CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-077

MEDICAL REVIEW

Medical Officer Review

Division of Pulmonary Drug Products (HFD-570)

Application #:	NDA 21-077	**Category of Drug:**	Long acting β_2-agonist /corticosteroid
Sponsor:	GlaxoWellcome	**Route of Administration:**	Oral Inhalation
Proprietary Name:	Advair Diskus	**Medical Reviewer:**	Susan Johnson, Ph.D.
USAN/Established Name:	Salmeterol/Fluticasone propionate	**Review Date:**	August 23, 2000

Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
February 25, 2000	February 27, 2000	Response to AE	
February 25, 2000	February 27, 2000	Safety Update	
April 18, 2000	April 19, 2000	Labeling	
July 17, 2000	July 18, 2000	Labeling	
August 18, 2000	August 21, 2000	Labeling	

Related Applications (if applicable)

Overview of Application and Review:
Application is clinically approvable, pending completion of labeling negotiation.

Outstanding Issues:

Recommended Regulatory Action

New Clinical Studies: _____ Clinical Hold
_____ May Proceed

NDA/Supplements: __X__ Approval
_____ Approvable

Signature: /S/ Medical Reviewer **Date:** 8/22/2000

Concurrence: /S/ ___, Div Dir **Date:** 8/23/2000

cc: Div File
NDA 21-077
HFD-570/Jani

This document contains reviews of four elements: the six-month safety update, case report forms from the original NDA, the sponsor's response to the January 27, 2000 approvable letter and proposed draft labeling.

I. Safety Update (February 25, 2000)

The safety update submission covers the time period from April 1, 1999 to January 15, 2000. Deaths, serious adverse events, withdrawals due to adverse events, pregnancies and other safety information from 13 on-going and 10 completed studies are reported for Advair Diskus and the MDI combination formulation. Spontaneously reported adverse events are included for patients using either Advair Diskus or salmeterol and fluticasone concurrently. A summary of eosinophilic events is included.

Reports of **deaths** were provided from all clinical trials (6 cases) and spontaneous reports (9 cases) that occurred subsequent to use of the combination product (dry powder or the MDI formulation). Case narratives reported that the deaths were considered by the investigators or reporters to be unrelated (or have an unlikely relationship to the combination product) except in Case B0073512A. The presenting symptom for this 78 year old male patient was a short episode of right sided, sharp thoracic pain following inhalation of the study drug. The study medication was discontinued and the patient died approximately four months following this event of multiple diseases including metastatic prostate cancer. Overall, it appears that combination therapy was not closely associated with any fatal cases reported in this safety update.

Patient ID	Treatment	Cause of Death
71 yo female / B0060091A		Leukemia
70 yo male / B0071256A	Diskus 500/50	Postoperative complications from surgical bypass
48 yo male / B0069956A	Diskus 500/50	Edemato-ascitic cirrhosis, septicemia, ARDS
76 yo female / B0068359A	Diskus 250/50	Pneumonia / right heart failure
69 yo male / B0069602A	Diskus 250/50	Small cell carcinoma
78 yo male / B0073512A	Diskus 250/50	Metastatic prostate cancer, chronic bronchitis, CIHD
68 yo male / B0068434	Diskus 250/50	Myocardial infarction
? yo female / B0068639A	Diskus 250/50	Right heart failure
86 yo male / B0069909A	Diskus 250/50	Cardiac failure
78 yo female / B0069949A	Diskus 250/50	Cachexia, cor pulmonale, COAD
80 yo male / B0068141A	Diskus 250/50	Gastric ulcer with perforation
87 yo male / B0069910A	Diskus 250/50	Cancer of colon
64 yo male / B0074235A	Diskus 100/50	Pneumothorax
46 yo male / B0068789A	Diskus 250/50	Unknown
79 yo female / B0069442A	Diskus 250/50	Underlying multiple diseases

Serious adverse events were reported for 16 active combination Diskus users and nine active combination MDI users from completed trials. The 16 Diskus cases occurred in patients using either 250/50 or 100/50 and consisted of: myocardial infarction/coronary bypass surgery, atrial fibrillation, fractured upper limb, overdose with paracetamol, subacute intestinal obstruction, prostatitis, breast cancer, pulmonary mycobacterium tuberculosis and exacerbation of asthma (8 cases). Four of the asthma exacerbation cases were considered to be potentially related to drug use / lack of effect. The nine MDI cases included: leukemia (fatal), appendicitis (2 cases), asthma exacerbation (3 cases), influenza, arthritis of the knee, infective exacerbation (non-site specific). One of the asthma exacerbations was considered related to the potential lack of efficacy of the study medication.

In addition, 302 serious adverse events were reported from ongoing trials (for asthma or other indications). Limited interpretation of these events is possible, given that the identity of the products used by reporting patients remained blinded at the time of submission. There appears to be no single event type that showed a notably high incidence of reports, with the exception of acute asthma / asthma exacerbation, as expected in the treatment populations of these trials.

Serious adverse events were also identified in 34 spontaneous reports. Twelve of these events were considered by the reporter to be potentially related to the medication including: acute asthma (2 cases), eosinophilic pneumonia (see subsequent discussion of eosinophilic conditions), tachycardia/tremor (2 cases), possible cardiac arrest/focal convulsions/loss of consciousness, exacerbation of angina, anaphylactic shock, spontaneous abortion, and muscle cramp/lockjaw.

Pediatric patients were reported to have experienced two serious adverse events in clinical trials: a six year old child was reported to have had appendicitis and a 10 year old child was reported to have had chest pain.

Patients withdrawn from clinical trials due to adverse events numbered 31 active combination Diskus patients and 18 active combination MDI patients. The most frequently reported reason for withdrawal was asthma exacerbation. Local reactions, including oral candidiasis, oral swelling, and hoarseness/dysphonia (2 cases) were also reported. These events are adequately addressed in the propsed ADVERSE EVENTS section of the labeling.

Pregnancies were reported in one patient using the combination product during clinical trials (pregnancy outcome unknown) and in three spontaneous reports (outcome unknown for two pregnancies and a spontaneous abortion occurred in the third case). Sixteen additional pregnancies were reported in ongoing trials for which information regarding assigned treatment remained blinded at the time of submission.

An **eosinophilic condition** was reported in one spontaneously submitted report. A 67 year old male with a history of coronary heart disease, myocardial infarction and multiple allergies received the combination powder for two weeks before being

hospitalized for exclusion of myocardial infarction. Examinations showed eosinophilic pneumonia, pulmonary infiltrate right upper lobe and eosinophilia (up to 51 percent eosinophils in blood). Treatment with the combination was discontinued and the event resolved after 16 days of treatment with "steroids" (presumably oral corticosteroids). Currently proposed PRECAUTIONS and ADVERSE EVENTS sections of the labeling adequately address the potential for such cases associated with Advair.

A summary of non-serious adverse events and other safety endpoints examined in the completed or ongoing clinical trials, including laboratory tests, HPA axis function and ECGs, were reported. There appear to be no new safety concerns (that have not been previously reported in the NDA review).

The sponsor reported on the outcome of a comprehensive **literature** search for the time period referenced by this submission and found only publications of GW clinical studies or secondary information (review articles, letters, bulletins).

As of January 21, 2000, three strengths of the combination product were **approved in 40 countries worldwide**, including Canada and the U.K. and applications were pending in another 30 countries. The tradenames Seretide, Viani and Advair are used and the delivery device is referred to as Diskus or Accuhaler.

There were 168 complaints regarding **device durability** through December 31, 1999 from approximately ——— devices manufactured. The sponsor considers 157 to be "unsubstantiated" or "inconclusive". Of the 11 substantiated complaints, five were caused by device jamming and six were reported when the device clicked more than once when the lever was actuated. The sponsor claims to have instituted measures to address both issues and this information will be validated by Dr. Koble, the chemistry reviewer.

In conclusion, the safety update provided information regarding deaths, serious adverse events, adverse events leading to withdrawals from clinical trials, pregnancies and other safety parameters in clinical trials. No information was reported which appears to suggest previously unidentified events which have the potential to be associated with use of the combination.

II. Case Report Forms (CRFs)

This section documents that CRFs were reviewed for patients who discontinued from the pivotal trials due to death or adverse events, as described below. See the Medical Officer review dated January 24, 2000 for discussion of these cases.

Trial SFCA3002:

- No Deaths
- 3 Serious Events
  - 1 Placebo Pt. #0074
  - 2 Salmeterol Pts. # 0221, 0232
- 1 Non-Serious Event (Fluticasone Pt. # 0145)
- 3 Adverse Event as Secondary Reason for Withdrawal
  - 1 Placebo Pt. # 0042 -- use of excluded medications
  - 1 Combination Pt. # 0374 -- use of excluded medications
  - 1 Fluticasone Pt. # 0039 -- lack of efficacy

Trial SFCA3003:

- No Deaths
- 3 Serious Events
  - 1 Fluticasone Pt. # 0739
  - 2 Salmeterol Pts. # 0913, 1256
- 3 Non-Serious Events
  - 2 Salmeterol Pt. # 0761, 1017
  - 1 Fluticasone Pt. # 0722

Trial SFCB3019:

- 2 Deaths (Pts. #2749 and #2872);
- 5 Serious Events
  - 2 Combination Pts. # 2067, 2654;
  - 3 Concurrent Therapy Pts. # 2630, 2653, 2765
- 26 Non-Serious Events, Deemed by Investigators as Potentially Drug Related
  - 8 Combination Pts. # 2094, 2161, 2179, 2183, 2354, 2439, 2472, 2763;
  - 7 Concurrent Therapy Pts. # 2162, 2252, 2306, 2349, 2428, 2435, 2453;
  - 11 Fluticasone Pts. # 2046, 2069, 2121, 2127, 2129, 2173, 2258, 2260, 2353, 2424, 2900
- 21 Non-Serious Events, Considered Unrelated to Drug – CRFs not reviewed

III. Response to Approvable Letter (February 25, 2000) Labeling Submissions (July 17, April 18, & August 18, 2000)

Comments 17 – 30 from the January 27, 2000 approvable letter have clinical implications and were responded to in the February 25 submission. This submission, as well as subsequent labeling negotiations with the sponsor, have contributed toward resolution of these issues. The attached draft labeling is current as of August 18, 2000, but is not the approvable version of the labeling. Additional negotiation with the sponsor is underway.

Response to Comments:

17. The tradename currently proposed by the sponsor is acceptable.
18. The established name currently proposed by the sponsor is acceptable.
19. Information included in the labeling about the clinical effect of inhalation flow rate has been revised in the labeling.
20. Disposal instructions have been revised in the labeling.
21a. The PPI has been revised, but is not completely consistent with other Glaxo products. Differences among the labels are intentional and designed to optimally convey information regarding Advair.
21b. Instructions for patient inhalation procedures are acceptable.
22. In-use dating has been changed to a one-month period and is acceptable.
23. The expiration date format has been modified and is acceptable.
24. The overwrap discard date format has been modified and is acceptable.
25. The device discard date format has been modified and is acceptable.
26. Changes to the CLINICAL TRIALS section of the labeling are acceptable and, in particular, reflect current preferences regarding the portrayal of secondary endpoints, including "asthma quality of life" data, and tertiary endpoints in labeling.
27. The INDICATION for Advair Diskus has been substantially revised and is acceptable. Specifications for product use are particularly emphasized in the DOSAGE and ADMINISTRATION section.
28. The box warning has been revised to reflect that Advair should not be used when transferring patients from oral corticosteroids. This statement is reemphasized in the PRECAUTIONS and DOSAGE AND ADMINISTRATION sections where implications for use of oral corticosteroids may be pertinent.
29. The DOSAGE and ADMINISTRATION has been significantly modified. Of primary concern is that the section not emphasize [redacted] since data supporting the use of Advair for this purpose have not been submitted.

The attached draft labeling also incorporates the Division's responses to consultations received from the Office of Post-Marketing Drug Risk Assessment (dated January 27, 2000), regarding medication error prevention / product name, and two consults from the Division of Drug Marketing, Advertising and Communications, dated December 29, 1999, regarding the "asthma quality of life" labeling proposals, and January 22, 2000, regarding patient information in the PI and the PPI.

IV. Proposed Draft Labeling (Current as of August 18, 2000)

Modifications to the attached draft labeling were conveyed to the sponsor in a telecon on August 22, 2000. Final labeling has not yet been agreed upon.

APPEARS THIS WAY
ON ORIGINAL

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Draft labeling

Medical Officer Review

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

Application #:	NDA 21-077	**Category of Drug:**	Long-Acting β_2-Agonist
Sponsor:	Glaxo Wellcome Inc.	**Route of Administration:**	Dry Powder for Oral Inhalation
Proprietary Name:	Advair (3 strengths)	**Medical Reviewer:**	Susan Johnson, Ph.D.
USAN/Established Name:	Salmeterol xinafoate/ Fluticasone propionate	**Review Date:**	January 24, 2000

Submissions Reviewed in This Document

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
March 24, 1999	March 25, 1999	Original NDA	
July 16, 1999	July 19, 1999	Safety Update	
January 13, 2000	January 14, 2000	Draft Labeling	

Related Applications (if applicable)

Overview of Application and Review: **See Executive Summary, page ii.**

Outstanding Issues: **Application is clinically approvable. Comments to sponsor regarding labeling are provided on page 72.**

Recommended Regulatory Action

New Clinical Studies: _____ **Clinical Hold**
_____ **May Proceed**

NDA/Supplements: _____ **Approval**
__X__ **Approvable**

Signature: /S/ **Medical Reviewer** **Date:** 1-24-00
Susan Johnson, Ph.D.

Concurrence: /S/ **Division Director** **Date:** 1/24/00
Robert Meyer, M.D.

EXECUTIVE SUMMARY

Glaxo Wellcome, Inc. is seeking approval of three strengths of Advair Diskus, a combination dry powder inhaler containing salmeterol xinafoate 50 mcg per inhalation plus fluticasone propionate in doses of 100 mcg, 250 mcg or 500 mcg per inhalation. The proposed dose of each strength is one inhalation twice daily. The proposed indication is in "the maintenance treatment of asthma [redacted] in patients 12 years of age and older where combination therapy is appropriate."

Pivotal clinical trials in this application were designed to demonstrate the safety and efficacy of Advair Diskus as compared to placebo or active controls. In addition, two of the pivotal trials were required to provide data that meets the evidentiary standard set in 21 CFR 300.50 for fixed combinations of prescription drugs. Specifically, the regulation states that "two or more drugs may be combined in a single dosage form when each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug."

There were three pivotal trials in the application, including two U.S. trials (SFCA3002 and SFCA3003) and one European trial (SFCB3019). Trial SFCA3002 was a randomized, double blind, parallel group design in adults and adolescents age 12 and older, involving four treatment arms: Advair Diskus 50/100 (n=92), salmeterol 50 mcg (n=92), fluticasone 100 mcg (n=90) and placebo (n=82). Patient enrollment was stratified by pre-study use of either salmeterol or specified doses of inhaled corticosteroids. The design of Trial SFCB3003 was similar to that of SFCA3002, however, all patients enrolled had previously been using specified doses inhaled corticosteroids. Treatment arms included Advair Diskus 50/250 (n=84), salmeterol 50 mcg (n=88), fluticasone 250 mcg (n=84) and placebo (n=93). In both trials, a two-week run in period was followed by a 12 week treatment period. The three primary efficacy endpoints in each study were mean FEV_1 AUC after one week of treatment, change from baseline in morning predose FEV_1 at endpoint (Week 12 or time of discontinuation) and probability of patients remaining in the study over time.

Results of both studies showed that Advair Diskus was statistically superior to placebo for each primary endpoints. In addition, Advair Diskus was statistically superior to both salmeterol alone and fluticasone alone for most endpoints. Secondary endpoints, including AM and PM PEFR, use of Ventolin MDI, asthma symptom severity and nocturnal awakenings were consistently supportive of the primary endpoint outcomes during both SFCA3002 and SFCA3003.

Trial SFCB3019 evaluated the safety and efficacy of Advair Diskus 50/500 (n=167) as compared to salmeterol 50 mcg administered concurrently with fluticasone 500 mcg (n=171) and to fluticasone 500 mcg (n=165) administered alone during a 28 week treatment period. The primary endpoint was mean change from baseline in morning PEFR during the first 12 weeks of treatment. Advair Diskus was statistically superior to

fluticasone alone, but no difference was observed between Advair Diskus and concurrent therapy.

Safety data in each of the pivotal trials, including adverse events, ECGs, Holter monitoring and clinical laboratory data (including HPA axis function assessment), did not show that the Advair combination was associated with an increased incidence of safety issues, or with unexpected outcomes, as compared to the individual ingredients given alone or concurrently.

The clinical utility of the Advair Diskus products was discussed with the Pulmonary-Allergy Drugs Advisory Committee on November 23, 1999. The committee's primary recommendation was to create labeling that is reflective of the population studied and to appropriately identify patients in whom these products should be indicated for optimal benefit. Further communication with the sponsor will be undertaken to clarify these issues. The products are clinically approvable at this time.

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I. BACKGROUND

The three Advair Diskus products proposed in this application are dry powder inhaler combinations of doses of salmeterol xinafoate 50 mcg with different amounts of fluticasone propionate (100 mcg, 250 mcg or 500 mcg). Support for the Advair 50/100, 50/250 and 50/500 combinations are based in part on the previously approved products:

Serevent Inhalation Aerosol	(NDA 20-236, approved February 1994),
Serevent Diskus	(NDA 20-692, approved September 1997),
Flovent Inhalation Aerosol	(NDA 20-548, approved March 1996),
Flovent Rotadisk	(NDA 20-549, approved November 1997),
Flovent Diskus	(NDA 20-833, application pending).

At present, the Flovent Diskus formulation appears to be clinically approvable and is likely to be approved pending resolution of remaining CMC concerns. Doses are consistent with the fluticasone propionate component of the proposed Advair formulations. The combination products are approved in 28 countries worldwide.

Given that the individual ingredients of the Advair products have been clinically established safe and effective in alternate formulations, the primary regulatory issues for this application are to verify that the formulations of Advair provide the expected safety and efficacy profiles and that the combination products meet the requirements set forth in the Code of Federal Regulations (21 CFR 300.50) regarding fixed combinations of prescription drugs. In essence, this regulation requires sponsors of a combination product that contain ingredients which have not previously been dosed in a single combination formulation to establish that each ingredient of that combination provides benefit, i.e., that there is sufficient rationale for each component to be contained in the combination. Therefore, this application contains pivotal trials which were designed to compare the safety and efficacy of the combination to placebo and both of the individual ingredients administered alone. Specifically, the regulation states that "two or more drugs may be combined in a single dosage form when each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug."

The sponsor proposes the product for use in "the maintenance treatment of asthma [redacted] in patients 12 years of age and older where combination therapy is appropriate." Proposed dosing of each strength is twice daily.

II. CHEMISTRY, MANUFACTURING AND CONTROLS (CMC)

The proposed formulations are doses of 50 mcg [redacted] salmeterol xinafoate with either 100, 250 or 500 mcg of [redacted] fluticasone propionate, [redacted] lactose to a total weight [redacted]. Each dose is contained in an individual foil blister, part of a blister strip linking 60 blisters (28 blisters for hospital/sample packs). Doses are administered via a plastic Diskus device which opens each blister and disperses medication when patients generate an air stream by inspiring through the device's mouthpiece.

At present, the CMC section of this application is under review by Dr. Koble. The division and sponsor have had considerable communication regarding the Diskus formulation containing various drug substances and it is anticipated that pending issues, primarily related to manufacturing controls to ensure consistent product quality, are resolvable. Dr. Koble has confirmed that the formulations used in the pivotal trials of this application appear comparable to the formulation proposed for marketing.

III. PHARMACOLOGY/TOXICOLOGY

This application is currently under review by Dr. Sancilio. Given the previous experience of the division with the proposed ingredients and the formulation, it is anticipated that all pending preclinical issues will be adequately resolved. These issues are not expected to have substantive clinical implications.

IV. CLINICAL PHARMACOKINETICS

Dr. Chen, of the Office of Clinical Pharmacology and Biopharmaceutics (DPEII), has completed a draft review of the clinical pharmacokinetics and pharmacodynamic data (to determine systemic exposure) submitted in this application. Three studies were designed to compare the pharmacokinetics of the combination product with that of the single ingredients and/or the single ingredients given concurrently in healthy volunteers. The goal of these studies was primarily to establish whether the Diskus combination formulation results in different bioavailability of the ingredients than previously reviewed formulations given concurrently. These studies also addressed the potential drug-drug interaction between salmeterol and fluticasone.

Trial SFCB1002 was a single dose study comparing doses of 5 inhalations of Advair 50/100 mcg with 5 inhalations of fluticasone 100 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 given alone. In Trial SFCB1004, a 10 day multiple dose study, 2 inhalations BID of the combination 50/250 mcg were compared with fluticasone 250 mcg and salmeterol 50 mcg, each administered alone as 2 inhalations BID. Trial SFCB1005 showed that the combination product had a higher Cmax for salmeterol than with concurrent administration. This finding was not confirmed by Trial SFCB1004, the multiple dose comparison. Significant differences in fluticasone bioavailability were not seen among the various dosing regimens.

A single pharmacokinetic evaluation of asthma patients was undertaken, during the pivotal safety and efficacy trial SFCB3019. This trial compared BID dosing of the Advair combination 50/500 mcg for 28 weeks with concurrent administration of salmeterol 50 mcg and fluticasone 500 mcg and with fluticasone 500 mcg alone. It appeared that no significant drug interactions altered bioavailability among the three treatments. In cross-study comparisons, Dr. Chen noted that the combination product appeared less bioavailable in asthmatics than in healthy subjects. Also, Trial SFCB3019 showed a gender difference, with males having approximately a 40 percent reduction in AUC and

Cmax for fluticasone compared to females. The efficacy outcomes for this trial will be compared based on gender subgroups in the Integrated Summary of Efficacy. In addition, the pharmacodynamic aspects of the pharmacokinetic trials will be further reviewed in Section VII.B.

V. CONDUCT OF THE REVIEW

The pivotal clinical trials for this application were conducted in adults and children age 12 and older. There were two U.S. safety and efficacy trials, SFCA3002 and SFCA3003 which directly addressed the required comparison of the combination with its individual ingredients. Each of these trials were placebo controlled, with SFCA3002 evaluating the combination 50/100 mcg dose and SFCA3003 evaluating the 50/250 mcg dose. Advair 50/500 was principally evaluated in the European Trial SFCB3019. This trial was not placebo controlled, but compared the combination to concurrent administration of the individual components and to fluticasone 500 mcg alone.

These pivotal trials are supported by eight active control trials in adults. A single active control trial was conducted in children, age 4 to 11 years, [redacted] Five additional trials were submitted in support of the concurrent use of salmeterol and fluticasone and will be discussed in the Integrated Summary of Safety.

The clinical review has been conducted in conjunction with the biometrics review by Dr. Elashoff of the Division of Biometrics II, particularly for the primary endpoints of Trials SFCA3002 and SFCA3003, in which the sponsor's analyses are were replicated and evaluated. In some instances, alternate analyses were conducted, using modified decision-rules regarding missing data, censoring, dropouts, etc. Dr. Elashoff's review should be consulted for details. Her overall conclusion was that the outcomes of her analyses support comparable conclusions as the sponsor's original analyses.

VI. PIVOTAL CLINICAL TRIALS

A. TRIAL SECA3002

TITLE: A Randomized, Double-Blind, Parallel-Group Trial Evaluating the Safety and Efficacy of Salmeterol 50 mcg BID and Fluticasone Propionate 100 mcg BID Individually and in Combination and Placebo in Subjects with Asthma.

OVERVIEW: The purpose of this study was to determine the effectiveness of the combination of salmeterol 50 mcg and fluticasone proprionate 100 mcg, administered BID as the proposed Advair 50/100 mcg formulation, relative to treatment with either single agent or placebo. A screening clinic visit and a two week run-in period were followed by 12 weeks of treatment with one of the four randomly assigned treatments. Primary efficacy analyses were based on FEV_1 data collected at clinic visits at Day 1, Week 1, Week 12 and the endpoint of the treatment period. The rate at which patients discontinued the trial for lack of effect was also a primary endpoint. (Volumes 55-63)

STUDY DATES: August 1, 1996 – July 15, 1997

INVESTIGATORS: Forty two investigators in the U.S. agreed to participate and 35 of these enrolled patients. See Appendix A.

PATIENT POPULATION:

General – Male and female asthmatic patients age 12 years or older were eligible for enrollment if they were current non-smokers with ≤ 10 pack year history and otherwise in generally in good health as ascertained by history, physical exam, 24-hour Holter monitoring (at selected sites), 12-lead ECG, chest x-ray and clinical laboratory parameters. Patients who had experienced a sinus, middle ear or viral or bacterial respiratory tract ear infection in the two weeks prior to screening were not eligible for enrollment.

Asthma – For enrollment into the **run-in phase**, patients were required at screening to have received pharmacotherapy for asthma for the preceding six months, have a best FEV_1 of 40 to 85 percent of predicted normal and to demonstrate at least 15 percent reversibility in FEV_1 within 30 minutes following two puffs of Ventolin. Patients' prior asthma therapy was required to have been either:

> **Inhaled corticosteroids** for the 3 months preceding screening in doses of beclomethasone dipropionate (BDP) 252-420 mcg per day, triamcinolone acetonide (TAA) 600-1000 mcg per day, flunisolide 1000 mcg per day or fluticasone propionate 176 mcg per day, **OR**
> **Salmeterol** for at least 1 week prior to screening, without the use of inhaled corticosteroids concomitantly for at least 1 month prior to screening.

Enrollment into the **double-blind phase** of the trial and randomization to treatment was limited to patients whose best FEV_1 at the clinic visit subsequent to the run-in period (Day 1) was within 15 percent of the screening visit value and within 40 to 85 percent of predicted normal. For patients who were using inhaled corticosteroids at screening,

those who used more than 12 puffs per day of Ventolin on more than 3 of their last 7 run-in days were excluded. For patients who were using salmeterol at screening, those who used more than 6 puffs per day of Ventolin on more than 3 of their last 7 run-in days were excluded. Finally, any patient who awakened due to asthma on more than 3 of their last 7 run-in nights was excluded.

Concomitant medication - Patients who were eligible for enrollment were required to withhold the following medications for the specified time prior to screening and for the duration of the trial:

Oral corticosteroids	1 month
Parenteral corticosteroids	1 month
Inhaled anticholinergics	24 hours
Inhaled cromolyn or nedocromil sodium	1 month
Oral short-acting β_2-agonists	12 hours
Oral long-acting β_2-agonists	24 hours

Patients were allowed to continue during the trial on stable doses of theophylline, provided that adequate washouts were observed prior to clinic visits. Patients were also eligible if they continued throughout the trial to receive stable doses of antihistamines, immunotherapy or Flonase (fluticasone propionate) Nasal Spray.
Patients were not enrolled if they were receiving β-blockers, oral decongestants, benzodiazepines, digitalis, phenothiazines, polycyclic antidepressants, MAO inhibitors.

PROCEDURES / ENDPOINTS:

Following assessment of enrollment criteria at the screening visit, eligible patients were instructed to use a single inhalation from a placebo Diskus device (single blind) at approximately 12 hour intervals, use two puffs of Ventolin as needed, and complete their daily diary card, including a record of AM and PM PEFR, for a period of two weeks. Following the run-in period, patients returned to the clinic for evaluation of their asthma stability (see previous section) and, if eligible, to be randomly assigned to one of four treatments:

- Advair 50 mcg salmeterol / 100 mcg fluticasone Diskus – one inhalation BID.
- Serevent (salmeterol) 50 mcg Diskus – one inhalation BID.
- Fluticasone propionate 100 mcg Diskus – one inhalation BID.
- Placebo Diskus – one inhalation BID.

During the 12 week treatment period, patients completed diary cards daily and returned to the clinic for interim evaluations at Weeks 1, 2, 3, 4, 6, 8, 10 and 12.
Efficacy data included:

- **Pulmonary function testing.** On Day 1 of the treatment period and at Weeks 1 and 12, twelve hour serial FEV_1 assessments were performed at 30 minutes and immediately prior to morning dosing, then at 30 minutes and 1, 2, 3, 4, 6, 8, 10 and 12 hours postdose. At other clinic visits, a single predose assessment was made.

  FEV_1 data were analyzed in several ways. There were two **primary endpoints** based on FEV_1 data, defined as **area under the serial FEV_1 -time curve relative to pre-treatment baseline at Week 1** and **mean change from baseline at endpoint in morning predose FEV_1**. For AUC, analyses at Week 12 were also conducted,

but were not identified as primary due to confounding from the disproportionate dropout rates among treatment groups. Pre-treatment baseline was defined as the average of the two predose timepoints from Day 1 (a new baseline was not established at each clinic visit, although predose data were collected). Study endpoint was Week 12 for completers and the discontinuation visit for those patients who did not complete the treatment period.

Both AUC and morning predose FEV_1 were analyzed using ANOVA models. In addition to the primary endpoints, serial FEV_1 data were analyzed based on change from pre-treatment mean with regard to the individual timepoints and a weighted (by time interval) average of all timepoints (compared to 0) using ANOVA. The ANOVA model employed the factors "cluster" (of investigators, by region) and "stratum" (based on prior salmeterol or inhaled corticosteroid use).

- **Discontinuation from the trial for lack of effect.** After randomization, patients were discontinued from the study for lack of efficacy if the patient experienced a clinical exacerbation or if at any clinic visit the patient's 30 minute pre-dose FEV_1 was less than 20 percent below the randomization clinic visit value. In addition, patients were discontinued for lack of efficacy if, in the 7 days immediately preceding each clinic visit, any of the following occurred:
  There were more than 2 days in which 12 or more puffs of Ventolin were used.
  There were more than 2 nights in which awakenings due to asthma required treatment with Ventolin.
  There were more than 3 days when PEFR values fell below the lower limit, defined at the randomization clinic visit as a 20 percent decline from the mean PEFR for 7 days the days preceding the randomization clinic visit.

Probability of remaining in the study was defined as the third **primary endpoint.** This parameter was analyzed using a log-rank test based on Kaplan-Meier estimates of the number of patients who withdrew from the study due to lack of efficacy. This number included patients who met the specified discontinuation criteria or had a clinical exacerbation. Patients who discontinued for reasons other than lack of efficacy were censored from these analyses.

Since many of the patients in this trial were discontinued prematurely, an endpoint value was used in many of the analyses. Endpoint values that were comprised of a single data point collected at the visits during which it was determined that patients were to be discontinued. Other endpoint values, such as diary data, are an average over the last seven days of the evaluable period.

Subgroup data were summarized for the three primary endpoints, serial FEV_1 AUC, morning pre-dose FEV_1 and probability of remaining in the study, based on whether patients did or did not use concurrent intranasal fluticasone. A second subgroup analysis was conducted based on pre-study asthma treatment (inhaled corticosteroid or salmeterol). No statistical analyses were conducted.

- **PEFR** was recorded on daily diary cards. It was measured throughout the run-in and treatment periods prior to morning and evening dose of study medication. Change from baseline (the average of the 10 days immediately prior to randomization) in morning and evening PEFR, percent predicted morning and evening PEFR and morning/evening differential were analyzed by treatment group at regular timepoints during the trial.

- **Asthma Quality of Life Questionnaire (AQLQ)** was administered in clinic on Day 1 and Week 12. The questionnaire contained 32 items in four domains: activity limitations (11 items), symptoms (12 items), emotional function (5 items) and environmental stimuli (4 items). In addition, an overall score was derived from the 32 items. See sample in Appendix B. ANOVA was used to analyze differences between and within treatment groups for individual domains and the overall score.

  The **secondary efficacy endpoints** were defined as change in PEFR (baseline versus endpoint) and AQLQ (Day 1 versus Week 12). For the purposes of this review, all other efficacy data are also considered secondary efficacy endpoints.

- **Sleep Related Quality of Life Questionnaire** was administered in clinic on Day 1 and Week 12. It was a 3-item scale which results in a 0-100 point rating, with higher scores reflecting improved sleep. This scale is also shown in Appendix B. ANOVA was used to analyze differences between treatments with regard to change between Day 1 and Week 12.

- **Symptom severity scores** were recorded prior to PEFR. Patients used a 6-point scale to describe any asthma-related symptoms such as wheeze, shortness of breath or cough experienced during the day.
  0 = No symptoms during the day.
  1 = Symptoms for one short period during the day.
  2 = Symptoms for two or more short periods during the day.
  3 = Symptoms for most of the day which did not affect my normal daily activities.
  4 = Symptoms for most of the day which did affect my normal daily activities.
  5 = Symptoms so severe that I could not go to work or perform normal daily activities.

- **Nights with awakenings due to asthma** were recorded each morning as the number of times a patient was awakened the previous night with asthma symptoms.

- **Supplemental Ventolin use** was recorded as the number of Ventolin puffs used over the past 24 hours. Cochran-Mantel-Haenszel tests were used to analyze percentages of rescue free days, as well as nights without awakenings and symptom-free days. The change from baseline (average over the 10 days immediately prior to randomization) to endpoint (last seven days of the evaluable period) in Ventolin use, nighttime awakenings and symptom scores were analyzed in the same manner.

Safety data collected during the trial included:

- Medical history (screening),
- Physical examinations (screening and Week 12),
- Oropharyngeal examinations for clinical evidence of candidiasis (screening and Weeks 4, 8 and 12),
- Chest x-ray (screening),
- ECG (screening, Day 1 and Week 12),
- Clinical laboratory tests including eosinophilic cationic proteins (ECP) at selected sites (screening and Week 12),
- Vital signs (screening and with PFT at Day 1 and Week 12),
- 24-hour Holter monitoring (at selected sites during screening and at Week 12)
- Clinical adverse events (at each clinic visit during treatment phase).

A **sample size** of 80 subjects per treatment was based on having 80 percent power to detect a 0.25 L difference in FEV_1 for any pairwise treatment comparison, assuming a standard deviation of 0.55 L and a significance level of 0.05. This N was determined to provide 88 percent power to detect a difference of 0.5 in the overall AQLQ score for any pairwise treatment comparison (assuming a standard deviation of 1.0). Also, assuming that 10 percent of Advair and 30 percent of salmeterol patients would discontinue due to lack of efficacy, there would be 85 percent power to detect this 20 percent difference in dropout rates.

PROTOCOL AMENDMENTS:

There were four protocol amendments. Two were made prior to initiation of the trial. Amendment 3 was made October 31, 1996 and it primarily raised the accepted upper bound of predicted normal FEV_1 from 80 to 85 percent for enrollment purposes. Amendment 4 was made January 17, 1997 and lowered the minimum acceptable pre-study doses of BDP from 336 to 252 mcg per day and TAA from 800 to 600 mcg per day, also for enrollment purposes. Neither Amendment 3 or 4 are expected to have substantially modified the eligible patient population. It is anticipated that if these amendments had any effect on the trial outcomes it would have been to decrease the likelihood of showing differences between treatments by allowing the enrollment of patients with slightly less severe asthma.

PATIENT DISPOSITION / DEMOGRAPHICS:

A Total Population of 527 patients were screened at 35 of the 42 investigational sites. An additional 7 sites were to have been involved in the trial, however, the investigators at these sites did not screen any patients. Of patients screened, 356 were randomized after the run-in period. The majority of the 171 patients who were screened, but failed to enter the treatment phase, did so because they were unable to meet pulmonary function criteria. Four of these patients experienced adverse events.

There were 356 patients randomized to treatment (**Intent to Treat Population / ITT**, N = 356) and 221 (62 percent) completed the study. Table 1 on the following page shows the disposition of the ITT population.

Table 1: Patient Disposition (ITT Population)

	Placebo (N = 82)	Advair 50/100 (N = 92)	Salmeterol (N = 92)	Fluticasone 100 (N = 90)	Total (N = 356)
# (%) Complete	28 (34%)	75 (82%)	51 (55%)	67 (74%)	221 (62%)
# (%) Withdrawn	54 (66%)	17 (18%)	41 (45%)	23 (26%)	135 (38%)
Reason for Withdrawal					
Failed entrance criteria	1 (1%)	4 (4%)	2 (2%)	3 (3%)	10 (3%)
Lack of Efficacy	41 (50%)	3 (3%)	32 (35%)	9 (10%)	85 (24%)
Adverse Event	1 (1%)	0	2 (2%)	1 (1%)	4 (1%)
Failed to Return	1 (1%)	0	0	0	1 (<1%)
Non-compliance	2 (2%)	0	1 (1%)	3 (3%)	6 (2%)
Other	8 (10%)	10 (11%)	3 (3%)	5 (6%)	26 (7%)
Reason Not Recorded	0	0	1 (1%)	2 (2%)	3 (1%)

The placebo group experienced the greatest number of discontinuations, followed by salmeterol, fluticasone and Advair. These differences will be discussed further in a subsequent section as they constitute a primary endpoint of this trial. Few patients discontinued due to adverse events (none from the Advair group). "Other" reasons for discontinuation were most prevalent among the placebo and Advair groups. These occurrences were attributed to a variety of issues, including scheduling conflicts, use of exclusionary medication, withdrawal of consent, etc. Since none of the four groups showed a predominance of a particular issue type, the difference among the groups related to "other" factors does not appear to be attributable to a predominant cause.

Overall, 53 percent of the ITT patients were male. Eight four percent of patients were Caucasian, 8 percent were Black, 5 percent were Hispanic and the remainder were Oriental or Other. Patient ages ranged from 12 to 70 years, with approximately 11 percent under the age of 18 and 2 percent over the age of 65. Most patients had no history of tobacco use (82 percent) and were atopic (73 percent). Fifty six percent of patients had an asthma history of at least 15 years duration. Mean screening FEV_1 was approximately 2.10 L, or 63 percent of predicted normal. Demographic factors and asthma parameters were relatively comparable among treatment groups.
During treatment, xanthine formulations were used by 11 percent of the ITT population. There was a difference among treatment groups with respect to concomitant xanthine use, with 11 percent of placebo patients, 12 percent of Advair patients, 7 percent of salmeterol patients and 16 percent of fluticasone patients on treatment. Use of concomitant non-asthma medications during the treatment period appeared similar among treatment groups. One notable exception is the use of fluticasone nasal spray in 40 percent of placebo, 16 percent of Advair, 25 percent of salmeterol and 27 percent of fluticasone patients. Further discussion of the impact of intranasal fluticasone is associated with review of the efficacy outcomes.

In addition to the ITT population, an **efficacy population** was identified. This group consisted of 334 patients at 34 investigational sites. Twenty two patients from the ITT population were excluded from the efficacy population due significant protocol violations (5 placebo, 5 Advair, 3 salmeterol, and 9 fluticasone patients). Parallel analyses were conducted on primary efficacy endpoints for the ITT and efficacy populations. Results

for the efficacy population will be discussed in this review only if they showed important differences from the ITT population.

Compliance with dosing regimen was assessed by comparing the dose counter indicator values on each returned Diskus device to the total number of doses that were to have been taken. Compliance rates ranged from 93 to 100 percent among the treatment groups and 10 percent or fewer of each group had compliance rates of less than 80 percent. It would appear from these data that differences in study outcomes among treatments are not attributable to compliance with assigned treatment.

EFFICACY OUTCOMES:

Primary Efficacy Outcomes

Table 2 summarizes the primary efficacy outcomes for the ITT population. For reference purposes, actual values for baseline FEV_1 and mean morning predose FEV_1 at endpoint are also included. Efficacy population results were comparable to those of the ITT population on each of the primary endpoints.

Table 2: Primary Efficacy Outcomes, ITT Population

	Placebo (n = 82)	Advair 50/100 (n = 92)	Salmeterol (n = 92)	Fluticasone 100 (n = 90)
Baseline FEV_1, L (SE)	2.17 (0.06)	2.20 (0.06)	2.14 (0.06)	2.12 (0.06)
Mean Morning Predose FEV_1 at Endpoint, L (SE)	2.17 (0.09)	2.71 (0.08)	2.28 (0.08)	2.40 (0.08)
Mean FEV_1 AUC at Week 1, L-hrs[a]	2.23	7.94[b,c,d]	5.09[b]	3.26
Mean Change from Baseline in Morning Predose FEV_1 at Endpoint, L[a]	-0.06	0.52[b,c,d]	0.16	0.30[b]
Patients withdrawn due to lack of efficacy, N[a]	41	3[b,c]	32[b]	9[b]

[a]overall treatment effect ($p<0.001$)
[b]differs from placebo ($p\leq0.007$)
[c]differs from salmeterol ($p<0.001$)
[d]differs from fluticasone ($p\leq0.007$)

Mean serial **FEV_1 AUC** at Week 1 relative to Day 1 baseline showed a significant overall treatment effect. In addition, both Advair and salmeterol were statistically superior to placebo. Advair was statistically superior to both salmeterol and fluticasone. No statistical difference was observed between salmeterol and fluticasone. Appendix C[1] contains a plot of hourly mean change from baseline FEV_1 at Week 1. At Week 12, the

[1] Dr. Elashoff, of the Division of Biometrics II, has reviewed Trials SFCA3002 and SFCA3003 to verify the sponsor's analyses. Appendices C – H and J – L have been generated as part of Dr. Elashoff's review. These figures differ from the sponsor's presentation and the numerical outcomes contained in the tables in this review only in minor respects that are documented thoroughly in the biometrics review. N is shown for each clinic visit by treatment.

four treatment responses were ranked the same as at Week 1, however, each response curve was shifted slightly upward. This appears to suggest that chronic therapy and/or patient discontinuations affected the responses for each treatment group at Week 12.

Mean change from baseline in **morning predose FEV_1** at endpoint showed a significant overall treatment effect. Advair was statistically superior to placebo, salmeterol and fluticasone. Fluticasone was statistically superior to placebo. No statistical difference was seen between salmeterol and either fluticasone or placebo.

Mean change from baseline data from clinic visits throughout the treatment period are plotted in Appendix D, although none of the individual weekly timepoints shown on the plot are representative of the actual endpoint data for each treatment (as shown in Table 1). Statistical analyses at endpoint of mean percent change from baseline in morning predose and change from baseline in morning predose, expressed as percent predicted FEV_1, also show statistical superiority of Advair relative to each of the other treatments.

It is notable that salmeterol was numerically superior to fluticasone with regard to FEV_1 AUC at Week 1, but that fluticasone was superior to salmeterol for morning predose FEV_1 at endpoint. This is likely reflective of the respective pharmacologic mechanisms of each drug, with salmeterol producing a greater change in response to individual doses and fluticasone providing a greater change in baseline lung function. The sponsor chose these co-primary endpoints for this reason.

In addition to the primary endpoint analyses of serial FEV_1 data, other analyses were conducted on data from Day 1, Week 1 and Week 12. FEV_1 AUC was analyzed using ANOVA (in addition to the primary analyses of change from baseline). Also, ANCOVA (with baseline FEV_1 as a covariate) was used to analyze individual timepoints as well as an average of all timepoints, weighted by time interval. These outcomes generally supported that Advair and salmeterol were associated with a greater FEV_1 response in the 12 hour postdose period than fluticasone or placebo. Again, this outcome is likely to be due to the bronchodilatory activity of salmeterol and is expected. Statistical superiority was noted in association with Advair treatment relative to salmeterol at some timepoints after Day 1, however, interpretation of these analyses is confounded by patient discontinuations.

Survival curves are shown in Appendix E based on **patient discontinuations**. Kaplan-Meier survival estimates were used to determine that each active treatment was statistically superior to placebo. Among the active treatment pairwise comparisons, the only statistically significant difference was Advair's superiority to salmeterol. However, treatment survival among Advair patients was greater than among any of the other treatment groups. Given the disparity among treatment groups in the proportion of premature discontinuations, the probability of remaining in the study appears to be the best representation of the performance of the treatment groups at the end of the treatment period (Week 12).

Descriptive analyses were undertaken to compare the outcomes of the primary endpoints based on stratum (prior asthma therapy) and on use of intranasal flunisolide. The results are shown in Table 3. No statistical analyses were undertaken for these subgroups.

Table 3: Primary Outcomes by Stratum and Intranasal Fluticasone Use

	Placebo	Advair 50/100	Salmeterol	Fluticasone 100
Mean FEV_1 AUC at Week 1, L-hrs				
ITT Population	2.37	7.61	5.07	3.48
Inhaled corticosteroids at entry	1.66 (N=55)	7.25 (N=66)	4.47 (N = 66)	2.67 (N = 63)
Salmeterol at entry	3.68 (N = 27)	8.52 (N = 26)	6.70 (N = 26)	5.37 (N = 27)
Taking intranasal FP	1.65 (N = 34)	6.15 (N =17)	3.51 (N = 23)	3.11 (N = 24)
Not taking intranasal FP	2.83 (N = 48)	7.96 (N = 75)	5.62 (N = 69)	3.61 (N = 66)
Mean Change from Baseline in Morning Predose FEV_1 at Endpoint, L				
ITT Population	0	0.50	0.13	0.29
Inhaled corticosteroids at entry	-0.16	0.45	0.04	0.18
Salmeterol at entry	0.29	0.65	0.35	0.53
Taking intranasal FP	-0.09	0.41	0.04	0.32
Not taking intranasal FP	0.06	0.53	0.16	0.27

With regard to **prior medication use**, those patients in each treatment group who had been taking salmeterol prior to entry had higher AUCs at Week 1 than either inhaled corticosteroid users or the ITT population (see Appendix F). Pre-study salmeterol users showed also more improvement on morning predose FEV_1 at endpoint than did the patients who were using inhaled corticosteroids prior to entry or the ITT population (see Appendix G). It appears that prior salmeterol patients benefited more from beginning Advair or other treatments than did prior corticosteroid users. For prior salmeterol users, fluticasone alone was nearly as beneficial as fluticasone in combination with salmeterol (Advair).

Prior salmeterol use did not appear to significantly affect dropout rates in the salmeterol or fluticasone groups (see Appendix H). However, the dropout rate of prior salmeterol users in the placebo group was considerably lower than among the prior inhaled corticosteroid users or the ITT population. It appears that prior corticosteroid users were less tolerant of the placebo than salmeterol users. Since the overall dropout rate from the Advair group was low, it is difficult to interpret the effect of prior medication use on this group.

With regard to **concomitant use of intranasal fluticasone**, those who were not taking intranasal fluticasone appeared to show more improvement in morning predose FEV_1 for all treatments except fluticasone than did Flonase users. Non-users showed

somewhat more improvement in AUC at Week 1 than did users among all the treatment groups. Discontinuation rates did not appear to be affected by use of intranasal corticosteroids in the placebo or salmeterol groups, but were lower for non-users in the Advair and fluticasone groups. These analyses are confounded by the difference in Flonase use among the groups (40 percent of the placebo group, 16 percent of the Advair group, 25 percent of the salmeterol group and 27 percent of the fluticasone group used Flonase).

Secondary Efficacy Outcomes

Table 4 (on the following page) shows a summary of the secondary efficacy outcomes. Baseline values are represented with change from baseline at endpoint for the ITT population. An efficacy population analysis was not reported for these endpoints.

An overall treatment effect was shown in analyses of AM PEFR, PM PEFR and AM/PM PEFR differential. Change from baseline in **AM PEFR** is presented in graphical form in Appendix I for the entire duration of the treatment period. Statistical superiority of the combination relative to salmeterol and fluticasone was observed as early as Week 1 and consistently thereafter. Fluticasone was also shown to be consistently superior to placebo. It is noted that no statistical differences were observed between salmeterol and fluticasone at regular analysis intervals, but were observed in the endpoint analyses. Outcomes of the analyses of **AM PEFR as percent of predicted** were comparable to those of AM PEFR.

PM PEFR and PM PEFR as percent of predicted analyses again showed Advair to be consistently statistically superior to placebo and salmeterol throughout the trial and at endpoint. Advair was not shown to be consistently superior to fluticasone throughout the trial, however, endpoint analyses favored Advair.

AM/PM PEFR differential was significantly improved with Advair treatment relative to the other treatments. However, unlike the previous PEFR endpoints, the differential was more responsive to treatment with salmeterol alone than with fluticasone alone. This outcome may again be anticipated based on the respective pharmacologic mechanisms.

Table 4: Secondary Efficacy Outcomes, ITT Population
(Baseline and Change from Baseline at Endpoint)

		Placebo (N = 82)	Advair 50/100 (N = 92)	Salmeterol (N = 92)	Fluticasone 100 (N = 90)
AM PEFR, L/min[a]	Baseline	384	400	371	377
	Change	-22.2	54.4[b,c,d]	-2.3[b]	18.1[b]
% Predicted AM PEFR[a]	Baseline	81	82	79	80
	Change	-5	11[b,c,d]	-1	4[b]
PM PEFR, L/min[a]	Baseline	401	424	397	393
	Change	-10.5	36.6[b,c,d]	-7.6	19.2[b]
AM/PM Differential, L/min[a]	Baseline	18	24	25	15
	Change	11	18[b,c,d]	4[b]	1
AQLQ Global[a]	Baseline	4.85	5.03	4.95	4.73
	Change	-0.33	0.99[b,c,d]	-0.03[b]	0.56[b]
Activity Limitation[a]	Baseline	5.00	5.17	5.09	4.72
	Change	-0.13	0.99[b,c,d]	-0.06	0.74[b]
Asthma Symptoms[a]	Baseline	4.74	4.97	4.88	4.75
	Change	-0.51	1.04[b,c,d]	-0.08[b]	0.55[b]
Emotional Function[a]	Baseline	4.66	4.91	4.84	4.67
	Change	-0.45	1.07[b,c,d]	0.00[b]	0.42[b]
Environmental Exposure[a]	Baseline	4.98	5.00	4.87	4.78
	Change	-0.14	0.87[b,c,d]	0.14	0.45[b]
% Days with no Ventolin[a]	Baseline	22.6	30.5	27.2	27.2
	Change	-9.1	30.7[b,c,d]	4.7[b]	10.1[b]
% Nights with no awakenings[a]	Baseline	89.5	91.8	91.8	91.8
	Change	-16.7	4.7[b,c]	-6.9[b]	2.2[b]
% Days with no symptoms[a]	Baseline	17	25	13	19
	Change	-4	25[b,c,d]	8[b]	7
Sleep Scale Scores[a]	Baseline	77.7 (N = 81)	81.6 (N = 86)	81.2 (N = 90)	80.3 (N=86)
	Change	-6.18	13.55[b,c,d]	1.58[b]	8.14[b]

[a]Overall treatment effect ($p<0.001$)
[b]Differs from placebo ($p \leq 0.05$)
[c]Differs from salmeterol ($p \leq 0.05$)
[d]Differs from fluticasone ($p \leq 0.05$)

AQLQ outcomes, both the global score and scores for the four individual dimensions, are contained in Table 4. Change from baseline was consistently greatest for the Advair group, followed by fluticasone and salmeterol. Scores worsened on each dimension in the placebo group. Clinically meaningful differences are considered a validated aspect of this instrument and are defined as a change of 0.5, either within or between treatment groups. Clinically meaningful differences were observed with Advair and fluticasone for the global score and all dimensions, with the exception of fluticasone's effect on emotional function. Differences in change from baseline between groups showed that Advair achieved clinically meaningful increases in global scores

and all dimension scores relative to salmeterol and placebo. Advair was similarly superior to fluticasone only on the emotional function dimension (not on the global score).

Ventolin use was diminished in each active treatment group, however Advair patients showed more improvement than the other active treatments. Table 4 includes the analyses of change from baseline in percent of days in which no Ventolin was used. All active treatments were statistically superior to placebo, however, Advair was also statistically superior to salmeterol and fluticasone. Analyses were also conducted on actual number of puffs used and were generally consistent with the previous analysis. Of note, however, is that in the comparisons of Advair with salmeterol, analyses at Weeks 1, 2, 3, and 4 do not show Advair to be statistically superior, despite superiority in the endpoint analyses.

Nighttime awakenings, when analyzed as change from baseline in percentage of nights with no awakenings (Table 4) or actual number of nights with no awakenings, did not separate the Advair from fluticasone. Advair was statistically superior to the other treatments. Nighttime awakenings were not prevalent in this population.

Asthma symptoms were generally low, with mean values ranging among the treatment groups from 1.5 to 1.8 at baseline (0 to 5 scale). Advair was statistically superior to each of the other treatments (see Table 4). Salmeterol was statistically superior to placebo, however fluticasone was not.

Mean scores on the **sleep scale** were relatively high, at approximately 80 points of a possible 100. Advair was statistically superior to each of the other treatments (see Table 4).

Overall, the secondary endpoints were very consistent with the primary efficacy outcomes. In particular, nearly all secondary endpoints presented a comparable trend, with the Advair group showing the greatest benefit, followed in rank order by fluticasone, salmeterol and placebo.

Efficacy Conclusion

In the analyses of primary efficacy outcomes, mean FEV_1 AUC at Week 1 and mean change from baseline in morning predose FEV_1 at endpoint, Advair was statistically superior to placebo, salmeterol and fluticasone. Advair was also superior to placebo and salmeterol with regard to rate of patient discontinuation for lack of effect. Although Advair was not statistically superior to fluticasone on this endpoint, it was numerically superior. Patients who used pre-study salmeterol tended to show more improvement on Advair with regard to the primary endpoints than did patients who used prestudy inhaled corticosteroids.

The primary endpoint outcomes were strongly supported by each of the secondary endpoints, including AQLQ and sleep scale, use of Ventolin, nighttime awakenings and asthma symptoms. For each endpoint, except nighttime awakenings, Advair was

shown to be statistically superior to the other treatments. Advair was not statistically superior, but was numerically superior to fluticasone with regard to reduction of nighttime awakenings. These outcomes support the benefit of the combination over the individual components, salmeterol and fluticasone.

SAFETY OUTCOMES:

Exposure

As a result of the disparity in discontinuation rates among treatment groups, total exposure to treatment was highly variable. Mean exposure was 43 days for placebo, 77 days for Advair, 61 days of salmeterol and 72 days for fluticasone.

Adverse Events

There were **no deaths** reported during this trial. There were six patients who experienced **serious adverse events** during the treatment phase, including one placebo, two Advair, two salmeterol and one fluticasone patient. A seventh patient (Pt # 8) experienced an asthma exacerbation during the run-in and was not randomized.

- Placebo Pt # 74, a 13 yo male, experienced an asthma exacerbation 8 hours after his initial dose of study medication. He was hospitalized and the event resolved 3 days later. Non-compliance with his previous asthma regimen was suspected as the cause of the event. This patient was withdrawn from the study.
- Advair Pt # 530, a 12 year old male, was discontinued due to appendicitis and appendectomy after 18 days on treatment.
- Advair Pt # 1474, a 54 year old female was hospitalized for surgical correction of a herniated disk related to a previous car accident.
- Salmeterol Pt # 221, a 45 yo female, was hospitalized for an asthma exacerbation related to a URI 32 days after initiation of treatment. This patient was withdrawn from the study.
- Salmeterol Pt #232, a 62 year old female, was hospitalized after two months on treatment for persistent nausea and upset stomach. Diverticulitis and temporal arteritis were ruled out . Her final diagnosis was fever of unknown origin, who received treatment with cefizoxime, metronidazole and ketrolac and the event resolved within 2 months.
- Fluticasone Pt #509, a 43 year old female, developed arm and chest pain and felt cold and clammy seven hours after her dose on her 67th day of treatment. She was hospitalized, but relevant tests were negative. The event was considered musculoskeletal in origin.

Four patients were **withdrawn due to adverse events** (1 placebo, 2 salmeterol and 1 fluticasone patient). The placebo and salmeterol patients experienced serious adverse events (above) and the fluticasone patient experienced a prolonged PR interval (to be discussed subsequently).

Adverse events that were experienced by at least 3 percent of any treatment group, and in a higher proportion of patients in any active treatment group than in the placebo group, are reported in Table 5 on the following page.

Table 5: Adverse Events[a] ITT Population, N (%)

	Placebo (N = 92)	Advair 50/100 (N = 92)	Salmeterol (N = 92)	Fluticasone 100 (N = 90)
Pts. with any event	38 (46)	65 (71)	57 (62)	63 (70)
Any ENT Event	26 (32)	48 (52)	35 (38)	44 (49)
URT Infection	15 (18)	25 (27)	16 (17)	26 (29)
Throat Irritation	7 (9)	11 (12)	6 (7)	6 (7)
UR Inflammation	2 (2)	6 (7)	9 (10)	6 (7)
Sinusitis	4 (5)	4 (4)	4 (4)	5 (6)
Hoarseness/Dysphonia	1 (1)	5 (5)	1 (1)	2 (2)
Pharyngitis/throat infection	0	1 (1)	3 (3)	0
Any Gastrointestinal Event	8 (10)	17 (18)	10 (11)	16 (18)
Nausea and vomiting	2 (2)	4 (4)	2 (2)	3 (3)
Diarrhea	2 (2)	4 (4)	1 (1)	2 (2)
Gastrointestinal Discomfort and Pain	1 (1)	4 (4)	2 (2)	0
Any Neurology Event	5 (6)	13 (14)	11 (12)	17 (19)
Headache	5 (6)	11 (12)	10 (11)	13 (14)
Dizziness	0	0	1 (1)	4 (4)
Any Lower Respiratory Event	10 (12)	13 (14)	10 (11)	6 (7)
Viral Respiratory Infection	6 (7)	4 (4)	6 (7)	4 (4)
Cough	2 (2)	3 (3)	1 (1)	0
Muscoloskelatal/Muscle Pain	3 (4)	4 (4)	6 (7)	1 (1)

[a]Events which occurred in 3 percent or more of any active treatment group and in a higher proportion of patients in any active treatment group than among placebo patients.

Survival in the trial is expected to have had an impact on the relative rates of event occurrence among the four treatment groups and it is anticipated that the overall rate of adverse events might be highest among the Advair patients, due to them generally remaining in the study for the longest period. However, local events, such as throat irritation and hoarseness/dysphonia may not necessarily have been related to total exposure time, perhaps being equally likely to occur with early exposures as with later exposures. It appears that these events occurred most frequently among Advair patients and suggest that the combination product may have had increased local effects. Other events did not appear to have elevated incidence rates among the Advair population relative to the other active treatments.

Oropharyngeal candidiasis infections with both clinical evidence and positive cultures were observed in four Advair and three fluticasone patients.

Clinical Laboratory Values

There were 16 patients whose laboratory values exceeded threshold values (defined a priori) after initiation of treatment, following normal baseline levels. These included 2 (3 percent) placebo patients, 4 (4 percent) Advair patients, 2 (2 percent) of salmeterol patients and 8 (9 percent) of fluticasone patients.

One **Advair** patient experienced a decrease in RBC, to below threshold at Week 12. Three Advair patients experienced increased LFTs at Week'12 as compared to screening. These are summarized below.

- Pt #151 (35yof)

Used concomitant estradiol patch, acetaminophen, TPM/SMT and cefprozil

	AST	ALT
Screening	WNL	45 U/L (high normal)
Week 12	105 U/L	255 U/L
Follow-up (3 weeks later)	19 U/L	22 U/L

- Pt #438 (62 yom)

Used concomitant calcium carbonate antacid and chlorpheniramine / acetaminophen

	GGT
Screening	40 U/L - WNL
Week 12	139 U/L
1st follow-up, 12 days later	66 U/L
2nd follow-up, 2 wks after 1st	38 U/L

- Pt # 28 (25 yof)

Used concomitant desogestrel ethinylestradiol and actetominophen

	AST	ALT
Screening	57 U/L	59 U/L
Week 12	306 U/L	212 U/L
Follow-up, 11 days later	240 U/L	192 U/L

A fourth Advair patient had elevations above threshold at screening in ALT and GGT, as well has high normal AST. These values remained elevated at Week 12, but had decreased from screening values. The patient was reported to have concurrent fatty liver, obesity and pre-existing mild elevations in LFTs.

Two **salmeterol** patients experienced a decrease in neutrophils at Week 12 relative to screening, to below threshold levels. A third patient had elevated ALT (202 U/L) at baseline which fell to WNL (18 U/L) at the discontinuation visit.

There were two **fluticasone** patients who exceeded threshold values for LFTs, including one who had normal screening values. The latter case is summarized below.

Pt #505 (32yom)

No additional information or follow-up provided.

	AST	ALT
Screening	44 U/L	90 U/L
Week 12	WNL	145 U/L

Three fluticasone patients experienced elevations above threshold in serum glucose at withdrawal (1 patient) or Week 12 (two patients). The patient who discontinued prematurely also had elevated glucose levels at screening. No follow-up was available for these patients. One patient exceeded threshold values on each of the following at Week 12 or discontinuation: increased sodium, increased hemoglobin, decreased neutrophils, and increased eosinophils.

There were no significant differences among the treatment groups in **eosinophilic cationic proteins.**

Overall, clinical laboratory parameters did not appear to suggest unexpected adverse events associated with Advair. Given the disparity in discontinuation rates, it appears that increased LFTs occurred at approximately the same rate among the Advair and fluticasone populations and the nature of the cases was similar.

Cardiovascular Outcomes

ECGs were performed at screening, then one hour predose and 1.5 hours postdose on Day 1 and at Week 1 and Week 12 (or discontinuation). **Mean heart rate** ranged from 68 to 72 bpm among the treatment groups at Day 1 predose. The only statistically significant difference among treatments was seen postdose at Week 1, when the decline from predose was 5.2 bpm for placebo, 0.1 bpm for Advair, 3.1 bpm for salmeterol and 4.2 bpm for fluticasone. These differences do not appear to have clinical significance, but were associated with a statistically significant difference among treatments in **QTc interval.** At the same timepoint, changes from predose were –4.0 msec for placebo, 2.7 msec for Advair, –6.1 msec for salmeterol and –4.3 msec for fluticasone. Also at this timepoint, only 4 percent of placebo patients, compared to 13 percent of Advair patients, 10 percent of salmeterol patients and 12 percent of fluticasone patients, experienced a QTc of more than 440 msec duration. At other timepoints, the proportion of patients with prolonged QTc intervals was comparable among treatment groups.

ECG changes were interpreted by a central cardiologist. Only one patient was found to have a clinically significant abnormality. Pt # 145 was found at screening to have a normal sinus rhythm with a left axis deviation. At predose on Day 1, normal sinus rhythm with 1st degree AV block was detected and the patient was discontinued due to the adverse event of prolonged PR interval.

Twenty four hour **Holter monitoring** was conducted in a subset of patients at screening and at Week 12. N was approximately 30 per group at screening and ranged from 11 to 26 per group at Week 12. The findings were interpreted by a central cardiologist who found one patient to have had a clinically significant abnormality. This patient was a 41 yo female in the placebo group (Pt # 47) with an average of 121 VEs per hour at screening and 169 per hour at Week 12. Pt # 439, a 48 yo female in the fluticasone group, experienced 49,837 SVEs at screening and 52,570 SVEs at Week 12. (The figure 49,837 has also been reported by the sponsor as 4,983 and the sponsor will be asked to identify the correct number). This patient's recording was deemed abnormal, but clinically insignificant. Those who had 50 or more VEs or SVEs at Week 12 numbered 3 placebo patients, 2 Advair patients, 3 salmeterol patients and 9 fluticasone patients.

Vital signs were assessed at the same times as ECG. Mean pulse, diastolic and systolic blood pressure evaluations did not reveal clinically important differences among the four treatment groups.

Physical examinations

Unfavorable physical changes between Screening and Week 12 or discontinuation were observed in 22 (28 percent) placebo patients, 16 (18 percent) Advair patients, 29 (32 percent) salmeterol patients and 22 (28 percent) placebo patients. ENT changes were the most frequently reported changes.

Safety Conclusion

Overall, the safety of Advair was comparable to that of the individual active agents. Of note is an apparent increase in local events associated with dosing (e.g., throat irritation). EKG and Holter monitor findings did not appear to reveal extensive safety concerns, nor did clinical laboratory or other safety parameters. It is noted that this trial involved the lowest dose of Advair studied in this NDA and subsequent trials need to be reviewed for potential dose-related safety concerns.

CONCLUSION:

There was a consistent trend among both primary and secondary endpoints, reflecting both early and late study outcomes, that Advair had greater effect than either salmeterol or fluticasone 100 mcg. In addition, safety concerns do not appear to have been elevated with the combination as compared to the other active treatments. Other trials in this program, evaluating the effects of the 100 mcg and higher strengths, will be evaluated for confirmation of these findings.

B. TRIAL SFCA3003

TITLE: A Randomized, Double-Blind, Parallel-Group Trial Evaluating the Safety and Efficacy of Salmeterol 50 mcg BID and Fluticasone Propionate 250 mcg BID Individually and in Combination and Placebo in Subjects with Asthma.

OVERVIEW: The purpose of this study was to determine the effectiveness of the combination of salmeterol 50 mcg and fluticasone proprionate 250 mcg, administered BID as the proposed Advair 50/250 mcg formulation, relative to treatment with either single agent or placebo. Study design was similar to that of Trial SFCA3002 (Section I.A.), but the patient population differed in its asthma severity. (Volumes 64-72)

STUDY DATES: August 6, 1996 – July 15, 1997

INVESTIGATORS: Forty three investigators in the U.S. agreed to participate and 39 enrolled patients. See Appendix A.

PATIENT POPULATION:

General - See Trial SFCA3002.

Asthma - For enrollment into the **run-in** phase, patients were required at screening to have received pharmacotherapy for asthma for the preceding six months, have a best FEV_1 of 40 to 85 percent of predicted normal and to demonstrate at least 15 percent reversibility within 30 minutes following two puffs of Ventolin. Patients' were required to have received inhaled corticosteroids continuously for at least 12 weeks prior to screening. In the four weeks prior to screening, patients were required to have received doses of BDP 462-672 mcg per day, TAA 1100-1600 mcg per day, flunisolide 1250-2000 mcg per day or fluticasone propionate 440 mcg per day. Unlike Trial SFCA3002, patients continued on their fixed dose of inhaled corticosteroid throughout the run-in phase. They were also allowed to use Ventolin as needed.

Enrollment into the **double-blind phase** of the trial and randomization to treatment was limited to patients whose best FEV_1 at the clinic visit subsequent to the run-in period was within 15 percent of the screening visit value and within 40 to 85 percent of predicted normal. Patients who used more than 12 puffs per day of Ventolin on more than 3 of their last 7 run-in days were excluded. Finally, any patient who awakened due to asthma on more than 3 of their last 7 run-in nights was excluded.

Concomitant medication – Allowed use of concomitant medication was the same as in Trial 3002, except with regard to salmeterol. Patients were eligible for enrollment if they had a prior history of salmeterol use, however, they were required to discontinue salmeterol one week prior to screening. Enrollment was not stratified by previous salmeterol use, nor were analyses of prior use subgroups undertaken.

PROCEDURES / ENDPOINTS:

Procedures were largely the same as in Trial SFCA3002, including criteria for patient discontinuation due to lack of effect. Two additional safety endpoints were included in this trial. HPA axis function was assessed using plasma cortisol concentration. Fasting blood samples were collected prior to 10 AM and the administration of morning doses of study medication at screening and Week 12 (or discontinuation). In addition, short Cortrosyn (cosyntropin) stimulation tests were conducted at selected sites. At screening and Week 12 (or discontinuation), blood samples were drawn between 30 and 60 minutes following IM or IV administration of Cortrosyn doses, according to product labeling. While the protocol specified that samples were to be drawn 60 minutes following dosing, this procedure was not consistently followed. The Cortrosyn labeling, included for reference in the protocol, clarifies interpretation of the test outcomes at both the 30 and 60 minute timepoints. This issue will be further discussed in relationship to the endpoint outcomes.

PROTOCOL AMENDMENTS:

There were three protocol amendments and the first two were made prior to initiation of the protocol. Amendment 3 was made October 31, 1996. It modified the original protocol to specify that reversibility of ≥ 15 percent in FEV_1 be demonstrated by each patient at screening. The original protocol stated that reversibility of at least 15 or 20 percent was necessary, depending upon the patient's FEV_1 as a percent of predicted normal. Specifically, patients with higher lung function (81 to 85 percent of predicted normal) were to have demonstrated reversibility of at least 20 percent, while other needed to demonstrate only 15 percent reversibility. Amendment 3 also allowed for reproducibility to be demonstrated at either 30 minutes predose or immediately prior to dosing. Neither of the Amendment 3 changes are expected to have created significant bias in the trial. However, the subgroup analyses conducted by the sponsor with regard to predicted FEV_1 at baseline is not considered meaningful since this aspect of enrollment into the protocol was not maintained.

PATIENT DISPOSITION / DEMOGRAPHICS:

A total of 484 patients were screened. Of these, 137 patients were not randomized, primarily due to failure to meet pulmonary function and asthma criteria. Two of these patients actually were randomized, did receive one dose of study medication, and were mistakenly included in the non-randomized total. These two patients were, however, included in the ITT population which numbered 349 patients. Table 6 (on the following page) presents the disposition of the ITT population.

Table 6: Patient Disposition (ITT Population)

	Placebo (n = 93)	Advair 50/250 (n = 84)	Salmeterol (n = 83)	Fluticasone 250 (n = 84)	Total (n = 349)
# (%) Complete	26 (28%)	70 (83%)	43 (49%)	61 (73%)	220 (57%)
# (%) Withdrawn	57 (72%)	14 (17%)	45 (51%)	23 (27%)	149 (43%)
Reason for Withdrawal					
Failed entrance criteria	1 (1%)	2 (2%)	3 (3%)	2 (2%)	8 (2%)
Lack of Efficacy	58 (62%)	3 (3%)	33 (38%)	19 (23%)	114 (33%)
Adverse Event	0	0	2 (2%)	0	2 (<1%)
Failed to Return	0	1 (1%)	1 (1%)	1 (1%)	3 (<1%)
Non-compliance	1 (1%)	1 (1%)	1 (1%)	0	3 (<1%)
Other	7 (8%)	5 (6%)	4 (5%)	1 (1%)	17 (5%)
Reason Not Recorded	0	1 (1%)	1 (1%)	0	2 (<1%)

These outcomes are very similar to those reported for Trial SFCA3002. However, a lower proportion of salmeterol patients completed SFCA3003 (49 percent) than SFCA3002 (55 percent). Patients who discontinued due to lack of efficacy accounted for only a portion of this difference (35 percent of withdrawals in SFCA3002 versus 38 percent of withdrawals in SFCA3003). In addition, a greater proportion of fluticasone and placebo patients withdrew from SFCA3003 due to lack of efficacy (23 percent of fluticasone withdrawals and 62 percent of placebo withdrawals) than from SFCA3002 (10 percent of fluticasone withdrawals and 50 percent of placebo withdrawals). Disposition of Advair patients was largely comparable between the two trials.

Fifty two percent of the ITT population was male. Nearly 80 percent were Caucasian, 12 percent were Black, 6 percent were Hispanic and the remainder were Oriental or Other. Ages ranged from 12 to 69 years, with approximately 9 percent under the age of 17 and only 2 percent over the age of 65. Most patients had no history of tobacco use (76 percent) and were atopic (70 percent). Fifty six percent of patients had an asthma history of at least 15 years duration. Screening FEV_1 was approximately 2.15 L, or 66 percent of predicted normal. Demographic factors and asthma parameters were comparable among treatment groups.

There was some difference among the treatment groups with regard to **previous inhaled corticosteroid therapy**. The Advair group had the highest proportion of patients who had previous used TAA (range 35 to 49 percent of patients among the groups). The fluticasone group included the largest proportion of patients who had previously used fluticasone (range of 24 to 38 percent of patients). This appears to have been an artifact of randomization.

During treatment, xanthines were used by 13 percent of placebo patients, 12 percent of Advair patients, 18 percent of salmeterol patients and 20 percent of fluticasone patients. The impact of the different utilization rates can not be interpreted from the outcomes of this trial. However, despite higher use of xanthines, both the salmeterol and fluticasone groups had higher discontinuation rates that did the Advair group. Fluticasone nasal spray was used by 38, 33, 28 and 33 percent of the placebo, Advair, salmeterol and

fluticasone groups, respectively. Use of other non-asthma medications appeared comparable among groups.

Compliance was approximately 94 percent, with approximately 10 percent having less than an 80 percent compliance rate (range 8 to 14 percent). Of note, the Advair group had the lowest overall compliance rate (91 percent) and highest proportion of low-compliance patients (14 percent).

The **efficacy population** (N = 322) excluded 27 patients (8 percent) of the ITT population due to protocol violations. Primary efficacy outcomes for this population will be discussed only where they differ markedly from ITT outcomes.

EFFICACY OUTCOMES:

Primary Efficacy Outcomes

Table 7 summarizes the primary efficacy outcomes for the ITT population.

Table 7: Primary Efficacy Outcomes, ITT Population

	Placebo (N = 93)	Advair 50/250 (N = 84)	Salmeterol (N = 87)	Fluticasone 250 (N = 84)
Baseline FEV_1, L (SE)	2.20 (0.06)	2.25 (0.07)	2.20 (0.06)	2.13 (0.06)
Mean Morning Predose FEV_1 at Endpoint, L (SE)	2.10 (0.08)	2.73 (0.09)	2.24 (0.07)	2.36 (0.07)
Mean FEV_1 AUC at Week 1, L-hrs[a]	-0.00	6.70[b,c,d]	3.80[b]	1.83[b]
Mean Change from Baseline in Morning Predose FEV_1 at Endpoint, L[a]	-0.11	0.48[b,c,d]	0.03[b]	0.23[b,c]
Patients withdrawn due to lack of efficacy, N[a]	58	4[b,c,d]	33[b]	19[b]

[a]overall treatment effect ($p<0.001$)
[b]differs from placebo ($p\leq0.041$)
[c]differs from salmeterol ($p\leq0.007$)
[d]differs from fluticasone ($p<0.001$)

Mean serial **FEV_1 AUC** at Week 1 relative to Day 1 baseline showed a significant overall treatment effect. All active treatments were statistically superior to placebo. Advair was statistically superior to both salmeterol and fluticasone ($p<0.001$). See Appendix J for a graphical display of hourly mean change from baseline at Week 1.

Mean change from baseline in **morning predose FEV_1** is depicted in Appendix K for the entire treatment period. Advair was statistically superior to each of the other treatment groups ($p<0.001$) and fluticasone was superior to salmeterol at endpoint.

Showing similar trends as in Trial SFCA3002, fluticasone was statistically superior to salmeterol with regard to morning predose FEV_1, while salmeterol was numerically superior to fluticasone with regard to FEV_1 AUC. Other analyses of serial FEV_1 values,

and analyses of the efficacy population, were consistent with the previously described outcomes. Analyses of Week 12 data were again confounded by the discontinuation rates, such that they were less able to distinguish among placebo, salmeterol and fluticasone treatments.

Patient discontinuation rates are shown in Appendix L. The rank ordering of treatments, Advair, fluticasone, salmeterol and placebo, is consistent with Trial SFCA3002. However, there is a greater difference among treatments, particularly between Advair and fluticasone, as discussed with regard to patient distribution.

Use of concurrent intranasal fluticasone, and associated primary efficacy outcomes, are summarized in Table 8.

Table 8: Primary Efficacy Outcomes by Intranasal Fluticasone Use

	Placebo	Advair 50/250	Salmeterol	Fluticasone 250
Mean Change from Baseline in Morning Predose FEV_1 at Endpoint, L				
ITT Population	-0.11	0.48	0.03	0.23
Taking intranasal FP	-0.07	0.44	0.17	0.33
Not taking intranasal FP	-0.14	0.49	-0.02	0.18
Mean FEV_1 AUC at Week 1, L-hrs				
ITT Population	-0.00	6.70	3.80	1.83
Taking intranasal FP	0.00	5.87	3.63	2.40
Not taking intranasal FP	-0.01	7.41	3.88	1.55
Patients withdrawn due to lack of efficacy, N				
ITT Population	58/93 (62%)	4/84 (5%)	33/88 (38%)	19/84 (23%)
Taking intranasal FP	20/35 (57%)	0/29(0%)	9/26 (35%)	4/28 (14%)
Not taking intranasal FP	36/58 (62%)	4/55 (7%)	24/62 (39%)	15/56 (27%)

Although no statistical analyses were conducted, those patients who were using concurrent intranasal fluticasone appeared less likely to discontinue from the trial, independent of their treatment group. Using intranasal fluticasone concurrently appeared to be associated with an enhanced FEV_1 AUC response, only among the fluticasone group, but was associated with increased change from baseline for morning FEV_1 among both salmeterol and fluticasone users. The Advair group does not appear to show consistent outcomes, i.e., a reduction in FEV_1 responses with concurrent use, but a decline in discontinuation rate.

Secondary Efficacy Outcomes

Table 9 (on the following page) shows a summary of the secondary outcomes.

Table 9: Secondary Efficacy Outcomes, ITT Population
(Baseline and Change from Baseline at Endpoint)

		Placebo (N = 93)	Advair 50/250 (N = 84)	Salmeterol (N = 88)	Fluticasone 250 (N = 84)
AM PEFR, L/min[a]	Baseline	374	371	371	376
	Change	-16	52[b,c,d]	-12	14[b]
% Predicted AM PEFR[a]	Baseline	81	79	79	83
	Change	-3	11[b,c,d]	-2	3[b]
PM PEFR, L/min[a]	Baseline	397	391	393	390
	Change	-17	43[b,c,d]	-14	7[b]
AM/PM Differential, L/min	Baseline	24	20	22	13
	Change	-1	-9	-3	-5
AQLQ Global[a]	Baseline	4.75	4.90	4.94	5.04
	Change	-0.26	1.00[b,c,d]	-0.10	0.55[b]
Activity Limitation[a]	Baseline	4.81	4.91	5.04	5.08
	Change	-0.18	0.99[b,c]	0.01	0.63[b]
Asthma Symptoms[a]	Baseline	4.70	4.98	4.92	5.01
	Change	-0.36	0.93[b,c,d]	-0.22[b]	0.55[b]
Emotional Function[a]	Baseline	4.67	4.75	4.89	5.09
	Change	-0.33	1.24[b,c,d]	-0.21	0.49[b]
Environmental Exposure[a]	Baseline	4.81	4.75	4.80	4.93
	Change	-0.05	0.92[b,c,d]	0.08	0.47[b]
% Days with no Ventolin[a]	Baseline	26.8	32.2	21.7	28.0
	Change	-6.0	35.3[b,c,d]	8.5[b]	13.6[b]
% Nights with no awakenings[a]	Baseline	89.3	91.1	89.5	90.8
	Change	-12.0	6.3[b,c,d]	-8.3	2.3[b]
% Days with no symptoms[a]	Baseline	24.6	27.8	19.0	22.6
	Change	-8.9	31.7[b,c,d]	2.2[b]	15.7[b]
Sleep Scale Scores[a]	Baseline	76.8 (N = 88)	81.9 (N = 82)	80.2 (N = 85)	83.5 (N=81)
	Change	-3.61	9.53[b,c]	-4.40	6.56[b]

[a]Overall treatment effect ($p<0.001$)
[b]Differs from placebo ($p\leq 0.05$)
[c]Differs from salmeterol ($p\leq 0.036$)
[d]Differs from fluticasone ($p\leq 0.041$)

AM PEFR demonstrated an overall treatment effect and the statistical superiority of Advair relative to each of the other treatment groups. While fluticasone was also superior to placebo, salmeterol actually showed a decline from baseline. The same outcomes were found in analyses of **AM PEFR as a percent of predicted** and **PM PEFR**. All four treatments showed a reduction from baseline in **AM/PM PEFR differential**. Although there were no statistical differences among the groups, the Advair group demonstrated the greatest improvement (decline).

AQLQ outcomes (see Table 9) were comparable to those observed in Trial SLGA3002. Advair was shown to be consistently superior to placebo and salmeterol. Advair was

also statistically superior to fluticasone for the overall score and each individual dimension, with the exception of activity limitation. Fluticasone was statistically superior to placebo overall and on each dimension, but salmeterol was statistically superior to placebo only on the asthma symptom dimension. Clinically meaningful improvement (changes of at least 0.5) were consistently observed in the Advair group and overall for fluticasone. Change from baseline for Advair was consistently more than 0.5 units greater than that of placebo and salmeterol. However, Advair reached this value relative to fluticasone only for the emotional function dimension.

Ventolin use was statistically diminished in each of the active treatment groups relative to placebo and the Advair group showed the greatest improvement. In addition to the percent days with no Ventolin (Table 9), the decline in actual number of puffs used showed similar outcomes. No statistical differences were observed between salmeterol and fluticasone.

Both percent of **nights with no awakenings** (Table 9) and number of nighttime awakenings improved (declined) with Advair and fluticasone, but worsened with salmeterol and placebo. Statistical differences were observed between Advair and the other treatments and between fluticasone and placebo.

Percent of **days with no asthma symptoms** was significantly improved in each of the active treatment groups relative to placebo. In addition, Advair showed statistical superiority to the other active treatments. At endpoint, the salmeterol group did not show a reduction in actual symptom scores, with a 0.1 mean increase on a six point scale. The placebo mean was increased by 0.4 at endpoint relative to baseline and a statistical difference was observed between salmeterol and placebo.

Change in **sleep scores** was positive (improved) for Advair and fluticasone, but was negative for salmeterol and placebo. No statistical distinction was noted between Advair and fluticasone, although Advair was statistically superior to salmeterol and placebo.

Efficacy Conclusion

Both the primary and secondary efficacy outcomes in Trial SLGA3003 supported the superiority of Advair over placebo, salmeterol and fluticasone, both numerically and statistically for most endpoints. In this regard, the outcomes were similar to those observed in Trial SLGA3002. As a qualitative observation, Trial SLGA3003 showed somewhat less distinction between the Advair and fluticasone treatments than had the previous trial. This was particularly evident among the secondary endpoints. Concurrent use of intranasal fluticasone did not appear to have an important clinical effect on efficacy responses to Advair therapy.

On many endpoints used to assess asthma control (e.g., AM PEFR, predose FEV_1, nighttime awakenings) salmeterol showed either small or insignificant differences from placebo. Although not an objective of the trial, and therefore not appropriate for

rigorous interpretation, this is suggestive that in patients controlled on ICS pre-study, switching to salmeterol alone and stopping ICS did not produce clinically favorable outcomes and may not be an appropriate clinical practice.

SAFETY OUTCOMES:

Exposure

There were **no deaths** reported during this trial. There were four **serious adverse events** reported during the treatment period, including one fluticasone patient (Pt. # 739, asthma exacerbation) and three salmeterol patients (Pt # 913, surgical removal of breast implants due to infection; Pt # 1256, asthma exacerbation; Pt # 1523, chest pain diagnosed as musculoskeletal pain). There were two patients **withdrawn due to adverse events** during the treatment period, both in the salmeterol group. The first was Pt # 913 and the second was Pt #761, who withdrew due to bilateral subcapsular cataracts. No patients experienced serious events on Advair therapy or were withdrawn from Advair therapy due to adverse events.

Adverse events that were experienced by at least 3 percent of any treatment group, and in a higher proportion of patients in any active treatment group than in the placebo group, are reported in Table 10.

Table 10: Adverse Events[a] ITT Population, N (%)

	Placebo (N = 93)	**Advair 50/250 (N = 84)**	**Salmeterol (N = 88)**	**Fluticasone 250 (N = 84)**
Pts. with any event	48 (52)	58 (69)	51 (58)	67 (80)
Any ENT Event	27 (29)	35 (42)	34 (39)	43 (51)
URT Infection	9 (10)	18 (21)	19 (22)	21 (25)
Throat Irritation	3 (3)	8 (10)	5 (6)	9 (11)
Sinusitis/sinus infection	5 (5)	5 (6)	6 (7)	4 (5)
Nasal Congestion/Blockage	3 (3)	2 (2)	1 (1)	4 (5)
Nasal signs & symptoms	0	1 (1)	1 (1)	3 (4)
Hoarseness/Dysphonia	0	2 (2)	0	3 (4)
Any Gastrointestinal Event	5 (5)	13 (15)	4 (5)	15 (18)
Nausea and vomiting	0	5 (6)	0	3 (4)
Candidiasis mouth/throat	0	3 (4)	0	2 (2)
Any Neurology Event	9 (10)	11 (13)	10 (11)	10 (12)
Headache	7 (8)	11 (13)	9 (9)	7 (8)
Any Lower Respiratory Event	5 (5)	16 (19)	12 (14)	12 (14)
Viral Respiratory Infection	0	3 (4)	4 (5)	8 (10)
Bronchitis	2 (2)	7 (8)	3 (3)	2 (2)
Cough	2 (2)	5 (6)	4 (5)	0
Fever	1 (1)	2 (2)	3 (3)	1 (1)
Candidiasis unspecified site	2 (2)	0	0	3 (4)
Muscoloskelatal Pain	2 (2)	2 (2)	2 (2)	4 (5)
Muscle Injury	0	1 (1)	1 (1)	3 (4)
Injury	0	0	3 (3)	1 (1)

[a]Events which occurred in 3 percent or more of any active treatment group and in a higher proportion of patients in any active treatment group than among placebo patients.