submitted with the complete response is a study report SAS30023 for a comparison between Advair and Fluticasone HFA administered once daily. Because once daily dosing is not approved, the efficacy data from this study will not be reviewed.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The data for this review were all obtained from the updated safety review. This included data submitted since the last update until May 2005. During that time the fluticasone/salmeterol combination product (FSC) was administered in two completed clinical pharmacology studies (SAS10007, SAS101877) and two ongoing studies (SAS10017, SAS104449). Fluticasone/salmeterol was also administered in three completed clinical trials (SAS30023, SAS30033, SAS30019), and in three non-US regional studies (SAM30013, SAM30022, SAM40120). Various formulations of fluticasone/salmeterol were used in these studies: Advair HFA, Seretide (fluticasone/salmeterol HFA MDI [non-US product]), Advair Diskus/Accuhaler, and fluticasone/salmeterol MDI formulated with propellants 11 and12 -

100 mcg/actuation Only severe adverse events and deaths were reported for the incomplete studies.

Study SAS30023 was a randomized, double blind comparison of fluticasone/salmeterol MDI 100/50 and Fluticasone HFA 100 mcg both administered once daily. The study was international and subjects had mild asthma (FEV1 >80% predicted) and were ≥ 12 years of age. Study SAS 30033 was an open-label evaluation of satisfaction with Advair HFA 220/42 in subjects with asthma and COPD who were ≥ 12 years of age. Study SAS30019 was a randomized, double-blind comparison of Advair HFA 88/42 and Advair Diskus 100/50 in subjects 4 to 11 years of age. The subjects were on maintenance inhaled corticosteroids at the time of enrollment.

In study SAS30023 155 subjects were randomized to receive fluticasone/salmeterol MDI and 144 completed the study. In study SAS30033 237 subjects were randomized and 97% completed the trial. In study SAS30019 215 subjects were randomized to receive Advair HFA.

7.1.1 Deaths

There were no deaths in any of the pharmacology studies. There were no deaths in the completed fluticasone/salmeterol HFA trials (SAS30023, SAS30033, SAS30019).

In the 14 completed trials with the Advair Diskus formulation 3 subjects died during treatment: 2 with myocardial infarction and 1 with lobar pneumonia. Two subjects died of myocardial infarction while being treated with Fluticasone Diskus. Five subjects died in ongoing trials: one each with coagulopathy asthma, still birth, Mucormycosis, drowning, and cardiac arrest. The cardiac arrest followed an episode of DVT that progressed to a clinical picture that was thought to represent Churg-Strauss syndrome. He was treated with methylprednisolone but developed seizures possibly due to an intracerebral hemorrhage and died. The investigator attributed the Churg-Strauss syndrome to previous ingestion of systemic corticosteroids. The mucormycosis occurred in a 61 year-old diabetic who had been treated with blinded study medication for one year.

There were no deaths in the two completed HFA MDI local studies. There were three deaths in the completed Advair Diskus local studies: one case each of coronary artery insufficient, pulmonary embolism, and myocardial infarction.

Two deaths were reported in nine ongoing Fluticasone/salmeterol (FSC) Diskus local studies. One subject had metastatic carcinoma and one died in her sleep.

7.1.2 Other Serious Adverse Events

There were no serious adverse events in the completed or ongoing pharmacology studies. Three subjects treated with fluticasone/salmeterol HFA in the three completed clinical trials suffered serious adverse events: One gastroenteritis and broken arm in study SAS30019

(fluticasone/salmeterol 100/50) and one broken ankle in study SAS30033 (Advair HFA 220/42). In study SAS30019 two subjects treated with Advair Diskus 100/50 had serious events (concussion, asthma), and 4 subjects not treated with fluticasone/salmeterol in study SAS30023 had serious events. There was one case each of influenza, headache, and premature labor in the placebo treated subjects and one case of pleuritic pain in an FP treated subject.

There was one case of muscle weakness an Advair Diskus pharmacology study that was considered serious. Serious adverse events were recorded in 31 subjects treated with Advair Diskus in completed clinical safety and efficacy studies (Table 3).

Table 3. Number of Subjects with Serious Adverse Events

Event	Studies Designed for Registration (N=4261)	Local Non-US Studies (N=2020)
Atrial fibrillation	3	1
Chest pain	1	
Appendicitis	1	
Cholelithiasis	2	
Urinary tract infection	1	
Cellulitis	1	
Lower respiratory infection	1	2
Malignancy	3	
Angina/myocardial infarction	2	3
Cerebrovascular accident	1	
Nephrolithiasis	1	
Abdominal hernia	1	
Tonsillitis	2	
Leptospirosis	1	
Musculoskelatal injury	3	2
Asthma	2	2
Hypertension	1	
Wound infection	1	
Lipoma	1	
Abortion	2	
Gaaastrointestinal hemorrhage		3
Anxiety		1
Arteritis		1
Anaphylactic shock		1

Study SAM40027 was reported separately because of its unique study design. It was a randomized, blinded comparison of Advair and FP Diskus with doses stepped up to achieve a 'well-controlled' or 'total-controlled' status. Subjects were treated for up to 52 weeks. There

were 1700 subjects in each treatment group and serious adverse events were equally common (53 [3%] and 67 [4%] of the FP and Advair subjects, respectively). No specific event (preferred term) occurred in >1% of subjects, but infections and infestations (9 and 15 in the FP and Advair groups, respectively), and respiratory disorders (13 and 10 in the FP and Advair groups, respectively) were the most commonly seen.

In the ongoing Advair Diskus clinical trials, 159 serious adverse events were reported. The most common SOC affected was the respiratory tract.

There were three serious adverse events in the two completed local fluticasone/salmeterol HFA studies (SAM30022, SAM40120): one case each of anaphylactic shock, neuralgia, and syncope. In the completed local fluticasone/salmeterol Diskus studies, 17 subjects suffered serious adverse events. In five subjects treated with FSC 500/50 Diskus, three had an acute respiratory complaint (asthma or COPD/bronchitis) and 2 had gastrointestinal hemorrhage. Of the 12 reported in subjects treated with FSC 250/50 Diskus, 4 reported cardiovascular events (2 with ASCVD, 1 atrial fibrillation, and one pulmonary embolus), 2 had respiratory events (1 each asthma and bronchitis), 2 had injuries and there was 1 each of rectal hemorrhage, anaphylactic shock, anxiety, and arteritis.

A total of 23 serious adverse events have been reported in the unblinded and ongoing FSC Diskus local trials: arrhythmia (3), asthma (2), attempted suicide (2), heart failure (2), respiratory infection (2), musculoskeletal abnormalities (2), syncope (1), missed abortion (1), abdominal abnormalities (3), AVM (1).

7.1.3 Dropouts and Other Significant Adverse Events

No subject withdrew prematurely due to adverse events in study SAS101877. However 1 subject withdrew from study SAS10007 due to viral gastroenteritis and one withdrew due to an exacerbation of asthma that occurred after 2 weeks of placebo treatment.

Six subjects were withdrawn from study SAS30023 due to adverse events. Three subjects who received once daily fluticasone/salmeterol HFA were withdrawn: two complained of pharyngeal irritation and one developed nausea and tachycardia. One subject who received daily fluticasone withdrew due to pharyngeal irritation and difficulty breathing and two placebo subjects withdrew due to an "allergic reaction" and influenza.

In study SAS30033 a 50 year old female developed an upper respiratory infection after treatment with fluticasone/salmeterol HFA 25/125, two actuations twice daily for one month.

Seven subjects withdrew prematurely from study SAS30019. One subject in the Advair HFA group had an abnormally high urinary cortisol at the beginning of treatment and another developed a muscle cramp during treatment. Five subjects treated with Advair Diskus withdrew due to adverse events: one each with low urinary cortisol, increased heart rate, headache, psychomotor hyperactivity and asthma.

7.1.5 Common Adverse Events

In study SAS10007 5/15(33%) experienced adverse events while taking Advair HFA compared with 2/14 (14%) while taking FP-HFA and 2/13 (15%) while taking Advair Diskus.

Because of the differences in study design, no attempt was made to integrate the safety data from the completed clinical trials. The events were similar to those seen with other formulations of fluticasone and salmeterol. They were not more frequent than were seen in the placebo or Diskus treated subjects.

Table 4. Adverse events occurring in ≥ 3% of subjects in study SAS30023

Adverse Event	Placebo (N=155) n (%)	FP 100 HFA MDI QD (N=154) n (%)	FSC 100/50 HFA MDI QD (N=149) n (%)
Number of subjects with any event	75 (48)	57 (37)	49 (33)
Nasopharyngitis	20 (13)	19 (12)	11 (7)
Headache	13 (8)	13 (8)	7 (5)
Upper Respiratory Tract Infection	10 (6)	3 (2)	7 (5)
Rhinitis	7 (5)	3 (2)	3 (2)
Influenza	6 (4)	1 (<1)	3 (2)
Respiratory Tract Infection (NOS)	4 (3)	4 (3)	2 (1)
Back Pain	3 (2)	2 (1)	4 (3)
Pharyngolaryngeal Pain	4 (3)	1 (<1)	4 (3)
Cough	1 (<1)	4 (3)	2 (1)
Dizziness	0	4 (3)	0

Source: SAS30023 CSR; Table 13.05

Table 5. Adverse events occurring in ≥ 3% subjects in study SAS30033

Adverse Event	FSC 220/42 HFA MDI BID Asthma N=128 n (%)	FSC 220/42 HFA MDI BID COPD N=109 n (%)
Number of subjects with any event	31 (24)	31 (28)
Headache	6 (5)	2 (2)
Pharyngolaryngeal pain	2 (2)	4 (4)

Source Data: SAS30033 CSR; Table 13.9

Table 6. Adverse events occurring in ≥ 3% subjects in study SAS30019

Adverse Event	FSC 100/50 DISKUS BID N=213 n (%)	FSC 100/50 HFA MDI BID N=215 n (%)
Number of subjects with any event	91 (43)	93 (43)
Nasopharyngitis	16 (8)	19 (9)
Upper respiratory tract infections NOS	7 (3)	6 (3)
Cough	12 (6)	10 (5)
Rhinitis, NOS	12 (6)	9 (4)
Rhinitis allergic, NOS	7 (3)	0
Headache	13 (6)	6 (3)
Pyrexia	7 (3)	8 (4)

Source data: SAS30019 CSR; Table 13.03

7.1.6 Less Common Adverse Events

At week 8 there were two subjects treated with fluticasone/salmeterol HFA MDI once daily in study SAS30023 who had clinical evidence of oropharyngeal candidiasis and one subject at week 12. None of the cultures was positive. In study SAS30019 physical examination of the throat was positive at some time during the study in 5 subjects in each treatment group. Five subjects had cultures taken and one in each treatment group was positive.

7.1.7 Laboratory Findings

Urinary cortisol/creatinine ratios were measured in study SAS30019. The ratio of week 12 to baseline for 12-hour cortisol/creatinine was 1.01 for Advair 100/50 Diskus and 0.97 for Advair 100/50 HFA.

7.1.8 Vital Signs

One subject treated with Advair Diskus withdrew from the study due to an increased heart rate. See above.

7.1.14 Human Reproduction and Pregnancy Data

There were no pregnancies reported in any of the pharmacology studies. One pregnancy was reported in study SAS30023 on the last day of the study. The outcome was not reported.

Forty-six pregnancies occurred during treatment with Advair Diskus in clinical trials, five of which resulted in spontaneous abortion. One of these was accompanied by vaginal hemorrhage and was assessed as related to treatment. One subject with previously complicated pregnancies suffered an intrauterine death. The investigator determined that there was *no possibility* the event was related to study medication (emphasis added).

There were 31 pregnancies reported for subjects currently enrolled in Advair Diskus clinical trials. Of the pregnancies reported, 2 resulted in a spontaneous abortion and 1 in an intraurterine death of one twin.

There was one pregnancy in completed FSC Diskus local trials. The outcome of the pregnancy is unknown. There were seven pregnancies in the incomplete FSC Diskus local trials and one spontaneous abortion.

7.1.17 Postmarketing Experience

Between February 1, 2004 and May 31, 2005 there were 47 spontaneous reports of death for all formulations of the fluticasone/salmeterol combination product. Eight deaths were reported in subjects less than 18 years of age. By comparison, only 9 deaths were reported to the FDA MedWatch during that same time period. In most of the reported deaths, detailed treatment histories were not available. However, at least three teen-ages died of asthma and one had an autopsy where the only changes in the lungs were compatible with the diagnosis of asthma.

There were 567 reports of serious adverse events for the Diskus formulation: 23% were in the respiratory tract, 21% were described as genera; disorders and administration site conditions, 7% were located in the nervous system and 7% were infectious diseases.

Exposure during pregnancy was reported 80 times and 17 of these reports included adverse events. There was one stillbirth and one spontaneous abortion, a variety of complications of delivery including vaginal hemorrhage and abnormal uterine contractions, and a variety of congenital malformations. None of the malformations occurred in more that one subject.

7.2 Adequacy of Patient Exposure and Safety Assessments

This summary of the world wide experience with Advair in all formulations is sufficiently detailed to assess the risks of adverse events and death.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The review of deaths and adverse events has revealed no new safety signals. There is no clustering of deaths in any particular diagnostic category and most are the result of common pathologic processes. The listing of severe and common adverse events resulted in a distribution of events that is similar to that seen in other studies with these drug products. Respiratory tract abnormalities and infections are the most common manifestations. Of note, was the low incidence of oropharyngitis either non-specific or associated with candidasis. There were no cases of adrenal insufficiency reported in the clinical trials. The one study that included measurement of urinary cortisol showed only trivial differences between the treatment groups.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The doses will be 90/42, 230/42, and 460/42 mcg fluticasone and salmeterol. Each dose will consist of two inhalations of a solution of 45/21, 115/21, and 230/21 mcg per actuation of fluticasone and salmeterol. The recommended starting dose is [redacted] for patients not on maintenance corticosteroids prior to starting Advair and [redacted] for those switching to Advair from another inhaled corticosteroid.

8.4 Pediatrics

The original application was submitted to support approval of Advair HFA for the maintenance treatment of asthma in subjects ≥ 12 years of age. A meeting was held with the FDA to discuss the applicant's ongoing program to study Advair HFA in subjects 4 to 11 [redacted] With minor additions, the Agency concurred with the plans to study 4 to 11 year olds.

The applicant is requesting a deferral for studies in subjects < 4 years of age, and the Division agreed to the deferral at a meeting held on February 19, 2002. The Division has previously noted that the combination product is not appropriate for patients < 4 years of age.

8.6 Literature Review

The applicant has submitted a list of 45 recent publications that discuss the safety of Advair.

9 OVERALL ASSESSMENT

9.1 Conclusions

The safety review has revealed no new safety concern.

9.2 Recommendation on Regulatory Action

From the clinical perspective, the application is approvable

9.3 Recommendation on Postmarketing Actions

No postmarketing actions are required

9.4 Labeling Review

Four specific comments were sent to the applicant with the last approvable letter. These have all been satisfactorily addressed by the applicant. For details see the line by line review of the label.

9.5 Comments to Applicant

None

1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

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/s/

Carol Bosken
6/1/2006 03:43:22 PM
MEDICAL OFFICER

Lydia McClain
6/5/2006 08:26:15 AM
MEDICAL OFFICER
I concur

MEDICAL OFFICER REVIEW

Division of Pulmonary Drug Products (HFD-570)

APPLICATION #:	N 21-254	APPLICATION TYPE:	NDA
SPONSOR:	GlaxoSmithKline	PROPRIETARY NAME:	Advair HFA Inhalation Aerosol
CATEGORY OF DRUG:	Corticosteroid/Bronchodilator	USAN / Established Name:	Fluticasone propionate/salmeterol
		ROUTE:	Inhaled
MEDICAL REVIEWER:	Lydia I. Gilbert-McClain, M.D.	REVIEW DATE:	09/10/2002

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
April 15, 2002	Electronic Document	Complete Response to Approvable letter	1st 6-month cycle

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments
December 20, 2000	NDA 21-254	Advair HFA- Original NDA
August 31, 2001	NDA 21-077/S -002	120-Day Safety Update for Advair Diskus
April 20, 2001	NDA 21-254	120-Day Safety Update for Advair HFA. Reporting period 8/1/00 – 12/31/00

Overview: NDA 21-254 was given an approvable action on October 18, 2001. The majority of issues that prevented approval were chemistry issues. Additionally, there were 2 biopharm issues relating to dose proportionality that needed to be addressed. From a clinical standpoint, the product was approvable and no specific clinical issues were identified that would prohibit approval. Initial labeling comments were sent to the sponsor and this response constitutes a complete response to those specific comments. However, as we indicated in the approvable letter, these were only preliminary labeling comments and more comments would be forth coming once the chemistry issues are resolved and the drug is ready for approval. The sponsor submitted the final safety update, and the proposed revised labeling with this submission.

Outstanding Issues: CMC, Biopharmceutics

Recommended Regulatory Action: Approvable

Signed: Medical Reviewer: _____ Date:

Medical Officer Review

NDA: # 21-254
Product: ADVAIR™ HFA (fluticasone propionate/salmeterol Inhalation Aerosol)
Sponsor: GlaxoSmithKline
Material Reviewed:

Submitted:	April 15, 2002
PDUFA due	October 16, 2001

Overview

This submission is a complete response to the Approvable letter of October 18, 2001. The sponsor has submitted a final safety update and revised proposed labeling.

I. FINAL SAFETY UPDATE REVIEW

Reporting Period

This final Safety Update is for the period of June 1, 2001 – October 31, 2001. Other safety information pertinent to Advair HFA that have been submitted comes from:

- Safety information up to the NDA 21-254 cut-off date of July 31, 2000 submitted December 20, 2000 to the NDA.
- The 120-day Safety update to NDA 21-254 submitted April 2001 for the reporting period of August 1, 2000 – December 31, 2000.
- The 120-Day Safety Update to S-002 to NDA 21-077 containing safety information relevant to Advair HFA for the period January 1, 2001 – May 31, 2001.

Data used in this report

The safety data presented in this report, come from completed and ongoing clinical studies, post-marketing observational studies, and spontaneous reports. The data contains information from all formulations (powder and MDI) of the fluticasone propionate/salmeterol combination. There were no completed studies with Advair HFA during the reporting period. The table below summarizes the data presented in this report.

Table 1: Safety Data Source

Data source	Number of patients	Study Designs	Comments
Completed studies			
SAM40012, SAS40024, SAS40025	Number of subjects treated across studies = 930	Randomized, double-blind parallel group studies with Advair Diskus 100/50 and 250/50. Age range ≥ 12 - 51 years of age in two studies. One study SAM40012 was done in subjects aged 4 –11 years	Study design in SAM40012 (in 4 – 11 year olds) was also double-dummy using Advair 100/50, with FP 100 and FP 200 as active controls. Study Duration was 6 months
12 Completed Local (non-regional) studies)	Number of subjects treated across studies = 4,629	Various study designs including open-label studies, randomized studies with double-dummy, double-blind studies and randomized open-label cross-over studies	
Ongoing clinical studies			
15 controlled studies	Enrollment not completed for all of the studies. At the time of reporting total number of subjects across studies exposed = 6,547	Randomized double-blind parallel group with various dose of Advair Diskus 100/50, 250/50 and 500/50. Age range across studies ≥12 – 85 years	One study of 4 years duration is an open-label study
12 local asthma studies	Number treated across studies 1,191	Advair Diskus or Rotacap used in 11 studies, 1 study used Advair HFA	
Post-marketing observational studies			
2 studies identified as SEROBS completed between the period September 2000 - September 2001	Number of patients in both studies total 15,577	Conducted in Germany using the Advair Diskus product. One study was a patient satisfaction study and included 5, 849 patients. The other study was an efficacy and tolerability study and included 9,728 patients	Deaths, SAEs, and pregnancies are reported
2 ongoing studies and EPI40067	Studies are ongoing	The [redacted] tudy is with Advair Diskus The EPI40067 observational study is being conducted with Advair HFA MDI	
Spontaneous reports between June 1, 2001 and October 31, 2001		All formulations and unknown formulations of fluticasone propionate/salmeterol combination	
other			Other post-marketing observational studies reported from Germany

Deaths, Serious Adverse Events and Pregnancies in the controlled and uncontrolled clinical studies

DEATHS

Four deaths were reported during the reporting period. One death occurred in the ongoing controlled clinical studies (using Advair Diskus). The subject (ID#10999) was a 53 year-old female with a history of hypertension who experienced a fatal ruptured cerebral aneurysm during the run-in period. The patient was randomized but had not received study medication. Three deaths occurred in the completed local studies with Advair Diskus. The three subjects were elderly patients aged 68 to 90. The cause of death was coronary insufficiency and possibly uncontrolled diabetes (subject 1045), fatal pulmonary embolism (subject 1357) and acute pulmonary edema and myocardial infarction (subject 1262).

SERIOUS ADVERSE EVENTS (SAEs)

Completed controlled clinical studies

Nine (9) subjects reported a total of 13 SAEs in the completed clinical studies SAM40012 and SAS40024. All of these events resolved. These events are shown in the table below as copied from the sponsor's submission. It should be noted that the 4th column in the table refers to the sponsor's assessment of causality of the AE, and not the Agency's. In reviewing the case narratives this reviewer believes that the two events of severe laryngitis could possibly be related to the study drug. One of these events occurred in a 5 year-old-boy subject # 3548 who had been on FP 200 mg BID for treatment of asthma. Nine weeks into treatment, he developed a viral infection that progressed into severe laryngitis and bronchitis for which he was hospitalized. The other event occurred in a 4 year-old female subject # 3562 who was taking FP 200 mg BID for the treatment of asthma. Three months later she developed severe acute laryngitis and status asthmaticus for which she was hospitalized. The status asthmaticus resolved 2 hours later and the laryngitis resolved 5 days following onset. The other SAEs do not appear to be drug related in the opinion of this reviewer. The case of multiple fractures was as a result of a motor vehicle accident. The case of salmonella infection occurred 3 days following treatment with FP 200 mg BID in a 5 year-old boy.

Serious Adverse Events in Completed Controlled Studies

Protocol	Subject #	Serious Adverse Event	Drug-Related? Y/N	Resolved? Y/N
SFC 100/50 BID				
SAM40012	4375	Coeliac disease	N	Y
SAM40012	3820	Abdominal injury	N	Y
		Laceration	N	Y
		Lung injury	N	Y
SAS40024	21384	Bipolar disorder	N	Y
FP 100 BID				
SAM40012	4329	Pneumonia	N	Y
FP 200 BID				
SAM40012	3408	Salmonella infection	N	Y
SAM40012	3548	Viral infection	N	Y
		Laryngitis	N	Y
SAM40012	3562	Laryngitis acute	N	Y
		Status asthmaticus	N	Y
SAM40012	6761	Multiple fractures	N	Y
SAM40012	6492	Contusion	N	Y

Source Data: Listing 6.1

FP= fluticasone propionate; FSC= Fluticasone propionate/salmeterol combination powder

Ongoing Controlled Clinical Studies

The data from the ongoing clinical studies are blinded. A total of 29 SAEs were reported in 28 subjects using powder formulations of the combination product. A causality assessment cannot be made at this time given that the data are blinded.

Non-US Regional (Local) Studies

a. Completed studies

For the completed regional studies, a total of 73 events occurred in 58 subjects during the reporting period. There were 3 events of femur fractures. One event occurred in a 56 y/o man who fell off a scaffold and sustained a femoral neck fracture. He had been on Advair Diskus 250/50 BID for 7 weeks. An 81 y/o man sustained a fractured neck of femur after a fall after being on Advair Diskus 250/50 BID for 5 weeks. An 84 y/o female sustained a fall about 1 week after being on Advair Diskus 250/50 BID and sustained a trochanteric fracture of the femur. All the fractures were treated surgically. Given the duration of treatment when these fractures occurred it is unlikely that they are related to the study medication. The other serious adverse events do not appear to be related to the study medication but in most cases to the underlying conditions such as known coronary artery disease in subjects who experience a myocardial infarction while on the study medication.

b. Ongoing local studies

The data from the ongoing local studies remain blinded and although no assessment of causality can be made at this time, given the nature of the events

it would be unlikely that they would be related to the study medication. During the reporting period a total of 3 serious adverse events in three subjects were reported. These events were pituitary tumor, asthma aggravated, and venous thrombosis deep limb.

Pregnancies

A total of 16 pregnancies were reported during this reporting period. Four (4) of these pregnancies occurred during the run-in period and the subjects did not receive active study drug. One of the pregnancies in the run-in period ending in a spontaneous abortion. Of the 16 pregnancies, 12 resulted in normal deliveries of healthy babies. One subject in one of the ongoing studies had an elective termination of the pregnancy. One subject in one of the completed studies who was taking Advair Diskus 250/50 BID for 8 months had a spontaneous abortion at approximately 10 weeks of gestation. The outcome of one pregnancy was unknown at the time of this reporting.

Post-marketing Observational studies

a. Completed post-marketing Observational studies

Two German post-marketing studies identified as SEROBS were completed during the review period. The VIANI DISKUS patient's satisfaction and asthma management study was a German study of patient satisfaction and management of bronchial asthma. The sponsor did not clarify whether patient satisfaction was in reference to their asthma management, or to the device. The study included 5, 849 patients. The other study was the "VIANI DISKUS for Asthma Control" study and included 9,728 patients in Germany. Additionally, there were other post-marketing observational studies reported from Germany.

Deaths: A total of 8 deaths were reported in the completed post-marketing observational studies. Four of the 9,728 subjects in the completed efficacy and tolerability study died and four subjects in other post-marketing observational studies reported from Germany died. No information is available on the details of these additional studies. The cause of death in the post-marketing observational studies are summarized in the table below copied from the sponsor's submission, again reflecting the sponsor's assessment of causality.

Deaths in Completed Post-Marketing Observational Studies

Case Id	Subject #	Age/ Gender	Serious Adverse Event	Drug-Related? Y/N
Efficacy and Tolerability Study				
B0094980A	8232[a]	60's/M	Arrhythmia	N
B0094808A	6507	U/U	Acute myocardial infarction	N
B0094367A	6461[a]	65/F	Gastric cancer	N
B0094982A	1280[a]	60's/F	Shock	N
Other Studies				
B0060158A	04673	70's/F	Gastrointestinal haemorrhage	N
B0086970A	33272	U/M	Ill-defined disorder[b]	N
B0085312A	41209	72/F	Pneumonia	N
B0059890A	03150	72/F	Respiratory failure	N

Eight deaths were reported in the ongoing study EPI40067. Three of the deaths occurred in elderly subjects (> 70 years of age) who were using Seretide Evohaler (equivalent to Advair HFA) and were cardiac events. Cause of death for 5 subjects was not ascertained.

Serious adverse events: A small number of SAEs (23 events in 21 subjects) were reported in the completed post-marketing observational studies and none appeared to be drug–related. In the ongoing observational studies 11 SAEs were reported in 4 subjects. One case of oral candidiasis in a subject on Advair Diskus 250/50 is probably drug-related.

Pregnancies: One pregnancy was reported for the ongoing observational study and the outcome was unknown at the time of reporting.

Spontaneous Reports

All spontaneous reports of deaths, SAEs, exposure during pregnancy and Churg-Strauss Syndrome for all formulations including those reported as unknown formulation, initially reported between the dates of 01 June 2001 and 31 October 2001 were presented in this report. There were four case reports of death during the reporting period. The causes of death were cardiac-related in all 4 cases. Fifty-six reports of SAEs with the dry powder formulation, 7 reports with the formulation not identified, and one report with the HFA formulation were collected during the reporting period. The SAE with the HFA formulation was a case of arthralgia in a patient with a history of metatarsalgia, asthma and joint pain. Seven reports of pregnancy were received. No events were reported with the pregnancies and the outcome of each pregnancy is unknown.

Churg-Strauss Syndrome (CSS) and Related Events

Five cases meeting the search criteria for CSS were identified in the Glaxo safety data base. Four of the cases were reported from Germany. One case was that of a 29 year old male who received the combination product and developed swelling of the leg after 3 months of treatment. Seven months later a punch

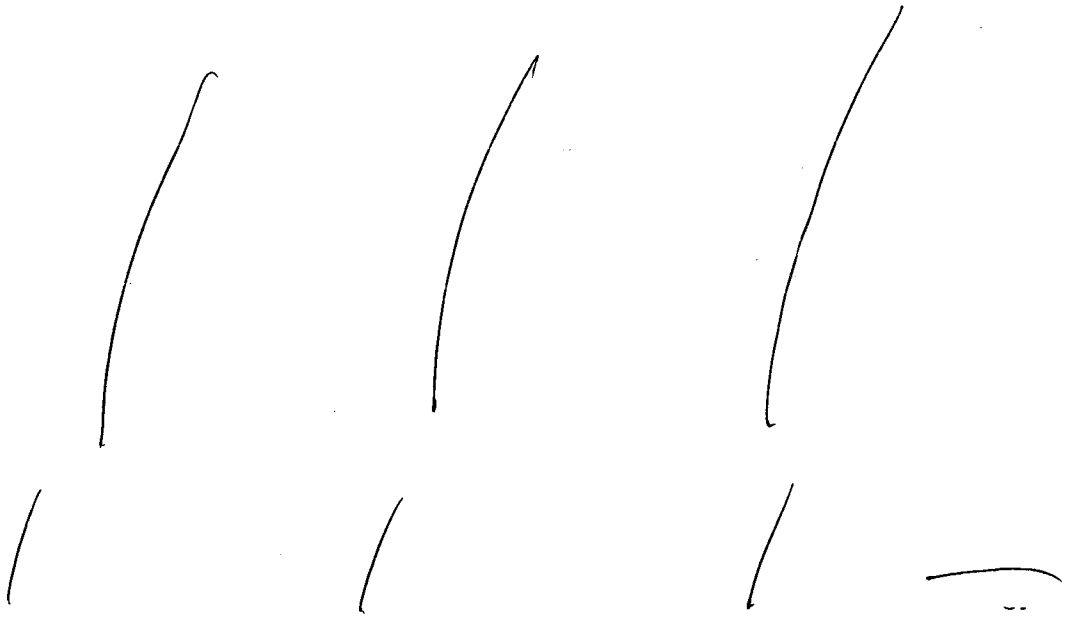
biopsy revealed a necrotizing vasculitis with severe eosinophilic infiltration. The other cases did not have biopsy confirmation.

Reports from other regulatory authorities
The sponsor communicated with the Agency on October 29, 2001 (correspondence to NDA 21-254) to notify the Agency of a voluntary recall in European Mutual Recognition (MR) markets and Norway of several batches of the low strength (50/25 ex-valve) Seretide/Viani Inhaler/Evohaler which is the non-US Advair HFA. A number of stability and retention samples of the low strength Seretide/Viani Inhaler/Evohaler failed the approved European Union end of life lower limit for FP fine particle mass.

Conclusions to the Safety Update Report (SUR)
The majority of the safety information in the final safety update is with Advair Diskus. There was very little information available with Advair HFA. The information provided does not warrant any changes in the current label for Advair Diskus. Advair HFA is not approved in the US and an approved label is still pending. The data presented in this SUR does not necessitate any specific labeling changes to the proposed labeling for Advair HFA.

II. RESPONSES TO QUESTIONS IN THE AE LETTER of October 19, 2001
The Agency's questions/comments are written in bold and the sponsor's response follows followed by reviewer comments and conclusions.

Question 32. In the CLINICAL PHARMACOLOGY Section,



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CONCLUSIONS

The sponsor's responses to the initial labeling comments in the AE letter (October 18, 2001) are generally acceptable except for the response to Questions 32, 37 and 35. For question 35, the sponsor should delete

. The sponsor should remove the words from the paragraph on the Asthma Quality of Life Questionnaire in the CLINICAL TRIALS section of the label. Additional changes to the responses submitted with this complete response as well as further labeling changes may be needed.

COMMENTS TO BE SENT TO THE SPONSOR

1. Delete

2. Delete the words form the paragraph on the Asthma Quality of Life Questionnaire in the Clinical Trials section of the label.

3. In the **DOSAGE AND ADMINISTRATION SECTION**, delete the

4. In the **CLINICAL PHARMACOLOGY SECTION,** change the statement

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/s/

Lydia McClain
9/30/02 02:28:48 PM
MEDICAL OFFICER

Mary Purucker
9/30/02 02:39:39 PM
MEDICAL OFFICER
concur

Division Director's Memorandum

Date:	Friday, October 19, 2001
NDA:	21-254
Sponsor:	GlaxoSmithKline
Proprietary Name:	ADVAIR (fluticasone propionate/salmeterol xinaphoate inhalation aerosol) HFA 44/21; 110/21 and 220/21

Introduction: This is a new NDA submitted on December 20, 2000 to support a line of combination metered-dose inhalers (MDIs) that provide salmeterol xinaphoate 21 mcg (expressed as the base) and either 44, 110 or 220 mcg of fluticasone proprionate in an HFA-134a propelled MDI blend. Though ADVAIR DISKUS (a similar dry-powder inhaler formulation) was discussed at an advisory committee meeting and is now approved and marketed, the application for the HFA MDI was developed as a stand-alone product (i.e., it was not a "switch" study, but GSK set about to reprove the combination policy). It should be noted, however that the division had extensive discussions with the company on the development of this line of products. As a part of developmental discussions, DPADP encouraged the sponsor to submit the higher strength products for the Diskus and the HFA MDI for approval, to allow more prescribing flexibility to the care-giver in assuring that patient needs are met. For this highest dose, no discreet replication of the combination policy was asked for, and none was undertaken.

Administrative: No outstanding administrative issues. The regulatory due date is October 20th, 2000.

Chemistry/Manufacturing and Controls: See Dr. Schroeder's reviews for details. There are many remaining CMC issues that preclude approval this cycle (including outstanding DMFs), although many appear to be resolvable in the near-term. Amongst these is the need to better evaluate the institution of — testing and any effects it may produce on stability.

Pharmacology/Toxicology: Due to this product containing two approved drug substances in a combination that is fairly common clinically (albeit separately administered), there are relatively few unique toxicology issues for this product. The sponsor has satisfactorily addressed the specific combination preclinically and, except for some changes to the proposed package insert, the product is approvable from the Pharm/Tox standpoint.

Biopharmaceutics: See Dr. Suarez's review for details. There are a few notable issues emanating from the biopharmaceutics review. First is an unexplained lack of consistency in salmeterol exposure across the dosage forms. By CMC, the emitted dose of salmeterol from the 3 strengths is relatively comparable, yet the systemic exposure to salmeterol rises considerably in normal subjects given the 3 different formulations, such that the lowest dosage strength provides only about 70% of the salmeterol exposure of the higher doses. The sponsor has been asked to explain this. Otherwise, the FP component appears to be dose-proportional. The comparative exposures from the HFA MDI, the Diskus and the single ingredient CFC MDIs shows some variations, but overall the exposure from the

ADVAIR HFA and Diskus products were largely similar for fluticasone, and somewhat higher for salmeterol for the MDI compared to the Diskus.

Clinical / Statistical: See Gilbert-McClain's primary review and Dr. Gebert's primary statistical reviews for details. Essentially, the results for the three pivotal studies establish the efficacy and the safety of all three dosage strengths. The studies done with the 44/21 and 110/21 product were placebo and active-controlled and were intended to meet the combination policy, which they did – with Advair HFA being statistically superior to its components and placebo on the primary endpoints and many of the secondaries. This is notable, since the primary endpoints were chosen with differing comparisons for the Advair vs. salmeterol alone comparison and the Advair vs. fluticasone alone comparisons. In fact Advair provided better results on the primary endpoints regardless of the comparison. The 220/21 study compared Advair HFA, Advair Diskus (500/50) and Flovent at a comparable dose (i.e., the MDIs were dosed at 2 puffs, or 440 mcgs and the Diskus with one blister/dose). Advair was superior to fluticasone alone on many endpoints, and the Advair HFA and Diskus groups looked largely comparable.

EER: There is an overall acceptable EER recommendation on April 9th, 2001, with site inspections signed off in early April for all sites of drug substance manufacture, micronization, and release-testing.

Labeling: There will still need to be revisions to the labeling prior to this product being approved, with only a few general and specific comments being conveyed at this time. However, since many of the issues related to the labeling and nomenclature have been worked out in individually labeling for the components and the Advair Diskus, it is not anticipated that there should need to be major revisions.

Conclusions: This NDA is approvable, pending resolution of the CMC issues and revision of the proposed labeling. It is anticipated that the remaining issues, though significant, can be resolved in a reasonable time frame.

Robert J. Meyer, MD
Director,
Division of Pulmonary and Allergy Drug Products.

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/s/

Robert Meyer
10/19/01 04:09:49 PM
MEDICAL OFFICER

CLINICAL TEAM LEADER REVIEW MEMORANDUM

***Memorandum to*:**	**NDA 21-254 file**
Product:	**Advair HFA Inhalation Aerosol**
Memo date:	**16 October 2001**
Memo from:	**Mary Purucker, MD, PhD, Medical Team Leader DPADP**

This memorandum is to document the secondary review conclusions for NDA 21-254 for Advair HFA Inhalation Aerosol, a new dosage formulation of the mono-therapies fluticasone propionate and salmeterol xinafoate. The combination is proposed for the long-term, twice-daily, maintenance treatment of asthma in patients 12 years of age and older. This is the same indication as for the previously approved Advair Diskus® (NDA 21-077), which contains the same fixed combination of active moities.

This application for Advair HFA Inhalation Aerosol is approvable from a clinical perspective.

Introduction and Background: NDA 21-254 was submitted on 20 December 2000. It has a nominal PDUFA date of 20 October 2001, although since this date falls on a Saturday, an action date of 19 October is planned.

Advair® HFA Inhalation Aerosol is an orally inhaled, fixed combination of fluticasone propionate and salmeterol xinafoate formulated as a micronized suspension in the hydrofluoroalkane propellant HFA-134a and delivered from a [redacted], pressurized metered dose inhaler via a valve-actuator system. There are no excipients in the formulation. The sponsor seeks marketing approval for three strengths of this product, 44, 110, or 220 µg ex actuator of fluticasone formulated with 21 µg ex actuator of salmeterol (as the base). The proposed unit dose is two actuations BID per product. The proposed to-be-marketed MDI products each contain 120 actuations or 60 doses per device.

Advair® HFA is considered a first line extension of the already approved fixed combination product Advair® Diskus dry powder inhaler, which is also available as three dosage strengths expressed as µg fluticasone/µg salmeterol, 100/50, 250/50, and 500/50. The unit dose of Advair® Diskus is one puff compared to two puffs for the MDI. As the first fixed combination of a corticosteroid and a long-acting β-agonist, Advair® Diskus was presented to the DPADP Advisory Committee in November 1999. The committee recommended approval, with minor labeling changes, and final marketing approval was granted 24 August 2000.

The clinical development program for Advair® HFA was conducted under IND 57,151, submitted to the Agency on 23 October 1998. There was substantial interaction between the Division and the sponsor during this time (see pre-IND meeting minutes 28 October 1997, letter to sponsor 25 November 1998, meeting minutes 8 May 2000). The program is primarily (although not entirely) a "stand alone" program, as opposed to a "switch", and therefore relies upon the fulfillment of the "combination policy" for drug product approval (21 CFR 300.50). As with Advair® Diskus, the contribution of fluticasone to the combination was assessed by change from baseline in FEV_1 while that of salmeterol relied upon 12-hour FEV_1 AUC.

Efficacy: The primary data for this NDA is contained in six studies, five of which were designed and powered for efficacy determination and three of which were conducted in the US. The six clinical trials appear in the table, below.

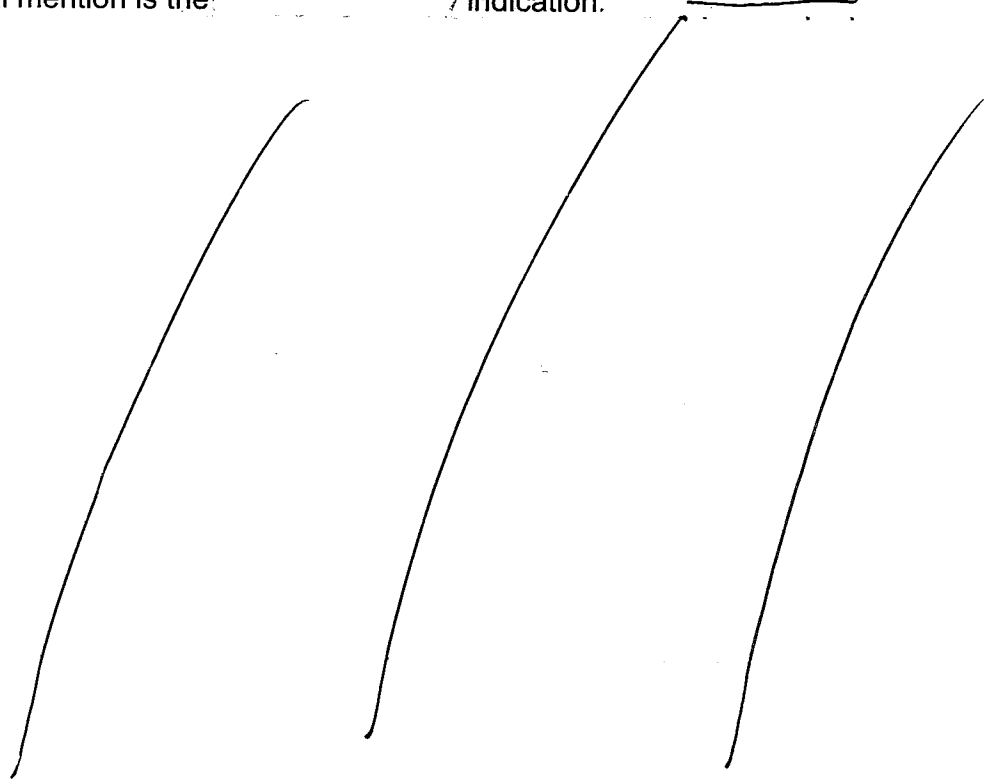
NDA 21-254 ADVAIR® HFA INHALATION AEROSOL

Trial	Design	Patient Population	Treatment Arms	Comments
SAS30001 (US)	R, DB, AC, 12-wk	ICS(-) subjects	FP 44µg 2 puffs BID SX 21µg 2 puffs BID Advair 44/21µg " "	"First-line" indication Fulfill 21 CFR 300.50
SAS30003 (US)	R, DB, PC, 12-wk	ICS(±) subjects	Placebo 2 puffs BID FP 44µg 2 puffs BID SX 21µg 2 puffs BID Advair 44/21 " "	"First-line" indication Fulfill 21 CFR 300.50
SAS30004 (US)	R, DB, PC, 12-wk	ICS(+) subjects	Placebo 2 puffs BID FP 110µg 2 puffs BID SX 21µg 2 puffs BID Advair 110/21µg " "	Fulfill 21 CFR 300.50
SFCB3023 (non-US)	R, DB, AC, 12-wk,	ICS(+) subjects	FP CFC 220µg 2 puffs BID Advair HFA 220/21µg " " Advair Diskus 500/50µg one puff BID	Clinical "comparability"
SFCB3022 (non-US)	R, DB, AC, 12-wk,	ICS(+) subjects	FP CFC 44µg 2 puffs BID Advair 44/21µg " " Advair Diskus 100/50µg one puff BID	Clinical "comparability"
SAS30005 (non-US)	52-wk, OL, uncontrolled	ICS(+) subjects	Advair 44/21µg 2 puffs BID Advair 110/21µg " " Advair 220/21µg " "	Pivotal safety study

Two important aspects of this development program are worth mention. First, as noted above, although the Advair HFA NDA should be considered primarily a "stand alone" as opposed to a "switch" program, the highest strength of the three products (Advair HFA 220/21 two puffs BID) depends upon a demonstration of clinical "comparability" to the approved Advair Diskus 500/50. Superiority over monotherapy with each of the two components was not demonstrated. The

sponsor successfully employed an "equivalency" clinical trial design with PEFR as the primary efficacy parameter. The two lower strength products, Advair HFA 110/21 and 44/21, each showed superiority over the single components in pivotal clinical trials SAS30001, SAS30003, and SAS30004. Additionally, the lowest strength product, Advair® HFA 44/21 two puffs BID, demonstrated clinical "comparability" to Advair® Diskus 100/50 in non-pivotal trial SAS3022, but did not rely upon this finding to support approval.

The second aspect of the Advair® HFA development program that is worth special mention is the indication.



Safety: Limited safety information was requested for Advair® HFA, because the long-term safety of the two active components have each been extensively studied in earlier programs. Potential cardiac safety concerns unique to the HFA formulation were identified in pre-clinical studies (see pharmacology-toxicology review, Dr. Lawrence Sancilio). Therefore Holter monitoring and 12-lead ECG with QT and QT_c determinations were required of several of the pivotal clinical trials. No specific cardiac toxicities were identified using these assessments.

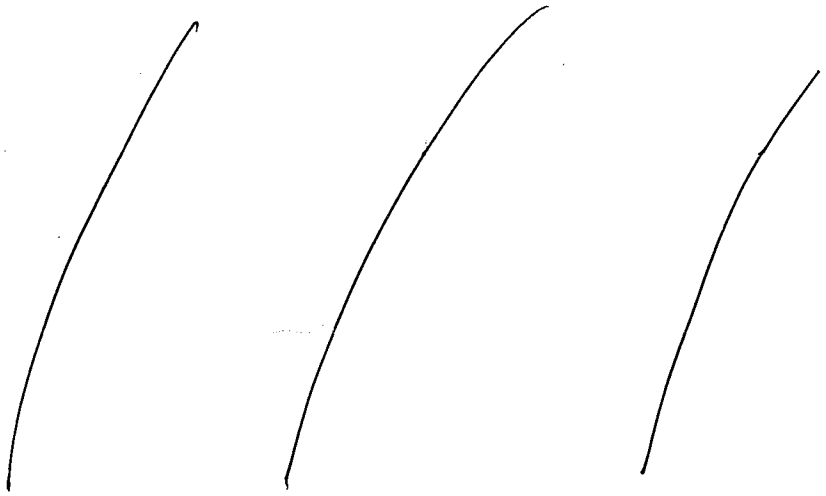
With regard to fluticasone propionate, the dose-related systemic effects of this corticosteroid have been extensively documented by numerous published and unpublished clinical trials, and reflected in the labeling for most drug products containing this moiety. The sponsor provided limited HPA axis assessment in a

subset of patients in several of the clinical trials submitted with this application. Tests included 24-hour urinary free cortisol and "short" cosyntropin stimulation testing, conducted according to the package insert supplied by the manufacturer. Due to serious methodological flaws, these studies add little to the overall body of knowledge for fluticasone. Urine collections were incomplete for substantial numbers of patients for SAS30005 and SAS3023 (based on review of total urine volumes) and total urinary cortisol was improperly "creatinine corrected." As would be expected, cosyntropin stimulation testing did show a greater number of abnormal tests for patients randomized to fluticasone 110µg two puffs BID or Advair 110/21µg two puffs BID than for patients receiving placebo. The sponsor supplied labeling [redacted]. Labeling adjustments will be required, in addition to reanalysis of urinary cortisol data, if feasible.

With regard to adverse events, these generally paralleled those identified in clinical trials and post-marketing experience with Advair Diskus. There were no new or unexpected AE's, based upon the known pharmacological properties of the active moieties of Advair HFA, nor any unique AE's attributable to the combination of these moieties with the hydrofluoroalkane propellant.

Overall Conclusions and Recommendation:

I am in agreement with Dr. Gilbert-McClain's assessment that this application is approvable from the clinical standpoint. Although substantial CMC problems await satisfactory resolution before final approval can be granted (see CMC review, Dr. Alan Schroeder), the following labeling issues should still be addressed during this cycle.



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/s/

Mary Purucker
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MEDICAL OFFICER

Robert Meyer
10/17/01 04:58:53 PM
MEDICAL OFFICER
I am in agreement with the substance of Dr. Purucker's review

Medical Officer Review

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

Application #:	NDA 21-254	**Category of Drug:**	Corticosteroid/Long-Acting β_2-Agonist
Sponsor:	GlaxoWellcome Inc.	**Route of Administration:**	Oral Inhalation
Proprietary Name:	Advair™ HFA	**Medical Reviewer:**	Lydia I. Gilbert-McClain, MD, FCCP
USAN/Established Name:	Fluticasone propionate/salmeterol xinafoate	**Review Date:**	September 27, 2001 Revised 10/04/01

Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
December 20, 2000	December 21, 2000	Original NDA	
April 20, 2001	April 21, 2001	Safety Update	

Related Applications (if applicable)

March 24, 1999		NDA 21-077	Original NDA for Advair™ Diskus approved August 24, 2000
October 23, 1998		IND 57,151	Original IND for Advair™ HFA

Overview of Application: See Executive Summary. The safety and efficacy findings of the clinical development program for Advair™ HFA submitted to NDA 21-254 support the approval of Advair™ HFA 44/21, Advair™ HFA 110/21, and Advair™ 220/21 for the long-term maintenance treatment of asthma in patients 12 years of age and older.

Outstanding Issues: The application is clinically approvable. Several CMC issues need to be addressed before the application can be approved. Comments on the proposed labeling are to be forwarded to the sponsor.

Recommended Regulatory Action

NDA/Supplements:

_____Approval

___X___Approvable

_____ Not Approvable

Signature:_____ Date_____

Lydia I. Gilbert-McClain, MD, FCCP
Medical Reviewer

Concurrence:_____ Date_____

Mary E. Purucker, MD, PhD
Medical Team Leader

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. RECOMMENDATIONS

A. Recommendation on Approvability

Advair™ HFA 44/21 (fluticasone propionate 44 mcg and salmeterol 21 mcg inhalation aerosol), Advair ™ HFA 110/21 (fluticasone propionate 110 mcg and salmeterol 21 mcg Inhalation Aerosol) and Advair ™ HFA 220/21 (fluticasone propionate 220 mcg and salmeterol 21 mcg Inhalation Aerosol) are approvable from a clinical standpoint for the long-term, twice daily maintenance treatment of asthma in patients 12 years of age and older.

B. Recommendation on Phase 4 studies and Risk Management Steps

No phase 4 studies are being requested for Advair HFA. Glaxo has an ongoing phase 4 commitment for Advair Diskus the first approved combination product of salmeterol xinafoate and fluticasone propionate. Glaxo will provide a summary of the existing pharmacokinetics and pharmacodynamic data on fluticasone propionate in patients with asthma to place in context the apparent gender effects that were observed in one of the studies [study SFCB3019] in the Advair Diskus clinical development program. In the event that the available data are inadequate to determine if a gender effect does or does not exist, Glaxo will conduct a clinical pharmacology trial to examine the pharmacokinetic and pharmcodynamic effect of fluticasone propionate administration to male and female asthma patients in an attempt to definitively assess for gender effects. These data will be provided to the Agency by February 2002.

II. SUMMARY OF CLINICAL FINDINGS

A. Overview of clinical program

Advair HFA is a combination product comprised of two drug substances that have each been approved individually for use as single agents for the maintenance treatment of asthma. The two drug substances- salmeterol xinafoate and fluticasone propionate, are each available as dry powder formulations as well as inhalation aerosols in pressurized MDIs. Serevent™ Inhalation Aerosol (NDA 20-236), approved for the treatment of asthma February 04, 1994, and Serevent Diskus (NDA 20-692) approved September 19, 1997, each contain salmeterol xinafoate as the active moiety. Flovent™ Inhalation Aerosol (NDA 20-548) approved March 26, 1996, Flovent™ Rotadisk (NDA 20-549), approved November 7, 1997, and Flovent™ Diskus (NDA 20-833), approved September 29, 2000, each contain fluticasone propionate as the active moiety, the latter two as DPI formulations.

The first combination product of salmeterol xinafoate and fluticasone propionate was Advair Diskus (NDA 21-077), which was approved August 24, 2000 for the long-term maintenance treatment of asthma in patients 12 years of age and older. Advair HFA contains these same active moieties, but has been

reformulated as an inhalation aerosol using hydrofluroalkane –134a (HFA) as a propellant. The two active moieties produce different pharmacological actions in the asthmatic airway. Salmeterol xinafoate is a long-acting $beta_2$-receptor agonist that produces bronchodilation while fluticasone propionate is a high potency corticosteroid with anti-inflammatory properties, as would be expected of this class of drugs.

Given that Advair HFA is a combination product, the sponsor's development program was designed to fulfill the regulatory requirements set forth in the Code of Federal Regulations 21 CFR 300.50 regarding fixed combinations of prescription drugs. Although Advair Diskus (NDA 21-077) has already been approved as a fixed combination of the active moieties fluticasone propionate and salmeterol xinafoate, Advair HFA is considered to be a new drug product by virtue of its new formulation and new delivery device. Since the sponsor did not relate these programs definitively, i.e. this is not a "switch program", Advair HFA must satisfy the regulatory requirements for approval of a combination product as was required of Advair Diskus. Specifically, to establish that each component makes a contribution to the claimed effects of the combination and the dosage of each component is such that the combination is safe and effective for the population requiring such concurrent therapy. Therefore, the primary objective of the drug development program was to assess the efficacy and safety of Advair HFA 44/21, Advair HFA 110/21, and Advair HFA 220/21-inhalation aerosol compared to its individual components and placebo. One non-U.S. pivotal trial was designed to establish the clinical comparability of the highest dosage strength of Advair HFA 220/21 administered as two puffs twice daily and the highest dosage strength of Advair Diskus 500/50 administered as one puff twice daily, and the efficacy of Advair HFA 220/21 two puffs twice daily compared to fluticasone propionate 220 mcg two puffs twice daily.

All four pivotal studies were conducted in asthmatics 12 years of age and older for the indication of the long-term maintenance treatment of asthma. One study, SAS30001 sought to evaluate [redacted] or Advair HFA, that is [redacted]

A total of 1,517 patients were enrolled in the four pivotal trials. Of these, 1,008 patients were enrolled in the three U.S. studies and the remaining 509 patients were enrolled in the non-U.S. study. The total number of patients exposed to Advair HFA in the four pivotal studies was 457. Of these, 176 patients were exposed to Advair HFA 220/21 mcg strength, 94 were exposed to Advair HFA 110/21 mcg strength, and 187 patients were exposed to Advair HFA 44/21 mcg strength. The sponsor also conducted one supporting study to assess the clinical comparability of Advair HFA 44/21 two puffs twice daily to Advair Diskus 100/50 1 puff twice daily in a 12-week non-U.S. study. In this study 165 subjects received Advair HFA.

B. Efficacy

All three U.S. pivotal studies showed that Advair HFA was more efficacious compared to treatment with the individual components alone at the same nominal doses in the population studied. Advair HFA was significantly superior to placebo in the two placebo-controlled trials conducted. In the equivalence study, Advair HFA 220/21 administered as 2 puffs twice daily was comparable to Advair Diskus 500/50 administered as one puff twice daily.

The 3 U.S. studies were: (I) Study SAS30001, an active-controlled study with Advair HFA 44/21 mcg strength conducted in asthmatics managed on as needed short-acting $beta_2$- agonist only, (ii) Study SAS30003, which evaluated the same dose of Advair HFA as study SAS30001 but was a placebo-controlled study in patients previously on inhaled corticosteroids or on long- or short-acting $beta_2$-agonist; and (iii) Study SAS30004, which studied patients poorly controlled on inhaled corticosteroids and evaluated the Advair HFA 110/21 mcg strength product. All three studies were designed with a 2-week placebo run-in period followed by a 12-week Treatment period.

Because the combination product is comprised of two drugs with different effects on clinical, physiological, and inflammatory indices of asthma, different primary efficacy endpoints were established for these studies which reflect both the bronchodilatory properties of salmeterol, and the anti-inflammatory properties of fluticasone propionate. Mean change from baseline in morning pre-dose FEV_1, AND the probability of remaining in the study over time were the primary endpoints for comparison of the combination product to salmeterol to evaluate the effects of fluticasone in the combination product in studies SAS30003 and SAS30004. In study SAS30001, only the mean change from baseline in morning pre-dose FEV_1 was evaluated to assess the FP effect. The probability of remaining in the study was evaluated as a secondary endpoint in study SAS30001. The area under the 12-hour serial FEV_1 curve relative to baseline [AUC (bl)] at Treatment Day 1 AND Treatment Week 12 were used as the primary endpoints for comparison of the combination product to FP to evaluate the effects of salmeterol in the combination. Adjustments for multiple comparisons were established *a priori* for the efficacy analyses.

The three U.S. studies showed that Advair HFA 44/21 mcg and 110/21 mcg strength administered twice daily were effective for the maintenance treatment of asthma in patients 12 years of age and older in the population studied. Subjects in the Advair HFA treatment group had significant improvements in FEV_1 measures compared to salmeterol, fluticasone propionate, or placebo. In study SAS 30001 the change from baseline in mean morning pre-dose FEV_1 at endpoint was 0.69L(33%) for Advair HFA compared to 0.47L (22%) for salmeterol [$p = 0.004$] and 0.51L (25%) for Flovent [$p= 0.016$]. The area under the 12-hour serial FEV_1 curve relative to Treatment Day 1 baseline [AUC (bl)] on Treatment Day one and Treatment Week 12 was significantly greater compared to FP ($p<0.001$). Similar improvements in FEV_1 measures in the Advair HFA-

treated group were seen in studies SAS 30003 and 30004 compared to the individual components salmeterol and fluticasone administered at the same nominal dose. At the end of the 12-week treatment period, subjects randomized to Advair HFA had a significantly higher probability of remaining in the study without discontinuation due to worsening asthma compared to those subjects receiving placebo or salmeterol [$p<0.001$].

In study SFCB 3023 Advair HFA 220/21 administered as 2 puffs twice daily was clinically comparable to Advair Diskus 500/50 administered as 1 puff twice daily. The mean change from baseline in morning peak flow over the 12-week treatment period was 50L/min ± 3.2 for Advair HFA and 48 L/min ± 3.4 for Advair Diskus adjusted for baseline, center, age and sex. This corresponds to an adjusted treatment difference Advair Diskus – Advair HFA of – 2L/min and the 95% confidence interval was –11 to 7 L/min. This interval falls inside the sponsor's prespecified comparability rule (95% confidence limit completely contained within ± 15 L/min). Advair HFA 220/21 2 puffs bid was superior to FP 220 2 puffs bid ($p<0.001$).

The indication for the long-term maintenance treatment of asthma is supported by the results of these studies.

C. Safety

Given that the individual components in this combination are already approved individually and together as a combination product (Advair™ Diskus®) for the treatment of asthma, and given that the safety profile of $beta_2$-agonists and corticosteroids is fairly well understood, the focus of the safety review was to identify any safety concerns unique or unusual with this formulation.

The sponsor conducted safety assessments in all the 12-week efficacy [pivotal and supporting] studies. In addition, a 12-month open label study [SAS3005] in 325 patients to assess the long-term safety of Advair was conducted. The safety data from all the studies support the safety and tolerability of Advair HFA. There was no evidence that treatment with the combination product was associated with an increased risk of adverse events including cardiovascular events compared to treatment with the individual agents. The most common events were in the upper respiratory system [URTI, throat irritation, viral respiratory infection, asthma, sinusitis, pharyngitis/throat infection] and headache, and occurred with comparable frequency across all the efficacy studies. In the long-term safety study the adverse event profile was similar to that seen in the efficacy studies. Adverse events occurring within 15 minutes following dosing were monitored as an indicator of potential propellant (HFA-134a) or formulation-related events and were collected in the U.S. efficacy studies. These adverse events were infrequent (≤ 5%) during both the run-in (propellant only) period and the active treatment (propellant + active drug) period. Only one death occurred during the entire study and it was unrelated to the study medication or the

underlying disease under study. Of the total number of patients [2,104] treated in al the efficacy studies, 1% (25) reported 30 serious adverse events and only 4 of these events were probably drug-related.

No formal drug interaction studies were performed with Advair HFA. Over the course of the 12-week clinical trials no increase in frequency of cardiovascular events was noted among patients taking the short-acting beta$_2$-agonist Ventolin® as needed. Patients using a theophylline product or Flonase ® nasal spray concomitantly with Advair HFA had similar adverse event profiles to patients who were not taking these medications.

D. Dosing

Advair HFA comes in three strengths 44/21, 110/21, and 220/21 measured at the ex-actuator. In the nomenclature the FP dose is written first followed by the salmeterol dose. Advair HFA is formulated for oral inhalation only. The recommended dosing regimen is two inhalations (puffs) twice a day. The lowest effective dose of corticosteroid should be employed depending on asthma severity.

E. Special Population

Formal pharmacokinetic studies using Advair HFA were not conducted to examine gender differences or in special populations, such as elderly patients specifically, or patients with hepatic, or renal impairment. Of the 622 patients exposed to Advair HFA in the five 12-week efficacy trials, females represented 53 –63% of subjects across treatment groups. Eight-five percent (85%) of the patients were Caucasian. However the minority races were poorly represented and while there appear to be no differences in safety or effectiveness, no definitive conclusions can be made about ethnic origin-related effects. There were no gender differences in effectiveness. In the clinical efficacy studies, the percentage of subjects who reported at least one adverse event in the Advair HFA treatment group was higher for females (55%-75%) compared to males (51%-59%). Similarly in the placebo group, a higher percentage of females (59%) compared to males (56%) reported at least one adverse event. The adverse event profile analyzed by gender was similar to that of the overall safety population.

Pediatric subjects 12 years of age and older were included in this clinical development program. [redacted]. For patients 4 to < 12 years of age, GSK has proposed to conduct a pharmacokinetic and pharmacodynamic study of Advair HFA and Advair Diskus. GSK had a meeting with the Division to discuss their pediatric program on April 26, 2001. At that meeting, the sponsor requested waiver or deferral for pediatric studies with Advair HFA in subjects [redacted] the Division agreed to grant a deferral at the time of NDA approval.

List of Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
AM	Morning
ANOVA	Analysis of Variance
AQLQ	Asthma Quality of Life Questionnaire
ATS	American Thoracic Society
AUC(bl)	Area under the serial FEV_1 curve relative to baseline
BID/bid/BD	Twice daily
CFC	Chloroflurocarbons
CRF	Case report form
DPI	Dry powder inhaler
DSI	Division of Scientific Investigations
EIR	Establishment Inspection Report
FEV_1	Forced expiratory flow rate in one second
FP	Fluticasone propionate
GI	Gastrointestinal
HFA 134a	Hydrofluroalkane propellant
ICS	Inhaled corticosteroid
ITT	Intent to treat
IRB	Institutional Review Board
ISS	Integrated summary of safety
ISE	Integrated summary of efficacy
L	Liter
L-hours	liter-hours
LLN	Lower limit of normal range
Mcg	microgram
MDI	Metered Dose Inhaler
Mins	Minutes
NAEPP	National Asthma Education Prevention Program
P11/12	propellant 11 and 12
PEF/PEFR	Peak expiratory Flow [Peak expiratory flow rate]
PFT	Pulmonary function test
PD	Pharmacodynamic
PK	Pharmacokinetic
PM	Evening
PRN/prn	As needed
PVC	Premature ventricular contraction
SAE/SE	Serious adverse event/Serious event
SAL	Salmeterol
ULN	Upper limit of normal
VAI	Voluntary Action Indicated

CLINICAL REVIEW

I. INTRODUCTION AND BACKGROUND

A. Drug Name, Indication, Dose, Regimens, Age Groups

Advair ™ HFA 44/21 (fluticasone propionate 44 mcg and salmeterol 21 mcg inhalation aerosol), Advair ™ HFA 110/21 (fluticasone propionate 110 mcg and salmeterol 21 mcg Inhalation Aerosol) and Advair ™ HFA 220/21 (fluticasone propionate 220 mcg and salmeterol 21 mcg Inhalation Aerosol) is a combination of two previously approved drugs- salmeterol xinafoate, and fluticasone propionate. The proposed indication is for the long-term maintenance treatment of asthma in patients 12 years of age and older. The recommended dose is 2 puffs by oral inhalation bid.

B. State of Armamentarium for Indication

The two-drug substances, salmeterol xinafoate and fluticasone propionate are approved and marketed individually as products for the long-term maintenance treatment of asthma. Salmeterol [SAL] has been approved as Serevent inhalation aerosol [in a pressurized MDI with CFC propellants] NDA 20-236, and as a dry powder formulation, Serevent Diskus NDA 20-692. Fluticasone [FP] has been approved as Flovent inhalation aerosol [in a pressurized MDI with CFC propellant, [NDA20-548], a dry powder inhaler [(DPI) as Flovent Rotadisk [NDA 20-549], and as Flovent Diskus [NDA 20-833] for the maintenance treatment of asthma. Salmeterol and fluticasone propionate were approved in combination as a DPI [Advair Diskus, NDA 21-077], on August 24, 2000 for the long- term maintenance treatment of asthma.

There are several inhaled corticosteroids available in the U.S. market for the maintenance treatment of asthma, including DPIs, MDIs, and a suspension for nebulization. Additionally, a second long-acting $beta_2$ - receptor agonist fomoterol fumarate [Foradil ® Aerolizer ®, (Norvatis)] was approved for the long-term maintenance treatment of asthma earlier this year. Advair HFA will be the second combination product albeit containing the same drug substances as Advair™ Diskus ® for the long-term maintenance treatment of asthma.

C. Important Milestones in Product Development

At the time of submission the sponsor was GlaxoWellcome (GW). The sponsor has since merged with SmithKline and is now GlaxoSmithKline (GSK). In a pre-IND meeting held on March 11, 1996, the Agency agreed that the proposed toxicology program for the Advair HFA formulation was acceptable and would be adequate to support an NDA submission. Following discussions with the Agency on October 28, 1997, study SAS30001 was added to the clinical development program to address the use of Advair HFA [redacted]
Clinical development was conducted under IND 57,151 which was submitted to the Agency on October 23, 1998.

A pre-NDA package was submitted on January 14, 2000 (Serial no. 51). After that, there were several pre-NDA meetings/telecons to discuss CMC-related issues. Additionally, a meeting was held August 4, 2000 in response to a meeting request dated June 12, 2000 (Serial No. 71) to discuss plans to submit this NDA in an electronic format. Agreement was reached as to the format and content of the electronic submission and the NDA was submitted in electronic format on December 20, 2000.

D. *Other Relevant Information*

See "Postmarketing Experience" section on page 15.

E. Important Issues with Pharmacologically Related Agents

N/A

II. Chemistry, Pharmacology/Toxicology, Statistics

Advair HFA inhalation Aerosol, is a combination of fluticasone propionate and salmeterol xinafoate. Fluticasone propionate is a potent fluorinated glucocorticoid having the chemical name S-fluoromethyl 6α-methyl-3-oxo-17α-propionyloxyandrosta-1, 4-diene-17β-carbothioate. Fluticasone propionate is a white to off-white powder with a molecular formula of $C_{24}H_{31}F_3O_{5S}$ and molecular weight of 500.6. Salmeterol is a long-acting, potent, selective beta$_2$ adrenergic agonist. The xinafoate salt of salmeterol is used in the combination product and has the chemical name 4-hydroxy-α^1-[((6-(4-phenylbutoxy) hexyl)-amino)methyl]-1,3-benzenedimethanol, 1-hydroxy-2-napthoate. It is a white to off-white powder with a molecular formula of $C_{25}H_{37}NO_4C_{11}H_8O_3$. Advair HFA Inhalation Aerosol is a pressurized, metered-dose aerosol unit intended for oral inhalation only. Each unit consists of an aluminum canister, [redacted] containing a suspension of micronized fluticasone propionate and salmeterol xinafoate in the liquefied hydrofluroalkane (HFA) propellant 1,1,1,2, -Tetrafluoroethane (GlaxoWellcome code GR 106642X). The unit is sealed with a metering valve. The canister is contained in a plastic actuator, fitted with a dust cap. The drug substances and propellant are the only components of the formulation. The drug product does not contain excipients or chlorofluorocarbon (CFC) propellants.

The sponsor proposes to market three strengths of product formulated to deliver the following mean quantities of fluticasone propionate/salmeterol per actuation through the actuator:

- Advair HFA 44/21 mcg
- Advair HFA 110/21 mcg
- Advair HFA 220/21 mcg

The proposed dosage is two puffs twice daily. The 42-mcg ex-actuator dose of salmeterol is equivalent to the ex-valve dose of 50 mcg. The ex-actuator doses of

fluticasone propionate of 88 mcg, 220 mcg and 440 mcg are equivalent to the ex-valve doses of 100 mcg, 250mcg, and 500 mcg respectively.

Dr. Lawrence Sancilio conducted a detailed pharmacology/toxicology review. Briefly, in preclinical studies with salmeterol, changes observed were characteristic of beta$_2$-agonist activity, i.e. hypoglycemia, hypokalemia, increased body weight and leomyomas. Additionally, tachycardia, vasodilation and myocardial papillary necrosis were observed in dogs receiving salmeterol orally and by inhalation. Findings in preclinical studies with fluticasone propionate were similar to those seen with glucocorticoids, i.e. weight loss, decreased thymus weight and/or decreased cortisol levels. Preclinical studies with salmeterol and fluticasone propionate in combination formulated as Advair HFA showed changes characteristic of beta$_2$-agonist and glucocorticoid activity. Inhalation studies in dogs with salmeterol and fluticasone propionate alone and in combination as Advair HFA showed that the glucocorticoid enhanced the increase in pulse rate seen with salmeterol.

Dr. James Gebert, Biostatistician conducted a detailed statistical review of the NDA.

III. Human Pharmacokinetics and Pharmacodynamics

Dr. Shinja Kim did a detailed review of the clinical pharmacology program. The individual clinical pharmacology of salmeterol and fluticasone propionate has been previously investigated and the effects of these two drugs in humans are well established. Therefore, the clinical pharmacology program for Advair HFA was designed mainly to evaluate the effects of the two components given together in an MDI propelled by HFA-134a and to compare the effects when salmeterol and fluticasone are given individually from a MDI propelled by CFC or together as the combination product propelled by HFA-134a. The results of the studies conducted show lower systemic exposure estimates of salmeterol and fluticasone propionate from the HFA combination compared with the individual inhalers. The systemic exposure of fluticasone propionate from Advair HFA and Advair Diskus were similar. Systemic exposure for salmeterol was higher from Advair HFA than from Advair Diskus, however pharmacodynamic effects [changes in heart rate, blood pressure, potassium, glucose and QTc intervals] were similar.

IV. Description of Clinical Data and Sources

A. Overall Data

The data used in the review were obtained from the U.S. and non-U.S. clinical program. The U.S. clinical program consists of three studies: SAS30001, SAS30003, and SAS 30004. Studies SAS30003 and SAS30004 were active and placebo-controlled 12-week studies comparing Advair HFA 44/21 and Advair HFA 110/21 2 puffs bid, to 2 puffs bid of the individual components FP and

salmeterol as CFC MDIs at the same nominal dose, and placebo. Study SAS30003 included adult and adolescent patients whose asthma was previously treated with either bronchodilators (short-acting or long-acting) alone or inhaled corticosteroids, while study SAS30004 included patients whose asthma was previously treated with inhaled corticosteroids alone and as needed short-acting $beta_2$-agonists. The non-U.S. clinical program consisted of three studies: SFCB3023, SFCB3022 and SAS30005. Study SFCB3023, another pivotal study, was an active-controlled study with a 12-week treatment period followed by a two-week follow-up period in patients whose asthma was previously treated with inhaled corticosteroids. The study was primarily designed to evaluate the equivalence of Advair HFA 220/21 2 puffs bid to Advair [Seretide[1]] Diskus 500/50 1 puff bid. This study also evaluated the efficacy of Advair HFA 220/21 2 puffs bid compared to fluticasone propionate 220 mcg 2 puffs bid. Study SAS30005, conducted in Canada, was a 52-week, open-labeled safety study that evaluated all three strengths of Advair HFA. Study SFCB3022, which was a supporting efficacy study of similar design to SFCB3023 compared Advair HFA 44/21 Inhalation Aerosol two puffs twice a day to fluticasone propionate MDI 44 mcg two puffs twice a day and Seretide Diskus 110/50 one puff twice a day. Only the safety results of study SFCB3022 were reviewed.

B. Table of Clinical Studies

APPEARS THIS WAY
ON ORIGINAL

[1] Seretide Diskus is the European name for Advair Diskus

TABLE 1. CLINICAL STUDIES

Study #	Location	Study Objective	Prior Asthma Therapy	Treatments Arms/ BID Dosage (mcg)	Primary Endpoints	N Randomized	N Completed
SAS30001 (Pivotal)	US	Demonstrate superiority of the combination product over the individual components	As needed β-agonists only	Advair HFA 88/42 SAL (CFC MDI) 42 FP (CFC MDI) 88	AUC [bl] at Treatment Day 1 and Week 12, Change from baseline in AM pre-dose FEV_1	283	257
SAS30003 (Pivotal)	US	Demonstrate superiority of the combination product over the individual components and placebo	ICS, salmeterol, or short-acting β-agonists.	Advair HFA 88/42 SAL (CFC MDI) 42 FP (CFC MDI) 88 Placebo HFA	AUC (bl) at Treatment Day 1 and Week 12, Change from baseline in AM pre-doseFEV_1, Probability of remaining in the study	360	279
SAS30004 (Pivotal)	US	Demonstrate superiority of the combination product over the individual components and placebo	ICS [all patients]	Advair 220/42 SAL (CFC MDI) 42 FP (CFC MDI) 220 Placebo HFA	AUC(bl)at Treatment Day 1 and Week 12, Change from baseline in AM pre-dose FEV_1, probability of remaining in the study	365	243
SFCB3023 (Pivotal)	Europe	Demonstrate the equivalence of the HFA MDI combination product with the Diskus combination product. Demonstrate superiority of the HFA MDI combination product over FP CFC MDI	ICS (BPD, budesonide or flunisolide 1500-2000 µg/day or FP 750-1000 µg/day)	Advair HFA 440/42 Advair Diskus 550/50 FP (CFC MDI) 440	Mean morning PEFR over Treatment Weeks 1-12	510	448
SFCB3022 (supporting)	Europe	Demonstrate the equivalence of the HFA MDI combination product with the Diskus combination product. Demonstrate superiority of the HFA MDI combination product over FP CFC MDI	ICS (BPD, budesonide or flunisolide 400-500 µg/day or FP 200-250 µg/day)	Advair HFA 88/42 Advair Diskus 100/50 FP (CFC MDI) 88	Mean morning PEFR over Treatment Weeks 1-12	497	430
SAS30005 (Long term safety)	Canada	Demonstrate the long-term safety of Advair HFA over 52 weeks	As needed β-agonists, salmeterol, ICS	Advair HFA 88/42 Advair HFA 220/42 Advair HFA 440/42	Safety	325	274

C. Postmarketing Experience

As of January 31, 2001, approval has been obtained for the fluticasone propionate/salmeterol HFA MDI combination product in 13 countries outside the U.S – Austria, Belgium, Denmark, Finland, Gibraltar, India, Malta, Netherlands, New Zealand, Peru, Switzerland, UK, and Venezuela. The earliest approval was in Venezuela on October 04, 2000. No marketing application has been rejected on the grounds of safety or effectiveness. There have been no withdrawals of the fluticasone propionate/salmeterol HFA MDI or Diskus combination product from marketing for any reason related to safety or effectiveness. Postmarketing data were obtained from information submitted in the 120-day safety update report submitted to the Agency on April 11, 2001. This report covered the period August 01, 2000- to December 31, 2000. The information in the 120-safety update report supports the safety and tolerability of Advair HFA for the maintenance treatment of asthma.

D. Literature Review

The sponsor submitted an extensive review in support of the use of corticosteroids in asthma, and the benefits of this combination therapy in asthma. For the purposes of the NDA review the following articles were reviewed:

(I) The NAEPP guidelines for the diagnosis and treatment of asthma (NIH publication 1998)

(II) Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Elizabeth F. Juniper et al; Thorax 1992; 47: 76-83

(III) Determining a minimal important change in a disease-specific quality of life questionnaire. Elizabeth F. Juniper et.al; J Clin Epidemiol (1994) Vol 47, No.1 81--87

(IV) Measurement of Health Status. Ascertaining the minimal clinically important difference. Roman Jaeschke et.al. Controlled Clinical Trials (1989) 10: 407-415

(V) The evaluation of multiple clinical endpoints with application to asthma. Markus Neuhauser and Volker W. Steinijans. Drug Information Journal (1999),Vol 33; 471-477

V. CLINICAL REVIEW METHODS

A. Conduct of the Review

The three U.S. trials SAS30001, SAS30003, and SAS30004 and the non-U.S. trials SFCB3023, and SAS30005 were reviewed in detail. Only the safety results of study SFCB3022 were reviewed. All trials were reviewed separately and discussed with the Medical Team Leader. A detailed review of each trial was

written and is included as an Appendix to this review. Only the efficacy results are presented in the Appendix, as the safety results of these trials are fully discussed in the safety section of the review. Throughout the review, the doses of Advair and other MDIs referred to will be the ex-actuator doses and not the ex-valve doses.

B. Overview of Materials Consulted in the Review

The NDA was submitted in electronic format and these materials were used to conduct the review. In addition, the Medical Officer Review of NDA 21-077 Advair™ Diskus® conducted by Dr. Susan Johnson and the Medical Officer Review of IND 57,151 done by Dr. Shan Chu under which the clinical program was developed were reviewed.

C. Overview of Methods used to Evaluate Data Quality and integrity

An audit by the Division of Scientific Investigations (DSI) was conducted at 4 U.S. study sites and checked the sponsor's data and analyses. Two sites each from studies SAS30001 and SAS 30004 were audited. No specific concerns were noted in the initial 45-day review of the NDA however, these sites were selected for various reasons. Study SAS30001 was designed [redacted] and study SAS30004 had the largest percent of withdrawals due to asthma. The DSI conducted a general survey of the trial, the IRB approval process, and the conduct of internal auditing by the sponsor. As part of the DSI audit, raw data were compared to data provided by the Agency from the line listings in the NDA and no discrepancy was noted. Work sheets with data from the SAS transport files from studies SAS30001 and SAS30004 were compared against the original data source. There were a few minor discrepancies but these did not have any bearing on the integrity of the data. For instance, in one subject, in study SAS30001 Investigator #9913 [Dr. [redacted], the heart rate from the ECG was 77 as read by an independent cardiologist but the computer-read ECG tracing was 81. For study SAS30004, Investigator #3893 [Dr. [redacted] had a protocol violation of having three informed consent documents missing from the file. One of the subjects entered the study and the other two subjects were screening failures. There were no other problems noted at the site and the classification of the Establishment Inspection Report [EIR] was VAI [voluntary action indicated]- no response required. Investigator #9072 Dr. [redacted], also had minor citations at the study site. The syringe used to calibrate the [redacted] Spirometer testing system used throughout the study for pulmonary function testing had not been re-calibrated annually. The syringe was originally calibrated when manufactured on 12/2/98. One subject with cataracts was randomized despite the fact that the protocol lists historical or current cataracts as exclusion. No discrepancies were observed with data submitted in the NDA compared with source documents. The classification of the EIR was VAI-no response required.

D. Ethical Conduct of Trials

The studies were conducted in accordance with "Good Clinical Practice" (GCP) guidelines and all applicable regulations including, the Declaration of Helsinki [JAMA 1997]. The U.S. studies were conducted in compliance with Title 21, parts 50, 56 [treatment of human subjects in clinical trials] and 312 [regulations governing conduct of studies under INDs] of the Code of Federal Regulations of the United States of America. All Principal Investigators provided GSK with a fully executed Form FDA 1572 (Statement of Investigator) and all updates were submitted on a new fully executed Form FDA 1572. Informed consent was obtained from all subjects or the subject's legal representative. Subjects were free to discontinue participation in the study at any time. All study protocols and amendments that required pre-approval were reviewed by an IRB or by a national, regional or investigational center ethics committee.

E. Evaluation of Financial Disclosure

GlaxoSmithKline states in an organization-wide policy statement that "Glaxo does not compensate clinical investigators in such a way as the total amounts could vary with the outcome of the study". With regard to "significant payments of other sorts" from the sponsor, the $25,000 threshold for "payments of other sorts" was exceeded in the case of one investigator participating in clinical trial [redacted]. This sponsor received $42,859.74 in total payments for honoraria and "other" on or after February 2, 1999. There were [redacted] (2.8%) subjects enrolled at this site of [redacted] subjects in the study. For each primary efficacy measure, GSK conducted an analysis on a subset of patients from the other investigative sites. The results from these analyses were no different from the original analyses of all subjects in terms of descriptive measures and inferential conclusions. Relying on information available internally, GSK determined that no clinical investigator has a proprietary interest in the fluticasone propionate/salmeterol HFA MDI combination product.

Two clinical investigators have a significant equity interest [> $50,000] in GSK- [redacted] in study [redacted]), and [redacted] in [redacted]). In order to assess whether the results from the investigator site in [redacted] affected the overall results of the study, the primary efficacy variables were analyzed on a subset of subjects from all other investigator sites. [redacted] of [redacted] subjects in the study from site [redacted] were excluded. The results from the analyses were no different from the original analyses of all subjects. No analyses were conduced to explore the effect of the investigator in [redacted] since only [redacted] enrolled at that site representing less than 1% of [redacted] randomized subjects. In summary, the contribution of the

study centers cited in the financial disclosures should not have had any meaningful impact on the overall outcome of clinical program.

VI. INTEGRATED REVIEW OF EFFICACY

A. Conclusions

Advair™ HFA 44/21, Advair 110/21, and Advair™ HFA 220/21 administered as two puffs twice daily are effective in the maintenance treatment of asthma. Advair HFA 44/21 and Advair HFA 110/21 administered as two puffs BID were superior to placebo and to the individual components salmeterol xinafoate and fluticasone propionate administered alone at the same nominal dose as two puffs BID. In asthmatic patients 12 years of age and older previously treated with as-needed short-acting beta$_2$ agonists [study SAS3001], Advair HFA 44/21 administered as 2 inhalations twice daily produced a significant improvement in the primary endpoints change from baseline in mean morning pre-dose FEV_1 and the AUC (bl), compared to salmeterol 42 mcg bid or FP 88 mcg.

In asthmatic patients previously managed on long-acting beta$_2$- agonists, or inhaled corticosteroids [study SAS30003], Advair HFA 44/21 administered as 2 inhalations twice daily had a statistically significant improvement in FEV_1 measures compared to each of the individual components administered at the same nominal dose and compared to placebo. These improvements in FEV_1 were achieved regardless of baseline asthma therapy. Survival analyses showed that patients treated with Advair had a significantly higher probability of remaining in the study without discontinuation due to worsening asthma compared to those subjects receiving placebo or salmeterol alone [$p<0.001$]. The probability of remaining in the study for patients on FP alone was comparable to patients on Advair.

In study SAS30004, asthmatic patients maintained on inhaled corticosteroids showed significantly greater improvement in FEV_1 measures when administered Advair HFA 110/21, 2 puffs BID, compared to subjects randomized to the individual components or placebo. Similar to the finding in study SAS30003, patients on Advair had a significantly higher probability of remaining in the study without discontinuation due to worsening asthma compared to those subjects receiving placebo or salmeterol [$p<0.001$].

Improvements in the secondary efficacy measures morning and evening peak flow (PEF) measurements at endpoint in patients on Advair HFA were numerically superior to patients on SAL, FP, or placebo in all the trials and are supportive of the primary efficacy findings. This is not an unexpected finding as PEF measurements also assess lung function and would be expected to be similar to FEV_1 measurements. Asthma symptom scores, nighttime awakenings due to asthma, and Ventolin® use were evaluated as secondary endpoints as

well, and the Advair-treated group achieved numerical superiority over the groups treated with the individual components or placebo. However, these improvements were generally very small and are difficult to assess from a clinical standpoint. The patients enrolled in these clinical trials were relatively stable and not very symptomatic consistent with an asthmatic population that is stable upon enrollment. In study SAS30003 and SAS30004, patients receiving Advair HFA had clinically meaningful improvements in overall asthma-specific patient-reported outcomes compared to patients on placebo as assessed by the Asthma Quality of Life Questionnaire.

In study SFCB3023, Advair HFA 440/42 mcg bid had comparable clinical efficacy to Advair Diskus 500/50 mcg bid and superior efficacy to FP MDI 440 mcg bid. In the long-term safety study SAS3005, improvements in FEV_1 were sustained over 52 weeks of treatment.

Advair HFA had a median time to onset of effect that was similar to that of salmeterol [24 –30 minutes]. Advair had a mean duration of effect of 12 hours.

The data support the efficacy of Advair HFA for the long-term treatment of asthma in patients 12 years and older.

. In study 30001, the mean baseline FEV_1 of patients enrolled was 65% to 67% of predicted normal. This degree of asthma severity is consistent with moderate persistent asthma as defined by the NAEPP guidelines and treatment with inhaled corticosteroids is recommended for these patients. In study SAS30003 where patients were stratified by prior asthma therapy, patients on short-acting $beta_2$-agonists alone had comparable significant improvements in lung function compared with patients who were on ICS or salmeterol at baseline.

B. General Approach to the Review of the Efficacy of the Drug

Described in section IV "Description of Clinical Data Sources" and section V "Clinical Review Methods".

C. DETAILED REVIEW OF CLINICAL TRIALS

The following efficacy studies conducted in the U.S, were reviewed in detail:

SAS 30001: "A randomized, double-blind, active-controlled parallel-group 12-week trial evaluating the safety and efficacy of the fluticasone propionate/salmeterol combination in GR106642X MDI, 44/21 two puffs BID and salmeterol in propellant 11/12 MDI 21 mcg two puffs BID and fluticasone

propionate in propellant 11/12 MDI 44 mcg two puffs BID, in adolescent and adult subjects with asthma".

SAS 30003: "A Stratified, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group 12-Week Trial Evaluating the Safety and Efficacy of the Fluticasone Propionate/Salmeterol Combination in GR106642X MDI, 88/42mcg BID, and Salmeterol in Propellant 11/12 MDI, 42mcg BID, Fluticasone Propionate in Propellant 11/12 MDI, 88mcg BID, and Placebo Propellant GR106642X MDI in Adult and Adolescent Subjects with Asthma".

SAS 30004: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group 12-Week Trial Evaluating the Safety And Efficacy Of Fluticasone Propionate/Salmeterol Combination in GR106642X MDI, 220/42 mcg BID, and Salmeterol in Propellant 11/12 MDI, 42 mcg BID, and Fluticasone Propionate in Propellant 11/12 MDI, 220 mcg BID, and Placebo in Propellant GR106642X MDI in Adolescent and Adult Subjects with Asthma".

TRIAL DESIGN
These trials were randomized double blind active and placebo controlled studies. The studies had 2 phases. The first phase was a 2-week run-in period where patients were placed on GR106642X [HFA] placebo MDI 2 puffs BID. During the two-week run-in period, subjects who were taking inhaled corticosteroids [ICS] or long-acting beta$_2$-agonists continued on their previous dose of these medications. At randomization (Visit 2), these medications were discontinued and subjects were randomized to one of the following treatment arms for a 12-week treatment period:

SAS 30001
- Advair HFA 44/21 inhalation aerosol two puffs[88/42 mcg] BID
- SAL two puffs (42mcg) BID
- FP two puffs (88mcg) BID

SAS 30003
- Advair HFA 44/21 inhalation aerosol two puffs [88/42 mcg] BID
- SAL MDI two puffs (42mcg) BID
- FP 44 mcg MDI two puffs (88mcg) BID
- Placebo inhalation aerosol two puffs BID

SAS 30004

- Advair HFA 110/21 inhalation aerosol two puffs [220/42 mcg] BID
- SAL MDI two puffs (42mcg) BID
- FP 110 mcg MDI two puffs (220 mcg) BID
- Placebo inhalation aerosol two puffs BID

Patients were allowed to take Ventolin® MDI as rescue medication for asthma symptoms during the two-week run-in period and during the treatment period. Patients were followed every week for the first 4 weeks and then every 2 weeks for the rest of the 12-week period.

PATIENT POPULATION
The inclusion and exclusion criteria were similar for all three studies. The differences are outlined in Table 2.

Inclusion Criteria
General – Male and female asthmatic patients age 12 years or older were eligible for enrollment. Female patients of childbearing potential were required to be on a reliable contraceptive method. Subjects were eligible for the study if they were current non-smokers with ≤ 10 pack- year history and were otherwise in good health as ascertained by history, physical exam, 12-lead ECG, chest x-ray and clinical laboratory parameters.

Asthma- Patients enrolled in these studies would be asthmatics with FEV_1 40-85% predicted. They should have had a documented history of asthma that had required therapy for at least 6 months. Disallowed asthma controller medications were leukotriene modifiers and cromones 2 weeks before screening, oral anticholinergics, methotrexate, gold, cyclosporine and azathioprine 12 months before Visit 1. Subjects treated with inhaled corticosteroids must have been treated for at least 3 months prior to Visit 1 [run-in period] and must have been on a consistent daily dose for at least one month prior to Visit 1 with no change in regimen.

Exclusion Criteria
Subjects were excluded if they had smoked for more than 10 pack-years or if they had used tobacco products (cigarettes, cigars, or pipe tobacco) within the past year. In addition to the general exclusion criteria in clinical trials, patients could not have had a viral or bacterial upper or lower respiratory tract infection, sinus, or middle ear infection within 2 weeks of the screening visit. They could not have had an abnormal chest X-ray due to conditions other than asthma within 12 months of screening and they could not have a clinically significant abnormal 12-lead ECG during the run-in period. Patients were also excluded if they required beta-blockers (including ophthalmic formulations), benzodiazepines, digitalis, phenothiazines, polycyclic antidepressants, MAO inhibitors, cough suppressants, intranasal corticosteroids [except Flonase®] or topical corticosteroids.

TABLE 2. Inclusion and Exclusion Criteria Differences for SAS30001, SAS30003, SAS30004

	SAS30001	**SAS30003**	**SAS30004**
Prior Asthma Rx	Prn $beta_2$-agonists only. No ICS	ICS, or long-acting or short-acting $beta_2$-agonists	ICS
Concomitant theophylline use	No	Yes	Yes

*Prior ICS dosage (mcg/day)	N/A		
Beclomethasone dipropionate		252-336	378-840
Triamcinolone acetonide		600-800	900-1600
Flunisolide		1000	1250-2000
Fluticasone propionate MDI		176	440-660
Fluticasone propionate DPI		200	400-600
Budesonide		400-600	800-1200
*Subjects must have been on ICS for at least 3 months and receiving a consistent dose without change in regimen for at least 1 month prior to Visit 1			

STUDY PROCEDURE

Patients were required to have an asthma severity of 40-85% predicted FEV_1 at screening and demonstrate reversibility by an increase in FEV_1 of 15% within 30 minutes following treatment with 2 puffs albuterol [Ventolin®] MDI. Randomization to study medication was done after the 2-week run in period [Visit 2]. Patients were eligible to be randomized if they met pre-set criteria based on symptom scores, best FEV_1, reproducible lung function, compliance with diary card recordings, and if they met a pre-specified PEF and FEV_1 stability limit. The PEF stability limit was calculated using the mean morning PEF from the 7 days preceding Visit 2. A 20% decrease in this mean was calculated and used for the duration of the study. The FEV_1 stability limit was calculated by taking a 20% decrease in the best FEV_1 obtained at the Visit 2 zero time point. This value was used for the remainder of the study. Patients should have had a total symptom score of ≥ 7 during the 7 days prior to Visit 2 [Randomization] based on the following symptom scale:

Asthma Symptom Scale

0 = No symptoms during the day.
1 = Symptoms for one short period during the day.
2 = Symptoms for two or more short periods during the day.
3 = Symptoms for most of the day which did not affect my normal daily activities.
4 = Symptoms for most of the day which did affect my normal daily activities.
5 = Symptoms so severe that I could not go to work or perform normal daily activities.

They should have had a best FEV_1 of 40% to 85% of the predicted value during Visit 2, reproducible lung function at Visit 2.

STATISTICAL AND ANALYTICAL PLAN

Primary Efficacy Endpoints

Area under the 12-hour serial FEV_1 curve relative to baseline [AUC (bl)] at Treatment Day 1 AND at Treatment Week 12, change from baseline at endpoint in the morning pre-dose FEV_1 and probability of remaining in the study were the primary efficacy endpoints.

The area under the 12-hour serial FEV_1 curve relative to baseline [FEV_1 AUC (bl)] at treatment day 1 AND at Treatment Week 12 were analyzed as the primary efficacy measure to evaluate the effects of salmeterol in the combination product. To assess this effect the comparison was made between the combination

product and FP. The baseline value was the average of the FEV_1 measurements taken at 30 minutes prior [-30 mins] and immediately prior [0 mins] to the morning dose on Treatment Day 1. This same baseline value measured on Treatment Day 1 was used to evaluate the AUC (bl) at week 12. At Treatment Day 1 and at Treatment Week 12, FEV_1 was measured at –30 minutes, and 0 minutes (prior to dosing), and at 30 minutes, 1, 2, 3, 4, 6, 8, 10, and 12 hours after the morning dose of study medication. At Week 12, the –30 minutes and 0 minutes FEV_1 measurements were called pre-dose measurements. These measurements were not used as Baseline [but were used to calculate the morning pre-dose FEV_1 at week 12].

The change from baseline at endpoint in the morning pre-dose FEV_1 AND the probability of remaining in the study were used to assess the effect of FP in the combination product in studies SAS30003 and SAS 30004. In study SAS30001, only the morning pre-dose FEV_1 was used to assess the effect of FP in the combination product. To assess this effect the comparison was made between the combination product and salmeterol.

The endpoint value for FEV_1 measurements was the measurement recorded at Treatment Week 12. If subjects discontinued prior to week 12, then the endpoint was the last on-treatment measurement recorded regardless of the duration of study participation with the following restrictions:

- Endpoint only came from a scheduled visit or a discontinuation visit.
- Endpoint never came from pre-randomization FEV_1 values recorded at either Visit 1 or Visit 2.
- Endpoint did not come from a visit more than one day after discontinuation from study drug.

If a discontinuation visit occurred more than 2 days after the last dose of study drug, then endpoint was assigned the FEV_1 value from the last scheduled visit and not from the discontinuation visit.

For both Treatment Day 1 and Treatment Week 12 AUC (bl) was calculated for each subject using the trapezoidal rule. AUC (bl) and morning predose FEV_1 were summarized by treatment group and visit. Overall and pairwise treatment comparisons were made using F-tests from ANOVA models that included terms for treatment, Investigator cluster, and stratum. The probability of remaining in the study over time was assessed using Kaplan-Meier product-limit estimators and overall and pair-wise treatment comparisons were made using log rank tests.

To address the multiplicity issues associated with testing multiple primary efficacy measures the sponsor used the intersection-union method of Neuhauser which means that in order to reject the null hypothesis of no treatment difference between the combination product and the individual component, at least one of the two p-values must be significant at the 0.025 level OR both p-values must be significant at the 0.05 level.

Secondary Efficacy Parameters

- AM and PM PEF
- Daily asthma symptom score
- Ventolin use
- Nighttime awakenings requiring Ventolin ® use
- Asthma Quality of Life Questionnaire(AQLQ) [SAS30003 and SAS30004 only]
- Withdrawal due to worsening asthma [SAS30001 only]

The secondary efficacy parameters were considered as supportive of the primary efficacy measures. Statistical tests on these secondary efficacy measures focused on the comparisons of the combination product to each of its individual components. No adjustments were made for multiple comparisons of any secondary efficacy parameters. Baseline for diary data (PEF, daily asthma symptom score, Ventolin® use, nighttime awakenings, etc) was defined as the average of the available data collected during the 10 days prior to treatment start or, as the average of all available data collected prior to treatment start, if fewer than 10 days of recorded data were available. Endpoint for the diary data was calculated as the last 7 days of available data where the subject was still on study drug, ending at Day 84 [week 12].

The subjective impact of asthma on patients' perception of health was evaluated using the Asthma Quality of Life Questionnaire [AQLQ]. The AQLQ uses a 7-point scale where 1 = maximum impairment and 7= none. Questions are grouped into four domains- Activity Limitation, Asthma Symptoms, Emotional Function and Environmental Exposure. The minimal important difference defined as the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, [in the absence of troublesome side-effects and excessive cost], a change in the patient's management was previously determined to be close to 0.5 (0.42-0.58)[2] .The sponsor selected a change of 0.5 *a priori* as clinically meaningful. A reduced ITT population with quality of life impairment at baseline as defined by an overall AQLQ score of ≤5.8 was defined *a priori* as the primary analysis population. Statistical analyses of AQLQ scores were based on mean change in response scores from baseline to endpoint. Treatment groups were compared using an ANCOVA model with baseline response as the covariate. Terms for treatment, Investigator, cluster, and stratum were included in the model.

Power and Sample Size Considerations

For sample size calculations, comparisons were done between the combination product and each active comparator using two-sided t-tests with $\alpha = 0.05$. From

[2] Determining a minimal important change in a disease-specific quality of life questionnaire. Elizabeth F. Juniper et.al. J Clin Epidemiol (1994) Vol 47, No. 1 pg. 81-87

previous studies with the combination product, a sample size of 80 subjects per treatment arm would provide more than 85% power to detect a difference of 0.25 L in mean change from baseline at endpoint in morning predose FEV_1, assuming a standard deviation of 0.5L. This sample size would also provide more than 90% power to detect a treatment difference in AUC (bl) on Treatment Day 1, of 3.6L-hours assuming a standard deviation of 4.1 L-hr, and a difference in AUC (bl) after 12 weeks treatment of 3.5L-hrs assuming a standard deviation of 5.3L-hrs. These power calculations were not adjusted for multiple comparisons.

Analysis populations

The Intent-to Treat [ITT] population was used for analysis of all efficacy and safety measures. For any subject who withdrew prematurely from the study, all available data up to the time of discontinuation were included in the ITT analysis. If a subject could not complete a 12-hour period of serial FEV_1 measurements the last observed pre-intervention FEV_1 was carried forward to replace missing values at each post-intervention observation time. Likewise, missing data at individual timepoints were carried forward from the previous timepoint. Of note is that no pre-treatment values were ever carried forward to a post-treatment timepoint.

Interaction Terms

Prior to unblinding the study treatments, the sponsor combined the investigative sites into clusters based on geographic proximity. The sponsor used this approach because of the large number of investigators participating in these studies, and the possibility of small numbers of subjects randomized at some sites. Therefore, instead of using individual investigators for adjustment in statistical analyses the sponsor used these clusters instead. And instead of "treatment-by-Investigator" interactions, the sponsor assessed "treatment-by-cluster" interaction for statistical significance. In the Clinical Study Report for primary efficacy measures, "by-cluster" summaries replaced the usual "by-Investigator" summaries. In order to check for investigator, cluster, or stratum, effects across treatment groups for the primary analyses, the sponsor used an interaction model incorporating Investigator, cluster, and treatment. In studies where the subjects were stratified, stratum was included in the model. If interaction terms were not significant, it meant that there was no evidence of treatment interaction with investigator cluster or stratum.

EFFICACY RESULTS

The primary efficacy results for these 3 pivotal trials will be discussed separately followed by a joint discussion of the secondary endpoints.

The baseline asthma characteristics of the patients were similar across the three trials. The baseline FEV_1 was between 65% and 69% predicted normal. Reversibility following Ventolin ® treatment range from 27% to 35% and over half of the patients had asthma for more than 15 years.

Primary Efficacy Results SAS30001

Evaluation of FP effect in the combination product

The comparison of interest is Advair vs. salmeterol. Mean improvement at endpoint was 0.69 L(33%) for Advair HFA, 0.47 L (22%) for salmeterol, and 0.51 (25%) for Flovent. There was an overall treatment effect, with Advair having significant improvement in morning pre-dose FEV_1 at endpoint compared to salmeterol (p=0.004) and FP (p=0.016).

Evaluation of salmeterol effect in the combination

The comparison of interest is Advair vs. FP. On Treatment Day 1 and at Treatment week 12, Advair had a significantly greater mean AUC (bl) compared to FP (p <0.001). On Treatment Day 1 there was no significant difference between Advair and salmeterol as expected due to the early bronchodilatory effect of salmeterol. However, at Treatment Week 12 Advair had a significantly greater mean AUC (bl) compared to salmeterol (p=0.013). These results are displayed in Table 3.

Table 3. Primary Efficacy Results SAS30001

	Advair 88/42 n = 95	**Salmeterol 42 n=91**	**Fluticasone 88 n = 97**
Change from baseline in mean morning pre-dose FEV_1 at endpoint			
Baseline FEV_1 L (SE)	2.37	2.34	2.31
Mean morning predose FEV_1 at Endpoint L (SE)	3.06	2.81	2.82
Mean change from Baseline in morning pre-dose FEV_1 L	0.69 L (33%) [a]	0.47 L (22%)	0.51 (25%)
Area under the 12-hour serial FEV_1 curve relative to Treatment Day 1 baseline [AUC (bl)]			
AUC(bl) at Treatment day 1 L-hrs	7.2 L [b]	7.6 L	2.9 L
AUC (bl) at treatment week 12	10.6 L [bc]	8.2 L	7.2 L

[a] differs from salmeterol and FP (p =0.004 and p =0.016 respectively)
[b] differs from FP (p < 0.001)
[c] differs from salmeterol (p=0.013)

Subset analyses in subjects with FEV_1 < 70% and subjects with FEV_1 >70% by Dr. James Gebert, Biostatistician showed similar results as the overall intent to treat population. Because the patient numbers were small in these subsets, no inferential statistical analyses were conducted.

Primary Efficacy Results SAS30003

Efficacy results for the intent to treat population are depicted in Table 4.

Table 4. Primary Efficacy Results SAS30003

	Placebo n = 87	**Advair 42/88 n = 92**	**Salmeterol n=92**	**Fluticasone n = 89**
Treatment day 1 n				
Baseline FEV_1 L (SE)	2.27 [0.07]	2.29 [0.06]	2.33 [0.07]	2.20 [0.06]
Mean morning predose FEV_1 at Endpoint L (SE)	2.40	2.86	2.58	2.55
Mean change from Baseline in morning pre-dose FEV_1 (L) [%]	0.14 [5%]	0.58 a [27%]	0.25 [12%]	0.36 [18%]
Mean AUC (bl) at Treatment day 1 L-hrs	2.0	6.7 b	6.1	2.7
Mean AUC (bl) at treatment week 12	2.6 [n=56]	9.0 c n=85	6.5 n=63	5.6 n=75
Subjects withdrawn due to lack of efficacy N	24 [28%]	2 [2%]d	23 [25%]	7 [8%]

[a] differs from placebo, salmeterol, and fluticasone ($p \leq 0.004$)
[b] differs from placebo and fluticasone ($p < 0.001$)
[c] differs from placebo, salmeterol, and fluticasone ($p \leq 0.006$)
[d] differs from placebo and salmeterol ($p < 0.001$)

To assess the effect of FP in the combination, change in predose FEV_1 at endpoint and probability of remaining in the study were the co-primary endpoints. The comparison of interest is Advair Vs. salmeterol. For the Advair arm, the mean morning pre-dose FEV_1 at endpoint increased from 2.29 L at baseline to 2.86 L at endpoint equivalent to a mean increase of 0.58 L. By comparison, there was a mean increase of 0.25 L in the salmeterol group [from 2.33 L at baseline to 2.58 L at endpoint] ($p \leq 0.004$ Advair vs. SAL).

Probability of Remaining in the Study

The number of subjects discontinued due to worsening asthma was similar in the placebo group [n=24, (28%)] and the salmeterol group [n=23, (25%)]. Whereas, the number of discontinuations due to worsening asthma was similar in the Advair group [n = 2, (2%)] and the fluticasone group [n= 7, (8%)]. Withdrawals due to asthma were categorized as clinical exacerbations, or withdrawal due to lack of efficacy. A clinical exacerbation was one where the subject required emergency intervention, hospitalization due to asthma, treatment with excluded asthma medication, or at the discretion of the Investigator. Lack of efficacy was determined by pre-defined criteria. Subjects were discontinued from the study for lack of efficacy [worsening asthma] if one of the following criteria were met during the 7 days preceding the visit:

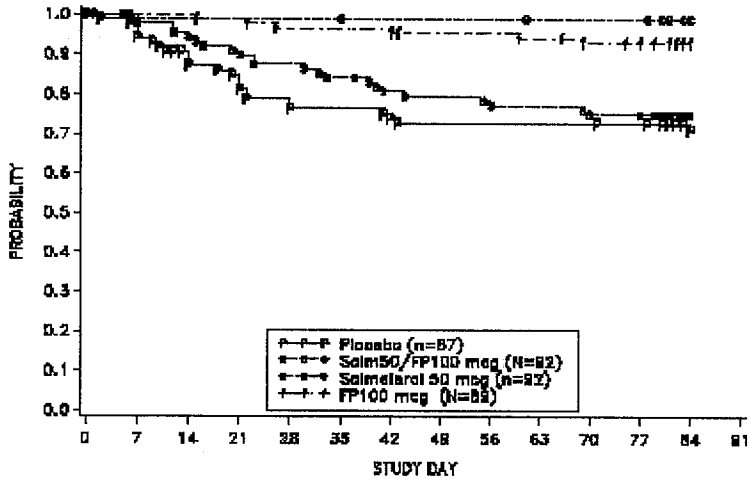
1. More than 3 days in which the PEF had fallen below the PEF Stability Limit calculated at Visit 2
2. More than 2 days in which ≥12 puffs/day of Ventolin ® were used. [6 puffs/day for subjects on baseline salmeterol]
3. More than 2 nights with awakenings due to asthma requiring treatment with Ventolin®
4. $FEV_1 \leq$ the FEV_1 Stability Limit calculated at Visit 2 [if no adequate improvement following trial of rescue Ventolin®]

In the placebo group, the FEV_1 stability limit and nighttime awakenings were the most frequent reasons for withdrawal due to worsening asthma. In the salmeterol group, clinical exacerbations were the most frequent reason for withdrawal due to worsening asthma. In the combination product group, no patient withdrew due to a clinical exacerbation but one patient each withdrew due to nighttime awakenings, and FEV_1 stability limit.

At the end of the 12-week treatment period, subjects randomized to Advair had a significantly higher probability of remaining in the study without discontinuation due to worsening asthma compared to those subjects receiving placebo or salmeterol [p<0.001]. The probability of remaining in the study was comparable for subjects treated with Advair and FP. Kaplan Meier estimates of survival curves are used to display the results of the survival analyses. The Kaplan-Meier survival estimates are based on the proportion of subjects withdrawn due to lack of efficacy and are depicted in the figure copied from the sponsor's submission. [*Source: SAS30003.pdf pg. 158]*

Protocol: SAS30003
Population: Intent-to-Treat

Figure 2
Probability of Remaining in the Study



AUC [bl] at Treatment Day 1 AND Treatment Week 12

For these endpoints the comparison of interest is Advair vs. FP to assess the salmeterol effect in the combination. On Treatment Day 1, subjects in the Advair

group had a significantly greater mean AUC [bl] value than subjects in the placebo and the fluticasone group [p <0.001]. At Treatment Week 12, the AUC (bl) showed an overall treatment effect. Advair was significantly superior to placebo, salmeterol, and fluticasone [p≤ 0.006].

Relationship between Prior Asthma Therapy and Primary Efficacy
The results of the primary efficacy analyses were similar regardless of prior β_2-agonists or ICS use. When the primary efficacy results were analyzed by prior treatment with short-acting beta$_2$-agonists Vs. salmeterol, the efficacy results were similar except that subjects previously on salmeterol had the highest number of withdrawals due to lack of efficacy. The patient numbers were too small for inferential statistical analyses to be made. *[See Table 14 Appendix 1.B. SAS30003 pg. 86.]*

Primary Efficacy Results SAS30004

The efficacy results for the intent to treat population are depicted in Table 5 for the primary efficacy outcomes. The mean morning predose FEV_1 at endpoint increased from 2.23 L to 2.64 L in the Advair group, compared to an increase from 2.22 L to 2.36 L in the SAL group and from 2.18 L to 2.36 L in the FP group (p<0.001).

The probability of remaining in the study at Week 12 was greatest for the Advair group compared to the SAL group (p <0.001). Kaplan Meier curves of survival estimates were similar to the survival estimates seen in SAS30003.

The mean AUC (bl) at Treatment Day 1 and Week 12 for Advair was statistically superior to placebo and fluticasone (p < 0.001). At Treatment Week 12 Advair also had significantly greater (p=0.020) mean AUC (bl) compared to salmeterol.

Table 5: Primary Efficacy Results SAS30004

	Placebo n = 89	**Advair 220/42 n = 94**	**Salmeterol 42 n=91**	**Fluticasone 220 n = 91**
Baseline FEV_1 L (SE)	2.17 [0.07]	2.23 [0.07]	2.22 [0.06]	2.18 [0.06]
Mean morning predose FEV_1 at Endpoint L (SE)	2.06 [0.08]	2.64 [0.08]	2.36 0.08]	2.36 [0.07]
Mean change from Baseline in morning pre-dose FEV_1 L [%change]	-0.12 [-6%]	0.41 [a] [20%]	0.15 [8%]	0.19 [9%]
Mean AUC (bl) at Treatment day 1 L-hrs	0.6	5.4 b	6.1	2.1
Mean AUC (bl)at treatment week 12	1.4 n=34	7.0 [b c] n=81	5.3 n=57	3.6 n=71
Subjects withdrawn due to lack of efficacy N	48 [54%]	7 [7%][d]	22 [24%]	10 [11%]

[A] differs from placebo, salmeterol, and fluticasone (p < 0.001)
[b] differs from placebo and fluticasone (p<0.001)

[c] differs from salmeterol (p = 0.020)
[d] differs from placebo and salmeterol (p ≤0.001)

Secondary Efficacy Results for SAS30001, SAS30003 and SAS30004

AM and PM PEF
Subjects treated with Advair HFA had numerically greater improvements in AM and PM PEF compared with subjects on SAL, FP, or placebo. Subjects on placebo either had no change in PEF [SAS3003] or a worsening of their PEF [SAS30004] measurements at endpoint. In study SAS3004 patients on placebo had a 3.5% decrease from baseline in AM PEF and a 3.7% decrease from baseline in PM PEF. In study SAS30003, patients on Advair had a mean % increase in AM and PM PEF of 16.6% and 13.1 % respectively, while in study SAS30004, patients on Advair had an increase of 16.5 % and 11.2 % in the AM and PM PEF respectively. In study SAS30001, the mean % increase in PEF in the Advair group was 20.1% for AM PEF and 14.1 % for PM PEF. [*See Table 6 pg.74, Table 15 pg.87, and Table19 pg. 94 respectively in the Appendix].*

Ventolin Use, Nighttime Awakenings, Symptom Scores
Although the subjects in the Advair treatment group had numerically greater improvements in all of these endpoints compared to its individual components and to placebo, the overall changes were very small. Given that patients enrolled in these studies were relatively asymptomatic, these findings are not unexpected.

Asthma Quality of Life Questionnaire (AQLQ) The results of the reduced intent to treat population (AQLQ Overall score at Baseline of ≤ 5.8) were reviewed in detail since these were the focus of the sponsor's primary analyses defined *a priori*. In both study SAS30003 and SAS30004 a clinically meaningful change of >0.5 at endpoint was seen in the overall score and in all domains in the Advair treatment group compared to placebo. In study SAS30003 the change in the overall score was 1.45 in the Advair group compared to –0.32 in the placebo group. In study SAS30004 the change in the overall score was 1.01 in the Advair group compared with –0.09 in the placebo group. [*See Table 16 pg. 89 and Table 20 pg. 97 respectively in the Appendix.].*

STUDY SFCB 3023

"A multicentre, randomised, double-blind, double-dummy, parallel-group, three-month comparison of the salmeterol/fluticasone propionate combination product 2x 250/25mcg strength bd *via* the pressurized metered dose inhaler [Advair HFA 440/42 mcg] with salmeterol/fluticasone propionate combination product (1x 500/50 mcg strength) bd *via* the Diskus/Accuhaler™ [Advair Diskus 500/50] inhaler and with fluticasone propionate (2x 250mcg strength) alone bd *via* the

pressurised metered dose inhaler [FP 500 MDI] in adolescents and adults with reversible airways obstruction". This study was conducted in the U.K.

TRIAL DESIGN
Similar to the other pivotal studies, this study was designed with a 2-week run-in period, followed by a 12-week randomization period. There was also a 2-week follow up visit at the end of the study or sooner if subjects were discontinued prior to completion of the study. Patients continued their prior doses of ICS during the run-in period and were given Ventolin® MDI to use as needed. At randomization previous ICS were discontinued and patients were randomized to one of the following treatments arms for a 12-week treatment period:

- Advair HFA 220/21 mcg Inhalation Aerosol 2 puffs BID
- Advair Diskus 500/50 mcg one puff BID
- FP 220 mcg MDI two puffs BID

Patients continued to use Ventolin ® as needed throughout the trial.

PATIENT POPULATION
Males and females ≥ 12 years who had a documented clinical history of reversible airways obstruction, who had received the following doses on ICS for at least four weeks prior to Visit 1:

Beclomethasone dipropionate	1500-2000mcg/day
Budesonide or flunisolide	1500-2000mcg/day
Fluticasone propionate	750-1000 mcg/day.

Other inclusion and exclusion criteria were similar to those of the previously described U.S. protocols. Excluded medications were the same as described for the U.S. protocols except that all regular non-corticosteroid therapy for asthma such as anticholinergics, theophyllines, and sodium cromoglycate could be continued provided that the dose remained constant throughout the study.

STUDY PROCEDURE
During the last seven days of the run-in period, subjects were required to have a mean morning PEFR of > 50% and < 85% of their PEFR measured 15 minutes after administration of 400 µg of Ventolin at randomization (Visit 2), and a cumulative total recorded symptom score (daytime plus nighttime) of ≥ 8 *[See nighttime symptom score below].* In order to enter the treatment period, subjects were required to have an FEV_1 of >50% and <100% of their predicted normal. During the run-in and the treatment period, patients recorded morning and evening PEFR, daily use of Ventolin® and daytime and nighttime symptom scores in a Daily Record Card [DRC]. Morning PEFR was measured upon waking, prior to taking any rescue or study medication. The daytime symptom score was based on the 0 to 5 scale previously described for the other trials. Nighttime symptom scores were assessed using the following scale:

Nighttime Symptoms Score
0 = No symptoms during the night
1 = Symptoms causing me to wake once or wake early

2 = Symptoms causing me to wake twice or more (including waking early)
3 = Symptoms causing me to be awake for most of the night
4 = Symptoms so severe that I did not sleep all night.

FEV_1 was measured at Screening, Treatment Day 1, and clinic visits which occurred at Weeks 2, 4, and 12. Subjects could be withdrawn from the study at the Investigator's discretion for significant laboratory abnormalities or other reasons, or if the subject required a change in their asthma medication during the run-in period, or had an exacerbation requiring additional medication during the treatment period. All subjects who were withdrawn had a 2-week follow up visit.

STATISTICAL AND ANALYTICAL PLAN

Primary Efficacy Endpoints
There was a single primary efficacy endpoint for this study - mean morning PEFR over Treatment Weeks 1-12. Two comparisons were performed:

1. Advair HFA 220/21 2 puffs bid Vs. Advair *Diskus 500/50 mcg bid.* The null hypothesis was that of a treatment difference of ± 15L/min in morning PEFR. The sponsor defined these treatments as equivalent if the 95% confidence interval for the treatment difference fell within ±15L/min. *The term "clinically comparable" instead of "equivalent" better reflects the objective of the sponsor's program.*
2. Advair HFA 220/21 2 puffs bid versus FP MDI 220 2 puffs bid. The aim was to compare the efficacy of Advair HFA to fluticasone propionate. The null hypothesis of no treatment difference was tested using a significance level of $\alpha = 0.05$. Confidence intervals for this difference used a confidence level of 95%.

No adjustments for multiple comparisons were made.

The secondary efficacy measures were evening PEFR, and daytime and nighttime asthma symptom scores. These were considered of secondary importance and no adjustments for multiple comparisons were made.

Sample Size
In order to have 90% power to establish equivalence if the treatments were in fact equally effective, 165 subjects per treatment group would be sufficient given a standard deviation of 35L/min.

Analysis Populations
The sponsor used both the ITT and the Per Protocol Population for confirmation of equivalence on the primary variable. The reviewer focused on the results of the ITT population.

Interaction Terms
Investigators who randomized fewer than 19 subjects were grouped in clusters based on geographical proximity of sites. Investigators who randomized 19 or

more subjects were defined as stand-alone clusters. Treatment-by-cluster interaction was assessed for statistical significance in lieu of treatment-by-investigator interactions. Interactions of treatment with cluster; age, sex, and baseline were tested for statistical significance at the 0.05 level in both populations when analyzing the primary efficacy variable. In addition, two further variables not normally in the model were tested for interactions with treatment in both the Intent-to-Treat and Per Protocol Populations. These were Volumatic Spacer Use and Type of Previous Inhaled Corticosteroids (FP/Other) used. An interaction would have only been considered meaningful if consistent for both populations.

EFFICACY RESULTS SFCB 3023

The table below summarizes the mean morning PEFR for the ITT population. A total of 691 patients were recruited of whom 510 were randomized and 509 actually received treatment. One subject (#34965) was identified as having been randomized to FP MDI but did not take any medication and so was not included in the ITT population. Therefore 176 patients received Advair HFA, 161 received Advair Diskus and 172 received FP. The adjusted mean change is the estimate of the population mean change obtained after adjusting the sample mean for baseline, center, age, and sex via the ANCOVA model. Baseline PEFR value is the mean of the 7 days before randomization visit (i.e. run-in Week 2).

Table 6. Morning PEFR

Morning PEFR	**Advair 42/440 HFA**	**Advair Diskus 50/500**	**FP 500 mcg**
Baseline n	N= 176	N=161	N=172
Mean Baseline (L/min) [SD]	327 [94]	341 [100]	345 [98]
Week 1-12 n	173	159	171
Mean Week 1-12 (L/min)	377 [104]	388 [108]	371 [104]
Mean change from Baseline, Weeks 1-12 (L/min) [SD]	49 [47]	46 [46]	25 [35]
Mean PEFR % change from baseline [SD]	17 [18]	15 [17]	8 [11]
Adjusted Change from Baseline Weeks 1-12 (L/min) [se]	50 [3.2]	48 [3.4]	27 [3.3]

The adjusted treatment difference Advair Diskus minus Advair HFA was –2 L/min. The 95% confidence interval was –11 to 7 L/min. This interval falls inside the prespecified limits of ± 15 L/min and therefore the two products are statistically comparable. The results of the per protocol population were similar to the ITT population results and support the conclusion of statistical equivalence.

D. OVERALL EFFICACY CONCLUSIONS

The efficacy results for Advair HFA Inhalation Aerosol in studies SAS30001, SAS30003, and SAS30004, fully satisfy the regulatory requirements for establishment of efficacy for combination drugs as set forth in the Code of

Federal Regulations 21 CFR 300.50 Advair HFA 44/21 and 110/21 were superior to each of their individual components and to placebo in all the studies reviewed. In study SAS30001 patients maintained on as needed beta$_2$-agonists were moderate persistent asthmatics by FEV_1 criteria and would be appropriate candidates for Advair. The recommendation for using Advair in patients [redacted], must be made in the context of the severity of asthma.

The median onset of action of Advair is similar to salmeterol [24 –30] minutes and the duration of action of 12 hours supports twice daily dosing.

Advair 220/21 mcg administered as 2 puffs twice a day is clinically comparable to Advair Diskus 500/50 mcg one puff twice a day and superior to FP MDI 220 mcg two puffs twice daily. The efficacy of Advair HFA 220/21 was only compared to FP. However, given that Advair HFA 44/21 and 110/21 fulfill the efficacy requirements for combination products, and given that Advair HFA 220/21 has comparable efficacy to Advair Diskus 500/50 and is superior to FP, an additional trial is unnecessary.

VII. INTEGRATED REVIEW OF SAFETY

A. CONCLUSIONS

The safety data from the five 12-week clinical trials SAS30001, SAS30003, SAS30004, SFCB3022, and SFCB3023, and the 52-week trial SAS30005, demonstrate that Advair HFA is safe and well tolerated in asthmatic patients 12 years of age and older when taken as recommended as two inhalations twice daily. There was no evidence that treatment with the combination product was associated with an increased risk of adverse events, compared to treatment with the individual agents. There were no new or unusual adverse events or other sequelae to suggest that subjects receiving salmeterol and fluticasone propionate in combination in this new formulation were at greater risk than those patients receiving either treatment alone. The most common events were in the upper respiratory system [URTI, throat irritation, viral respiratory infection, asthma, sinusitis, pharyngitis/throat infection] and headache, and occurred with comparable frequency across all the efficacy studies.

The adverse events leading to withdrawal of subjects treated with the HFA product were similar to the adverse events leading to withdrawal for subjects receiving the individual components in the clinical efficacy studies. Of the 2,014 patients treated in the 5 efficacy studies, a total of 73 (3.6%) subjects ranging from 1-8% of subjects across all treatment groups, were withdrawn from a study due to an adverse event. Of the subjects who were withdrawn due to an AE, nine (9) were in the Advair HFA 44/21 mcg 2 puffs bid treatment group, 1 was in the Advair HFA 110/21mcg 2 puffs bid treatment group, and 11 were in the Advair HFA 220/21 mcg two puffs bid treatment group. Of all the AEs leading to withdrawal (86 events in 73 subjects), 37 AEs (43%) reported in 31 subjects were

considered by the Investigator to be related to study drug. Upon review of the case narratives, the AEs reported by 2 of the subjects are unlikely to be related to study drug. One patient who developed upper GI bleeding during the study had a history of peptic ulcer disease and was on placebo and another patient was a 31 year-old black man who reported palpitations 12 hours after taking FP. Of these 37 events considered drug-related by the Investigators, the most common was asthma exacerbation/asthma worsening reported by 10 subjects. From the case narratives it appears that these were probably exacerbations of the underlying disease process. Therefore upon review, a total of 25 events that led to withdrawal from the study are probably related to study drug. Of these events only one occurred in the Advair HFA treatment group. This was a case of an allergic reaction of the mouth in a 66-year-old female one day following treatment with Advair HFA 220/21. The event resolved after 11 days.

Of the 325 subjects treated in the long-term safety study, 20 (5% to 7%) across treatment arms were withdrawn from the study due to an adverse event. The total number of AEs that led to withdrawal in the long-term study was 26. Of these AEs, five (5) occurring in 4 subjects were considered serious but were not drug-related. The most common AEs leading to withdrawal were in the lower respiratory system and were related to worsening asthma. Four AEs that led to withdrawal were possibly drug-related. These were muscle soreness and headache in one subject, hyperglycemia in one subject, and edema of the lips in one subject. The Investigators reported an additional event [increased PVCs in one subject] as possibly drug-related. This is unlikely as the subject also had a history of migraine headaches and ulcerative colitis and was concurrently taking medications for both of these conditions which could have precipitated the PVCs.

Adverse events occurring within 15 minutes of dosing were collected in the U.S. efficacy studies SAS30001, SAS30003, and SAS30004 as an indicator of potential propellant (HFA-134a)-related or formulation-related events. These adverse events were infrequent (≤5%) during both the run-in (propellant alone) and the 12-week treatment (propellant +active) periods. The most commonly reported event was headache.

One death occurred in the entire study population in a 71-year-old female who was diagnosed with leukemia 8 days following randomization. Of the 2,104 subjects treated in the clinical efficacy studies, 30 SAEs were reported in 25 (1%) subjects. The most common body system affected was the respiratory system. Only 3 of the 30 serious adverse events were possibly related to study medication. All three were asthma exacerbations and occurred in, one patient taking Advair HFA 44/21 mcg 2 puffs bid, one patient taking Advair Diskus 100/50 mcg 1 puff bid and one patient taking Advair Diskus 500/50 mcg 1 puff bid. In the long-term safety study 12 SAEs occurred in 11 subjects (3%). It is unlikely that any of these SAEs were related to the study medication.

No significant difference was observed in AM plasma cortisol levels in the combination product compared to the other treatment groups and the proportion of subjects with abnormal ACTH stimulation test results was similar across treatment groups although both tests are relatively insensitive measures of systemic corticosteroid effects.

A greater percentage (56%) of subjects participating in the clinical efficacy studies was female. The frequency of adverse events in the clinical efficacy studies reported in the Advair HFA groups in females was slightly higher (55 to 75%) than males (51to 59%) but similar to the overall safety population. There were no obvious age-related differences in the types of adverse events reported across treatment groups. The 12- to 17- year-old age group and the > 65 year-old age group had the smallest numbers of subjects enrolled making comparisons difficult. The most commonly reported adverse events in all age groups were similar to the overall safety population. The majority of subjects were Caucasian and because of the low representation of the other ethnic groups, interpretation of a relationship between ethnicity and adverse events is difficult to make. However, the most commonly reported adverse events in all races were similar to the overall safety population, and there were no obvious ethnic origin-related differences in the types of adverse events reported across treatment groups.

B. PATIENT EXPOSURE AND DEMOGRAPHICS

Of the 2,014 patients treated in the five 12-week efficacy trials, 622 received Advair HFA. Of these, 352 [187 in the U.S. and 165 in the U.K.] received Advair HFA 44/21 mcg two puffs bid, 94 U.S. patients received Advair 110/21 mcg two puffs bid, and 176 U.K. patients received Advair 220/21 mcg two puffs bid. The mean duration of exposure to Advair HFA was 80 days for Advair HFA 44/21 mcg 2 puffs bid, 78.6 days for Advair HFA 110/21 mcg 2 puffs bid, and 79.3 days for Advair 220/21 mcg two puffs bid.

Female subjects represented 53% to 63% of the subjects across the various treatment groups. Of the 622 patients who received treatment with Advair, 531 (85%) were Caucasian, 40 (6.4%) were black, 28 (4.4%) were Asian, 18 (2.8%) were Hispanic and <1% were of another race. The mean age of the subjects ranged from 35 to 48 years of age. Of all the patients exposed to Advair in the clinical efficacy trials, 70 (11.2%) were 12-17years of age and 41 (6.5%) were >65 years of age.

A total of 325 patients participated in the 52-week safety study conducted in Canada. Of these, 98 patients were treated with Advair HFA 44/21 mcg 2 puffs bid, 109 were treated with Advair HFA 110/42 mcg 2 puffs bid, and 118 patients were treated with Advair 220/42mcg 2 puffs bid. The mean duration of exposure was 320 days for patients receiving Advair HFA 88/42 mcg bid, 343 days for

patients receiving Advair HFA 220/42 mcg bid, and 345 days for patients receiving Advair HFA 440/42 mcg bid.

The mean age ranged from 37 to 45 years in the long-term study. Fifteen (4.5%) patients were 12-17 years old and 27 (8.28%) were over 65 years of age. Demographics in the long-term safety study were similar as for the 12-week efficacy studies. Female subjects represented 46% to 55% of subjects across treatment groups. The majority of the subjects (90%) were Caucasian, 5.2% were black, 3% were Asian, and Hispanics and other races made up the remaining < 2%.

Table 7. Summary of Exposure and Demographics

Summary of Exposure and Demographics		
Patients in Advair treatment arms	12-Week Efficacy Trials (U.S. and U.K.)	52-week safety study SAS30005 [Canada]
# Patients	622	325
Mean Exposure	78.6 -80 days	320 –345 days
Mean Age	35-48	37-45 years
# (%)12-17 years old	70 (11.2%)	15 (4.5%)
# (%) >65 years old	41 (6.5%)	27 (8.28%)
# (%)Caucasian	531(85%)	(90%)

C. METHODS AND SPECIFIC FINDINGS OF SAFETY REVIEW

The safety profile of each individual component of Advair has been well characterized. In addition, a combination product in a dry powder formulation (Advair Diskus) was approved for marketing in the U.S. Therefore; the safety assessment of Advair HFA is mainly to identify safety issues unique to this new formulation. Safety assessments were conducted in the five 12-week efficacy trials [SAS30001, SAS30003, SAS30004, SFCB3022, and SFCB3023] and in one 52-week open label safety study [SAS30005].

The safety profile was determined by monitoring of adverse events, clinical laboratory analyses, EKGs, Holter monitoring, physical examinations, and vital signs. Adverse events occurring within 15 minutes after dosing were monitored as an indicator of potential propellant (HFA-134a) -related events during the run-in (propellant only) phase and the treatment (propellant + active drug) period in the U.S. 12-week efficacy trials and in the long term safety study.

Given that $beta_2$-agonists and corticosteroids have known effects on the cardiovascular system and the HPA axis respectively, the sponsor conducted a focused assessment of these effects.12-lead EKGs were done on patients at screening and at week 12 and evaluated by an independent cardiologist for heart rate, arrhythmias, and QTc intervals using Bazette's correction formula. In two clinical trials (SAS30003 and SAS30004), 24-hour Holter monitoring in a subset of patients was done at screening and at week 12.

Evaluation of AM (8:00 – 10:00) cortisol levels, and the short [conventional] ACTH stimulation testing were done in studies SAS30004, SAS30005, and

SFCB3023. While predictive of adrenal insufficiency, neither of these tests is considered sensitive measures of systemic corticosteroid effects. In addition, 24-hour urinary cortisol excretion was performed in studies SAS30004 and SFCB3023. While this test is a sensitive measure of HPA axis function when performed correctly the methodological flaws noted in these studies limit the value of these data.

The safety data from Advair Diskus from ongoing COPD trials were presented in the sponsor's ISS in response to the Agency's request to include those data in the NDA. Spontaneous reports, and safety data from ongoing marketing studies with Advair HFA in non-U.S. countries, were presented in the 120-day safety update and covered the reporting period from August 1, 2000 to December 31, 2000.

The design and safety findings of the long-term safety study SAS30005 are described first followed by the safety findings of studies SAS30004, SAS30003, SAS30001, SFCB3023 and SFCB3022 in that order.

SAFETY RESULTS STUDY SAS30005

"A 12-Month, Open-Label, Stratified Study to Assess the long-term Safety of Advair HFA [Fluticasone Propionate/salmeterol /GR106642X] Inhalation Aerosol at Doses of 88/42 mcg [Advair HFA 44/21 2 puffs bid], 220/42 mcg [Advair HFA 110/21 2 puffs bid] and 440/42 mcg BID [Advair HFA 220/21 2 puffs bid] in Adolescent and Adult Subjects with Asthma".

Summary

A Total of 325 patients were treated in this 52-week safety trial. The majority of subjects (79%) were on study treatment for more than 360 days. The safety profile of Advair HFA in the long-term safety study was similar to the safety profile seen in the 12-week efficacy studies. The five most common adverse events were upper respiratory tract infections [URTI], throat irritation, viral infections, headache and musculoskeletal pain. There were no deaths during the study. Only 3 % of subjects reported serious adverse events, none of which appeared to be related to the study drug.

Trial design

The study was a multicenter open-label study conducted in Canada using the to-be-marketed U.S. product. Male and female patients with asthma for at least 6 months duration managed with prn short-acting $beta_2$-agonist, long-acting $beta_2$-agonists and/or inhaled corticosteroids were enrolled. Subjects completed a one-to two-week run-in period. At the end of the run-in period, they were assigned to one of the following treatments for 12 months in accordance with their asthma severity:

Advair HFA 88/42 (2 puffs Advair HFA 44/21) BID
Advair HFA 220/42 (2 puffs Advair HFA 110/21) BID

Advair HFA 440/42 (2 puffs Advair HFA 220/21) BID
This treatment assignment allowed for enrollment of subjects with mild asthma to the 88/42 mcg dose group, while subjects with moderate and severe asthma were enrolled in the 220/42 mcg and the 440/42 mcg dose group respectively. Patients were allowed to use Ventolin® for relief of asthma symptoms, and Flonase® for allergy relief. The study had a total of 15 clinic visits including the screening visit and the Treatment Day 1visit. Subsequent visits were at 4-week intervals.

Safety Analyses
The primary endpoint for this study was safety. This was assessed by collecting and summarizing subject-reported adverse event details throughout the 12 months of the study and by the following assessments:

- Routine clinical chemistry, hematology and urinalysis at the start of the study (Visit 1) and after Treatment Weeks 24 (Visit 8) and 52 (Visit 15) or premature discontinuation.

- 12-lead electrocardiogram (ECG/EKG) at the start of the study (Visit 1), after Treatment Weeks 24 (Visit 8) and 52 (Visit 15) or premature discontinuation.

- Oropharyngeal examination for clinical evidence of infection at all visits.

- 24-hour urinary free creatinine- corrected cortisol excretion, and cortisol/creatinine ratio at baseline, after Treatment Week 24 (Visit 8) and at Week 52 (Visit 15). Participation in this analysis was voluntary.

- FEV_1 and peak expiratory flow (PEF) measured at each visit and summarized descriptively.

SAFETY RESULTS SAS30005
Three hundred and twenty five (325) patients received treatment with Advair HFA. Subject disposition is depicted in Table 8.

Table 8: Subject Disposition/ Accountability per Treatment Arm

	Advair HFA 88/42 BID	**Advair HFA 220/42 BID**	**Advair HFA 440/42 BID**	**Total N (%)**
Subjects treated	98	109	118	325
Withdrawals	20 (20%)	15 (14%)	16 (14%)	51 (16%)
Completers	78 (80%)	94 (86%)	102 (86%)	274 (84%)
# of subjects on treatment > 360 days	73 (75%)	87 (80%)	97 (82%)	257 (79%)
REASON FOR WITHDRAWAL				
Adverse event	5 (5%)	7 (6%)	8 (7%)	20 (6%)
Worsening asthma	0	5 (5%)	4 (3%)	9 (3%)

Lost to follow-up	7 (7%)	0	0	7 (2%)
Consent withdrawn	2 (2%)	3 93%)	2 (2%)	7 (2%)
Protocol violation	1 (1%)	1 (<1%)	2 (2%)	4 (1%)
Other	5 (5%)	4 (4%)	4 (3%)	13 (4%)
Worsening asthma is reported from the "other" and "adverse event" categories. Therefore, these subjects also reported another reason for withdrawal.				

Extent of Exposure

The mean duration of exposure was 320 days in the Advair 88/42mcg group, 343 days in the Advair 220/42 mcg group and 345 days in the Advair 440/42 mcg group. The majority of subjects 257 (79%) were on study treatment for more than 360 days.

Compliance

Treatment compliance was assessed from diary data as for all the other clinical studies. The number of subjects who had compliance rates of > 80% was 67 (68%) in the 88/42 mcg dose group, 86 (79%) in the 220/42 mcg dose group and 84 (71%) in the 440/42 mcg dose group. Three patients were withdrawn for non-compliance with study medication.

Serious Adverse Events

There were no deaths during the study. Eleven (3%) subjects reported at least one serious AE during the study. The case narratives of these events were reviewed and it is possible that two subjects had events that might have been exacerbated by the steroid component in Advair. One patient # 4599 experienced a major depressive episode, and panic attacks after 5 months on study drug. However, this patient had suffered from depression and panic attacks for 10 years and was on antidepressants and anxiolytics. She was receiving the lowest dose of Advair 88/42 mcg bid and had a recurrence of the panic attack and major depressive episode 19 days after discontinuation from the study. Subject # 4429 is a 77-year-old female who developed bleeding from a duodenal ulcer 11months into treatment with Advair 440/42 mcg. She had a history of duodenal ulcer and also lost her husband one week prior to the adverse event.

Pregnancies

One subject in the 440/42 mcg dose had a pregnancy after 3.5 months in the study. She was discontinued from the study and gave birth to a normal infant.

Adverse Events Incidence

The percentage of subjects in the study reporting at least one adverse event during the treatment period was high, as expected for a study of this duration, and was similar across treatment groups: 92% in the 88/42 mcg dose group, 92% in the 220/42 mcg dose group and 96% in the 440/42 mcg dose group. The adverse event profile was similar across treatment groups with the exception of upper respiratory inflammation, cough, asthma, and candidiasis of the mouth/throat, which were lower in the 88/42 mcg dose group compared with the 220/42 mcg and 440/42 mcg dose groups as depicted in Table 9 below. The

increased frequency of asthma in the higher dose group is consistent with the enrollment of more severe asthmatics to the higher dosage groups.
The body systems with the most commonly occurring adverse events [regardless of causality] were in descending order of frequency the ear, nose and throat, lower respiratory, gastrointestinal, neurological, and musculoskeletal systems. The five (5) most common (≥3%) adverse events in each of these body systems are displayed below in Table 9. The five most common adverse events overall depicted in **bold** were (I) upper respiratory tract infections, (ii) throat irritation, (iii) viral respiratory infections, (iv) headache and (v) musculoskeletal pain.

Table 9. Most common Adverse Events SAS30005

	Advair 88/42 n = 98	**Advair 220/42 n= 109**	**Advair 440/42 n= 118**	**Total 325**
Ear, Nose, and Throat System				
Upper respiratory tract infection	**51 (52%)**	**40 (37%)**	**58 (49%)**	**149 (45.8%)**
Throat Irritation	**20 (20%)**	**25 (23%)**	**23 (19%)**	**68 (20.9%)**
Upper respiratory inflammation	8 (8%)	20 (18%)	23 (19%)	51 (15.7%)
Sinusitis	12 (12%)	15 (14%)	11 (9%)	38 (11.7%)
Hoarseness/ dysphonia	1 (1%)	13 (12%)	11 (9%)	25 (7.7%)
Lower Respiratory				
Viral respiratory infections	**26 (27%)**	**28 (26%)**	**39 (33%)**	**93 (28.6)**
Asthma	7 (7%)	16 (15%)	24(20%)	47 (14.4%)
Cough	9 (9%)	16 (15%)	16 (14%)	41 (12.6%)
Lower respiratory infections	3 (3%)	7 (6%)	10 (8%)	20 (6.15%)
Bronchitis	8 (8%)	6 (6%)	4 (3%)	18 (5.5%)
Gastrointestinal				
Candidiasis mouth/throat	3 (3%)	13 (12%)	13 (11%)	29 (8.9%)
Nausea and vomiting	7 (7%)	10 (9%)	10 (8%)	27 (8.3%)
Diarrhea	5 (5%)	6 (6%)	9 (8%)	20 (6.15%)
GI discomfort and pain	5 (5%)	4 (4%)	5 (4%)	14 (4.3%)
Dental discomfort and pain	5 (5%)	4 (4%)	3 (3%)	12 (3.7%)
Neurology				
Headaches	**36 (37%)**	**26 (24%)**	**30 (25%)**	**92 (28.3%)**
Sleep disorders	2 (2%)	2 (2%)	5 (4%)	9 (2.7%)
Migraines	0	5 (5%)	3 (3%)	8 (2.4%)
Musculoskeletal				
Musculoskeletal pain	**14 (14%)**	**22 (20%)**	**22 (19%)**	**58 (17.8%)**
Arthralgia & articular rheumatism	4 (4%)	9 (8%)	8 (7%)	21 (6.4%)
Muscle pain	7 (7%)	5 (5%)	3 (3%)	15 (4.6%)
Muscle cramps and spasms	3 (3%)	1 (<1%)	5 (4%)	9 (2.7%)