U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Pulmonary and Allergy Drug Products (HFD-570) Backgrounder for sNDA 21-077 – Advair Diskus 250/50, Advair Diskus 500/50

Application #:	NDA 21-077/SE1-003	**Category of Drug:**	Corticosteroid/Long-Acting β_2-Agonist
Sponsor:	GlaxoSmithKline	**Route of Administration:**	Oral Inhalation
Proprietary Name:	Advair Diskus 250/50 and Advair Diskus 500/50	**Medical Reviewer:**	Lydia I. Gilbert-McClain, MD, FCCP
USAN/Established Name:	Fluticasone propionate/salmeterol xinafoate	**Submission Date:**	May 4, 2001

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS

A. Recommendation on Approvability

Withheld pending Pulmonary and Allergy Drug Products Advisory Committee [PADAC] meeting January 17, 2002.

B. Recommendation on Phase 4 studies and Risk Management Steps

Recommendations on phase 4 studies and risk management steps would be addressed after the Pulmonary and Allergy Drug Products Advisory Committee meeting. The sponsor has an ongoing 3-year international study to evaluate the effect of Advair Diskus 500/50 mcg bid and fluticasone propionate 500 mcg bid via Diskus on survival in COPD patients. The sponsor is evaluating bone mineral density and ophthalmologic effects of inhaled corticosteroids over the 3-year period. This study should provide critical safety information about the long-term use of inhaled corticosteroids in COPD patients. Recommendations such as ophthalmologic examinations, monitoring of bone density [by DEXA], and concomitant use of calcium supplements and/or other therapies to reduce bone loss would depend on the final approval decision.

II. SUMMARY OF CLINICAL FINDINGS

A. Overview of clinical program

The clinical development program for the indication for COPD for Advair® Diskus was done concurrently with the development program for the Diskus formulations of fluticasone [Flovent®] and salmeterol [Serevent®]. Three clinical trials of similar design conducted in a similar manner have been submitted as supplements to three separate NDAs; NDA 21-077(Advair Diskus), NDA 20-833 (Flovent Diskus) and NDA 20-692 (Serevent Diskus). The patient population was similar in all three studies. With this clinical program the sponsor is seeking approval of all three products for the long-term maintenance treatment of COPD. Two of the clinical studies [SFCA3006 and SFCA3007] were conducted with Advair Diskus 500/50 and Advair Diskus 250/50 respectively and one study [FLTA3025] was conducted with Flovent® Diskus 500 and Flovent® Diskus 250. The focus of this review will be on the clinical studies with Advair Diskus with references to study FLTA3025 as appropriate.

Advair Diskus is the combination product comprised of the two drug substances-salmeterol xinafoate and fluticasone propionate [FP] in a dry powder formulation in the Diskus device. The two active moieties produce different pharmacological actions in the airway. Salmeterol xinafoate is a long-acting beta$_2$-receptor

agonist that produces bronchodilation, while fluticasone propionate is a high potency corticosteroid with anti-inflammatory properties, as would be expected of this class of drugs. Salmeterol Inhalation Aerosol (Serevent® MDI) was approved in 1998 for the treatment of bronchospasm associated with COPD but neither fluticasone propionate or any other corticosteroid has been approved for the treatment of COPD.

Given that Advair Diskus is a combination product, the clinical studies with Advair® Diskus were designed to fulfill the regulatory requirements set forth in the Code of Federal Regulations 21 CFR 300.50 regarding fixed combinations of prescription drugs. Specifically, to establish that each component makes a contribution to the claimed effects of the combination and the dosage of each component is such that the combination is safe and effective for the population requiring such concurrent therapy. Therefore, the primary objective of these studies was to assess the efficacy and safety of Advair Diskus 250/50 and Advair Diskus 500/50, compared to its individual components and placebo.

In selecting the Advair dose for these trials, the sponsor relied on previous clinical experience from other non-U.S. clinical trials with fluticasone propionate. Previous clinical studies in patients with COPD using fluticasone propionate 500 mcg bid have been reported to show some benefit.[1] The approved dose of salmeterol xinafoate is 50 mcg bid. Therefore the sponsor elected to study Advair Diskus 500/50 mcg bid and 250/50 mcg bid. The lowest strength Advair Diskus 100/50 mcg was not evaluated in this clinical program.

The two pivotal studies with Advair Diskus were conducted in male and female subjects 40 years of age and older. Subjects were current or former smokers with a FEV_1 between 40% - 42% of predicted normal, a ratio of FEV_1 to force vital capacity (FEV_1/FVC) of 47% -51% as well as a history of chronic bronchitis. Subjects were stratified by reversibility [reversible vs. non-reversible] based on their response to bronchodilators as defined by the ATS [see pg. 25]. Study SFCA3006 was done with Advair Diskus 500/50 and study SFCA3007 was done with Advair Diskus 250/50. These studies had 4 arms; Advair Diskus 500/50 or 250/50, Flovent ® Diskus 500 or 250, Serevent® Diskus 50, and placebo. The contribution of fluticasone and salmeterol in the combination were each assessed using a different primary endpoint. Change from Baseline in pre-dose FEV_1 was the primary endpoint used to evaluate the contribution of fluticasone in the combination by comparing Advair Diskus vs. salmeterol. Change from Baseline in 2-hr post dose FEV_1 was the primary endpoint used to evaluate the contribution of salmeterol in the combination by comparing Advair Diskus vs. fluticasone. The asthma trials with Advair Diskus were similarly designed except

[1] PS Burge et.al Randomized double blind placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ vol 320 13 May 2000; 1297-1303*
Pier Luigi Paggiaro et.al. Multicentre randomized placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. The Lancet Vol 351 March 14, 1998; 773-779

that FEV_1 AUC over 12 hours was used to assess the salmeterol effect and not 2-hr post-dose FEV_1. At the end of phase 2 meeting for the COPD program, [April 21, 1998] the Division agreed that it was acceptable to use the 2-hr post dose FEV_1 but that the sponsor should collect serial FEV_1 measurements in at least one study to confirm the 12-hour duration of action and the durability of that action over time. Therefore, the sponsor collected serial FEV_1 measurements over 12 hours on Treatment Day 1 and at Week 12 in a subset of patients at 30 sites in study SFCA3006.

A total of 1,414 patients were enrolled in these two pivotal trials. Of these, 347 patients were exposed to Advair Diskus, 356 to Flovent® Diskus, 341 to Serevent ® Diskus and 370 to placebo. Of the subjects exposed to Advair Diskus, 169 received Advair Diskus 500/50 mcg bid and 178 received Advair Diskus 250/50 mcg bid. The mean duration of exposure was 141.3 days for Advair Diskus 500/50 mcg bid and138.6 days for Advair Diskus 250/50 mcg bid.

B. Efficacy

Advair Diskus 500/50 and Advair Diskus 250/50 both met the efficacy criteria for combination drug products as stated in the Code of Federal Regulations. However the efficacy of Advair Diskus was not demonstrated for any of the supportive secondary endpoints relevant to the COPD indication. There was no treatment difference in COPD-related quality of life, the frequency or severity of COPD exacerbations, or in the chronic bronchitis symptom questionnaire. This finding seriously questions the overall clinical significance of the FEV_1 improvements seen in these trials to the COPD population.

For the primary endpoints both, Advair Diskus 500/50 and 250/50 were superior to placebo. In study SFCA3006 with Advair Diskus 500/50 mcg bid the fluticasone effect in the combination was represented by a model-adjusted mean difference of 67 mL [$p \leq 0.012$] and the salmeterol effect was represented by a model-adjusted mean difference of 129 mL [$p \leq 0.024$]. Similarly, in study SFCA3007 with Advair Diskus 250/50, the fluticasone effect was demonstrated by a model-adjusted mean difference of 69 mL [$p=0.012$] and the salmeterol effect had an adjusted mean difference of 124 mL [$p<0.001$].

The results seen for the primary efficacy endpoints were not affected by smoking status.

In study SFCA3006 the effect size [Advair vs. placebo] for Advair for the reversible group for the mean change from Baseline in mean morning pre-dose FEV_1 was 192 mL compared to 124 mL for the non-reversible population. Therefore, the reversible population had an effect size that was [numerically] 1.5 times that of the non-reversible population. In study SFCA3007, the effect size for the reversible population was [numerically] more than twice [211 mL] the effect size of the non-reversible population [97 mL] for the mean change from

Baseline in mean morning pre-dose FEV_1. For the mean change from Baseline in post-dose FEV_1 the effect size of the reversible population was [numerically] 1.5 times that of the non-reversible population in both studies.

Of the multiple secondary endpoints evaluated, the ones of clinical relevance to the COPD population were COPD exacerbations, a revised Chronic Bronchitis Symptom Questionnaire [CBSQ], COPD-related quality of life as assessed by the Chronic Respiratory Disease Questionnaire (CRDQ) and the assessment of dyspnea. The sponsor used the Baseline Dyspnea Index/Transitional Dyspnea Index [BDI/TDI] to assess dyspnea. Except for the assessment of dyspnea, Advair Diskus did not demonstrate a treatment advantage over its individual components or placebo. In The BDI/TDI Advair Diskus 500/50 had a clinically meaningful improvement compared to placebo and salmeterol at Endpoint, but not compared with fluticasone. In study SFCA3007, the incidence of COPD exacerbations of any severity, and moderate/severe exacerbations were similar in the Advair 250/50 and placebo groups. Of the number of discontinuations, the percentage of withdrawals due to COPD exacerbations was greater in the Advair 250/50 group compared to the placebo group [Advair 250/50 28% vs. placebo 24%]. In study SFCA3006 subjects in the salmeterol treatment group had the lowest incidence of exacerbations [SAL 63 (39%) vs. Advair 68 (41%)] and the lowest number of withdrawals [SAL 9 (20%) vs. Advair 14 (27%)] due to COPD exacerbations. The incidence of COPD exacerbations of any severity was similar in the Advair 500/50 group and the placebo group. However, of the number of withdrawals, the percentage due to COPD exacerbations was higher in the Advair 500/50 [27%] group compared to the placebo group [23%]. Although Advair had a clinically meaningful change at Endpoint in the CBSQ and the CRDQ, no treatment difference was demonstrated when compared with its individual components or placebo.

Other secondary endpoints evaluated were AM peak flow, Ventolin use and nighttime awakenings requiring Ventolin use. As expected, the AM peak flow results were concordant with the FEV_1 findings. The results were similar in both studies. In study SFCA3006, the mean change in AM PEF at Endpoint was 31.9 L/min for Advair Diskus 500/50 compared with 12.9 L/min for Flovent ® Diskus 500 and 16.8 L/min for Serevent ® Diskus. In study SFCA3007, the improvement in AM PEF was 30.6 L/min for Advair 250/50 compared with 11.3 L/min for Flovent ® Diskus 250, and 14.7 L/min for Serevent ® Diskus. Although there were improvements in Ventolin use and nighttime awakenings, these changes were very small and difficult to put in a clinical perspective. Also, these secondary endpoints and in particular, nighttime awakenings are of more clinical relevance in an asthmatic population.

Although Advair Diskus 500/50 and Advair Diskus 250/50 met the efficacy criteria for combination drug products as set forth in the Code of Federal Regulations, the data do not appear to be robustly supportive of an indication for the long-term maintenance treatment of COPD. Additionally, Advair Diskus 500/50 does not

appear to offer a treatment advantage over Advair Diskus 250/50. This finding is noteworthy in dose selection considerations given the risks associated with long-term corticosteroid use.

C. Safety

The safety profile of beta$_2$-agonists and corticosteroids is fairly well understood and characterized in the asthma population. However, although salmeterol has been approved for use in patients with COPD, neither fluticasone propionate nor any other corticosteroid has been approved for use in this patient population in the U.S. Although three large multicenter studies conducted outside of the U.S. provide some safety assessment of the use of inhaled corticosteroids for $\geq$ 6 months in this population the long term safety effects of inhaled corticosteroids in COPD patients is still not fully known.

Safety in the pivotal studies was assessed by monitoring AEs, routine clinical laboratory tests, Cosyntropin stimulation testing [selected sites], ECGs, 24-hour Holter monitoring [selected sites], vital signs and oropharyngeal examinations. This reviewer incorporated relevant safety information from study FLTA3025 in the safety review.

Adverse events more frequent in the active treatment groups than placebo and occurring ≥3% included upper respiratory tract infection [URTI], headache, throat irritation, viral respiratory infection, sinusitis/sinus infection, candidiasis mouth/throat, muscle cramps and spasms, muscle pain, hoarseness/dysphonia, upper respiratory inflammation, and nasal congestion and blockage. Adverse events seen more commonly in subjects receiving fluticasone either alone or in combination with salmeterol included candidiasis mouth/throat, hoarseness/dysphonia, throat irritation, sinusitis, viral respiratory infections, and muscle cramps and spasms. A similar adverse event profile was noted in the Flovent ® study FLTA 3025. A higher frequency of pneumonia was noted in subjects receiving FP than for placebo [FP 250 (1%), FP 500 (2%), Advair 500/50 (1%), placebo (<1%)].

There were 4 deaths in placebo-treated patients in these studies. There were no deaths in any of the active treatment arms in any of the pivotal studies.

There were no clinically meaningful changes in vital signs during the study. Cardiovascular findings were similar among treatment groups and did not suggest that subjects on salmeterol alone or in combination were at increased risk of arrhythmias or cardiac-related adverse events. A drug effect on QTc intervals assessed by Bazetts' and Fridericia's correction formulae was not observed.

Cosyntropin (ACTH) stimulation testing results were not suggestive of clinically significant adrenal suppression. There was some decrease in post-stimulation

serum cortisol levels compared to Treatment Day one levels, but these differences were not clinically significant but tended to suggest [as expected] that with higher doses of inhaled corticosteroids there is some systemic exposure. In study FLTA3025, measurements of serum cortisol AUC at treatment Week 4 showed a dose dependent decrease in serum cortisol in subjects treated with Flovent compared to placebo. Mean cortisol AUC_{12} was 21% lower than placebo for FP 500 and 10% lower than placebo for FP 250.

Specific monitoring of bone mineral density or for ophthalmologic effects were not done in this clinical program. Fractures and ocular-related events were rare in all three studies. There were 13 reports of fractures in the Advair studies one of which was a fractured femur in a 68-year-old female who sustained a fall. There were 10 reports of fractures in study FLTA3025. Five (5) were in the placebo group, 3 were in the FP 500 group, and 2 were in the FP 250 treatment group. Two reports of ocular pressure disorders occurred in the Advair 500/50 treatment group and 3 reports of cataracts occurred in the FP 500 group, 2 in study SFCA3006 and one in study FLTA3025. These pivotal studies were not of sufficient duration and power to detect differences between treatment groups for these uncommon events.

The sponsor is conducting a 3-year study with Advair 500/50, FP 500, salmeterol 50 and placebo bid via Diskus in COPD patients [SCO30003] to evaluate the effect of FP and Advair on survival in COPD. Bone density will be evaluated over three years in a subpopulation of 600 patients. The study will assess fractures and ocular events in the entire study population of 5000 patients. The results of this study will be critical in assessing the long-term risk/benefit analysis for Advair in the COPD population.

D. Dosing

Advair Diskus comes in three strengths 100/50, 250/50, and 500/50. The approval of the latter two strengths is being sought for COPD. In the nomenclature the FP dose is written first followed by the salmeterol dose. Advair Diskus is formulated for oral inhalation only. The proposed dosing regimen is one inhalation twice a day.

E. Special Population

Formal pharmacokinetic studies using Advair Diskus were not conducted to examine gender differences or in special populations, such as elderly patients specifically, or patients with hepatic, or renal impairment.

Pediatric subjects were not included in this clinical development program. COPD as defined by the ATS is not a disease of the pediatric age group. GlaxoSmithKline has asked for a waiver from the pediatric study requirements with Advair Diskus for COPD. The Division stated at the pre-sNDA meeting held

December 1, 2000 that a waiver would most likely be granted at the time of NDA approval.

List of Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
AM	Morning
CRDQ	Chronic respiratory disease questionnaire
ATS	American Thoracic Society
BID/bid/BD	Twice daily
BDI/TDI	Baseline dyspnea index/transitional dyspnea index
CBSQ	Chronic bronchitis symptom questionnaire
CRF	Case report form
DPI	Dry powder inhaler
DSI	Division of Scientific Investigations
FEV_1	Forced expiratory flow rate in one second
FP	Fluticasone propionate
GI	Gastrointestinal
ICS	Inhaled corticosteroid
ITT	Intent to treat
IRB	Institutional Review Board
ISS	Integrated summary of safety
ISE	Integrated summary of efficacy
L	Liter
L-hours	liter-hours
LLN	Lower limit of normal range
Mcg	microgram
MDI	Metered Dose Inhaler
Mins	Minutes
PEF/PEFR	Peak expiratory Flow [Peak expiratory flow rate]
PFT	Pulmonary function test
PD	Pharmacodynamic
PK	Pharmacokinetic
PM	Evening
PRN/prn	As needed
PVC	Premature ventricular contraction
SAE/SE	Serious adverse event/Serious event
SAL	Salmeterol
ULN	Upper limit of normal

CLINICAL REVIEW

I. INTRODUCTION AND BACKGROUND

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

Advair Diskus 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg), and Advair 250/50 (fluticasone propionate 250 mcg and salmeterol 50) are combination products of two previously approved drugs - fluticasone propionate and salmeterol xinafoate. The proposed indication is for the long-term maintenance treatment of COPD (including emphysema and chronic bronchitis). The proposed dose is one oral inhalation bid.

B. State of Armamentarium for Indication

The drugs currently approved for use in COPD are only for the relief of dyspnea associated with the disease. These drugs include short acting and long acting β_2-agonists such as albuterol, salmeterol, and most recently [September 2001] formoterol. The long and short acting theophylline preparations and the anticholinergic drug ipratropium bromide alone, and in combination with albuterol sulphate [Combivent®] are also approved medications for the relief of bronchospasm associated with COPD. The only therapy to date that has been shown to improve survival in COPD is long term oxygen therapy in hypoxemic patients[2]. Oral and inhaled corticosteroids are used off label for this disease however; the benefit of corticosteroids in the long-term maintenance treatment of COPD in contrast to their value in asthma is unclear. The benefit of a short course of systemic corticosteroids in COPD patients hospitalized with acute exacerbations has been reported in the literature.[3]

C. Important Milestones in Product Development

The sponsor consulted with the Division of Pulmonary and Allergy Drug Products at an end of phase 2 meeting held April 21, 1998 to discuss the design of the pivotal trials. The Division informed the sponsor that the proposed clinical trials were acceptable for Advair Diskus provided that the combination policy requirements were met. Additionally, concerns about the long-term use of the individual products (FP and salmeterol) for COPD also needed to be satisfied. Specifically, the Division raised concerns about the potential systemic effect of FP over time in elderly patients and how to link the safety databases from the FP asthma NDA to an older more fragile COPD population. In the case of

[2] Report of the Medical Research Council Working Party. 1981. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet* **1**: 681-685 Nocturnal Oxygen Therapy Trial Group (NOTT) 1980. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. *Ann Intern. Med*. **93**: 391-398

[3] Dennis E. Niewoehner et.al. For the Department of Veterans Affairs Cooperative Study Group. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *NEJM* vol 340 no. **25** 1941-1947

salmeterol, the Division commented that the data from Serevent Diskus asthma trials suggest that dose-response and dose-delivery are somewhat different from the Diskus compared to the MDI and therefore the dose response of salmeterol in the COPD population with the Diskus device should be characterized.

The Division accepted the sponsor's primary efficacy endpoint - 2-hr post-dose FEV_1 to assess the salmeterol effect in the combination product. However the Division asked the sponsor to confirm the 12-hour duration of action of salmeterol and the durability of that action over time in at least one study. A meeting was held August 4, 2000 to discuss electronic submissions and a pre-NDA meeting was held December 1, 2000 to discuss submission of the sNDAs. The sponsor initially intended to submit a single sNDA containing all of the clinical data for all three products [Advair, salmeterol, and fluticasone propionate] but this was not acceptable to the Agency and the sponsor was asked to submit all of the clinical data to three separate NDAs.

At the pre-NDA meeting the Division informed the sponsor of the concern about the benefit/risk of administering a corticosteroid on a regular basis to the COPD population and that the discussion of the use of Flovent Diskus and Advair Diskus will likely be undertaken with an Advisory Committee. The sponsor requested a priority review designation at the pre-NDA meeting. The Division indicated that the preliminary data did not warrant a priority review however, the decision would be made at the time the sNDA is submitted. This sNDA was submitted in electronic format on May 4, 2001 and the sNDA for Flovent Diskus and Serevent Diskus were submitted on May 25, 2001. In a Telecon held Friday September 28, 2001, the Division informed the sponsor that the discussion of the use of Advair and Flovent Diskus in the COPD population will be taken to the Pulmonary and Allergy Advisory Committee meeting to be held January 17th, 2002.

D. *Other Relevant Information*

See "Postmarketing Experience" section on page 15.

E. Important Issues with Pharmacologically Related Agents

N/A

II. Chemistry, Pharmacology/Toxicology, Statistics

Advair Diskus is a combination of fluticasone propionate and salmeterol xinafoate in a Diskus device. Fluticasone propionate is a potent fluorinated glucocorticoid having the chemical name S-fluoromethyl 6α-methyl-3-oxo-17α-propionyloxyandrosta-1, 4-diene-17β-carbothioate. Fluticasone propionate is a white to off-white powder with a molecular formula of $C_{24}H_{31}F_3O_{5S}$ and molecular weight of 500.6. Salmeterol is a long-acting $beta_2$ adrenergic agonist. The xinafoate salt of salmeterol is used in the combination product and has the chemical name 4-hydroxy-α^1-[((6-(4-phenylbutoxy) hexyl)-amino)methyl]-1,3-benzenedimethanol, 1-hydroxy-2-napthoate. It is a white to off-white powder with

a molecular formula of $C_{25}H_{37}NO_4C_{11}H_8O_3$. The Diskus is a breath-actuated powder delivery system containing 60 doses of the combination product. Each dose of Advair is hermetically sealed in an individual double-foil blister strip. Each blister on the double-foil strip within the device contains 100, 250, or 500 mcg of microfine fluticasone propionate powder and 72.5 mcg of microfine salmeterol xinafoate salt powder, equivalent to 50 mcg of salmeterol base, in 12.5 mg of formulation containing lactose. The device is equipped with a dose counter. After a blister containing medication is opened by activating the device, the medication is dispersed into the airstream created by the patient inhaling through the mouthpiece.

Three strengths of Advair Diskus are currently marketed in and outside of the U.S. for the long-term maintenance treatment of asthma. They are:

- Advair Diskus 100/50 mcg
- Advair Diskus 250/50 mcg
- Advair Diskus 500/50 mcg

The sponsor is seeking approval of the 2 higher strengths for the long-term maintenance treatment of COPD. The proposed dosage is one inhalation twice daily. Under standardized *in vitro* test conditions, Advair Diskus 250/50 and 500/50 delivers 233 and 465 mcg of fluticasone respectively and 45 mcg of salmeterol base per blister when tested at a flow rate of 60 L/min for 2 seconds. In 9 adult patients with obstructive lung disease and severely compromised lung function [FEV_1 20% -30% predicted] mean peak inspiratory flow through a Diskus device was 80.0 L/min [range 46.1 to 115.3 L/min].

Pharmacology/toxicology data were not submitted to this sNDA.

Dr. Ted Guo Biostatistician conducted a detailed statistical review of the sNDA.

III. Human Pharmacokinetics and Pharmacodynamics

Dr Sandra Suarez conducted the biopharmacology review of the sNDA. The same biopharm studies were submitted to all three sNDAs. The sponsor did not conduct clinical pharmacology studies with Advair Diskus during this development program. The sponsor submitted the results of a previous five-way crossover study [SAS1005] in 15 healthy subjects with Advair HFA, Advair Diskus, FP, and salmeterol. In that study, the systemic exposure from Advair HFA and Advair Diskus were similar. Systemic exposure for salmeterol was lower from Advair Diskus compared with Advair HFA. A dose proportionality study [FLTA 1003] was conducted with FP to examine the comparability of FP pharmacokinetics and pharmacodynamics following administration of 1000 mcg of fluticasone propionate via the 50, 100, 250, and 500 mcg Diskus formulation. Additionally, the sponsor conducted a randomized two-period cross-over trial in COPD and healthy subjects with inhaled FP 500 mcg bid for 7 days followed by a single inhaled dose of FP 1000 mcg and placebo infusion, or inhaled BDP 1000

mcg bid from a metered dose inhaler for 7 days followed by inhaled placebo and FP 1000 mcg infusion. [Study fms40243]. The sponsor also evaluated systemic exposure of FP in a subset of patients in the clinical study FLTA3025. This study showed a dose-related reduction in serum cortisol levels. From Dr. Saurez's review, dose proportionality of the 500 mcg strength of FP was not demonstrated in study FLTA1003. This finding will influence the decision on the approvability of FP 500 mcg BID administered via Flovent Diskus 250 as 2 inhalations bid however, for the combination product Advair 500/50 this finding is not as crucial

IV. Description of Clinical Data and Sources

A. Overall Data

The data used in this review were obtained from the sNDA 21-077/SE1-03 submission. Three pivotal trials were submitted: SFCA3006, SFCA3007, and FLTA3025. All three studies are randomized, double blind placebo-controlled multicenter trials conducted in a similar manner. All three trials were submitted to 3 separate supplemental NDAs as was required by the Agency. For the purpose of the Advair Diskus, the clinical program must fulfill the combination policy requirements for approval. To this end, this review will focus on studies SFCA3006 and SFCA3007 with evaluation of the following assessments:

- Advair Diskus 250/50 and 500/50 compared with salmeterol 50 to evaluate the contribution of FP to the combination product

- Advair Diskus 250/50 and 500/50 compared with FP Diskus 250 and 500 respectively to evaluate the contribution of salmeterol in the combination.

- Advair Diskus 250/50 and 500/50 versus placebo to evaluate the overall safety and efficacy profile of the combination product.

Dr. Charles Lee reviewed the supplemental application for Flovent Diskus [sNDA 20-833/SE1-04]. Relevant safety and efficacy findings from study FLTA3025 will be referenced from his review. In addition to safety assessments in the efficacy trials, the sponsor has submitted an extensive safety database that includes data from the European 3-year study in patients with COPD with Flovent 500 mcg bid [ISOLDE], 2 completed studies with FP in asthmatic patients, and the 120-safety day update submitted August 31, 2001. This reviewer reviewed the 120-day safety update and Dr. Charles Lee reviewed the safety information from the FP studies. Relevant safety information from Dr. Lee's review is referenced.

B. Table of Clinical Studies

TABLE 1. PIVOTAL CLINICAL STUDIES

Study #	Location	Study Objective	Treatments Arms/ BID Dosage (mcg)	Primary Endpoints	N Randomized	N Completed
SFCA3006	US	Demonstrate efficacy of the combination product over the individual components and placebo	Advair Diskus 500/50 SAL Diskus 50 FP Diskus 500 Placebo Diskus	Change from Baseline in 2-hr post-dose FEV_1 [to assess the salmeterol effect in Advair] Change from baseline in AM pre-dose FEV_1 [to assess the FP effect in Advair]	691	440
SFCA3007	US	Demonstrate efficacy of the combination product over the individual components and placebo	Advair Diskus 250/50 SAL Diskus 50 FP Diskus 250 Placebo Diskus	Change from Baseline in 2-hr post-dose FEV_1 [to assess the salmeterol effect in Advair] Change from baseline in AM pre-dose FEV_1 [to assess the FP effect in Advair]	723	505
FLTA3025	US	Demonstrate efficacy of Flovent Diskus over placebo	FP Diskus 500 , FP Diskus 250, placebo	Change from baseline in pre-dose FEV_1	640	414

C. Postmarketing Experience

The fluticasone propionate /salmeterol combination product has not received approval for COPD in any country. Fluticasone propionate has obtained approval for COPD in several developing countries in the West Indies, Africa, and South America, and in Pakistan, the Philippines, Romania, Slovakia, Turkey, and Yugoslavia. Salmeterol has been approved for use in patients with COPD in the U.S., Albania, Bulgaria, China, Greece, Hong Kong, Korea, Malaysia, Moldova, Pakistan, Philippines, Singapore, and Taiwan. Deaths reported in cases where salmeterol, FP, or Advair were stated as used for COPD were reported in the 120-day safety update in the "Post-Marketing Experience" Section. Three deaths in patients taking Advair and one death in a patient taking FP were reported. None of the deaths appear to be drug-related. Three of the deaths were from cardiac causes and one was due to malignancy. Serious adverse events that were reported in the post-marketing observational studies either appear to be unrelated to Advair or in some cases causality was unable to be established.

D. Literature Review

The sponsor submitted an extensive review in support of the use of corticosteroids in COPD, and the benefits of this combination therapy in COPD. For the purposes of the sNDA review the following articles were reviewed in detail. Other references are cited in footnotes as appropriate throughout the review.

(I) Long term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease that continue smoking. *Romain A. Pauwels et.al for the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease [EUROSCOP]. NEJM 1999;340:1948-53*

(II) Randomised, double-blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary diseases: the ISOLDE trial. PS Burge et.al on behalf of the ISOLDE study investigators. *BMJ Vol 320; 1297-1303*

(III) Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. Pier Luigi Paggiaro et.al. On behalf of the international COPD study group. *Lancet Vol 351;773-779*

(IV) Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med. 1987; 106:196-204*

(V) Standards for the diagnosis and care of patients with chronic obstructive pulmonary diseases. *Am J Respir Crit care Med. 1995; Vol 152 pp s77-s120*

(VI) Global Initiative for chronic obstructive lung disease [GOLD]. Executive summary based on April 1998 meeting. *National Institutes of Health/National Heart, Lung and Blood Institute.*

V. CLINICAL REVIEW METHODS

A. Conduct of the Review

The two trials SFCA3006, and SFCA3007 and the 120-day safety update were reviewed in detail. Safety results of study FLTA3025 were referenced from Dr. Charles Lee's review. The two trials were reviewed separately and discussed with the Medical Team Leader.

B. Overview of Materials Consulted in the Review

The sNDA was submitted in electronic format and these materials were used to conduct the review. The sNDA contained the safety and efficacy findings of the three controlled clinical studies SFCA3006, SFCA3007, and FLTA3025 and an ISS and ISE. During the review cycle, 4 additional submissions from the sponsor in response to FDA questions related to the sNDAs and the 120-day safety update were reviewed. Safety information from the asthma studies with Flovent® submitted to the sNDA was referenced from Dr. Charles Lee's review. The Medical officer Review of NDA 21-077 for Advair Diskus for the indication for the long term maintenance treatment of asthma was consulted.

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

An audit by the Division of Scientific Investigations (DSI) was conducted at 2 U.S. study sites and checked the sponsor's data and analyses. One site from study SFCA3007 and one site from study FLTA3025 were audited. Dr. Charles Lee requested this audit as part of his review of sNDA20-833/SE1-04. Therefore, this reviewer did not request additional sites for auditing. The sites chosen were site #15557 UCLA - Principal Investigator Donald P. Tashkin, and site # 13564 Scripps Clinical/Research Foundation - Principal Investigator Darlene Joan Elias. Each of these two sites enrolled the largest number of patients in both studies. The findings of the DSI audit did not preclude the use of these data in the assessment of approvability. [*See Dr. Charles Lee's review for details of DSI inspection]*

D. Ethical Conduct of Trials

The studies were conducted in accordance with "Good Clinical Practice" (GCP) guidelines and all applicable regulations including the Declaration of Helsinki [June 1964] as modified by the 48th World Medical Association, Republic of South Africa, October 1996. All study sites were registered with the FDA. The decision to participate in the study was entirely voluntary. The subject or the subject's legally authorized representative signed and dated the informed consent form before the subject could participate in the study.

E. Evaluation of Financial Disclosure

GlaxoSmithKline states in an organization-wide policy statement that “Glaxo does not compensate clinical investigators in such a way as the total amounts could vary with the outcome of the study”. With regard to “significant payments of other sorts” from the sponsor, the $25,000 threshold for “payments of other sorts” was exceeded in the case of one investigator participating in clinical trial SFCA3006 – [ ]. Of the 691 subjects in the study there were [ ] (<1%) subjects enrolled at this investigator’s site. Because the number of subjects was so small GSK did not conduct an analysis to explore the effect of this Investigator on the results of study SFCA3006. This reviewer concurs that such a small number of subjects should not have the potential to bias the outcome and/or conclusions of the study. GSK determined that no investigator participating in the Advair studies had a proprietary interest in Advair Diskus. Additionally, no investigators in the Advair studies had a significant equity interest [> $50,000]. In summary, the contribution of the one study center cited in study SFCA3006 in the financial disclosure statement should not have had an impact on the overall outcome or conclusions of the clinical program.

VI. INTEGRATED REVIEW OF EFFICACY

A. Conclusions

Advair Diskus 500/50 and Advair Diskus 250/50 were statistically superior to placebo. For the primary efficacy endpoint “mean change from Baseline in pre-dose FEV_1” both Advair 500/50 and Advair Diskus 250/50 had a statistically significant treatment effect when compared with salmeterol establishing the contribution of fluticasone in the combination product. The model-adjusted treatment effect was 67 mL [$p \leq 0.012$] for Advair Diskus 500/50, and 69 mL [$p=0.012$] for Advair Diskus 250/50.

For the primary efficacy endpoint “mean change from Baseline in 2-hr post-dose FEV_1 the model adjusted treatment effect of Advair Diskus compared to FP was 129 mL [$p<0.001$] for Advair Diskus 500/50, and 124 mL [$p<0.001$] for Advair Diskus 250/50. The comparison of Advair vs. FP establishes the contribution of salmeterol in the combination product.

In both studies subjects on Advair in the reversible population had a numerically greater treatment effect than subjects in the non-reversible population. Inferential analyses were not conducted for these subgroup analyses.

Improvements in AM peak flow (PEF) measurements at Endpoint in patients treated with Advair Diskus were numerically superior to patients treated with SAL, FP, or placebo in both studies and are supportive of the FEV_1 results. This is not an unexpected finding as PEF measurements also assess lung function and would be expected to be similar to FEV_1 measurements. Nighttime

awakenings and Ventolin® use were evaluated as secondary endpoints as well; however, numerical improvements were generally very small and are difficult to assess from a clinical standpoint. Also, nighttime awakenings requiring Ventolin use are of more clinical relevance in an asthmatic population.

COPD-related quality of life was assessed with the Chronic Respiratory Disease Questionnaire [CRDQ]. Although Advair Diskus 500/50 and 250/50 each had a clinically meaningful change [>10] in the Overall score, a clinically meaningful difference was not achieved between placebo or any of the individual components. In the Chronic Respiratory Disease Questionnaire, a clinically meaningful difference was not seen at Endpoint between Advair Diskus and any of its individual components or placebo.

The frequency of COPD exacerbations and withdrawals due to COPD exacerbations were lowest in the salmeterol treatment group and similar for the Advair Diskus and placebo groups in study SFCA3006. Of the number of withdrawals, the percentage due to COPD exacerbations in SFCA3006 was 20% in the salmeterol group compared with 23% in the placebo group and 27% in the Advair 500/50 group. In study SFCA3007 of the number of withdrawals due to COPD exacerbations 30% was in the salmeterol group, 28% in the Advair 250/50 group, and 24% in the placebo groups. The time to onset of COPD exacerbations and the number of severe exacerbations were similar across treatment groups in SFCA3006. In SFCA3007 the percentage of subjects with severe COPD exacerbations was highest in the FP 250 group [38%] followed by the placebo and Advair Diskus 250/50 groups [34%] and lowest in the salmeterol group [31%].

The Baseline Dyspnea Index/Transitional Dyspnea Index [BDI/TDI] was used to evaluate dyspnea. At Endpoint there was a clinically meaningful improvement in dyspnea in the Advair 500/50-treatment group compared with placebo and salmeterol in study SFCA3006 but not with Advair Diskus 250/50 in study SFCA3007.

In summary Advair Diskus 500/50 and Advair Diskus 250/50 both met the efficacy criteria for combination drug products as stated in the Code of Federal Regulations. However except for dyspnea as evaluated with the BDI/TDI with the 500/50 mcg dose, the efficacy of Advair Diskus was not demonstrated for any of the secondary endpoints relevant to the COPD indication. The patient population studied was not representative of the COPD population at large in that > 50% of the subjects showed significant reversibility and the study was limited to only patients with confirmed chronic bronchitis. The failure of Advair to demonstrate a treatment effect in the secondary endpoints of relevance to COPD [i.e. exacerbations, CRDQ, CBSQ] calls into question the clinical significance of the FEV_1 findings. Taken together, These data do not appear to be robustly supportive of efficacy in the COPD population.

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

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

C. DETAILED REVIEW OF CLINICAL TRIALS

The three trials for the COPD indication are:

SFCA3006. “A Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Safety and Efficacy of the Diskus Formulations of Salmeterol 50 mcg bid and Fluticasone Propionate 500 mcg BID Individually and in Combination as Compared to Placebo in COPD Subjects. ”

SFCA 3007 “A Randomized, Double-Blind, Placebo-Controlled Trial Evaluating the Safety and Efficacy of the Diskus Formulations of Salmeterol 50 mcg bid and Fluticasone Propionate 250 mcg BID Individually and in Combination as Compared to Placebo in COPD Subjects. ”

FLTA3025: “A Randomized, Double-Blind, Placebo-Controlled, Trial Evaluating the Safety And Efficacy Of Fluticasone Propionate 500 mcg BID, and 250 mcg BID Compared with Placebo in COPD Subjects”.

For the purpose of the indication for Advair Diskus for the treatment of COPD, studies SFCA3006 and SFCA3007 were reviewed in detail. The comparison of the Advair Diskus 500/50 and Advair Diskus 250/50 with SAL 50 to evaluate the contribution of FP to the combination product, and with FP 500 and 250 to evaluate the contribution of SAL 50 in the combination product are critical to satisfy the regulatory requirements for combination drug products. The Comparison of Advair Diskus to placebo is helpful in determining the overall efficacy and safety of the combination product. As previously stated study FLTA3025 will not be reviewed in this document.

TRIAL DESIGN of STUDIES SFCA3006 AND SFCA 3007

<u>OBJECTIVES</u>

1. To compare the efficacy of salmeterol 50 mcg bid, FP 500 mcg or FP 250 mcg bid, Advair 500/50 mcg or Advair 250/50 mcg bid, and placebo when administered via the Diskus over a 24-week treatment period for the treatment of COPD subjects.

2. To compare the safety of salmeterol 50 mcg bid, FP 500 mcg or 250 mcg bid, Advair 500/50 mcg or 250/50 mcg bid, and placebo when administered via the Diskus over a 24-week treatment period for the treatment of COPD subjects.

3. To compare the quality of life in COPD subjects receiving salmeterol bid, FP 500 mcg or FP 250 mcg bid, Advair 500/50 mcg or 250/50 mcg bid or placebo when administered via the Diskus over a 24-week treatment period.

These trials were randomized, double blind, placebo-controlled, parallel group studies of 24 weeks duration. The studies had 2 phases. The first phase was a 2-week run-in period where patients who met the entrance criteria were placed on placebo via Diskus device one puff BID. During the two-week run-in period, concurrent inhaled or oral sympathomimetic or anticholinergic bronchodilator and corticosteroid therapies were discontinued. Subjects on theophylline were permitted to continue it if the dose had been stable for at least one month. During the run-in period and throughout the study, subjects were allowed to take Ventolin ® MDI, or nebules as needed. The 2-week run-in period was used to establish a baseline for AM peak flow, supplemental Ventolin use, nighttime awakenings requiring Ventolin use, and compliance. At randomization subjects were randomized to one of the following treatments via Diskus for a 24-week treatment period:

SFCA3006
- Advair 500/50 mcg BID
- SAL 50mcg BID
- FP 500 mcg BID
- Placebo BID

SFCA3007
- Advair 250/50 mcg BID
- SAL 50 mcg BID
- FP 250 mcg BID
- Placebo BID

Patients were followed every week for the first 4 weeks, every 2 weeks through Treatment Week 8, and then at 4-week intervals for the remainder of the treatment period. Subjects who developed an exacerbation of COPD after randomization were treated with antibiotic therapy as an outpatient for up to two exacerbations but were withdrawn from the study if a third exacerbation occurred, or if they required hospitalization to treat an exacerbation.
Reviewer Comment: The sponsor did not define COPD exacerbation per se but defined the severity of an exacerbation based on the treatment the subject received. [See pg.26]

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

Inclusion Criteria

Subjects had to be male and female patients diagnosed with COPD (ATS definition)[4] age 40 years or older and had to meet ALL of the following inclusion criteria to be eligible for inclusion in the study:

- Female subjects had to be of non-child-bearing potential or if of childbearing potential must have a negative serum pregnancy test and must use an approved contraceptive, undergo female sterilization, or their male partner must have undergone sterilization.

- Subjects had to have a current or prior history of ≥ 20 pack-years of cigarette smoking. Subjects who were ex-smokers must have discontinued smoking for at least 6 months prior to Screening.

- Subjects must have a history of cough productive of sputum on most days for at least 3 months of the year for at least 2 years, that was not attributable to another disease process.

- Subjects had to have a baseline FEV_1 of < 65% predicted normal but > 0.70 L OR $FEV_1 \leq 0.70$ L AND >40% but still < 65% of predicted normal value [according to Crapo et al.][5] AND FEV_1/FVC ratio of ≤70%.

- Subjects also had to achieve a score of ≥ 2 on the Modified Medical Research Council Dyspnea Scale [MMRCD] (see Appendix on pg. 83) at screening

- Subjects had to have a score of ≥4 [out of possible 16] on the Chronic Bronchitis Symptoms Questionnaire [CBSQ] (see Appendix on pg. 75 for CBSQ) at Treatment Day 1 to qualify for the study.

- Subjects could be on inhaled corticosteroids not exceeding the doses outlined in Table 2, below.

Exclusion Criteria

In addition to the usual exclusion criteria in clinical trials, subjects were excluded for any of the following criteria:

- A diagnosis of asthma as defined by the ATS[6]

[4] Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by the presence of airflow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyperreactivity, and may be partially reversible. *Am J Respir Crit Care Med Vol 152. pp S77-S120, 1995*

[5] Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis 1981; 123: 659-64*

[6] Asthma is a clinical syndrome characterized by increased responsiveness of the tracheobronchial tree to a variety of stimuli. The major symptoms of asthma are paroxysms of dyspnea, wheezing and cough, which may vary from mild and almost undetectable to severe and unremitting (status asthmaticus). *Am J Respir Crit Care Med Vol 152. pp S77-S120, 1995*

- Alpha-1-antitripsin deficiency
- Lung cancer, bronchiectasis, sarcoidosis, tuberculosis, lung fibrosis
- A lobectomy within 1 year of the Screening visit
- Current smokers who decided to quit smoking at the Screening Visit
- Subjects with specific causes of airflow obstruction such as localized disease of the upper airways, bronchiectasis, and cystic fibrosis
- Patients who required CPAP or BIPAP for COPD or sleep apnea
- Patients who had significant concurrent diseases that placed them at risk or interfered with clinical evaluations or influenced their participation in the study
- Patients who required supplemental oxygen with the exception of those who live at high altitudes (i.e. above 3000 feet) and did not require oxygen for more than 12 hours per day and the maximum rate during the 12-hour period was not more than 2 liters/minute, or did not require more than 2 L/min of oxygen for more than 2 hours per day for exertion.
- Patients with a history of drug or alcohol abuse
- Patients with chest x-ray abnormalities not believed to be due to COPD
- Patients with a clinically significant abnormal 12-lead ECG during the run-in period.
- Patients who required beta-blockers digitalis, ketoconazole or fluconazole, phenothiazines, tricyclic antidepressants, MAO inhibitors, or immunosuppressive agents including cyclosporine, methotrexate and gold.
- Patients with glaucoma requiring treatment with non-selective beta blockers
- History of symptomatic or clinically significant pathological fractures
- Subjects with a moderate or severe exacerbation during the Run-in period.

TABLE 2. Prior ICS Use - Differences for Study SFCA 3006 and SFCA3007

	SFCA3006	**SFCA3007**
Prior ICS dosage (mcg/day)		
Beclomethasone dipropionate (Beclovent®, Vanceril®)	≥1008 mcg/day (12/24 puffs)	378-840

Triamcinolone acetonide (Azmacort®)	≥1600 mcg/day (16 puffs)	900-1600
Flunisolide (Aerobid®)	≥2000mcg/day (8 puffs)	1250-2000
Fluticasone propionate MDI (Flovent®)	≥ 880 mcg/day	440-660
Fluticasone propionate DPI (Flovent Rotadisk®)	≥1000 mcg/day	400-600
Budesonide (Pulmicort® Turbuhaler)	≥1600 mcg/day (8 puffs)	800-1200

STUDY PROCEDURE

To ensure an even distribution of reversible and non-reversible subjects in each treatment group, assignment to study drug the sponsor stratified according to the subjects' response to reversibility testing with Ventolin at screening. Reversibility was defined as per the ATS criteria for reversibility stated below.

Reversible: Subjects that demonstrated a bronchodilator response (post albuterol) of ≥200 mL AND 12% improvement in FEV_1 over Baseline.

Non reversible: Subjects that demonstrated a bronchodilator response (post albuterol) of <200 mL or < 12% improvement in FEV_1 over Baseline.

Note: Bronchodilator response = percent improvement over Baseline, calculated as follows:
(post-bronchodilator FEV_1 - pre-bronchodilator FEV_1)/pre-bronchodiator FEV_1 X 100

In the data analysis, the sponsor also defined a **poorly reversible population** that they have indicated as applicable to the rest of the world (ROW). The **poorly reversible population** was defined as subjects that demonstrated an increase in **percent predicted** FEV_1 of < 10% after 4 puffs of albuterol inhalation aerosol at Screening**.**

Reviewer's Comment: When reversibility is defined as a function of percent-predicted FEV_1 some patients defined as Reversible by ATS criteria could be defined as "Poorly Reversible" leading to potential misunderstanding of the degree of individual patient responsiveness to bronchodilators (see examples in the table below). Because this definition of reversibility is seldom used in this country, details of this population will not be discussed in this review.

Table3. Reversibility Results for selected subjects Expressed as per ATS criteria and as Percent Predicted [Data from Listing 7.1 SFCA3006.pdf]

Subject #	% Predicted FEV_1 [Pre]	FEV_1 [Pre]	FEV_1 [Post]	% Predicted FEV_1 [Post]	Reversibility [% change in FEV_1 and Absolute mL]	Reversibility [Change in % predicted]
9029	20.1	0.71	1.01	28.61	42.3% , 300mL	8.5%
9254	39.8	1.44	1.74	48.1	20.8% , 300 mL	8.3%
9532	61.6	2.04	2.30	69.4	12.7%, 260mL	7.8%
9729	38.2	1.48	1.78	46.0	20.3%, 300mL	7.7%

Withdrawal Criteria
Subjects were discontinued from the study if any of the following occurred:

- Three exacerbations requiring treatment with antibiotics
- An exacerbation which required treatment with corticosteroids
- Hospitalized for an exacerbation
- An AE which led to study withdrawal
- Not benefiting from treatment [lack of efficacy/treatment failure]
- Used corticosteroids or other prohibited medication for another indication
- Initiated use of CPAP device
- Withdrew consent
- Former smoker who started smoking during the study and smoked at least 7 consecutive days
- Current smoker who stopped smoking during the study for > 4 weeks
- Inability to attend scheduled clinic visits.

Exacerbations of COPD
The investigator assessed the severity of COPD exacerbations at each clinic visit. Each COPD exacerbations was categorized according to one of the following three levels of severity:

Mild: Defined as use of relief bronchodilator of more than 12 puffs [or more than 4 nebules] per day for 2 consecutive days, but without the need for any other additional medication [this information collected from subject diary records]

Moderate: defined as requiring, per investigator judgement, either oral antibiotics and/or corticosteroids.

Severe: Defined as requiring, per investigator judgement, inpatient admission for treatment of an exacerbation of COPD. Subjects who developed a severe exacerbation were discontinued from the study.

STATISTICAL AND ANALYTICAL PLAN

EFFICACY
Primary Efficacy Endpoints
The mean change from Baseline at Endpoint in the Pre-dose FEV_1 and 2 hr-post-dose FEV_1 were the primary efficacy analyses. The pre-dose FEV_1 was the primary endpoint used to evaluate the effect of FP in the combination product, while the 2 hr-post-dose FEV_1 was the endpoint used to evaluate the effect of SAL in the combination product. The comparison was made between Advair Diskus [500/50 and 250/50] and SAL 50 to evaluate the effect of FP. The comparison was made between Advair Diskus 500/50 and FP 500 in study SFCA3006 and between Advair Diskus 250/50 and FP 250 in study SFCA3007 to evaluate the effect of SAL.

Baseline FEV_1 was the pre-dose FEV_1 at Treatment Day 1.The endpoint value for FEV_1 measurements was the last on-treatment measurement recorded excluding data from discontinuation visits for each subject.

Sample size and power calculations

The standard deviation of the change from pre-dose Treatment Day 1 Baseline in pre-dose FEV_1 at each treatment visit was assumed to be 0.28 L. Using a two sample t-test with an α of 0.05 a sample size of 175 patients per treatment arm would provide $\geq$ 91% power to detect a difference of 0.1 L for any pairwise treatment comparisons. A total of 692 subjects in 65 centers were randomized to study SFCA3006 and 723 subjects in 76 centers were randomized to study SFCA3007. The sponsor indicated that the standard deviation of change from Baseline at Endpoint in pre-dose FEV_1 ranged from 220 mL to 239 mL for the ITT population for study SFCA3006 and ranged from 204 mL to 277 mL for study SFCA3007. For post-dose FEV_1 the standard deviation of change from Baseline at Endpoint ranged from 134 mL to 212 mL for the ITT population for study SFCA3006 and ranged from 211 mL to 313 mL for study SFCA3007. Therefore, the studies were adequately powered to show a 100 mL difference for both pre-dose and post-dose FEV_1 for the ITT population.

Secondary Efficacy Endpoints

The sponsor evaluated multiple secondary endpoints. Of these, the secondary endpoints most relevant to COPD are:

- Chronic Bronchitis symptom Questionnaire [revised]
- Transition Dyspnea Index
- COPD exacerbations

Chronic Bronchitis Symptom Questionnaire [CBSQ]

The CBSQ combined selected questions from the Petty Subject Evaluation Questionnaire and the Revised Global Petty Questionnaire for Ease of Cough and Sputum Clearance[7]. The CBSQ evaluated the COPD symptoms of cough frequency and severity, chest discomfort, and sputum production on a scale of 0-4 where a rating of 0 reflected no symptoms (see Appendix On pg. 75). Subjects had to have a score of $\geq$4 out of possible 16 at Treatment Day 1 to qualify for the study. The test was given at every study visit as well as the discontinuation visit where possible. Individual scores were added to provide a Global Assessment Score (GAS). The minimal clinically important change (MCIC) for the CBSQ was determined to be a change from baseline of 1.4 in the CBSQ GAS. The MCIC was determined by matching changes from Baseline in the CBSQ GAS with a separate measure of change in chronic bronchitis symptoms called the Global Rate of Change [GRC]. The GRC was a 2-part question asked by the

[7] Petty TL. The national mucolytic study: results of a randomized, double blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. Chest 1990;97:75-83
Rubin Bk, Ramirez O, Ohar JA. Iodinated glycerol has no effect on pulmonary function, symptom score, or sputum properties in patients with stable chronic bronchitis. Chest 1996;109348-52

investigator independent of the CBSQ of all available patients at the Week 8, 16, and Discontinuation visit. Patients were first classified as to whether their chronic bronchitis had improved, stayed the same or deteriorated by asking the following question: “Since the beginning of this study, has there been any change in your symptoms of chronic bronchitis, that is, your cough, OR sputum production, OR chest discomfort? If the patient indicated that there had been no change, a score of 0 was given. If the patient indicated that there had been an improvement or deterioration, the change was scored on the scale outlined below: The investigator recorded a single number between –7 and 7.

-7:	A very great deal worse
-6:	A great deal worse
-5:	A good deal worse
-4:	Moderately worse
-3:	Somewhat worse
-2:	A little worse
-1:	Almost the same, hardly any better at all
0:	No change
1:	Almost the same, hardly any better at all
2:	A little better
3:	Somewhat better
4:	Moderately better
5:	A good deal better
6:	A great deal better
7:	A very great deal better

Baseline/Transition Dyspnea Index (BDI/TDI)

The BDI/TDI scale was developed to provide a clinical measurement of dyspnea. The Baseline (BDI) scale was given on Treatment Day 1 and rated the Baseline severity of dyspnea on a scale of 0 –4 where 0 was most severe. The BDI total score was the sum of the individual category scores. The maximum possible BDI score was 12. The TDI measured the change from Baseline using a –3 to +3 scale where negative numbers indicated deterioration and 0 indicated no change. The TDI total score could range from –9 to +9. [see Appendix on pg. 77].

Health Outcomes

COPD related quality of life was evaluated using the Chronic Respiratory Disease Questionnaire [CRDQ]. The CRDQ contains 20 questions each scored 0-7 in four domains: dyspnea, fatigue, emotional function, and mastery [see Appendix on pg.81]. The domains can be grouped as physical summary [dyspnea and fatigue] and emotional summary [emotional function and mastery]. The primary quality of life endpoint is the overall score [sum of all 20 questions] and this score can range from 0-140. Higher CRDQ scores indicate better COPD-related qualify of life. The CRDQ was administered at Baseline (Treatment Day 1), and at Treatment Weeks 2, 4, 8, 24, and at the Premature Discontinuation Visit as appropriate. A mean score improvement of 0.5 points per

item was considered to be clinically meaningful based on published literature[8]. Therefore, for this study, an improvement of at least 10 in the Overall score was considered an overall improvement in COPD-specific quality of life. For treatment group comparisons, a difference of at least 10 in the Overall score in the mean change from Baseline at Endpoint between treatment groups was considered clinically meaningful. A reduced ITT population was used for the analysis of the CDRQ data. Subjects were excluded from the analyses based on their scores as follows:

1. overall Baseline score greater than 130
2. dyspnea score greater than 32
3. fatigue score greater than 26
4. emotional function score greater than 45
5. mastery score greater than 26

Subjects with physical summary score greater than 58 and emotional summary score greater than 71 were excluded from the analysis of their corresponding domains. The Overall score was the primary measure for all analyses.

SAFETY

Safety assessments include adverse event reporting, clinical chemistry and hematology, ECG, and Holter monitoring [at selected sites], vital signs, oropharyngeal examinations, and Cosyntropin [ACTH] stimulation testing at selected sites.

EFFICACY RESULTS

RESULTS STUDY SFCA3006

Patient Disposition

A total of 1,352 patients were screened, and 691patients were randomized. Of the 1,352 subjects screened, 661 failed screening. The most common reason for screening failure was not meeting the entrance criteria of disease severity [i.e. an FEV_1/FVC of ≤70% and Baseline FEV_1 of ≤ 65% predicted but >0.70L].

Because of data integrity concerns the sponsor excluded all subjects (n = [ ]) enrolled with Investigator #[ ] from the efficacy analyses. The [ ] subjects included [ ] each in the placebo, Advair 500/50, and SAL treatment groups and [ ] in the FP 500 group. Therefore data from 674 patients were analyzed for efficacy and the ITT population for the efficacy analyses refers to these 674 patients. For the safety analyses all 691 randomized patients were included.

Of the 674 subjects analyzed in the ITT population, 165 were in the Advair Diskus 500/50 group, 160 in the salmeterol group, 168 were in the Flovent Diskus 500 group, and 181 were in the placebo group. Two hundred and thirty-

[8] Jaeschke R, Singer J, Guyatt GH. Measurement of health status: ascertaining the minimal clinically important difference. Controlled Clinical Trials 1989;10:407-15

four (234) of the 674 subjects withdrew from the study prior to completion and 440 (65%) completed the study.

Table -4. Patient Disposition ITT Population SFCA 3006

	Placebo n=181	SAL 50 n=160	FP 500 n=168	Advair Diskus 500/50 n =165	Total N =674
# (%) Complete	112 (62%)	115 (72%)	100 (60%)	113 (68%)	440 (65%)
# (%) Withdrawn	69(38%)	45 (28%)	68 (40%)	52 (32%)	234 (35%)[a]
Reason for Withdrawal					
Lack of Efficacy[b]	11 (6%)	7 (4%)	3 (2%)	3 (2%)	24 (4%)
Adverse Event	17 (9%)	11 (7%)	21 (12.5%)	11 (7%)	60 (9%)[c]
Protocol violation	8 (4%)	10 (6%)	14 (8%)	8 (5%)	40 (6%)
Consent withdrawn	11 (6%)	4 (2.5%)	5 (3%)	10 (7%)	30 (4.5%)
Lost to follow up	2 (1%)	1 (<1%)	3 (2%)	1 (<1%)	7 (1%)
COPD exacerbation[d]	16 (9%)	9 (6%)	17 (10%)	14 (8.4%)	56 (8%)
***Other**	4 (2%)	3 (2%)	5 (3%)	5 (3.5%)	17 (2.5%)

*Other: include noncompliance, subject relocation, or treatment needed for concurrent disease
[a] Deaths = 3 bring the total number of withdrawals to 247
[b] The sponsor did not provide a definition for "lack of efficacy"
[c] From data listings a total of 59 subjects withdrew due to AE [not counting the 3 deaths]
[d] COPD exacerbations are also included in "Adverse Events"

The percentage of withdrawals due to COPD exacerbations was lowest [6%] in the SAL group compared to the other groups [placebo 9%, FP 10%, Advair 8%].

Medication Compliance

Compliance was assessed from the reading on the dose counter on the Diskus device. Median compliance ranged from 95% to 96% across treatment groups. In 502 (75%) subjects the compliance rate was assessed as ≥90% and 61 (~10%) had compliance rates assessed as < 80%.

Demographics

Four hundred and forty-five (66%) of the ITT patients were male. The percentage of males was similar across treatment groups and ranged from 61% to 75%. Ninety-three percent (93%) of patients were Caucasian, 5 percent were Black, and the remainder were Asian or of other races. Patients' ages ranged from 40 to 90 years. There were 324 [48%] current smokers and 350 [52%] former smokers. The placebo group had a higher percentage of current smokers [54%] compared to the other treatment groups [46%]. The median number of pack-years smoked was similar among treatment groups and ranged from 52.5 to 60.0 pack-years. Former smokers tended to be older (42 –90 yrs) than current smokers (40-81 yrs) and had a higher incidence of inhaled corticosteroids [ICS] use (27-40%) than current smokers (10-23%). The majority of subjects [75%] were not taking ICS prior to screening and the majority [76%] reported having emphysema. The demographic characteristics for the reversible and the non-reversible population

were similar to that of the overall ITT population. A total of 361 patients were stratified as reversible, and 313 were non-reversible [per ATS criteria].

Table 5 - Characteristics of the Intent-to Treat population SFCA3006

	Placebo N = 181	**SAL 50 N= 160**	**FP 500 N= 168**	**Advair Diskus N =165**
Age (yrs) Mean Range	 64.0 44-90	 63.5 40-84	 64.42 42-82	 61.9 40-86
Gender Male Female	 136 (75%) 45 (25%)	 103 (64%) 57 (36%)	 103 (61%) 65 (39%)	 103 (62%) 62 (38%)
Race Caucasian Black Asian/Other	 166 (92%) 11 (6%) 4 (2%)	 152 (95%) 6 (4%) 2 (1%)	 156 (93%) 8 (5%) 4 (2%)	 156 (95%) 7 (4%) 2 (1%)
Median Duration of COPD (yr.)	6.00	6.00	5.00	5.00
Inhaled steroids at screening No Yes	 148 (82%) 33 (18%)	 111 (69%) 49 (31%)	 126 (75%) 42 (25%)	 119 (72%) 46 (28%)
Former Smoker Current Smoker	84 (46%) 97 (54%)	86 (54%) 74 (46%)	91 (54%) 77 (46%)	89 (54%) 76 (46%)
Emphysema Yes No	 142 (78%) 39 (22%)	 125 (78%) 35 (22%)	 125 (74%) 43 (26%)	 123 (75%) 46 (25%)
MMRC Dyspnea Score 2 3 4	 129 (71%) 47 (26%) 5 (3%)	 90 (56%) 62 (39%) 8 (5%)	 112 (67%) 51 (30%) 5 (3%)	 108 (65%) 55 (33%) 2 (1%)

The screening spirometry results were consistent with airflow obstruction with FEV_1% predicted ranging from 40.25% to 41.48% across treatment groups. The FEV_1/FVC x100 ratio ranged from 47.64% to 49.41%. The FEV_1 % predicted and the FEV_1/FVC ratio were similar for the reversible and the non-reversible population. The table below summarizes the screening spirometry results for the overall ITT population and the reversible and non-reversible population. The bronchodilator response ranged from 19.23% to 21.18% across treatment groups. The reversible subjects had a bronchodilator response ranging from 28.05% to 31.56%, while the non-reversible population had a bronchodilator response ranging from 8.04% to 10.28%. Screening spirometry and bronchodilator response data were similar between the former smokers and current smokers. Table 6 summarizes the spirometry and bronchodilator response results.

Table 6 - Spirometry and Bronchodilator Response Results SFCA 3006

	Placebo	SAL 50	FP 500	Advair 500/50
	ITT Population			
Randomized n	181	160	168	165
Mean FEV_1 [mL]	1282	1192	1174	1254
FEV_1 % predicted	41.48	40.25	41.40	40.85
FEV_1/FVC x 100	49.02	48.58	47.64	49.41
Bronchodilator response [%]	19.33	21.18	19.23	20.58
	Reversible Population			
Randomized n	101	82	90	88
Mean FEV_1 [mL]	1322	1250	1228	1366
FEV_1 % predicted	40.85	39.12	40.82	41.25
FEV_1/FVC x 100	48.91	48.32	47.74	50.20
Bronchodilator response [%]	28.05	31.55	28.56	31.56
	Non-Reversible Population			
Randomized n	80	78	78	77
Mean FEV_1 [mL]	1230	1132	1114	1129
FEV_1 % predicted	42.29	41.44	42.09	40.40
FEV_1/FVC x 100	49.17	48.45	47.52	48.51
Bronchodilator response [%]	8.33	10.28	8.46	8.04

Reviewer's Comments:

There are a number of concerns regarding the patient population enrolled in this study and hence whether it is appropriate to generalize the results of this trial to the COPD population as a whole. The proportion of patients enrolled in the study with reversibility (54%) is much higher than the approximately 30% reported in the population of COPD patients at large[9]. Secondly, all patients had to have a diagnosis of chronic bronchitis to be enrolled in the study. While chronic bronchitis and emphysema can occur together, the study entry criteria specifically eliminated those COPD patients with relatively "pure" emphysema. The diagnosis of emphysema was captured by patient self-reporting without pre-defined objective criteria.

EFFICACY RESULTS SFCA3006

Primary Efficacy Results

Change from baseline in mean morning pre-dose FEV_1 at endpoint

This analysis evaluated the effects of FP 500 in the combination product. The comparison was between Advair 500/50 and salmeterol 50. The mean changes are displayed in the table below. Endpoint refers to the last post-Baseline assessment (excluding the Discontinuation visit), the post-Baseline N's stated were used for the mean change calculation.

[9] Standards for the Diagnosis and Care of Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med Vol 152. Pp. S77-S120, 1995*

Table 7 Mean Change [mL] from Baseline in Pre-Dose FEV_1 SFCA3006

	Placebo	SAL	FP 500	Advair 500/50
	ITT Population			
Baseline n	181	159	166	163
Mean FEV_1	1282	1192	1174	1254
Endpoint n	171	158	161	157
Mean FEV_1 [mL]	1292	1303	1298	1410
Mean Change	-4	107[a]	109[a]	156[abc]
	Reversible Population			
Baseline n	101	81	88	86
Mean FEV_1	1322	1250	1228	1366
Endpoint n	97	81	86	84
Mean FEV_1 [mL]	1334	1382	1367	1545
Mean Change	-1	132	123	191
	Non-reversible Population			
Baseline n	80	78	78	77
Mean FEV_1	1230	1132	1114	1129
Endpoint n	74	77	75	73
Mean FEV_1 [mL]	1238	1220	1219	1256
Mean Change	-8	80	93	116

a $p \leq 0.028$ vs. placebo
b $p \leq 0.016$ vs. SAL
c $p \leq 0.038$ vs. FP500

For the ITT population, mean improvement in pre-dose FEV_1 at Endpoint was 156 mL (14.5% change) for Advair Diskus 500/50, and 107 mL (10.0% change) for SAL 50 representing a mean difference of 49 ml [$p \leq 0.028$]. The model-adjusted mean difference was 67 mL [$p \leq 0.012$].

The mean treatment difference between Advair 500/50 and placebo for the reversible and non-reversible population was 192 mL and 124 mL respectively. Numerically, this is equivalent to a treatment effect size for the reversible population that is 1.5 times the effect size for the non-reversible population. Because the study was designed and powered based on the ITT population inferential testing for these two subgroups was not performed.

Table 8 summarizes the actual change from Baseline in Pre-Dose FEV_1 across multiple timepoints for each treatment group. Over the 24 weeks of treatment, mean changes from Baseline in AM pre-dose FEV_1 ranged from 159 mL to 192 mL for the Advair Diskus 500/50 group, 110 mL to 134 mL for the SAL 50 group, 69 mL to 131 mL for the FP 500 group and 18 mL to 28 mL for the placebo group.

Table 8 - Summary of Pre-Dose FEV_1 [mL] Across Multiple Timepoints SFCA3006 [Data Table 7.3 SFCA3006.pdf] (All timepoints not shown)

	Placebo		**SAL 50**		**FP 500**		**Advair Diskus 500/50**	
	n	Change (mL) [SE]	n	Change (mL) [SE]	n	Change (mL) [SE]	n	Change (mL) [SE]
Week 1	168	-7 [12] **0.3%**	155	127 [14] **11.8%**	160	76 [14] **8.2%**	156	173 [19] **16.7%**
Week 4	147	-4 [15] **1.2%**	141	130 [15] **12.0%**	148	78 [15] **7.8%**	147	178 [19] **16.8%**
Week 6	141	15 [17] **2.9%**	138	114 [17] **10.9%**	141	96 [18] **9.4%**	142	192 [22] **17.5%**
Week 12	127	-12 [19] **0.7%**	131	110 [20] **10.7%**	121	81[21] **8.2%**	132	186 [20] **17.1%**
Week 16	119	19 [19] **3.0%**	123	115 [19] **10.9%**	106	103 [23] **9.4%**	125	159 [22] **14.4%**
Week 20	113	7 [21] **2.5%**	120	121 [20] **11.0%**	103	122 [25] **11.6%**	117	163 [23] **15.2%**
Week 24	112	-18 [22] **0.3%**	114	116 [21] **10.7%**	99	131 [26] **11.9%**	113	180 [24] **16.5%**

Advair Diskus 500/50 had numerically greater improvements in Pre-dose FEV_1 at all timepoints throughout the study compared to its individual components and placebo, although Endpoint was selected *a priori* to assess the contribution of fluticasone to the combination.

Mean Change From Baseline at Endpoint in 2-hr Post-Dose FEV_1

This variable was analyzed as the primary measure of efficacy to evaluate the effect of salmeterol in the combination product. The comparison of interest is Advair Diskus 500/50 vs. FP 500.

Table 9 - Mean Change (mL) from Baseline in 2-Hour Post-Dose FEV_1 ITT Population SFCA 3006

	Placebo N= 181	**SAL 50 N=160**	**FP 500 N=168**	**Advair Diskus 500/50 N=165**
Baseline N	181	159	166	163
Baseline mean FEV_1 [mL] (SD)	1282 [491]	1192 [441]	1174 [445]	1254 [546]
Endpoint n	171	158	160	156
Mean 2-hour Post-Dose FEV_1 at Endpoint [mL] (SD)	1324 [504]	1429 [532]	1327 [501]	1515 [616]
Mean change from Baseline in morning 2-hour post-dose FEV_1 [mL] [SD]	28 [231]	233[a] [283]	138[a,b] [231]	261[a,c] [261]
Percent change	3.7%	21.6%	13.1%	24.2%

a $p \leq 0.024$ vs. placebo
b $p \leq 0.043$ vs. SAL 50
c $p \leq 0.001$ vs. FP 500

The p-values are based on comparisons of estimated (model adjusted) means rather than the actual mean changes shown in the table.

There was a greater increase in the 2-hr post-dose FEV_1 at Endpoint in the Advair 500/50 treatment group (261 mL) compared with the FP 500 treatment group (138 mL). The mean treatment difference is 123 mL [p≤ 0.024]
The model-adjusted mean treatment difference was 129 mL. The mean treatment difference between Advair 500/50 and placebo for the reversible and the non-reversible population was 290 mL and 167 mL respectively. Numerically, these results demonstrate an effect size for the reversible population that was 1.5 times the treatment effect for the non-reversible population. No inferential statistics on the subgroup analyses were performed.

Table 10 - Mean Change from Baseline in Post-Dose FEV_1 Reversible and Non-Reversible Population SFCA3006

	Reversible				**Non-Reversible**			
	Placebo N=101	SAL 50 N=82	FP 500 N=90	Advair Diskus 500/50 N=88	Placebo N=80	SAL 50 N=78	FP 500 N=78	Advair Diskus 500/50- N=77
Baseline n	101	81	88	86	80	78	78	77
Mean (mL)	1322	1250	1228	1366	1230	1132	114	1129
Endpoint n	97	81	86	84	74	77	75	73
Mean (mL)	1363	1538	1405	1672	1274	1315	1237	1335
Mean change (mL)	29	287	161	319	28	175	111	195

Onset of Effect and Duration of Effect

Onset, offset, and duration of effect were defined based on the serial FEV_1 measurements collected on Treatment Day 1, and at Treatment Week 12. Onset of effect was defined as the time point within 4 hours post-dose at which the increase of FEV_1 achieved 100 mL or greater above Day 1 Baseline. The duration of effect was defined as the difference between time of onset to time of offset of effect. The time to offset was defined as the time point post dose at which a given subject's FEV_1 dropped below the 100 mL improvement threshold for two consecutive timepoints. Most patients in the Advair Diskus and salmeterol groups [≥ 87%] achieved ≥100 mL improvement in FEV_1 over Baseline within 4 hours on Treatment Day 1 and Treatment Week 12 compared to 61.1% and 67.7% of subjects in the FP 500 group and 49.5% and 61.5% of subjects in the placebo group on Treatment Day 1, and Treatment Week 12 respectively.

Reviewer's comment. In previous COPD studies with salmeterol MDI an improvement of 12% in FEV_1 was used to define onset of effect and not an absolute increase of 100 ml as is being used here. The onset of effect of Advair is driven by the salmeterol component. The Baseline mean FEV_1 for the SAL 50 group was 1192 ml and for Advair 500/50 was 1254. Therefore, an increase of

100 ml would be equivalent to an improvement of about 8%. The sponsor should reanalyze the data using a 12% improvement to evaluate onset and duration of effect as was done for other COPD studies with salmeterol.

Reviewer Comment:
The sponsor explained that since 12% of the mean Baseline FEV_1 for all treatment groups was less than 200 mL the greater of a mean 12% increase and a mean increase of 200 mL is 200 mL for every treatment group. From data submitted via Facsimile on December 12, 2001, the sponsor showed that at 0.5 hrs, 38% of subjects in the Advair group reached or exceeded the threshold of at least 12% and at least 200 mL above the subject's pre-dose value on Treatment Day 1. The mean time to reach an increase of at least 12% and at least 200 mL above the subject's pre-dose value on Treatment Day 1 was 2.01 hrs for the Advair group, 1.74 hrs for the salmeterol group and 3.96 hours for the placebo group. The percentage of subjects reaching that threshold was 74% in the Advair group, 67% in the salmeterol group and 26% in the placebo group.

Secondary Efficacy Measures SFCA3006

Diary Data

AM PEF

Patients in the placebo group had a higher mean AM PEFR [measured pre-dosing] at Baseline compared to subjects in the active treatment groups. There were greater improvements in AM PEF in the Advair group overall and throughout the study compared with the placebo, SAL 50, and FP 500 groups. The mean change from baseline in AM PEF was 31.9 L/min for Advair Diskus 500/50, 16.8 L/min for SAL 50, and 12.9 L/min for FP 500 [see table below].

Table 11 - AM PEF Results SFCA3006

	Placebo	SAL 50	FP 500	Advair Diskus 500/50
Baseline n	181	158	167	162
*Baseline Mean (L/min)	269.5	252.1	243.7	254.0
Month 3 n	141	135	138	138
Mean (L/min)	276.2	272.7	263.7	287.2
Month 6 n	116	123	102	118
Mean L/min	283.5	281.4	273.4	286.1
**Overall				
N	179	157	166	162
Mean (L/min)	267.1	268.7	256.6	284.7
Mean Change	-2.7	16.8	12.9	31.9

**Baseline for AM PEFR is the average of the values between Screening and Day 1.*
***Overall = the entire treatment period.*

Ventolin® Use

The total symptomatic Ventolin use at baseline was similar across treatment groups and ranged from 4.2 puffs/24 hrs in the Advair Diskus 500/50 group to 4.9 /24 hrs in the placebo group. Over the course of the study, subjects in all the

active treatment groups had slight decreases in Ventolin® use compared with placebo. The overall changes were small with Ventolin use in the Advair group decreasing by 1.2 puffs/24 hours and by 0.9 puffs/24 hrs and 0.4 puffs/24 hrs in the SAL 50 and FP 500 groups respectively.

Nighttime Awakenings /Night Requiring Ventolin

At Baseline there were very few nighttime awakenings across treatment groups. The mean number of nighttime awakenings ranged from 0.22 to 0.27 equivalent to one nighttime awakening every 4.5 to 3.7 nights. All the active treatment groups had a reduction in nighttime awakenings requiring Ventolin use however, the overall changes were very small. For example, in the Advair Diskus 500/50 group the number of nighttime awakenings decreased from 0.22/night at baseline to 0.19/night equivalent to a change from one awakening every 4.5 nights to one awakening every 5.2 nights. In the SAL 50 group, there was a decrease from 0.26 awakenings/night at Baseline to 0.17 awakenings/night overall, equivalent to a decrease from one awakening every 3.8 nights to one awakening every 5.8 nights.

Chronic Bronchitis Questionnaire [CBSQ GAS]
Please refer to the "Statistical and analytical" section for description of the CBSQ GAS. There was a mean minimal clinically important change of >1.4 from Baseline in the CBSQ GAS for all treatment groups including placebo. The difference between placebo and Advair Diskus or its individual components did not constitute a clinically meaningful difference.

Table 12 - Summary of Mean Change from Baseline in CBSQ GAS
ITT Population SFCA3006

Time Point	Placebo n = 181	SAL 50 N=160	FP 500 N=168	Advair Diskus N=165
Treatment Day 1 (Baseline)				
n	180	159	167	164
mean	7.3	7.4	7.0	6.9
Week 12				
n	127	131	120	132
mean	5.7	5.6	5.0	4.8
mean change	1.3	1.8	2.0	2.1
Week 24				
n	112	120	100	112
mean	5.4	5.0	5.2	4.8
mean change	1.6	2.0	1.9	2.1
Endpoint				
n	172	158	161	157
mean	5.7	5.6	5.5	5.1
mean change	1.5	1.9	1.6	1.8

Baseline Dyspnea Index/Transitional Dyspnea Index [BDI/TDI

At Baseline [Treatment Day 1] the BDI scores ranged from 5.8 to 6.2. This corresponds to a moderate level of dyspnea at Baseline. At Endpoint the mean TDI score for the Advair Diskus 500/50 group was numerically greater than the mean TDI score for the SAL 50, FP 500, and placebo groups. Advair Diskus 500/50 had a clinically meaningful difference [>1] compared to placebo and salmeterol but not FP. The summary of the BDI/TDI Dyspnea Index score is shown in the table below.

Table 13 - Summary of BDI/TDI Total Score ITT Population SFCA3006

Time point	Placebo N=181	SAL 50 N=160	FP 500 N=168	Advair Diskus 500/50 N=165
Day1 (BDI)				
N	179	154	164	160
Mean	5.8	5.9	6.0	6.2
Week 12 (TDI)				
N	127	131	120	132
Mean	0.6	1.3	1.4	2.0
Week 24 (TDI)				
N	112	116	100	113
Mean	0.6	1.6	1.9	2.7
Endpoint (TDI)				
N	172	158	161	157
Mean	0.4	0.9	1.3	2.1

Exacerbations of COPD

Four secondary endpoints related to COPD exacerbations were evaluated. They were:

- Severity of exacerbation
- Time to first exacerbation
- Time to first moderate or severe exacerbation
- Number of withdrawals due to COPD exacerbation

Of note is that the sponsor did not state in the protocol how a COPD exacerbation would be defined. However, the sponsor defined the severity of COPD exacerbations predicated on the use of self-administered rescue Ventolin, and Investigator use of antibiotics, corticosteroids or hospitalization. [see page 26]

Reviewer comment: Most published definitions of COPD exacerbations encompass some combination of three clinical findings: worsening dyspnea, increase in sputum purulence, and increase in sputum volume. A severity scale for acute exacerbations developed by Anthonisen and colleagues is based on these findings as well as others.[10]

[10] Severity of COPD exacerbations: Type 1 (severe) – Increased dyspnea, sputum volume, and sputum purulence (ii) Type 2 (moderate) – Two of these three symptoms are present (iii) Type 3 (mild) – One of these three symptoms are present in addition to at least one of the following findings: upper respiratory infection within the past 5 days; fever without other cause; increased wheezing; increased cough; or increase in respiratory rate or heart rate by 20% as compared with baseline. *Anthonisen et.al Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Int Med; 1987* ***106****: 196-204*

The incidence and frequency of exacerbations as defined by the sponsor was similar across the treatment groups but was lowest in the SAL group. A total of 79 (44%) subjects in the placebo group, 63 (39%) in the SAL 50 group, 77 (46%) in the FP 500 group and 68 (41%) in the Advair Diskus group had at least one COPD exacerbation. There was no difference in the time to the onset of a COPD exacerbation among treatment groups and no difference in the number of moderate/severe exacerbations among treatment groups.

Table 14 - Incidence of COPD exacerbations. ITT Population SFCA3006

	COPD Exacerbation of Any Severity					**Moderate/severe COPD Exacerbation**			
No of Exac. N (%)	Placebo N=181	SAL N=160	FP N=168	Advair N=165		Placebo N=181	SAL N=160	FP 168	Advair N=165
None	102 (56%)	97 (61%)	91(54%)	97 (59%)		118 (65%)	100 (63%)	101 (60%)	104 (63%)
1	50 (28%)	45 (28%)	52 (31%)	47 (28%)		48 (27%)	46 (29%)	54 (32%)	45 (27%)
2	13 (7%)	11 (7%)	16 (10%)	12 (7%)		12 (7%)	12 (8%)	11 (7%)	13 (8%)
3	2 (1%)	3 (2%)	1 (<1)	4 (2%)		2 (1%)	2 (1%)	2 (1%)	1 (<1%)
≥4	14 (8%)	4 (3%)	8 (5%)	5 (3%)		1 (<1)	0	0	2 (1%)

Subgroup analysis in Current smokers and Former smokers

Summary statistics showed that the combination group had similar results for the primary efficacy endpoints regardless of smoking status. For the primary endpoint mean change in pre-dose FEV_1 at Endpoint, the mean treatment difference between Advair and SAL was 47 mL in former smokers compared with 52 mL in current smokers. For the primary endpoint change in 2-hr post-dose FEV_1 at Endpoint the mean treatment difference between Advair and FP was117 mL in former smokers and 132 mL in current smokers. These results are displayed in the table below.

Table 15 - Summary of Results Displayed by Smoking Status

	Former Smokers				Current Smokers			
Efficacy Variable	**Placebo N=84**	**SAL 50 N=86**	**FP 500 N=91**	**Advair 500/50 N=81**	**Placebo N=97**	**SAL 50 N=74**	**FP 500 N=77**	**Advair 500/50 N=76**
Pre-Dose FEV_1 (mL) Change from Baseline								
Mean change at Endpoint	16	132	139	179	- 21	78	73	130
Post-Dose FEV_1 (mL) Change from Baseline								
Mean Change at Endpoint	45	243	140	257	15	221	134	266
Transition Dyspnea Index (TDI)								
Mean at Endpoint	-0.1	1.0	1.3	1.9	0.7	0.9	1.3	2.2

HEALTH OUTCOMES RESULTS

COPD-related Quality of Life assessed by the CRDQ

See discussion of secondary endpoints in "Statistical and Analytical" section for description. One of the objectives of the pivotal studies was to compare the quality of life in COPD subjects receiving Advair, its individual components, or placebo for 24-weeks.

Results

A total of 663 of the 674 subjects [excluding Investigator 1403] in the ITT population were included in the reduced ITT population for the CRDQ analyses. The results of the Overall score at Endpoint and at other timepoints are summarized in the table below.

Table 16. Mean Change from Baseline in Overall CRDQ Score at Endpoint and other Timepoints. Reduced ITT Population Study SFCA3006 [data from Table 8.1 SFCA3006.pdf]

Timepoint	**Placebo**	**SAL 50**	**FP 500**	**Advair 500/50**
Day 1	N=177	N=157	N=166	N=163
Mean [SD]	86.2 [17.1]	87.6 [17.5]	88.5 [17.4]	87.1 [18.3]
Endpoint	N=175	N=155	N=163	N=161
Mean[SD]	91.3 [24]	95.8[22]	93.5 [21.2]	97.1 [22]
Mean change from Baseline	5	8	4.8	10
Week 2	N=154	N=150	N=157	N=153
Mean change from Baseline	3.3	6	5.8	8.5
Week 4	N=149	N=138	N=147	N=144
Mean change from Baseline	7.8	8.5	6.1	11.6
Week 8	N=140	N=132	N=138	N=135
Mean change from Baseline	8.9	9	9.4	14.3
Week 24	N=102	N=107	N=95	N=100
Mean change from Baseline	8.9	11.5	10.1	13.1

At Endpoint, subjects in the Advair Diskus 500/50 treatment group had a mean change from Baseline of 10 in Overall score. This improvement meets the predefined minimal change of 10 to be considered as an overall improvement in COPD-specific quality of life. However, there was no clinically meaningful difference in improvement between Advair and any treatment group at Endpoint nor at any other timepoint. When Overall scores were analyzed by smoking status, a clinically meaningful improvement at Endpoint was seen in former smokers in the Advair Diskus 500/50 group but not in the current smokers in the Advair Diskus 500/50 treatment group. A clinically important improvement in the Overall score was seen at all timepoints except at Week 2 for the Advair Diskus 500/50 group. However, there was no clinically important difference between treatment groups at any timepoint. [*See Table 17 below]*

Table 17 - Summary of CRDQ Overall Score Results from Baseline at Endpoint and other Timepoints by Smoking Status [data from tables 8.29 –8.85 SFCA3006.pdf]

	Current Smokers					**Former Smokers**			
Timepoint	**Placebo N=97**	**SAL N=74**	**FP 500 N=77**	**Advair 500/50 N=76**		**Placebo N=84**	**SAL 50 N=86**	**FP 500 N=91**	**Advair 500/50 N=89**
Endpoint	N=94	N=73	N=74	N=74		N=81	N=82	N=89	N=87
Mean change	6.6	7.4	6.3	8.5		3.1	8.5	3.5	**11.2**
Week 2	N=89	N=69	N=71	N=71		N=65	N=81	N=86	N=82
Mean change	4.4	4.8	7.2	7.7		1.8	7.1	4.6	9.1
Week 4	N=84	N=65	N=67	N=66		N=65	N=73	N=80	N=78
Mean change	9	6.6	6.5	**10**		6.2	**10.2**	5.7	**13**
Week 8	N=78	N=62	N=62	N=63		N=62	N=70	N=76	N=72
Mean change	9.8	6.9	**10.8**	**12.8**		7.7	**10.8**	8.1	**15.6**
Week 24	N=53	N=47	N=39	N=46		N=49	N=60	N=56	N=54
Mean change	**10.1**	**12.3**	**11.7**	**11.4**		7.6	**10.9**	9	**14.5**

For the individual domains a difference in the mean change from Baseline at Endpoint among treatment groups was considered clinically meaningful if the difference between groups was statistically significant and met the ≥ 0.5 point improvement per item criterion. Using the ≥ 0.5 point improvement per item criterion, an improvement in the domains and the summary score was determined by the number of items in the domain x 0.5 points. Therefore, a clinically meaningful improvement in a domain would be as follows:

Dyspnea domain	≥2.5 point improvement
Emotional function domain	≥ 3.5 point improvement
Fatigue domain	≥ 2.0 point improvement
Mastery domain	≥ 2.0 point improvement

Subjects in the Advair Diskus 500/50 group achieved clinically important improvements at Endpoint in the Dyspnea and Fatigue domains only whereas, subjects in the SAL 50 group achieved a clinically important improvement at Endpoint in the Dyspnea domain only. None of the other treatment groups achieved clinically important improvements at Endpoint in any of the domains. However, in across treatment comparisons, Advair Diskus 500/50 did not have a clinically important improvement in any domain at Endpoint or at any other timepoint.

Table 18 Summary of Mean Change from Baseline at Endpoint in CRDQ Domains

	Placebo N=81	SAL 50 N=160	FP 500 N=168	Advair Diskus 500/50 N=165
Dyspnea domain [clinically important change ≥2.5]				
Day 1 mean	17.4	17.9	18.2	18
Endpoint mean	19.5	20.8	20.7	22.1
Mean Change	2.1	**2.9**	2.4	**4.2**
Fatigue domain [[clinically important change ≥2.0]				
Day 1 mean	15.1	15.5	15.6	15.5
Endpoint mean	15.7	17.3	16.6	17.5
Mean change	0.5	1.8	0.9	**2**
Emotional function [clinically important change ≥3.5]				
Day 1 mean	33.4	33.1	33.3	32.7
Endpoint mean	35	35.8	34.4	35.2
Mean change	1.4	2.6	0.9	2.5
Mastery domain [clinically important change ≥2.0]				
Day 1 mean	19.6	19.6	20.2	19.6
Endpoint	20.7	21	20.8	21.3
Mean change	1.1	1.3	0.6	1.8

RESULTS STUDY SFCA3007

Patient Disposition

A total of 1,489 patients were screened, and 723 patients were randomized and 766 failed screening. The most common reason for screening failure [516 subjects (67%)] was not meeting the entrance criteria of an FEV_1/FVC of ≤70% and Baseline FEV_1, of ≤ 65% predicted but >0.70 L. Of the 723 subjects randomized 178 were in the Advair Diskus 250/50 group, 177 in the salmeterol group, 183 were in the fluticasone Diskus 250 group, and 185 were in the placebo group. Two hundred and eighteen subjects [30%] withdrew from the study prior to completion and 505 (70%) completed the study.

Table 19 - Patient Disposition ITT Population SFCA 3007 [*Data source SFCA3007.pdf pg. 81*]

	Placebo n=-185	SAL 50 n=177	FP 250 n=183	Advair Diskus 250/50 n =178	Total N =723
# (%) Complete	126 (68%)	121 (68%)	133 (73%)	125 (70%)	505 (70%)
# (%) Withdrawn	59(32%)	56 (32%)	50 (27%)	53 (30%)	218 (30%)a
Reason for Withdrawal					
Lack of Efficacy	14 (7.5%)	8 (4.5%)	6 (3%)	3 (2%)	31 (4%)
[a]Adverse Event	7 (4%)	6 (3%)	9 (5%)	9 (5%)	31 (4%)[b]
Protocol violation	9 (5%)	8 (4.5%)	9 (5%)	7 (4%)	33 (4.5%)
Consent withdrawn	11 (6%)	9 (4.5%)	5 (3%)	10 (5%)	35 (5%)
Lost to follow up	0	3 (2%)	4 (2%)	6 (3%)	13 (2%)
COPD exacerbation	14 (7.5%)	17 (9.6%)	13 (7%)	15 (8.4%)	59 (8%)
*****Other	4 (2%)	5 (3%)	4 (2%)	3 (2%)	17 (2 %)

*Other: include noncompliance, subject relocation, site closure, and surgery
a The number of subjects withdrawing due to AE is 37 per data listing 9.4 pg. 5770 –5785 SFCA3007.pdf. This number of withdrawals includes 7 COPD exacerbations. Excluding the COPD exacerbations listed in listing 9.4 the number of withdrawals due to AE is 30 and not 31 as stated in the table. Other difficulties in interpreting these data include the lack of a definition of "lack of efficacy", and the failure to explain when a COPD exacerbation is counted as AE and when it is not. In the in-text table on page 81 from which the data in this table are obtained, withdrawals due to AE, and due to COPD are counted separately. However, in the listing "withdrawals due to AEs" [listing 9.4] 7 COPD events are included.

The number of withdrawals due to COPD exacerbations were similar across treatment groups but was slightly higher in the Advair Diskus 250/50 and SAL 50 groups compared to placebo.

Medication Compliance

Compliance was assessed based on the dose counter on the Diskus device. The median compliance was 96% in each treatment groups. A total of 560 (77%) of subjects had a compliance rate of ≥90%. Fourteen percent (99) of subjects had compliance rates of 80% to <90%, and 54(~9%) had compliance rates of < 80%.

Demographics

Overall, 63 % [457] of the ITT patients were male. The percentage across treatment groups ranged from 58% to 68%. Ninety-three percent of patients [675] were Caucasian, 4% were Black, and the remainder were Asian or of other races. Patient ages ranged from 40 to 87 years. There were 342 [47%] current smokers and 381 [53%] former smokers. The majority of subjects [541, 75%] were not taking inhaled corticosteroids prior to screening. The majority of subjects [483; 67%] reported having emphysema. A slightly higher percentage of patients in the Advair Diskus 250/50 treatment group were former smokers (57%) compared to the other treatment groups (range 49% -53%). The median number of pack-years smoked was similar among treatment groups and ranged from 53 to 60 pack-years. A total of 398 patients were stratified as reversible, and 324 were non-reversible. The demographic characteristics for the reversible and the

non-reversible population were generally similar to that of the overall ITT population.

Table 20 - Characteristics of the Intent-to Treat population [SFCA 3007]

	Placebo **N = 185**	**SAL 50** **N= 177[a]**	**FP 250** **N= 183**	**Advair Diskus 250/50** **N =178**
Age (yrs) Mean Range	 64.8 40-81	 64.2 42-87	 63.3 40-84	 63.4 40-87
Gender Male Female	 126 (68%) 59 (32%)	 102 (58%) 75 (42%)	 121 (66%) 62 (34%)	 108 (59%) 70 (41%)
Race Caucasian Black Asian/Other	 173 (94%) 6 (3%) 6 (3%)	 165 (93%) 7 (4%) 5 (3%)	 167 (91%) 9 (5%) 7 (4%)	 170 (95%) 5 (3%) 3 (2%)
Median Duration of COPD (yrs)	6.00	6.00	6.00	6.00
Emphysema Yes No	 126 [68] 59 [32]	 142 [80] 35 [20]	 132 [72] 51 [28]	 137 [77] 41 [23]
Inhaled steroids at screening No Yes	 130 (70%) 55 (30%)	 142 (80%) 35 (20%)	 132 (74%) 51 (26%)	 137 (77%) 41 (23%)
Former Smoker Current Smoker	98 (53%) 87 (47%)	87 (49%) 90 (51%)	95 (52%) 88 (48%)	101 (57%) 77 (43%)
*MMRC Dyspnea Score 2 3 4	 118 (64%) 58 (31%) 9 (5%)	 120 (68%) 49 (28%) 8 (4%)	 116 (63%) 63 (34%) 2 (3%)	 109 (61%) 63 (35%) 6 (4%)

[a] Total number in SAL 50 group 176 [79 non-reversible, 97 reversible] per sponsor's submission 10/17/2001 *response.pdf* pg. 13 making total subjects in ITT population 722 and not 723
*Two subjects in the FP 250 group had missing data

The screening spirometry results for the ITT population were consistent with moderate airflow obstruction with FEV_1% predicted ranging from 41.37% to 42.05% across treatment groups. The FEV_1/FVC x100 ratio ranged from 49. 48% to 51.29%. The spirometry results for the reversible and the non-reversible population were also consistent with moderate airflow obstruction with FEV_1 % predicted ranging from 40.37% to 42.67 % for the reversible population and 41.19% and 42% for the non-reversible population. The bronchodilator response for the ITT population ranged from 19.53% to 21.31% across treatment groups. The reversible subjects had a bronchodilator response ranging from 29.88% to 30.87%, while the non-reversible population had a bronchodilator response ranging from 7.93% -8.58%. The table below summarizes the screening

spirometry and bronchodilator response results for the ITT, reversible and non-reversible populations.

Table 21 - Screening Spirometry and Bronchodilator Response SFCA3007

	Placebo	SAL	FP 250	Advair 250/50
	ITT Population			
Randomized n	185	177	183	178
Mean FEV_1 [mL]	1289	1245	1313	1252
FEV_1 % predicted	42.05	41.94	41.96	41.37
FEV_1/FVC x100	49.63	50.83	51.29	49.48
Bronchodilator response [%}	20.24	21.31	19.53	20.14
	Reversible Population			
Randomized n	102	97	100	99
Mean FEV_1 [mL]	1313	1235	1359	1286
FEV_1 % predicted	42.67	40.37	42.59	40.87
FEV_1/FVC x100	51.01	50.81	52.16	49.56
Bronchodilator response [%}	29.72	30.87	28.93	29.88
	Non-reversible Population			
Randomized n	83	79	83	79
Mean FEV_1 [mL]	1259	1245	1256	1208
FEV_1 % predicted	41.29	43.64	41.19	42.00
FEV_1/FVC x100	47.94	50.69	50.19	49.37
Bronchodilator response [%}	8.58	9.56	8.19	7.93

EFFICACY RESULTS SFCA3007

Primary Efficacy Results

Change from baseline in mean morning pre-dose FEV_1 at endpoint

This endpoint evaluates the effect of FP 250 in the combination product. The comparison of interest is between Advair 250/50 and salmeterol 50. The mean changes are displayed in the table below. Endpoint refers to the last post-Baseline assessment (excluding the Discontinuation Visit), the post-Baseline Ns stated were used for the mean change calculation.

Table 22 - Mean Change [mL] from Baseline in Pre-Dose FEV_1 SFCA3007

	Placebo	SAL	FP 250	Advair 250/50
	ITT Population			
Baseline n	185	177	183	178
Mean FEV_1 [mL]	1232	1205	1236	1207
Endpoint n	172	168	175	171
Mean FEV_1 [mL]	1240	1303	1351	1375
Mean change	1	91[a]	109[a]	165[ab]
	Reversible Population			
Baseline n	102	97	100	99
Mean FEV_1 [mL]	1327	1237	1350	1284
Endpoint n	93	93	96	96
Mean FEV1 [mL]	1325	1389	1500	1476
Mean change	-15	141	138	196
	Non-reversible Population			
Baseline n	83	79	83	79
Mean FEV_1 [mL]	1116	1151	1098	1111
Endpoint n	79	74	79	75
Mean FEV_1 [mL]	1141	1176	1170	1245
Mean change	19	26	74	116

a p≤0.005 vs. placebo
b p=0.012 vs. SAL 50

For the ITT population, mean improvement in AM pre-dose FEV_1 at Endpoint in the Advair Diskus 250/50 group was 165 mL compared with 91mL in the SAL 50 group [p = 0.012]. The model-adjusted mean difference was, 69 mL[p=0.012].

For the primary endpoint "mean change from Baseline in pre-dose FEV_1", the mean treatment difference between Advair 250/50 and placebo was 211 mL for the reversible population and 97 mL for the non-reversible population. Numerically, this is equivalent to a treatment difference in the reversible population that was twice the treatment effect seen in the non-reversible population. Inferential statistics were not done on these subgroups.

Over the 24 weeks of treatment, mean changes from Baseline in AM pre-dose FEV_1 ranged from 153 mL to 189 mL [15.8% to 19.2%] for the Advair Diskus 250/50 group, 102 mL to 129 mL [9.2% to 12.8%] for the SAL 50 group, 83 mL to 118 mL [7.3% to 11.3%] for the FP 250 group and 3 mL to 49 mL [0.5% to 5.6%] for the placebo group. Similar to study SFCA3006, Advair Diskus 250/50 had numerically greater improvements in AM Pre-dose FEV_1 at all timepoints throughout the study compared to its individual components and placebo.

Mean Change from Baseline in 2-hour Post-Dose FEV_1

The comparison of interest is Advair 250/50 vs. FP 250. There was a statistically significant greater increase in the 2-hr post-dose FEV_1 at Endpoint in the Advair 250/50 treatment group [281 mL, 27.0%] compared with FP 250 [147 mL, 13.8%], placebo [58 mL, 5.9%], and SAL 50 [200 mL, 19.0%] p≤0.007.The results are displayed in the table below.

Table 23 - Mean change [mL] from Baseline in 2-hour Post-Dose FEV_1 ITT Population-Study SFCA3007 [Data from Tables 7.4-7.5 SFCA3007.pdf]

	Placebo N=185	SAL 50 N=177	FP 250 N=183	Advair Diskus 250/50 N=178
Baseline n	185	177	166	163
Mean FEV_1 [mL]	1232	1205	1236	1207
Endpoint n	172	168	175	171
Mean 2-hour post-dose FEV_1 at Endpoint [mL]	1298	1413	1389	1490
Mean change from Baseline in morning 2-hour post-dose FEV_1 [mL]	58 .	200	147	281

The mean change in post-dose FEV_1 for the Advair 250/50 group compared with placebo was numerically greater [282 mL] in the reversible population compared with the non-reversible population [150 mL]. Again no inferential analyses were conducted in these subgroups.

Table 24 - Summary of mean Change [mL] in Post-Dose FEV_1

	Reversible					Non-Reversible			
	Placebo	SAL 50	FP 250	Advair 250/50		Placebo	SAL 50	FP 250	Advair 250/50
Baseline n	102	97	100	99		83	79	83	79
Mean [mL]	1327	1237	1350	1284		1116	1151	1098	1111
Endpoint n	93	93	96	96		79	74	79	75
Mean	1386	1510	1541	1608		1194	1270	1203	1340
Mean change [mL]	46	262	179	328		71	119	107	221

SECONDARY EFFICACY MEASURES

Diary Data

AM PEF

There were numerically greater improvements in AM PEF in the Advair Diskus 250/50 group throughout the study compared to all other treatment groups. The mean change from Baseline in AM PEF at Endpoint was 30.6 L/min for the Advair Diskus 250/50 group compared with 0.8 L/min for the placebo group, 11.3 L/min for the SAL 50 group and 14.7L/min for the FP 250 group. The AM PEF results are summarized in Table 25.

Table 25 - AM PEF Results SFCA3007

Time Point	Placebo	SAL 50	FP 250	Advair Diskus 250/50
Baseline				
N	184	176	182	175
Mean	220.3	210.3	220.0	206.1
Month 3				
N	149	146	154	152
Mean	225.2	228.9	231.5	240.2
Mean change	2.1	15.8	12.2	34.7
Month 6				
N	128	124	136	130
Mean	230.0	235.9	242.6	246.4
Mean change	6.9	17.0	17.9	38.6
Overall				
N	183	174	177	173
Mean	220.2	225.3	230.7	236.3
Mean change	0.8	14.7	11.3	30.6

Ventolin Use

The mean number of puffs of Ventolin used per day was similar across treatment groups and ranged from 5.1 to 4.8 puffs. Over the course of the study, mean changes from Baseline in daily Ventolin use were very small and ranged from –1.1 puffs to –0.9 puffs for the Advair Diskus 250/50 group to –0.1 puffs to 0.1 puffs for the placebo group.

Nighttime Awakenings/Night Requiring Ventolin

At Baseline there were very few awakenings at night requiring Ventolin use. The mean number of nighttime awakenings ranged from 0.20 to 0.24 awakenings/night equivalent to one nighttime awakening every 5 to 4.2 nights. The overall changes in mean number of nighttime awakenings were –0.12 for Advair Diskus 250/50, -0.03, -0.06, and 0.02 for FP 250, SAL, and placebo respectively. These changes correspond to one nighttime awakening requiring Ventolin use every 8, 5, 7, or 4 nights for the Advair Diskus 250/50, FP 250, SAL 50 and placebo group respectively.

Chronic Bronchitis Symptoms Questionnaire

The results for study SFCA3007 are shown in table 26. The results are similar to the results seen in SFCA3006. All treatment groups [including placebo] had a mean change at endpoint that met the MCIC. However, the difference between placebo and Advair Diskus, or its individual components did not constitute a clinically meaningful change.

Table 26 - Summary of Mean Change from Baseline in CBSQ GAS
ITT Population SFCA3007

Time Point	Placebo	SAL 50	FP 250	Advair 250/50
Treatment Day 1 (Baseline)				
N	185	177	183	178
Mean	7.5	7.0	7.4	7.3
Week 12				
N	139	136	147	144
Mean	6.0	5.4	5.2	5.0
Mean change	1.4	1.6	2.2	2.3
Week 24				
N	126	121	133	125
Mean	5.6	5.2	4.9	4.8
Mean change	1.8	1.9	2.5	2.5
Endpoint				
N	172	169	175	172
Mean	6.1	5.6	5.2	5.2
Mean change	1.4	1.5	2.2	2.1

Baseline/Transition Dyspnea Index (BDI/TDI)

Baseline scores (Treatment day 1) ranged from 5.7 to 6.2 Mean TDI scores were comparable for all three active treatment groups at Endpoint as shown in Table 27.

Table 27 - Summary of BDI/TDI Total Score ITT Population SFCA3007

Time Point	Placebo	SAL 50	FP 250	Advair Diskus 250/50
Day 1 (BDI)				
N	183	176	179	174
Mean	5.7	6.1	6.2	6.1
Week 12				
N	139	136	147	144
Mean	1.5	1.5	1.6	1.8
Week 24 (TDI)				
N	126	121	132	125
Mean	1.7	1.8	2.0	2.4
Endpoint (TDI)				
N	172	169	175	172
Mean	1.0	1.6	1.7	1.7

Exacerbations of COPD

The highest incidence of COPD exacerbations occurred in the FP 250 and Advair 250/50 groups and lowest in the SAL group. Thirty-seven (37%) percent of subjects in the SAL group, 39% in the placebo group, 40% in the Advair 250/50 group and 43% in the FP 250 group experienced one or more COPD exacerbations. The SAL group also had the lowest percentage of moderate/severe exacerbations. Based on the sponsor's definition of severity [*see pg.25*], 31% of subjects in the SAL group, 34% of subjects in the placebo and Advair Diskus 250/50 groups, and 38% of subjects in the FP 250 group had moderate/severe exacerbations. The time to first COPD exacerbation and the

number of withdrawals due to COPD exacerbations were similar among treatment groups.

Subgroup Analysis by Smoking Status

For the primary endpoint change from Baseline in pre-dose FEV_1 current smokers had a numerically greater mean treatment effect [107 ml] compared with former smokers [31 m] for the comparison Advair 250/50 vs. SAL. For the primary endpoint change from Baseline in 2-hr post-dose FEV_1, former smokers had a numerically similar effect [138 ml] compared with current smokers [124 ml] for the comparison Advair 250/50 vs. FP 250. No inferential analyses for these subgroups were done. The primary efficacy results by smoking status are displayed in the table.

Table 28 - Summary of Efficacy Results Displayed by Smoking Status

	Former Smokers				Current Smokers			
Efficacy Variable	Placebo N=87	SAL N=90	FP 250 N=88	Advair 250/50 N=77	Placebo N=98	SAL N=87	FP250 N=95	Advair 250/50 N=101
Pre-Dose FEV_1 (mL) Change from Baseline								
Mean change at Endpoint	4	96	80	127	-3	86	136	193
2-Hr Post-Dose FEV_1 (mL) Change from Baseline								
Mean Change at Endpoint	52	222	115	253	64	177	176	301
Transition Dyspnea Index (TDI)								
Mean at Endpoint	1.1	1.7	1.6	1.6	0.9	1.5	1.8	1.8

HEALTH OUTCOMES RESULTS

COPD-related quality of life was evaluated using the CRDQ in the same manner as for study SFCA3006. The same criteria were used to define the Reduced ITT Population. A total of 705 out of 723 randomized subjects were included in the Reduced ITT Population. At Endpoint, subjects in the Advair Diskus 250/50 and FP 250 treatment group had a mean change from Baseline in the Overall CRDQ score of ≥ 10 thereby meeting the predefined minimal change considered as an overall improvement in COPD-related quality of life. There was no clinically meaningful improvement between any treatment group neither at Endpoint or any other timepoint. When Overall scores were analyzed by smoking status, a clinically meaningful improvement at Endpoint was seen in current smokers in the Advair Diskus 250/50 group and in former smokers in the FP 250 group. The results of the Overall score are summarized in the table below.

Table 29 - Mean Change from Baseline in Overall CRDQ Score at Endpoint and other Timepoints SFCA3007 ITT population

Timepoint	Placebo	SAL 50	FP 250	Advair Diskus 250/50
Day1 N Mean [SD]	 180 84.8 [17.8]	 173 86.3 [18]	 177 85.5 [17.4]	 175 84.1 [17.6]
Endpoint N Mean [SD] Mean Change	 177 89.6 [24.9] 5.0	 170 93.0 [21.3] 6.4	 170 96.4 [20.3] 10.4	 169 93.9 10
Week 2 N Mean change from Baseline	 161 3.8	 158 6.2	 161 5.2	 162 7.5
Week 4 N Mean change from Baseline	 148 7.5	 158 6.2	 155 9.2	 162 7.5
Week 8 N Mean change from Baseline	 138 9.4	 136 7.7	 142 10.1	 145 11.2
Week 24 N Mean change from Baseline	 116 9.4	 113 10.3	 122 13.6	 119 13.3

	Current Smokers				Former Smokers			
	Placebo N=83	SAL N=87	FP 250 N=84	Advair 250/50 N=76	Placebo N=98	SAL N=86	FP 250 N=94	Advair 250/50 N=99
Mean Change in Overall CRDQ Score								
Mean change at Endpoint	5.2	6.6	9.5	11.2	4.9	6.3	11.1	9.1

Similar to the results in study SFCA3006, a clinically important improvement in the Overall score was seen at all timepoints except at Week 2 for the Advair Diskus 250/50 group. There was no clinically important difference between treatment groups at any timepoint. In the analysis of the individual Domains, all treatment groups [including placebo] achieved A MCIC at Endpoint in the Dyspnea Domain. Advair Diskus 250/50 also achieved a MCIC in the Fatigue Domain. Table 30 summarizes the changes at Endpoint in the individual domains.

Table 30 - Summary of Mean Change from Baseline at Endpoint in CRDQ Domains

	Placebo	SAL 50	FP 250	Advair Diskus 250/50
Dyspnea Domain [MCIC ≥2.5] Mean change	2.8	2.9	3.3	4.1
Fatigue Domain [MCIC ≥2.0] Mean Change	1.5	0.9	1.7	2.5
Emotional Function Domain [MCIC ≥3.5] Mean Change	1.1	1.4	2.5	2.4
Mastery Domain [MCIC ≥ 2.0] Mean Change	1	0.9	1.8	1.9

EFFICACY CONCLUSIONS

Summary

Advair Diskus 500/50 mcg and Advair Diskus 250/50 mcg both met the established efficacy criteria for combination drug products as stated in the Code of Federal Regulations. However except for dyspnea as evaluated with the BDI/TDI with the 500/50 mcg dose, the efficacy of Advair Diskus was not demonstrated for any of the secondary endpoints relevant to the COPD indication. The patient population studied was not representative of the COPD population at large in that > 50% of the subjects showed significant reversibility and the study was limited to only patients with confirmed chronic bronchitis. The failure to demonstrate efficacy with the secondary endpoints of relevance to COPD [i.e. exacerbations, CRDQ, CBSQ] calls into question the clinical significance of the FEV_1 findings. Taken together the efficacy data do not appear to support broad-based efficacy conclusions in the proposed population. The efficacy conclusions are outlined below in bulleted text.

Both Advair Diskus 500/50 mcg and Advair Diskus 250/50 mcg bid showed statistically significant effect compared to placebo for each of the primary endpoints “mean change from Baseline in pre-dose FEV_1 and 2-hr post-dose FEV_1”. Compared to their individual components FP 500 mcg and 250 mcg and SAL 50 mcg, Advair Diskus 500/50 and Advair Diskus 250/50 had a statistically significant treatment effect. This finding established from a regulatory standpoint the efficacy requirement for Advair as a combination drug product in that both components contributed to the effect of the combination.

- When the primary efficacy endpoints were assessed by populations [reversible vs. Non-reversible], the reversible population had a treatment effect that was numerically greater [63%] than the treatment effect seen in the non-reversible population for both primary endpoints in both studies.

- Advair Diskus 500/50 and 250/50 did not have a clinically meaningful change compared with placebo or any of its components in the chronic bronchitis questionnaire

- Both studies failed in their quality of life objective. Compared to placebo or their individual components, neither Advair Diskus 500/50 nor Advair Diskus 250/50 had a clinically meaningful change in COPD-related quality of life as assessed by the CRDQ.

- In the assessment of dyspnea using the BDI/TDI, using a score of ≥1.0 as clinically meaningful Advair 500/50 had a meaningful improvement in dyspnea compared with placebo and salmeterol, but Advair 250/50 did not.

- Treatment with Advair 500/50 and Advair 250/50 did not result in a significant decrease in the frequency or severity of COPD exacerbations nor the time to COPD exacerbations.

- The percentage of withdrawals due to COPD exacerbations was similar for Advair Diskus and placebo in both studies.

- Changes in nighttime awakenings requiring Ventolin use were numerically small and of questionable clinical value in assessing effect of therapy for the COPD population.

- Inferential analyses in former smokers and current smokers were not conducted but the results seen for Advair Diskus in the overall ITT population did not appear to be affected by smoking status.

- In study SFCA3006 74% of subjects on Advair 500/50 mcg bid achieved a 12% increase in FEV_1 and at least 200 mL improvement above pre-dose FEV_1 values on Treatment Day $_1$.

VII. INTEGRATED REVIEW OF SAFETY

A. CONCLUSIONS

The safety findings in the two pivotal studies SFCA3006, SFCA3007 were similar. Safety findings in these two studies that were consistent with corticosteroid effects were similar to findings in the Flovent study FLTA3025.

The majority of the patients in the Advair studies were male Caucasians. Minority races represented only 5% of the study population. Median age was ~ 63 years and most patients had extensive smoking histories and had a long-standing

history of COPD. Exposure to study treatment was adequate to assess safety over the 24-week active treatment period.

The frequency of adverse events was relatively high in the two studies. A total of 1000 [71%] subjects from the two Advair studies reported at least one adverse event. Subjects in the Advair and FP groups had the highest incidence of adverse events [75%] compared to placebo 66%] or salmeterol. [68%] The incidence of AEs with Advair 250/50 was 70% compared with 64% for placebo while in study SFCA3006 the incidence of AEs with Advair 500/50 was 78% compared with 69% for placebo. There was a high [30% -36%] dropout rate across all three studies].

Adverse events occurring in Advair 500/50 and 250/50, FP 250, FP 500 or salmeterol at a frequency ≥ 3% and more frequently than in placebo included headache, upper respiratory tract infection, throat irritation, upper respiratory inflammation, sinusitis/sinus infection, candidiasis, hoarseness/dysphonia, musculoskeletal pain, muscle cramps and spasms and viral infections.

Candidiasis of the mouth/throat, hoarseness/dysphonia, throat irritation, and muscle cramps and spasms were highest in the in Advair treatment groups compared to the other treatment arms in both studies. Subjects treated with FP 250 and 500 in the two studies had higher incidences of candidiasis, sinusitis, hoarseness/dysphonia, and viral respiratory infections compared to placebo and salmeterol. Across studies subjects treated with Advair or FP had higher incidences of candidiasis, hoarseness/dysphonia and viral respiratory infections. These AEs are listed in the current labeling for Flovent and Advair Diskus.

Three deaths occurred in the placebo group during the study. Two were related to malignancy and one was due to aspiration pneumonia following surgery. There were no deaths in any active treatment group during the study. A total of 74 [5%] patients [including the 3 deaths mentioned] had a least one serious AE. None of the serious AEs appear to be drug-related. Excluding deaths a total of 50 [3.5%] patients withdrew from the study due to serious AEs.

There were some discrepancies in the number of subjects withdrawing from the study due to adverse events in the sponsor's data tables and in-text tables. However, the overall number of withdrawals due to AEs were [approximately 98(7%]. None of the adverse events that led to withdrawal appear to be drug-related. In general drug-related adverse events were mainly limited to events that are known to be associated with corticosteroid use [i.e. candidiasis mouth/throat, hoarseness/dysphonia, and throat irritation].

The sponsor did not monitor bone mineral density in the Advair studies. There were 13 reports of fractures. Six occurred in the Advair Diskus groups, 2 in the FP 250/50 group, 4 in the placebo group, and one in the salmeterol group. Case narratives were not provided for all the patients who sustained fractures. One

patient who received Advair 250/50 sustained a broken femur after a fall and two patients who received Advair 500/50 were reported to have osteoporosis.

There were only 3 reports of cataracts and ocular pressure disorders during the study. However, these adverse events were not specifically monitored for during the studies.

The sponsor did an extensive cardiovascular evaluation with 12-lead ECGs and 24-hour Holter monitoring. The cardiovascular-related adverse events did not appear to be causally related to Advair and in. study SFCA3007, the highest incidence of cardiovascular events was reported in the placebo group, while in study SFCA3006 the incidence was similar across treatment groups. An independent cardiologist evaluated QTc intervals. There did not appear to be a relationship with QTc prolongation and Advair in the two studies reviewed.

Relatively few reports of hyperglycemia were noted in the two studies. However, the sponsor's threshold for hyperglycemia was > 175 mg/dl. With this liberal definition, a meaningful assessment of the effect of Advair on blood glucose could not be made. Similarly, given the sponsor's threshold for hypokalemia [<3.0] it was difficult to assess the effect [if any] of Advair on potassium levels. Changes in liver function tests were generally similar among treatment groups.

The effect of Advair Diskus on HPA axis in COPD patients was evaluated in a subset of patients in both Advair studies. The number of subjects studied was relatively small. Neither of the studies had findings suggestive of adrenal suppression, however Cosyntropin stimulation testing is primarily intended for the diagnosis of adrenal insufficiency rather than to detect or quantify the more subtle finding of HPA-axis suppression. Therefore, these negative findings do not rule out the occurrence of systemic corticosteroid effects due to inhaled fluticasone in COPD patients, particularly with more long-term exposure.

In several supportive studies there has been substantial evidence of systemic exposure. For example in an open-label 4-way crossover study [FLTA1003] in which normal subjects received single doses of1000 mcg of Flovent Diskus via four different dosage strengths, the mean 24-hour urinary cortisol excretion was decreased by 42% to 62% compared to baseline in all treatment groups. In pivotal study FLTA3025 serum cortisol AUC_{12} measured at Week 4 was reduced in subjects in the FP 250 and FP 500 groups compared with subjects in the placebo group. A dose response effect was noted with the FP 500 and FP 250 groups having mean cortisol AUC_{12} values that were 21% and 10% lower than placebo respectively.

In the ISOLDE trial [FLIT78][11] 12 subjects [3%] in the FP 500 mcg treatment group compared with 2 subjects [<1%] in the placebo group had decreased cortisol reported as an AE. Skin hemorrhage was reported by 9 [2%] subjects in the FP group compared with 1 [<1%] subject in the placebo group. Reports of hyperglycemia were similar in the FP and placebo group (6[2%] FP vs. 5 [1%] placebo). [*Medical Officer Dr. Charles Lee's sNDA20-833/SE1-04 review]*

The sponsor evaluated the effects on bone mineral density in two controlled long-term studies of FP [FLTA3001 and FLTA3017] in patients with asthma. The lumbar spine was the only area in these studies that underwent prospective quality assurance from the osteoporosis central laboratory while results from the proximal femur; a more sensitive area for corticosteroid effect did not. In these studies the lumbar spine bone mineral density measurements did not show a difference between FP and placebo. The patient population in these studies was younger and probably less sensitive than older COPD patients to bone effects of corticosteroids. [*Medical Officer Dr. Charles Lee's sNDA20-833/SE1-004]*

The 120-safety update contained blinded data from ongoing controlled clinical studies, non-US regional studies and clinical pharmacology studies. An assessment of adverse events could not be made from these blinded data.

B. PATIENT EXPOSURE AND DEMOGRAPHICS

Of the 1,414 patients treated in the two Advair trials, 347 received Advair Diskus, 356 received Flovent ® Diskus, 341 received salmeterol, and 370 received placebo. Of the subjects receiving Advair, 169 received Advair Diskus 500/50 mcg bid, and 178 patients received Advair 250/50 mcg bid. Of the subjects receiving Flovent® 173 received Flovent Diskus 500 mcg bid and 183 received Flovent ® Diskus 250 mcg bid. The mean duration of exposure to active treatment was 137.8 days for Advair Diskus 500/50, 141.3 days for Advair Diskus 250/50 bid, 126.5 days for Flovent ® 500 mcg bid, 138.5 days for Flovent ® 250 mcg, and 138.6 for salmeterol. The dropout rate was relatively high and ranged from 30% to 36%.

In both studies the majority of the subjects were male and made up 63% of the study population. The minority races were underrepresented in both studies and made up approximately 5% [3.5% black, 1.5% Asian or Other] of the study population. Subjects had a mean age of approximately 63 years with ages ranging from 40 to 90 years of age. Most patients were long time smokers with a long-standing history of COPD ranging from 1 to 51 years [median duration 6 years]. Patients were heavy smokers with a 20 – 220 pack-year smoking history [median range 53-60 pack-years]. Objective criteria for diagnosing emphysema

[11] The ISOLDE [Inhaled steroids in obstructive lung disease] trial was a 3-year Non-U.S. multicenter, double blind, placebo-controlled, parallel group study of the efficacy and tolerability of long-term FP 500 mcg BID in COPD.

were not defined in the trials but most patients [63% -78%] reported having a diagnosis of COPD. All patients had to have chronic bronchitis by definition to be in the trials. Approximately half of the patients [46% -54%] were current smokers. The majority of subjects [69% -82%] were not using inhaled corticosteroids at Screening. Most patients had a MMRC dyspnea Score of 2 or 3 signifying dyspnea while walking on level group or while walking on level ground for 100 yards or less.

C. METHODS AND SPECIFIC FINDINGS OF SAFETY REVIEW

The safety findings for studies SFCA3006 and SFCA3007 were reviewed in detail. The safety findings of study FLTA3025 was reviewed by Dr. Charles Lee in his review of the supplemental NDA for Flovent ® Diskus [sNDA 20-833/SE1-04]. Safety findings from his review that are related to the use of corticosteroids are referenced in this review. The sponsor provided additional safety information from several other studies. These studies were four completed non-U.S. studies with Flovent® [MDI formulation] 500 mcg bid in subjects with COPD, data from two long-term asthma studies using Flovent ® [MDI and Rotadisk], adverse events and HPA axis data from a completed clinical pharmacology study FLTA 1003, and blinded data from two ongoing controlled clinical trials and 23 non-US regional trials. A 120-safety day update was submitted on August 31, 2001 that included blinded data from the ongoing controlled clinical studies, pharmacology studies, and the non-U.S. regional studies. Dr. Charles Lee did a review of the completed non-US studies with Flovent and this Medical Officer reviewed the 120-day safety update. Safety findings from the Flovent studies that are relevant to the use of corticosteroid therapy will be referenced from Dr. Charles Lee's review.

The safety findings of SFCA3006 are presented first followed by the safety findings of SFCA3007, and the 120-safety update.

SAFETY RESULTS SFCA3006

Extent of Exposure

A total of 100 (55%) patients were exposed to Advair Diskus for ≥ 24 weeks, 23 (14%) patients were exposed for 20 to <24 weeks 9(5%) patients were exposed for 16 to <20 weeks and the remainder for <16 weeks. The mean number of treatment days was 137.8 with a median range of 2 to 191. A total of 97 (56%) patients were exposed to FP 500 for ≥ 24 weeks with a mean exposure of 126.5 days. Mean exposure to SAL 50 was 141.1 days with 109 (66%) subjects exposed to treatment for ≥ 24 weeks. Exposure for ≥ 24 weeks in the placebo group was noted in 101 (55%) patients.

Adverse Events Incidence

A total of 515 (74%) subjects reported at least one adverse event. The percentage of subjects that reported at least one AE was highest in the FP 500 (80%) and Advair Diskus (78%) groups. As expected, candidiasis of the mouth/throat was seen mostly in the FP 500 group (10%) and the Advair Diskus 500/50 group (7%) compared to <1% each for the Salmeterol and placebo groups. Muscle cramps were reported most frequently in the Advair Diskus 500/50 group (8%). The 10 most common events were headaches, upper respiratory tract infections (URTI), musculoskeletal pain, throat irritation, upper respiratory inflammation, viral respiratory infections, candidiasis of the mouth/throat, cough, nasal congestion/blockage, and muscle cramps and spasms. Five fractures were reported during the treatment period. One in the placebo group, 1 patient in the SAL 50 group who fell of a ladder, and three patients in the Advair Diskus group. The sponsor did not provide case narratives for these cases except to mention that 2 of the cases [#9688 and 10292] had a diagnosis of osteoporosis. Table 31 shows the adverse events more frequent than placebo and occurring ≥3%.

Table 31 - Adverse Events more Frequent than Placebo and Occurring ≥ 3% SFCA3006 [data table 9.2 SFCA3006.pdf]

Adverse event	Placebo N=185	SAL 50 N=164	FP 500 N=173	Advair 500/50 N=169
Any adverse event	127[69%]	119[73%]	138[80%]	131 [78%]
Headaches	25[14%]	30[18%]	35[20%]	30[18%]
Upper respiratory tract infection [URTI]	18[10%]	20[12%]	25 [14%]	28 [17%]
Throat irritation	14[8%]	17 [10%]	11[6%]	19[11%]
Musculoskeletal pain	23[12%]	21[13%]	13[8%]	20[12%]
Viral respiratory infections[a]	6[3%]	12[7%]	17[10%]	14[8%]
Candidiasis mouth/throat	1[1%]	1[1%]	17[10%]	12[7%]
Upper respiratory inflammation[b]	12[6%]	12[7%]	11[6%]	15[9%]
Nasal congestion/blockage	7[4%]	10[6%]	13[8%]	7[4%]
Muscle cramps & spasms	4[2%]	8[5%]	3[2%]	13[8%]
Chest symptoms	6[3%]	8[5%]	7[4%]	6[4%]
Sinusitis/sinus infection	4[2%]	5[3%]	6[3%]	7[4%]
Hoarseness/dysphonia	4[2%]	1[<1%]	9[5%]	5[3%]
Dizziness	5[3%]	6[4%]	5[3%]	5[3%]
Muscle pain	1[<1%]	1[<1%]	5[3%]	7[4%]
Pain [non-site specific]	6[3%]	7[4%]	3[2%]	5[3%]
Hypertension*	4[2%]	7[4%]	5[3%]	5[3%]
Anxiety	2[1%]	6[4%]	2[1%]	5[3%]
Chronic obstructive airways disease	2[1%]	2[1%]	5 [3%]	2[1%]
Lower respiratory signs & symptoms	2[1%]	6[4%]	2[1%]	2[1%]
Sputum abnormalities	4[2%]	2[1%]	1[<1%]	5[3%]
*One other patient was listed as having “high blood pressure”				
a The preferred term for flu or flu symptoms b Includes all AEs of cold symptoms				

Deaths and Serious Adverse Events

Three subjects in the placebo group died. One patient died of adenocarcinoma of the small intestine. One patient died of recurrent thyroid cancer and the other patient died due to aspiration pneumonia two months following surgery for multiple colonic tumors.

Serious AEs

Thirty-nine subjects [including the three subjects who died] experienced at least one SAE during the treatment period. Twelve (7%) subjects were in the FP 500 treatment group and 9 (5%) subjects were in the Advair 500/50 treatment group. The SAEs are summarized in the following table. None of these SAEs appear to be drug-related.

Table 32. Serious Adverse Events SFCA3006

	Placebo N =185	SAL 50 N =164	FP 500 N=173	Advair 500/50 N=169	Totals 691
Serious Adverse Event [SAE] n (%)	11 (6%)	7 (4%)	12 (7%)	9 (5%)	39 (6%)
Withdrawal due to SAE n (%)	6 (3%)	6 (3.6%)	12 (7%)	7 (4%)	31 (4.5%)
SAE					
COPD exacerbation/worsening COPD	2	2[a]	5	2	11 (1.6%)
Respiratory failure	0	0	1	0	1
Chest pain/atypical chest pains	2			2	4
Angina	0	1	1	0	2
Pneumonia	0		2[b]	2	4

a Also reported atrial flutter
b Also reported COPD exacerbation.
The other serious adverse events each reported once in one patient were pericarditis, ischemic cardiomyopathy, deep vein thrombosis, adenocarcinoma of the intestine, colon tumor, recurrent thyroid cancer, anxiety and withdrawal symptoms, spontaneous pneumthorax, diverticulitis, codeine overdose, stroke, concussion and fractured vertebrae, small bowel obstruction, tennis elbow, cellulitis, cholecystitis and diverticular disease

Adverse Events leading to withdrawal

The Adverse events leading to study discontinuation were listed in listing 9.6 pg. 6692. The total numbers listed in the in-text table on page 181 SFCA3006.pdf are slightly different from the data listing. Additionally, there are differences in the number of subjects withdrawing due to an adverse event in the in-text table on page 93 SFCA 3006.pdf. The withdrawals due to AEs are discussed from the data obtained from data listing 9.6 pg. 6692 SFCA 3006 and are discussed by treatment group.

A total of 61 subjects are listed as withdrawn from the study due to AEs. This number includes 2 of the deaths previously discussed.

Placebo

A total of 18 subjects are listed as discontinuing due to an AE. These include 7 of the SAEs discussed above including 2 of the 3 deaths. Two cases of COPD exacerbation are listed. Events in two subjects might be related to the formulation [bad taste in mouth, hoarseness, dry mouth (1 subject), nausea and vomiting (1 subject)].

SAL 50
Nine (9) subjects in the SAL 50 group are listed as discontinuing due to AEs. Five of these are listed as serious. It is unlikely that any of these events are related to the study drug although the case of angina occurring 5 weeks after starting study medication [#9060] in a 71 year old male with a history of coronary artery disease could have been aggravated by the use of salmeterol.

FP 500
Twenty-two (22) subjects are listed as discontinuing due to AEs. Of these subjects 12 had SAEs. The SAEs include 5 cases of COPD exacerbation, 3 cases of pneumonia, and 1 case of respiratory failure. Also among the AEs leading to withdrawal are 2 cases of candidiasis of the mouth/throat, 2 cases of hoarseness, and one case of cough. Candidiasis of the mouth/throat and hoarseness are known corticosteroid-related effects.

Advair Diskus 500/50
Twelve (12) subjects in the Advair Diskus 500/50 discontinued due to AEs. Of these, 7 subjects had SAEs. The serious events include 2 cases of pneumonia, 2 cases of chest pain/atypical chest pain, 1 case of cholecystitis, and 2 cases of COPD exacerbations.

Drug-related Events
Reviewer Comment: The sponsor did not provide case narratives of the adverse events considered by the Investigator to be drug-related therefore it was difficult to assess causality for most of these events except for events that are know to be associated with inhaled corticosteroid or beta-agonist use.

Candidiasis, throat irritation, and hoarseness/dysphonia occurred more frequently in the FP 500 and Advair 500/50 treatment groups compared with salmeterol and placebo. Seventeen (10 percent) of subjects in the FP 500 treatment group and 11 (7%) of subjects in the Advair Diskus 500/50 treatment group reported candidiasis of the mouth/throat. There were 4 cases of candidiasis at an unspecified site in the Advair Diskus 500/50 treatment group and 2 (1%) in the FP 500 group. When candidiasis was reported together as candidiasis of the mouth/throat, candidiasis unspecified, and unspecified oropharyngeal plaques a total of 19 cases in the FP 500 group and 19 cases in the Advair Diskus group were reported. Throat irritation was experience by 11 (7%) of subjects in the Advair Diskus group, 2 (1%) of subjects in the FP 500 group, 5 (3%) subjects in the placebo group and 4 (2%) subjects in the SAL 50 group. Throat irritation could probably be formulation-related as well as drug related. More subjects in the FP group (8 [5%]) reported hoarseness/dysphonia compared to the other treatment groups (Advair 500/50 4 [2%], SAL 1 [<1%], and placebo 4 [2%). Other events reported as drug-related by the Investigator that are possibly related to the study drug are muscle cramps and spasms occurring in the SAL group [4 (2%)] and the Advair Diskus group [2 (1%)]. Three cases of

cataracts and 3 cases of ocular pressure disorders were reported. Two cases of cataracts were reported in the FP 500 group and 1 in the placebo group and 2 cases of ocular pressure disorders were reported in the Advair 500/50 group and 1 case in the placebo group. Although these adverse events are known to associate with corticosteroid use, without case narratives it is difficult to establish causality.

Cardiovascular Safety

Adverse Events

The incidence of cardiovascular events was similar across treatment groups; 14 (8%) in the placebo group, 12 (7%) in the SAL 50 group, 13 (8%) in the FP 500 group and 14 (8%) in the Advair Diskus 500/50 treatment group. The most frequent cardiovascular events were hypertension and palpitations. There were 21 reported AEs of hypertension 4 (2%) in the placebo group, 7 (4%) in the SAL 50 group, 5 (3%) in the FP 500 group and 5 (3%) in the Advair Diskus 500/50 group. There were 6 reports of palpitations, 3 (2%) in the placebo group, 1(<1%) in the FP 500 group and 2 (1%) in the Advair Diskus 500/50 group. There were 2 (1%) cases each of tachycardia and tachyarrhythmias in the SAL 50 group. All the other cardiovascular-related events each occurred in < 1% of patients across treatment groups.

ECGs

An abnormal and clinically significant ECG was defined *a priori* as a 12-lead tracing with any of the following:

- Myocardial ischemia
- Left or right ventricular hypertrophy
- Clinically significant conduction abnormalities (e.g. LBBB, WPW)
- Clinically significant arrhythmias (e.g. atrial fibrillation, ventricular tachycardia)

Four subjects in the placebo group, 2 in the SAL 50 group, 4 in the FP 500 group, and 3 in the Advair Diskus 500/50 treatment group had abnormal clinically significant ECGs at screening or during the study. One subject in the placebo, SAL 50, and Advair Diskus treatment groups and 3 subjects in the FP group had clinically significant abnormal ECGs at screening but were allowed to participate in the study. These patients had no clinically significant changes in their ECG tracing when their ECGs were repeated during the study. Three patients in the placebo group with ECG abnormalities during the treatment period were withdrawn. One patient was discontinued due to a myocardial infarction, another was discontinued due to COPD exacerbation and had an episode of ventricular tachycardia, and one patient had atrial enlargement on a repeat ECG tracing [*Data from CRFs*]. One subject in the SAL group was discontinued after Treatment Week 8 due to ischemic changes and left atrial enlargement. One subject in the FP 500 group also experienced a left atrial abnormality, and was discontinued due to pneumonia. One subject in the Advair Diskus 500/50 treatment group was discontinued due to atrial flutter and one subject who experienced nodal tachycardia was discontinued due to pneumonia. Heart rate

as measured by ECG was similar across treatment groups and did not change significantly during the course of the 24 weeks of treatment.

QTc Intervals

QTc intervals were calculated using Bazett's square root formula [QTcB] and Fridericia's formula [QTcF]. The sponsor defined prolonged QTc intervals as > 440 msecs. The majority of subjects across treatment groups had normal QTc intervals at screening and throughout the study. Using Bazett's formula, 84% - 88% of subjects had QTc interval <440 msecs and using Fridericia's formula 94% -96% had QTc < 440 msecs. Using Bazett's formula 1% - 2% of patients across treatment groups at screening had QTc intervals >470 msec. No patient in the placebo group had a QTc interval > 470 msecs during the treatment period. Five (5) patients in the Advair Diskus 500/50 group had QTc intervals > 470 msecs during the study. Four of these subjects had QTc intervals >470 msecs at screening. One subject with QTc interval of 440.0 msecs at screening had a QTc interval of 471.4 msecs at week 24. The two subjects in the FP 500 group with QTc intervals > 470 msecs during the study had QTc intervals > 440 msecs at screening. One of these subjects was later discontinued from the study due to COPD exacerbation. Two (2) patients in the SAL 50 group had QTc intervals > 470 msecs. Both of these subjects had QTc intervals > 440 msecs at screening. Using Fridericia's formula only 4 subjects in the Advair Diskus treatment group had QTc intervals > 470 msecs. The QTc interval changes that occurred during the study were not associated with QTc-related events and were not the reason for discontinuation from the study in any subject.

Holter Monitoring

The sponsor conducted Holter monitoring over a 24-hour period at screening and at Week 4 in a subset of patients. A total of 158 subjects at screening and 130 patients at Treatment Week 4 had 24-hour Holter monitoring. Most subjects (≥ 95%) in each treatment group had ECG data from Holter monitoring within normal limits. Five subjects [one subject each in the placebo, SAL, and Advair group, and 2 subjects in the FP group] experienced significant changes from screening in Holter monitoring. One subject in the FP group experienced atrial flutter/atrial fibrillation, and one subject in the Advair Diskus group experience heart block. There were three cases of ventricular tachycardia one each in the placebo, SAL, and FP 500 group treatment groups.

Vital Signs (pulse, blood pressure)

There were no significant changes in vital signs across treatment groups during the study. At Baseline pulse and blood pressure were similar across treatment groups.

Clinical Laboratory Results

Clinical laboratory tests were conducted at screening, Week 12, and Week 24. A threshold range for each laboratory measurement was defined by factors greater

than and less than the upper and lower limits of the normal range for that measurement. The factors for calculating these ranges were pre-specified.

Few subjects (≤2% in each treatment group) had hematology parameters that were outside sponsor-defined threshold values. Of these subjects, 2 in the Advair Diskus group had eosinophils values above the sponsor-defined threshold [>20%] and 3 had WBC counts above the sponsor-defined threshold [>16x10^3/uL]. No patients in the Advair Diskus 500/50 or FP 500 treatment groups had lymphocyte or monocyte counts outside of the sponsor-defined threshold [>60% for lymphocytes and > 15% for monocytes]. In clinical chemistry parameters, less than 1% of subjects had values outside of the sponsor-defined threshold values for LFTs, calcium, creatinine, phosphorous and potassium. A higher percentage of subjects [≤ 4%] had values outside the sponsor-defined threshold value for glucose. Seven (4%) subjects in the Advair Diskus 500/50 group, 6 (4%) subjects in the FP 500 group and 5 (3%) subjects in the placebo and SAL groups had glucose levels greater than the threshold value. The sponsor's pre-defined threshold for high and low values is significantly different from what would prompt treatment and/or medical evaluation in clinical practice [see table 33 below]. For example, with the sponsor's threshold limits, patients with fasting glucose values of ≥ 120 mg/dL but ≤ 175 mg/dL would not be outside the threshold for high glucose. However, a fasting glucose value of ≥ 120 mg/dL in the clinical setting would prompt an evaluation for diabetes. Similarly a potassium of <3.5 or >5.5 meq/L would be addressed in clinical practice. However, the sponsor's threshold for a low potassium is <3.0 mEq/l.

Table 33 - Sponsor-Defined Laboratory Threshold Values *[Data from Listing 9.7 pg. 6719-6721 SFCA 3006.pdf Lab. references ranges obtained from SAS transport files]]*

Analyte		Sponsor-defined threshold values		Lab reference range		Range in traditional units
	Units	Low	High	Low	High	
ALT	U/L		>120		>35 U/L	
AST	U/L		>120		>36 U/L	
Alkaline phosphatase	U/L		>300		>115 U/L	
Bilirubin	mg/dl		≥2	<3 (μmol/L)	>21 (μmol/L)	0.3 –1.0 mg/dL
Calcium	mg/dl	<8	>12	<2.1 (nmol/L)	>2.57 (nmol/L)	9 –10.5 mg/dL
Creatinine	mg/dl		>2	<40 (μmol/L)	>110 (μmol/L)	<1.5 mg/dL
Glucose	mg/dl	<55	>175	<3.9 (mmol/L)	6.7 (mmol/L)	70 –120 mg/dL
WBC		2.8 x10^3/μL	16x10^3/uL			
Potassium	mEq/l	<3.0	>6.0	3.4 (mmol/l)	5.4 (mmol/L)	Same as mEq/L
Eosinophils	%		>20		6.8%	
Lymphocytes	%		≥60	15.4%	48.5%	
Monocytes	%		>15	2.6%	10.1%	

Cosyntropin Stimulation Testing

The effect of Advair Diskus 500/50 on HPA Axis was evaluated by morning plasma cortisol concentration and short cosyntropin stimulation testing at Treatment Day 1 and Endpoint at selected sites. Morning plasma cortisol values of < 4 mcg/dL, peak post stimulation cortisol of < 14.5 mcg/dL, and change from baseline of < 5.6 mcg/dL were considered abnormal *a priori*. The threshold values in the Cosyntropin package insert was 18.0 mcg/dL and 7 mcg/dL however the sponsor used lower values because the sponsor used the HPLC assay and not the less specific radioimmunoassay [RIA] upon which the values in the package insert were based. The results are obtained from data table 9.10 and 9.11 on pg. 1462 and 1463 SFCA3006.pdf.

Table 34 - ACTH Stimulation Testing Results SFCA3006

	Placebo)		SAL 50		FP 500 (		Advair Diskus 500/50	
Day 1 N	44		38		39		39	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Mean	12.75	24.19	12.37	24.12	13.09	24.01	13.66	24.71
Endpoint N	35		36		37		36	
Mean	12.89	23.61	11.77	23.20	12.04	21.42	12.14	21.92

Normal pre-stimulation plasma cortisol > 4 mcg/dL
Normal post-stimulation cortisol > 14.5 mcg/dL
Endpoint: Week 24, or discontinuation

The mean basal and post-ACTH stimulation plasma cortisol levels were comparable among treatment groups on Treatment Day 1 and at Endpoint. The post-stimulation cortisols for the FP 500 and the Advair Diskus 500/50 treatment groups at Endpoint were slightly lower compared with post-stimulation cortisols on Day 1. The overall results are not suggestive of clinically significant adrenal suppression.
Reviewer Comment: There are discrepancies in the subject numbers in several of the data tables with the cortisol results. Most of these discrepancies are small and is not expected to affect the overall results. However, the sponsor has been asked to clarify these discrepancies and submit corrected data tables.

Six (6) subjects had abnormal ACTH stimulation testing results [pre-stimulation cortisol < 4 mcg/dL and/or post-stimulation cortisol < 14.5 mcg/dl] during the treatment period. One subject each was in the placebo and SAL group, and 2 patients each were in the FP 500 and Advair Diskus 500/50 group. [*Data from Listing 9.12 pg. 9090 –9095 SFCA3006.pdf]* The results for these patients are outlined below. The results for subjects 11179 in the FP group and 11178 in the Advair group seem odd. However, taken as is they support the fact that there is as expected systemic exposure with FP doses of 500 mcg.

Table 35. Subjects with Abnormal ACTH stimulation results SFCA3006

Treatment Group	Subject
Placebo	Subject 8929 At Discontinuation [29 days] Pre =14.61 Post=13.20
SAL 50	Subject 10797 At discontinuation [54 days] Pre=12.61 Post=14.01
FP 500	Subject 10884 at discontinuation [79 days] Pre=0.50 Post=8.80 Subject 11179 at discontinuation [18 days] Pre=9.50 Post=9.50
Advair Diskus 500/50	Subject 11178 at week 24 Pre = 7.90 Post =7.10 Subject 11287 at discontinuation [56 days] Pre=4.70 Post =13.61

SAFETY RESULTS SFCA 3007

Extent of Exposure

Of the 178 patients who received Advair Diskus 250/50, 112 (63%) were exposed to the drug for ≥ 24 weeks, 19 (11%) patients were exposed for 20 to <24 weeks 10 (6%) patients were exposed for 16 to <20 weeks and 37 patients were exposed for <16 weeks. The mean number of treatment days was 141.3 days with a median range of 1 to 186 days. A total of 116 (63%) patients were exposed to FP 250 for ≥ 24 weeks with a mean exposure of 138.5 days. Mean exposure to SAL 50 was 136.1 days with 108 (61%) of subjects exposed to treatment for ≥ 24 weeks. A total of 110 (59%) patients in the placebo group were exposed for ≥ 24 weeks.

Adverse Events Incidence

A total of 485 (67%) subjects reported at least one adverse event. The percentage of subjects reporting at least one AE was highest in the FP 250 and Advair Diskus 250/50 groups [70% in each group]. As expected, candidiasis of the mouth/throat occurred more frequently in the Advair Diskus 500/50 group (10%) and in the FP 250 group (6%). The 10 most common [≥3%] events regardless of causality were headaches, upper respiratory tract infections (URTI), candidiasis mouth/throat, diarrhea, chest symptoms, and hoarseness/dysphonia. Eight (8) fractures were reported during the treatment period. Three occurred each in the placebo group, and Advair Diskus 250/50 treatment groups and 2 in the FP 250 group. Of the 3 subjects in the Advair/Diskus group who sustained

fractures one was a 58 year-old woman [#16741] who fractured her femur due to a fall and withdrew from the study. Another subject [#16636] sustained 3 broken ribs in a car accident and withdrew from the study.

The highest incidence of AEs occurred within the first month of treatment in all treatment groups. Thirty-five percent of subjects in the placebo group, 38% in the SAL 50 group 44% in the FP 250 group and 41% in the Advair 250/50 Diskus group reported at least one AE within the first month of treatment. Table 36 list the most common [≥3%] events that occurred during the treatment period.

Table 36 - Adverse Events more Frequent than Placebo and Occurring ≥ 3% SFCA3007 [data table 9.2 SFCA3007.pdf]

Adverse event	Placebo N=185	SAL 50 N=177	FP 250 N=183	Advair 250/50 N=178
Any adverse event	118 [64%]	114 [64%]	129 [70%]	124 [70%]
Headaches	22[12%]	17[10%]	21[11%]	28[16%]
Candidiasis	2[1%]	5[3%]	11[6%]	17[10%]
Throat irritation	13 [7%]	7 [4%]	10 [5%]	15 [8%]
Sinusitis	5 [3%]	8 [5%]	14 [8%]	6 [3%]
Fever	5 [3%]	0	5 [3%]	8 [4%]
Hoarseness/dysphonia	0	1 [<1%]	5 [3%]	9 [5%]
Dizziness	3[2%]	6[3%]	1 [<1%]	7 [4%]
Viral respiratory infections	6 [3%]	5 [3%]	8 [4%]	10 [6%]
Upper respiratory inflammation	6[3%]	5 [3%]	7 [4%]	4 [2%]
Muscle cramps & spasms	2[1%]	2 [1%]	5 [3%]	6 [3%]
Rhinorrhea/post nasal drip	3[2%]	5[3%]	2 [1%]	3 [2%]
Nasal congestion/blockage	4[2%]	2[1%]	1 [<1%]	5 [3%]
Epistaxis	2[1%]	3[2%]	5[3%]	1[<1%]
Pain	3[2%]	2 [1%]	5 [3%]	2 [1%]
Cough	2 [1%]	7 [4%]	1 [<1%]	2 [1%]

Deaths and Serious Adverse Events

There were no deaths during the study.

Serious Adverse Events

Thirty-five subjects experienced at least one SAE during the treatment period. Eleven (5%) subjects were in the FP 250 treatment group and 8 (4%) subjects were in the Advair 250/50 treatment group. The SAEs are listed in the table below.

Note: The sponsor's in-text table and text on page 159 reports a total of 34 SAEs with 10 occurring in the FP 250 treatment group. The sponsor acknowledged [pg160] that because of a recording error in the medication stop date 2 SAEs experienced by subject #12438 in the FP group should have been considered as SAEs during the treatment period.

On review of the case narratives none of the SAEs appear to be drug-related.

Table 37 - Serious Adverse Events SFCA 3007

	Placebo N =185	SAL 50 N =177	FP 250 N=183	Advair 250/50 N=178	Totals 723
Serious Adverse Event [SAE] n (%)	11 (6%)	5 (3%)	*11 (5%)	8 (4%)	35 (5%)
Withdrawal due to SAE n (%)	5 (3%)	5 (3.6%)	7 (7%)	4 (4%)	21 (3%)
SAE					
Chronic obstructive airways disease (COAD)[a]	1 (<1%)	2 (1%)	4 (2%)*	0	7 (<1%)
Cholelithiasis	1 (<1%)	0	2 (1%)	0	3 (<1%)
Chest pain	2 (1%)	0	0	1 (<1%)	3 (<1%)
Pneumonia	0	1 (<1%)	1 (<1%)	0	2 (<1%)
Cholecystitis	0	0	1 (<1%)	1 (<1%)	4 (<1%)
[b]Fractures	1 (<1%)	0	0	1 (<1%)[b]	2 (<1%)

*One subject experience a COPD exacerbation and worsening sinusitis during the treatment period but was incorrectly recorded as occurring after discontinuing treatment.
a The preferred term for COPD
b The patient in the Advair group was a 58-year old female who sustained a fractured femur after a fall while attempting to climb into her locked home. The patient in the placebo group had chest contusions and rib fractures following a motor vehicle accident.
The other serious adverse events each reported once in one patient were appendicitis, coronary artery disease, worsening depression, right breast cancer, epistaxis, and prostate cancer (placebo group), hemorrhagic cerebral infarction and possible TIA (SAL 50 group), splenic enlargement, myocardial infarction, suspected hypoglycemia, and acute pancreatitis (FP 250 group), basal cell carcinoma of the nose, streptococcal bacteremia/infection of the pharynx, myeloid leukemia, spontaneous pneumothorax, and cardiac arrhythmia (Advair Diskus 250/50).

Adverse Events leading to withdrawal

See page 42 Table 19 for discussion on the discrepancy with the number of subjects with AEs leading to withdrawal. Also there is a discrepancy in the number of subjects with withdrawal due to AEs in the text and in-text table on page 160-161 and in Listing 9.4 pg. 5770-5785. The number of subject withdrawals due to AEs is stated as 34 with 10 subjects in the FP group on pages 160-161.However, in the data listing 9.4 pg. 5778- 5782 the total number of subjects listed as withdrawing due to AEs in the FP 250 group is 13. The AEs leading to withdrawals are discussed based on data from listing 9.4 pg. 5770 – 5785. Based on those data the total number of subject withdrawals due to AEs is 37.

Of the 37 subjects who withdrew due to AEs, 10 were in the placebo group, 7 were in the SAL 50 group, 13 were in the FP 250 group and 9 were in the Advair Diskus 250/50 group. None of these events that led to withdrawal appear to be drug related.

Drug-related Events

The sponsor did not provide case narratives for the adverse events considered by the Investigator to be drug-related therefore it was difficult for this reviewer to assess causality for most of these events. However, except for events such as candidiasis or hoarseness/dysphonia that are know to be associated with inhaled corticosteroid use, the other events described as drug-related by the Investigator

[e.g. wounds and lacerations in a patient on SAL and depression in a patient on placebo] are unlikely by this reviewer's assessment to be drug-related.

Candidiasis, throat irritation, and hoarseness/dysphonia occurred more frequently in the FP 250 and Advair 250/50 treatment groups compared with salmeterol and placebo. Seventeen (10 percent) of subjects in the Advair Diskus 200/50 group and 11 (6%) subjects in the FP 250 treatment group reported candidiasis of the mouth/throat. There were 4 cases (2%) of candidiasis at an unspecified site in the FP 250 group and 2 (1%) in the Advair Diskus 250/50 treatment group. No cases of unspecified oropharyngeal plaques were reported in the Advair or FP groups but 1 case was reported each in the placebo and SAL groups. Throat irritation was experience by 15 (8%) subjects in the Advair Diskus 250/50 group, by 10 (5%) of subjects in the FP 250 group, by 7 (4%) subjects in the SAL group and by 13 (7%) subjects in the placebo group. More subjects in the Advair Diskus 250/50 group (9 [5%]) reported hoarseness/dysphonia compared to the other treatment groups (FP 250 5 [3%] subjects, SAL 1[<1%] subject. No cataracts or glaucoma were reported however the sponsor did not specifically monitor patients for these adverse events. Other events reported as drug-related by the Investigator that by this reviewer's assessment are possibly related to the study drug are hyperglycemia [1] and abnormal liver function tests [1] in the FP 250 group, and muscle cramps and spasms [1] in the SAL group. Two cases of oral itching and irritation [one each in the SAL and FP group] and one case of oral lesions [Advair 250/50 group] could possibly be drug or formulation-related.

Cardiovascular Safety

Adverse Events

The incidence of cardiovascular events was highest in the placebo group [16 subjects (9%)] followed by the SAL 50 group [11 (6%)] The FP 250 and Advair Diskus 250/50 groups had the lowest percentage [4%] of cardiovascular events. The most frequent [≥2%] cardiovascular events were hypertension and syncope. There were 5 (3%) reported AEs of hypertension in the placebo and in the SAL 50 group, 4 [2%] in the Advair Diskus 250/50 group and 2 [1%] in the FP 250 group. There were 2 reports of syncope (1%) in the SAL group and 3 (2%) reports in the Advair Diskus 250/50 group. Each of the other cardiovascular-related events occurred in < 1% of patients across treatment groups.

ECGs

An abnormal and clinically significant ECG was defined *a priori* as described in study SFCA3006 [*See pg.60*]

Most subjects had normal ECG tracings or had abnormal tracings that were not clinically significant at screening. Only 3 subjects [one each in the placebo, SAL and FP 250 group] had an abnormal ECG tracing that was clinically significant at screening. No Subjects in the FP 250 or Advair Diskus 250/50 groups had clinically significant changes from baseline in their ECG tracings during the study.

Two subjects were discontinued due to clinically significant ECG changes. One subject was in the placebo group and had left bundle branch block and QTc prolongation and one subject was in the SAL group and had QTc prolongation. The QTc prolongation in the patient in the SAL group did not exceed 470 msecs.

QTc Intervals

QTc intervals were calculated using Bazett's square root formula [QTcB] and Fridericia's formula [QTcF]. The sponsor defined prolonged QTc intervals as > 440 msecs. The majority of subjects across treatment groups had normal QTc intervals at screening and throughout the study. Using Bazett's formula mean QTc ranged from 414.64 msecs to 417.56 msecs. Using Bazett's or Fridericia's formula only 5 patients at screening had QTc intervals >470 msecs. Two of these patients were in the Advair Diskus 250/50 treatment group. The QTc intervals were not significantly changed during the study. One subject in the placebo group discontinued because of the onset of LBBB and QTc prolongation. The QTc at screening in this subject was 407.9 msecs and at discontinuation was 475.3. The QTc findings overall were not suggestive of any drug-related effects.

Vital Signs (pulse, blood pressure)

At Baseline pulse and blood pressure were similar across treatment groups. There were no significant changes in vital signs across treatment groups during the study.

Clinical Laboratory Results

Clinical laboratory tests [fasting] were performed on samples collected at screening, Week 12 and Week 24. The sponsor defined a threshold range for each laboratory measurement by factors greater than and less than the upper and lower limits of the normal range for that measurement *[See Table 33 pg. 62]*. The majority of subjects (≥ 91%) had either no change in hematology parameters or a shift into the normal range at Treatment Weeks 12 and 24. Few subjects [≤2%] in each treatment group had hematology parameters that were outside sponsor-defined threshold values. The majority of subjects [≥87%] had either no change in clinical chemistry parameters or a shift into the normal range at Weeks 12 and 24 and at the Discontinuation visit. The most common shifts observed were shifts to "high" in glucose and ALT values. Seventeen subjects had glucose values above the sponsor's pre-defined threshold [>175 mg/dl]. Three subjects were in the Advair Diskus 250/50 group, 5 were in the FP 250 group, 6 were in the SAL group and 3 were in the placebo group. Elevated glucose as an AE was reported in 8 subjects two of whom were in the Advair Diskus 250/50 treatment groups. As mentioned for study SFCA3006, the sponsor's threshold for high glucose of >175 mg/dl would have failed to capture high glucose levels that generally would be addressed in clinical practice.

Cosyntropin Stimulation Testing

The effect of Advair Diskus 500/50 on HPA Axis was evaluated by morning plasma cortisol concentration and short cosyntropin stimulation testing at Treatment Day 1 and Endpoint at selected sites as was done in study SFCA3006. The mean pre and post-stimulation cortisol results were similar across treatment groups at Day 1 and Endpoint. Results are depicted in table 38. [Data obtained from data table 9.10 and 9.11 in pg. 965 and 966 SFCA3007. A total of 4 subjects had post-stimulation cortisols < 14.5 mcg/dl at Endpoint. Two subjects were in the placebo group, and 1 subject each was in the SAL and Advair 250/50 group [Data table 9.16 pg. 973].

Reviewer comment: There were minor discrepancies in the patient numbers [± 1 patient in some treatment groups] in some of the tables with cortisol results. The sponsor has been asked to clarify these discrepancies but these are not expected to affect the overall results.

Table 38 ACTH Stimulation Testing Results SFCA3007

	Placebo (n=185)		SAL 50 (n=177)		FP 250 (n=183)		Advair Diskus 250/50 (n=178)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Day 1 N	54	53	51	53	50	50	44	45
Mean	12.43	25.94	12.98	24.61	11.56	23.96	13.40	23.89
Endpoint N	27	25	29	28	26	24	32	29
Mean	11.13	23.23	12.24	23.57	10.55	22.14	12.38	23.19

Normal pre-stimulation plasma cortisol > 4 mcg/dl
Normal post-stimulation cortisol > 14.5 mcg/dL
Endpoint: Week 24, or discontinuation

120-Safety Update

The cut-off date for collection of all safety information in the supplemental NDA was 30 September 2000. The 120-day safety update includes all safety information reported during the period of 01 October 2000 to 31 May 2001. The safety update includes data from 4 clinical pharmacology studies, 2 controlled clinical studies, 23-non U.S. regional studies and selected safety information from a completed long-term FP asthma study FLTA3001.

No clinically relevant adverse events were reported for the completed clinical pharmacology studies. There were no completed clinical studies within this reporting period that evaluated SAL, FP, or Advair in the treatment of COPD. Therefore no analyses of AEs can be conducted for the 120-safety day report since treatment assignment remains blinded. Two controlled clinical studies with Advair Diskus 500/50 mcg and its individual components [SAL 50 and FP 500

mcg] are ongoing. Twenty-three non-US regional studies including a total of 4 studies with the combination product [Advair] in COPD subjects are ongoing. There have been 16 deaths reported to date in the two controlled clinical trials and 11 deaths in the 23 non-U.S. regional studies. The majority of the deaths were due to cardiac causes [cardiac arrest, myocardial infarction, and chest pain]

A 2 year study to assess the long term safety of FP Inhalation Aerosol 100 mcg bid and 500 mcg bid versus placebo bid in adult subjects with moderate asthma [Study FLTA3001] was mentioned in the 120-safety update but no data from that study were provided.

Eight SAEs [including 4 deaths] were reported in post-marketing observational studies. Three of these deaths were due to cardiac causes and one was due to metastatic cancer of the stomach. There have been 42 spontaneous reports of deaths from September 18, 1998 through May 05, 2000 from the New Zealand Regulatory Authority and New Zealand's Intensive Medicine Monitoring Program. The patients had been on salmeterol. A causality assessment has not been determined.

VIII. Dosing, Regimen, and Administration Issues

Advair Diskus comes in three strengths 100/50 mcg, 250/50 mcg, and 500/50 mcg. The sponsor is seeking approval for the 250/50 and the 500/50mcg strengths only. The proposed dosing regimen is one inhalation twice daily.

IX. Use in Special Populations

A. Gender Effects

A greater percentage (63%) of subjects participating in the efficacy clinical studies was male. The incidence of candidiasis mouth/throat and hoarseness/dysphonia was lower in males [5% -6% with candidiasis and < 1% - 2% with hoarseness] than females [9% to 14% with candidiasis and 5% to 7% with hoarseness]. The incidence by gender was comparable for other adverse events. There were no gender-related differences in effectiveness.

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

Subjects age in the clinical studies ranged from 40 to 90 years and the majority of subjects were Caucasian. There was not a representative number of patients in the other ethnic groups to allow for meaningful statistical comparisons. Although there were some scattered differences in the incidence of individual AEs, there did not appear to be any age-related or ethic origin-related differences in efficacy or safety.

C. Pediatric Program

In compliance with 21 CFR 314.55(c)(3) Glaxo has requested a waiver of submission of an assessment of pediatric use with Advair ® Diskus in subjects 0 to 16 years of age for COPD. The reason the sponsor gives for the waiver request is that the disease being studied COPD as defined by the ATS does not occur in this age group. The sponsor further states that COPD occurs in patients who have usually been smoking for 20 or more years and that symptoms commonly present in the 5th decade of life. Progressive airflow obstruction is also observed in patients with COPD. The Clinical program for COPD studied only subjects aged 40 years and older with a substantial smoking history.

Safety data and dosing recommendations are available for pediatric subjects 12 years of age and older from asthma studies with Advair Diskus. The sponsor currently has a pediatric program addressing safety and dosing recommendations for Advair Diskus in asthmatic patients 4 to 11 years of age. Pediatric studies in subjects with asthma 6 months to 4 years of age are currently ongoing with both active components [salmeterol, FP] of Advair.

The sponsor's request for a waiver for studies with Advair Diskus for the indication of COPD in the pediatric population is appropriate.

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

Formal studies were not conducted in subjects with renal impairment or hepatic compromise. Since FP is predominantly cleared by hepatic metabolism impairment of liver function may lead to accumulation of FP in plasma. Therefore, patients with hepatic disease should be closely monitored. There are no adequate and well-controlled studies with Advair Diskus in pregnant women. No pregnancies were reported during the conduct of the Advair studies or the Flovent study FLTA3025. Because subjects with COPD tend to be older pregnancy might be less of an issue for the use of Advair Diskus for this indication than it is for the asthma indication. Nevertheless, Advair Diskus should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

X. Conclusions and Recommendations

A. Conclusions

- Advair Diskus 500/50 and Advair Diskus 250/50 met the efficacy criteria for combination drug products as set forth in the Code of Federal regulations but approval for the treatment of COPD remains questionable.
- The efficacy results for Advair Diskus 500/50 were similar to the efficacy results for Advair Diskus 250/50.

- The improvement in lung function (FEV_1) seen in the clinical trials was not accompanied by improvements in clinically relevant endpoints such as reduction in the frequency or severity of COPD exacerbations, or symptom scores,
- Advair did not demonstrate a treatment advantage for COPD-related quality of life
- There was a clinically meaningful change in the TDI at Endpoint with Advair 500/50 compared to placebo and salmeterol but not with FP.
- The patient population studied did not represent the general COPD population as a whole. Over 50% of the patients had significant reversibility compared with up to 30% in the COPD population and all patients in these studies had chronic bronchitis. This brings into question the efficacy of this therapy in COPD patients whose clinical presentation is predominately emphysema without associated chronic bronchitis.
- There was a relatively high incidence of oral candidiasis in the FP and Advair groups and respiratory infections tended to be higher in the FP and Advair groups compared to placebo and SAL.
- The sponsor's threshold for laboratory values were very liberal making it difficult to evaluate the true incidence of hyperglycemia and hypokalemia in the pivotal studies.
- Monitoring for decreased bone mineral density and ocular pressure disorders and cataracts was not done in these studies.

B. Recommendations

A recommendation on approval is withheld pending the Advisory Committee meeting January 17th 2001.

XI. Appendix

Chronic Bronchitis Symptoms Questionnaire (CBSQ)

The CBSQ scale combined selected questions from the Petty subject Evaluation Questionnaire And the Revised Global Petty Questionnaire for Ease of Cough and Sputum Clearance. The CBSQ evaluated the COPD symptoms of cough frequency and severity, chest discomfort, and sputum production on a scale of 0-4, where a rating of 0 reflect no symptoms. Subjects had to have a score of ≥4 out of a possible 16 at Treatment Day 1 to qualify for the study.

Cough Frequency

"How frequently were you coughing during a typical 24-hour day during the past week?"		
0	None	Unaware of coughing
1	Rare	Cough now and then during the day, unaware of or rarely at night
2	Occasional	Less than hourly during the day, rarely at night
3	Frequent	One or more times an hour during the day, occasionally at night
4	Almost constant	Never free of cough or feeling free of the need to cough

Cough Severity

"How severe were your cough episodes during a typical day during the past week?"		
0	None	Unaware of coughing
1	Mild	Did not interfere with usual morning or daily activities
2	Moderate	Must stop activity during coughing episode
3	Marked	Must stop activity during and for a brief period after coughing episode
4	Severe	Stops all activity for some time and is exhausting; may be accompanied by dizziness, headache, and/or pain in the chest or abdomen

Sputum Release

"How easy was it to cough up sputum when you coughed during a typical day during the past week?"		
0	None	Unaware of coughing
1	Easy	Sputum comes up without difficulty after only one or two coughs
2	Somewhat difficult	Most of the sputum comes up but only after several hard coughs
3	Very difficult	Some sputum comes up after hard coughing but there is the feeling that most is still sticking down there
4	Impossible	There is sputum down there but no matter how hard the coughing nothing comes up

Chest Discomfort

"How much chest tightness or discomfort did you have during a typical day during the past week?"		
0	None	Unaware of any discomfort
1	Mild	Noticeable now and then but is not bothersome and passes quickly; does not limit activity
2	Moderate	Noticeable during light activity such as walking one block or up one flight of stairs
3	Marked	Noticeable while washing or dressing in the morning
4	Severe	Almost constant and limits all activity; present even while resting

Baseline/Transition Dyspnea Index

The BDI scale administered on Treatment Day 1 rate the Baseline severity of dyspnea on a graded scale from 0 to 4 where Grade 0 was most severe. The scores depended on ratings for three different categories: functional impairment, magnitude of task, and magnitude of effort as shown below.

Baseline Functional Impairment		
_____Grade 4	*No Impairment*	Able to carry out usual activities and occupation without shortness of breath.
_____Grade 3	*Slight Impairment*	Distinct impairment in at least one activity but no activities completely abandoned. Reduction, in activity at work *or* in usual activities, that seems slight or not clearly caused by shortness of breath.
_____Grade 2	*Moderate Impairment*	Subject has changed jobs *and/or* has abandoned at least one usual activity due to shortness of breath.
_____Grade 1	*Severe Impairment*	Subject unable to work or has given up most or all usual activities due to shortness of breath.
_____Grade 0	*Very Severe Impairment*	Unable to work *and* has given up most or all usual activities due to shortness of breath.
_____W	*Amount Uncertain*	Subject is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.
_____X	*Unknown*	Information unavailable regarding impairment.
_____Y	*Impaired for Reasons Other than Shortness of Breath*	For example, musculoskeletal problem or chest pain.

Usual activities refer to requirements of daily living, maintenance or upkeep of residence, yard work, gardening, shopping, etc.

Baseline Magnitude of Task		
_____Grade 4	*Extraordinary*	Becomes short of breath only with extraordinary activity such as carrying very heavy loads on the level, lighter loads uphill, or running. No shortness of breath with ordinary tasks.
_____Grade 3	*Major*	Becomes short of breath only with such major activities as walking up a steep hill, climbing more than three flights of stairs, or carrying a moderate load on the level.
_____Grade 2	*Moderate*	Becomes short of breath with moderate or average tasks such as walking up a gradual hill, climbing fewer than three flights of stairs, or carrying a light load on the level.
_____Grade 1	*Light*	Becomes short of breath with light activities such as walking on the level, washing, or standing.
_____Grade 0	*No Task*	Becomes short of breath at rest, while sitting, or lying down.
_____W	*Amount Uncertain*	Subject's ability to perform tasks is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.
_____X	*Unknown*	Information unavailable regarding limitation of magnitude of task.
_____Y	*Impaired for Reasons Other than Shortness of Breath*	For example, musculoskeletal problem or chest pain.

Baseline Magnitude of Effort		
_____Grade 4	*Extraordinary*	Becomes short of breath only with the greatest imaginable effort. No shortness of breath with ordinary effort.
_____Grade 3	*Major*	Becomes short of breath with effort distinctly submaximal, but of major proportion. Tasks performed without pause unless the task requires extraordinary effort that may be performed with pauses.
_____Grade 2	*Moderate*	Becomes short of breath with moderate effort. Tasks performed with occasional pauses and requiring longer to complete than the average person.
_____Grade 1	*Light*	Becomes short of breath with little effort. Tasks performed with little effort or more difficult tasks performed with frequent pauses and requiring 50-100% longer to complete than the average person might require.
_____Grade 0	*No Effort*	Becomes short of breath at rest, while sitting, or lying down.
_____W	*Amount Uncertain*	Subject's exertional ability is impaired due to shortness of breath, but amount cannot be specified. Details are not sufficient to allow impairment to be categorized.
_____X	*Unknown*	Information unavailable regarding limitation of effort.
_____Y	*Impaired for Reasons Other than Shortness of Breath.*	For example, musculoskeletal problems, or chest pain.

The Transition (TDI) scale administered at each subsequent visit denoted changes from Baseline in functional impairment, magnitude of task, and magnitude of effort. The scale ranged form –3 to + 3 where negative numbers indicated deterioration, 0 was no change, and positive numbers indicated improvement as shown below.

Transition Dyspnea Index

Change in Functional Impairment		
_____-3	*Major Deterioration*	Formerly working and has had to stop working *and* has completely abandoned some of usual activities due to shortness of breath.
_____-2	*Moderate Deterioration*	Formerly working and has had to stop working *or* has completely abandoned some of usual activities due to shortness of breath.
_____-1	*Minor Deterioration*	Has changed to a lighter job *and/or* has reduced activities in number or duration due to shortness of breath. Any deterioration less than preceding categories.
_____ 0	*No Change*	No change in functional status due to shortness of breath.
_____+1	*Minor Improvement*	Able to return to work at reduced pace or has resumed some customary activities with more vigor than previously due to improvement in shortness of breath.
_____+2	*Moderate Improvement*	Able to return to work at nearly usual pace *and/or* able to return to most activities with moderate restriction only.
_____+3	*Major Improvement*	Able to return to work at former pace *and* able to return to full activities with only mild restriction due to improvement of shortness of breath.
_____ Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has stopped working, reduced work, or has given up or reduced other activities for other reasons. For example, other medical problems, being "laid off" from work, etc.

Change in Magnitude of Task		
_____-3	*Major Deterioration*	Has deteriorated two grades or greater from Baseline status.
_____-2	*Moderate Deterioration*	Has deteriorated at least one grade but fewer than two grades from Baseline status.
_____-1	*Minor Deterioration*	Has deteriorated less than one grade from Baseline. Subject with distinct deterioration within grade, but has not changed grades.
_____ 0	*No Change*	No change from Baseline.
_____+1	*Minor Improvement*	Has improved less than one grade from Baseline. Subject with distinct improvement within grade, but has not changed grades.
_____+2	*Moderate Improvement*	Has improved at least one grade but fewer than two grades from Baseline.
_____+3	*Major Improvement*	Has improved two grades or greater from Baseline.
_____ Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has reduced exertional capacity, **but** not related to shortness of breath. For example, musculoskeletal problem or chest pain.

Change in Magnitude of Effort		
_____-3	*Major Deterioration*	Severe decrease in effort from Baseline to avoid shortness of breath. Activities now take 50-100% longer to complete than required at Baseline.
_____-2	*Moderate Deterioration*	Some decrease in effort to avoid shortness of breath, although not as great as preceding category. There is greater pausing with some activities.
_____-1	*Minor Deterioration*	Does not require more pauses to avoid shortness of breath, but does things with distinctly less effort than previously to avoid breathlessness.
_____ 0	*No Change*	No change in effort to avoid shortness of breath.
_____+1	*Minor Improvement*	Able to do things with distinctly greater effort without shortness of breath. For example, may he able to carry out tasks somewhat more rapidly than previously.
_____+2	*Moderate Improvement*	Able to do things with fewer pauses and distinctly greater effort without shortness of breath. Improvement is greater than preceding category, but not of major proportion.
_____+3	*Major Improvement*	Able to do things with much greater effort than previously with few, if any, pauses. For example, activities may be performed 50-100% more rapidly than at Baseline.
_____ Z	*Further Impairment for Reasons Other than Shortness of Breath*	Subject has reduced exertional capacity, but not related to shortness of breath. For example, musculoskeletal problem or chest pain.

The Chronic Respiratory Disease Questionnaire

From " A measure of quality of life for clinical trials in chronic lung disease". Gordon H Guyatt et.al. Thorax 1987; **42**: 773-778

Appendix: Summary of the Chronic Respiratory Disease Questionnaire

The questionnaire begins by eliciting five activities in which the patient experiences dyspnoea during day to day activities:

1 I would like you to think of the activities that you have done during the last 2 weeks that have made you feel short of breath. These should be activities which you do frequently and which are important in your day to day life. Please list as many activities as you can that you have done during the last 2 weeks that have made you feel short of breath.

[Circle the number on the answer sheet list adjacent to each activity mentioned. If an activity mentioned is not on the list, write it in, in the respondent's own words, in the space provided.]

Can you think of any other activities you have done during the last 2 weeks that have made you feel short of breath?

[Record additional items]

2 I will now read a list of activities which make some people with lung problems feel short of breath. I will pause after each item long enough for you to tell me if you have felt short of breath doing that activity during the last 2 weeks. If you haven't done the activity during the last 2 weeks, just answer "No." The activities are:

[Read items, omitting those which respondent has volunteered spontaneously. Pause after each item to give respondent a chance to indicate whether he/she has been short of breath while performing that activity during the last week. Circle the number adjacent to appropriate items on answer sheet.]

1 Being *angry* or upset
2 Having a *bath* or shower
3 *Bending*
4 *Carrying*, such as carrying groceries
5 *Dressing*
6 *Eating*
7 *Going* for a walk
8 Doing your *housework*

9 *Hurrying*
10 *Lying* flat
11 *Making a bed*
12 *Mopping* or scrubbing the floor
13 *Moving* furniture
14 *Playing* with children or grandchildren
15 *Playing* sports
16 *Reaching* over your head
17 *Running*, such as for a bus
18 *Shopping*
19 *Talking*
20 *Vacuuming*
21 *Walking* around your own home
22 *Walking* uphill
23 *Walking* upstairs
24 *Walking* with others on level ground
25 *Preparing* meals
26 While trying to *sleep*

If more than five items have been listed the interviewer then helps the subject determine the five activities which are most important in the subject's day to day life.

3(*a*) Of the items which you have listed, which is the most important to you in your day to day life? I will read through the items, and when I am finished I would like you to tell me which is the most important.

[Read through all items spontaneously volunteered and those from the list which patient mentioned.]

Which of these items is most important to you in your day to day life?

[List item on response sheet.]

This process is continued until the five most important activities are determined. The interviewer then proceeds to find out how much shortness of breath the subject has experienced during the prior two weeks. Throughout the questionnaire, response options are printed on different colour cards with which the subject is presented.

4 I would now like you to describe how much shortness of breath you have experienced during the last 2 weeks while doing the five most important activities you have selected.

(*a*) Please indicate how much shortness of breath you have had during the last 2 weeks while *[Interviewer: Insert activity list in 3a]* by choosing one of the following options from the card in front of you *[green card]:*

1 Extremely short of breath
2 Very short of breath
3 Quite a bit short of breath
4 Moderate shortness of breath
5 Some shortness of breath
6 A little shortness of breath
7 Not at all short of breath

This process continues until the subject's degree of dyspnoea on all five of his or her most important activities has been determined. The remainder of the questionnaire asks 15 standard questions, which are identical for each subject. The wording is deliberately repetitious, experience having taught us that the repetition ensures subjects' understanding. Response options are consistently presented as seven point scales. An example of the way the questions are structured follows.

5 In general, how much of the time during the last 2 weeks have you felt frustrated or impatient? Please indicate how often during the last 2 weeks you have felt frustrated or impatient by choosing one of the following options from the card in front of you *[blue card]:*

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

The wording structure of the other questions is identical, and appropriate seven points scales are offered for each question. The content of the remaining 14 questions is as follows:

6 How often during the past 2 weeks did you have a feeling of fear or panic when you had difficulty getting your breath?

7 What about fatigue? How tired have you felt over the last 2 weeks?

8 How often during the last 2 weeks have you felt embarrassed by your coughing or heavy breathing?

9 In the last 2 weeks, how much of the time did you feel very confident and sure that you could deal with your illness?

10 How much energy have you had in the last 2 weeks?

11 In general, how much of the time did you feel upset, worried, or depressed during the last 2 weeks?

12 How often during the last 2 weeks did you feel you had complete control of your breathing problems with shortness of breath and tiredness?

13 How much of the time during the last 2 weeks did you feel relaxed and free of tension?

14 How often during the last 2 weeks have you felt low in energy?

15 In general, how often during the last 2 weeks have you felt discouraged or down in the dumps?

16 How often during the last 2 weeks have you felt worn out or sluggish?

17 How happy, satisfied, or pleased have you been with your personal life during the last 2 weeks?

18 How often during the last 2 weeks did you feel upset or scared when you had difficulty getting your breath?

19 In general, how often during the last 2 weeks have you felt, restless, tense, or uptight?

Modified Medical Research Council Dyspnea Scale

Grade	Degree	
0	None	Not troubled with breathlessness except with strenuous exercise
1	Slight	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
2	Moderate	Walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level
3	Severe	Stops for breath after walking about 100 yards or after a few minutes on the level
4	Very severe	Too breathless to leave the house or breathless when dressing or undressing