Unlike Trial SLGA3002, local reactions such as hoarseness/dysphonia were not predominant among Advair patients. This would suggest that there is no clear dose-relationship for this event and, based on the fluticasone group response in this trial, may be most related to the fluticasone component. Advair does not appear to be associated with other adverse events to a significantly greater degree than the single agent treatments.

Oral candidiasis that was clinically observable and confirmed with a culture was considered an adverse event. Although Advair was associated with the highest rate (4 percent), fluticasone also was associated with a similar rate (2 percent) of this expected adverse event.

Clinical Laboratory Values

There were 23 patients who experienced clinical laboratory values that exceeded threshold values during the treatment period, as shown in Table 11. None were considered serious adverse events.

Table 11: Patients with Threshold Laboratory Abnormalities

	Placebo (N = 93)	Advair 50/250 (N = 84)	Salmeterol (N = 88)	Fluticasone 250 (N = 84)
Total	4 (4)	7 9	9 11	3 (4)
Increased serum glucose	0	1 (1)	3 (4)	1 (1)
Low serum potassium	0	1 (1)	0	0
Increased LFT	1 (1)	1 (1)	1 (1)	1 (1)
Increased urea	0	1 (1)	0	0
Decreased hemoglobin	0	1 (1)	0	0
Decreased RBC	1 (1)	2 (2)	0	0
Decreased platelets	0	0	1 (1)	0
Decreased neutrophils	1 (1)	0	3 (4)	1 (1)
Increased eosinophils	1 (1)	0	2 (2)	0

There was a single patient in each treatment group who experienced threshold elevations in **LFTs** post-treatment. Among Advair patients, Pt # 946, a 46 yo female, had an elevated GGT at screening (122 U/L) and again one week after screening. At Week 12, GGT and was elevated above threshold (342 U/L), but diminished one week later (296 U/L). In addition to the post-treatment changes, Advair Pt # 886, a 17 year old male, had an elevated GGT that met threshold at screening, on repeat 10 days after screening and at Week 12. Week 12 values were lower than those at the preceding timepoints. One patient (Pt # 794) in the fluticasone group was diagnosed with Hepatitis C following discontinuation from the trial.

There were no significant differences among the treatment groups with respect to serum **eosinophilic cationic proteins** at baseline or endpoint, or in changes between these timepoints.

HPA axis function was assessed using morning plasma cortisol and short ACTH stimulation testing in a subset of patients. **Mean morning cortisol** results are summarized in Table 12.

Table 12: Mean Morning Cortisol

	Placebo (N = 93)	Advair 50/250 (N = 84)	Salmeterol (N = 88)	Fluticasone 250 (N = 84)
Screening				
N	39	37	36	35
Mean (SD)	399.1 (239.2)	433.4 (223.5)	437.8 (235.2)	349.3 (187.4)
# Pts(%) with values < 5 mcg/dl	1 (3)	0	1 (3)	1 (3)
Endpoint				
N	34	36	34	32
Mean (SD)	467.6 (288.8)	460.0 (219.6)	476.5 (247.3)	373.5 (170.4)
# Pts(%) with values < 5 mcg/dl	2 (6)	1 (3)	0	2 (6)

All treatment means were increased at endpoint relative to screening, but no significant differences were detected among the treatments at either screening or endpoint. Table 13 shows outcomes of the **short cosyntropin stimulation test** at screening and endpoint.

Table 13: Short Cosyntropin Stimulation Test

	Placebo (N = 93)	Advair 50/250 (N = 84)	Salmeterol (N = 88)	Fluticasone 250 (N = 84)
Screening				
N	39	37	36	35
# Pts(%) w/ pre-stimulation cortisol < 5 mcg/dL	1 (3)	0	1 (3)	1 (3)
# Pts(%) post-stimulation cortisol change < 7 mcg/dL	2 (5)	0	4 (11)	2 (6)
# Pts(%) post-stimulation cortisol < 18 mcg/dL	1 (3)	0	0	1 (3)
# Pts(%) post-stimulation cortisol change < 7 mcg/dl & cortisol < 18 mcg/dL	1 (3)	0	0	1 (3)
Endpoint				
N	36	36	34	34
# Pts(%) w/ pre-stimulation cortisol < 5 mcg/dL	2 (6)	1 (3)	0	2 (6)
# Pts(%) post-stimulation cortisol change < 7 mcg/dL	3 (8)	4 (11)	5 (15)	3 (9)
# Pts(%) post-stimulation cortisol < 18 mcg/dL	2 (6)	1 (3)	0	2 (6)
# Pts(%) post-stimulation cortisol change < 7 mcg/dl & cortisol < 18 mcg/dL	1 (3)	1 (3)	0	1 (3)

Of the five patients with post-stimulation cortisol levels less than 18 mcg/dl, only one was an Advair patient. This patient (#1012) had pre- and post-stimulation cortisols of 9 and 18 mcg/dL, respectively, at screening and 12 and 16 mcg/dL at endpoint (Week 12). This patient was taking intranasal fluticasone, as were the two placebo patients in this category. The two inhaled fluticasone patients were not using inhaled fluticasone.

Both placebo patients, and one of the fluticasone patients, were discontinued prematurely for lack of efficacy and had received oral prednisone prior to discontinuation. Overall, it does not appear that Advair at a dose of 50/250 BID was more likely than the other treatments to have been associated with HPA axis suppression.

Cardiovascular Outcomes

Mean heart rate ranged from 67 to 69 bpm among the treatment groups at Day 1 predose. There was a statistically significant overall treatment effect at 1.5 hours postdose at Week 1 and Week 12. At both timepoints, the fluticasone mean fell (2.2. and 0.8 bpm, respectively), while salmeterol and Advair means increased (up to 3 bpm). Statistically significant differences were also seen postdose at Week 1 for **QTc interval**. Mean changes from baseline were –9.1, -0.6, 1.6 and –0.7 msec for placebo, Advair, salmeterol and fluticasone, respectively. At this same timepoint, there were 6, 7, 11, and 6 percent of the respective treatment groups with QTc intervals exceeding 440 msec. **ECG changes** which were found clinically significant during treatment occurred in two placebo patients and one salmeterol patient.

Holter monitoring was conducted in a subset of 153 patients: 37 to 40 per treatment group at screening and 12 to 32 per treatment group at Week 12. Two patients were found to have had clinically significant abnormalities. Pt # 1043, a 59 yo female in the Advair group, was found to have an average of 29, 222 and 99 VEs per hour at screening, Week 12 and 3 months after Week 12, respectively. Possible episodes of junctional rhythm were noted at each timepoint. This patient significantly skewed the mean findings for the Advair treatment group relative to the other treatments. Pt # 993, a 30 yo in the placebo group, had an average of 17 VEs per hour at screening, but did not have a Holter follow-up after discontinuation. **Vital signs** did not reveal clinically important differences among the four treatment groups.

Physical Examinations

Unfavorable changes from screening were noted at Week 12 or discontinuation in 16, 4, 13 and 6 percent of the placebo, Advair, salmeterol and fluticasone groups, respectively. ENT and respiratory changes were the most numerous.

Safety Conclusion

This trial does not appear to corroborate the findings of increased local / application site reactions found in Trial SFCA3002. Further evaluation of this safety aspect will be undertaken in review of the Integrated Summary of Safety. Overall, the safety profile of Advair does not appear to be distinguishable from that of salmeterol and fluticasone.

CONCLUSION:

Trial SFCA 3003 supports the efficacy of Advair relative to placebo and to each of the individual active ingredients, salmeterol 50 mcg and fluticasone 250 mcg. Safety of Advair 50/250 appears comparable to that of the individual active ingredients.

C. TRIAL SFCB3019

TITLE: A Multicentre, Randomised, Double-Blind, Double-Dummy, Parallel-Group Comparison of the Salmeterol/Fluticasone Propionate Combination Product (50/500 mcg strength) BID via one Diskus/Accuhaler Inhaler with Salmeterol 50 mcg BID via one Diskus/Accuhaler Inhaler and Fluticasone Propionate 500 mcg BID via another Diskus/Accuhaler Inhaler and with Fluticasone Propionate 500 mcg BID via one Diskus/Accuhaler Inhaler in Adolescents and Adults with Reversible Airways Obstruction.

OVERVIEW: This active control trial lacked a placebo control and is considered pivotal primarily because it is the principal evaluation of Advair 50/500 contained in this application. The sponsor had not planned to develop this dosage strength for the U.S. market, but was encouraged to do so by the division in order to maximize flexibility in dosing titration. The division asked that the sponsor submit this study despite its design limitations. The study was designed to compare the individual moieties given as the Advair combination product and given concurrently from separate delivery systems. The single agent active control is fluticasone. There is no salmeterol-only treatment arm. A two week run-in period was followed by 28 weeks of active treatment, then a two week follow-up period. Pharmacokinetic and pharmacodynamic analyses were undertaken with a subgroup of patients. (Volumes 73 - 90)

STUDY DATES: May 31, 1996 – November 10, 1997

INVESTIGATORS: There were 55 study centers in three countries: Germany, France and the Netherlands. There were administrative and protocol differences among the participating countries that are not considered to be within the scope of this review. The outcomes of this trial will be factored into the consideration of this products' approvability with appropriate recognition of the potential issues associated with generalization from the study population to the U.S. population.

PATIENT POPULATION:

Males and females age 12 years or older were eligible for enrollment into the run-in phase if they had received BDP or budesonide at doses of 1500 – 2000 mcg per day, fluticasone propionate at doses of 750 – 1000 mcg per day or flunisolide at doses of 1500 – 2000 mcg per day for the 4 weeks prior to screening. Patients were also required to have received inhaled corticosteroids continuously for 12 weeks prior to screening. Patients were not enrolled if they were currently taking long-acting β_2-agonists.

In order to enter the treatment period, patients' Day 1 PEFR (measured 15 minutes after administration of 400 mcg doses of Ventolin on Day 1) was required to be between 50 and 85 percent of their mean morning PEFR (calculated from the last seven run-in days). In addition, patients were required to have recorded a total score of at least 2 for daytime and nighttime symptoms on four of the last seven days of run-in. Other entry

criteria were similar to those of Trial SLGA3002. Concurrent therapy was similar to that of Trial SFCA3002, with ongoing asthma therapy allowed only if it was not a β_2-agonists or inhaled or oral corticosteroid formulation (intranasal formulations of corticosteroids were allowed).

Patients were withdrawn from the study if they "experienced significant worsening of symptoms and required additional treatment during the run-in or the 28 week randomized treatment period."

PROCEDURES / ENDPOINTS:

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. Morning PEFR was to be measured upon waking, prior to any rescue or study medication.

The daytime symptom score was based on the 0 to 5 scale previously described for Trial SFCA3002. 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.

PFTs were assessed at screening, Day 1, and clinic visits which occurred at Weeks 2, 4, 12, 20 and 28. "Humanistic measures," including impact on patients' usual activities, satisfaction with medication and willingness to use the treatment again and a 3-item sleep scale were assessed at screening and Week 28. Use of medical resources, i.e., unscheduled healthcare contacts, were recorded. At Week 12, plasma pharmacokinetics were assessed over a 10 hour period in a subgroup of patients for Cmax, Tmax and AUC. A pharmacodynamic endpoint, area under the plasma cortisol concentration curve, was assessed over the same period.

The **primary efficacy endpoint was mean morning PEFR during the first 12 weeks of treatment**. Secondary efficacy measures were evening PEFR, rescue Ventolin use, symptoms scores (day and nighttime) and FEV_1 at clinic visits.

Safety endpoints included morning serum cortisol and 24 hour urinary cortisol (at a subset of centers), clinical laboratory tests, vital signs, 12 lead ECGs and oropharyngeal exams at Day 1 and Weeks 12 and 28. Physical exams were conducted at screening and Week 28 and adverse events were monitored throughout the study at each clinic visit.

A **sample size** of 150 patients (450 total) was based on having 90 power to detect a 15 L/min difference between treatment groups in morning PEFR, using a two-sided significance level of 5 percent and assuming a standard deviation of 40 L/min.

Confidence limits of 90 and 95 percent were constructed on the 12 week mean morning PEFR. Treatments were considered "equivalent" if the interval was ± 15 L/min.

PATIENT DISPOSITION / DEMOGRAPHICS:

There were 659 patients screened, 509 were randomized, 503 received treatment (six were randomized but did not receive treatment) and 403 completed the study. Table 14 summarizes patient disposition.

Table 14: Patient Disposition

	Advair 50/500	Concurrent Tx	Fluticasone 500 mcg
# Pts randomized	167	171	165
# Pts (%) withdrawn after randomization	31 (19)	28 (16)	41 (25)
# Pts (%) who completed the study	136 (81)	143 (84)	124 (75)
Reasons for withdrawal			
Adverse event	16 (10)	16 (9)	22 (13)
Failure to return	6 (4)	6 (4)	4 (2)
Lack of efficacy	3 (2)	1 (<1)	4 (2)
Non-compliance	3 (2)	3 (2)	3 (2)
Other	2 (1)	2 (1)	8 (5)
Did not fulfill entry criteria	1 (<1)	0	0

The rate of completion was comparable between the Advair combination and concurrent treatment regimen. Overall, the rates of continuation are similar to those seen in Trials SFCA 3002 and 3003. However, the rate of discontinuation for lack of efficacy among fluticasone patients is considerably lower in this trial while the rate of discontinuation for adverse events is increased. The reason for this is unclear, but may be related to the lack of strict discontinuation criteria or increased efficacy and/or adverse events associated with the higher strength (500 mcg) formulation. Overall, it is notable that the discontinuation rates are not higher than the previous trials, given that the treatment period was 28 rather than 12 weeks.

Fifty three percent of the patients were male and 96 percent were Caucasian. Patient ages ranged from 12 to 79 years, with a mean of approximately 48 years. There were only 6 patients (1 percent) enrolled who were under the age of 17 and 78 patients (15 percent) at least 65 years of age. Approximately 15 percent of the population were current tobacco users, although approximately 47 percent of the study population had never used tobacco.

It is reported that nearly 90 percent of patients were more than 80 percent **compliant** with both of their inhalers (in the double-dummy design) over Weeks 1 through 12.

An ITT and efficacy population were defined, with the latter excluding patients with protocol violations. This review considers only ITT outcomes.

EFFICACY OUTCOMES:

Table 15 shows a summary of the **morning PEFR** outcomes. Mean morning PEFR is shown graphically in Appendix M as change from baseline for the first 12 weeks of the treatment period.

Table 15: Morning and Evening PEFR

	Advair 50/500 (N = 167)	Concurrent Tx (N = 171)	Fluticasone 500 mcg (N = 165)
Morning PEFR			
Mean Baseline (L/min)	359	345	351
Mean Week 1-12 (L/min)	396	380	365
Change from Baseline, Weeks 1-12 (L/min)	37	34	13
Adjusted Change from Baseline[a], Weeks 1-12 (L/min)	35	33	15
Evening PEFR			
Mean Baseline (L/min)	379	366	368
Mean Week 1-12 (L/min)	410	391	377
Change from Baseline, Weeks 1-12 (L/min)	31	24	8
Adjusted Change from Baseline[a], Weeks 1-12 (L/min)	29	23	9

[a]Adjusted for baseline, age, sex and centre amalgamation.

Statistical analyses of morning PEFR outcomes showed that the 95 percent confidence limits on the difference between Advair and concurrent treatment adjusted mean change from baseline were within ± 15 L/min, although the difference between Advair and fluticasone exceeded that limit ($p<0.001$).

Secondary analyses were conducted on morning PEFR data, involving different timepoints of the study and percent predicted PEFR values. These data were largely supportive of the primary findings and some of these secondary analyses also established a statistical difference between Advair combination and concurrent treatments.

Table 15 also includes **evening PEFR** values. The 95 percent confidence limits on the difference between Advair combination and concurrent therapy showed no statistical difference between treatments, however, a statistical difference was observed between Advair combination and fluticasone therapy.

Adjusted mean change from baseline FEV_1 is plotted in Appendix N from data collected at clinic visits at Weeks 2, 4, 12, 20 and 28. Ninety five percent confidence limits on the difference in change from baseline were analyzed at Weeks 12 (0.22, 0.17 and 0.13L for the Advair combination, concurrent treatment and fluticasone groups, respectively) and 28 (0.26, 0.15 and 0.21L for the same respective three groups). No statistically significant differences were found among the three treatments at either timepoint, although it is noted that the Advair combination treatment is favored numerically.

Median **daytime symptom scores** were 2 during baseline and 1 during Weeks 1-12 for each of the treatment groups. Distribution of scores was slightly different within the groups such that the difference between Advair combination and concurrent treatment was not shown to be statistically significant, however, the difference between the Advair combination and fluticasone was (favoring the Advair combination). Percentage of symptom free days was 24 percent for the Advair combination, 27 percent for concurrent treatment and 7 percent for fluticasone.

Median **nighttime symptom scores** for each of the treatment groups were 1 during baseline and 0 during Weeks 1-12. No statistical differences were observed. The percentage of symptom free nights was 73 percent for the Advair combination, 66 percent for concurrent treatment and 57 percent for fluticasone.

Median values for **percent of days with no Ventolin use** were 50, 45 and 13 percent for the Advair combination, concurrent treatment and fluticasone, respectively, but had been 0 percent at baseline for all three groups. The change from baseline was significantly greater for the Advair combination than for fluticasone, but no difference was found between the Advair combination and concurrent therapy. Similar statistical outcomes were seen for **percent of nights with no Ventolin use**, with median values of 50, 43 and 43 percent for the Advair combination, concurrent treatment and fluticasone groups, respectively.

The **humanistic measures** conducted in this trial did not appear to include the AQLQ used in Trials SFCA3002 and SFCA3003. The sleep scale may have been comparable (scores of 0 – 100), but language translation issues may impede direct correlation. Overall, no significant differences were seen among the three treatments with regard to impact on activities or the sleep scale outcomes. Patient satisfaction was reported as "very satisfied" by 49, 39 and 40 percent of the Advair combination, concurrent treatment and fluticasone groups, respectively, and 34, 27 and 24 percent of the same respective treatment groups said that they would ask their doctors again for the medication. Approximately 35 percent of each treatment group had an unscheduled healthcare contact during the study. Ninety percent of these patients had only one such visit. Outcomes were comparable among the treatment groups.

Efficacy Conclusion - It is noted that this trial does not provide for efficacy analyses which take into account the variability in discontinuation rates among treatment groups. Such an analysis might have enhanced the ability to interpret difference between the fluticasone group and two-component treatments. As analyzed, this trial consistently favors the Advair combination over fluticasone and fails to discriminate between the Advair combination and concurrent treatment.

SAFETY OUTCOMES:

Mean **exposure** was 178 days for both Advair and concurrent treatment patients and 167 days for fluticasone patients.

There were **two deaths** in this trial. Study medication was stopped on the day of cataract surgery for Pt # 2872, a 72 year old male with a history of hypertension and heart failure, who was randomized to Advair combination treatment. Assigned treatment was replaced with terbutaline and theophylline on the day of cataract surgery, involving local anesthetic. Following the procedure, the patient experienced status asthmaticus and died after 14 days on a ventilator. The second death, Pt # 2749, was due to bronchial carcinoma. The death occurred three months after withdrawal from the study following 134 days on treatment with concurrent therapy. A significant breath sound was detected after 84 days on treatment, but the diagnosis was not made for an additional 50 days.

A total of 20 patients experienced **serious adverse events**. In addition to the two fatal events, there were 3 events during Advair combination therapy, 8 during concurrent therapy, 5 during fluticasone therapy and 2 after fluticasone therapy (during follow-up). Of note, one Advair combination patient experienced a "cerebral insult." One patient on concurrent therapy experienced sinubronchial syndrome and a second patient experienced a severe cold / asthma exacerbation. Among fluticasone patients, two patients had events during treatment that appear potentially related to treatment. One patient developed iridochoroditis and a second patient had a one minute black out 12 days after starting treatment.

Adverse events leading to **withdrawal** were experienced by 8 Advair combination patients, 7 concurrent therapy patients and 11 fluticasone patients. Most of these events were related to asthma deterioration.

Adverse events were experienced by 70 to 73 percent of the patients in each treatment group. The six most common adverse events were upper respiratory infection, viral respiratory infection, asthma, cough, bronchitis and headaches. Without a placebo control, it is difficult to assess the relative incidence of these events, however, no strong trends were observed. The fluticasone group had the highest incidence of asthma (12 percent) as compared to Advair (8 percent) and concurrent therapy (6 percent).

Throat irritation occurred in four Advair combination patients, 10 concurrent therapy patients and 11 fluticasone patients. Skin rashes were reported by five patients: 1 Advair combination patient, 2 concurrent therapy patients and 2 fluticasone patients. Incidence of oral candidiasis was low and comparable among treatment groups.

During the follow-up period, 9 patients (6 percent) of the Advair combination group, 11 patients (7 percent) of the concurrent therapy group and 8 patients (5 percent) of the fluticasone group reported adverse events. Asthma or breathing disorders were observed in 4, 3 and 1 patient in the respective treatment groups.

There were no patients withdrawn due to abnormal **laboratory values**. Twenty four percent of Advair patients, 21 percent of concurrent therapy patients and 26 percent of fluticasone patients had laboratory values that exceeded threshold levels. The most

prevalent abnormalities were in serum glucose or potassium and LFTs. Data were consistent with the description of findings in Trials SFCA3002 and SFCA3003.

Morning serum cortisol, 24 hour urinary cortisol outcomes and plasma cortisol AUCs are presented in Table 16.

Table 16: HPA Axis Function Endpoints

	Advair 50/500 (N = 167)	Concurrent Tx (N = 171)	Fluticasone 500 mcg (N = 165)
Serum Cortisol, # Pts (%) with cortisol < lower limit of nl			
Screening	15 (9)	13 (8)	15 (9)
Week 12	7 (4)	11 (6)	16 (10)
Week 28	9 (5)	18 (11)	15 (9)
Follow-up	0	0	1 (<1)
Mean 24 Hour Urinary Cortisol (corrected for creatinine) nmol/24 hrs			
Screening	20	19	19
Week 12	19	20	19
Week 28	20	19	17
Plasma cortisol AUC_{0-10} at Week 12 nmol.h/L	2767 N = 17	2960 N = 16	2442 N = 12

No statistical differences were observed among the treatment groups for any of the endpoints used to assess HPA axis function. Interpretation of these outcomes is confounded by the lack of an ICS-free comparator group.

Pharmacokinetic data on fluticasone propionate were also collected during this study and will be reviewed by Dr. Chen of DCPB. In population pharmacokinetic/pharmacodynamic analyses, neither plasma cortisol AUC or urinary cortisol appear correlated to systemic exposure, clearance or volume of distribution.

Physical examinations and **vital signs** did not appear to convey clinically meaningful differences among the treatments. There were 3 patients in the Advair group who were considered to have had clinically significant changes from baseline **ECG** at Week 12 or 28. Each of these events was resolved at the subsequent visit (Week 28 or follow-up).

Safety Conclusion – None of the safety measures included in this trial appeared to show important clinical differences among treatments. Most importantly, the Adair therapy did not appear to show increased safety concerns relative to fluticasone alone.

CONCLUSION:

While the design of Trial SFCB3019 (50/500) is limited by its lack of placebo and salmeterol controls, it adequately allows for some extension of the efficacy findings with the 50/100 product in Trial SFCA3002 and the 50/250 product in Trial SFCB3003 to the highest strength product. In addition, the 50/500 product did not appear to have a substantially different safety profile than fluticasone alone.

VII. SUPPORTIVE TRIALS

A. Safety and Efficacy (Adult)

Other supportive trials evaluating the use of Advair in adult or adolescent asthmatics were mentioned in the original application and/or safety update. All were conducted outside of the U.S. Of these, two trials (SFCB3017 and SFCB3018) are completed, considered to provide substantial relevant information and will be discussed subsequently. The remaining 11 trials (SFCF10001, SFCB3022, SFCB3023, SERL03, SERL04, SERL05, FLIQ43, SFCF3001, SFCF3002, SAS40015, SAS40018) are ongoing and have less impact on this review, primarily due to their design limitations.

TRIAL SFCB3017

TITLE: : A Multicentre, Randomised, Double-Blind, Double-Dummy, Parallel-Group Comparison of the Salmeterol/Fluticasone Propionate Combination Product (50/100 mcg strength) BID via one Diskus/Accuhaler Inhaler with Salmeterol 50 mcg BID via one Diskus/Accuhaler Inhaler and Fluticasone Propionate 100 mcg BID via a second Diskus/Accuhaler Inhaler in Adolescents and Adults with Reversible Airways Obstruction.

OVERVIEW: This trial is similar in design to SFCB3019, but compares Advair 50/100 combination therapy only with concurrent therapy. No single ingredient treatment arms are included. The primary contribution of this trial to the determination of Advair's approvability is as a supplemental safety and efficacy trial to support the findings from pivotal Trial SFCA3002. (Volumes 91-94)

STUDY DATES: July 17, 1996 – May 9, 1997

INVESTIGATORS: There were 44 study centers in four countries: United Kingdom, Spain, Portugal and South Africa. As with Trial SFCB3019, interpretation of the outcomes of this study for the U.S. population will be undertaken with an awareness of the diversity of the study population.

PATIENT POPULATION:

Males and females age 12 years or older were eligible for enrollment into the run-in phase if they had received BDP or budesonide at doses of 400-500 mcg per day or fluticasone propionate at doses of 200-250 mcg per day for the 4 weeks prior to screening. Other enrollment criteria were similar to those of Trial SFCB3019. Patients were enrolled into the treatment period if their FEV_1 at the randomization visit was between 50 and100 percent of predicted normal and PEFR met the criteria as stated in Trial SFCB3019.

PROCEDURES / ENDPOINTS:

Procedures and endpoints were essentially identical to those used in Trial SFCB3019, with the exception that there were only two treatment arms in this trial and Advair 50/100 was studied.

PATIENT DISPOSITION / DEMOGRAPHICS:

There were 383 patients screened, 244 were randomized and 209 completed the trial. Of the 35 patients who withdrew from the study after randomization, 18 (15 percent) were from the Advair combination group and 17 (14 percent) were from the concurrent treatment group. No patients were reported to have withdrawn for lack of efficacy.

Fifty six percent of the Advair combination group were female, as were 59 percent of the concurrent therapy group. Mean age was 33 years and ranged from 12 to 76 years. Twenty percent of the patients were under the age of 18 and two percent were over 65. Eighty eight percent of the population was Caucasian, six percent were Asian and the remainder were Black or Other.

Approximately 90 percent of the patients were at least 80 percent compliant with both double dummy devices.

EFFICACY OUTCOMES:

Mean morning PEFR at baseline was 368 L/min for the Advair combination group and 365 L/min for the concurrent treatment group. Mean changes for Weeks 1-12 were 44 and 35 L/min for the two groups, respectively. A statistically significant difference was found in this primary analysis, based on the 90 percent confidence interval having exceeded the specified range of ±15 L/min. Similar outcomes were not consistently seen in other analyses of morning PEFR data (i.e., other time intervals, percent of predicted). A plot of change from baseline in morning PEFR is presented in Appendix O.

Evening PEFR was 381 L/min for the Advair combination and 376 L/min for concurrent therapy at baseline and changed 36 and 30 L/min during Weeks 1 –12 for the same groups, respectively. The 90 percent confidence intervals on the difference in change between the two treatments did not exceed ±15 L/min, although the 95 percent confidence limits did. Analyses of AM/PM PEFR differential did not show statistical differences between treatments, but did show a similar trend with change from baseline for Weeks 1-12 in the Advair combination group of 7 L/min and 4 L/min in the concurrent treatment group.

Adjusted mean change from baseline FEV_1 was 0.20L and 0.17L for the Advair combination and concurrent treatment, respectively (baseline 2.42 and 2.33L, respectively). No statistically significant differences were observed.

Secondary endpoints reflected that patients experienced minimal asthma symptoms. Median daytime asthma score was 0 at baseline and for Weeks 1-12 in both groups, although the proportion of patients with 0 scores rose from approximately 17 percent at baseline to 60 percent for Weeks 1-12 in both treatment groups. No statistically significant differences were observed. Similar outcomes were seen for nighttime asthma symptoms. Percentage of days with no Ventolin rose from 14 and 23 percent at baseline in the Advair combination and concurrent treatment groups, respectively, to 76 and 82 percent for Weeks 1-12. Nights with no Ventolin use rose from 57 to 93 percent in both treatment groups between baseline and Weeks 1-12.

Efficacy Conclusion – The primary endpoint, change from baseline morning PEFR, showed statistical superiority for the Advair combination group versus the concomitant treatment group. Without additional control treatments (e.g., single ingredient treatments or placebo) it is difficult to gauge the clinical relevance of this finding since the actual difference is quite small. The secondary efficacy endpoints did not suggest clinically important differences between the treatments.

SAFETY OUTCOMES:

The mean number of days of exposure was 80 for the Advair combination and 79 for concurrent therapy.

There were **no deaths** reported during this trial. During treatment, three Advair combination patients experienced **serious adverse events** (acute asthma exacerbation, respiratory infection, road traffic accident), as did two concurrent group patients (tachycardia, increased platelet count). There were 11 patients (9 percent) of the Advair combination group and 9 patients (7 percent) of the concurrent treatment group who withdrew due to adverse events. Seven of the Advair patients and four of the combination patients withdrew due to respiratory events. One patient in the concurrent therapy group withdrew due to oral thrush.

A total of 88 (73 percent) of Advair combination patients and 69 (56 percent) of concurrent patients experienced adverse events during the treatment period. URTI, LRTI, viral respiratory infections and headaches were the most **common adverse events**. Headaches occurred in 15 (12 percent) of Advair combination patients and only 5 (6 percent) of concurrent use patients. This difference in incidence was statistically significant (p=0.02).

Adverse events during follow-up occurred in 13 (11 percent) of Advair combination patients and 16 (14 percent) concurrent treatment patients. The most common event was URTI and incidence rates were comparable between treatments for this and other events.

Sixteen patients (14 percent) of the Advair combination group and 14 (13 percent) of the concurrent group experienced a **laboratory value** that exceeded threshold values. One patient was withdrawn due to an increased platelet count at baseline. Eosinophil

concentrations were increased above threshold levels in 4 (4 percent) of Advair combination patients and 7 (7 percent) of concurrent therapy patients. Cortisol levels decreased to lower than threshold in 5 Advair combination and 3 concurrent treatment patients. One patient on concurrent therapy was reported as having had an adverse event (possible adrenal suppression). Cortisol levels increased above threshold in 3 Advair combination patients. Two patients in each group had increased LFTs that were not associated with adverse events. Finally, one patient using the combination product experienced potassium concentrations below threshold.

At the initiation of treatment, 19 (16 percent) of the Advair combination patients and 24 (20 percent) of the concurrent therapy patients had **morning serum cortisol** values less than the lower limit of normal. At Week 12, 11 and 12 percent of the groups, respectively, exceeded the lower limit of normal with mean values of 351 and 299 nmol/L in the two respective groups. At follow-up, only two patients in the concurrent treatment group continued to have lower than normal values.

Physical examinations and vital signs did not show appreciable differences between treatment groups.

Safety Conclusion – No safety parameters appear to suggest clinically important differences between Advair combination and concurrent therapy of 50/100 mcg BID doses. These data are supportive of the safety of the Advair combination given the limited interpretation possible from this trial design.

CONCLUSION:

The primary efficacy outcome, change from baseline in morning PEFR, was statistically superior for the Advair 50/100 combination relative to concurrent salmeterol 50 mcg plus fluticasone 100 mcg therapy. These trends were reflected in other analyses of morning PEFR, evening PEFR, AM/PM differential and clinic visit FEV_1, although no statistically significant differences were observed. Neither secondary efficacy data, nor safety data appeared to support the clinical importance of these findings.

TRIAL SFCB3018

TITLE: : A Multicentre, Randomised, Double-Blind, Double-Dummy, Parallel-Group Comparison of the Salmeterol/Fluticasone Propionate Combination Product (50/250 mcg strength) BID via one Diskus/Accuhaler Inhaler with Salmeterol 50 mcg BID via one Diskus/Accuhaler Inhaler and Fluticasone Propionate 250 mcg BID via a second Diskus/Accuhaler Inhaler in Adolescents and Adults with Reversible Airways Obstruction.

OVERVIEW: This trial is similar in design to SFCB3019, but compared Advair 50/250 combination therapy with concurrent therapy only. It differs somewhat from SFCB3017, primarily with regard to dose, patient asthma severity at enrollment and duration (treatment period was 28 weeks instead of 12). The primary contribution of this trial to the determination of Advair's approvability is as a supplemental safety and efficacy trial to support the findings from pivotal Trial SFCA3003. Efficacy was evaluated primarily during the first 12 weeks of treatment. (Volumes 95-98)

STUDY DATES: July 3, 1996 – July 23, 1997

INVESTIGATORS: There were 43 study centers in five countries: Canada, Denmark, Finland, Norway and Sweden. As with Trial SFCB3019, interpretation of the outcomes of this study for the U.S. population will be undertaken with an awareness of the diversity of the study population.

PATIENT POPULATION:

Males and females age 12 years or older were eligible for enrollment into the run-in phase if they had used ICS for 12 weeks prior to entry and received BDP or budesonide at doses of 800-1200 mcg per day or fluticasone propionate at doses of 400-600 mcg per day for at least 4 weeks prior to screening. Other enrollment criteria were similar to those of Trial SFCB3019. Patients were enrolled into the treatment period if their FEV_1 at the randomization visit was between 50 and100 percent of predicted normal and PEFR met the criteria as stated in Trial SFCB3019.

PROCEDURES / ENDPOINTS:

Procedures and endpoints were essentially identical to those used in Trial SFCB3019. This study used doses of 250 mcg fluticasone and the treatment period was 28 weeks in duration. However, efficacy evaluations were comparable to those used in Trial SFCB3017, in that they assessed the first 12 weeks of treatment.

PATIENT DISPOSITION / DEMOGRAPHICS:

There were 523 patients screened, 371 were randomized and 335 completed the trial. Of the 36 patients who withdrew from the study after randomization, 20 (11 percent) were from the Advair combination group and 16 (8 percent) were from the concurrent

treatment group. No patients were reported to have withdrawn for lack of efficacy and the most common reason for withdrawal was adverse events.

Forty nine percent of the Advair combination group was female, as was 57 percent of the concurrent therapy group. Mean age was 42 years and ranged from 13 to 75 years. Two percent of the patients were under the age of 18 and eight percent were over 65. Ninety eight percent of the population was Caucasian and the remainder were Asian.

Approximately 94-96 percent of the patients were at least 80 percent compliant with both double dummy devices.

EFFICACY OUTCOMES:

Mean morning PEFR at baseline was 398 L/min for the Advair combination group and 391 L/min for the concurrent treatment group. Mean changes for Weeks 1-12 were 44 and 36 L/min for the two groups, respectively. Despite a trend similar to that seen in Trial SFCB3017, no statistically significant differences were seen in the primary analyses or other analyses of morning PEFR data. A plot of these data is shown in Appendix P.

Evening PEFR was 415 L/min for both the Advair combination and concurrent treatment at baseline and changed 35 and 25 L/min for the two groups respectively during Weeks 1 –12. The 90 percent confidence intervals on the difference in change between the two treatments exceeded the pre-specified limit of ±15 L/min. Analyses of AM/PM PEFR differential did not show statistical differences between treatments, with a change from baseline of 17 L/min in the Advair treatment group and 23 L/min in the concurrent treatment group. It is noted that the PEFR differential trended in the opposite direction from morning and evening PEFR outcomes.

Adjusted mean change from baseline **FEV_1** was 0.21 L for both treatment groups, with no statistical difference observed. Baselines were 2.51L and 2.77L, for the Advair combination and concurrent treatment, respectively.

Secondary endpoints showed markedly higher values in this trial than in SFCB3017. Median daytime asthma score was 2 at baseline and 1 for Weeks 1-12 in both groups. The median percentage of symptom-free days was 0 percent for both groups at baseline and was 22 percent for Advair combination treatment versus 16 percent for the concurrent treatment over Weeks 1-12. No statistically significant differences were observed. Median nighttime symptom scores were 1 at baseline and 0 at Week 12 for both treatments.

Percentage of days with no Ventolin rose from 0 for both groups at baseline to 67 and 52 percent in the Advair combination and concurrent treatment groups, respectively, over Weeks 1-12. Nights with no Ventolin use rose from 71 and 57 at baseline to 94 and 90 percent over Weeks 1-12 in the same respective treatment groups.

Efficacy Conclusion – No statistically significant difference was observed between treatment groups for the primary endpoint, morning PEFR, although Advair was statistically superior to concurrent treatment for evening PEFR. AM/PM differential, clinic FEV_1 and secondary efficacy endpoints failed to support a meaningful clinical difference between treatments.

SAFETY OUTCOMES:

The mean number of days of exposure was 184 for the Advair combination and 188 for concurrent therapy.

There were **no deaths** reported during this trial. During treatment, eight patients in each treatment group experienced **serious adverse events**. Among the Advair combination group, there were two patients with respiratory events (acute asthma and pneumothorax), as well as a patient who discontinued due to increased blood glucose. In the concurrent treatment group, there were four respiratory events (asthma exacerbation with infection and three pneumonia cases). One Advair combination patient suffered acute paroxysmal atrial fibrillation and one concurrent treatment patient had a myocardial infarction. Twelve (seven percent) of Advair patients and nine (five percent) of concurrent treatment patients discontinued due to adverse events. Five patients from both groups withdrew due to asthma exacerbations/worsening asthma. Of note, one Advair combination patient discontinued after five days of treatment because he experienced throat constriction for a 30 minute period that he attributed to the medication.

A total of 160 (89 percent) of Advair combination patients and 164 (85 percent) of concurrent patients experienced adverse events during the 28 week treatment period. URTI, LRTI, viral respiratory infections, headaches, cough, throat irritation and asthma were the most **common adverse events**. Rates of occurrence appeared comparable between the two treatment groups.

Adverse events during follow-up occurred in 21 (13 percent) of Advair combination patients and 22 (12 percent) concurrent treatment patients. The most common event was asthma, reported by two percent of each treatment group.

Thirty three patients (19 percent) in the Advair combination group and 48 (26 percent) of the concurrent group experienced a **laboratory value** which exceeded threshold values. One patient was withdrawn due to an increased platelet count at baseline. Neutrophil concentrations were decreased below threshold levels in 8 (5 percent) of Advair combination patients and 11 (6 percent) of concurrent therapy patients. Cortisol levels decreased to lower than threshold in 7 patients (4 percent) of each treatment group. Cortisol levels increased above threshold in 2 Advair combination patients and 9 concurrent treatment patients. Four patients in each group had increased LFTs that were not associated with adverse events. Two patients on concurrent treatment had decreased potassium values and glucose was elevated above threshold in 2 Advair patients and 3 concurrent treatment patients.

At the initiation of treatment, 11 (6 percent) of the Advair combination patients and 14 (7 percent) of the concurrent therapy patients had **morning serum cortisol** values less than the lower limit of normal. At Week 12, 4 and 3 percent of the groups, respectively, exceeded the lower limit of normal with mean values of 383 and 436 nmol/L in the two respective groups. At Week 28, values were 368 and 381nmol/L for the same respective groups.

Physical examinations and vital signs did not show appreciable differences between treatment groups.

Safety Conclusion – No safety parameters appear to suggest clinically important differences between Advair combination and concurrent therapy of 50/250 mcg BID doses. These data are supportive of the safety of the Advair combination given the limited interpretation possible from this trial design.

CONCLUSION:

The primary efficacy outcome, change from baseline in morning PEFR, was not statistically different for the Advair 50/250 combination relative to concurrent salmeterol 50 mcg plus fluticasone 250 mcg therapy. Secondary efficacy endpoints and safety data also failed to support a difference between treatments.

A. Safety and Efficacy (con't) – Pediatric

TRIAL SFCB3020

A single pediatric trial was submitted to this application for patients age 4 to 11.

TITLE: A Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Comparison of the Salmeterol/Fluticasone Propionate Combination Product (50/100 mcg Strength) BID via One Diskus/Accuhaler Inhaler with Salmeterol 50 mcg BID via One Diskus/Accuhaler Inhaler and Fluticasone Propionate 100 mcg BID via a Second Diskus/Accuhaler Inhaler in Children Age 4 – 11 Years with Reversible Airway Obstruction. (Volumes 103-105)

OVERVIEW: This pediatric trial was similar in design to SFCB3019, which was conducted in adults. The purpose of this trial was to compare Advair combination and concurrent therapies and there are no treatment arms for individual therapies. Although both safety and efficacy data were collected during this trial, the primary contribution of this trial to the application was to verify the safety and appropriate dose of the Advair combination formulation in children ages 4 to 11.
(Volumes 103-106)

STUDY DATES: November 11, 1996 – September 10, 1997

INVESTIGATORS: 35 centers in nine countries: Estonia, Finland, Lithuania, Netherlands, Norway, Portugal, Spain, South Africa and Sweden. As with Trial SFCB3019, interpretation of the outcomes of this study for the U.S. population will be undertaken with an awareness of the diversity of the study population.

PATIENT POPULATION:

Males and females age 4 to 11 were eligible for enrollment if they had received BDP, budesonide or flunisolide at a dose of 400-500 mcg per day, or fluticasone propionate at a dose of 200-250 mcg per day for at least four weeks prior to the start of the run-in. Other enrollment criteria were comparable to those in Trial SFCB3019.

PROCEDURES / ENDPOINTS:

As in Trial SFCB3019, patients continued on their pre-study inhaled corticosteroid throughout the two week run-in period. The treatment period was 12 weeks long, instead of 28 weeks as in the previous study. Endpoints were largely the same, with some exceptions. FEV_1 data were collected in all children age 8 to 11 and in younger children if they could perform the maneuver. Assessment of 24 hour urinary cortisols was not conducted in this trial, nor were plasma fluticasone or cortisol AUCs assessed. ECGs were also not conducted.

A sample size of 120 per treatment group was projected to provide 90 percent power to detect a treatment difference of ± 15L/min in PEFR for Weeks 1-12 based on a 90 percent confidence interval and a standard deviation of 35 L/min.

PATIENT DISPOSITION / DEMOGRAPHICS:

A total of 402 patients were screened and 257 were randomized (125 to Advair combination and 132 to concurrent treatment). Five patients (4 percent) of each treatment group failed to complete the study. Sixty four percent of the Advair combination group were male, while 54 percent of the concurrent therapy group were male. Ninety percent of both groups were Caucasian and approximately five percent were Asian (not Oriental). Ages ranged from 4 to 11 years, with 21 percent of the population age 4-5 years, 27 percent age 6-7 years and 52 percent age 8-11 years. Approximately 65 percent were atopic.

Over 90 percent of the patients were more than 80 percent compliant with both double-dummy devices.

[redacted]

SAFETY OUTCOMES:

The mean number of days of exposure was 84 for Advair and 83 for the concurrent therapy.

There were no deaths during this study. Four **serious adverse events** were reported during Advair combination therapy: asthmatic crisis (leading to withdrawal), appendicitis, enlargement of tonsils and coxitis fugax of the right hip. No patients on concurrent therapy experienced a serious adverse event. Two patients in each treatment group were discontinued due to adverse events. In the Advair combination group, the serious asthmatic crisis caused discontinuation in Pt # 3814, as did a coronary sinus arrhythmia in Pt # 4271. The latter was thought to be possibly due to treatment. In the concurrent therapy group, Pt # 3991 discontinued due to stomatitis and Pt # 4138 discontinued due to an asthma exacerbation with a common cold.

The six most **common adverse events** were URTI, rhinitis, fever, viral respiratory infection, cough and headache. Both rhinitis and fever were more prevalent among the Advair combination users (14 and 12 percent, respectively) than among the concurrent therapy group (7 percent for both events). One patient developed a "full moon face" after 10 days on Advair combination treatment. Oral candidiasis was confirmed with cultures in four Advair combination patients.

A total of 31 (26 percent) of the Advair combination patients and 30 (24 percent) of the concurrent therapy patients experienced a **laboratory value** which exceeded threshold. Approximately half of these patients (16 per group) experienced a decline in lymphocytes. Seven Advair combination patients and six concurrent therapy patients fell below the lower threshold (— x lower limit of normal) for cortisol.

At screening, 36 and 43 percent of the Advair combination and concurrent therapy groups, respectively had serum cortisol values less than the lower limit of normal. At Week 12, percentages had fallen to 26 and 23 percent of the respective treatment groups, with mean values of 232 and 247 nmol/L, respectively.
Physical examinations and vital signs did not show appreciable differences between treatment groups.

Safety Conclusion - These data appear to support the safety of Advair 50/100 in the pediatric population (ages 4 to 11) and do not suggest clinically important differences between combination and concurrent use.

CONCLUSION:

This trial is supportive of the safety and efficacy of Advair 50/100 BID in children ages 4 to 11. However, it is a single trial with a less than informative design [redacted]

B. Pharmacodynamics

The pharmacodynamics and tolerability of the Advair formulation were evaluated in Trial SFCB1001 and C92-029. Pharmacodynamics were also assessed concurrently with Advair's pharmacokinetic profile in Trials SFCB3019, SFCB1002, SFCB1004 and SFCB1005. Each trial was conducted in Europe. As noted in Section IV of this review, the pharmacokinetic outcomes of these trials were further reviewed by Dr. Chen of the Division of Clinical Pharmacology and Biopharmaceutics. Additional safety data will be reviewed subsequently in the Integrated Summary of Safety (e.g., adverse events.)

Trial SFCB1001 was a cumulative dose study, crossover comparison of Advair 50/500 mcg, salmeterol 50 mcg and placebo. Tolerability and pharmacodynamics were assessed, as a total of 8 puffs were given at 60 minute intervals over 3 hours (total Advair dose 400/4000 mcg.) Pulse rate, blood pressure, 12-lead ECG, tremor, and plasma potassium and glucose were assessed at predose and 30 and 55 minutes after dosing. Results are shown on the following page in Table 24. Change is expressed as slope of the linear regression line per 100 mcg of cumulative dose of salmeterol between baseline and the final value (after the last cumulative dose.)

Table 24: Pharmacodynamic Responses from Trial SFCB1001

	Advair 50/500 (N = 12)	Salm (N = 12)	Placebo (N = 12)
Pulse (bpm)			
Baseline	57	58	57
Final value	68	65	57
Slope per 100 mcg increase	2.9	2.2	0.2
Systolic Blood Pressure (mmHg)			
Baseline	121	121	124
Final value	123	122	126
Slope per 100 mcg increase	0.7	0.5	1.1
Diastolic Blood Pressure (mmHg)			
Baseline	73	73	73
Final value	65	65	72
Slope per 100 mcg increase	-2.0	-2.0	-0.2
QTc (msec)			
Baseline	401	405	405
Final value	425	420	414
Slope per 100 mcg increase	n/a	n/a	n/a
Potassium (mEq/L)			
Baseline	3.93	3.94	3.86
Final value	3.54	3.58	3.81
Slope per 100 mcg increase	-0.13	-0.11	-0.04
Glucose (mg/dL)			
Baseline	90.2	90.9	91.1
Final value	101.3	99.0	86.9
Slope per 100 mcg increase	0.19	0.14	-0.04
Tremor (arbitrary units)			
Baseline	93.4	126.2	107.7
Final value	250.9	226.9	121.6
Slope per 100 mcg increase	1.29	1.18	1.05

Dose related increases were observed in association with salmeterol and Advair treatment for pulse rate, QTc interval, tremor and blood glucose. Dose related decreases were observed for diastolic blood pressure and plasma potassium. Similar findings were observed in Trial C92-029.

Trial SFCB1002 was a three-way crossover, single dose study comparing 5 inhalations of Advair 50/100 mcg with 5 inhalations of fluticasone 100 mcg and placebo. Pharmacodynamic assessment of 24 hour urinary cortisols was made on the day prior to and following each treatment. Comparisons of pre and post treatment values revealed a 4.4, 6.7 and 2.1 percent decline for the 250/500 Advair dose as compared to fluticasone 500 mcg and placebo.

Trial SFCB1005 was also a single dose study, comparing 2 inhalations of combination 50/500 mcg with 2 inhalations each of salmeterol 50 mcg and fluticasone 500 mcg administered concurrently and 2 inhalations of fluticasone 500 mcg. Pharmacodynamic endpoint included those studied in Trial SFCB1001 and 24 hour urinary cortisol assessments, as in Trial SFCB1002. In addition, plasma cortisol AUCs were measured. Consistent with the expected outcomes based on Trial SFCB1001, statistically significant differences were observed between Advair and fluticasone alone for pulse

rate, QTc interval, potassium and glucose (effects attributable to salmeterol.) Such differences were not observed between Advair and the concurrently administered salmeterol and fluticasone. No statistically significant differences were observed among the treatments with regard to urinary or plasma cortisol, although fluticasone showed the smallest decline in plasma cortisol AUC and the greatest decline in 24 hour urinary cortisol.

In Trial SFCB1004, a 10 day multiple dose study, 2 inhalations BID of the combination 50/250 mcg were compared with fluticasone 250 mcg, salmeterol 50 mcg, and placebo each administered alone as 2 inhalations BID. The combination product and salmeterol groups showed comparable changes in pulse rate, QTc, potassium and glucose. No predose urinary cortisols were assessed, but after nine days of dosing, fluticasone, alone or in combination, was statistically different from placebo.

Pharmacodynamic outcomes for Trial SFCB3019 are described in Section VI.C. and are generally consistent with those reported in this section.

Overall, it appears that both the salmeterol and fluticasone components of Advair generate similar pharmacodynamic profiles as the individual agents given alone, i.e., the extrapulmonary effects of salmeterol are unaffected by the presence of fluticasone and vice versa.

C. Concurrent Use of Salmeterol and Fluticasone

Five study reports (FLTA3015, FLTA4012, FLTA4022, SLGA5021, SLGA5022) were submitted to this application that address the concurrent use of salmeterol and fluticasone in asthma. An additional study (SERL01) is reported as ongoing. These trials involved only previously marketed products, Serevent Diskus and Inhalation Aerosol and Flovent Inhalation Aerosol. None of the trials included treatment with the Advair formulation, hence these trials will not be reviewed at length in association with this application. Safety data from these trials is included in the Integrated Summary of Safety and will be summarized Section VIII of this review.

[redacted]

D. COPD

There are three ongoing studies of the Advair combination in patients with COPD. SFCA3006 – A randomized double blind, placebo controlled, parallel group trial evaluating the safety and efficacy of the Diskus formulations of salmeterol 50 mcg BID and fluticasone propionate 500 mcg BID individually and in combination as compared to placebo in COPD subjects (U.S.).

SFCA3007- A randomized double blind, placebo controlled, parallel group trial evaluating the safety and efficacy of the Diskus formulations of salmeterol 50 mcg BID and fluticasone propionate 250 mcg BID individually and in combination as compared to placebo in COPD subjects (U.S.).
SFCB3024 – A multicenter, randomized, double blind, parallel group, placebo controlled study to compare the efficacy and safety of the salmeterol/fluticasone propionate combination product at a strength of 50/500 mcg BID with salmeterol 50 mcg BID alone and fluticasone propionate 500 mcg BID alone, delivered via the Diskus/Accuhaler Inhaler, in the treatment of subjects with COPD for 12 months.
Since this indication has not been proposed for approval at the present time and because the safety and efficacy questions of this product are distinctly different in this population, these studies have not been reviewed in their entirety. Safety data from these trials has been included in the Integrated Summary of Safety and will be reviewed with that section.

X. INTEGRATED SUMMARY OF EFFICACY

This section of the review is based primarily on the pivotal adult and adolescent Trials SFCA3002 (Advair 50/100), SFCA3003 (Advair 50/250) and SFCB3019 (Advair 50/500). Other efficacy trials submitted to this application can at best be considered supportive, given significant design limitations. Trials SFCA3002 and SFCA3003 were conducted in the U.S. and were specifically designed to address the regulatory requirements of the policy for fixed combination prescription products. These studies were designed to compare the combination formulation to each of the individual components (salmeterol and fluticasone) and placebo.

Trial SFCB3019 was not designed in a similar fashion, but is considered pivotal to this application because it is the principal study of Advair 50/500. The division encouraged the sponsor to pursue development of Advair 50/500 in the U.S. to offer a wider range of product strengths for titration purposes in the clinical setting.

In Trial SFCA3002, there were four treatment arms: Advair 50/100, salmeterol 50 mcg, fluticasone propionate 100 mcg and placebo. In Trial SFCA3003, there were also four treatment arms: Advair 50/250, salmeterol 50 mcg, fluticasone propionate 250 mcg and placebo. In both trials, the primary efficacy endpoints were change from baseline at endpoint in morning pre-dose FEV_1, area under the serial FEV_1 curve relative to pre-treatment baseline and probability of remaining in the study. Secondary endpoints included morning predose FEV_1 from clinic visits, morning and evening PEFR, diary efficacy card parameters (asthma symptom scores, use of Ventolin MDI, nighttime awakenings), the Asthma-Specific Quality of Life scale (global dimension and four individual dimensions) and the Sleep Scale.

For both SFCA3002 and 3003, the Advair treatment was consistently statistically superior to placebo for all primary and secondary efficacy endpoints. In SFCA3002, Advair 50/100 was also consistently statistically superior to salmeterol 50 mcg on both primary and secondary endpoints. Advair 50/100 was statistically superior to fluticasone 100 mcg for all endpoints except probability of remaining in the study and percent of nights with no awakenings. In Trial SFCA3003, Advair 50/250 was statistically superior to placebo and salmeterol 50 mcg for all endpoints. Advair 50/250 was also statistically superior to fluticasone 250 mcg except on the AQLQ activity limitation dimension and sleep scale scores.

Trial SFCB3019 was conducted in three European countries with Advair 50/500. This trial involved three treatments: Advair 50/500, salmeterol 50 mcg given concurrently with fluticasone propionate 500 mcg from two separate devices and fluticasone 500 mcg administered alone. The primary efficacy endpoint in this trial was change from baseline in mean morning PEFR over treatment Weeks 1-12. Morning predose FEV_1, evening PEFR, asthma symptom severity, use of Ventolin MDI and nocturnal awakening were secondary efficacy endpoints. Statistically significant differences were not observed between the Advair combination and concurrent treatment. However, the

Advair combination was statistically superior to fluticasone with regard to most secondary endpoints.

Compliance with assigned treatment appeared to be generally high, approximately ninety percent of patients used over 80 percent of their required doses and compliance was consistent among the various treatment groups in the pivotal trials. It does not appear to have been an important factor in determining treatment outcomes.

Efficacy was examined in three population subsets. Analyses of efficacy by age and gender were undertaken for all three pivotal studies. Analyses of efficacy by ethnic origin was undertaken for Trials SFCA3002 and 3003 only because nearly all of the patients in Trial SFCB3019 were Caucasian. Statistical analyses were prohibited in each case because of the small subgroup sizes.

Means for the each of the primary endpoints were reported for the pivotal trials by **age** group. In SFCA3002, 37 (11 percent) of 335 patients were under the age of 18 and 9 (3 percent) were age 65 or over. In SFCA3003, 28 (8 percent) or 336 patients were under the age of 18 and 8 (2 percent) were over the age of 65. Trial SFCB3019 had only 6 (1 percent) of patients under the age of 18 and 78 (16 percent) of patients over the age of 65. Numerical trends almost universally favored Advair relative to the other treatment groups for both older and younger patients, as they did in the primary analyses.

Analyses by **gender** were also conducted on the primary endpoints. In Trial SFCA3002, 48 percent of patients were female (162 of 335), in Trial SFCA3003, 54 percent of patients were female (183 of 336) and in Trial SFCB3019, 47 percent were female (234 of 503). Advair showed numerical superiority relative to the other treatments for each endpoint in each study. In Trials SFCA3002 and 3003, Advair outcomes were numerically worse for females than males. This is inconsistent with the pharmacokinetic outcomes which found In Trial SFCB3019, a lower bioavailability, and therefore potentially less efficacy, among males.

In analyses by **ethnic origin**, Trial SFCA3002 had a Black subgroup of 30 (nine percent) of patients and an "Other" subgroup of 23 (7 percent) of patients. Trial SFCA3003 had a Black subgroup of 41 (12 percent) of patients and an "Other" subgroup of 28 (8 percent) of patients. Among Caucasians and Blacks, the Advair treatment was consistently numerically superior to the other treatments. Among "Other" patients, the fluticasone treatment groups were generally as good if not better than the Advair treatment. It unclear that this finding has any clinical significance given the small number of diverse patients included in the "Other" category.

The influence of use of concomitant intranasal fluticasone and the influence of prestudy asthma therapy (**drug-drug interactions**) were discussed within the individual trial reviews for Trials SFCA3002 and 3003. Neither of these factors appeared to alter the advantage seen among Advair patients relative to the other treatments.

Long term effectiveness was evaluated by the sponsor by comparing FEV_1 clinic data from Weeks 2, 12 and 28 of Trials SFCB3018 and 3017. Numerically, the response to Advair was consistent throughout the trial. **Tolerance** was evaluated by comparing functions of FEV_1 from Trials SFCA3002 and 3003 with regard to Day 1, Week 1 and Week 12. Within the Advair treatment groups, responses appeared to remain stable or increase over time. These analyses are confounded by the difference among treatment groups with regard to patient discontinuation. An alternate mode of evaluating tolerance is to examine the Kaplan-Meier survival curves for these pivotal study which appear to suggest a decline in the rate of patient discontinuation at the end of the trials, particularly among Advair patients (see Appendices E and L). These outcomes appear to confirm that there was a significant proportion of patients who continued to receive benefit from therapy throughout the trial.

Withdrawal effects on efficacy were not studied in the pivotal or other trials in this submission. The sponsor suggests that an appropriate surrogate may be the frequency of adverse events during follow-up, but event rates are not necessarily correlated to the efficacy outcomes of primary interest.

The pivotal trials were not specifically designed to explore the question of **onset of effectiveness**. In post hoc analyses of FEV_1 data from the clinic visit on Day 1 and diary data, the sponsor has presented an analysis of onset. For both Trials SFCA3002 and 3003, the percent of patients who achieved a 15 percent increase in FEV_1 after their first dose of Advair was determined. For Advair 50/100, 57 and 75 percent of patients reached this threshold at the 30 and 60 minute timepoints, respectively, following dosing. For Advair 50/250, 46 and 63 percent of patients reached this threshold at the same timepoints, respectively.

Other FEV_1 parameters also showed Advair superiority to other treatments on Day 1 treatment. However, this bronchodilatory response does not characterize full onset of effect from the combination.

In addition to FEV_1 responses, diary data were analyzed on a daily basis for the first week of treatment. For SFCA3002 and 3003, Advair was statistically better than placebo on Day 1 of treatment for change in AM and PM PEFR, change in symptom scores and change in Ventolin use. Advair was also statistically superior to fluticasone on Day 1 in SFCA3002 and superior to both fluticasone and salmeterol on Day 1 in SFCA3003 for most endpoints.

Conclusion - The pivotal trials submitted to this application (SFCA3002, SFCA3003 and SFCB3019) provide a scientific rationale for combining salmeterol and fluticasone in a fixed combination from an efficacy standpoint. Further evaluation of the regulatory and clinical implications of such therapy was discussed at the November 23, 1999 meeting of the Pulmonary Allergy Drugs Advisory Committee. The primary outcome of that meeting was a consensus that the Advair products appear to be effective compared to single ingredient products and placebo, but that the appropriate indication for labeling purposes requires further refinement.

IX. INTEGRATED SUMMARY OF SAFETY

The original NDA submission contained data through a cut-off date of October 31, 1998. There were five safety data groupings discussed in the submission, including the completed Advair studies in adults and pediatrics, the completed MDI concurrent use studies, ongoing trials [redacted]; and the clinical pharmacology studies. Although the ISS submission was reviewed with regard to the pediatric trial (see Section VII.A.) and the [redacted] trials (see Section VIII.C.), these trials will not be routinely addressed in this section, except in instances in which there were important findings.

The 120-day safety update, dated June 16, 1999, included data from November 1, 1998 through March 31, 1999. The safety update contained information from ongoing clinical and clinical pharmacology trials worldwide of Advair and [redacted], in asthma and COPD.

Exposure

In the adult and adolescent Trials SFCA3002, SFCA3003, SFCB3019, SFCB3017 and SFCB3018, there were 644 patients exposed to Advair. Mean exposure time is shown below for the various treatment groups in these trials.

Treatment	Number of Pts	Mean Treatment Days
Placebo	175	43
Advair 50/100	213	79
Advair 50/250	264	150
Advair 50/500	167	178
Concurrent 50 Salm + 100 Fl	123	79
Concurrent 50 Salm + 250 Fl	192	188
Concurrent 50 Salm + 500 Fl	171	178
50 Salm	180	60
100 Fl	90	72
250 Fl	84	70
500 Fl	165	167

Demographics

The demographic factors gender, age and race are summarized on the following page for the Advair treatment groups. As discussed in the individual study reports, these demographic factors were largely consistent across treatment groups within a given study.

	Advair 50/100	Advair 50/250	Advair 50/500
Gender			
Female	106 (50%)	132 (50%)	71 (43%)
Male	107 (50%)	132 (50%)	96 (57%)
Age			
Mean years	35.3	41.1	46.2
12-17 years	38 (18%)	13 (5%)	3 (2%)
18-64 years	169 (79%)	234 (84%)	143 (86%)
≥ 65 years	6 (3%)	17 (6%)	21 (13%)
Ethnic Origin			
Caucasian	185 (87%)	238 (90%)	158 (95%)
Black	8 (4%)	15 (6%)	6 (4%)
NonCaucasian – Non Black	20 (9%)	11 (4%)	3 (2%)

Patient Disposition

The disposition of patients who were exposed to Advair formulations is shown below. As discussed in the individual study reviews there were disparities among treatment groups with regard to study discontinuation rates, particularly for trials SFCA3002 and 3003. The use of salmeterol with fluticasone, either in the Advair formulation or as concurrent treatment, was associated with lower discontinuation rates than treatment with individual agents or placebo.

	Advair 50/100	Advair 50/250	Advair 50/500
Number Completed	178 (84%)	230 (87%)	136 (81%)
Number Withdrawn	35 (16%)	34 (13%)	31 (19%)
Did Not Fulfill Entry Criteria	6 (3%)	4 (2%)	1 (<1%)
Lack of Efficacy	3 (1%)	4 (2%)	3 (2%)
Adverse Event			
Non-serious asthma	3 (1%)	4 (2%)	4 (2%)
Serious asthma or other	8 (4%)	8 (3%)	12 (7%)
Failed to Return	1 (<1%)	2 (<1%)	6 (4%)
Non-compliance	2 (<1%)	1 (<1%)	3 (2%)
Other	12 (6%)	10 (4%)	2 (1%)
Reason Not Recorded	0	1 (<1%)	0

Descriptive subset analyses were conducted to determine the effect of gender, age and ethnic origin. Overall, these factors did not appear to show a consistent correlation with discontinuation rates among the various treatments in the adult and adolescent trials.

Adverse Events

Adverse events that occurred among the completed adult clinical trials at a rate of at least 3 percent (by body system) of any combination treatment group appear in Appendix Q. ENT events were most frequent, followed by lower respiratory events. As in the reviews of the individual trials, there appears to be no indication that the Advair combination was associated with an overall higher rate of adverse events than concurrent administration or individual component therapy, particularly when differential

mean treatment time is considered. This was also true of the incidence of local effects such as hoarseness / dysphonia, pharyngitis and throat irritation.

Dose response among the Advair strengths was observed for the total number of lower respiratory events (26, 39 and 41 percent of the 50/100, 50/250 and 50/500 treatment groups, respectively.) This outcome is consistent with the severity of asthma among these three populations and may be unrelated to treatment.

There were 41 ocular events reported during the five adult trials. These events did not appear to occur at an increased incidence among the Advair patients. Three patients were diagnosed as having cataracts during the studies, including one patient on salmeterol, one on concurrent salmeterol 50 plus fluticasone 250 and one on Advair 50/500.

Cardiovascular events were reported by 51 patients (68 events). Of these, 31 were among Advair users, 22 were associated with concurrent use, two were reported in patients taking salmeterol, 12 were among fluticasone user and one event was reported in a placebo user. These numbers reflect inconsistency among the treatments with Advair appearing to have a higher overall rate of such events. However, differences in discontinuation rates (particularly between combination and salmeterol groups) again must be factored in and may account for much of the disparity.

Deaths

Reports of 22 deaths are included in the original submission and safety update. Among the five adult studies involving Advair formulations, two deaths were reported during Trial 3019. The first case was a 72 year old male with a history of hypertension and heart failure who discontinued Advair 50/500 for cataract surgery, experienced status asthmaticus and died after 14 days on a ventilator. The second death was a 61 year old male who died two months after being diagnosed with bronchial carcinoma while on concurrent salmeterol 50 mcg plus fluticasone 500 mcg. In neither of these deaths is Advair implicated in a causal manner.

Three deaths were reported during the MDI concurrent use studies (none of the patients were using Advair). The first patient (receiving TAA 600 mcg) died from a bilateral pulmonary embolism after hospitalization for sepsis. The second patient was hospitalized for cardiac tamponade and an aortic tear with dissection. Post-surgically, she developed severe coagulopathy and acute renal failure. The third case was a vehicle accident fatality. Again, the circumstances of these deaths do not appear to implicate Advair as a problem.

One death has been reported in the ongoing trials [redacted]
A patient using salmeterol [redacted] fluticasone 250 mcg was diagnosed with leukemia and died after 20 days on medication.

Three additional deaths were reported in the safety update submission from ongoing clinical trials. A placebo patient experienced a myocardial infarction after approximately two weeks of treatment for cardiac decompensation and influenza (Trial SFCB3024.) A second patient died from a severe COPD exacerbation during the run-in period of Trial SFCB3024. The third patient was a 70 year old female in Trial SAS40011 with a history of arterial hypertension and coronary artery disease who was found dead from acute cardiac failure by emergency services on her second day of treatment with Advair Diskus 50/250. It does not appear that the association of this event with treatment can be ruled out.

A total of 13 deaths have been received by the sponsor as spontaneous reports (12 in the original submission, 1 in the safety update) for patients using concurrent or combination treatment with salmeterol and fluticasone. Of these, five did not appear to be potentially related to treatment, including two in which the cause of death was unknown. Of the remaining eight reports, six were reports of acute respiratory distress, status asthmaticus or apnea, associated with cardiac arrest. The seventh event was a fatal myocardial infarction. The eighth report was of a 68 year old male who suffered asystolic cardiac arrest four days after adding salmeterol to a fluticasone regimen.

Of the 22 reports of death submitted to this application, eight appear to be potentially related to treatment with Advair or concurrent therapy, although none can be definitively linked to treatment or treatment failure. Such events are expected in a subset of patients with severe asthma and/or COPD and similar events have been observed in association with single agent treatment. It is not possible from these data to conclude whether Advair or concurrent therapy is associated with an increased risk of death relative to single agent treatment. It is noted that the sponsor is currently conducting an large, post-marketing study of the use of salmeterol to investigate any relation with its use and severe asthma events, including death. However, at the current time, there are no definitive data to suggest that salmeterol plays a causal role in the severe asthma events and/or cardiac events reported during clinical investigations and post-marketing experience.

Serious Adverse Events

The original submission and safety update describe 327 serious adverse events from various sources: adult clinical trials (71), pediatric clinical trial (4), ongoing [redacted] trials (13), MDI concurrent use studies (27), spontaneous reports (101), safety update/clinical trials (87) and safety update/spontaneous reports (24). Each event has been reviewed. It is noted that these events encompass a wide variety of products, use settings and outcomes and that events reported in ongoing trials generally cannot be associated with a treatment due to the blinded nature of the reported data. From each data source, the predominant effects were lower respiratory in nature.

Among the completed adult trials, there were 71 serious adverse events reported. Of these, 16 were considered lower respiratory events and nine were cardiovascular. Six lower respiratory events occurred in Advair patients, including 4 asthma exacerbations,

one LRTI and one disorder of the pleura. Asthma exacerbations also occurred in two concurrent use, two salmeterol, one fluticasone and one placebo patient. Of the nine cardiovascular events, three occurred during use of Advair. Each was an atrial fibrillation event and all three occurred in the same patient. Other events included myocardial infarction (1 concurrent use and two fluticasone patients) and tachycardia (in one concurrent use patient). See individual study summaries for details of all serious events in the adult trials.

Pregnancies

There were three pregnancies reported in the five adult trials of Advair. One was terminated in an elective abortion and the other two resulted in normal births. Seven additional pregnancies were reported during trials while patients were using [redacted] or concurrent treatment. One resulted in a missed spontaneous abortion, two in normal births and the remainder of the outcomes are unknown. Twenty seven pregnancies were reported via spontaneous reports, including 19 in patients using the [redacted] or concurrent therapy. Of the latter group, there were three spontaneous abortions, one missed spontaneous abortion and the remainder of pregnancies ended in normal births or the outcomes were unknown. Six pregnancies were reported in the safety update. Outcomes in two cases were elective terminations, were unknown in two cases and were normal births in the last two cases. There appears to be no information in the application that associates Advair with an increased incidence of abnormal pregnancies.

Eosinophilic Syndromes

Eosinophilic syndromes have been investigated by the division to a greater degree recently due to increased reports of Churg-Strauss syndrome and related syndromes occurring in asthma patients using or tapering from oral or inhaled corticosteroid doses.

Among the adult clinical trials, nine patients had eosinophil counts of at least 2000/mm^3 at some time during a trial. Of these, two cases were noted at randomization and the remainder were observed after treatment (discontinuation, Week 12 or during follow-up.) There were two Advair 50/250 patients, one Advair 50/500 patient, four concurrent therapy patients (one fluticasone 100, two fluticasone 250 and one fluticasone 500 patient), one salmeterol patient and one fluticasone 500 patient. All but two of these events were associated with a reported adverse event, primarily infection. These data may suggest that the [redacted] and concurrent treatments resulted in a greater number of patients with high eosinophil counts than fluticasone alone, but there appeared no difference between [redacted] and concurrent therapy and no cases of Churg-Strauss syndrome were reported.

There were seven patients identified in the sponsor's spontaneous event database who received salmeterol and fluticasone (either concurrently or as Advair) and experienced eosinophilic syndromes. In three of these cases, patients were receiving or decreasing concomitant oral corticosteroids. The first case was a 64 year old male who was

hospitalized 14 months after initiating fluticasone due to eosinophilia, sinusitis and pulmonary infiltrates. A 41 year old male was diagnosed with probable Churg-Strauss syndrome (peripheral eosinophilia, exudative pleural effusion, pericardial effusion and adrenal insufficiency) eight months after initiating inhaled fluticasone and simultaneously decreasing his dose of oral corticosteroid. A third patient was a 16 year old male who developed eosinophilia and sinusitis after being weaned off oral corticosteroids. It is unknown whether the four additional patients were using concomitant oral corticosteroids, although one patient is known to have been using concomitant montelukast.

Two additional spontaneous reports of eosinophilic syndromes were discussed in the safety update, both in patients using concurrent salmeterol plus fluticasone. In the first case, a 78 year old male experienced eosinophilia after several months on fluticasone (stable dose), which worsened following the addition of zafirlukast and phenytoin (for a possible seizure disorder.) Subsequently, fluticasone was discontinued and phenytoin was decreased, after which his eosinophil count dropped. The second case was reported in a 67 year old male whose fluticasone dose was lowered from four to two puffs twice daily during a prednisone taper. The patient developed neuropathy, progressive weakness in the lower extremities, eosinophilia and possible Churg-Strauss syndrome.

The incidence of serious eosinophilic events [ ] [ ] It is not possible to conclude from the cases whether Advair may have an association with such events nor whether any association might differ any association seen with fluticasone alone

Drug-Demographic Interactions

Adverse event data from the five adult clinical trials was evaluated for effects of gender, age and ethnic origin for each strength of Advair. In the gender effects evaluation, Advair 50/500 was associated with more adverse events in females (85 percent) versus males (63 percent.) This difference was largely attributable to an increased incidence of lower respiratory events (largely infections and increased asthma symptoms) that were experienced by 82 percent of females and 38 percent of males. This difference appears somewhat inconsistent with the data arising from the review of the pharmacokinetic data, which showed that males may have experienced lower bioavailability than females, hence may have had the potential for less efficacy and/or adverse events due to poorer asthma control. On the other hand, if exposure to fluticasone is in someway causal for lower respiratory infections (i.e., bronchitis, pneumonias), then this observation would be consistent with the PK observations.

Age did not appear to have an effect on the overall incidence of adverse events. Some disproportionate outcomes were noted due to the very small numbers of patients over age 65 in Advair 50/100 trials and of patients under the age of 18 in Advair 50/500 trials. The incidence of adverse events by ethnic origin was also greatly influenced by the relatively small number of non-Caucasian participants in these trials. No clinically

significant findings were apparent. Overall, the demographic factors of gender, age and ethnic origin did not appear to have an effect on incidence of adverse events.

Drug-Drug Interactions – Adverse Events

Qualitative evaluations of the effect of concomitant use of intranasal fluticasone, methylxanthines and six or more puffs per day of Ventolin on the incidence of adverse events were evaluated. With regard to intranasal fluticasone use, hoarseness/dysphonia, sinusitis and diarrhea were more frequent among users (approximately 18 percent) than non-users (approximately 2 percent) for Advair 50/100. This disparity was not seen at higher doses, and the observation for sinusitis may is likely confounded by indication (i.e., patients with SAR/PAR are more likely to suffer sinusitis and more likely to be on intranasal corticosteroids)For Advair 50/250, upper respiratory tract infections were more frequent among non-users (29 percent) than users (7 percent). These disparities are somewhat influenced by the fact that at each dose level there were significantly fewer users than non-users.

Only 5 (5 percent) of Advair 50/100 patients and 3 (4 percent) of Advair 50/250 patients used an average of six or more puffs of Ventolin per day, thus interpretation of the relative incidence of adverse events is limited. It appears that those with increased Ventolin use may have had higher rates of sinusitis, hoarseness/dysphonia and throat irritation.

Headache appeared less frequent among patients who did not use methylxanthines compared to those who did. Interpretation of these analyses are also confounded because only approximately 12 percent of patients used methylxanthines.

Long-Term Adverse Events

The rate of adverse events during the first and second 84 days of treatment during Trials SFCB3018 and 3019 were examined to determine whether treatment duration had an apparent effect. This analysis was confounded by discontinuations from the trial. However, the rate of adverse events appeared consistent between the two periods. Predominant adverse events reported in both periods were URTI, viral LRTI and headache.

Withdrawal Adverse Events

Four non-US studies included follow-up periods after cessation of treatment (SFCB3017, 3018, 3019 and 3020.) Adverse events that occurred during this period were described for each trial in Section VII.A. Twelve percent or less of the patients in each trial experienced adverse events during follow-up. The predominant events were respiratory, including infection and worsening asthma symptoms. Four of these event were considered serious, including two cases of asthma and two cases of pneumonia. Overall, the occurrence of these events did not appear convincingly related to the previously assigned treatment.

Cardiovascular Outcomes

ECGs were conducted in Trials SFCA3002, SFCA3003, SFCB3018 and SFCB3019. Clinically significant abnormalities associated with treatment were observed in 1, 3, 3 and 4 patients respectively in each of the trials. Of these, three patients in Trial 3019 were using combination therapy (Advair 50/500.) For each of these patients, ECGs returned to normal following cessation of therapy. Overall, the incidence of abnormal ECGs does not appear to have been elevated in association with Advair therapy relative to the other treatments.

QTc was determined in Trials SFCA3002 and 3003. Analyses of means, ranges and number of patients with prolonged QTc values showed no differences between Advair, combination and individual treatments. There were four or fewer patients in any of the treatment groups who experienced an observed prolongation event at any timepoint (pre- or postdose at screening, Week 1 or Week 12.)

Mean heart rates did not appear to show differences among the treatment groups of Trials SFCA3002 or 3003 (approximately 67 – 70 bpm for each group.) Ranges for heart rate values were also consistent among groups (max — for any patient), with the absolute highest values seen among salmeterol 50 mcg patients.

Holter monitoring showed the number of patients with ≥50 VEs and/or ≥50 SVEs in Trials SFCA3002 and 3002 was low and is summarized below.

Trial SFCA3002		Trial SFCA3003	
Placebo	3	Placebo	2
Advair 50/100	2	Advair 50/250	6
Salm 50	3	Salm 50	4
Flutic 100	9	Flutic 250	6

The maximum number of VEs per group at Screening and Week 12 is shown below.

	Trial SFCA3002		Trial SFCA3003	
	Screening	Week 12	Screening	Week 12
Placebo	**2269**	**3920**	1142	142
Advair 50/100	**190**	**1745**	**685**	**5091**
Salm 50	378	92	1186	11
Flutic 100	433	200	**244**	**276**

The maximum number of SVEs per group at Screening and Week 12 is shown below.

	Trial SFCA3002		Trial SFCA3003	
	Screening	Week 12	Screening	Week 12
Placebo	78	58	388	64
Advair 50/100	7010	93	**925**	**1015**
Salm 50	311	78	5819	2678
Flutic 100	**4983**[a]	**52570**	5561	280

[a]This value was also reported as 49,837 on pg 100 of Volume 55 and page 151 of Volume 120. The sponsor will be asked to verify the correct number.

Instances in which maximum values increased between screening and Week 12 are shown in bold. For Trial SFCA3002, each bolded pair was derived from a single patient.

In Trial SFCA3003, the maximums for VEs among Advair patients were also derived from the same patient at screening and Week 12. Maximum data among the treatment groups were not routinely observed in the Advair treatment groups. Overall, these data do not suggest that Advair is associated with increased electrocardiographic abnormalities relative to other treatment groups.

Vital signs were evaluated pre- and postdose at each clinic visit in Trials SFCA3002 and 3003. Pulse rate, diastolic and systolic blood pressure were analyzed for mean changes and categorical shifts. Advair 50/100 and Advair 50/250 did not appear to be associated with a greater effect on these parameters than the individual therapies, particularly salmeterol.

Clinical Laboratory Evaluations

Clinical laboratory data were collected during the five adult trials. Threshold laboratory abnormality analyses were conducted in each trial and shift analyses were also conducted in Trials SFCA3002 and 3003. As described for the individual trials, the occurrence of laboratory abnormalities was infrequent. With regard to shift analyses, the most frequent changes were: A shift from normal baseline to high serum glucose (7 to 12 percent of each treatment group), eosinophils (1 to 10 percent of each treatment group) or LFTs (up to 7 percent of each treatment group) or a shift to low RBC (2 to 7 percent of each treatment group) or neutrophils (2 to 5 percent of each treatment group). These shifts occurred in the placebo and each of the active treatment groups. None appeared to occur predominantly among Advair patients. Cases in which individual patients exceeded threshold values were described for each individual study. Overall, the Advair treatment groups did not appear to be associated with a higher incidence of such values than concurrent or individual therapy groups.

HPA Axis Effects

Morning cortisol assessments were conducted in Trials SFCA3003 and SFCB3017, 3018 and 3019. As discussed in the individual study reports, the overall incidence of abnormalities was low and not apparently increased in association with Advair use relative to concurrent or fluticasone use. However, AM cortisols are not very reliable in their sensitivity nor specificity for predicting HPA effects of steroids. However, the same lack of apparent effect was observed for outcomes of short cosyntropin testing in Trial SFCA3003.

The effects of concurrent intranasal fluticasone use on HPA axis outcomes were evaluated for SFCA3003. Overall, it appeared that the use of intranasal fluticasone was not associated with increased mean plasma cortisols or increased incidence of abnormal AM cortisol or ACTH stimulation.

Conclusion

Since the components of the Advair combination are marketed drug products, a significant related safety database had been established prior to submission of this application. The primary purpose of conducting safety evaluations in the combination product trials was to establish whether the combination is uniquely associated with unexpected safety concerns or safety events that occur with an increased frequency with respect to the individual components. None of the safety outcomes included in these trials suggest that there is a clinically important difference between Advair and the individual agents, nor from their separate, but concurrent administration.

X. CONCLUSION

Trials SFCA3002 (Advair 50/100) and SFCA3003 (Advair 50/250) have adequately demonstrated the effect of the combinations with respect to placebo. In addition, they appear to have provided ample data to support the evidentiary standard for 21 CFR 300.50 regarding fixed combinations of prescription products. Specifically for both trials, Advair was superior to fluticasone alone on the primary endpoint mean FEV_1 AUC after one week of treatment (reflecting primarily the effect of salmeterol), was superior to salmeterol on change from baseline in morning predose FEV_1 at endpoint (reflecting primarily the effect of fluticasone) and showed some superiority with regard to probability of patients remaining in the study over time (reflective of the overall action of the product). The secondary safety endpoints served as metrics of the clinical importance of the differences seen among the primary endpoints and were also supportive of the Advair combinations.

Trial SFCB3019 was supportive of the efficacy of Advair 50/500, both in its similarity to the performance of a concomitant use regimen and its relative superiority to fluticasone alone.

Safety endpoints in each of the pivotal trials, as well as in the supportive clinical program, did not appear to suggest increased incidence or the occurrence of unexpected safety findings relative to individual ingredient or concurrent therapy.

The Advair Diskus products are clinically approvable at this time. Further refinement of the labeling will be requested based in part on the discussion with the Pulmonary-Allergy Drugs Advisory Committee on November 23, 1999. The Committee provided input on the clinical utility of the fixed combination product and helped to identify appropriate labeling parameters, such as the patient populations that might be expected to receive optimal benefit from the products. The sponsor will be asked to revise their proposed labeling based on these recommendations.

XI. AUDITING FUNCTIONS / FINANCIAL DISCLOSURE

For the purposes of the clinical review, each of the study reports detailed in this document were inspected. The study reports, protocols, figures and most tables were routinely reviewed and supplementary tables and other appendices were consulted as necessary.

The reviewing biometrician, Dr. Elashoff, has confirmed that the results of Trials SFCA3002 and SFCA3003, both with and without data from Dr. Thomas Edwards' study site support comparable conclusions. Dr. Edwards' participation has been "Restricted" by CDER's Division of Scientific Investigation (DSI) due irregularities in the clinical trial conduct procedures found on inspection of his study site (for a different application). Twenty one patients were enrolled from this site into Trial SFCA3002 and 12 were enrolled into Trial SFCA3003. Safety data from Dr. Edward site were included in the ISE and ISS.

At the request of the division, as part of routine auditing procedures, DSI has been asked to inspect Dr. Chervinsky's site for Trials SFCA3002 and SFCA3003, as well as Dr. Windom's site for Trial SFCA3003. These sites were selected based primarily on their relatively high patient enrollment and related influence on the study analyses. The official response from DSI has not yet been received by the division.

A financial disclosure statement was provided by the sponsor. It states that there were 11 "covered clinical studies," "Glaxo Wellcome does not compensate clinical investigators in such a way as the total amount would vary with outcome of the study," no payments were made on or after February 2, 1999 (the initial time of the relevant reporting window), and "no clinical investigator participating in the 'covered studies' has a proprietary interest in salmeterol / fluticasone propionate Discus Inhalation Powder." The latter assessment was said to be based on "information available internally" at Glaxo Wellcome. A signed form FDA 3454 was included.

XII. LABELING COMMENTS

The proposed package insert was reviewed for accuracy and completeness and compared to the approved version of Serevent Diskus and Flovent Rotadisk, as well as the proposed version of Flovent Diskus labeling. The following comments are noted.

DESCRIPTION:

- Information regarding drug delivery at various inspiratory flow rates differs in the proposed labeling from that of Serevent or Flovent Diskus. These data will need to be confirmed with the chemistry reviewer for final labeling review.

CLINICAL PHARMACOLOGY:

- Each subsection in this section is organized to provide information regarding salmeterol alone, fluticasone alone and Advair (with separate descriptions for each ingredient). It is very lengthy and, although DCPBP reviewers asked that the January 13, 2000 labeling version use this format, additional revisions are needed to to condense this information. Dr. Uppoor has agreed that this can be accomplished in a team meeting / labeling re-write session for the final labeling.
- Mechanism of action for salmeterol and fluticasone are identical to the labeling of the single ingredient products. The mechanism for Advair Diskus describes that the two drugs have [redacted] This text may imply an [redacted] claim for salmeterol and should be revised for clarity in the final labeling.
- Pharmacokinetics have been reviewed by Drs. Chen and Uppoor and comments are being forwarded to the sponsor.
- A Drug-Drug Interaction subsection conveys information contained in the Flovent labels, with an additional general statement about [redacted]
- Pharmacodynamics are described for salmeterol with a condensed version of the Serevent section. Specific information regarding [redacted]