Asthma Exacerbations
Forty-seven (14%) subjects reported asthma as an adverse event. The number of subjects reporting asthma as an adverse event increased with product strength: (7) 7% subjects in the 88/42 mcg dose group, 16 (15%) subjects in the 220/42 mcg dose group and 24 (20%) subjects in the 440/42 mcg dose group. This dose ordering is not unexpected given the assignment to higher dose with increasing asthma severity.

Corticosteroid-Related Adverse Events
Candidiasis of the mouth/throat, hoarseness/dysphonia, and throat irritation are known effects of ICS. Candidiasis appeared to be drug-related in 2% of subjects in the 88/42 mcg dose group, 9% of subjects in the 220/42 mcg dose group, and 7% of subjects in the 440/42 mcg dose group. Hoarseness/dysphonia was probably drug-related in 1% of subjects in the 88/42 mcg dose group, 7% of subjects in the 220/42 mcg dose group and 5% of subjects in the in the 440/42 mcg dose group. Throat irritation was probably drug-related in 6% of subjects in the 220/42 mcg group and 2% of subjects in the 440/42 mcg group compared to no patients in the 88/42 mcg group. Other possibly drug-related adverse events reported by 0 to 3% of subjects in each treatment group were headaches, tremors, tachycardia and cough.

Adverse Events Leading To Withdrawal
Twenty (6%) subjects discontinued from the study due to an adverse event. Four of these subjects had serious adverse events. None of the SAEs appear to be drug-related. These SAEs were subdural hematoma (subject # 4569), major depressive episodes (subject # 4599), multiple sclerosis (subject # 4449)), and asthma exacerbation (subject #4476). Three (1%) subjects withdrew due to events that were possibly drug-related. These events were: muscle soreness and headache (subject #4562), hyperglycemia (subject # 4567), and edema of the lips (subject # 4683).

Adverse Events occurring within 15 minutes of dosing
A comparable low number of subjects in each treatment group 4(4%) in the 88/42 mcg dose group, 4 (4%) in the 220/42 mcg dose group, and 6 (5%) in the 440/42 mcg dose group reported an adverse event within 15 minutes of dosing. No subject reported cough as an adverse event within 15 minutes of dosing. One subject in the 88/42 mcg- and 440/42 mcg- dose group reported throat irritation and one subject in the 220/42 and 440/42 treatment group reported an allergic reaction within minutes of dosing. Of all the adverse events reported, no specific adverse event affected more than one subject in a treatment group. Three adverse events tremor (subject #4446 in the 220/42 mcg dose group), tachycardia (subject #4507 in the 440/42 mcg dose group) and palpitations (subject #4461 in the 440/42 mcg dose group) were possibly drug-related. These

three events were mild in intensity and resolved spontaneously and the three subjects continued in the study.

Clinical Laboratory Results

A threshold range for each laboratory measurement was defined by factors greater than and less than the upper and lower limits of the normal range for that measurement. The factors for calculating these ranges were pre-specified. A total of 18 (6%) subjects had laboratory results that were outside the threshold at the 6-month study visit or at Treatment Week 52. Only 2 of the laboratory abnormalities were reported as adverse events. Both were cases of increased blood glucose in two female patients [subject #4349 in the Advair 220/42 mcg dose group and subject #4457 in the Advair 440/42 mcg dose group]. One was diagnosed with underlying diabetes. For HPA Axis assessments, 24-hour urine samples for urinary cortisol were collected from a total of 159 patients. Participation was voluntary and there was an unequal representation across treatment groups. Data concerning urine volumes for the 24-hour collections were not provided and incomplete collections cannot be excluded. Given that cortisol excretion is not continuous but follows a diurnal pattern, one cannot correct urinary cortisol excretion for creatinine. Because of these limitations the value of data from this assessment is highly questionable.

SAFETY RESULTS STUDY SAS30004

SUMMARY

Advair HFA 220/42 mcg bid was well tolerated during the 12-week study. There were no new or unusual adverse events or other sequelae to suggest that subjects receiving the combination product were at greater risk than subjects receiving placebo or the individual components.

There were no deaths during the study. Two subjects reported serious adverse events in the treatment phase. The two SAEs were viral meningitis and upper GI bleeding. The subject with the upper GI bleed was on placebo, and the subject with viral meningitis was on salmeterol. Both were withdrawn from the study. Laboratory abnormalities were similar in the Advair HFA group and the salmeterol and FP group. Most of the clinical laboratory changes were not clinically significant, or were associated with underlying abnormalities (e.g. hyperglycemia in a patient with underlying diabetes mellitus).

There was no significant difference in the mean AM plasma cortisol levels in the Advair group compared to the individual components, or placebo. Although there are limitations to these data, the mean post-ACTH stimulation cortisol levels at Screening and at Treatment Week 12 were similar across treatment groups. The sponsor adjusted the urinary cortisol excretion for creatinine and did not provide information on incomplete urine collections. Therefore no reliable conclusions can be made from the urinary cortisol excretion data.

Exposure

The mean duration of exposure to study medication was 49 to 79 days across treatment groups. A greater percentage (82%) of subjects in the Advair group completed ≥ 82 days of treatment compared with 38% of the subjects in the placebo group, 65% of the subjects in the salmeterol group, and 80% of the subjects in the FP group.

Deaths and Withdrawals due to adverse events

There were no deaths during the study. Only 9 subjects discontinued the study due to adverse events. One subject in the Advair group, 2 each in the placebo and FP groups, and 4 patients in the SAL group. Two of these events were deemed by the investigator to be related to the study drug however, on review of the case narratives it is unlikely that these events were drug related. One was a case of palpitations in a subject on FP, and the other a case of upper GI bleeding in a subject on placebo with a prior history of peptic ulcer disease.

Adverse Events Incidence

The most commonly affected body system was the ear, nose and throat and the most common adverse event was upper respiratory tract infection. The five most common (>3%) adverse events occurring during the treatment period are displayed below in Table10.

Table10. Most Common Adverse Events Study SAS30004

	Placebo n=89	**Advair 220/42 n= 94**	**SAL 42 n= 91**	**FP 220 n=91**
Number (%) of subjects with any event	53 (60%)	65 (69%)	60 (66%)	63 (69%)
URTI	11 (12%)	23 (24%)	17 (19%)	14 (15%)
Headaches	11 (12%)	14 (15%)	19 (21%)	15 (16%)
Nausea/vomiting	4 (4%)	5 (5%)	5(5%)	5 (5%)
Viral respiratory infections (lower respiratory tract)	4(4%)	5 (5%)	5 (5%)	5 (5%)
Musculoskeletal pain	3 (3%)	7 (7%)	7 (8%)	2 (2%)

Adverse events generally associated with fluticasone propionate or other inhaled corticosteroids include pharyngitis and/or throat irritation, hoarseness/dysphonia, and oropharyngeal candidiasis. Throat irritation was most common in the FP group (13%) compared to 7% and 6% in the Advair and placebo group. Candidiasis of the throat and mouth was more common in the FP group (3%) compared to 1% in the Advair group.

Drug-related AEs

Thirty-one [31 out] of 365 (8%) subjects experienced adverse events classified as drug-related by the investigators. Two of these AEs were probably not drug-

related as previously mentioned. *[See discussion under "Deaths and withdrawals due to AEs].* Nine [10%] of the subjects were in the Advair group, 4% in the placebo group, 5% in the salmeterol group and 13 (14%) in the FP group. Two subjects in the Advair group reported throat irritation, and oropharyngeal plaques. One subject in the Advair group reported candidiasis of the mouth/throat.

Adverse Events within 15 minutes of Dosing
Events occurring during the run-in and treatment period within 15 minutes of dosing occurred in ≤ 1% of subjects. These events were cough, URTI and upper respiratory inflammation. Cough was reported in only one subject and was possibly related to the study drug. The subject was withdrawn from the study.

Pregnancies
Two pregnancies occurred during the study. One patient [Subject #4030] had an elective termination and one patient [Subject # 4220] carried to term and had a vaginal delivery. The baby had an Apgar score of 2 at one minute but had a score of 8 at 5 minutes. The low Apgar score at one minute was probably due to medication the patient received during labor.

Laboratory abnormalities
The most frequent abnormalities encountered were elevated blood glucose, increase eosinophil counts, and elevated liver function tests (ALT, AST, and bilirubin). Three of the 4 patients with elevated blood glucose [2 on FP (subjects # 4095 and #8683) and one on placebo (subject # 4299)] already had a history of diabetes mellitus on entering the study and were on oral medication for diabetes mellitus. No worsening of glucose control was mentioned in the case narratives. The fourth patient [#8989] who was randomized to placebo did not have a history of diabetes and was referred to her primary physician for follow up. The other laboratory abnormalities did not require medical intervention, and were not considered to be clinically significant.

HPA-Axis Assessments
These included AM plasma cortisol with short ACTH stimulation testing[3], and 24-hour urine collection for urine cortisol. A total of 126 patients had a morning plasma cortisol and short ACTH stimulation testing performed at screening and 113 patients had these tests repeated at endpoint or discontinuation visit. At screening both the mean morning plasma cortisol and the post-stimulation cortisol concentrations were similar across treatment groups and ranged form 10.8 to 12.8 mcg/dL [AM cortisol] and 25.0 to 26.5 mcg/dL [post-stimulation cortisol] respectively. At endpoint the cortisol measurements were also similar across treatment groups with AM (pre-stimulation) cortisol levels ranging from 11.9 to 13.8 mcg/dL and post-stimulation cortisol ranging from 26.3 to 28.9 mcg/dl. These data suggest that there was no apparent clinically significant adrenal suppression seen across treatment groups. Eight subjects had a post-

[3] 250 mcg of cosyntropin is given intravenously and plasma cortisol levels are obtained before, and 30, and 60 minutes later.

stimulation peak cortisol level of≤ 18 mcg/dL at endpoint. The data for these 8 patients are depicted in Table 11.

Table 11 [Data source SAS30004.pdf pg. 127]

Abnormal post-stimulation peaks at endpoint (<18mcg/dL)

Treatment	Subject #	Sex	HRT/ OC	Visit	Pre-stim. Cortisol (mcg/dL)	Post-stim. Cortisol (mcg/dL)
Placebo	3692	M	--	Scm	15.4	21.5
				Wk 12	5.7	14.8
Placebo	8840	M	--	Scm	8.7	20.9
				D/C	10.1	7.1
SFC 42/220mcg	3772	M	--	Scm	11.8	17.8
				Wk 12	1.4	12.7
SFC 42/220mcg	8723	M	--	Scm	4.5	22.0
				Wk 12	4.0	12.7
SFC 42/220mcg	4098	M	--	Scm	12.9	29.4
				D/C	9.1	15.2
				Repeat	13.7	23.8
Salm 42mcg	8683	F	No	Scm	2.9	14.1
				Wk 12	4.3	15.3
FP 220mcg	3798	F	No	Scm	1.0	6.6
				Wk 12	1.0	9.8
FP 220mcg	8711	F	No	Scm	9.7	18.5
				Wk 12	2.3	11.3

Source Data: Listing 8, HRT= Hormone replacement therapy OC=Oral contraceptive

HRT = hormone replacement therapy
OC = oral contraceptive
D/C = discontinuation
SCM = Screening
SFC = Advair

It is important to note that of the two patients in the placebo group, one was on prednisone 40 mgs for two days prior to the endpoint stimulation test, and there was possible mislabeling of the other patient's pre-and post-stimulation plasma samples. One subject in the Advair (subject # 3772), SAL (subject #8683) and FP (subject # 3798) treatment group also had an abnormal post-stimulation peak plasma cortisol level at Screening. However, 5 of the 8 patients received FP 220 bid (3 as Advair HFA 220/42 bid, and 2 as FP 220 bid) which strongly suggests, that in these 5 patients, the low post-stimulation cortisol level was due to adrenal suppression.

The urinary cortisol excretion data are difficult to interpret because of the adjustment for cortisol excretion for creatinine excretion which calls the data reported into serious question.

Cardiovascular effects

There were no clinically significant cardiovascular findings. A total of 124 patients had 24-hour Holter monitoring at Screening and at Treatment Week 12 and the majority [93% to 100%] were within normal limits at both timepoints. The few patients that had abnormal Holter results (3%-7%) did not have clinically significant findings. ECGs were done at Screening and Week 12 or discontinuation in all patients. No clinically significant abnormalities were noted and the mean heart rate across treatment groups ranged from 67.9 to 68.9 beats/minute at Screening with no clinically significant change at Treatment Week 12. The number of subjects with prolonged QTc [defined as >450msec for male subjects and > 470 msec for female subjects using Bazett's correction formula] was similar at Screening and throughout the study. Across treatment groups, 0% - 2% of males at Screening and throughout the study had prolonged QTc. While 0% -1% of females at Screening and 0%-2% during treatment had prolonged QTc.

SAFETY RESULTS SAS30003

SUMMARY

Similar to study SAS30004, Advair HFA 44/21mcg 2 puffs bid was well tolerated during the 12-week study. The adverse event profile in SAS30003 was similar to that of SAS30004. There were no deaths during the study. There was only one serious adverse event reported in this study (tachyarrhythmias) occurring in a 69-year-old female on FP. No HPA axis assessments were conducted in this study.

Exposure

The mean duration of exposure ranged from 64 days in the placebo group to 82 days in the Advair group.

Deaths, Serious Adverse Events, Withdrawals

No deaths were reported during the study. There was only one serious adverse event reported in this study (tachyarrhythmias) occurring in a 69-year-old female [subject # 3390] approximately 14 days after starting FP (88 mcg dose). The patient had atrial fibrillation, which from the case narrative appeared to be unrelated to the study drug.

A total of 4 subjects were withdrawn due to adverse events. None of these subjects were in the Advair group. Two of these subjects had adverse events possibly related to the study drug. Both subjects were randomized to salmeterol. One subject reported hoarseness/dysphonia, and the other reported exacerbations of anxiety that was pre-existing.

Pregnancies

Three pregnancies were reported in the study. One subject [#6362] was diagnosed in the run-in period and was discontinued. She later had a ruptured

ovarian cyst and a spontaneous abortion. The other 2 subjects [#6164 and 6230] both gave birth to healthy babies.

Adverse Events Incidence

The number of subjects who reported any adverse event during the treatment period was 49 (56%) in the placebo group, 62 (67%) in the Advair group, 55 (60%) in the salmeterol group, and 52 (58%) in the FP group. The 5 most common adverse events [≥3% frequency] were similar to those is study SAS 30004 and are summarized in Table 12.

Table 12. Most Common AEs SAS30003

	Placebo n=87	**Advair 88/42 n= 92**	**SAL 42 n= 92**	**FP 88 n=89**
Number (%) of subjects with any event	49 (56%)	62 (67%)	55 (60%)	52 (58%)
URTI	11 (13%)	15 (16%)	11 (12%)	12 (13%)
Headaches	9 (10%)	20 (22%)	17 (18%)	22 (25%)
Nausea/vomiting	2 (2%)	5 (5%)	1(1%)	2 (2%)
Viral respiratory infections (lower respiratory tract)	3(3%)	1 (1%)	4 (4%)	0
Musculoskeletal pain	4 (5%)	6 (7%)	1 (1%)	6 (7%)

Adverse Events occurring within 15 minutes of dosing

During the run-in and the treatment period the frequency of events occurring within 15 minutes of dosing was low and was reported in ≤ 2% of subjects. During the treatment period, of the 3 AEs occurring within 15 minutes of dosing only two appear to be drug-related. One was a case of throat irritation in the salmeterol group and the other a case of cough in the placebo group. The third event, a case of candidiasis of the mouth/throat could not have occurred within 15 minutes of dosing.

Drug-related AEs

Overall, adverse events considered to be drug-related by the investigators were low and similar across treatment groups affecting 5 [6%] of subjects in the placebo group, 6 [7%] of subjects in the Advair group, 10 [11%] of subjects in the salmeterol group and 5 [6%] of subjects in the FP group.

Corticosteroid-Related Events

A total of 5 subjects had positive evidence of oral candidiasis with positive cultures. Two (2) in the Advair group, 2 in the FP group and one in the placebo group. Seven (8%) subjects in the Advair group reported throat irritation compared to 11 (12%) subjects in the FP group, 8 (9%) subjects in the SAL and group and 7 (8%) subjects in the placebo group. Hoarseness/dysphonia was not reported in the placebo group but was reported by 1 patient in the Advair and FP group (1%) and 3 (3%) patients in the SAL group.

Cardiovascular events

There were no significant differences across the four treatment groups in mean heart rate at baseline and at endpoint or discontinuation. There were no subjects with clinically significant abnormal ECG findings prior to randomization and no subject had a clinically significant change in ECG at any post-dose assessment. There was no evidence of any increased risk in QTc prolongation associated with Advair. Holter monitoring was conducted at 10 sites at screening in 100 patients and at Treatment Week 12 in 81 patients. At screening, 92% of subjects had normal Holter results and. 9 subjects had abnormal Holter results. In seven of these subjects the abnormalities were not clinically significant and were unchanged upon repeat testing at the end of the study. The other two subjects had clinically significant abnormalities on Holter monitoring at Screening. They both had PVCs at Screening but on repeat testing, the Holter monitoring results were normal. Both subjects completed the study.

Clinical Laboratory Results There were minor changes in laboratory parameters during the study such as small increases in eosinophils, small decreases in neutrophils, small upward shifts in glucose and downward shifts in potassium. Some of these changes are expected effects of $beta_2$-agonists (decreases in potassium) and corticosteroids (increase glucose). With the exception of increases to high glucose (6% in the placebo and Advair group, and 8% in the FP group) the incidence of pre to post treatment changes in chemistry laboratory was low (≤ 3%) across treatment groups.

SAFETY RESULTS SAS30001

SUMMARY

The adverse event profile in study SAS30001 supports the safety and tolerability of Advair 44/21 2 puffs bid. The adverse event profile was similar to that seen in study SAS30003.

Exposure

Unlike studies SAS30004 and SAS30003, the mean duration of exposure was comparable across treatment groups ranging from 80.4 days to 80.9 days. The incidence of withdrawals was low. This is probably due to the fact that the patient population in this study had only been controlled with as needed $beta_2$-agonists, and all subjects in the study received an active medication.

Adverse Events Incidence

The five most common adverse events (≥ 3%) were headaches, upper respiratory tract infection, throat irritation, upper respiratory inflammation, and musculoskeletal pain. These events are depicted in the table below.

Table 13. Five most Common Adverse Events (≥3%)

	Advair 88/42 n= 95	SAL 42 n= 91	FP 88 n=97
Number (%) of subjects with any event	64 (67%)	66 (73%)	71 (73%)
Headaches	20 (21%)	18 (20%)	23 (24%)
URTI	15 (16%)	18 (20%)	12 (12%)
Throat irritation	10 (11%)	11 (12%)	11 (11%)
Upper respiratory inflammation	6 (6%)	6 (7%)	4 (4%)
Musculoskeletal pain	3 (3%)	3 (3%)	9 (9%)

Drug-related events

The incidence of events deemed to be drug-related by the investigator was relatively low and similar across all treatment groups affecting 46 of the 283 (16%) of subjects. Of these 16 (17%) subjects were in the Advair group, 14 (15%) were in the salmeterol group and 16 (16%) were in the FP 88 mcg dose group.

Adverse Events occurring within 15 minutes of Dosing

Adverse events occurring within 15 minutes of dosing during the run-in period was reported by 3% of subjects in the Advair group compared with 7% of subjects in the salmeterol and FP groups. Headache was the most frequent event reported (3% in the FP group and 1% in the Advair and salmeterol group). Fewer subjects in the Advair HFA group (5%) reported adverse events within 15 minutes of dosing compared to subjects receiving salmeterol (12%) or FP (13%) during the treatment period. Cough was reported by 3 (3%) subjects in the salmeterol group, with no reports of coughing reported in the Advair group. The remaining events, throat irritation, hoarseness/dysphonia, headaches, sleep disorders, and muscle cramps and spasms were reported by 1% of less of subjects in each treatment group.

Pregnancies

One pregnancy was reported during the study. The patient had an elective termination.

Laboratory results

No subject in the Advair group experienced a clinical laboratory value outside of the pre-defined threshold. Overall, 4% of subjects in the salmeterol group and 1% in the FP group experienced laboratory results outside of the predefined normal threshold but none of these laboratory results were clinically significant.

Cardiovascular Events

At screening, 12-lead ECGs were performed predose and 1.5 hours post-dose on Treatment Day 1, and Treatment Week 12. For patients who discontinued prematurely, one reading was done at the discontinuation visit. Mean heart rate at Screening ranged form 67.9 to 69 beats/min. There were no clinically significant changes in mean heart rate or ECG findings at Treatment Week 12. No subjects had clinically significant abnormal ECGs at Screening or Treatment week 12. There was no evidence of any increased risk of QTc prolongation with Advair HFA. Pulse and blood pressure remained essentially unchanged throughout the study.

SAFETY RESULTS SFCB3023

Summary

Advair 220/21mcg two puffs bid was well tolerated and had a comparable safety profile to both Advair Diskus 500/50 bid and FP [CFC MDI] 220 mcg two puffs bid No treatments resulted in a decrease in mean serum cortisol levels and there was no evidence of any effect on mean QTc interval.

Extent of Exposure
Mean exposure was 79 days for the three treatment arms. The number of subjects exposed to > 84 days of study drug were 68 (39%) for Advair HFA, 67 (42%) for Advair Diskus and 76 (44%) for FP. The maximum number of days' study medication provided for each subject was 90 days.

Deaths and Serious Adverse Events
There was one death during the study, which was not related to the study drug. Subject #4715 was a 71-year of female who was diagnosed with leukemia 8 days after randomization to the Advair HFA arm. Study medication was discontinued and the subject was withdrawn form the study and died 20 days after the diagnosis of leukemia was made.

Including the death described above, a total of 13 subjects experienced serious adverse events during the treatment period and/or after completion of the treatment period. Three subjects experienced SAEs after completion of the treatment period. One of these subjects [subject #4343] also had a SAE reported during the treatment period. Six subjects were withdrawn from the study because of the SAE. The SAEs that led to withdrawal from the study were leukemia (subject #4715), arthritis (subject #5038), acute bronchitis, asthma exacerbation, and atrial fibrillation (subject #4343), tuberculosis (subject #4994), sinusitis, pneumonia, and asthma exacerbation (subject #7963), and asthma exacerbation (subject #4807). These SAEs are further described below.

Subject 05038 is a 33-year-old female randomized to Advair HFA who developed arthritis in the left knee. No infectious etiology was identified. She was hospitalized and treated with prednisolone, and was withdrawn from the study. The event was unresolved after 7 months.

Subject 04343 is an 81 year old female randomized to Advair Diskus who developed acute asthma exacerbation, and acute bronchitis after being on treatment with study drug for one month. The subject was hospitalized and study drug was withdrawn. She was treated with corticosteroids, antibiotics and theophylline. The asthma exacerbation resolved after 5 days but the patient developed atrial fibrillation, which subsequently resolved. This subject was described as developing a serious event both on and off study drug.

Subject 04994 is a 60 year old male randomized to Advair Diskus who was hospitalized five days after starting study drug with suspected tuberculosis which was confirmed. The patient was discontinued from the study.

Subject 07963 is a 40 year old female randomized to Advair Diskus who developed asthma exacerbation, pneumonia, and sinusitis [confirmed radiologically] 8 days after being on the study medication. She was hospitalized for treatment and was withdrawn from the study.

Subject 04807 is a 24 year old male subject randomized to FP who developed an acute asthma exacerbation requiring hospitalization 7 weeks after treatment with study drug. The study drug was discontinued and the subject was withdrawn.

Frequency of Adverse Events

The type and incidence of adverse events was generally similar between the treatment groups. A total of 94 subjects (53%) on Advair HFA, 73 (45%) subjects on Advair Diskus and 90 subjects (52%) on FP MDI experienced at least one AE. The most commonly reported AEs [reported by ≥ 3% of subjects] were upper respiratory tract infection reported by 18 (10%) subjects receiving Advair HFA, by 17 (11%) subjects receiving the *Diskus* combination and by 20 (12%) subjects receiving the fluticasone propionate MDI. Tremor was rare occurring in only one subject on Advair HFA and FP MDI. No cases of tremor were reported for Advair Diskus. There were 3 cases of muscle cramps and spasms in the Advair HFA group but none in the other treatment groups. The following table summarizes the most common adverse events that occurred during treatment.

Table 14. Most Common Adverse Events SRCB3023

	Advair HFA 42/440 N= 176	**Advair Diskus 50/500 N= 161**	**FP MDI 500 172**
Any adverse event	94 (53%)	73 (45%)	90 (52%)
Upper respiratory tract infection	18 (10%)	17 (11%)	20 (12%)
Headaches	15 (9%)	16 (10%)	9 (5%)
Asthma	6 (3%)	11 (7%)	10 (6%)

Rhinitis	12 (7%)	6 (4%)	7 (4%)
Viral respiratory infection	8 (5%)	8 (5%)	7 (4%)
Hoarseness/dysphonia	6 (3%)	9 (6%)	3 (2%)
Throat irritation	6 (3%)	3 (2%)	9 (5%)
Bronchitis	6 (3%)	7 (4%)	3 (2%)
Lower respiratory infections	8 (5%)	2 (1%)	4 (2%)
Cough	5 (3%)	2 (1%)	4 (2%)
Candidiasis mouth/throat	6 (3%)	2 (1%)	2 (1%)
Musculoskeletal pain	4 (2%)	5 (3%)	1 (<1%)
Fever	5 (3%)	1 (<1%)	2 (1%)
Arthralgia	5 (3%)	0	0

Pregnancies

Two pregnancies were reported during the study. One patient [subject #4773] had an extrauterine pregnancy during the run-in phase and was withdrawn. The other subject [#4880] had a positive pregnancy test 5 days after randomization to FP MDI and was withdrawn. She gave birth to a healthy infant.

Withdrawals due to adverse events

Thirty-four (34) subjects were withdrawn from the study due to adverse events. Six of these subjects had serious adverse events previously described. Of the 34 patients who withdrew because of adverse events 11 were in the Advair HFA group, 9 were in the Advair Diskus group, and 14 were in the FP MDI group. The most common event leading to withdrawal was asthma exacerbations/asthma worsening/increased dyspnea reported by a total of 18 subjects. Of these events 6 [3 each in the Advair Diskus and FP groups] were considered by the Investigator to be related to the study drug. It is unclear if these events were really drug-related or simply worsening of the underlying disease process. One subject (#4645) reported a hypersensitivity reaction in the mouth on the first day of starting Advair HFA. The study medication was discontinued and the event resolved after 11 days. The event was not serious but was probably related to the study drug.

Corticosteroid-Related events

A total of 6 cases (3%) of candidiasis of mouth and throat occurred in the Advair MDI group, 2 cases (1%) in the Advair Diskus group and 2 cases (1%) in the FP MDI group. Hoarseness/dysphonia occurred at a frequency of 6 cases (3%) in Advair HFA, 9 cases (6%) in Advair Diskus and 3 cases (2%) in FP MDI Throat irritation occurred at a frequency of 3% (6 cases) with Advair HFA, 2% (3 cases) with Advair Diskus, and 5% (9 cases) with FP 500 MDI.

Cardiovascular Events

Palpitations occurred rarely 2% (3 cases) in the FP MDI group, 1 case in the Advair HFA group but none in the Advair Diskus group. Three cases of tachycardia, one in Advair HFA and 2 in FP MDI were reported. There was one report of extrasystoles in the FP MDI group. Four patients [one in each of the HFA and Diskus groups and two in the FP group] had normal QTc interval at

baseline and a prolonged QTc interval at the end of treatment or withdrawal. These four cases are summarized in the table below. These cases are too few in numbers to draw any conclusions. Overall there was no mean effect on QTc during the study.

Table 15. Cases with QTc prolongation in study SFCB3023

Subject	Study Medication	Baseline QTc [msecs]	Follow-up QTc [msecs]
4411 50 y/o W F	FP 440	449	477 at follow up visit
4987 49 y/o W M	Advair HFA 220/21	444	451 at follow up visit
*4700 54 y/o W M	Advair Diskus 500/50	393	472 at discontinuation visit
*5026 79 y/o W F	FP 440	440	451 at end of treatment visit
*Subjects withdrawn due to an AE not related to QTc interval. # 4700 withdrew due to worsening asthma 15 days into the study, and # 5026 was listed as withdrawn due to polymyalgia rheumatic but had completed 84 days of treatment at withdrawal.			

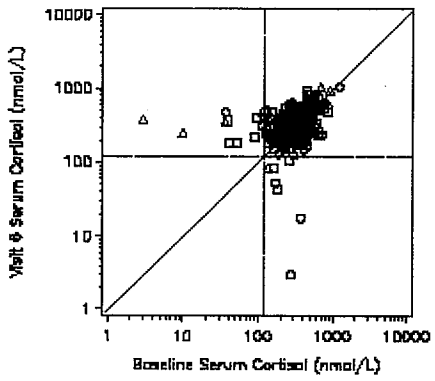
Laboratory abnormalities

In the majority of subjects (>90%) results of hematological variables were within the normal range or did not change from baseline. Abnormalities were found only in neutrophil, eosinophil, or monocyte counts and were attributed to the underlying disease state. There were infrequent changes in biochemistry abnormalities. The most frequent changes were in glucose, urea, and liver enzyme levels. Glucose levels were increased in 5 (3%) subjects in the Diskus combination product, 7 (5%) in the HFA group, and 6 (4%) subjects in the FP group. Blood urea increased in 6 (4%) of HFA subjects, 7 (5%) of Diskus subjects, and 4 (3%) of FP subjects. AST levels increased in 9 (6%), 5 (3%) and 3 (2%) subjects respectively in the HFA, Diskus, and FP treatment groups. Most of these biochemistry abnormalities were attributed to underlying disease states. None were attributed to the study drug.

Cortisol levels

The baseline means for AM cortisol (collected between 0800 and 10:00 hours) were 305.2 nmol/L for the HFA combination, 316.4 nmol/L for the Diskus, and 310.0nmol/L for the FP MDI group. The geometric mean ratios at the end-of-treatment visit were 1.14, 0.94, and 1.03 for the HFA, Diskus and FP groups respectively showing that mean cortisol levels increased slightly in the MDI combination and the FP groups and decreased slightly in the Diskus group. A Scatter plot of the results showed that the majority of subjects had cortisol levels within the reference range both before and after treatment. This is depicted in the above figure *[Source: Figure 14,file 3023.pdf pg. 136]*

Figure 14
Serum Cortisol (nmol/L) (8–10am samples only)



Similar to study SAS30004, 24-hour urinary cortisol excretion corrected for creatinine was done on a subset of patients. It is difficult to make conclusions from these data because of inappropriate adjustments for creatinine, and incomplete urine collections.

SAFETY RESULTS SFCB 3022

Summary

This study similar to study SFCB3023 was conducted in the U.K. and was identical in design and objectives except that the treatment arms of the study were Advair HFA 88/42 mcg bid [Advair HFA 44/21 2 puffs bid], Advair Diskus 100/50 mcg bid, and FP MDI 88 mcg bid [FP 44 mcg 2 puffs bid]. The safety findings were similar to that of the other studies. Mean AM serum cortisol levels did not decrease during the course of the study.

Exposure
Of the 497 subjects receiving study medication, 165 received Advair HFA, 167 received Advair Diskus, and 165 received FP. The mean number of days of exposure to study medication was 78.74 (Advair HFA), 78.45 (Advair Diskus) and 77.04 (FP). Sixty-four (39%) patients in the Advair HFA group, 76 (46%) in the Advair Diskus group and 81 (49%) in the FP group were exposed to study drug for > 84 days.

Deaths, Serious Adverse events, Withdrawals
There were no deaths in this study. One serious adverse event leading to withdrawal was reported prior to randomization. This subject had a myocardial infarction. Nine (9) subjects [3 in each treatment arm] reported a SAE during the Treatment period. Additionally, One of these subjects in each of the MDI treatment groups reported a SAE in the post-treatment period. Therefore a total of 12 SAEs were reported by 10 patients in the study - 1 in the run-in period, 9 in

the treatment period, and 2 in the post treatment period. All the SAEs resolved. Table 16 below gives a summary of the SAEs in the treatment period. [*Source: 3022.pdf pg. 82.The MDI combination refers to Advair HFA.]*

Summary of Serious Adverse Events

Subject	Treatment	Treatment period	Adverse event	Drug-related	Resolved	Withdrawn
7087	MDI combination	During	Asthma exacerbation	No	Yes	Yes
7374	MDI combination	During	Asthma exacerbation	Yes	Yes	Yes
7046[1]	MDI combination	During	Asthma exacerbation	No	Yes	Yes
		Post	Hyperglycemia	No	Yes	Yes
7279	*Diskus* combination	During	Asthma exacerbation	Yes	Yes	Yes
7583	*Diskus* combination	During	Asthma exacerbation	No	Yes	Yes
7081	*Diskus* combination	During	Breast cancer	No	Yes	No
7582	Fluticasone propionate MDI	During	Throat infection	No	Yes	No
7483	Fluticasone propionate MDI	Post	Spontaneous abortion	No	Yes	No
7501	Fluticasone propionate MDI	During	Infectious gastroenteritis	No	Yes	No
7410	Fluticasone propionate MDI	During	Inguinal hernia	No	Yes	No

Subject # 7046 on Advair HFA also had an URTI. The patient was hospitalized for the asthma exacerbation and was treated with systemic corticosteroids. She developed hyperglycemia while in hospital. The hyperglycemia resolved after 8 days. Upon review of the case narratives none of these SAEs appear to be attributable to the study drug.

A total of 27 subjects discontinued from the study because of an adverse event 7 (4%) in the Advair HFA group, 8 (5%) in the Advair Diskus group and 12 (7%) in the FP group. Five subjects had serious events [see table above]. The most common AE leading to withdrawal from the study was asthma exacerbations.

Adverse Events Incidence

A total of 82 subjects (50%) from the Advair HFA group, 95 (57%) from the Advair Diskus group, and 90 (55%) from the FP group experienced at least one AE. The most commonly reported (≥3%) adverse events were in the respiratory system (URTI, viral respiratory infection, rhinitis, throat irritation, asthma, pharyngitis/throat infection and sinusitis), and in the neurological system (headaches). These adverse events are depicted in Table17.

Table 17. Most common Adverse Events SFCB3022

Adverse Event	**Advair HFA88/42 n= 165**	**Advair Diskus 50 N= 168**	**FP 88 n= 165**
URTI	19 (12%)	29 (17%)	21 (13%)
Headaches	14 (8%)	14 (8%)	10 (6%)
Viral respiratory infection	6 (4%)	6(4%)	9 (5%)
Rhinitis	1 (<1%)	9 (5%)	5 (3%)
Throat irritation	5 (3%)	5 (3%)	5 (3%)
Asthma	4 (2%)	5 (3%)	5 (3%)
Pharyngitis/throat infection	5 (3%)	3 (2%)	6 (4%)
Sinusitis	3 (2%)	6(4%)	5 (3%)

Corticosteroid-Related Events

Candidiasis was seen in two subjects on Advair HFA, 4 subjects on Advair Diskus and 2 subjects on FP.

Vital Signs

No difference in vital signs was seen during the study among the treatment groups.

Laboratory results

The most common chemistry laboratory abnormalities were liver function tests and blood glucose abnormalities. Most liver abnormalities were due to underlying disease or alcohol. Less than 1% of subjects in any group had a laboratory value below or above the threshold value at any visit after baseline.

Morning serum cortisol measurements

The mean serum cortisol values measured between 0800 and 1000 hours rose slightly during the course of the study in all treatment groups. The baseline geometric means of each group were 335.1nmol/L, 349.7nmol/L and 328. nmol/L for the HFA combination, *Diskus* combination and fluticasone propionate MDI groups respectively. There was a small increase in geometric mean by the end of treatment, the geometric ratio of the end of treatment vs. the beginning of treatment being 1.08, for the HFA combination group, 1.09 for the *Diskus* combination group and 1.21 for the fluticasone propionate MDI group. At the end of treatment three subjects (2%) in the Advair HFA group, 2 (1%) subjects in the Advair Diskus group and 3 (2%) subjects in the FP group had a decrease in cortisol values to below the reference range.

120-day Safety Update [SUR]

A 120-day safety report covering the period August 1 2000 – December 31, 2000 was submitted in April 2001. The safety data in the NDA submission covered the period up to July 31, 2000. The SUR included safety information from two on-going non-U.S. studies with Advair HFA SAS30015 and SAM30013, safety information from ongoing Advair Diskus studies for COPD not submitted in the ISS of the NDA, and spontaneous reports from August 1, 2000 to December 31, 2000. The data in the SUR provide additional evidence of the safety and tolerability of the combination product when used for the maintenance treatment of asthma.

There was a report via Schwarz Pharma Germany of one death in a 78-year-old man who was receiving Advair Diskus (Atmadisk). The suspected cause of death was pulmonary embolism.

There were a total of 15 serious adverse events [including the death mentioned] that were spontaneously reported. Four reports were for asthma exacerbations/lack of efficacy. There was one case of Churg-Strauss syndrome in patients with bronchial asthma who had received fluticasone propionate/salmeterol combination product via Diskus (case D0010462A) and one case of possible vasculitis in patients with asthma who received fluticasone propionate/salmeterol Diskus (case A0126648A). There was one SAE in SAM30013. SAM30013 is a 12-week multicenter randomized double-blind parallel group study comparing the efficacy and safety of fluticasone propionate/salmeterol HFA MDI 88/42 mcg dose BID with fluticasone 220 mcg dose BID in adolescent and adult patients with mild to moderate asthma. One patient developed headache, which was diagnosed as occipital neuralgia. There was also one case of angioneurotic edema with a positive dechallenge while the patient was on Seretide® (Advair) HFA however the patient was taking other medications including enalapril.

There were 4 spontaneous reports of pregnancies while on study medication. No safety issues have been reported.

Safety information for the combination product in COPD studies

The Agency requested that the sponsor provide deaths and serious adverse events for the ongoing Advair Diskus studies in COPD. To fulfill this request, the sponsor submitted cumulative safety data for all ongoing Advair Diskus studies in COPD as of the cut-off date of July 31, 2000. There are no ongoing or completed studies with Advair HFA in COPD. The ongoing clinical studies in COPD are listed below.

Table 18. Advair Diskus Ongoing Clinical Studies in COPD

Study	Doses (mcg) bid	Duration	Planned # subjects
SFCA3006	Advair Diskus 500/50	24 weeks	691
SFCA3007	Advair Diskus 250/50	24 weeks	722
SFCB3024	Advair Diskus 500/50	54 weeks	1468
SCO30001	Advair Diskus 500/50	12 weeks	270
SCO40002	Advair 5 Diskus 500/50	135 weeks	500

Deaths

Twenty-eight deaths (16 previously reported to the FDA) have been reported in ongoing Advair Diskus studies in COPD as of July 31, 2000. Treatment remains blinded. The majority of the deaths [[fourteen] are cardiovascular system -related deaths.

Serious Adverse Events

There were 414 serious adverse events occurring in 413 subjects (28 of which were the deaths mentioned above). Two hundred and eighty-two of the 414 SAEs were previously reported to the FDA. Forty-six of these SAEs were reported during the run-in period. Nineteen of all the SAEs were deemed by the Investigator to be related to the study medications or relationship to study medication was unknown at the time of reporting.

VIII. Dosing, Regimen, and Administration Issues

Advair HFA comes in three strengths 44/21 mcg, 110/21 mcg, and 220/21 mcg [measured at the ex-actuator]. The recommended dosing regimen is two inhalations (puffs) twice a day for patients 12 years of age and older. Advair HFA is recommended for asthma patients not currently on ICS whose asthma severity warrants therapy with ICS, or for patients currently on ICS or other controller therapy. The lowest effective dose of corticosteroid should be employed. Advair is not recommended for asthmatics with mild intermittent asthmatics that are controlled on, as needed β-$_2$ agonists only. Advair should not be used for transferring patients from systemic corticosteroid therapy.

IX. Use in Special Populations

A. Gender Effects

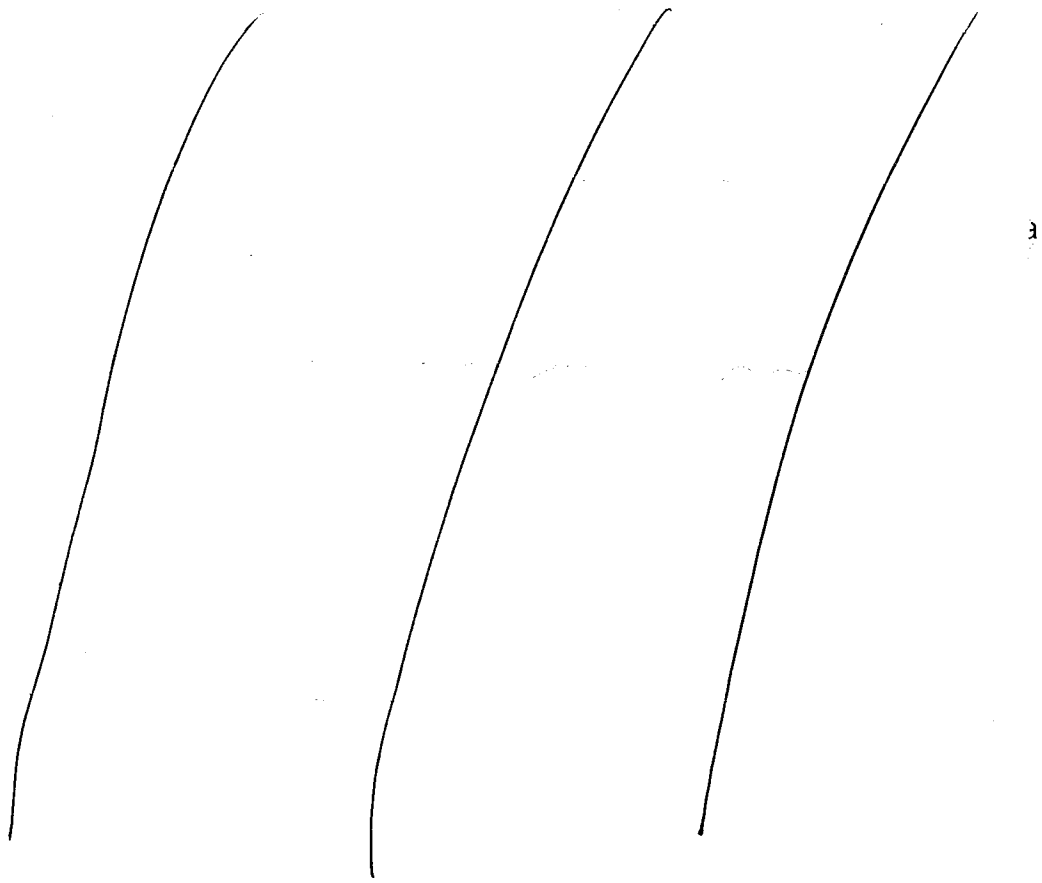
A greater percentage (56%) of subjects participating in the efficacy clinical studies was female. Female subjects represented 46 –55% of subjects in the long-term safety study. The frequency of adverse events reported in the Advair

HFA groups in females was slightly higher across studies (55 to 75%) than males (51to 59%). The adverse event profile in female subjects was similar to the overall population. There was no gender-related differences in effectiveness were noted.

B. Age, Race/Ethnicity effects on Safety or Efficacy

The mean age in the clinical studies ranged from 37 to 45 years and the majority of subjects were Caucasian. There was not a representative number of patients in the other ethnic groups to allow for meaningful statistical comparisons. However, there did not appear to be any age-related or ethic origin-related differences in efficacy or safety. There were no obvious age-related differences in the types of adverse events reported across treatment groups. The > 65 year-old and the 12 to 17 year-old age groups had the smallest numbers of subjects (68 and 85 respectively from a total of 2,429 subjects) enrolled making comparisons difficult. The most commonly reported adverse events in all age groups were similar to the overall safety population.

C. Pediatric Program



D. Other Populations i.e. Pregnancy, Renal, or Hepatic Compromise

No formal studies were conducted in subjects with renal impairment or hepatic compromise. Since FP is predominantly cleared by hepatic metabolism impairment of liver function may lead to accumulation of FP in plasma. Therefore, patients with hepatic disease should be closely monitored. There are no adequate and well-controlled studies with Advair HFA in pregnant women. A total of 9 pregnancies occurred in subjects participating in this clinical program but none of these patients was taking Advair HFA. All subjects were discontinued. Two subjects had elective terminations, one subject had an extrauterine pregnancy, and one subject had a spontaneous abortion in the run-in period. The other 5 subjects delivered healthy babies although one baby had a low Apgar (2) at one minute secondary to medications given to the mother shortly before delivery. Advair HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

X. Conclusions and Recommendations

A. Conclusions

- Advair HFA Inhalation Aerosol 44/21 110/21, and 220/21 administered twice daily is effect for the maintenance treatment of asthma in patients 12 years of age and older.

- Advair 220/21 mcg administered as 2 puffs twice a day is comparable to Advair Diskus 500/50 mcg one puff twice a day.

- There are no data to show [redacted]

- Advair HFA was safe and well tolerated in asthmatic patients 12 years of age and older when taken as recommended as two inhalations twice daily in the clinical studies.

- Treatment with the Advair HFA was not associated with an increased risk of adverse events compared to treatment with the individual components.

- There were no new or unusual adverse events or other sequelae to suggest that subjects receiving salmeterol and fluticasone propionate in combination are at greater risk than patients receiving either treatment alone.

- Patients on Advair HFA did not have an increase in cardiovascular events.

- The AM plasma cortisol and ACTH stimulation data did not show evidence of adrenal suppression. However these tests are relatively insensitive measures of systemic corticosteroid effects. The 24-hour urinary cortisol excretion data are inconclusive due to deficiencies in the conduct of the analyses. However, PD and systemic data are already available for FP and PK data showed less exposure from Advair HFA compared to Advair Diskus or single component devices.

B. Recommendations

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. The lowest effective dose of Advair HFA should be used depending on the degree of asthma severity.

2 Page(s) Withheld

_____ Trade Secret / Confidential

__/__ Draft Labeling

_____ Deliberative Process

XI. Appendix

This Appendix contains a detailed description of the clinical trials and the efficacy results. The safety results for these trials were extensively discussed in section VII.C "Methods and Specific Findings of Safety Review" and therefore are not repeated here.

Appendix 1.A. Study SAS 30001

"A randomized, double-blind, active-controlled parallel-group 12- week trial evaluating the safety and efficacy of the salmeterol/fluticasone propionate 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".

OVERVIEW: The purpose of this study was to determine the effectiveness of the combination of salmeterol 21 mcg [SAL] and fluticasone propionate 44 mcg [FP] administered BID as the proposed combination product Advair™ HFA Inhalation aerosol formulation relative to treatment with either single agent alone. Primary efficacy analyses were based on FEV_1 data namely, area under the 12-hour serial FEV_1 curve relative to baseline [AUC (bl)] on Treatment Day 1, and at Treatment Week 12 and change from baseline at endpoint in morning predose FEV_1. The AUC (bl) was used as the primary endpoint for comparison of the combination product to FP to evaluate the effects of salmeterol in the combination. The change from baseline in morning predose FEV_1 was the primary endpoint for comparison of the combination product to salmeterol to evaluate the effects of fluticasone in the combination product.

Study Dates: December 10, 1998 – August 07, 1999

INVESTIGATORS: Thirty-three (33) investigators in the US enrolled patients in this study.

Amendments

There was one study amendment dated December 16th 1998 that provided clarification of some inclusion and exclusion criteria, excluded Ventolin® use with spacers, and added further instructions on the management of subjects with declining FEV_1 during the 12-hour serial PFTs.

Protocol

This was a randomized double blind active controlled study conducted at 33 US sites. The study 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 followed by a 12-week period of active treatment where patients were randomized to Advair HFA 44/21 inhalation aerosol two puffs BID, SAL two puffs (42mcg) BID, or FP 44 mcg formulation, two puffs (88mcg) BID. Patients were allowed to take Ventolin® MDI as rescue medication for asthma symptoms.

Patients were followed every week for the first 4 weeks and then every 2 weeks for the rest of the 12-week period. Clinic visits were scheduled as follows in table 1 below: [*copied from page 21 SAS30001.pdf*]

Clinic Visit	Treatment Week	Time of Occurrence
Visit 1	----------	14 ±2 days prior to Visit 2 (Treatment Day 1)[a]
Visit 2 (randomization)	0	Treatment Day 1
Visit 3	1	Treatment Day 7 ±2 days
Visit 4	2	Treatment Day 14 ±2 days
Visit 5	3	Treatment Day 21 ±2 days
Visit 6	4	Treatment Day 28 ±2 days
Visit 7	6	Treatment Day 42 ±2 days
Visit 8	8	Treatment Day 56 ±2 days
Visit 9	10	Treatment Day 70 ±2 days
Visit 10	12	Treatment Day 84 ±2 days

a If a subject did not meet the inclusion criteria based upon FEV_1 percent predicted or reversibility, the subject could return to repeat the PFTs once within 7 days.

PATIENT POPULATION

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 generally good health as ascertained by history, physical exam, 12-lead ECG, chest x-ray and clinical laboratory parameters.

Asthma- Patients enrolled in this study would be asthmatics with FEV_1 40-85% predicted not well controlled on $beta_2$--agonists alone. They should have had a documented history of asthma that had required therapy for at least 6 months prior to Visit 1. There could not have had any corticosteroids oral or inhaled in the month preceding the screening period, or long-acting $beta_2$-agonists 3 days before the screening period. Other disallowed asthma controller medications were leukotriene modifiers, theophylline, and cromones 2 weeks before screening, oral anticholinergics and long-acting $beta_2$-agonists, for 24 hours before Visit 1, methotrexate, gold, cyclosporine and azathioprine 12 months before Visit 1, and short-acting $beta_2$-agonist at least 12 hours prior to Visit 1. Subjects were given Ventolin® MDI for rescue treatment of asthma symptoms throughout the study.

Exclusions- 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.

Study Procedure

Patients were required to have an FEV_1 of 40-85% predicted at screening and demonstrate reversibility by an increase in FEV_1 of 15% within 30 minutes following treatment with albuterol [Ventolin ®] 2 puffs via 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. Patients should have had a total symptom score of ≥ 7 during the 7 days prior to Visit 2 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 defined as best baseline FEV_1 at the –30 minute or 0 hour time point PFT within ± 15% of the best pre-Ventolin® Visit 1 FEV_1. 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.

Statistical and Analytical Plan

See section VI. C." Detailed Review of Clinical Trials" for full description of statistical and analytical plan.

Efficacy

Primary efficacy endpoints

1. Area under the 12-hour serial FEV_1 curve relative to baseline [AUC (bl)] on Treatment Day 1 and Treatment Week 12 as the primary endpoint for comparison of the combination product to FP, to assess the effect of salmeterol in the combination product.

2. Change from baseline at endpoint in the morning pre-dose FEV_1 for comparison of the combination product to salmeterol to assess the effect of FP in the combination product.

Baseline for FEV_1 measurements: The average of the –30-minute and 0 hour FEV_1 measurements on Treatment Day 1. If only one value was obtained, then that one value was used as the baseline value.
Endpoint for FEV_1 measurements: The measurement recorded at Treatment Week 12 or for subjects who discontinued prior to Week 12 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.

Serial FEV_1 measurements were performed at baseline, 30 minutes post dose, every hour for the first 4 hours and then every 2 hours for up to 12 hours post dose. FEV_1 values recorded at each timepoint were weighted by length of time interval (in hours) as outlined in the following table [*reproduced from the sponsor's table pg. 53 SAS30001.pdf]*

Table 2

Timepoint	Interval	Weight
30 minutes	15-45 minutes	0.5
1 hour	45 –90 minutes	0.75
2 hours	1.5 –2.5 hours	1.0
3 hours	2.5 –3.5 hours	1.0
4 hours	3.5 – 5 hours	1.5
6 hours	5-7 hours	2
8 hours	7 – 9 hours	2
10 hours	9 – 11 hours	2
12 hours	11 –12 hours	1

Serial FEV_1 collected at these timepoints were used to calculate the AUC (bl) using the trapezoidal rule.
For the weighted average, the mean change from baseline FEV_1 was calculated by subtracting each subject's baseline FEV_1 from his/her weighted average FEV_1, and then summarising the resulting differences by treatment group. Mean percent change from baseline was derived by dividing each subject's weighted change from baseline by their baseline, multiplying the result by 100 and then summarising by treatment group.

Secondary Endpoints: With the exception of survival these were comprised of parameters recorded on diary cards and were assessed as change from baseline at endpoint
Secondary Endpoints

1. AM and PM PEF (recorded prior to medication)
2. Daily asthma symptoms (assessed in the AM before dosing)
3. PRN Ventolin use

4. Nighttime awakenings requiring the use of Ventolin (recorded in the morning). Note: The only diary measure recorded in the evening was evening PEF.
5. Withdrawals due to worsening asthma

Baseline for diary data: The average of the available data collected during the 10 days prior to treatment start or 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: The last 7 days of available data where the subject was still on study drug, ending at Day 84 [week 12].

Safety endpoints and analysis
Adverse events, vital signs, 12-lead ECGs, adverse events assessed within 15 minutes of dosing in the run-in period and the active treatment period.

Medication Compliance
Compliance was assessed by diary data. Subjects had to place a check mark in the "yes" or "no" box on the subject diary card as to whether he/she administered each dose of the study medication.

RESULTS

Patient Disposition
A total of 525 patients were screened, and 283 patients were randomized. One hundred and sixty two (162) subjects were excluded at Visit 1. The most common reason for exclusion at the Screening visit was not meeting the entrance criteria of an FEV_1 of 40% to 85% of predicted at Visit 1 (101) subjects. A total of 80 subjects were excluded at Visit 2. The most common reason for exclusion at Visit 2 was lack of reproducible lung function. Of the 283 subjects randomized 95 were in the Advair HFA group, 91 in the salmeterol group and 97 were in the fluticasone group. Two hundred and fifty seven (257 [90.8%]) of the randomized patients completed the study. Twenty-six subjects withdrew from the study prior to completion, 9 subjects each in the Advair and salmeterol group and 8 in the fluticasone group. The most common reason for withdrawal was lack of efficacy and occurred most frequently in the salmeterol group (7 subjects).

Table 3. Patient Disposition SAS30001

	Advair 88/42 (N = 95)	Salmeterol 42 (N = 91)	FP 88 (N = 97)	Total (N = 283)
# (%) Complete	86 (91%)	82 (90%)	89 (92%)	257 (91%)
# (%) Withdrawn	9 (9%)	9 (10%)	8 (8%)	26 (9%)
Reason for Withdrawal				
Lack of Efficacy (worsening asthma)	1 (1%)	7 (8%)	3 (3%)	11 (3.88%)
Adverse Event	3 (3%)	0	0	3 (1%)
Protocol violation	2 (2%)	0	1 (1%)	3 (1%)
Consent withdrawn	2 (2%)	0	2 (2%)	4 (1.4%)

Lost to follow up	0	0	1 (1%)	1 (0.35%)
***Non-compliance**	0	2 (2%)	0	2 (0.70%)
Other	1 (1%)	0	1 (1%)	2 (0.70%)
*Not medication compliance				

Medication Compliance

Overall compliance was high with mean compliance rates ranging from 96% to 97% across treatment groups.

Demographics

Overall, 53 percent [148] of the ITT patients were male. Seventy-eight percent of patients were Caucasian, 10 percent were Black, 7 percent were Hispanic 3 percent were Asian and 2 percent were of other races. Patient ages ranged from 12 to 77 years, with approximately 14 percent [39] under the age of 18 and only 3 patients (1%) over the age of 65. Most patients [225] had no history of tobacco use (79 percent). Sixty-one percent of patients [174] had an asthma history of at least 15 years duration and 54 percent had a history of atopy. Mean FEV_1 at screening ranged from 2.28L to 2.37L representing a mean baseline percent predicted FEV_1 of 64% to 67%. All treatment groups were responsive to Ventolin® at screening with a mean percent reversibility following Ventolin® treatment within 30 minutes ranging from 30% to 33%. Demographic factors and asthma parameters were relatively comparable among treatment groups. However, the elderly were not well represented in this trial.

Table 4. Characteristics of the Intent-to Treat population

	Advair HFA (n = 95)	**Salmeterol (n=91)**	**FP (n=97)**
Age (median) Age 12-17 Age > 65	28 n=20 n=1	32 n =7 n=1	31 n=11 n=1
Gender Female Male	 46 (48%) 49 (52%)	 43 (47%) 48 (53%)	 46 (47%) 51 (53%)
Race Caucasian/White Black Hispanic Asian	 76 (80%) 8 (8%) 7 (7%) 3 (3%)	 70 (77%) 8 (9%) 9 (10%) 3 (3%)	 75 (77%) 12 (12%) 6 (6%) 4 (4%)
Asthma history >15 yrs ≥10 ≤15 yrs ≥5 ≤10 yrs < 5 yrs	 51 (54%) 20 (21%) 13 (14%) 11 (11%)	 60 (66%) 11 (12%) 14 (15%) 6 (7%)	 63 (65%) 13 (13%) 10 (10%) 11 (12%)
Mean FEV_1 L (% predicted) Baseline (Visit 2)	2.37 (67.21%)	2.34 (66.12)	2.31(65.19)
% reversibility	30.52	33.58.	33.71

Primary Efficacy results

Change from baseline in mean morning pre-dose FEV_1 at endpoint
This analysis evaluated the effects of FP in the combination product. The comparison was between Advair and salmeterol. The changes are displayed in the table below.
Mean improvement at endpoint was 0.69L(33%) for Advair HFA, 0.47L (22%) for salmeterol and 0.51 (51%) 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). Improvements in morning pre-dose FEV_1 was numerically greater for Advair compared with salmeterol and FP at all timepoints. (Source: Tables 14 and 15, SAS30001.pdf pg. 66)

Area under the 12-hour serial FEV_1 curve relative to treatment day 1 baseline [AUC (bl)]
This is the area under the curve generated by serial measurement of FEV_1 over 12 hours relative to baseline. This variable was analyzed as a primary measure of efficacy to evaluate the effects of salmeterol in the combination product on Treatment Day 1 and Treatment Week 12. Advair had a significantly greater mean AUC value relative to baseline compared to FP (88 mcg) ($p < 0.001$) on Treatment day 1 and at Treatment week 12. On Treatment Day 1 there was no significant difference between Advair and salmeterol, however at Treatment Week 12 Advair had significantly greater mean AUC (bl) compared to salmeterol (p=0.013)

Table 5. Efficacy Results SAS30001: Primary Endpoints

	Advair 42/88	**Salmeterol**	**Fluticasone**
Treatment day 1 n	n = 95	n=91	n = 97
Change from baseline in mean morning pre-dose FEV_1 at endpoint			
Baseline FEV_1 L (SE)	2.37 [0.06]	2.34 [0.07]	2.31 [0.07]
Mean morning predose FEV_1 at Endpoint L (SE)	3.06 [0.08]	2.81 [0.09]	2.82 [0.09]
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)]			
Mean FEV_1 AUC at Treatment day 1 L-hrs [SEM]	7.2 L [b] [0.4]	7.6 L [0.6]	2.9 L [0.4]
Mean FEV_1 AUC at treatment week 12 [SEM]	10.6 L [bc] [0.6]	8.2 L [0.8]	7.2 L[0.6]
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)			

The FDA statistician, Dr. James Gebert did subgroup analyses of FEV_1 AUC and mean change from Baseline in morning pre-dose FEV_1 at Treatment Day 1 and at Week 12 for subjects with FEV_1 < 70% and subjects with FEV_1 >70%. Because the patient numbers were small no inferential statistical analyses were conducted in these subsets. Nevertheless the results were similar as the overall intent to treat population and it did not appear that one subgroup was "driving" the results.

Serial FEV_1 measurements

The mean pre-dose baseline FEV_1 on Treatment Day 1 was similar across treatment groups and ranged from 2.31L to 2.37L[see table above]. As expected, there was no significant difference between Advair and salmeterol on Treatment Day 1 at any timepoint or in the time-weighted serial FEV_1 average. Whereas, compared with FP, Advair showed significant differences on Treatment Day 1 at all timepoints. (P <0.001). This finding demonstrates the acute bronchodilatory effects of salmeterol. At treatment week 12 the Advair group had significantly greater increases in FEV_1 than the salmeterol or fluticasone group at most timepoints ($p \leq 0.033$), with the exception of the 1, 2 and 3 hour timepoints for Advair compared to the salmeterol group. A similar pattern was seen when serial FEV_1 data was expressed as change from baseline in percent predicted FEV_1 at Treatment Day 1 and Treatment Week 12.

Response to Treatment, Onset of Effect and Duration of Effect
Response to treatment, onset, offset and duration of effect were defined based on the serial FEV_1 measurements collected on Treatment Day 1 and at Treatment Week 12. Response to treatment was defined as an increase over baseline FEV_1 of 15% or greater within the first 4 hours after treatment. Effect was defined as an increase in FEV_1 over baseline of 15% or greater, regardless of time of occurrence. The time to onset of effect was the first time during the 12-hour serial FEV_1 that the subject achieved a response. If no response was achieved in the 12 hours then time of onset was assessed as 12 hours. The duration of effect was defined as the difference between time of onset to time of offset of effect. The time to offset was defined as the time just before a given subject's FEV_1 drops below the 15% improvement threshold for two consecutive timepoints.

Most patients in the Advair and salmeterol group [70%] achieved more than 15% improvement in FEV_1 within 60 minutes on Treatment Day 1 compared to only 24% of subjects in the FP group indicative of the acute bronchodilatory effect of salmeterol. At Treatment Week 12, 76% and 86% of subjects in the salmeterol and Advair group respectively had an improvement of 15% or greater in FEV_1 compared to 64% of subjects in the FP group. Eighty seven percent [87%] of subjects in the Advair and salmeterol groups responded [$\geq$ 15% increase in FEV_1 over baseline within the first 4 hours] to treatment on Day 1 with a median time to

onset of 18 minutes for salmeterol and 24 minutes for Advair. The effect was sustained for a median duration of up to 11.7 hours. At Treatment Week 12 ninety three percent [93%] of subjects in the Advair group responded to treatment compared with 87% in the salmeterol group and 75% in the FP group. The median duration of effect was 12.0 hours in the Advair and FP group and 11.7 in the salmeterol group.

SECONDARY EFFICACY MEASURES

AM and PM PEF Results
Overall there was no difference across treatment groups in mean PEF values at baseline. There were greater improvements in AM and PM PEF in the Advair group compared with the salmeterol and fluticasone groups at endpoint. The mean change from baseline in AM PEF was 66.5Lmin for Advair, 29.2L/min for salmeterol, and 43.0L/min for fluticasone [see table below]. The mean percent change from baseline was higher 20% in the Advair group compared with 9% in the salmeterol group and 14% in the fluticasone group. Morning PEF expressed as mean percent predicted was also increased in the Advair group compared with salmeterol and fluticasone at week 12. Similar changes were seen in the PM PEF measurements with a mean increase from baseline of 51L in the Advair group measured at endpoint compared an increase of 22 L and 30L in the salmeterol and FP groups respectively.

Table 6. AM and PM PEF Results SAS30001

	Advair 42/88 (n= 95)		**Salmeterol 42 (n=91)**		**FP 88 (n=97)**	
	AM PEF	PM PEF	AM PEF	**PM PEF**	AM PEF	**PM PEF**
Baseline Mean (L/min) [%predicted]	356 [74.5]	385 [80.6]	364[74]	391 [79.4]	361 [74]	394 [80.6]
Endpoint Analyses						
n	94		91		97	
Mean (L/min) [% predicted]	423 [88.3]	436 [91.2]	393 [80.1]	413.0 [84]	404 [82.6]	424 [86.5]
Mean change L/min	67	51.5	29	22	43	30
Mean % change	20.1	14.1	8.7	6.1	13.5	8.9
Mean change % predicted PEF	14.1	10.8	6.2	4.6	8.6	5.9

Ventolin® Use
The total symptomatic Ventolin use at baseline was similar across treatment groups and ranged from 3.2 puffs/24 hrs in the salmeterol group to 3.9 /24 hrs in the FP group. At endpoint, the subjects in the Advair group had a decrease in Ventolin® use compared with the other treatment groups. The changes were small with Ventolin use in the Advair group decreasing by 2.4 puffs/24 hours and by 1.6 puffs/24hrs and 1.8 puffs/24 hrs in the salmeterol and FP groups respectively.
Nighttime Awakenings due to Asthma

At baseline there were very few nighttime awakenings across treatment groups. The mean number of nighttime awakenings was 0.4 equivalent to one night awakening every 2.5 days. At endpoint there was essentially no difference.

Asthma symptoms

The mean scores for the patients across treatment groups were low and ranged from 2.1 to 2.2 at baseline. There was no difference in change from baseline in daily asthma symptom scores for the combination product group compared with the neither salmeterol group nor fluticasone at endpoint. Neither was there any difference in change from baseline in percent days with no asthma symptoms in any of the treatment groups.

Withdrawal due to worsening asthma

There was only one withdrawal due to worsening asthma in the combination group (1%) compared with 7 (8%) in the salmeterol group and 3 (3%) in the FP group.

Subgroup analysis in patients taking intranasal Flonase®

No statistical comparisons were conducted for this subgroup analysis because the number of patients taking intranasal fluticasone was too small. The results were similar as the results seen in the intent to treat population. Summary statistics showed that the combination group did better than the individual components regardless of intranasal steroid use. These results are displayed in the table below.

Table 7. Primary Efficacy Endpoints Results Displayed By Concomitant Intranasal FP Use

		Advair 88/42		**Salmeterol 42**		**FP 88**
Mean change from baseline at Endpoint in morning pre-dose FEV_1 (L) by concomitant intranasal FP use	N	Mean change at endpoint (L)	N	Mean change at endpoint (L)	N	Mean change at endpoint (L)
Intent to treat population	94	0.69	91	0.47	97	0.51
Taking intranasal FP	27	0.75	22	0.54	26	0.45
No taking intranasal FP	67	0.67	69	0.45	71	0.53
AUC (bl) at Treatment Day 1 and Treatment Week 12		Mean AUC (bl) L-hrs		Mean AUC (bl) L-hrs		Mean AUC (bl) L-hrs
Treatment Day 1						
Intent to Treat population	95	7.2	91	7.6	97	2.9
Taking intranasal FP	28	7.7	22	6.6	26	2.4

Not taking intranasal FP	67	7.0	69	7.9	71	3.1
Treatment Week 12						
Intent to treat Population	86	10.6	82	8.2	88	7.2
Taking intranasal FP	24	11.2	21	8.5	23	7.4
Not taking intranasal FP	62	10.3	61	8.1	65	7.1

Efficacy Conclusions

- Advair 44/21 administered as two puffs bid showed a significantly greater improvement in both mean morning pre-dose FEV_1 at endpoint and mean serial FEV_1 AUC on treatment Day 1 and at Treatment Week 12 compared with its individual components salmeterol and fluticasone at the same nominal dose. These findings support the conclusion that treatment with Advair was significantly better than either component alone.

- Salmeterol was primarily responsible for the first day effect on FEV_1 seen with Advair. Median time to onset of effect was 24 minutes with a median duration of 11.7 hours on Treatment Day one and 12 hours at Treatment Week 12.

- Peak flow results (AM and PM were consistent with the changes seen with FEV_1. Improvements in the other secondary endpoints Ventolin® use, asthma symptoms, nighttime awakenings were numerically quite small.

- Overall the patient population studied was not very symptomatic at baseline although frequency of use of short-acting β-agonists at baseline and mean baseline FEV_1 define these patients as moderate persistent asthmatics by NAEPP criteria. Although subjects were using albuterol on an as needed basis at baseline this moderate level of severity would have argued for use of at least one controller therapy.

APPENDIX 1.B. STUDY SAS30003

"A Stratified, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group 12-Week Trial Evaluating the Safety and Efficacy of the Salmeterol/Fluticasone Propionate Combination in GR106642X MDI, 42/88mcg 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".

STUDY OBJECTIVES

To demonstrate the efficacy and safety of the fluticasone propionate/salmeterol GR106642X [HFA] inhalation aerosol 88/42 mcg BID compared with the individual components (via the P11/12 [CFC] pressurized MDI) and with placebo/ [HFA] MDI in subjects with asthma treated with inhaled corticosteroids, inhaled short-acting $beta_2$-agonists or salmeterol.

Study Dates: December 07, 1998 – November 05, 1999

Amendments: The original protocol dated July 13, 1998 was amended three times. The first two amendments were made prior to initiation of the trial. The first one provided clarification of the secondary efficacy endpoints, redefined how Visit 2 reproducibility would be met and provided a statement about the power of the study in the statistical section in order to establish consistency across the three protocols. Amendment 2 allowed for optional participation (by center and subject) in subject genotyping during the course of the clinical study. This amendment essentially allowed for the collection of one blood sample (10 ml) and the recording of phenotypic information at Visit 10 from subjects who completed the study. Amendment 3 was dated December 11, 1998 and resulted from comments received from physicians participating at the Investigator meeting for SAS30003. The changes were minor and included modification of the inclusion criteria to allow female subjects of childbearing potential using barrier methods of birth control in combination with spermicide to participate in the study, modification of the concurrent medications to allow for long-acting oral decongestants, guaifenesin, and antihistamines as needed during the study, as well as further instructions on the management of subjects with declining FEV_1 during the serial PFTs. These amendments will not have any substantive impact on the study results.

STUDY DESIGN

This was a stratified, randomized, double blind, placebo-controlled, parallel-group trial conducted on an outpatient basis. Similar to study SAS30001, subjects who meet the inclusion criteria completed a two-week run-in period. During the run-in period subjects who were previously taking inhaled corticosteroids or salmeterol continued taking those medications but discontinued all other asthma medication. All subjects received single-blind placebo (GR106642X Aerosol Inhaler) and

Ventolin® to relieve symptoms of acute asthma. Subjects who complete the run-in period and meet all randomization criteria were stratified according to previous asthma therapy and then randomly assigned to one of the following treatment groups:

1. Advair ™ HFA 44/21 mcg two puffs BID
2. Salmeterol MDI 21 mcg two puffs BID
3. Fluticasone propionate MDI 44mcg two puffs BID
4. Placebo HFA 2 puffs BID

Subjects discontinued inhaled corticosteroid therapy and salmeterol on the day prior to randomization (Visit 2).

STUDY POPULATION

The study was conducted in 36 centers in the U.S. And 360 subjects were randomized to treatment.

Inclusion Criteria

Inclusion criteria are the same as those in Study SAS30001 except for the following Concurrent Anti-Asthma Therapy:

a) Eligible Treatment at Baseline: Two groups of subjects were eligible to participate based on previous treatment as described below and the study population was stratified according to whether or not subjects were currently taking inhaled corticosteroids or beta-agonists.

Group 1

Inhaled Corticosteroids: Subjects must have been using inhaled corticosteroids for at least 3 months prior to Visit 1; and, must be on a consistent daily dose of one of the following for at least one month prior to Visit 1:

Table 8. ICS prior to Visit I SAS30003

Drug	Dose (mcg/day)
Beclomethasone dipropionate	252-336
Triamcinolone acetonide	600-800
Flunisolide	1000
Fluticasone propionate MDI	176
Fluticasone propionate **ROTADISK**	200
Budesonide	400-600

Subjects using salmeterol with inhaled corticosteroids were eligible to participate if they were able to replace salmeterol with as-needed, short-acting beta$_2$ agonist for at least 72 hours prior to Visit 1.

Group 2:

Baseline Salmeterol: Subjects must have been using salmeterol and as needed, short-acting beta$_2$-agonists for at least one week prior to Visit 1. Subjects should not have received concurrent inhaled corticosteroids for at least one month prior to Visit1. Each subject had to be able to withhold salmeterol 24 hours prior to Visit 1 and prior to Visit 2 and then discontinue its use for the remainder of the study.

Baseline PRN Short-Acting Beta$_2$-Agonist Only: Subjects must have been using only, as-needed, short-acting beta$_2$-agonists for at least 1 week prior to Visit 1. Subjects should not have received concurrent salmeterol for at least 72 hours prior to Visit1 nor inhaled corticosteroids for at least one month prior to Visit 1. Each subject had to be able to withhold short-acting beta$_2$-agonist therapy for at least 6 hours prior to Visit 1 and 2. During the 7 days prior to Visit 2, subjects must have a total symptom score (scale 0-5) of ≥ 7[4]

b) Theophylline: Subjects currently using theophylline medications had to be able to continue taking the following agents without a significant adjustment of dosage, formulation or dosing interval for the duration of the study; and, must have been judged by the investigator to be able to withhold theophylline for the specified minimum time intervals prior to each visit:
   - Short-acting forms of theophylline: 12 hours
   - Twice-a-day controlled-release forms of theophylline: 24 hours
   - Once-a-day controlled-release forms of theophylline: 36 hours

Exclusion Criteria

Same as those in Study SAS30001.

Statistical and Analytical Plan

Same as for SAS30001. The endpoints specific to SAS30003 are noted in bold Italics. The multiplicity issues associated with testing the primary efficacy endpoints were addressed in the same manner as for study SAS30001.

Primary Efficacy Endpoints

To evaluate the effects of salmeterol in the combination product, the comparison is made between Advair and FP for the following endpoint (s)

- Area under the 12-hour serial FEV_1 cure relative to baseline on treatment Day 1 and Treatment Week 12.

To evaluate the effects of FP in the combination product the comparison is made between Advair and salmeterol for the following endpoints

- Change from baseline at endpoint in AM pre-dose FEV_1 AND
- Probability of remaining in the study over time

Secondary Efficacy Endpoints

- AM & PM peak flow (PEF)
- Daily asthma symptom scores
- PRN Ventolin® use
- Nights with awakenings due to asthma requiring Ventolin®
- Quality of life evaluation conducted using the Asthma Quality of Life Questionnaire (AQLQ)

The AQLQ is a disease-specific questionnaire that contains 32 items in four domains: activity limitation (11 items), asthma symptoms (12 items),

[4] See Asthma symptom score described in study SAS30001 page 68

emotional function (5 items), and environmental exposure (4 items). For the AQLQ the mean Overall score as well as the mean score in all four domains [Activity Limitation, Asthma symptoms, Emotional Function and Environmental Exposure] were analysed. 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.

Safety Endpoints

Safety analysis was similar to SAS30001 but also included 24-hour Holter monitoring at selected sites at screening and at Week 12. Holter monitoring results included cardiac rates, cardiac rhythm abnormalities, listing of subjects with 50 or more ventricular ectopic events, or 50 or more supraventricular events during the 24-hour monitoring period.

RESULTS

Patient Disposition

A total of 360 subjects were randomized of the 799 subjects screened for entry into the study. A total of 326 subjects failed screening (Visit 1) and 113 subjects failed randomization criteria at Visit 2. The disposition of the randomized subjects and treatment assignment by stratum is displayed in the table below. Of the 360 randomized subjects 134 (37%) were using inhaled corticosteroids and 226 (63%) were using beta$_2$-agonists as baseline therapy.

Table 9. Subject Disposition by Baseline Asthma Therapy *(Data source: supporting tables 2-5 SAS 30003)*

	Total	**Group 1 (ICS)**	**Group 2 (Beta$_2$-agonists)**		
			All Beta-agonists	**Salmeterol**	**Short-acting β_2 agonists**
Randomized	N= 360	N= 134 [37%]	N= 226 [63%]	N= 84 [23%]	N=142 [40%]
Withdrawn	81 (22.5%)	42 (31.3%)	39 (17.2%)	19 (22.6%)	20 (14%)
Completed	279 (77.3%)	92 (68.7%)	187 (82.8%)	65 (77.4%).	122 (86%)

Table 10. Treatment Assignment By study Group

	Placebo n = 87	**Advair 88/42 n = 92**	**Salmeterol 42 n = 92**	**FP 88 n = 89**
Group 1 (ICS)	29 (33%)	33 (36%)	38 (41%)	34 (38%)
Group 2 (Beta-agonists [Total])	58 (67%)	59 (64%)	54 (59%)	55 (62%)
Group 2 : Short-acting Beta-agonists	41 (47%)	37 (40%)	32 (35%)	32 (36%)
Group 2: Salmeterol	17 (20%)	22 (24%)	22 (24%)	23 (26%)

A total of 279 subjects [77.5%] completed the double-blind treatment period and 81 subjects [22.5%] were withdrawn early. The percentage of randomized subjects who completed the study was higher for subjects who were on baseline $beta_2$-agonists [51.8%] than for those on baseline inhaled corticosteroids [25.5%].

Table 11. Reasons for Withdrawal

	Placebo (n=87)	Advair 42/88 (n= 92)	Salmeterol (n= 92)	FP (n = 89)	Total n= 360
Number (%) completed	56 (64%)	85 (92%)	63 (68%)	75 (84%)	279 (77.5%)
Number (%) Withdrawn	31 (36%)	7 (8%)	29 (32%)	14 (16%)	81 (22.5%)
Reason for withdrawal					
Lack of Efficacy [worsening asthma]	25 (29%)	2 (2%)	23 (25%)	7 (8%)	57 [16%]
Protocol Violation	0	0	2 (2%)	2 (2%)	4 [<1%]
Consent withdrawn	2 (2%)	1 (1%)	0	1 (1%)	4 [<1%]
Adverse event	1 (1%)	0	2 (2%)	1 (1%)	4 [<1%]
Failed to return	0	1 (1%)	0	0	1 [<1%]
Other	3 (3%)	3 (3%)	2 (2%)	3 (3%)	11 [3%]

A total of 81 randomized subjects (22.5%) withdrew from the study. Of these 81 subjects 57 (70%) withdrew because of lack of efficacy [worsening asthma]. Most of the withdrawals due to worsening asthma were in the placebo and salmeterol group. This will be discussed further in the efficacy results since it relates to one of the primary efficacy endpoints.

Compliance
Compliance was assessed as described for study SAS30001. Compliance with study medication was high with mean compliance rates of 97% to 98% across treatment groups.

Table 12. Characteristics of the Intent-to Treat population

	Placebo N = 87	Advair 44/88 (n = 92)	Salmeterol (n=92)	FP 88 (n=89)
Median age (yrs)	32 yrs	33 yrs	32 yrs	34 yrs
No. subjects (%) in age range				
12-17 yrs	14 [16%]	11 [12%]	15 [16%]	17 [19%]
16-64 yrs	70 [80%]	81 [88%]	74 [80%]	67 [75%]
> 65 yrs	3 [4%]	0	3 [3%]	5 [6%]
Gender				
Female	46 [53%]	57[62%]	46 [50%]	52 [58%]
Male	41 [47%]	35 [38%]	46 [50%]	37 [42%]
Race				
Caucasian/White	73 [84%]	67[73%]	74 [80%]	74 [83%]
Black	7 [8%]	17[18%]	11 [12%]	9 [10%]
Hispanic	2 [2%]	6 [7%]	7 [8%]	2 [2%]
Asian & other	5 [6%]	2 [2%]	0	4 [5%]
Asthma history >15 yrs	49 [56%]	50 [54%]	47 [50%]	39 [44%]

≥10 ≤15 yrs ≥5 ≤10 yrs <5 yrs	18 [21%] 14 [16%] 6 [7%]	16 [17%] 17 [19%] 9 [10%]	19 [21%] 17 [19%] 9 [10%]	23 [26%] 17 [19%] 10 [11%]
Mean FEV_1 L (% predicted) Baseline (Visit 2)	2.27 L (66.74%)	2.29L (68.13%)	2.33L (67.79%)	2.20 (67.05%)
% reversibility	35%	32%	30.73%	29.22%
Smoking History Former smoker Non-smoker	 14 [16%] 73 [84%]	 21[23%] 71 [77%]	 19 [21%] 73 [79%]	 18 [20%] 71 [80%]
Subjects with atopy	42 [48%]	47 [51%]	45 [49%]	45 [51%]
Baseline Asthma symptom scores (median)	12	13	12	12
Note: Percentages are rounded up to the nearest whole number				

Demographics of the Randomized Subjects

There were no significant differences in demographic and subject characteristics of subjects randomized into each treatment group. A total of 201 subjects (56%) were female and 159 (44%) were male. The majority of the subjects (288, 80%) were Caucasians, 44 (12%) were black and the remaining 28 subjects (8%) were of other races. There were 57 [16%] subjects aged 12 to 17 years of age, and 11 [3%] subjects over age 65. Two hundred and ninety-two [81%] of the randomized subjects were between the age of 18 – 64 years. There were no current smokers in the study and most of the subjects (288 [80%]) were non-smokers.

Asthma Characteristics of the Randomized Subjects

One hundred and eighty five [51%] subjects had asthma for over 15 years and only 2 subjects had asthma for less than one year. The other 173 subjects had asthma for 1 to 15 years duration. The 7-day asthma symptom score at entry was similar across treatment groups with a mean symptom score of 12 –13. The FEV_1 at screening (Visit 1) and at Baseline (Visit 2) was similar across treatment groups and there was no significant difference in FEV_1 measured at Screening and FEV_1 measured at baseline. FEV_1 at baseline was 2.27L [66.74% predicted] in the placebo group, 2.29 L [68.13% predicted] in the Advair group, 2.33L [67.79% predicted] in the salmeterol group, and 2.20L [67.05% predicted] in the FP group.

Subjects previously taking inhaled corticosteroids [ICS] or salmeterol continued their usual dose of these medications during the placebo run-in period but discontinued them before the first dose of double-blind study drug. A total of one hundred and thirty-four subjects were taking ICS and these subjects were relatively evenly distributed among the 4 study treatment groups. Subjects on ICS were on the following treatments prior to enrollment in the study:

Fluticasone propionate MDI 176-220 mcg	41 subjects
Becomethasone diproprionate 252-336 mcg	38 subjects
Triamcinolone acetonide 600-800 mcg	35 subjects
Budesonide 400-600 mcg	10 subjects

Flunisolide 1000 mcg	9 subjects
Fluticasone propionate Rotadisk 200mcg	1patient

Of the 226 subjects on beta$_2$-agonists, 142 were receiving short acting beta$_2$-agonists while 84 were receiving salmeterol.
Theophylline was allowed during the study with no change in dose or frequency. A total of 12 subjects continued taking theophylline during the study.

Primary Efficacy Results SAS30003

The efficacy results for the intent to treat population are depicted in the table.

Table 13. Primary efficacy outcomes, ITT population (n =360)

	Placebo	Advair 42/88 mcg	Salmeterol 42 mcg	Fluticasone 88 mcg
Treatment day 1 n	**n = 87**	**n = 92**	**n=92**	**n = 89**
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 [0.10]	2.86[0.07]	2.58 [0.09]	2.55 [0.08]
Mean change from Baseline in morning pre-dose FEV_1 L	0.14 [0.05]	0.58 [a] [0.05]	0.25[0.06]	0.36 [0.05]
Mean FEV_1 AUC at Treatment day 1 L-hrs [SEM]	2.0 [0.4]	6.7 [b] [0.4]	6.1[0.5]	2.7 [0.4]
Mean FEV_1 AUC at treatment week 12 [SEM]	2.6 [0.6] [n=56]	9.0 [c] [0.6] n=85	6.5 [0.8] n=63	5.6 [0.7] 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 ($p < 0.001$)

Assessment of the FP effect in the combination product

Mean change from baseline in morning predose FEV_1 at endpoint AND probability of remaining in the study. The comparison of interest for these endpoints is Advair Vs salmeterol. The mean change from baseline in morning predose FEV_1 at endpoint, showed a significant overall treatment effect. Advair was significantly superior to placebo, salmeterol, and fluticasone [$p \leq 0.004$]. Statistical analyses at endpoint of mean percent change from baseline in morning predose FEV_1 and change from baseline in morning predose FEV_1, expressed as percent predicted FEV_1, also showed statistical superiority of Advair relative to each of the other treatments. The difference in mean effect size between Advair and salmeterol [330 cc] was slightly lower but similar [360cc] to that seen for Advair Diskus 50/100 in trial SFCA 3002 [NDA 21-077].

Probability of remaining in the Study (Survival in the Study)

The number of subjects discontinuing 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 lowest 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 had an exacerbation at the discretion of the Investigator.

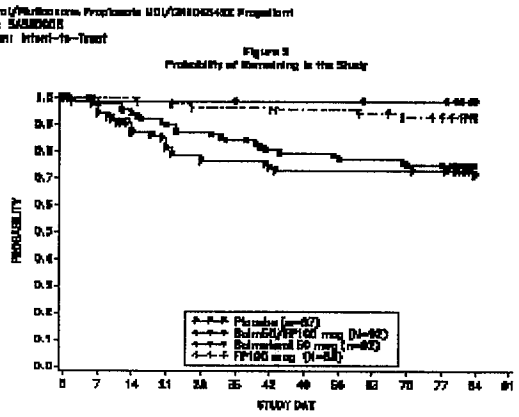
Lack of efficacy was determined by pre-defined criteria. Any subject who did not meet any of the criteria outlined below was discontinued from the study for lack of efficacy.

Stability Criteria: During the 7 days immediately preceding the clinic visit, the subject must have experienced:

- No more than 3 days in which the PEF had fallen below the PEF stability Limit calculated at Visit 2
- No more than 2 days in which ≥12 puffs/day of Ventolin ® were used.
- No more than 2 nights with awakenings due to asthma requiring treatment with Ventolin
- $FEV_1 \geq$ the FEV_1 Stability Limit calculated at Visit 2

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 weeks treatment, 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 in the figure below. The Kaplan-Meier survival estimates are based on the proportion of subjects withdrawn due to lack of efficacy.



Serial FEV_1 Measurements

Serial FEV_1 was measured at Treatment Day 1 and Week 12 at 30 minutes prior to dosing, immediately 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 all timepoints on Treatment Day one, subjects in the Advair group and the salmeterol group experienced greater increases in serial FEV_1 compared to subjects in the placebo or fluticasone groups. The improvement in FEV_1 over all time points on Treatment Day one was similar in the Advair and the salmeterol group. This is not unexpected given that the bronchodilatory effect of salmeterol would be responsible for the initial effect of Advair. At Treatment week 12, all subjects on Advair experience greater increases in serial FEV_1 at all time points than did subjects in the placebo, salmeterol and fluticasone groups. Similar results were seen for the percent predicted serial FEV_1 on Treatment Day 1 and Week 12
On Treatment Day one the weighted average FEV_1[5] was greater for the subjects in the Advair and SAL groups compared with subjects in the placebo and FP groups. At Treatment Week 12, the weighted average serial FEV_1 was greater (2.98L) for subjects in the combination product compared with subjects in the other treatment groups [2.57L placebo, 2.88L salmeterol, 2.6L fluticasone].

Assessment of the salmeterol effect in the combination product

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

For these endpoints the comparison of interest is Advair vs. FP.

On treatment Day 1, after the first dose of study drug, 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]. The mean AUC (bl) on Treatment Day 1 was 6.7 L-hrs for Advair, compared to 2.7 L-hrs for FP and 2.0 L-hrs for placebo. There was no significant difference between the AUC (bl) for subjects in the Advair group [6.7 L-hrs] and subjects in the salmeterol group [6.1 L-hrs] on Treatment Day 1. At Treatment Week 12, the AUC (bl) showed an overall treatment effect. Subjects in the Advair group had a mean AUC (bl) of 9.0 L-hrs

[5] See definition of weighted average FEV_1 outlined in SAS30001 page 69

which was significantly greater [p≤ 0.006] than placebo [2.6 L-hrs], salmeterol [6.5 L –hrs], and fluticasone [5.6 L-hrs].

Response to treatment, onset of effect and duration of effect[6]
Results were similar to what was seen in SAS30001. Over half of the subjects in the Advair [69%] and the salmeterol group [66%] achieved ≥ 15% increase in FEV_1 within the first 60 minutes on Treatment Day 1 compared to only 17% of subjects in the FP group.
The median time to onset of effect was 24 minutes for Advair and 30 minutes for salmeterol, with a median duration of effect of 11.6 hours. Up to 85% of subjects in the Advair treatment arm had a response to treatment (responders) [i.e. an increase in $FEV_1 \geq 15\%$ within the first 4 hours], compared to 41 % of subjects in the placebo group and 39% of subjects in the FP group. At Treatment Week 12 eighty-nine percent [89%] of subjects in the Advair group responded to Treatment compared to 70% in the Advair group and 60% in the FP group.

Effect of prior asthma therapy corticosteroids vs. $beta_2$-agonists
On entering the study, subjects were stratified into two groups by prior use of ICS- Group 1) or $beta_2$-agonists (Group 2- short-acting $beta_2$- agonists alone or salmeterol). The improvements seen in FEV_1 in the Advair group were achieved regardless of baseline asthma therapy.

Table 14. Relationship between Prior Asthma Therapy and Primary Efficacy Variables

Prior Asthma Treatment	**Placebo** N = 87	**Advair 88/42** N =92	**Salmeterol 42** N = 92	**FP 88** N =89
ICS	N=29	N=33	N=34	38
Withdrawals	12 (41%)	1 (3%)	14 (37%)	4 (12%)
Change from baseline in Pre-dose FEV_1 at endpoint	0.09L	0.46L	0.02L	0.21L
AUC(bl) Day 1 [L-hrs]	1.6	6.4	5.3	2.2
AUC (bl) Wk 12 [L-hrs]	2.3	7.7	3.6	3.8
Short-acting β_2-agonist	N=41	N=37	N=32	N=32
Withdrawals	5 (12%)	1 (3%)	3 (9%)	3 (9%)
Change from baseline in Pre-dose FEV_1 at endpoint	0.14L	0.66L	0.42L	0.50L
AUC(bl) Day 1 [L-hrs]	1.9	6.9	6.2	3.6
AUC (bl) Wk 12 [L-hrs]	2.5	9.7	7.5	7.3
Salmeterol	N=17	N=22	N=22	N=23
Withdrawals	7 (41%)	0	6 (26%)	0
Change from baseline in Pre-dose FEV_1 at endpoint	0.21L	0.61L	0.40L	0.37L
AUC(bl) Day 1 [L-hrs]	3.2	6.9	7.1	2.3
AUC (bl) Wk 12 [L-hrs]	3.4	9.6	9.2	5.5
N = n at randomization. Endpoint n is not displayed in the table				

[6] Same definitions and assessments methods as in SAS30001

Secondary Efficacy Results

The mean morning and evening PEF values for subjects randomized into the study was similar across treatment groups and ranged from 369 to 382 L/min. At endpoint, there was no change in the placebo group in the morning or evening PEF measurements. However, there was an improvement in all the treatment groups which was greater in the combination product group compared to the salmeterol and fluticasone groups as measured by change from baseline in percent predicted PEF, mean % change, and change from Baseline in % predicted These results are depicted in the table below. The data are obtained from the sponsor's supporting tables 41 through 50. The increase in AM and PEF at endpoint (L/min) in the Advair group is ≥ two-fold compared to the increase in the salmeterol and the FP group.

Table 15. AM and PM PEF Results SAS30003

	Placebo (n = 87)		Advair 88/42 (n= 92)		SAL (n=92)		FP 88 (n=89)	
	AM PEF	PM PEF	AM PEF	PM PEF	AM PEF	PM PEF	AM PEF	PM PEF
Baseline Mean (L/min) [%predicted]	382.3 [82.1]	407[87.6]	376.7 [81.2]	397.3 [85.6]	381.4 [80.8]	402 [85.1]	369.2 [80.8]	387.1 [84.8]
Endpoint Analyses								
Mean (L/min) [% predicted]	383.3 [82.1]	410.1 [89.1]	434.5 [93.5]	444.9 [95.9]	406.6 [86]	418.0 [88.3]	396.8 [86.9]	407.6 [89.4]
Mean change	1	3.2	58	47.6	25.2	15.9	27.6	20
Mean % change	0.7	1.4	16.6	13.1	7.4	4.5	8.0	5.8
Change form Baseline in % predicted PEF	0	0.5	12.3	10.3	5.2	3.3	6.1	4.4

Ventolin® Use

At Baseline, total Ventolin® use ranged from 2.4 to 3.1 puffs/24hr periods across treatment groups. In all analyses, subjects in the Advair [88/42] group had a greater reduction in Ventolin® use compared with subjects in the SAL and fluticasone group. There was no reduction in Ventolin® use in the placebo group. At Baseline the mean Ventolin® use (puffs/24hr) in the Advair group was 3.1 puffs which decreased to 1.0 puff at endpoint, Whereas, the baseline mean Ventolin® use in the placebo group of 2.7 puffs/24 hr, was slightly increased to 2.9 puffs/24 hrs at endpoint. There were small decreases in Ventolin® use in the Salmeterol and fluticasone group from 2.7 puffs to 1.9 puffs and from 2.4 puffs to 2.0 puffs respectively at endpoint. The percentage of days with no Ventolin® use increased to 42.1% in the Advair group, and 21.1% and 13.5% in the salmeterol and FP groups respectively compared to a 3.2% increase in number of days with no Ventolin® use in the placebo group. At the end of the study, all subjects in the treatment groups were using Ventolin® less frequently than at baseline.

Nighttime Awakenings

Subjects could not have had more than 3 nighttime awakenings requiring treatment with Ventolin® during the 7 days prior to randomization in order to

qualify for randomization. Additionally, during follow up visits, subjects were discontinued for worsening asthma if they had more than 2 nights with awakenings due to asthma during the 7 days prior to the visit. Of note is that ≥ 47% of subjects across treatment groups had no nighttime awakenings at baseline and were not used in the analysis to calculate the percentage change from baseline at endpoint in nighttime awakenings? In addition, the mean number of nighttime awakenings was low for all subjects in the treatment groups averaging 0.10 to 0.15 [equivalent to 1 night awakening every 9.1 to 6.7 days]. Consequently, The reduction in nighttime awakenings in the Advair group to 0.02 is so small that it lacks clinical significance.

Asthma Symptom Scores

Similarly, daily asthma symptom scores were very low in the study population. The mean daily score ranged from 1.6 to 1.8 at Baseline. The decrease in the mean asthma score from 1.8 to 0.8 in the Advair group is so small that the clinical significance is questionable.

Asthma Quality of Life Questionnaire (AQLQ)

The sponsor selected a change of ≥0.5 a *priori* as clinically meaningful. The results of the reduced intent to treat population (AQLQ Overall score at baseline of≤ 5.8) are displayed below as these were the focus of the sponsor's primary analyses defined *a priori*. The data are obtained from the sponsor's data table #70.

As shown in table 16 a clinically meaningful change of >0.5 was seen in the Overall score and in all domains in the Advair treatment group compared to placebo. A change of > 0.5 was also seen in the Advair group compared to placebo when the entire ITT population [baseline Overall Score > 5.8 and baseline Overall Score > 5.8] was analyzed.

Table 16. Within Treatment Group Changes in Mean AQLQ Scores From Baseline at Endpoint (Overall Baseline AQLQ ≤ 5.8) SAS30003

[Data compiled from data table 70 SAS30003.pdf]

	Placebo *N=87			Advair 42/88 N=92			Salmeterol N=92			FP 88 N=89		
	n	Mean (se)	Change (se)	n	Mean (se)	Change (se)	n	mean (se)	Change (se)	n	mean (se)	Change (se)
Overall AQLQ Score												
Baseline	73	4.67 (0.09)		82	4.35 (0.09)		75	4.56 (0.09)		74	4.53 (0.09)	
Endpoint	69	4.99 (0.13)	-0.32 (0.11)	80	5.81 (0.12)	1.45 (0.11)	71	5.23 (0.13)	0.63 (0.13)	71	5.51 (0.12)	0.97 (0.12)
Activity Limitation												
Baseline	72	4.79 (0.10)		82	4.48 (0.11)		75	4.69 (0.10		73	4.64 (0.10)	
Endpoint	68	5.21 (0.14)	0.42 (0.11)	79	5.92 (0.12)	1.43 (0.12)	71	5.39 (0.12)	0.65 (0.13)	71	5.63 (0.11)	0.97 (0.12)
Asthma symptoms												
Baseline	73	4.59 (0.09)		82	4.34 (0.08)		75	4.52 (0.10)		74	4.53 (0.09)	
Endpoint	69	4.88 (0.14)	0.29 (0.13)	80	5.88 (0.11)	1.55 (0.11)	71	5.16 (0.14)	0.62 (0.14)	71	5.52 (0.13)	0.99 (0.14)
Emotional function												
Baseline	73	4.57 (0.13)		82	4.18 (0.12)		75	4.49 (0.16)		74	4.33 (0.14)	
Endpoint	69	4.85 (0.17)	0.28 (0.15)	80	5.75 (0.14)	1.57 (0.16)	71	5.02 (0.18)	0.53 (0.17)	71	5.32 (0.14)	0.97 (0.15)
Environmental exposure												
Baseline	73	4.67 (0.13)		82	4.26 (0.13)		75	4.44 (0.13)		74	4.33 (0.14)	
Endpoint	69	4.93 (0.14)	0.24 (0.13)	80	5.44 (0.16)	1.18 (0.13)	71	5.24 (0.15)	0.76 (0.16)	71	5.32 (0.14)	0.97(0.15)

* Denotes number of randomized subjects.

Efficacy Conclusions

- The findings in study SAS30003 support the conclusion that treatment with Advair 44/21 two puffs bid was significantly better than its individual components at the same nominal dose and placebo.

- Similar to study SAS30001, the median time to onset of effect was 24 minutes for Advair with a median duration of effect of 11.6 hours at Treatment Day 1 and a median duration of 12 hours.

- Both AM and PM peak flow results were consistent with the improvements in FEV_1 measurements.

- In the AQLQ a clinically meaningful change was seen in the Overall Score and each of the individual domains for Advair 44/21 and each of its individual components. Numerically, the change with Advair HFA was greater; however, the clinical significance of this is unknown.

APPENDIX 1.C. STUDY SAS 30004

"A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group 12-Week Trial Evaluating the Safety And Efficacy Of Salmeterol/Fluticasone Propionate Combination in GR106642X MDI, 42/220 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".

STUDY OBJECTIVES
To demonstrate efficacy and c safety of the fluticasone propionate/salmeterol GR106642X inhalation aerosol 110/21 mcg two puffs BID compared with the individual components (via the propellant 11/12 pressurized MDI) and placebo/GR106642X MDI in subjects whose asthma is inadequately controlled with inhaled corticosteroids.

Study Dates: December 05, 1998- March 14, 2000

Amendments: The original protocol dated June 09, 1998 was amended three times. All three amendments were identical to the amendments made for protocol SAS30003.

Study design: The study was designed in a similar manner to study SAS30003 with a run-in period followed by a 12-week treatment period. However, there was no stratification because all subjects had to be using inhaled corticosteroids for at least 3 months prior to screening (Visit 1). Subjects continued on their previous dose of inhaled corticosteroids during the run-in period. At randomization (visit 2), inhaled corticosteroids were discontinued and subjects were randomized to on of the following treatment arms:
Advair ™ HFA 110/21 two puffs BID
Salmeterol (CFC) 42mcg BID
Fluticasone propionate (CFC) 220 mcg BID
Placebo HFA 2 puffs BID

Study Population
The study was conducted in 35 centers in order to complete 320 evaluable subjects with 80 subjects per treatment arm.

Inclusion and Exclusion Criteria
These criteria were similar as for protocol SAS30001 and SAS30003. Subjects must have been taking one of the following ICS at least one month before Visit 1

- Beclomethasone diproprionate (ex-actuator dose) 378-840mcg/day
- Triamcinolone acetonide 900-1600mcg/day

- Flunisolide 1250-2000mcg/day
- Fluticasone propionate MDI (ex-actuator dose) 440-660mcg/day
- Fluticasone propionate **Rotadisk** 400-600mcg/day
- Budesonide 800-1200mcg/day

Similar to protocol SAS30003, subjects previously taking theophylline preparations could continue on those medications as long as there was no change in dosage. In order to be eligible for randomization the subject must demonstrate relative asthma stability based on randomization criteria described for study SAS30001 and the following additional diary card criteria:

1. During the 7 days prior to Visit2 the subject must have no more than 3 days with more than 12 puffs/day of Ventolin®.
2. During the 7 days prior to Visit2 the subject must have no more than 3 nights with awakenings due to asthma requiring treatment with Ventolin®.

FEV_1 and PEF Stability and discontinuation criteria were calculated and applied as described for SAS30001.

The Statistical and Analytical Plan is the same as for study SAS30003.

The safety assessment was similar to study SAS30001 and SAS30003 with the addition of 24-hour Holter monitoring and 24-hour Urinary free cortisol and the short ACTH-stimulated plasma cortisol concentrations at selected sites.

RESULTS SAS 30004

Patient Population

A total of 755 subjects were screened. Of subjects screened, 365 were randomized after the run in period. The majority of the patients who failed eligibility for randomization did so because they were unable to meet the FEV1 or the reversibility criteria. Of the 365 randomized patients [ITT population], 243[67%] completed the study. The table below shows the disposition of the ITT population.

Table 17. Patient Disposition SAS30004

	Placebo (n = 89)	Advair 220/42 (n=94)	Salmeterol 42 (n = 91)	Fluticasone 220 (n = 91)	Total (n = 365)
# (%) Complete	34 (38%)	81 (86%)	57 (63%)	71 (78%)	243 (67%)
# (%) Withdrawn	55 (62%)	13 (14%)	34 (34%)	20 (22%)	122 (33%)
Reason for Withdrawal					
Lack of Efficacy (worsening asthma)	48 (54%)	7 (7%)	23 (25%)	11 (12%)	89 (24%)
Adverse Event	2 (2%)	1 (1%)	4 (4%)	2 (2%)	9 (2.5%)
Protocol violation	3 (3%)	3 (3%)	2 (2%)	2 (2%)	10 (2.7%)
Consent withdrawn	0	1 (1%)	0	1 (1%)	2 (0.5%)
Lost to follow up	0	0	0	1 (1%)	1 (0.27%)
Non-compliance	0	0	1 (1%)	0	1 (0.27%)
Other	2 (2%)	1 (1%)	4 (4%)	3 (3%)	10 (2.7%)

The placebo group experienced the greatest number of discontinuations, followed by salmeterol, fluticasone and Advair in that order. These differences will be discussed further in the efficacy results since they constitute one of the primary endpoints of this trial. Few patients discontinued due to adverse events. Withdrawals due to worsening asthma were categorized as clinical exacerbation if the subject required emergency intervention, hospitalization due to asthma, treatment with excluded asthma medications, or at the discretion of the investigator. Worsening asthma was also defined by FEV_1 and PEF stability limits, Ventolin® use and nighttime awakenings.

Demographics and Baseline asthma characteristics

Overall, 40 percent [145] of the ITT patients were male. Eighty four percent of patients [305] were Caucasian, 11 percent [42] were Black, 1% [4] Asian 3 % [11] were Hispanic and1% were of another race. Patient ages ranged from 12 to 82 years, with approximately % [32] of subjects under the age of 18 and 5 % [20] over the age of 65. Most patients had no history of tobacco use (74 %) 56 % had a history of atopy. Fifty nine percent of patients [214] had asthma for at least 15 years. Mean FEV_1 at screening ranged from 2.17L to 2.23L representing a mean baseline percent predicted FEV_1 of 67% to 69%. All treatment groups were responsive to Ventolin® at screening with a mean percent reversibility 30 minutes following Ventolin® treatment ranging from 27% to 30%. Demographic factors and asthma parameters were relatively comparable among treatment groups.

Compliance

Compliance was assessed from diary data. Every day each subject recorded in the diary every morning and evening whether or not the dose of study medication was taken. Overall compliance was high; mean compliance rates ranged form 95% to 98% across treatment groups. Non-compliance was not a reason for withdrawal in any subject.

Primary Efficacy Results SAS 30004

The efficacy results for the intent to treat population are depicted in table 18.

Table 18. Primary Efficacy Results SAS30004

	Placebo	**Advair 220/42**	**Salmeterol 42**	**Fluticasone 220**
Treatment day 1 n	**n = 89**	**n = 94**	**n=91**	**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 FEV_1 AUC at Treatment day 1 L-hrs	0.6	5.4 b	6.1	2.1
Mean FEV_1 AUC 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 ($p \leq 0.001$)

In the Mean FEV_1 AUC at Treatment Day 1 both Advair and salmeterol were statistically superior to placebo and fluticasone. There was no significant difference between Advair and salmeterol in the mean serial FEV_1 at Treatment Day 1. However, at Treatment Week 12 Advair had significantly ($p=0.020$) greater mean AUC relative to baseline compared to the salmeterol group. At treatment week 12, mean serial FEV1 AUC relative to day 1 Baseline showed a significant overall treatment effect.

Secondary Efficacy Results

AM and PM PEF results support the primary efficacy endpoint results. Subjects in the Advair HFA 220/42 treatment group had numerically greater improvements in both AM and PM PEF compared with subjects in the salmeterol and FP treatment group. Subjects in the placebo group showed a worsening of their AM and PM PEF results at endpoint compared to baseline.

Table 19. AM and PM PEF Analyses SAS30004

	Placebo (n = 87)		Advair 220/42 (n= 92)		SAL 42 (n=92)		FP 220 (n=89)	
	AM PEF	PM PEF	AM PEF	PM PEF	AM PEF	PM PEF	AM PEF	PM PEF
Baseline Mean (L/min) [%predicted]	347 [75.8]	372 [81]	343 [74.2]	369 [80]	344 [75.3]	367 [80]	344 [76.1]	368 [82]
Endpoint Analyses								
Mean (L/min) [% predicted]	332 [72.6]	357 [78.1]	393 [85.2]	406 [87.9]	357 [78.2]	371 [81.4]	358 [79.7]	377 [83.6]
Mean change	-15.5	-14.3	49.6	36.1	13.2	5.4	13.9	9.0
Mean % change	-3.5	-3.7	16.5	11.2	4.4	2.4	4.7	2.6
Change form Baseline in % predicted PEF	-4.2	-3.2	11.1	8.1	2.8	2.4	3.0	1.8

Similar to what was noted in SAS30001 and SAS30003, patients were generally not very symptomatic on entering the study. There were small numerical changes in the secondary endpoints Ventolin ® use, daily asthma symptom score, and nighttime awakenings. For example a large percentage of subjects had no nighttime awakenings at baseline. The mean number of nighttime awakenings

ranged form 0.09 to 0.15 equivalent to one night awakening every 7 to 11 days. At endpoint the mean number of nighttime awakenings due to asthma symptoms showed a numerical decreased by 0.04 in the Advair group (i.e. one nighttime awakening every 25 days) compared to an increase in the placebo, salmeterol, and fluticasone groups equivalent to one awakening every 3, 5 and 10 nights respectively. All active treatment groups had a numerical decrease in Ventolin use (puffs/24 hr) and daily asthma symptom score at endpoint.

Asthma Quality of Life Questionnaire
Similar to study SAS30003, a reduced ITT population with an overall baseline score of $p \leq 5.8$ was the primary focus for this secondary endpoint and. the sponsor defined a clinically meaningful change as a difference of ≥ 0.5 between treatments. The results for the reduced ITT population are displayed below in table ----. There was a clinically meaningful change in the Advair treatment group compared to placebo in both the Overall Score and in each individual domain. A change of > 0.5 was also seen in the Advair group compared to placebo when the entire ITT was analyzed.

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APPEARS THIS WAY
ON ORIGINAL

Table 20. Within Treatment Group Changes in Mean AQLQ Scores From Baseline at Endpoint (Overall Baseline AQLQ ≤ 5.8) SAS3004

[Data compiled from data table 70 SAS30004.pdf]

	Placebo			Advair 220/42			Salmeterol 42			FP 220		
	n	Mean (se)	Change (se)	n	Mean (se)	Change (se)	n	mean (se)	Change (se)	n	mean (se)	Change (se)
Overall AQLQ Score												
Baseline	71	4.51 (0.10)		78	4.65 (0.10)		74	4.54 (0.09)		75	4.81 (0.09)	
Endpoint	69	4.42 (0.13)	-0.09 (0.11)	77	5.68 (0.10)	1.01 (0.12)	72	5.00 (0.14)	0.44 (0.14)	73	5.32 (0.13)	0.50 (0.10)
Activity Limitation												
Baseline	71	4.51 (0.11)		78	4.73 (0.11)		74	4.61 (0.09)		74	4.79 (0.11)	
Endpoint	69	4.54 (0.13)	0.03 (0.11)	76	5.73 (0.12)	0.94 (0.11)	71	5.11 (0.14)	0.50 (0.13)	72	5.33 (0.14)	0.54 (0.11)
Asthma symptoms												
Baseline	71	4.67 (0.10)		78	4.66 (0.10)		74	4.53 (0.09)		75	4.84 (0.09)	
Endpoint	69	4.42 (0.14)	-0.25 (0.13)	77	5.75 (0.10)	1.06 (0.13)	72	5.00 (0.16)	0.45 (0.16)	73	5.34 (0.12)	0.50 (0.12)
Emotional function												
Baseline	71	4.20 (0.16)		78	4.51 (0.14)		74	4.58 (0.16)		75	4.80 (0.14)	
Endpoint	69	4.08 (0.19)	-0.12	77	5.60 (0.14)	1.06 (0.14)	72	4.89 (0.18)	0.31 (0.18)	73	5.29 (0.16)	0.49 (0.15)
Environmental exposure												
Baseline	71	4.40 (0.15)		78	4.54 (0.15)		74	4.58 0.16		75	4.84 (0.12)	
Endpoint	69	4.49 (0.17)	0.12 (0.13)	77	5.37 (0.15)	0.82 (0.17)	72	4.93 (0.15)	0.55 (0.13)	73	5.19 (0.17)	0.35 (0.12)

As shown in the table subjects in the Advair HFA group had a clinically meaningful change in the overall AQLQ score as well as in each domain. The results were similar when the entire ITT population was analyzed. In the FP group there was a clinically meaningful change in the Overall Score, and in the Activity Limitation and Asthma Symptoms domains for the population with an Overall baseline score of ≤ 5.8. There was no meaningful change in the Overall score or individual domains for the overall ITT population in the FP group. Subjects in the salmeterol group did not show a clinically meaningful change in the overall score but did so in the Activity Limitation and the Environmental Exposure domains in the population with a baseline score of ≤ 5.8 and only showed a clinically meaningful change in the Environmental Exposure domain for the entire ITT population.

Efficacy Conclusion

Efficacy findings of study SAS30004 satisfy the regulatory requirements of the combination policy and support the conclusion that Advair 110/21 administered as two puffs bid is more efficacious than its individual components at the same nominal dose and placebo.

APPENDIX 1.D STUDY SFCB 3023

"A multicentre, randomized, double-blind, double-dummy, parallel-group, three-month comparison of the fluticasone propionate/ salmeterol combination product 220/21 mcg strength [Advair HFA 220/21] 2 puffs bid *via* the pressurized metered dose inhaler with the fluticasone propionate/salmeterol combination product 500/50 mcg strength *via* the Diskus/Accuhaler™ [Advair Diskus 500/50] 1 puff bid and with fluticasone propionate 220mcg strength [FP 220 MDI] 2 puffs bid *via* the pressurized metered dose inhaler in adolescents and adults with reversible airways obstruction".

Overview
This active control study is also considered pivotal by the sponsor and it was designed to show the comparability of Advair™ HFA 220/21 two puffs bid to Advair Diskus 500/50 mcg 1 puff bid and to demonstrate the efficacy of Advair HFA 220/21 2 puffs bid compared to FP [CFC MDI] 220 mcg 2 puffs Bid. 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. The primary efficacy measure for this study was the change from baseline in mean morning PEFR averaged over Treatment Weeks 1-12. Treatment groups were defined by the sponsor to be equivalent if the 95% confidence intervals for the treatment difference fell with ±15L/min.

Study dates: December 02, 1997 –March 25, 1999

Patient Population
Males and females 12 years of age and older who had a documented clinical history of reversible airways obstruction, who had received beclomethasone diproprionate, budesonide or flunisolide at a dose of 1500-2000µg/day or fluticasone propionate at a dose of 750-1000 mcg/day for at least four weeks prior to Visit 1, and who had given written informed consent to participate in the study. During the last seven days of the run-in period, subjects were required to have had a mean morning PEFR of > 50% and < 85% of their PEFR measured 15 minutes after administration of 400µg of Ventolin® at randomization (Visit 2), and a cumulative total recorded symptom score (daytime plus nighttime) ≥8. [*See "Study Procedure" below for scale*] In order to enter the treatment period, subjects were required to have an FEV_1 of >50% and <100% of their predicted normal. Other inclusion and exclusion criteria were similar to those of the previously described protocols. 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.

There were no pre-specified stability criteria as was established for SAS30003 and SAS30004.

Concurrent asthma medication
Excluded medications were the same as described for study SAS30003. All regular therapy for asthma (i.e. not prn) such as anticholinergics, theophylline, and sodium cromoglycate could be continued provided that the dose remained constant throughout the study.

Study Procedure
Patients eligible for the run-in continued their pre-study doses of inhaled corticosteroids and used Ventolin® MDI as a rescue medication. During 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 awakening, prior to 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:
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, 8 and 12.

Statistical and Analytical plan
Statistical comparability was assessed using the data from the time interval Treatment Weeks 1-12. Both the ITT and the per-protocol population were used for confirmation of comparability. The per-protocol population (efficacy population) consisted of those subjects in the ITT population with no major protocol violation. Major violations were defined as violations that the sponsor considered as affecting the validity of the lung function efficacy measurements such as:

- Age <12 years
- No documented clinical history of reversible airways obstruction
- No treatment with beclomethasone diproprionate, budesonide or flunisolide at a dose of 1500-2000mcg/day or fluticasone propionate at a dose of 750-1000mcg /day for at least four weeks prior to Visit 1.
- Not meeting pre-defined PEFR criteria
- Not meeting asthma symptom score criteria
- Inability to use a mini-Wright peak flow meter and complete a DRC correctly
- Inability to use the *Diskus* inhaler and the pressurized MDI correctly

Primary Endpoints

There was a single primary efficacy measure for this study - mean morning PEFR over Treatment Weeks 1-12. Two analyses were performed:

- The comparison of Advair HFA versus Advair *Diskus.* For this comparison, the null hypothesis was that of a treatment difference of ± 15L/min in morning PEFR. These treatments would be statistically comparable if the 95% confidence interval for the treatment difference fell within the prespecified limit of ±15L/min.

- The comparison of Advair HFA 220/21 two puffs bid to FP MDI 220 2 puffs bid. The aim here was to demonstrate superiority of Advair HFA versus fluticasone propionate alone. 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%.

There was only one primary efficacy measure in this study, mean AM PEFR over Treatment Weeks 1-12, and two analyses, comparison of Advair HFA with Advair Diskus for "equivalence" and comparison of Advair HFA with FP MDI for superiority. Because the study was designed and powered as an equivalency study, and there was a single comparison for "equivalence" and all other efficacy measures were defined as secondary, no adjustments for multiple endpoints were made.

Sample Size

Previous studies had shown a standard deviation of 35L/min for this type of study. Using a confidence level of 95% is equivalent to testing two one sided hypotheses, achieving an overall significance level of $\alpha = 0.025$. 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.

Clusters

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 "*Volumetric* spacer use" and "type of previous inhaled corticosteroids" (FP/Other). An interaction would have only been considered meaningful if consistent for both populations.

The **secondary efficacy measures** were evening PEFR, and daytime and nighttime asthma symptom scores. No adjustments for multiple comparisons were made.

Safety was assessed by morning serum cortisol and creatinine-corrected 24-hour urinary cortisol (at a subset of centers), clinical laboratory tests, vital signs, 12 lead ECGs, oropharyngeal exams, Physical exams and adverse events monitoring.

RESULTS SFCB3023

Patient Disposition/Demographics

There were 691 subjects recruited to the study of which 510 were randomized and 509 actually received treatment. One subject, number 4965, was identified as having been randomized to treatment number 419 (fluticasone propionate MDI), but did not take any treatment medication, so was not included in the Intent-to-Treat Population. The table below summarizes the ITT patient disposition.

Table 21. Patient Disposition ITT population SFCB3023

	Advair HFA 440/42 n = 176	Advair Diskus 500/50 n = 161	FP 500 n = 172	Total 509
# (%) Complete				
# (%) Withdrawn	21	19	22	62
Reason for Withdrawal				
Lack of Efficacy (worsening asthma)	1			1
Adverse Event	11	9	14	34
Consent withdrawn	2	1	0	3
Protocol violation	6	3	6	15
Non-compliance	0	3	1	4
Other		1		1
Lost to follow up	1	1	1	3
Entry criteria not fulfilled		1		1

The per-protocol population was comprised of 420 patients. Of these, 144 received Advair HFA, 132 received Advair Diskus, and 144 received FP MDI.

Baseline Characteristics of the ITT population

The mean age of the study population was 47 years. In total 59% of the subjects were female and the majority were Caucasian. Thirty nine percent of subjects had reversible obstructive airway disease for 15 years or more in total, 58% of subjects had a positive history of atopy (55% in the MDI combination group, and 59% in each of the other groups). Approximately 20% of subjects were using a spacer device on entry to the study and they continued to do so throughout the study. The baseline characteristics of the per-protocol population were

comparable to the ITT population. Only 8% of subjects were current smokers with a mean smoking history of 6.26 pack years. The three treatment groups were comparable for all these characteristics. The mean FEV_1 at Visit 1(run-in) was 2.18L in the MDI combination group, 2.26L in the Advair Diskus group, and 2.30L in the FP group. The mean percent predicted FEV_1 was 70 –75% in all treatment groups. Mean reversibility at Visit 2 (randomization) was 18.4% in the Advair HFA group, 17.3% in the Advair Diskus group and 17.9% in the FP MDI group.

Table 22. Characteristics of the Intent-to Treat Population

	Advair HFA 440/42 n=176	**Advair Diskus 500/50 n=161**	**FP 500 n=172**
Age (median) Age 12-17 Age 18-64 Age > 65	49 yrs 4 [2%] 151 [86%] 21 [12%]	49 yrs 3 [2%] 139 [86%] 19 [12%]	46.3 yrs 6 [3%] 144 [84%] 22 [13%]
Gender • Female • Male	 106 [60%] 70 [40%]	 96 [60%] 65 [40%]	 100 [58%] 72 [42%]
Race • Caucasian/White • Black • Asian • Other	 163 [93%] 0 12[7%] <1%	 148[92%] 3 [2%] 9 [6%] <1%	 160 [93%] 2 [1%] 10 [6%] 0
Asthma* history • >15 yrs • ≥10 ≤15 yrs • ≥5 ≤10 yrs	 53 [37%] 19 [13%] 38 [26%]	 54 [41%] 13 [10%] 25 [19%]	 57 [40%] 30[21%] 26 [18%]
Mean FEV_1 L (% predicted) Baseline (Visit 2)	2.11 L (70.9%)	2.23 L (73.61%)	2.23L (72.48%)
% reversibility	18.43 %	17.30 %	17.90 %
Mean PEF at Baseline	327 L	341 L	345 L
Current smoker Former smoker Non-smoker	15 [9%] 50 [28%] 111 [63%]	12[7%] 54 [33%] 95 [60%]	12[7%] 43 [27%] 117 [66%]
Subjects with atopy	82 [57%]	72 [55%]	85 [59%]
Asthma symptom scores (median)			
Using spacers	29 [20%]	22 [17%]	25 [17%]
Concurrent asthma medications • Any medication • Xanthines	 42 [24%] 19 [11%]	 41 [25%] 18 [11%]	 37 [22%] 27 [13%]

Primary Efficacy Results

Although the sponsor defined and ITT and an efficacy population, this review focuses only on the ITT. The table summarizes the mean morning PEFR for the ITT population. 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 23. Efficacy Results SFCB3023

Morning PEFR	Advair HFA 440/42	Advair Diskus 500/50	FP 500
Baseline n	N= 176	N=161	N=72
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 –2L/min. The 95% confidence interval was –11 to 7 L/min. This interval falls inside the prespecified limits of ± 15L/min for comparability 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 clinical comparability.

The primary assessment period for the statistical analysis was week 1-12; however, results are also presented for Weeks 1, 2, 3, 4, 1-4, 5-8 and 9-12. For all treatment periods except period 9-12 the 95% confidence interval for the treatment difference of the Advair Diskus and the Advair HFA combination lie completely inside the limits of ±15L/min. For the period Weeks 9-12 the 95% confidence interval was –16 to 5 L/min.

Table 24. PEFR Over Weeks 1 through 12

	Advair 440/42 HFA	Advair Diskus 500/50
Week 1		
Number of subjects	173	159
Adjusted mean change from baseline (L/min) [se]	50 [3.2]	48 [3.4]
Treatment difference [se]		-2 [4.6]
95% CI		-11, 7
Week 4		
Number of subjects	167	153
Adjusted mean change from baseline (L/min) [se]	47 [3.6]	48 [3.8]
Treatment difference [se]		1
95% CI		-9, 11
Weeks 1-4		
Number of subjects	173	159
Adjusted mean change (L/min) [se]	46 [3.0]	44 [3.1]
Adjusted mean change (L/min)[se]		-2
95% CI		-10, 7
Weeks 5-8		

Number of subjects	165	151
Adjusted mean change (L/min) [se]	51 [3.6]	51 [3.8]
Adjusted mean change (L/min) [se]		0
95% CI		-10, 11
Week 9-12		
Number of subjects	159	147
Adjusted mean change (L/min) [se]	57 [3.8]	51 [4.0]
95% CI		-5
		-16, 5

For the comparison of Advair HFA 220/21 2puffs bid to FP 220 mcg 2 puffs bid, the adjusted mean change for the FP MDI over Weeks 1-12 was 27 L/min. The Advair HFA MDI had a statistically significant greater improvement in PEFR than FP 50 L/min [$p < 0.001$]. The adjusted treatment difference FP – MDI combination was –23 L/min with 95% CI of –32, -14.

Secondary Analyses

The secondary assessment evening PEFR supports the primary efficacy assessment. The adjusted treatment difference [Advair Diskus – Advair HFA] for the mean evening PEFR is -1 with a 95% confidence interval of -3 to 1.

Efficacy Conclusions

Advair HFA 220/21 administered as two puffs bid has comparable efficacy to Advair Diskus 500/50 administered as 1 puff bid and is superior to FP 220 two puffs bid. Although this study was not designed to satisfy the requirements of the combination policy, given the weight of evidence demonstrated for Advair 44/21 and Advair 110/21 and the superior efficacy of Advair 220/21 compared to FP220 alone which is an approved product that has demonstrated superiority over placebo it is reasonable to conclude that Advair HFA 220/21 would also fulfill the regulatory requirements for the combination product.

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