Backgrounder
Pulmonary and Allergy Drugs Advisory Committee

Application Number:	20-833, SE1-004	**Application Type:**	NDA
Sponsor:	GlaxoSmithKline	**Proprietary Name:**	Flovent® Diskus®
Category of Drug:	Corticosteroid	**USAN/Established Name**:	Fluticasone propionate
		Route of Administration:	Oral inhalation dry powder
Medical Reviewer:	Charles E. Lee, M.D.	**Review Date:**	12/14/01

REVIEW SUMMARY:

This is an NDA review for a chronic obstructive pulmonary disease (COPD) indication for Flovent® Diskus®. The sponsor is GlaxoSmithKline. The proposed indication is the long-term maintenance treatment of COPD. The proposed starting dose for adults is one inhalation (250 mcg) twice daily. The labeling allows for increasing the dose to 2 inhalations (500 mcg) twice daily in patients with an inadequate response. There were three pivotal studies submitted in this application, Studies FLTA3025, SCFA3006, and SFCA3007. Although statistical significance was shown for FP 500, the effect size was relatively modest, particularly for FLTA3025, where 24 weeks of treatment resulted in a net improvement in FEV_1 of only 50 mL. These studies do not appear to support the efficacy of FP 250 in the population studied, as a statistically significant difference from placebo was not noted in replicate studies. Most secondary efficacy endpoint variables did not support the efficacy of FP 500 or FP 250. The health-related quality of life instrument does not support the efficacy of FP 500 or FP 250. The sponsor does not appear to have established the safety of FP for this indication in the proposed population. The sponsor has not adequately studied the safety of FP in non-Caucasian patients with COPD. The pivotal studies were likely to be of insufficient duration to detect differences between treatment groups for time and exposure-related events such as fractures, cataracts, ocular pressure disorders, and disorders of glucose metabolism. The pivotal studies were not designed to specifically look for cataracts or systemic bone effects. Safety data from supportive studies raise concerns about a higher incidence of respiratory infections, pneumonia, HPA axis effects, among others, in FP-treated patients, and do not adequately address bone effects in the proposed population. The sponsor does not appear to have sufficiently established that the proposed dose of FP is effective or safe in the treatment of COPD.

SIGNED:

Medical Reviewer: **Date:**

Medical Team Leader: **Date:**

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EXECUTIVE SUMMARY

1. RECOMMENDATIONS

Recommendations will be added after the Pulmonary and Allergy Advisory Committee meeting, which is scheduled for January 17, 2002.

2. SUMMARY OF CLINICAL FINDINGS

2.1. Brief overview of clinical program

Fluticasone propionate is approved in the form of a dry powder inhaler as Flovent® Rotadisk, NDA 20-549, November 7, 1997, and as Flovent® Diskus®, NDA 20-833, September 29, 2000. The dry powder inhaler products are approved for use in adults and children ages 4 years and older for the maintenance treatment of asthma as prophylactic therapy. Fluticasone propionate inhalation aerosol (Flovent®, NDA 20-548) was approved March 27, 1996 in three dosage strengths (44 mcg, 110 mcg, and 220 mcg) for the maintenance treatment of asthma as prophylactic therapy.

The sponsor, GlaxoSmithKline, has submitted this NDA supplement for a chronic obstructive pulmonary disease (COPD) indication for Flovent® Diskus®. The proposed indication is the long-term maintenance treatment of COPD. The proposed starting dose for adults is one inhalation (250 mcg) twice daily. The proposed labeling allows for increasing the dose to 2 inhalations (500 mcg) twice daily to provide additional control for patients who do not respond adequately to the starting dose. The clinical program was also designed to pursue COPD indications for Serevent Diskus (salmeterol xinafoate 50 mcg) and Advair Diskus (fluticasone propionate 250 mcg /salmeterol xinafoate 50 mcg and fluticasone propionate 500 mcg/salmeterol xinafoate 50 mcg). Submissions similar to the Flovent Diskus NDA supplement have been simultaneously submitted to the Serevent Diskus NDA (NDA 20-692) and to the Advair Diskus NDA (NDA 21-077).

This submission refers to three pivotal clinical studies, Studies FLTA3025, SFCA3006, and SFCA3007. These studies are submitted in support of the efficacy of FP in the treatment of COPD. The pivotal studies were randomized, double-blind, parallel group, placebo-controlled, multicenter studies. Each of the pivotal studies had a 24-week treatment duration. Study FLTA3025 evaluated the efficacy of FP 250 and FP 500 compared with placebo. SAL 50/FP 500 and FP 500 were compared with each other and with placebo in SFCA3006. SAL 50/FP 250 and FP 250 were compared with each other and with placebo in SFCA3007. All three studies were similar in design, subject entrance criteria, and overall conduct to provide replication of treatment arms across studies. The sponsor provided safety data from the pivotal studies, supportive safety data from other studies, and a safety update, which included postmarketing reports and a literature review, in support of the safety of FP in the treatment of COPD.

2.2. Efficacy

The primary efficacy variable for the evaluation of FP in the pivotal studies was the pre-dose FEV_1. The primary analysis for FP was the comparison of the mean morning pre-

dose FEV_1 between treatment groups at endpoint. Comparisons of FP 500 with placebo showed statistically significant differences in mean change from baseline in pre-dose FEV_1 in both FLTA3025 and SFCA3006, although the effect size observed in FLTA3025 was only 50 mL, half of the "clinically significant" 100 mL the sponsor had powered the study to detect. The effect size reported in SFCA3006 was 113 mL. Comparisons of FP 250 with placebo showed statistically significant differences in mean change from baseline in pre-dose FEV_1 only for SFCA3006 with an effect size of 108 mL, but not for FLTA3025, which had an effect size of only 27 mL.

No active treatment group had a clinically significant difference from the placebo group in mean change from baseline in the Global Assessment Score (GAS) of the Chronic Bronchitis Symptom Questionnaire (CBSQ). FP 500 and FP 250 did not have a clinically significant difference from the placebo group in the mean Transition Dyspnea Index (TDI) score. In FLTA3025 there were slightly fewer COPD exacerbations in FP 500 and FP 250 groups than in placebo, with a dose-response effect noted. Otherwise, the incidence of COPD exacerbations in the three pivotal studies was fairly similar among treatment groups. The incidence of moderate or severe COPD exacerbations in the three pivotal studies was similar among treatment groups. There were no significant differences between the FP and placebo groups for time to withdrawal from the study, time to withdrawal due to COPD exacerbation, and time to withdrawal due to COPD-related condition. Small changes from baseline in AM PEFR, daily Ventolin use, and number of awakenings per night requiring Ventolin use were noted for FP 250 and FP 500 groups.

The Chronic Respiratory Disease Questionnaire (CRDQ) was used to compare changes in the COPD-related quality of life for treatment groups. No active treatment group had a clinically significant difference from the placebo group in mean change from baseline in the Overall score of the CRDQ.

Subgroup analysis by smoking status showed that former smokers had larger mean changes from baseline in FEV_1 at endpoint for all active study treatments than did current smokers. Subgroup analysis for the non-reversible and reversible groups showed that the non-reversible group had smaller mean changes from baseline in FEV_1 at endpoint for all active study treatments than did the reversible group.

These studies do not appear to sufficiently support the efficacy of FP 500 or FP 250 in the treatment of COPD. The main issues included the patient population studied, inconsistent findings in the three pivotal studies with the primary endpoint, the absence of strong support from the secondary endpoints, and the failure of the studies to fully support the clinical relevance of the primary endpoint, particularly with regard to the quality of life (QOL) instrument and COPD exacerbation.

With regard to the patient population, the sponsor has not adequately studied the efficacy of FP in non-Caucasian patients with COPD. Additional study of the efficacy of FP in a more racially diverse study population is indicated. There are serious questions about whether the patient population studied, of which 51% to 59% were highly reversible, is

representative of the US COPD population as a whole, for which a broad indication is sought. Although statistical significance was shown for FP 500, the effect size was relatively modest, particularly for FLTA3025, where 24 weeks of treatment resulted in a net improvement in FEV_1 of only 50 mL. It should be noted that this result was also heavily driven by the "reversible" subgroup and by subjects who had stopped smoking. These studies do not appear to sufficiently support the efficacy of FP 250 in the population studied, as a statistically significant difference from placebo was not noted in replicate studies. In general, most of the secondary efficacy variables did not support the efficacy of FP 500 or FP 250. Secondary efficacy variables that would be expected to be correlated to the primary endpoint, such as PEFR, showed modest treatment effects and therefore do not add substantially to the argument in favor of efficacy for this product.

The quality of life (QOL) instrument, the CRDQ, does not appear to support the efficacy of FP 500 or FP 250. This is particularly concerning because all three of the pivotal studies had evaluation of QOL as one of their primary objectives. This was included because relatively short-term (6 months) changes in FEV_1 have uncertain clinical significance and do not have the same correlation with mortality that long-term (3 year) changes would have. The small effect size in FEV_1 combined with the observation that the patients experienced no detectable benefit vs. placebo in a well-validated QOL instrument argues strongly against a conclusion of efficacy for FP for the COPD indication.

2.3. Safety

Safety data from the three pivotal studies in this application were integrated in support of this application. Adverse events (AEs) were fairly common in these studies. A dose response effect was noted when comparing all AEs for placebo (69%) with FP 250 (74%) and FP 500 (80%). AEs occurring at a frequency ≥3% and more frequently with FP 250, FP 500, SAL 50/FP 250, or SAL 50/FP 500 than with placebo included upper respiratory tract infection, headaches, musculoskeletal pain, throat irritation, viral respiratory infections, URI, candidiasis of the mouth or throat, nasal congestion/blockage, cough, sinusitis, nausea and vomiting, hoarseness/dysphonia, fever, malaise and fatigue, muscle cramps and spasms, rhinitis, dizziness, hypertension, sinusitis/sinus infection, and muscle pain.

When comparing placebo with FP 250 and FP 500, a dose response effect was noted for URTI, headaches, viral respiratory infections, URTI, candidiasis of the mouth or throat, nasal congestion/blockage, and muscle pain. Many of the AEs noted are also noted in the labels for Flovent MDI and Flovent Rotadisk. AEs reported in these studies that are not noted in current labeling for other Flovent products include musculoskeletal pain, nausea and vomiting, airway irritation (throat irritation, cough, rhinitis), dizziness, malaise and fatigue. Differences could be attributed to differences in patient population or in the magnitude of the dose of FP, which was high for COPD (500 mcg to 1000 mcg per day) when compared to the asthmatic population (100 mcg to up to 500 mcg per day for moderate persistent asthma; 500 mcg to 1000 mcg per day for the oral corticosteroid sparing indication).

AEs associated with use of inhaled and systemic corticosteroids were noted in these studies. Candidiasis, throat irritation, and hoarseness/dysphonia were more common in FP 250, FP 500, SAL 50/FP 250, and SAL 50/FP 500 than in placebo. A dose response effect for candidiasis was seen when comparing placebo (1%) with FP 250 (7%) and FP 500 (13%). There were a small number of AEs for fractures, cataracts, hyperglycemia, diabetes mellitus, and impaired glucose tolerance, and the frequencies of these AEs were similar among treatment groups. There was a higher frequency of pneumonia for FP 250 (1%), FP 500 (2%), and SAL 50/FP 500 (1%) than for placebo (<1%). There were four deaths in placebo-treated patients in these studies. There were no deaths in patients that received active treatment. There was a higher frequency of SAEs due to COPD for FP 250 and FP 500, and a suggestion of an association with SAEs due to pneumonia with FP treatment. Withdrawals due to any AE were more common in FP 500 and SAL 50/FP 500 than in placebo. Withdrawals due to AEs for COPD were more common in FP 500 and FP 250 than in placebo; dose response effect was noted. Withdrawals due to pneumonia were more common in FP 500, FP 250, and SAL 50/FP 500 than for placebo. Withdrawals due to candidiasis mouth/throat only occurred in FP 500-treated patients.

Plasma cortisol levels were studied in FLTA3025. FP treatment groups had lower mean cortisol AUC_{12} and mean C_{min} than the placebo group, with a dose response effect noted. Mean cortisol AUC_{12} was 21% lower than placebo for FP 500 and 10% lower than placebo for FP 250, indicating dose-related systemic absorption and systemic activity from Flovent Diskus. The plasma cortisol samples were taken at Week 4, early in the study. Cosyntropin stimulation testing was performed in SFCA3006 and SFCA3007 on a subset of patients (15% to 20%). The data for cosyntropin stimulation testing show no evidence of adrenal suppression, however, cosyntropin stimulation testing is intended as a means to diagnose adrenal insufficiency and is a relatively insensitive measure of adrenal suppression.

The sponsor also provided safety data from other studies to support this application. These data included blinded listings of deaths and SAEs from ongoing clinical studies, as well as safety information from completed clinical pharmacology and clinical studies. Blinded listings of deaths and SAEs from ongoing clinical studies provided no useful safety information. Many AEs and SAEs from the completed studies are similar to those that were noted in the three pivotal studies and those noted in current labeling of Flovent product formulations. However, both upper respiratory infections and lower respiratory infections, including pneumonia, were more frequent in FP-treated patients than in placebo. Patients treated with FP MDI 500 mcg BID over the 3-year course of FLIT78 (also known as ISOLDE) had a higher frequency of events associated with systemic effects of corticosteroids than patients treated with placebo. These events included gastrointestinal hemorrhage, diabetes mellitus, hyperglycemia, ocular pressure disorders, decreased cortisol, abnormal adrenal hormone levels, Cushing's syndrome/symptoms, hypofunction of the adrenal cortex, skin hemorrhage, acne and folliculitis, and muscle atrophy, weakness, and tiredness.

These supportive studies also included laboratory data that showed evidence of HPA-axis effects of inhaled FP. FLTA1003 was a open-label, single dose, 4-way crossover, PK/PD

study in normal subjects. Patients received 1000 mcg of FP in four different dosage strengths of the Diskus formulation. Compared to baseline, mean urinary cortisol excretion was decreased by 42% to 62% in all treatment groups in this study, and many individual patients had decreases in urinary cortisol excretion even after the first dose of study treatment.

The sponsor studied effects on bone mineral density in two controlled, long-term studies of FP in the treatment of asthma. These studies were FLTA3001 and FLTA3017. Lumbar spine bone mineral density measurements in FLTA3001 demonstrated no statistically different treatment effects at 24, 52, 76, and 104 weeks of double-blind treatment with placebo, FP MDI 88 mcg BID, or FP MDI 440 mcg BID. Lumbar spine bone mineral density measurements in FLTA3017 demonstrated no statistically different treatment effects at 24, 52, 76, and 104 weeks of double-blind treatment with placebo or FP 500 mcg BID with the Rotadisk formulation. The lumbar spine was the only area in these studies that underwent prospective quality assurance from the osteoporosis central laboratory. Results from the proximal femur had no prospective quality assurance. These studies were small (N=160 and N=64) and performed in a young population (18 to 40 years) of asthma patients who were primarily male. It is likely that these studies were underpowered to detect a difference in bone mineral density. In addition, the asthmatic population may have a different sensitivity to bone effects of corticosteroids, and have a far smaller risk of pathological fracture per decrement in bone mineral density than older COPD patients would have.

The sponsor does not appear to have established the safety of FP in the proposed population. The sponsor has not adequately studied the safety of FP in non-Caucasian patients with COPD. Additional study of the safety of FP in a more racially diverse study population is strongly suggested. Further study is also required to demonstrate the safety of this product in the COPD population, a population that would be at higher risk for systemic corticosteroid effects. The pivotal studies were likely to be of insufficient duration to detect differences between treatment groups for dose and duration-related events such as fractures, cataracts, ocular pressure disorders, and disorders of glucose metabolism. The pivotal studies were not designed to specifically look for cataracts or systemic bone effects and exclusion criteria specifically selected subjects with baseline bone or ocular problems. Safety data from the supportive studies raise concerns about a higher incidence of respiratory infections, pneumonia, HPA axis effects, among others, in FP-treated patients, and do not adequately address bone effects in the proposed population.

The sponsor has recently started a 3-year study of FP 500 mcg BID, SAL 50/FP 500 BID, SAL 50 BID, and placebo BID via the Diskus formulation in COPD patients (SCO30003). Bone density is to be evaluated over three years in a subpopulation of 600 patients. This study will also assess bone fractures and ocular events in the entire study population of 5000 patients. The long-term safety data that will be provided in this study will be critical in assessing the long-term risk/benefit analysis for this product in the proposed population.

2.4. Dosing

The FP Diskus 500 mcg is not an approved product, and the sponsor is not seeking approval of this product for this indication in this application. The sponsor's proposed starting dosage for COPD is 1 inhalation (250 mcg) twice daily. The proposed labeling allows for increasing the dose to 2 inhalations (500 mcg) twice daily to provide additional control for patients who do not respond adequately to the starting dose, although no data are provided to support this dose increase.

The sponsor has argued dose proportionality of the approved FP 250 mcg and proposed FP 500 mcg Diskus products in another study included in this submission, FLTA1003. Although still under review by OCPB, it appears that data from FLTA1003 indicate FP 250 X 2 puffs provides less active drug than FP 500 X 1 puff. However, in FLTA3025, a multiple dose, 4-week study, FP 250 Diskus appears to be more than dose proportional to the FP 500 Diskus. Since the latter trial is comprised of the population of interest, these results are more relevant to the proposed indication.

The primary efficacy endpoint data in the pivotal studies showed a statistically significant treatment effect for the FP 500 mcg BID when administered with the FP 500 Diskus. However, the effect was modest and was offset by the largely negative secondary efficacy endpoint data and by the lack of effect on health-related quality of life. Furthermore, most of the secondary efficacy variables and the health-related quality of life instrument did not support the efficacy of FP 500 mcg BID when administered with the FP 500 Diskus. The sponsor has not studied the efficacy or safety of FP 500 mcg BID when administered as 2 inhalations BID of the FP 250 Diskus. The fact that the FP 250 mcg Diskus may be more than dose proportional to the FP 500 mcg Diskus does raise additional safety concerns. The pivotal studies do not appear to support the efficacy of FP 250 BID when administered with the to-be-marketed FP 250 mcg Diskus product, as a statistically significant difference from placebo was not noted in replicate studies.

Examination of safety data for the pivotal studies reveals a dose response effect for FP 500 mcg BID and FP 250 mcg BID for upper respiratory tract infections (URTI), headaches, viral respiratory infections, candidiasis of the mouth or throat, nasal congestion/blockage, and muscle pain.

2.5. Special populations

The under-representation of non-Caucasian patients in this study is a serious deficiency of these studies. The sponsor has not adequately studied the efficacy or safety of FP in non-Caucasian patients with COPD. Additional study of the safety of FP in a more racially diverse study population is indicated. Efficacy and safety data from future studies should be examined to determine if the increases in COPD exacerbations in women and patients ≥ 65 years represent true safety signals.

The sponsor provided subgroup analyses of efficacy by gender, race, and age. Males had greater absolute mean changes from baseline in FEV_1 at endpoint than women for all active treatment groups. Mean percent change from baseline in FEV_1 at endpoint was similar for men and women, however, indicating the larger absolute mean change in men

was due to larger lung volumes. Women in the FP 500 and FP 250 groups had more slightly more moderate or severe COPD exacerbations than men, when compared with data for the placebo group. There was no consistent association of gender with AEs for any of the treatment groups. There was no association of gender for the four deaths in the pivotal studies.

Incidences of COPD exacerbations in the FP 500 and FP 250 groups relative to placebo were higher for patients ≥65 years than those <65 years. Incidences of COPD exacerbations in the FP 500 group relative to placebo were higher for patients ≥65 years than those <65 years. Pneumonia and withdrawals due to pneumonia appeared to be more common in patients ≤65 years of age who were treated with FP 500.

As noted in each of the individual study reviews in this document, the vast majority of patients in this study were of Caucasian race. The small number of Non-Caucasian patients makes it difficult to draw firm conclusions. The overall frequency of AEs differed by race. The overall frequency of AEs in Caucasian patients ranged from 69% (223/321) to 81% (298/367). The overall frequency of AEs in Black patients ranged from 47% (8/17) to 72% (13/18). The overall frequency of AEs in patients of Asian or Other race ranged from 33% (1/3) to 43% (3/7). The difference in frequencies between the races is likely to be a result of the small sample size of patients of Black and Asian/Other races. The small number of non-Caucasian patients did not allow for an analysis of SAEs, withdrawals due to AEs, laboratory results, or ECG results by race.

No patients were studied in the pediatric age group, and therefore there is no analysis of this subgroup. The sponsor has requested a waiver of pediatric studies in children 0-16 years of age. The sponsor's justification for this request for waiver is that COPD, as defined by the American Thoracic Society, does not occur in this age group [pediatricwaiverrequest.pdf, page 1].

There were no pregnancies reported in the conduct of the pivotal studies, and therefore there is no analysis of this subgroup.

CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

1.1. Introduction

This is an NDA supplement for a chronic obstructive pulmonary disease (COPD) indication for Flovent® Diskus®. The sponsor is GlaxoSmithKline. The proposed indication is the long-term maintenance treatment of COPD. The proposed starting dose for adults is one inhalation (250 mcg) twice daily. The proposed labeling allows for increasing the dose to 2 inhalations (500 mcg) twice daily to provide additional control for patients who do not respond adequately to the starting dose. The clinical program was also designed to pursue COPD indications for Serevent Diskus (salmeterol xinafoate 50 mcg) and Advair Diskus (salmeterol xinafoate 50 mcg/fluticasone propionate 250 mcg and salmeterol xinafoate 50 mcg/fluticasone propionate 500 mcg). Submissions similar to the Flovent Diskus NDA supplement have been simultaneously submitted to the Serevent Diskus NDA (NDA 20-692) and to the Advair Diskus NDA (NDA 21-077).

COPD is a disease in which airflow obstruction results from chronic bronchitis and/or emphysema. Symptoms include cough, increased sputum production, and dyspnea. The disease is characterized by intermittent acute exacerbations of these symptoms, and by an increase in the rate of the natural decline in pulmonary function that occurs with age. COPD is most commonly related to cigarette smoking.

Bronchodilators, both beta agonists and anticholinergics, are important medications approved for use in treatment of symptoms of COPD. Inhaled corticosteroids are widely used off-label in the treatment of COPD. Although inhaled corticosteroids have been clearly demonstrated as safe and effective in the treatment of asthma, and represent the mainstay of controller treatment in asthma, their role in COPD treatment is not clear. Systemic corticosteroids have been demonstrated as effective in the acute treatment of COPD exacerbations. However, varying degrees of benefit in the treatment of COPD, from some effect to no effect, have been noted in the literature.

The sponsor notes that corticosteroids attenuate chemotaxis and recruitment of neutrophils, which are important effector cells in COPD. Accordingly, the sponsor believes that the presence of airway inflammation serves as the primary scientific rationale for the proposed use of fluticasone propionate in the treatment of COPD [summary.pdf, page 4].

The sponsor also believes there is a role for salmeterol and the combination of salmeterol and fluticasone propionate in the maintenance treatment of COPD, and as noted above, has submitted efficacy supplements to these NDAs as well [summary.pdf, pages 4-5].

1.2. Foreign Marketing and Regulatory History

Fluticasone propionate has been approved for the treatment of COPD in the following countries [summary.pdf, page 10]:

Argentina
Austria
Belgium
Colombia
Czech Republic
Germany
Iceland
Ireland
Israel
Latvia
Lithuania
Luxembourg
Netherlands
Peru
Russia
Spain

Applications for fluticasone propionate are pending for the treatment of COPD in the following countries [summary.pdf, pages 11-12]:

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Applications for fluticasone propionate for the treatment of COPD have been withdrawn by the sponsor or rejected by regulatory authorities in the following countries [summary.pdf, pages 12-13]:

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Fluticasone propionate is approved in the form of a dry powder inhaler as Flovent® Rotadisk (50 mcg, 100 mcg, 250 mcg) NDA 20-549, November 7, 1997, and as Flovent®

Diskus®, (50 mcg, 100 mcg, 250 mcg) NDA 20-833, September 29, 2000. It should be noted that the Flovent Diskus 500 mcg product, which was used in pivotal clinical studies FLTA3025 and SFCA3006 in this application, is not approved in the US. The dry powder inhaler products are approved for use in adults and children ages 4 years and older for the maintenance treatment of asthma as prophylactic therapy. Fluticasone propionate inhalation aerosol (Flovent® NDA 20-548) was approved March 27, 1996 in three dosage strengths (44 mcg, 110 mcg, and 220 mcg) for the maintenance treatment of asthma as prophylactic therapy.

2. CLINICALLY RELEVANT FINDINGS FROM CHEMISTRY, TOXICOLOGY, MICROBIOLOGY, BIOPHARMACEUTICS, STATISTICS, AND/OR OTHER CONSULTANT REVIEWS

Chemistry, manufacture and controls information for this application was cross-referenced to NDA 20-833 for Flovent Diskus 50, 100, and 250 mcg per blister drug product. NDA 20-833 was previously approved for use in inhalation drug products on September 29, 2000. Flovent Diskus Inhalation Powder is formulated to contain either 50, 100, or 250 mcg of fluticasone propionate (micronized) per blister made up to 12.5 mg with lactose monohydrate [cmc\dpcrossreference.pdf, page 1].

The active component of Flovent Diskus 250 mcg is fluticasone propionate, a corticosteroid having the chemical name S-(fluoromethyl)6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate. Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6, and the empirical formula is $C_{25}H_{31}F_3O_5S$. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol. Flovent Diskus 250 mcg is a specially designed plastic device containing a double-foil blister strip of a powder formulation of fluticasone propionate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 250 mcg of microfine fluticasone propionate in 12.5 mg of formulation containing lactose. 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 [labeling/current.pdf, page 1].

The formulation is contained in a sealed double foil blister strip, which in turn is contained within the Diskus device. Flovent Diskus is supplied as a disposable two-tone, orange-colored device and is packaged within an orange-colored plastic-coated foil pouch. Flovent Diskus is also supplied in a sample and institutional size as a two-tone, orange-colored disposable Diskus inhalation device containing 28 blisters. Flovent Diskus is manufactured at Glaxo Wellcome Operations, Ware, United Kingdom. This manufacturing site was previously inspected and received satisfactory GMP status in conjunction with NDA 21-077 for Advair Diskus on February 8, 2000 [cmc\dpcrossreference.pdf, page 1].

The sponsor included a statement of categorical exclusion for the environmental assessment because they estimate that the concentration of the drug substance active

moiety will not be one part per billion or greater at the point of entry into the aquatic environment [cmc\environ.pdf, page 1].

The batch numbers of medication that were used in the pivotal studies in this application are displayed in Table 2.1. The sponsor states that the formulations of Flovent used in this study were representative of the commercial product in terms of input materials, scale of manufacture, manufacturing equipment, and manufacturing process. The only differences between the batches of Flovent that were supplied for this study and the commercial product were the device coloration and the overwrap. All batches of Ventolin nebules and Ventolin MDI used in this study were the approved commercial product. The placebo used in this study was identical to the active product used in this study except for the absence of active drug [NDA 20-833, SE1-004, 9/17/01, page 3; NDA 20-833, SE1-004, 12/5/01, page 1].

Table 2.1. Batch numbers of study medication, pivotal clinical studies, NDA 20-833 S004 [clinstat\copd\flta3025.pdf, page 44; clinstat\copd\scfa3006.pdf, page 56; clinstat\copd\scfa3007.pdf, page 47].

FLTA3025	
Product	**Batch numbers**
Placebo Diskus	WP1WF9 WP25L4
FP Diskus 250 mcg	U98/028A
FP Diskus 500 mcg	U98/024C
Ventolin MDI, 90 mcg/puff	8ZP0692 8ZP0909 8ZP1741 8ZP1924 8ZP1924 9ZP0124
Ventolin nebules, 0.098%, 2.5 mg/3 mL	970963 980904 980905 980911 980901
SCFA3006	
Product	**Batch numbers**
Placebo Diskus	WP25L4 WP31R9 WP2GHW
FP Diskus 500 mcg	U98/024C
SAL Diskus 50 mcg	WP2D8B WP2NLT WP2T35
SAL Diskus 50 mcg/FP Diskus 500 mcg	U97/061C WP2NPB B003371
Ventolin MDI, 90 mcg/puff	8ZP0909 9ZP0259
Ventolin nebules, 0.098%, 2.5 mg/3 mL	980905 990903 980901
Cortrosyn 0.25 mg injection	2240697731 2300199731 2310299731

SFCA3007	
Product	**Batch numbers**
Placebo Diskus	WP25L4 WP31R9 WP2GHW
FP Diskus 250 mcg	U98/028A B006597
SAL Diskus 50 mcg	WP2D8B WP2NLT WP2T35 B003516
SAL Diskus 50 mcg/FP Diskus 250 mcg	U97/060C WP2PY5 E99B157 E99B158
Ventolin MDI, 90 mcg/puff	7ZP0053 7ZP0727 8ZP0909 9ZP1288 0ZP0164
Ventolin nebules, 0.098%, 2.5 mg/3 mL	980905 990903
Cortrosyn 0.25 mg injection	2240697731 2300199731 2310299731

There was no nonclinical pharmacology and toxicology data submitted with this application. FP is currently approved at doses up to 1000 mcg BID for the maintenance treatment of asthma as prophylactic therapy, the latter dose (1000 mcg BID) for the oral corticosteroid-sparing indication only.

Clinically relevant findings from Dr. Suarez's Clinical Pharmacology and Biopharmaceutics review are discussed in the following section "Human Pharmacokinetics and Pharmacodynamics."

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

A brief review of pertinent human pharmacokinetics and pharmacodynamic data for FP follows.

3.1. Previously established data

The pharmacokinetics of FP has been well established in previous NDAs. A brief summary of these data follows. Systemic exposure of inhaled FP compared to intravenous administration from the individual Rotadisk, Diskus, and CFC-MDI devices is approximately 14%, 18%, and 30%, respectively. Systemic exposure from the Diskus inhaler is about half that seen with the CFC-MDI. These data are derived primarily from studies of normal volunteers and do not necessarily reflect the systemic availability or relative delivery of each of the three devices in the COPD population. Peak plasma concentrations occur within one hour, regardless of device. Incomplete absorption and high first pass hepatic metabolism result in oral bioavailability of less than 1%. The terminal elimination half-life after intravenous or inhaled administration is 6 to 8 hours. Plasma protein binding is 91%. Metabolism of FP to an inactive carboxylic acid metabolite occurs by the cytochrome P450 isoenzyme, CYP3A4. The major route of elimination is the feces. The renal excretion of FP is negligible (<0.02% of the dose) with less than 5% of a radiolabeled dose excreted in the urine as metabolites. FP does not

affect the metabolism of other drugs metabolized by the CYP3A4 enzyme system. Drugs that act as a substrate for (terfenadine) or as a moderate inhibitor (erythromycin) of the CYP3A4 system do not significantly alter the systemic exposure of FP. Ketoconazole increased the systemic exposure of FP and a similar potential exists for other strong inhibitors of the CYP3A4 enzyme system such as ritonavir. Systemic exposure and cortisol suppression following inhalation in asthma subjects is approximately half the exposure observed in healthy subjects. This is likely due to airflow obstruction. The accumulation factor following multiple dosing in asthma subjects is 1.7 and 1.5 in healthy subjects [hpbio\biosum.pdf, pages 13-14].

3.2. Pharmacokinetic and pharmacodynamic data in this application

The sponsor supported this application with PK and PD data from three studies. The PK and PD of FP in patients with COPD were examined in FLTA3025 and FMS40243. The systemic exposure to FP from the FP Diskus inhaler in the 50 mcg, 100 mcg, 250 mcg, and 500 mcg strengths in healthy subjects was examined in FLTA1003. The results of these studies are briefly summarized in the sections below.

3.2.1. FLTA3025

FLTA3025 was a randomized, double-blind, parallel group, placebo-controlled, comparative trial of inhaled FP 250 mcg BID and FP 500 mcg BID via the Diskus in patients with COPD. A subset of 86 patients was included in the PK/PD component of this study. Patients had blood samples taken for measurements of plasma FP and serum cortisol after 4 weeks of study treatment.

Key pharmacokinetic results are summarized in Table 3.1. FP AUC_{last} and FP C_{max} were higher for FP 500 than FP 250 and data suggest that 2 inhalations of FP 250 Diskus might be more than dose proportional than one inhalation of FP 500 Diskus.

Mean FP AUC_{last} was somewhat lower in current smokers than in former smokers. In addition, a linear relationship was observed between weight and FP AUC_{last} for FP 500, with lower FP levels for heavier patients. This association was not noted with FP 250 [clinstat\copd\flta3025.pdf, pages 166, 4857, 4881].

Table 3.1. Key pharmacokinetic results, FLTA 3025 [clinstat\copd\flta3025.pdf, page 166; hpbio\hpsum.pdf, page 17].

PK parameter	FP 250 N = 31	FP 500 N = 27
Mean AUC_{last}, pg.hr/mL	310.6	539.0
Ratio FP 500/FP 250		1.74
Mean C_{max}, pg/ml	52.9	83.6
Ratio FP 500/FP 250		1.58
T_{max}, h	1.08	1.00
Ratio FP 500/FP 250		-1.01

Key pharmacodynamic results are displayed in Table 3.2. FP 250 and FP 500 treatment groups had lower mean cortisol AUC_{12} and mean C_{min} than the placebo group (10% and 21%, respectively, for serum cortisol AUC). There was a dose-response effect noted with the lowest cortisol AUC_{12} and C_{min} in FP 500 patients [clinstat\copd\flta3025.pdf, pages

166, 4855]. Higher mean cortisol AUC_{12} levels were noted for current smokers than for former smokers, consistent with the lower serum FP levels measured in current smoking. There was no relationship noted between cortisol levels and weight [clinstat\copd\flta3025.pdf, page 4857]. These PK/PD data demonstrate measurable systemic effects of inhaled FP.

Table 3.2. Serum cortisol results, FLTA3025 [clinstat\copd\flta3025.pdf, pages 166, 4855].

Cortisol parameter	Placebo N = 28	FP 250 N = 31	FP 500 N = 27
Mean Cortisol AUC_{12}, pmol.hr/mL	2673.4	2404.2	2102.3
Δ vs. placebo	-	- 10.1%	- 21.4%
Mean C_{min}, pmol/mL	123.1	116.7	85.3

3.2.2. FMS40243

This study was a comparison of the PK and PD of inhaled FP in healthy volunteers and patients with COPD. It was a randomized, double-blind, double dummy, 2-way crossover study that was performed in 23 subjects. Subjects were randomized to inhaled FP 500 mcg BID from a HFA-MDI with a Volumatic spacer device for 7 days, followed by a single inhaled dose of 1000 mcg FP and a placebo infusion, or inhaled beclomethasone dipropionate 1000 mcg BID from a CFC-MDI with a spacer for 7 days, followed by a single dose of inhaled placebo and FP 1000 mcg intravenous infusion. Serial plasma FP and pre-and post-dose plasma cortisol concentrations were measured, and urinary cortisol excretion was calculated. Systemic exposure from inhaled FP in COPD patients was approximately 35% (AUC_{inf}) and 44% (C_{max}) less than that observed in healthy patients, but there was a large degree of variation among subjects. Mean post-dose serum cortisol levels were 83% lower in healthy subjects than in COPD patients [hpbio\biosum.pdf, pages 22-24]. Although these data give some suggestion of decreased systemic exposure to FP in COPD patients, they were performed with the CFC-MDI formulation and were delivered with a spacer device, and provide little relevant information applicable to the Diskus formulation in this application.

3.2.3. FLTA1003

This study was a single center, open label, randomized, 4-way crossover study performed in 22 healthy male and female subjects. Subjects were randomized to receive a single 1000 mcg FP dose from the four Diskus strengths (20 inhalations of FP Diskus 50 mcg, 10 inhalations of FP Diskus 100 mcg, 4 inhalations of FP Diskus 250 mcg, 2 inhalations of FP Diskus 500 mcg). Serial plasma FP concentrations were measured pre-dose and for 24 hours post-dose. Twenty-four hour urinary cortisol excretion was measured before and after dosing. The sponsor reported a proportional increase in systemic exposure was seen with increasing strength when the data were expressed as systemic exposure per inhalation. However, pairwise comparisons of mean ratio of AUC_{last} for 1000 mcg of FP via the FP 250 Diskus and the FP 500 Diskus was 0.87, indicating the FP 250 device was less than dose proportional to the FP 500 device in this single dose study in a population of healthy subjects. This is in contrast to the data in FLTA3025, which suggests that the FP 250 device was more than dose proportional to the FP 500 device. FLTA3025 was

multidose, 4-week study in patients with COPD, in contrast to FLTA1003, which was a single dose, 4-way crossover study in healthy subjects. These differences may be the reason for the discordance between these data. Of the two studies, FLTA3025 would be a closer approximation to the use, indication, and population proposed in this application.

Significant decreases in post-treatment urinary cortisol levels were noted across all treatment groups (. These data are displayed in Table 3.3. These data show strong evidence of systemic HPA-axis effects in normal subjects when given 1000 mcg FP by Diskus. Decreases in cortisol excretion were noted in many subjects as soon as after the first dose of study treatment.

Table 3.3. Urinary cortisol excretion data, FLTA1003 [hpbio\bio\flta1003.pdf, page 67].

Treatment group	Mean urinary cortisol excretion, pre-dose, mcg	Mean urinary cortisol excretion, post-dose, mcg	Difference, Post-dose minus pre-dose
50 mcg X 20 inhalations	18.5	9.6	8.9
100 mcg X 10 inhalations	22.3	13.8	8.5
250 mcg X 4 inhalations	19.1	12.4	6.7
500 mcg X 2 inhalations	18.0	7.3	10.7

3.3. Comments from Clinical Pharmacology and Biopharmaceutics review

The following comments are provided by Dr. Sandra Suarez's Clinical Pharmacology and Biopharmaceutics review.

1. No dose-proportional increase in AUC_t and C_{max} per inhalation was observed with increasing strengths of FP delivered from the Flovent Diskus. Study FLTA1003 showed that the same dose of FP (1000 mcg) delivered from the 250 mcg and 500 mcg strengths, produce significantly higher cortisol suppression when delivered from the 500 mcg strength compared to the one obtained when delivered from the 250 mcg strength. In addition, study FLTA3025 showed that ninety percent (90%) CI for the dose normalized log-transformed C_{max} and AUC_t values of FP following multiple administration of the treatments were out of the BE guidelines. In this case, the 250 mcg strength produced significantly higher C_{max} and AUC values than the 500 mcg strength. Therefore, strengths might not be interchanged with another, especially the 250 mcg and 1000 mcg strengths.

2. Higher FP systemic exposure and lower cortisol AUC_{12} was observed in former smokers. According to the sponsor, no significant differences in FP systemic exposure or cortisol changes were observed between current and former smokers. However, 95% CI range from 0.63 to 1.35. Also, higher FP systemic exposure was seen in poorly reversible subjects; although no significant differences in FP systemic exposure or cortisol changes were observed between poorly reversible subjects and those considered not poorly reversible, 95% CI ranged from 0.73 to 1.54. The medical reviewer should evaluate the clinical relevance of these findings.

3. No relationship was observed between FP systemic exposure and gender, race, elderly subjects (≥65 years), age, and pulmonary function. A relationship between

FP systemic exposure and weight was observed after FP 500 that was not observed after FP 250 or between cortisol AUC_{12} and weight. However, if the sponsor chooses to claim in the label a lack of gender and age effect on the pharmacokinetics of FP delivered from the Diskus, it is necessary to carry out a more complex analysis of the data (including 90% CI of the relevant PK parameters). The sponsor is encouraged to pool all the FP pharmacokinetic data generated in this submission and other submissions before making a statement of lack of gender and age effect on the PK of FP. This analysis should be conducted taking into account the weight of the subjects.

4. The sponsor used the FP HFA MDI with spacer to compare the PK and PD of inhaled FP in healthy subjects and subjects with COPD in study FMS40243. No study has been conducted to link the Flovent Diskus and the FP-HFA MDI with spacer. Therefore the relevance of the findings from this study to this NDA is questionable. If the sponsor wants to market the FP-HFA MDI device with spacer for the treatment of COPD, it might be necessary to conduct a complete clinical/safety and PK program.

Medical reviewer comment:
The trend to higher FP systemic exposure and lower cortisol AUC12 in former smokers and the trend to higher FP systemic exposure in the poorly-reversible population may indicate that these populations are at higher risk for systemic effects. These associations do not appear to be strong, and are not likely to have a large degree clinical relevance. Furthermore, the findings in the poorly reversible population are not relevant to approval of the product in the US. The sponsor performed a subgroup analysis of this population to support European applications. The definition of this population was based on the ERS definition of reversibility. Patients were considered to be "poorly-reversible" of they had an increase in percent predicted FEV_1 of less than 10% after albuterol at the screening visit.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

This submission refers to three pivotal clinical studies, Studies FLTA3025, SFCA3006, and SFCA3007. These studies are submitted in support of the efficacy of FP in the treatment of COPD. The pivotal studies were randomized, double-blind, parallel group, placebo-controlled, multicenter studies. Each of the pivotal studies had a 24-week treatment duration. Study FLTA3025 evaluated the efficacy of FP 250 and FP 500 compared with placebo. SAL 50/FP 500 and FP 500 were compared with each other and with placebo in SFCA3006. SAL 50/FP 250 and FP 250 were compared with each other and with placebo in SFCA3007. All three studies were similar in design, subject entrance criteria, and overall conduct to provide replication of treatment arms across studies [summary.pdf, page 1]. Replication of treatment arms is displayed in Table 4.1. The pivotal studies for this submission are summarized in Table 4.2.

Table 4.1. Treatment arms, pivotal clinical studies, NDA 20-833 [summary.pdf, page 2]

Study	Placebo, N	SAL 50, N	FP 250, N	FP 500, N	SAL50/ FP 250, N	SAL 50/ FP 500, N	Total, N
FLTA3025	206	0	216	218	0	0	640
SFCA3006	181	160	0	168	0	165	674
SFCA3007	185	177	183	0	178	0	723
Total, N	570	337	399	386	178	165	3037

The sponsor provided the following data in support of the safety of FP in the treatment of COPD:

- Safety data from the pivotal studies
  - FLTA3025
  - SFCA3006
  - SFCA3007
- Supportive safety data from other studies
  - AEs and HPA-axis data from clinical pharmacology study FLTA1003
  - Blinded listings of deaths and SAEs from ongoing clinical studies SFCB3024, SCO30003
  - Studies of Flovent MDI 500 mcg BID, FLIP63, FLIT78, FLIT97, FLIT98
  - Bone mineral density data from two long-term studies in asthma, FLTA3001 and FLTA3017
  - Blinded listings of deaths and SAEs from nine ongoing non-US studies used to support regional markets (SCO30001, SCO40002, SMS40026, SMS40130, SMS40308, SAM30001, FCO40003, FCO30002, and FCO40004)

A safety update, including postmarketing reports and a literature review, is reviewed in Dr. Gilbert-McClain's Medical Officer Review of the application for the COPD indication for the Advair product, NDA 21-077, S003.

Table 4.2. Summary of pivotal studies, NDA 20-833, S0004 [summary.pdf, page 20].

Study Number	Study Type	Treatment Groups	Duration of treatment	Design	Number of subjects	Diagnosis	Materials submitted in this application
FLTA3025	Pivotal Efficacy and Safety	FP 250 mcg BID FP 500 mcg BID Placebo BID	24 weeks	Multicenter, randomized, double-blind, placebo-controlled, parallel group	640	Physician-diagnosed COPD, smoking history, men and women	Protocol Study report Line listings Appropriate CRFs
SFCA3006	Pivotal Efficacy and Safety	SAL 50 mcg BID FP 500 mcg BID SAL 50/FP 500 mcg BID Placebo BID	24 weeks	Multicenter, randomized, double-blind, placebo-controlled, parallel group	691	Physician-diagnosed COPD, smoking history, men and women	Protocol Study report Line listings Appropriate CRFs
SCFA3007	Pivotal Efficacy and Safety	SAL 50 mcg BID FP 250 mcg BID SAL 50/FP 250 mcg BID Placebo BID	24 weeks	Multicenter, randomized, double-blind, placebo-controlled, parallel group	723	Physician-diagnosed COPD, smoking history, men and women	Protocol Study report Line listings Appropriate CRFs

5. CLINICAL REVIEW METHODS

A summary of review methods follows, and includes a description of the conduct of the review and an assessment of data quality.

5.1. Conduct of the review

This submission refers to three pivotal clinical studies, Studies FLTA3025, SFCA3006, and SFCA3007. These studies are submitted in support of the efficacy of FP in the treatment of COPD. All three studies were similar in design, subject entrance criteria, and overall conduct to provide replication of treatment arms across studies. The pivotal studies were reviewed in depth individually. The sponsor presented individual study results and integrated the results for the studies in the Integrated Summary of Efficacy. The integrated analysis was not examined for this reviewer's Integrated Review of Efficacy, as integrating the results obscured the differences in effect for the FP 250 and FP 500 groups between the studies.

Safety data was reviewed for the individual pivotal studies in depth. Safety data from the pivotal studies and supportive safety data from other studies were reviewed to provide this reviewer's Integrated Review of Safety. These supportive safety data included the following:

- AEs and HPA-axis data from clinical pharmacology study FLTA1003
- Blinded listings of deaths and SAEs from ongoing clinical studies SFCB3024, SCO30003
- Studies of Flovent MDI 500 mcg BID, FLIP63, FLIT78, FLIT97, FLIT98
- Bone mineral density data from two long-term studies in asthma, FLTA3001 and FLTA3017
- Blinded listings of deaths and SAEs from nine ongoing non-US studies used to support regional markets (SCO30001, SCO40002, SMS40026, SMS40130, SMS40308, SAM30001, FCO40003, FCO30002, and FCO40004)

The sponsor provided a safety update, including postmarketing reports and a literature review, to support the safety of this application. These data are reviewed in Dr. Gilbert-McClain's Medical Officer Review of the application for the COPD indication for the Advair product, NDA 21-077, S003.

5.2. Data quality

The following sites were identified for inspection by the Division of Scientific Investigation (DSI):

1. UCLA (15557)
   10833 Le Conte Avenue Pulmonary Division, Suite 32/170
   Los Angeles, CA 90024

   Principal Investigator:
   Donald P. Tashkin (3854)

   Subinvestigators:
   [ ]
   [ ]
   [ ]
   [other\financialinformation.pdf, page 68]

This center enrolled the greatest number of patients in Study FLTA3025 [clinstat\copd\flta3025.pdf, page 289].

2. Scripps Clinical/Research Foundation (13564)
   10666N. Torrey Pines Road, Room W-207
   La Jolla, CA 92037

   Principal Investigator:
   Darlene Joan Elias (9058)

   Subinvestigators:
   [ ]
   [ ]
   [ ]
   [ ]
   [other\financialinformation.pdf, page 47]

This center enrolled the greatest number of patients in Study SFCA3007 [clinstat\copd\sfca3007.pdf, page 336].

A request for DSI consultation was submitted. The consultation request included selected values from the submission for comparison with the original data source. Representative data from the NDA were provided for the DSI team for comparison with the original data source. Data were verified at both sites. Data from both sites appear to be acceptable for use in the support of this application.

The sponsor excluded data from patients enrolled at the site of Investigator #[ ] from population and efficacy analyses of SFCA3006as a result of a quality assurance assessment. The sponsor indicates that there was reason to doubt the integrity of the data

from patients enrolled at this site. Data for these patients were included in the analyses of safety [clinstat\copd\sfca3006.pdf, page 92]. Investigator #[ ] was Dr. [ ], of [ ], who was at study Site #[ ] [clinstat\other\listofinvestigators.pdf, page 8]. Dr. [ ]enrolled [ ] patients in the study [clinstat\copd\sfca3006.pdf, page 2235].

The sponsor received a letter from Investigator #[ ] stating that the data generated from SFCA3006 might be unreliable. The sponsor performed an impact analysis to determine if the removal of the data submitted by this investigator would change interpretation of the data. The impact analysis showed that there would be no change in the interpretation of the data, and included data from this investigator in the study report [clinstat\copd\sfca3006.pdf, page 92]. Investigator #[ ] was Dr. [ ], who was at Site #[ ] [clinstat\other\listofinvestigators.pdf, page 9]. Dr. [ ] enrolled [ ] patients in the study [clinstat\copd\sfca3006.pdf, page 2263-2264].

This reviewer compared results for the primary efficacy endpoint from the impact analysis with the data including Investigator #[ ] in the analysis. There was essentially no difference in the change from baseline in FEV_1 at endpoint and at other times for treatment groups during the treatment period. There was no impact on the inferential statistical analysis for the primary efficacy parameter. Overall, the data in this application appear to be acceptable for review in this reviewer's opinion.

5.2.1. Ethical standards and financial disclosure

The following items were included in this submission:

- Debarment certification [other\debar.pdf]
- Financial disclosure statement [other\financialinformation.pdf]

The sponsor certified that they did not and would not use in any capacity the services of any person debarred under Section 306 of the Act in connection with the application. The sponsor states that they did not compensate clinical investigators in such a way that the total amount could vary with the outcome of the study, and therefore there were no disclosures in this category [other\financialinformation.pdf, page 2].

Based on available financial data the $25,000 threshold for payments of other sorts was exceeded in the case of one investigator, [ ] (Investigator #[ ]). The sponsor conducted no analysis on the results on study SFCA3006, since the results for the [ ] patients enrolled at the site represented less than 1% of patients randomized to treatment and do not have the potential to bias the results of the study [other\financialinformation.pdf, page 3].

The sponsor stated that no clinical investigator participating in the covered studies had a proprietary interest in the products studied [other\financialinformation.pdf, page 3].

Based on available financial data the $50,000 threshold for equity interest was exceeded in the case of two subinvestigators, [ ] (Investigator #[ ]) and [ ] (Investigator #[ ]). The sponsor conducted no analysis on the results on study FLTA3025 since the results for the [ ] patients enrolled at Dr. [ ]'s site represented less

than 4% of patients randomized to treatment and do not have the potential to bias the results of the study. The sponsor conducted no analysis on the results on study FLTA3025 since the results for the [ ] patients enrolled at Dr. [ ]'s site represented less than 1% of patients randomized to treatment and do not have the potential to bias the results of the study [other\financialinformation.pdf, page 3].

The sponsor provided a statement of Good Clinical Practices for each of the pivotal clinical studies [clinstat\copd\flta3025.pdf, page 1, clinstat\copd\sfca3006.pdf, page 1, clinstat\copd\sfca3007.pdf, page 1].

Overall, the data in this application appear to be acceptable for review in this reviewer's opinion.

6. INTEGRATED REVIEW OF EFFICACY

Review of efficacy data supporting this application follows.

6.1. Summary and conclusions

This application included three pivotal clinical studies—FLTA3025, SFCA3006, and SFCA3007. These studies were randomized, double-blind, placebo-controlled, parallel group, multicenter trials that had a similar design and were conducted in a similar manner. The studies were designed to evaluate the safety and efficacy of SAL, FP, and the SAL/FP combination administered BID via the Diskus over 24 weeks for the treatment of COPD.

The majority of patients in these studies were male. The mean patient age ranged from 61.9 to 65.2 years. A large majority of patients in these studies were of Caucasian race, 91% to 95%. Non-Caucasian patients were not well represented in these studies. Patients had fairly severe dyspnea, with approximately one-third of patients experiencing dyspnea with walking 100 yards or less on level ground. Inhaled corticosteroids were used by 18% to 31% of patients in these studies, a fairly large minority. The percentage of patients who were former smokers ranged from 46% to 57%. Median history of smoking ranged from 50.0 to 60.0 pack-years. The majority of patients in each of these studies were considered to have reversibility. A patient was considered "non-reversible" if, after 4 puffs of Ventolin MDI, there was a change in FEV_1 of <12% from baseline or there was <200 mL absolute increase in the FEV_1. Compliance was adequate. More than 70% of patients in each treatment group were reported as taking 90% or more of the prescribed doses of medication. The mean number of doses taken was approximately 93% in each treatment group.

The primary efficacy variable for the evaluation of FP in these studies was the pre-dose FEV_1. The primary analysis for FP was the comparison of the mean morning pre-dose FEV_1 between treatment groups at endpoint. Comparisons of FP 500 with placebo showed statistically significant differences in mean change from baseline in pre-dose FEV_1 in both FLTA3025 and SFCA3006, although the effect size observed in FLTA3025 was only 50 mL, half of the "clinically significant" 100 mL the sponsor had powered the study to detect. The effect size reported for SFCA3006 was 113 mL. Comparisons of FP 250 with placebo showed statistically significant differences in mean change from baseline in pre-dose FEV_1 only for SFCA3006, with an effect size of 108 mL, but not for FLTA3025, which had an effect size of only 27 mL.

No active treatment group had a clinically significant difference from the placebo group in mean change from baseline in the Global Assessment Score (GAS) of the Chronic Bronchitis Symptom Questionnaire (CBSQ). FP 500 and FP 250 did not have a clinically significant difference from the placebo group in the mean Transition Dyspnea Index (TDI) score. In FLTA3025 there were slightly fewer COPD exacerbations in FP 500 and FP 250 groups than in placebo, with a dose-response effect noted. Otherwise, the incidence of COPD exacerbations in the three pivotal studies was fairly similar among treatment groups. The incidence of moderate or severe COPD exacerbations in the three

pivotal studies was similar among treatment groups. There were no significant differences between the FP and placebo groups for time to withdrawal from the study, time to withdrawal due to COPD exacerbation, and time to withdrawal due to COPD-related condition. Small changes from baseline in AM PEFR, daily Ventolin use, and number of awakenings per night requiring Ventolin use were noted for FP 250 and FP 500 groups.

The Chronic Respiratory Disease Questionnaire (CRDQ) was used to compare changes in the COPD-related quality of life for treatment groups. No active treatment group had a clinically significant difference from the placebo group in mean change from baseline in the Overall score of the CRDQ.

Subgroup analysis by smoking status showed that former smokers had larger mean changes from baseline in FEV_1 at endpoint for all active study treatments than did current smokers. Subgroup analysis for the non-reversible and reversible groups showed that the non-reversible group had smaller mean changes from baseline in FEV_1 at endpoint for all active study treatments than did the reversible group. The small number of Non-Caucasian patients makes it difficult to draw firm conclusions on subgroup analysis by race. Subgroup analyses for gender and age suggest that COPD exacerbations are more common in FP-treated women and in patients greater than 65 years of age.

These studies do not support the efficacy of FP 500 or FP 250 in the treatment of COPD. The main issues include the patient population studied, inconsistent findings in the three pivotal studies with the primary endpoint, the absence of strong support from the secondary endpoints, and the failure of the studies to fully support the clinical relevance of the primary endpoint, particularly with regard to the QOL instrument and COPD exacerbation.

With regard to the patient population, the sponsor has not adequately studied the efficacy of FP in non-Caucasian patients with COPD. There are serious questions about whether the patient population studied, of which 51% to 59% were highly reversible, is representative of the US COPD population as a whole, for which a broad indication is sought. Demonstration of the efficacy of FP in a more racially diverse and more representative COPD study population would provide more convincing evidence.

With regard to inconsistent findings on the primary endpoint, these studies fail to support the efficacy of FP 250 because a statistically significant difference from placebo was not noted in replicate studies. Although statistical significance was shown for FP 500, the effect size was relatively modest, particularly for FLTA3025, where 24 weeks of treatment resulted in a net improvement in FEV_1 of only 50 mL. It should be noted that this result was also heavily driven by the “reversible” subgroup and by subjects who had stopped smoking.

In general, most of the secondary efficacy variables did not support the efficacy of FP 500 or FP 250. Secondary efficacy variables that would be expected to be correlated to

the primary endpoint, such as PEFR, showed modest treatment effects and therefore do not add substantially to the argument in favor of efficacy for this product.

The quality of life instrument (QOL), the CRDQ, does not support the efficacy of the FP 500 or FP 250. This is particularly concerning because all three of the pivotal studies had evaluation of QOL as one of their primary objectives. This was included because relatively short-term (6 months) changes in FEV_1 have uncertain clinical significance and do not have the same correlation with mortality that long-term (3 year) changes would have. The small effect size in FEV_1 combined with the observation that the patients experienced no detectable benefit vs. placebo in a well-validated QOL instrument argues strongly against a conclusion of efficacy for FP for the COPD indication.

6.2. Content

The following data were reviewed in preparation of this overview of efficacy:

- Efficacy data from the following pivotal studies
  - FLTA3025
  - SFCA3006
  - SFCA3007

A review of efficacy data from these three pivotal clinical studies follows below.

6.3. Description of pivotal studies

This application included three pivotal clinical studies, FLTA3025, SFCA3006, and SFCA3007. These studies were randomized, double-blind, placebo-controlled, parallel group, multicenter trials that had a similar design and were conducted in a similar manner. The studies were designed to evaluate the safety and efficacy of SAL, FP, and the SAL/FP combination administered BID via the Diskus over 24 weeks for the treatment of COPD. These studies are summarized in Table 7.1.2.1 [clinstat\ise\ise.pdf, pages 45-46].

Table 6.1. Summary of pivotal studies in this application, NDA 20-833, S004.

Study number	Study type	Treatment groups	Duration of treatment	Design	Number of patients	Diagnosis, age of subjects
FLTA3025	Efficacy and safety	FP 250 mcg Diskus BID FP 500 mcg Diskus BID Placebo Diskus BID	24 weeks	Randomized, double-blind, placebo controlled, parallel group	640	COPD, ≥40 years
SFCA3006	Efficacy and safety	SAL 50 mcg Diskus BID FP 500 mcg Diskus BID SAL 50 mcg/FP 500 mcg Diskus BID Placebo Diskus BID	24 weeks	Randomized, double-blind, placebo controlled, parallel group	674	COPD, ≥40 years
SFCA3007	Efficacy and safety	SAL 50 mcg Diskus BID FP 250 mcg Diskus BID SAL 50 mcg/FP 250 mcg Diskus BID Placebo BID	24 weeks	Randomized, double-blind, placebo controlled, parallel group	723	COPD, ≥40 years

6.3.1. Primary efficacy endpoint

The primary efficacy variable for the evaluation of FP in these studies was the pre-dose FEV_1 collected at Day 1, and Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24. The primary analysis for FP was the endpoint analysis comparing the mean morning pre-dose FEV_1 between treatment groups. The endpoint was defined in the protocol as the final evaluable measurement for the patient. For patients who discontinued from the study the endpoint was the last evaluable measurement taken prior to withdrawal. The FEV_1 at the Discontinuation Visit was not used for any efficacy analysis.

For SFCA3006 and SFCA3007, the 2-hour post dose FEV_1 collected at Day 1, and Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 was used to assess the efficacy of SAL 50 and the SAL 50/FP 250 or SAL 50/FP 500 combinations [clinstat\ise\ise.pdf, pages 48-49]. It is not relevant to the efficacy of FP alone or in the combination and therefore will not be discussed further in this document.

For the primary efficacy measure to evaluate FP in these studies, treatments were compared as follows [clinstat\ise\ise.pdf, pages 48-49].

- FP 250 or FP 500 to placebo: Pre-dose FEV_1, to evaluate the efficacy of the individual component
- SAL 50/FP 250 or SAL 50/FP 500 to SAL 50: Pre-dose FEV_1, to evaluate the contribution of FP 250 or FP 500 to the combination product

Treatment groups were compared using ANCOVA F-tests with baseline, treatment group, and investigator as covariates [clinstat\ise\ise.pdf, page 64].

6.3.2. Secondary efficacy endpoints

Secondary efficacy variables included change from baseline in the global and individual domains of the Chronic Bronchitis Symptoms Questionnaire (CBSQ), the Baseline/Transition Dyspnea Index (BDI/TDI) score at each of the treatment visits, number and percent of exacerbations of COPD, time to first COPD exacerbation, number of withdrawals and time to withdrawals. Morning PEFR, daily use of Ventolin, percentage of nights with no awakenings requiring Ventolin, frequency of nighttime awakenings requiring Ventolin, and percent of days without using Ventolin were also summarized [clinstat\ise\ise.pdf, pages 50-59].

Summary statistics were provided for all secondary endpoints. Changes from baseline in the Global Assessment Score (GAS) of the CBSQ were compared between treatment groups using an ANCOVA F-test with baseline, investigator, and treatment group as covariates. Overall and pairwise treatment comparisons of the BDI/TDI scores were performed by ANOVA F-test. Time to first COPD exacerbation, number of withdrawals, and time to withdrawals were analyzed using survival analysis. [clinstat\ise\ise.pdf, page 64-67].

The Chronic Respiratory Disease Questionnaire (CRDQ) was used to compare changes in the COPD-related quality of life for treatment groups, as measured by an overall score and for each of the four domains. An improvement of at least 10 in overall score was

considered to be an overall improvement in COPD specific quality of life. At each visit, treatment group comparisons were made comparing the change from baseline using ANOVA, controlling for baseline and investigator. A difference between treatment groups in mean change from baseline was considered clinically meaningful if the difference was statistically significant and had a minimum of ≥0.5 point improvement per question per item [clinstat\ise\ise.pdf, pages 68-70].

6.3.3. Disposition, demographics, and baseline characteristics

Patient disposition for the three pivotal studies in this application is outlined in Table 6.2. Discontinuations were fairly frequent, ranging from 27% to 40%. The percentage of discontinuations was fairly similar among treatment groups, with no consistent association of discontinuation with treatment group.

Table 6.2. Patient disposition, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, page 71]

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025	**N = 206**		**N = 216**	**N = 218**		
Completed, %	62		65	67		
Discontinued, %	38		35	33		
SFCA3006	**N = 181**	**N = 160**		**N = 168**		**N = 165**
Completed, %	62	72		60		68
Discontinued, %	38	28		40		32
SFCA3007	**N = 185**	**N = 177**	**N = 183**		**N = 178**	
Completed, %	68	68	73		70	
Discontinued, %	32	32	27		30	

Patient demographics and baseline characteristics for the pivotal studies in this application are summarized in Table 6.3. The majority of patients in these studies were male, and the percentage of male patients ranged from 58% to 72%. The mean patient age ranged from 61.9 to 65.2 years. A large majority of patients in these studies were of Caucasian race, 91% to 95%. With regard to symptoms, approximately one-third of patients experienced dyspnea with walking 100 yards or less on level ground. Inhaled corticosteroids were used by 18% to 31% of patients in these studies. The percentage of patients who were former smokers ranged from 46% to 57%. Median history of smoking ranged from 50.0 to 60.0 pack-years. The majority of patients in each of these studies were considered to have reversibility. A patient was considered "non-reversible" if, after 4 puffs of Ventolin MDI, there was a change in FEV_1 of <12% from baseline or there was <200 mL absolute increase in the FEV_1. Reversible patients represented 51% to 59% of all patients in these studies. The effects of the high percentage of patients with reversibility in these studies are discussed further below.

Reviewer comment:
The population of patients recruited for these studies raises serious questions about the generalizability of results from this trial to the US COPD population as a whole. Under-representation of non-Caucasian patients in this study is a deficiency. The population studied is characterized by long smoking histories and significant dyspnea. A fairly large minority of the patients was taking inhaled corticosteroids at the time of screening. One would expect these patients to more likely to be corticosteroid-responsive than those not taking inhaled corticosteroids, as one would expect patients with no response or a poor response to have their treatment discontinued. It would be preferable to perform these studies on patients who were naïve to inhaled corticosteroids, to stratify by this variable, or recruit them to a percent that reflects the actual off-label use of inhaled corticosteroids in the COPD population.

Table 6.3. Patient demographics and baseline characteristics, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, page 72]

	Placebo	**SAL 50**	**FP 250**	**FP 500**	**SAL 50/ FP 250**	**SAL 50 /FP 500**
FLTA3025	**N = 206**		**N = 216**	**N = 218**		
Gender, % F/ M	32/68		28/72	34/66		
Mean age, years	64.8		65.2	63.3		
Race, % C/B/Other	95/3/2		94/4/1	94/4/1		
Dyspnea score, % 3 o4 4	33		34	36		
ICS use, %	31		31	31		
Former smokers, %	57		55	53		
Pack-years, Median	50.0		54.5	52.3		
Reversible, %	59		59	57		
SFCA3006	**N = 181**	**N = 160**		**N = 168**		**N = 165**
Gender, % F/ M	25/75	36/64		39/61		38/62
Mean age, years	64.0	63.5		64.4		61.9
Race, % W/B/Other	92/6/2	95/4/1		93/5/2		95/4/1
Dyspnea score, % 3 o4 4	29	44		33		34
ICS use, %	18	31		25		28
Former smokers, %	46	54		54		54
Pack-years, Median	60.0	52.5		54.0		55.0
Reversible, %	56	51		54		53
SFCA3007	**N = 185**	**N = 177**	**N = 183**		**N = 178**	
Gender, % F/ M	32/68	42/58	34/66		39/61	
Mean age, years	64.8	64.2	63.3		63.4	
Race, % W/B/Other	94/3/3	93/4/3	91/5/4		96/3/2	
Dyspnea score, % 3 o4 4	36	33	35		38	
ICS use, %	30	20	28		23	
Former smokers, %	53	49	52		57	
Pack-years, Median	56.0	57.0	60.0		53.0	
Reversible, %	55	55	55		56	

Spirometry results at the time of screening are presented in Table 6.4. The mean FEV_1 for each treatment group was about 1250 mL, mean FEV_1 % predicted was about 40%, and mean FEV_1/FVC % was about 49%. The degree of airway obstruction was fairly similar in each of the treatment groups.

Table 6.4. Spirometry at screening, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, page 74]

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025	**N = 206**		**N = 216**	**N = 218**		
n	206		216	217		
Mean FEV_1, mL	1254		1242	1266		
Mean FEV_1% predicted	41.0		39.8	41.3		
Mean FEV_1/FVC, %	47.2		46.6	47.8		
SFCA3006	**N = 181**	**N = 160**		**N = 168**		**N = 165**
n	181	160		168		165
Mean FEV_1, mL	1317	1237		1233		1268
Mean FEV_1% predicted	41.5	40.3		41.4		40.9
Mean FEV_1/FVC, %	49.0	48.6		47.6		49.4
SFCA3007	**N = 185**	**N = 177**	**N = 183**		**N = 178**	
n	185	177	183		178	
Mean FEV_1, mL	1289	1245	1313		1252	
Mean FEV_1% predicted	42.1	41.9	42.0		41.4	
Mean FEV_1/FVC, %	49.6	50.8	51.3		49.5	

Patient response to treatment with bronchodilator at screening is summarized in Table 6.5. Reversible patients represented from 55% to 59% of all patients in these studies. The mean % change in FEV_1 for reversible patients ranged from 29.8% to 32.4%. Non-reversible patients represented 41% to 46% of all patients in this study. The mean % change in FEV_1 for non-reversible patients ranged from 8.6% to 9.2%. The degree of reversibility in each of the treatment groups was similar. The mean % change in FEV_1 for all patients ranged from 20.0% to 22.9%.

Table 6.5. Mean change in FEV_1 after bronchodilator treatment at screening*, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, page 74, clinstat\copd\flta3025.pdf, pages 306-307, cllinstat\copd\sfca3006.pdf, pages 397-398, clinstat\copd\sfca3007.pdf, pages 354-356].

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500	All treatment groups**
FLTA3025							
Reversible patients % of population (Mean % change in FEV_1)	60 (31.5)		59 (32.2)	57 (33.5)			59 (32.4)
Non-reversible patients % of population (Mean % change in FEV_1)	40 (10.1)		41 (8.1)	43 (9.6)			41 (9.2)
All patients % of population (Mean % change in FEV_1)	100 (22.8)		100 (22.4)	100 (23.3)			100 (22.9)

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500	All treatment groups**
SFCA3006							
Reversible patients % of population (Mean % change in FEV_1)	56 (28.0)	51 (31.6)		54 (28.6)		53 (31.6)	54 (29.8)
Non-reversible patients % of population (Mean % change in FEV_1)	44 (8.3)	49 (10.3)		46 (8.5)		47 (8.0)	46 (8.8)
All patients % of population (Mean % change in FEV_1)	100 (19.3)	100 (21.2)		100 (19.2)		100 (20.6)	100 (20.0)
SFCA3007							
Reversible patients % of population (Mean % change in FEV_1)	55 (29.7)	55 (30.9)	55 (28.9)		56 (29.9)		55 (29.8)
Non-reversible patients % of population (Mean % change in FEV_1)	45 (8.6)	45 (9.6)	45 (8.2)		46 (7.9)		45 (8.6)
All patients % of population (Mean % change in FEV_1)	100 (20.2)	100 (21.3)	100 (19.5)		100 (20.1)		100 (20.3)

*Calculation of response: $\frac{\text{(Post-BD } FEV_1 \text{ minus Pre-BD } FEV_1\text{) X 100}}{\text{Pre-BD } FEV_1}$

Not reversible if result is <12% or <200 mL increase in FEV_1
Reversible if result is ≥12% and ≥200 mL increase in FEV_1

**Mean change derived from data for individual treatment group data

Reviewer comment:
The proportion of patients enrolled in these studies with reversibility is much higher than is found in the population of COPD patients at large. There were 54% to 59% of patients in these studies who had reversibility. One would expect that only up to 30% of patients to have in increase of ≥15% in FEV_1 after inhalation of a beta-agonist.[1, 2] In addition, the degree of reversibility for the reversible population in these studies is high—approximately 30%. The mean degree of reversibility in the non-reversible population was also high—approximately 9%.

The high proportion of patients with reversibility in this study is a critical consideration in determining whether the results of the study can be generalized to the COPD population as a whole. Reversible patients were over-represented relative to their prevalence in the COPD population as a whole, and the degree of reversibility in these patients is much higher than would be expected for the general population of patients with COPD[1, 2]. Enrichment for these highly reversible patients would be predicted to increase the effect size. This finding argues for restricted labeling, should the indication be granted, and against a broad "COPD" indication.

Although the sponsor stratified for reversible and non-reversible populations at randomization, initially the sponsor did not perform an analysis of efficacy for these subgroups. The subgroup analysis was provided by the sponsor in response to a request for information, and is discussed later in this section.

Compliance with study treatment is displayed in Table 6.6. The median number of doses reported as taken was approximately 95% in each treatment group [clinstat\ise\ise.pdf, page 76].

Reviewer comment:
Compliance seemed adequate to allow for assessment of efficacy, recognizing that compliance reporting is commonly unreliable. Compliance assessment was based on data from the Diskus dose counter, which cannot accurately assess whether patients actually received the drug that was dispensed.

Table 6.6. Compliance with study treatment, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, page 76].

	Placebo	SAL 50	FP 250	FP 50	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025 Median rate*, %	96.0		95.3	95.3		
SFCA3006 Median rate, %	95.2	96.4		95.9		95.8
SFCA3007 Median rate, %	96.0	96.4	95.9		96.0	

*Compliance rate = (Total doses from dose counter) / (2 X Number of days on treatment) X 100

6.3.4. Primary efficacy endpoint

The primary efficacy variable for the evaluation of FP in these studies was the pre-dose FEV_1 collected at Day 1, and Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24. The primary analysis for FP was the endpoint analysis comparing the mean morning pre-dose FEV_1 between treatment groups.

Because this application is concerned with the efficacy of FP and not the SAL 50/FP combination products, the following comparisons will be discussed:
- FP 250 and FP 500 to placebo
- SAL 50/FP 250 and SAL 50/FP 500 to SAL 50

The following comparisons will not be discussed in this section, as they are concerned with the evaluation of efficacy of the SAL 50 or the SAL 50/FP products:
- SAL 50/FP 250 and SAL 50/FP 500 to placebo
- SAL 50 to placebo
- SAL 50/FP 250 to FP 250 and SAL 50/FP 500 to FP 500

Primary efficacy endpoint data for the three pivotal studies in this application are summarized in Table 6.7. Comparisons of FP 500 with placebo showed statistically significant differences in mean change from baseline in pre-dose FEV_1 in both FLTA3025 (50 mL, $p = 0.010$) and SFCA3006 (113 mL, $p < 0.001$). Comparisons of FP 250 with placebo showed statistically significant differences in mean change from baseline in pre-dose FEV_1 for SFCA3006 (108 mL, $p<0.001$), but not for FLTA3025 (27 mL, $p = 0.140$). In FLTA 3025, there was a dose-response noted for the small magnitude of change from baseline in pre-dose FEV_1 for FP 500 (50 mL) and FP 250 (27 mL). The magnitude of change from baseline for pre-dose FEV_1 for FP 500 in SFCA3006 (113

mL) was similar to that noted for FP 250 in SFCA3007 (108 mL) [clinstat\ise\ise.pdf, pages 134, 532, 536, 540].

Comparisons with placebo showed statistically significant differences in mean change from baseline in pre-dose FEV_1 at endpoint for SAL 50/FP 500 and SAL 50/FP 250. Comparisons of SAL 50/FP 500 with SAL 50 showed statistically significant differences in mean change from baseline in pre-dose FEV_1 in SFCA3006 ($p < 0.001$), with an "added" effect size attributable to FP of 49 mL (see table, below). Comparisons of SAL 50/FP 250 with SAL 50 showed statistically significant differences in mean change from baseline in pre-dose FEV_1 in SFCA3007 ($p = 0.012$), with an "added" effect size attributable to FP of 74 mL (see table, below) [clinstat\ise\ise.pdf, pages 134, 532, 536, 540].

Differences from placebo in mean change from baseline in pre-dose FEV_1 were noted at Week 1 for the FP and SAL 50/FP products although the magnitude of the differences for FP 500 (36 mL) and FP 250 (18 mL) were quite small [clinstat\ise\ise.pdf, pages 509, 515, 521].

Reviewer comment:
A statistically significant difference from placebo in the primary efficacy endpoint was noted in replicate studies for FP 500 only, not for FP 250. There were large differences in the degree of effect noted in these studies, with a small effect in FLTA3025, particularly for FP 250. The reason for the large differences in the effect is unclear. Comparisons of the SAL 50/FP combination products with SAL 50 indicate that FP provided some efficacy to the combination product.

The sponsor integrated the results for the primary efficacy endpoint. This analysis will not be discussed, as integrating the results obscures the differences in effect for the FP 250 and FP 500 groups, and is not appropriate for efficacy data.

These studies fail to support the efficacy of FP 250, as a statistically significant difference from placebo was not noted in replicate studies. Although these primary efficacy endpoint data support the efficacy of FP 500, the modest effects on FEV_1 will need to be examined in light of secondary endpoint and quality of life results, and balanced against safety concerns for this high dose of FP.

Table 6.7. Mean change in pre-dose FEV_1 from baseline, primary efficacy variable, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, pages 134, 532, 536, 540].

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025						
Baseline Mean FEV_1, ml (n)	 1203 (204)		 1207 (215)	 1246 (218)		
Endpoint **Difference from placebo** **Mean change, ml** **p value vs. placebo** Mean FEV_1, ml (n)	 **0** 1221 (199)		 **27** **(0.140)** 1240 (211)	 **50** **(0.010)** 1301 (210)		

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
SFCA3006						
Baseline Mean FEV_1, ml (n)	 1282 (181)	 1192 (159)		 1174 (166)		 1254 (163)
Endpoint **Difference from placebo** **Mean change, ml** **p value vs. placebo** **p value vs. SAL 50** Mean FEV_1, ml (n)	 **0** 1292 (171)	 **111** **(<0.001)** 1303 (158)		 **113** **(<0.001)** 1298 (160)		 **160** **(<0.001)** **(<0.001)** 1410 (156)
SFCA3007						
Baseline Mean FEV_1, ml (n)	 1232 (185)	 1205 (177)	 1236 (183)		 1207 (178)	
Endpoint **Difference from placebo** **Mean change, ml** **p value vs. placebo** **p value vs. SAL 50** Mean FEV_1, ml (n)	 **0** 1240 (172)	 **90** **(<0.001)** 1303 (168)	 **108** **(<0.001)** 1351 (175)		 **164** **(<0.010)** **(0.012)** 1375 (165)	

ANCOVA, baseline as covariate
p values for overall comparisons at endpoint for each study:
FLTA3025: 0.035
SFCA3006: <0.001
SFCA3007: <0.001

6.3.5. Secondary efficacy endpoints

Secondary efficacy variables included change from baseline in the global and individual domains of the CBSQ, the BDI/TDI score at each of the treatment visits, number and percent of exacerbations of COPD, time to first COPD exacerbation, number of withdrawals and time to withdrawals. Morning PEFR, daily use of Ventolin, percentage of nights with no awakenings requiring Ventolin, frequency of nighttime awakenings requiring Ventolin, and percent of days without using Ventolin were also summarized [clinstat\ise\ise.pdf, pages 50-59]. These data are discussed below.

6.3.5.1. Chronic Bronchitis Symptom Questionnaire

The CBSQ evaluated cough frequency and severity, sputum release, and chest discomfort on a 0 to 4, 5-point scale. Individual scores were summed to provide a Global Assessment Score (GAS). The maximum possible GAS was 16. Patients were required to have a minimum score of 4 at baseline to qualify for randomization. The sponsor determined that the Minimally Clinically Important Change (MCIC) in the CBSQ was 1.4 points in an analysis of patients completing at least 8 weeks of this study [clinstat\other\cbsqvalidationdocument.pdf, page 11]. Results of the Chronic Bronchitis Symptom Questionnaire are displayed in Table 6.8.

Differences from placebo in the mean change from baseline in the GAS at endpoint were compared. No active treatment group had a clinically significant difference from the placebo group in mean change from baseline in the GAS.

Table 6.8. Mean change from baseline in the global assessment score (GAS) of the CBSQ, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, page 138].

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025						
Mean change in GAS at endpoint	0.9		1.4	1.4		
Difference from placebo	0		0.5	0.5		
SFCA3006						
Mean change in GAS at endpoint	1.5	1.9		1.6		1.8
Difference from placebo	0	0.4		0.1		0.3
SFCA3007						
Mean change in GAS at endpoint	1.4	1.5	2.2		2.1	
Difference from placebo	0	0.1	0.8		0.7	

*Minimal clinically significant change = 1.4 points

Reviewer comment:
The CBSQ does not support the efficacy of the FP 500 or FP 250, or for the SAL50/FP combination products. This is an important observation, as this endpoint evaluates symptoms of patients with COPD, and is not directly related to measures of bronchodilatation, as is the primary efficacy endpoint.

6.3.5.2. Baseline/Transition Dyspnea Indices

The degree of functional impairment at baseline due to dyspnea, the magnitude of task to provoke dyspnea, and the magnitude of effort that provoked dyspnea were rated on a 0 to 4, 5-point scale to derive the BDI. The maximum BDI score was 12. The TDI assessed changes from baseline in functional impairment, magnitude of task, and magnitude of effort and were assessed at each subsequent visit with a -3 to +3, seven-point scale. The sponsor considered a clinically important TDI score to be ≥1.0. Results of the BDI/TDI are presented in Table 6.9.

Differences from placebo in the mean TDIs at endpoint were compared. Only SAL50/FP 500 had a clinically significant difference from the placebo group. No other active treatment group had a clinically significant difference from the placebo group in mean TDI.

Table 6.9. Mean Transition Dyspnea Index (TDI) scores, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, page 140].

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025						
Mean TDI at endpoint	0.5		0.9	1.2		
Difference from placebo	0		0.4	0.7		
SFCA3006						
Mean TDI at endpoint	0.4	0.9		1.3		2.1
Difference from placebo	0	0.5		0.9		1.7
SFCA3007						
Mean TDI at endpoint	1.0	1.6	1.7		1.7	
Difference from placebo	0	0.6	0.7		0.7	

*Minimal clinically significant change = 1.0 points

Reviewer comment:
The TDI does not support the efficacy of the FP 500 or FP 250.

6.3.6. COPD exacerbations

The incidence of COPD exacerbations in these studies is summarized in Table 6.9. In FLTA3025 there were slightly fewer COPD exacerbations in FP 500 and FP 250 groups than in placebo, with a dose-response effect noted. Otherwise, the incidence of COPD exacerbations in the three pivotal studies was fairly similar among treatment groups. The incidence of moderate or severe COPD exacerbations in the three pivotal studies was similar among treatment groups [clinstat\ise\ise.pdf, pages 143-144].

Table 6.9. Incidence of COPD exacerbations, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, page 143, 144].

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025	**N = 206**		**N = 216**	**N = 218**		
At least one COPD exacerbation, %	51		48	45		
At least one moderate or severe COPD exacerbation, %	43		40	48		
SFCA3006	**N = 181**	**N = 160**		**N = 168**		**N = 165**
At least one COPD exacerbation, %	44	39		46		41
At least one moderate or severe COPD exacerbation, %	35	38		40		37
SFCA3007	**N = 185**	**N = 177**	**N = 183**		**N = 178**	
At least one COPD exacerbation, %	39	37	43		40	
At least one moderate or severe COPD exacerbation, %	34	31	38		34	

There were no significant differences between the FP and placebo groups for time to withdrawal from the study, time to withdrawal due to COPD exacerbation, and time to withdrawal due to COPD-related condition [clinstat\ise\ise.pdf, pages 146-147].

Reviewer comment:
With the exception of FLTA3025, these studies show no effect of FP on the incidence of all COPD exacerbations or moderate or severe COPD exacerbations. These data do not support the efficacy of FP 250 or FP 500 in this population.

6.3.6.1. AM PEFR

Mean change from baseline in AM PEFR in the three pivotal studies in this application is summarized in Table 6.10. Small changes from baseline in AM PEFR were noted for FP 500 and FP 250 groups. Larger changes from baseline in AM PEFR were noted for SAL 50, SAL 50/FP 250, and SAL 50/FP 500 groups [clinstat\ise\ise.pdf, page 148].

Table 6.10. Mean change from baseline in AM PEFR, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, page 148].

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025	**N = 205**		**N = 213**	**N = 218**		
Mean change, L/min	-1.9		8.8	9.4		
Difference from placebo	0		10.7	11.3		

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
SFCA3006	**N = 181**	**N = 160**		**N = 168**		**N = 165**
Mean change, L/min	-2.7	16.8		12.9		31.9
Difference from placebo	0	19.5		15.6		34.6
SFCA3007	**N = 185**	**N = 177**	**N = 183**		**N = 178**	
Mean change, L/min	0.8	14.7	11.3		30.6	
Difference from placebo	0	13.9	10.5		29.8	

Reviewer note:
These data are supportive of the efficacy of FP in this population, however PEFR results are likely to be fairly closely correlated with the FEV_1 results and other measures of bronchodilatation.

6.3.6.2. Daily Ventolin use

Mean change from baseline in daily Ventolin use in the three pivotal studies in this application is summarized in Table 6.11. Small changes from baseline in mean change from baseline in daily Ventolin use were noted for FP 500 and FP 250 groups. Larger changes from baseline were noted for SAL 50, SAL 50/FP 250, and SAL 50/FP 500 groups [clinstat\ise\ise.pdf, page 148].

Table 6.11. Mean change from baseline in daily Ventolin use, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, page 151].

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025	**N = 204**		**N = 212**	**N = 215**		
Mean change, puffs/day	0.7		-0.1	-0.2		
Difference from placebo	0		-0.8	-0.9		
SFCA3006	**N = 182**	**N = 174**		**N = 177**		**N = 172**
Mean change, puffs/day	0.5	-0.9		-0.4		-1.2
Difference from placebo	0	-1.4		-0.9		-1.7
SFCA3007	**N = 185**	**N = 177**	**N = 183**		**N = 178**	
Mean change, puffs/day	0.1	-0.7	-0.2		-1.0	
Difference from placebo	0	-0.8	-0.3		-1.1	

Reviewer note:
These data are supportive of the efficacy of FP in this population. However, as with AM PEFR data, Ventolin use results are likely to be fairly closely correlated with the FEV_1 results and other measures of bronchodilatation.

6.3.6.3. Awakenings requiring Ventolin use

Mean change from baseline in daily Ventolin use in the three pivotal studies in this application is summarized in Table 6.12. Small changes from baseline in mean change from baseline in number of awakenings per night requiring Ventolin use were noted for FP 500 and FP 250 groups. Larger changes from baseline were noted for SAL 50, SAL 50/FP 250, and SAL 50/FP 500 groups [clinstat\ise\ise.pdf, page 153].

Table 6.11. Mean change from baseline in number of awakenings per night requiring Ventolin use, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, page 153].

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025	**N = 202**		**N = 211**	**N = 212**		
Mean change, awakenings/night	0.11		-0.05	-0.05		
Difference from placebo	0		-0.16	-0.16		

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
SFCA3006	**N = 175**	**N = 153**		**N = 162**		**N = 157**
Mean change, awakenings/night	0.10	-0.09		-0.08		-0.04
Difference from placebo	0	-0.19		-0.18		-0.14
SFCA3007	**N = 181**	**N = 174**	**N = 177**		**N = 172**	
Mean change, awakenings/night	0.02	-0.06	-0.03		-0.12	
Difference from placebo	0	-0.08	-0.05		-0.14	

Reviewer note:
These data are supportive of the efficacy of FP in this population. However, as with AM PEFR data and Ventolin use, these data are likely to be fairly closely correlated with the FEV_1 results and other measures of bronchodilatation.

6.3.7. Health-related quality of life instrument

QOL assessment was one of the pre-specified objectives of all three pivotal studies. COPD-related quality of life was evaluated using the Chronic Respiratory Disease Questionnaire (CRDQ). The CRDQ contains 20 questions in 4 domains: dyspnea, fatigue, emotional function, and mastery. An overall score, the sum of the scores for all 20 questions, was the primary health-related quality of life endpoint. An improvement in the Overall score of at least 10.0 points was considered to be a clinically significant improvement in COPD-specific quality of life. Results of the Chronic Bronchitis Symptom Questionnaire are displayed in Table 6.12.

Differences from placebo in the mean change from baseline at endpoint in the Overall score of the CRDQ were compared. No active treatment group had a clinically significant difference from the placebo group in mean change from baseline in the Overall score of the CRDQ.

Table 6.12. Mean change from baseline for Overall score of CRDQ, pivotal studies in this application, NDA 20-833, S004, [clinstat\ise\ise.pdf, page 171].

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025						
Mean Overall score at endpoint	1.0		5.1	9.1		
Difference from placebo	0		4.1	8.1		
SFCA3006						
Mean Overall score at endpoint	5.0	8.0		4.8		10.0
Difference from placebo	0	3.0		1.8		5.0
SFCA3007						
Mean Overall score at endpoint	5.0	6.4	10.4		10.0	
Difference from placebo	0	1.4	5.4		5.0	

Minimal clinically significant change ≥ 10.0 points

Reviewer comment:
No active treatment group had a clinically significant difference from the placebo group in the Overall score. As there was no clinically significant differences from the placebo group in the Overall score, any changes in individual domains or summary scores provide little meaningful information. These data provide no additional support for the efficacy of FP in this population. This is an important negative finding, since one of the stated objectives of this study was to compare the health-related quality of life in COPD patients receiving active treatment compared to placebo over this 24-week study, in part to corroborate the clinical importance of relatively small, short-term changes in FEV_1.

6.4. Subgroup analyses, smoking status and reversibility

The sponsor provided subgroup analyses of efficacy by smoking status and for the reversible and non-reversible groups. These subgroup analyses are discussed below.

6.4.1. Smoking status, subgroup analysis

The sponsor provided a post-hoc analysis of efficacy by patient smoking status for exploratory purposes. The sponsor provided only integrated data for this analysis in the Integrated Summary of Efficacy (ISE), and did not provide the results for individual studies [clinstat\ise\ise.pdf, page 205]. This reviewer will not examine the sponsor's integrated data for the primary efficacy endpoint because of the large differences in effect size between these studies. This document will review the primary efficacy endpoint data from the individual studies for this subgroup analysis, instead. Integrated secondary efficacy endpoint data will be reviewed, as presented in the sponsor's ISE.

Former smokers had larger mean changes from baseline in FEV_1 at endpoint for all active study treatments than did current smokers. These data are displayed in Table 6.13. Current smokers showed responses to FP 500 and FP 250 that were smaller and more modest than did former smokers in SFCA3006 and SFCA3007. Current smokers showed no response to FP 500 or FP 250 in FLTA3025, in contrast to the other two studies.

Table 6.13. Mean change from baseline in FEV_1 at endpoint, by smoking status, pivotal studies in this application, NDA 20-833, S004, [clinstat\copd\flta3025.pdf, page 101; clinstat\copd\sfca3006.pdf, page 130; clinstat\copd\sfca.pdf, page 115].

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025						
Current smokers Mean change, mL Difference from placebo	31 0		-5 -36	17 14		
Former smokers Mean change, mL Difference from placebo	-5 0		72 77	100 105		
SFCA3006						
Current smokers Mean change, mL Difference from placebo	-21 0	78 99		73 94		130 151
Former smokers Mean change, mL Difference from placebo	16 0	132 116		139 123		179 163
SFCA3007						
Current smokers Mean change, mL Difference from placebo	4 0	96 92	80 76		127 123	
Former smokers Mean change, mL Difference from placebo	-3 0	86 89	136 139		193 196	

The sponsor also examined other efficacy endpoints by patient smoking status. As noted above, the sponsor presented integrated data from the three pivotal studies. These data are discussed below.

The GAS of the CBSQ showed no clinically significant differences from placebo for any treatment group in both former and current smokers. The GAS of the CBSQ numerically favored former smokers [clinstat\ise\ise.pdf, page 207].

Mean TDI scores showed clinically significant differences from placebo for former smokers for FP 500, SAL 50/FP 500, and SAL 50/FP 250. Mean TDI scores showed clinically significant differences from placebo for current smokers for SAL 50/FP 500. TDI scores numerically favored former smokers [clinstat\ise\ise.pdf, page 209].

The incidence of COPD exacerbations of any intensity was similar between smoking status subgroups. The incidence of moderate or severe COPD exacerbations was slightly lower in FP 500 and FP 250 groups when compared with placebo. There was no difference in survival analyses for time to first COPD exacerbation of any intensity or time to first moderate or severe COPD exacerbation for FP 500 or FP 500 with regards to smoking status [clinstat\ise\ise.pdf, pages 209-210].

The Overall score of the CRDQ, the health-related quality of life instrument, showed no clinically significant differences from placebo for any treatment group in both former and current smokers. The Overall score of the CBSQ numerically favored former smokers [clinstat\ise\ise.pdf, page 247].

Reviewer comment:
These data suggest that patients who stopped smoking prior to the conduct of the study had a greater treatment effect from FP 500 and FP 250. It is unclear why there is such a large discordance in the response to FP for the primary efficacy endpoint in current smokers between FLTA3025 and the other two studies. The most prominent treatment effects were noted for the primary efficacy endpoint, change in FEV_1 from baseline at endpoint. Secondary efficacy endpoint results showed smaller differences between current and former smokers.

It has been well established by the Lung Health Study[3] that smoking cessation has a far greater impact on lung function and long-term survival of the COPD patient than any pharmacological intervention. It is therefore not unreasonable to attribute some of the improvement in FEV_1 observed during the study to abstention from smoking.

6.4.2. "Non-reversible" population, subgroup analysis

Assignment to study drug was to be stratified according to the patients' response to reversibility testing with Ventolin at screening to a non-reversible group and a reversible group. Non-reversible patients were defined as having an absolute volume increase <200 mL or an absolute volume increase of ≥200 mL with baseline FEV_1 reversibility of <12%. Reversible patients were defined as having an absolute volume increase ≥200 mL with baseline FEV_1 reversibility of ≥12%. The sponsor provided only integrated data for this analysis in the Integrated Summary of Efficacy (ISE), and did not provide the results for individual studies [clinstat\ise\ise.pdf, page 212]. This reviewer will not examine the sponsor's integrated data for the primary efficacy endpoint because of the large differences in effect size between these studies. This document will review the primary efficacy endpoint data from the individual studies for this subgroup analysis, instead. Integrated secondary efficacy endpoint data will be reviewed, as presented in the sponsor's ISE.

The non-reversible group had smaller mean changes from baseline in FEV_1 at endpoint for all active study treatments than did the reversible group. These data are displayed in Table 6.13. Both the non-reversible and reversible groups in FLTA3025 showed responses to FP 500 and FP 250 that were much smaller than the same groups in SFCA3006 and SFCA3007.

Table 6.12. Mean change from baseline in FEV_1 at endpoint, non-reversible and reversible groups, pivotal studies in this application [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf page 18; NDA 20-833, S004, [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 9; NDA 20-833, S004, [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 14].

	Placebo	SAL 50	FP 250	FP 500	SAL 50/ FP 250	SAL 50/ FP 500
FLTA3025						
Non-reversible						
Mean change, mL	-17		-15	21		
Difference from placebo	0		2	38		
Reversible						
Mean change, mL	29		70	93		
Difference from placebo	0		41	64		
SFCA3006						
Non-reversible						
Mean change, mL	-8	80		93		116
Difference from placebo	0	88		101		124
Reversible						
Mean change, mL	-1	132		123		191
Difference from placebo	0	133		124		192
SFCA3007						
Non-reversible						
Mean change, mL	19	26	74		126	
Difference from placebo	0	7	55		107	
Reversible						
Mean change, mL	-15	141	138		196	
Difference from placebo	0	156	153		211	

The sponsor also examined other efficacy endpoints for the non-reversible and reversible subgroups. As noted above, the sponsor presented integrated data from the three pivotal studies. These data are discussed below.

The GAS of the CBSQ showed no clinically significant differences from placebo for any treatment group in the non-reversible and reversible groups. The GAS of the CBSQ was numerically favored in the reversible group [clinstat\ise\ise.pdf, page 215].

Mean TDI scores showed clinically significant differences from placebo for the non-reversible group for FP 500, SAL 50/FP 500, and SAL 50/FP 250. Mean TDI scores showed clinically significant differences from placebo for current smokers for SAL 50/FP 250 and SAL 50/FP 500. TDI scores numerically favored former smokers [clinstat\ise\ise.pdf, page 217].

The incidence of COPD exacerbations of any intensity and moderate or severe COPD exacerbations for all active treatments was slightly higher in the non-reversible subgroup than in the reversible subgroup. The incidence of moderate or severe COPD exacerbations was slightly lower for FP 500 and FP 250 in the reversible group than in the reversible group. There was no difference in survival analyses for time to first COPD

exacerbation of any intensity or time to first moderate or severe COPD exacerbation for FP 500 or FP 500 with regards to smoking status [clinstat\ise\ise.pdf, pages 218-219].

The Overall score of the CRDQ, the health-related quality of life instrument, showed no clinically significant differences from placebo for any treatment group in both the non-reversible and reversible groups. The Overall score of the CBSQ was numerically favored in the reversible group [clinstat\ise\ise.pdf, page 248].

Reviewer comment:
These data suggest that patients who had an absolute volume increase ≥200 mL with baseline FEV_1 reversibility of ≥12% had a greater treatment effect from FP 500 and FP 250. The most prominent treatment effects were noted for the primary efficacy endpoint, change in FEV_1 from baseline at endpoint. Secondary efficacy endpoint results showed smaller differences between the non-reversible and reversible groups.

6.5. Subgroup analyses, demographics

The sponsor provided subgroup analyses of efficacy by gender, race, and age. These are reviewed below.

Males had greater absolute mean changes from baseline in FEV_1 at endpoint than women for all active treatment groups. Mean percent change from baseline in FEV_1 at endpoint was similar for men and women, however, indicating the larger absolute mean change in men was due to larger lung volumes [clinstat\ise\ise.pdf, page 227]. The mean change from baseline in CBSQ GAS was similar in men and women for treatment groups. Women had slightly greater TDI scores at endpoint than men. Women in FP 500 and FP 250 groups had slightly more COPD exacerbations than did men, but this observation was also present in the placebo group. Women in the FP 500 and FP 250 groups had more slightly more moderate or severe COPD exacerbations than men, when compared with data for the placebo group [clinstat\ise\ise.pdf, page 228-238].

No consistent difference in mean change from baseline in FEV_1 was noted for all treatment groups when data for patients <65 years and ≥65 years were compared. Changes in the CGSQ GAS were similar among treatments for patients <65 years and ≥65 years. Changes in TDI scores were similar among treatments for patients <65 years and ≥65 years. Incidences of COPD exacerbations in the FP 500 and FP 250 groups relative to placebo were higher for patients ≥65 years than those <65 years. Incidences of COPD exacerbations in the FP 500 group relative to placebo were higher for patients ≥65 years than those <65 years [clinstat\ise\ise.pdf, page 233-240].

As noted in each of the individual study reviews elsewhere in this document, the vast majority of patients in this study were of Caucasian race. There were few patients of Black or Asian race. Non-Caucasian races represented 6% or less of each of the treatment groups. The small number of Non-Caucasian patients makes it difficult to draw firm conclusions. Mean percent change from baseline in FEV_1 at endpoint by race appeared to be greatest in patients of Other race, followed by patients of Black race, with the smallest in Caucasian patients [clinstat\ise\ise.pdf, page 240]. Changes in the CBSQ GAS

appeared to be similar among racial subgroups. COPD exacerbations and moderate or severe COPD exacerbations appeared to be most frequent in patients of Black race, followed by Caucasian patients, and lowest in patients of Other race [clinstat\ise\ise.pdf, page 241-246].

Reviewer comments:
The under-representation of non-Caucasian patients in these studies is problematic in that the sponsor has not adequately studied the efficacy of FP in non-Caucasian patients with COPD. Additional information on the efficacy of FP in a more racially diverse study population is recommended. Safety data from future studies should be examined to determine if the increases in COPD exacerbations in women and patients ≥ 65 years represent true safety signals.

6.6. References

1. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152:S77-S121.

2. Barnes PJ. Chronic Obstructive Pulmonary Disease. New Engl J Med 2000;343:269-280.

3. The Lung Health Study Research Group. Effect of Inhaled Triamcinolone on the Decline in Pulmonary Function in Chronic Obstructive Pulmonary Disease. New Engl J Med 2000;343:1902-1909.

7. INTEGRATED REVIEW OF SAFETY

Integrated review of safety data supporting this application follows below.

7.1. Summary and conclusions

Safety data from the three pivotal studies in this application were integrated in support of this application. These studies were randomized, double-blind, placebo-controlled, parallel group, multicenter trials that had a similar design and were conducted in a similar manner. The studies were designed to evaluate the safety and efficacy of SAL, FP, and the SAL/FP combination administered BID via the Diskus over 24 weeks for the treatment of COPD. FP 250, FP 500, and placebo were studied in FLTA3025. FP 500, SAL 50/FP 250, SAL 50, and placebo were studied in SFCA3006. FP 250, SAL 50/FP 500, SAL 50, and placebo were studied in SFCA 30007.

The majority of patients were males. Non-Caucasian patients were seriously under-represented in these studies, representing approximately 5% of patients studied. . Approximately one third of patients had dyspnea with walking on level ground for 100 yards or less. Drug exposure was adequate to assess safety over the 24-week study period.

Adverse events (AEs) were fairly common in these studies. A dose response effect was noted when comparing all AEs for placebo (69%) with FP 250 (74%) and FP 500 (80%). AEs occurring at a frequency ≥3% and more frequently with FP 250, FP 500, SAL 50/FP 250, or SAL 50/FP 500 than with placebo included upper respiratory tract infection, headaches, musculoskeletal pain, throat irritation, viral respiratory infections, URI, candidiasis of the mouth or throat, nasal congestion/blockage, cough, sinusitis, nausea and vomiting, hoarseness/dysphonia, fever, malaise and fatigue, muscle cramps and spasms, rhinitis, dizziness, hypertension, sinusitis/sinus infection, and muscle pain. When comparing placebo with FP 250 and FP 500, a dose response effect was noted for URTI, headaches, viral respiratory infections, URTI, candidiasis of the mouth or throat, nasal congestion/blockage, and muscle pain. Many of the AEs noted are also noted in the labels for Flovent MDI and Flovent Rotadisk. AEs reported in these studies that are not noted in current labeling for other Flovent products include musculoskeletal pain, nausea and vomiting, airway irritation (throat irritation, cough, rhinitis), dizziness, malaise and fatigue). Differences could be attributed to differences in patient population or in magnitude of the dose of FP, which was high for COPD (500 to 1000 mcg per day) when compared to the asthmatic population (100 to up to 500 mcg per day for moderate, persistent asthma; 500 to 1000 mcg per day for oral corticosteroid sparing indication).

AEs associated with use of inhaled and systemic corticosteroids were noted in these studies. Candidiasis, throat irritation, and hoarseness/dysphonia were more common in FP 250, FP 500, SAL 50/FP 250, and SAL 50/FP 500 than in placebo. A dose response effect for candidiasis was seen when comparing placebo (1%) with FP 250 (7%) and FP 500 (13%). There were a small number of AEs for fractures, cataracts, hyperglycemia, diabetes mellitus, and impaired glucose tolerance, and the frequencies of these AEs were

similar among treatment groups. There was a higher frequency of pneumonia for FP 250 (1%), FP 500 (2%), and SAL 50/FP 500 (1%) than for placebo (<1%).

There were four deaths in placebo-treated patients in these studies. There were no deaths in patients that received active treatment. There was a higher frequency of SAEs due to COPD for FP 250 and FP 500, and a suggestion of an association with SAEs due to pneumonia with FP treatment.

Withdrawals due to any AE were more common in FP 500 and SAL 50/FP 500 than in placebo. Withdrawals due to AEs for COPD were more common in FP 500 and FP 250 than in placebo; a dose response effect was noted. Withdrawals due to pneumonia were more common in FP 500, FP 250, and SAL 50/FP 500 than for placebo. Withdrawals due to candidiasis mouth/throat only occurred in FP 500-treated patients.

Plasma cortisol levels were studied in FLTA3025. FP treatment groups had lower mean cortisol AUC_{12} and mean C_{min} than the placebo group, with a dose response effect noted. Mean cortisol AUC_{12} was 21% lower than placebo for FP 500 and 10% lower than placebo for FP 250, indicating dose-related systemic absorption and systemic activity from Flovent Diskus. The plasma cortisol samples were taken at Week 4, early in the study. Cosyntropin stimulation testing was performed in SFCA3006 and SFCA3007 on a subset of patients (15 – 20%). The data for cosyntropin stimulation testing show no evidence of adrenal suppression, however, cosyntropin stimulation testing is intended as a means to diagnose adrenal insufficiency and is fairly insensitive as a measure of adrenal suppression.

Subgroup analyses of safety endpoints in the pivotal studies in this application reveal no gender effects associated with treatment group. SAEs due to pneumonia were more common in patients ≤65 years of age who were treated with FP 500 and SAL 50/FP 500. Withdrawals due to pneumonias were more common in patients ≥65 years of age who were treated with FP 500 and SAL 50/FP 500. The small number of non-Caucasian patients did not allow for an analysis of AEs, SAEs, or withdrawals due to AEs by race.

The sponsor also provided safety data from other studies to support this application. These data included blinded listings of deaths and SAEs from ongoing clinical studies, as well as safety information from completed clinical pharmacology and clinical studies. Blinded listings of deaths and SAEs from ongoing clinical studies provided no useful safety information. Many AEs and SAEs from the completed studies are similar to those that were noted in the three pivotal studies and those noted in current labeling of Flovent product formulations. However, both upper respiratory infections and lower respiratory infections, including pneumonia, were more frequent in FP-treated patients than in placebo. Patients treated with FP MDI 500 mcg BID over the 3-year course of FLIT78 (also known as ISOLDE) had a higher frequency of events associated with systemic effects of corticosteroids than patients treated with placebo. These events included gastrointestinal hemorrhage, diabetes mellitus, hyperglycemia, ocular pressure disorders, decreased cortisol, abnormal adrenal hormone levels, Cushing's syndrome/symptoms, hypofunction of the adrenal cortex, skin hemorrhage, acne and folliculitis, and muscle

atrophy, weakness, and tiredness. One patient in FLIT98 was noted as having a SAE for decreased cortisol. FLTI98 was a 4-week randomized, double blind, placebo controlled study of FP MDI 1000 mcg BID in patients with COPD exacerbations.

These supportive studies also included laboratory data that showed evidence of HPA-axis effects of inhaled FP. FLTA1003 was a open-label, single dose, 4-way crossover, PK/PD study in normal subjects. Patients received 1000 mcg of FP in four different dosage strengths of the Diskus formulation. Compared to baseline, mean urinary cortisol excretion was decreased by 42% to 62% in all treatment groups in this study, and many individual patients had decreases in urinary cortisol excretion event after the first dose of study treatment.

The sponsor studied effects on bone mineral density in two controlled, long-term studies of FP in the treatment of asthma. These studies were FLTA3001 and FLTA3017. Lumbar spine bone mineral density measurements in FLTA3001 demonstrated no statistically different treatment effects at 24, 52, 76, and 104 weeks of double-blind treatment with placebo, FP MDI 88 mcg BID, or FP MDI 440 mcg BID. Lumbar spine bone mineral density measurements in FLTA3017 demonstrated no statistically different treatment effects at 24, 52, 76, and 104 weeks of double-blind treatment with placebo or FP 500 mcg BID with the Rotadisk formulation. The lumbar spine was the only area in these studies that underwent prospective quality assurance from the osteoporosis central laboratory. Unfortunately, results from the proximal femur, a more sensitive area for corticosteroid effect, had no prospective quality assurance. These studies were performed in a younger population of asthma patients, a population that would be less sensitive to bone effects of corticosteroids than older COPD patients would be.

The sponsor does not appear to have established the safety of FP in the proposed population. The sponsor has not adequately studied the safety of FP in non-Caucasian patients with COPD. Additional study of the safety of FP in a more racially diverse study population is strongly suggested. Further study is also required to demonstrate the safety of this product in the COPD population, a population that would be at higher risk for systemic corticosteroid effects. The pivotal studies were likely to be of insufficient duration to detect differences between treatment groups for uncommon events such as fractures, cataracts, ocular pressure disorders, and disorders of glucose metabolism. The pivotal studies were not designed to specifically look for cataracts or systemic bone effects and exclusion criteria specifically selected subjects with baseline bone or ocular problems. Safety data from supportive studies raise concerns about a higher incidence of respiratory infections, pneumonia, HPA axis effects, among others, in FP-treated patients, and do not adequately address bone effects in the proposed population.

The sponsor has recently started a 3-year study of FP 500 mcg BID, SAL 50/FP 500 BID, SAL 50 BID, and placebo BID via the Diskus formulation in COPD patients (SCO30003). Bone density is to be evaluated over three years in a subpopulation of 600 patients. This study will also assess bone fractures and ocular events in the entire study population of 5000 patients. The long-term safety data that will be provided in this study

will be critical in assessing the long-term risk/benefit analysis for this product in the proposed population.

7.1.1. Content

The following data were reviewed in preparation of this overview of safety:

- Safety data from the following pivotal studies
  - FLTA3025
  - SFCA3006
  - SFCA3007
- Supportive safety data from other studies
  - AEs and HPA-axis data from clinical pharmacology study FLTA1003
  - Blinded listings of deaths and SAEs from ongoing clinical studies SFCB3024, SCO30003
  - Studies of Flovent MDI 500 mcg BID, FLIP63, FLIT78, FLIT97, FLIT98
  - Bone mineral density data from two long-term studies in asthma, FLTA3001 and FLTA3017
  - Blinded listings of deaths and SAEs from nine ongoing non-US studies used to support regional markets (SCO30001, SCO40002, SMS40026, SMS40130, SMS40308, SAM30001, FCO40003, FCO30002, and FCO40004)

The following data are reviewed in Dr. Gilbert-McClain's Medical Officer Review of the application for the COPD indication for the Advair product, NDA 21-077, S003.

- Safety update, including postmarketing reports and a literature review

7.1.2. Safety data from pivotal studies

A review of integrated safety data from the three pivotal clinical studies in this application, FLTA3025, SFCA3006, and SFCA3007, follows below.

7.1.3. Description of pivotal studies

This application included three pivotal clinical studies, FLTA3025, SFCA3006, and SFCA3007. These studies were randomized, double-blind, placebo-controlled, parallel group, multicenter trials that had a similar design and were conducted in a similar manner. The studies were designed to evaluate the safety and efficacy of SAL, FP, and the SAL/FP combination administered BID via the Diskus over 24 weeks for the treatment of COPD. These studies are summarized in Table 7.1. [clinstat\iss\iss.pdf, page 33].

Table 7.1. Summary of pivotal studies in this application, NDA 20-833, S004.

Study number	Study type	Treatment groups	Duration of treatment	Design	Number of patients	Diagnosis, age of subjects
FLTA3025	Efficacy and safety	FP 250 mcg Diskus BID FP 500 mcg Diskus BID Placebo Diskus BID	24 weeks	Randomized, double-blind, placebo controlled, parallel group	640	COPD, ≥40 years

Study number	Study type	Treatment groups	Duration of treatment	Design	Number of patients	Diagnosis, age of subjects
SFCA3006	Efficacy and safety	SAL 50 mcg Diskus BID FP 500 mcg Diskus BID SAL 50 mcg/FP 500 mcg Diskus BID Placebo Diskus BID	24 weeks	Randomized, double-blind, placebo controlled, parallel group	640	COPD, ≥40 years
SFCA3007	Efficacy and safety	SAL 50 mcg Diskus BID FP 250 mcg Diskus BID SAL 50 mcg/FP 250 mcg Diskus BID Placebo BID	24 weeks	Randomized, double-blind, placebo controlled, parallel group	640	COPD, ≥40 years

Integrated review of safety findings from these three pivotal studies follow.

7.1.3.1. Demographics

Patient demographics and baseline characteristics for the pivotal studies in this application are presented in Table 7.2. The mean age of patients was fairly similar in each of the treatment groups, approximately 62 to 64 years. Patients ranged from 39 to 90 years of age.

The majority of patients in these studies were of male gender. Males represented from 61% to 70% of patients in each of the treatment groups. The distribution of male and female patients was fairly similar in each of the treatment groups. The vast majority of patients in these studies were of Caucasian race, approximately 95%. There were very few patients of Black or Asian race. Non-Caucasian races represented less than 6% of most treatment groups, with the greatest proportion of Non-Caucasian patients in the FP 250 group (7%, 28/399).

With regard to symptoms, all patients experienced dyspnea with walking on level ground, and approximately one third of the patients in each of the treatment groups had dyspnea with walking on level ground for 100 yards or less (MMRC Dyspnea Score ≥3). The majority of patients were former smokers, but a fairly large minority of patients were current smokers. Mean history of smoking was approximately 60 pack-years in each of the treatment groups, much larger than the 20 pack-year history required for entry into the studies. Approximately 30% of each of the treatment groups were using corticosteroids at the time of screening. Use of inhaled corticosteroids at the time of screening ranged from 23% (SAL50/FP 250) to 29% (FP 250).

Reviewer comments:
The under-representation of non-Caucasian patients in these studies is a serious deficiency. The degree of dyspnea, duration of COPD, smoking status, and magnitude of smoking history were fairly similar among treatment groups. The population studied is characterized by long smoking histories, significant dyspnea, and longstanding COPD.

A fairly large minority of patients was taking inhaled corticosteroids at the time of screening. One would expect these patients to more likely to be corticosteroid-responsive than those not taking inhaled corticosteroids, as one would expect patients with no

response or a poor response to have their treatment discontinued. Patients with inhaled corticosteroid use were evenly distributed between treatment groups.

Table 7.2. Summary of patient demographics and baseline characteristics of this application, NDA 20-833, S004 [clinstat\iss\iss.pdf, page 41].

Characteristic	Placebo N = 576		SAL 50 N = 341		FP 250 N = 399		FP 500 N = 391		SAL 50/FP 250 N = 178		SAL 50/FP 500 N = 169	
Age, years	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Mean age		64.6		63.9		64.4		63.7		63.4		62.0
Range		40 – 90		40 – 87		40 – 88		39 – 85		40 – 87		40 – 86
Gender	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Female	171	(30)	133	(39)	122	(31)	141	(36)	70	(39)	64	(38)
Male	405	(70)	208	(61)	277	(69)	250	(64)	108	(61)	105	(62)
Race	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Caucasian	539	(94)	321	(94)	371	(93)	367	(94)	170	(96)	159	(94)
Black	23	(4)	13	(4)	18	(5)	17	(4)	5	(3)	7	(4)
Asian/Other	14	(2)	7	(2)	10	(3)	7	(2)	3	(2)	3	(2)
MMRC Dyspnea Score	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
2	385	(67)	211	(62)	257	(64)	253	(65)	109	(61)	108	(64)
3	168	(29)	113	(33)	133	(33)	120	(31)	63	(35)	59	(35)
4	23	(4)	17	(5)	7	(2)	18	(5)	6	(3)	2	(1)
Missing	0	(0)	0	(0)	2	(1)	0	(0)	0	(0)	0	(0)
Smoking status	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Former smoker	303	(53)	175	(51)	214	(54)	208	(53)	101	(57)	91	(54)
Current smoker	273	(47)	166	(49)	185	(46)	183	(47)	77	(43)	78	(46)
Pack-years smoked												
Mean	62.7		63.2		60.5		60.1		59.8		62.1	
Range	20 – 168		20-224		20-162		20-201		20-220		15-150	
Inhaled steroids at screening	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Yes	153	(27)	84	(25)	117	(29)	111	(28)	41	(23)	48	(28)
No	423	(73)	257	(75)	282	(71)	280	(72)	137	(77)	121	(72)

7.1.3.2. Disposition

Patient disposition for the pivotal studies in this application is presented in Table 7.3. There were a total of 2054 patients randomized and 1365 patients completed the studies. There were 689 patients that discontinued prematurely for an overall dropout rate of 33.5%. The largest percentage of discontinuations was in the FP 500 group (37%, 143/391). The smallest percentage of discontinuations was in the SAL 50 (30%, 103/341) and SAL 50/FP 250 (30%, 53/178) treatment groups. Although more of an efficacy than safety issue, it is notable that there is little if any difference in dropout rate between the active treatment groups and placebo, unlike what is typically observed in asthma trials using inhaled corticosteroids.

The most frequent reason for discontinuation for all groups was COPD exacerbation, which ranged from 25% in the SAL 50 and FAL 50/FP 500 groups to 30% in the placebo group. Adverse events (AEs) leading to discontinuation were most common in the FP 500 group (27%, 39/341) and least in the SAL 50, FP 250, and SAL 50/FP 250 groups (all 17%). Lack of efficacy as a reason for discontinuation was most frequent in the FP 250 (19%) and least frequent in the FP 500 and SAL 50/FP 500 groups (5%). Protocol violations were also more frequent in the FP 500 group (20%) compared with the other treatment groups (13% to 18%) [clinstat\iss\iss.pdf, page 49].

Reviewer comment:
Although discontinuations due to lack of efficacy occurred at low frequency in the FP 500 group, this group also had the highest frequency of discontinuation due to AEs of all the treatment groups.

Table 7.3. Patient disposition, pivotal studies in this application, NDA 20-833, S004 [clinstat\iss\iss.pdf, page 50]

	Placebo N (%)	SAL 50 N (%)	FP 250 N (%)	FP 500 N (%)	SAL 50/FP 250 N (%)	SAL 50/FP 500 N (%)
Patients randomized	576 (100)	341 (100)	399 (100)	391 (100)	178 (100)	169 (100)
Patients completed	367 (64)	238 (70)	273 (68)	248 (63)	125 (70)	114 (67)
Patients discontinued	209 (36)	103 (30)	126 (32)	143 (37)	53 (30)	55 (33)
Reason						
Adverse event	38 (18)	17 (17)	22 (17)	39 (27)	9 (17)	11 (20)
COPD exacerbation	62 (30)	26 (25)	35 (28)	39 (27)	15 (28)	14 (25)
Withdrawn consent	29 (14)	13 (13)	7 (6)	13 (9)	10 (19)	11 (20)
Lack of efficacy	35 (17)	16 (16)	24 (19)	7 (5)	3 (6)	3 (5)
Lost to follow-up	5 (2)	4 (4)	8 (6)	7 (5)	6 (11)	2 (4)
Protocol violation	27 (13)	18 (17)	23 (18)	29 (20)	7 (13)	8 (15)
Other	13 (6)	9 (9)	7 (6)	9 (6)	3 (6)	6 (11)

7.1.3.3. Exposure

Total drug exposure is summarized in Table 7.4. Approximately more than 50% of each group completed ≥24 weeks of study treatment. The mean duration of treatment was 128.9 days for placebo, 135.6 days for FP 250, and 131.9 days for FP 250.

Table 7.4. Total drug exposure, pivotal studies in this application, NDA 20-833, S004 [clinstat\iss\iss.pdf, page 58].

Duration of treatment	Placebo N = 576		SAL 50 N = 341		FP 250 N = 399		FP 500 N = 391		SAL 50/FP 250 N = 178		SAL 50/FP 500 N = 169	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	N	(%)
0 to <4 weeks	78	(14)	34	(10)	35	(9)	36	(9)	15	(8)	16	(9)
4 to <8 weeks	36	(6)	17	(5)	27	(7)	27	(7)	5	(3)	10	(6)
8 to <12 weeks	26	(5)	18	(5)	21	(5)	24	(6)	10	(6)	6	(4)
12 to <16 weeks	33	(6)	7	(2)	15	(4)	28	(7)	7	(4)	5	(3)
16 to <20 weeks	24	(4)	13	(4)	21	(5)	19	(5)	10	(6)	9	(5)
20 to <24 weeks	64	(11)	35	(10)	59	(15)	38	(10)	19	(11)	23	(14)
≥24 weeks	315	(55)	217	(64)	221	(55)	219	(56)	112	(63)	100	(59)
Treatment days, mean	128.9		138.5		135.6		131.9		141.3		137.8	

Reviewer comment:
Drug exposure appears to be adequate to allow for assessment of safety over the 24-week treatment period, given the recognition that compliance reporting is commonly unreliable, but should not be taken as supportive of the adequacy of safety assessment in the long-term.

7.1.3.4. Adverse events

Adverse events (AEs) were fairly common in these studies. AEs occurring at a frequency of ≥3% and more frequently in FP 250, FP 500, SAL 50/FP 250, or SAL 50/FP 500 than placebo are summarized in Table 7.5. A dose response effect was noted when comparing all AEs for placebo (69%) with FP 250 (74%) and FP 500 (80%). A dose response effect was noted when comparing all AEs for placebo (69%) with SAL 50/FP 250 (70%) and SAL 50/FP 500 (78%).

AEs occurring at a frequency ≥3% and more frequently with FP 250, FP 500, SAL 50/FP 250, or SAL 50/FP 500 than with placebo included upper respiratory tract infection, headaches, musculoskeletal pain, throat irritation, viral respiratory infections, URI, candidiasis of the mouth or throat, nasal congestion/blockage, cough, sinusitis, nausea and vomiting, hoarseness/dysphonia, fever, malaise and fatigue, muscle cramps and spasms, rhinitis, dizziness, hypertension, sinusitis/sinus infection, and muscle pain [clinstat\iss\iss.pdf, page 67].

When comparing placebo with FP 250 and FP 500, a dose response effect was noted for URTI, headaches, viral respiratory infections, URTI, candidiasis of the mouth or throat, nasal congestion/blockage, and muscle pain [clinstat\iss\iss.pdf, page 67].

When comparing placebo with SAL 50/FP 250 and SAL 50/FP 500, a dose response effect was noted for headaches, throat irritation, viral respiratory infections, sinusitis/sinus infection, and muscle cramps and spasms [clinstat\iss\iss.pdf, page 67].

Reviewer comment:
Many of these AEs are noted in the labels for Flovent MDI and Flovent Rotadisk. These include upper respiratory tract infection, headaches, candidiasis, viral respiratory infections, nasal congestion, dysphonia, sinusitis, diarrhea, and rhinitis. AEs reported in

these studies that are not noted in current labeling for other Flovent products include musculoskeletal pain, nausea and vomiting, airway irritation (throat irritation, cough, rhinitis), dizziness, malaise and fatigue.

Table 7.5. Adverse events occurring at a frequency of ≥3% and more frequently in FP 250, FP 500, SAL 50/FP 250, or SAL 50/FP 500 than in placebo, pivotal studies in this application, NDA 20-833, S004. Entries represent number (percent) of patients [clinstat\iss\iss.pdf, page 68].

Adverse event	Placebo N = 576		SAL 50 N = 341		FP 250 N = 399		FP 500 N = 391		SAL 50/FP 250 N = 178		SAL 50/FP 500 N = 169	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any event	397	(69)	233	(68)	294	(74)	312	(80)	124	(70)	131	(78)
URTI*	114	(20)	53	(16)	84	(21)	96	(25)	26	(15)	43	(25)
Headaches	66	(11)	47	(14)	51	(13)	65	(17)	28	(16)	30	(18)
Musculoskeletal pain	58	(10)	42	(12)	41	(10)	35	(9)	16	(9)	20	(12)
Throat irritation	36	(6)	24	(7)	35	(9)	36	(9)	15	(8)	19	(11)
Viral respiratory infections	23	(4)	17	(5)	20	(5)	36	(9)	10	(6)	14	(8)
Candidiasis mouth/throat	4	(<1)	6	(2)	23	(6)	46	(12)	17	(10)	12	(7)
Nasal congestion/ blockage	19	(3)	12	(4)	17	(4)	26	(7)	5	(3)	7	(4)
Cough	24	(4)	17	(5)	18	(5)	15	(4)	2	(1)	6	(4)
Sinusitis/ sinus infection**	24	(4)	20	(6)	30	(8)	19	(5)	9	(5)	12	(7)
Nausea & vomiting	18	(3)	11	(3)	16	(4)	16	(4)	4	(2)	6	(4)
Hoarseness/ dysphonia	6	(1)	2	<1)	18	(5)	19	(5)	9	(5)	5	(3)
Fever	18	(3)	4	(1)	12	(3)	11	(3)	8	(4)	6	(4)
Malaise & fatigue	17	(3)	7	(2)	11	(3)	12	(3)	6	(3)	6	(4)
Muscle cramps & spasms	7	(1)	10	(3)	9	(2)	8	(2)	6	(3)	13	(8)
Rhinitis	14	(2)	12	(4)	11	(3)	8	(2)	4	(2)	3	(2)
Dizziness	10	(2)	12	(4)	7	(2)	7	(2)	7	(4)	5	(3)
Hypertension	11	(2)	12	(4)	5	(1)	9	(2)	4	(2)	5	(3)
Muscle pain	5	(<1)	4	(1)	7	(2)	13	(3)	0	(0)	7	(4)

*Combines sponsor's numbers for URTI and URI
**Combines sponsor's numbers for sinusitis and sinusitis/sinus infection

A listing of AEs that have been attributed to local and systemic effects of corticosteroids is found in Table 7.6. With the exception of oropharyngeal candidiasis, small numbers of these AEs were observed. Candidiasis, throat irritation, and hoarseness/dysphonia were more common in FP 250, FP 500, SAL 50/FP 250, and SAL 50/FP 500 than in placebo. A dose response effect for candidiasis was seen when comparing placebo (1%) with FP 250 (7%) and FP 500 (13%). A dose response effect was seen for throat irritation when comparing placebo (6%) with SAL 50/FP 250 (8%) and SAL 50/FP 500 (11%) [clinstat\iss\iss.pdf, pages 68, 275-307]. There were a small number of AEs for fractures, cataracts, hyperglycemia, diabetes mellitus, and impaired glucose tolerance, and the frequencies of these AEs were similar among treatment groups. There appeared to be higher frequency of pneumonia for FP 250 (1%), FP 500 (2%), and SAL 50/FP 500 (1%) than for placebo (<1%).

Table 7.6. Selected adverse events of low frequency, pivotal studies in this application, NDA 20-833, S004. Entries represent number (percent) of patients [clinstat\iss\iss.pdf, pages 68, 275-307].

Adverse event	Placebo N = 576		SAL 50 N = 341		FP 250 N = 399		FP 500 N = 391		SAL 50/FP 250 N = 178		SAL 50/FP 500 N = 169	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any event	397	(69)	233	(68)	294	(74)	312	(80)	124	(70)	131	(78)
Candidiasis*	6	(1)	8	(2)	29	(7)	50	(13)	20	(11)	18	(11)
Throat irritation	36	(6)	24	(7)	35	(9)	36	(9)	15	(8)	19	(11)
Fractures	9	(2)	1	(<1)	4	(1)	4	(1)	3	(2)	3	(2)
Cataracts	1	(<1)	0	(0)	0	(0)	3	(<1)	0	(0)	0	(0)
Ocular pressure disorders	2	(<1)	0	(0)	0	(0)	0	(0)	0	(0)	2	(1)
Hoarseness/ dysphonia	6	(1)	2	(<1)	18	(5)	19	(5)	9	(5)	5	(3)
Pneumonia	4	(<1)	1	(<1)	5	(1)	7	(2)	0	(0)	2	(1)
Hyperglycemia	1	(<1)	4	(<1)	4	(1)	2	(<1)	1	(<1)	1	(<1)
Diabetes mellitus	1	(<1)	0	(0)	0	(0)	1	(<1)	0	(0)	2	(1)
Impaired glucose tolerance	0	(0)	0	(0)	0	(0)	1	(<1)	0	(0)	0	(0)

*Includes candidiasis mouth/throat, candidiasis unspecified, and unspecified oropharyngeal plaques.

Reviewer comment:
The large doses of FP used is underscored by the high frequency of candidiasis in the FP 500 (13%) and SAL 50/FP 500 groups (11%) in these 6-month studies. There appears to be an association of pneumonia with FP-treated patients. There is no signal for fractures, cataracts, ocular pressure disorders, and disorders of glucose metabolism in these 6-month studies. It is likely that these studies were of insufficient duration to detect differences between treatment groups for these uncommon events. Furthermore, these studies were not designed to specifically look for cataract or systemic bone effects, both known to be associated with systemic effects of corticosteroids. Ophthalmologic examination and studies to assess osteoporosis would have been helpful to address these concerns. There appears to be suggestion that pneumonia may be associated with FP.

7.1.3.5. Deaths

There were four deaths that occurred in patients in the pivotal clinical studies in this application. All four deaths occurred in patients treated with placebo. One of these four patients died after completing study FLTA3025, three of these deaths occurred during SFCA3006. There were no deaths in SFCA3007 [clinstat\iss\iss.pdf.83-84].

7.1.3.6. Serious adverse events

A total of 115 patients (6%, 115/2054) experienced SAEs during the treatment period of these studies. The frequency of SAEs was similar among treatment groups and ranged from 4% for SAL 50 and SAL 50/FP 250 to 7% for FP 500. SAEs occurring in more than one patient in any treatment group are summarized in Table 7.7.

Table 7.7. SAEs occurring in more than one patient in any treatment group, pivotal studies in this application, NDA 20-833, S004. Entries represent number (percent) of patients [clinstat\iss\iss.pdf, pages 84, 424-432].

SAE	Placebo N = 576		SAL 50 N = 341		FP 250 N = 399		FP 500 N = 391		SAL 50/FP 250 N = 178		SAL 50/FP 500 N = 169	
Any SAE	34	(6)	12	(4)	25	(6)	27	(7)	8	(4)	9	(5)
COPD	7	(1)	4	(1)	8	(2)	11	(3)	0	(0)	2	(1)
Pneumonia	1	(<1)	1	(<1)	3	(<1)	4	(1)	0	(0)	2	(1)

SAE	Placebo N = 576	SAL 50 N = 341	FP 250 N = 399	FP 500 N = 391	SAL 50/FP 250 N = 178	SAL 50/FP 500 N = 169
Chest symptoms	5 (<1)	1 (<1)	0 (0)	0 (0)	1 (<1)	2 (1)
Fractures	1 (<1)	0 (0)	2 (<1)	2 (<1)	1 (<1)	0 (0)
Cholelithiasis	1 (<1)	0 (0)	2 (<2)	0 (0)	0 (0)	0 (0)
Syncope	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Depressive disorders	2 (<1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

SAEs for COPD were more common in FP 250 and FP 500 than for placebo. A dose response effect was noted for COPD. There was a suggestion that SAEs for pneumonia were associated with FP.

Reviewer comment:
There was a higher frequency of COPD in FP 250 and FP 500, and a suggestion of an association with pneumonia with FP. Although these may be a chance occurrence, these data raise the concern that lower respiratory tract infections may be associated with FP. It should be noted that AEs for URTI were associated with FP in these studies, and are noted in current FP labeling.

7.1.3.7. Withdrawals due to AEs

Withdrawals due to any AE were more common in FP 500 (11%, 42/391) and SAL 50/FP 500 (7%, 11/169) than in placebo (6%, 36/576). Withdrawals due to AEs for COPD were more common in FP 500 (3%, 10/391) and FP 250 (2%, 8/399) than placebo (1%, 8/576); a dose response effect was noted. Withdrawals due to pneumonia were more common in FP 500 (1%, 4/391), FP 250 (1%, 4/399), and SAL 50/FP 500 (1%, 2/169) than for placebo (<1%, 1/576). Withdrawals due to candidiasis mouth/throat only occurred in FP 500-treated patients (<1%, 3/391). Withdrawals due to viral respiratory infections occurred only in FP 500 (<1%, 1/391), FP 250 (<1%, 1/399), and SAL 50/FP 250 (<1%, 1/178). Data for other withdrawals due to AEs do not suggest any safety signal.

Reviewer comment:
Withdrawals due to AEs also suggest that lower respiratory tract and viral infections may be associated with FP treatment in this population. Withdrawals due to candidiasis mouth/throat only occurred in FP 500-treated patients, which underscores the large dose of FP used and is concordant with other AE data from these pivotal studies.

7.1.3.8. Vital signs

The sponsor did not provide an integrated summary of vital signs results from the pivotal studies. The following is an integrated summary of this reviewer's analysis of vital signs results from the pivotal studies.

There were no clinically significant changes from baseline in median values of vital signs for any of the treatment groups in the pivotal studies in this application [clinstat\copd\flta3025.pdf, pages 147, 903-905; clinstat\copd\sfca3006.pdf, pages 1521-1520; clinstat\copd\sfca3007.pdf, pages 999-1004].

The sponsor provided a summary of 12-hour serial vital signs results from SFCA3006 in their Integrated Safety Summary. These results are pertinent to the SAL50, SAL 50/FP 250, and SAL 50/FP 500 products, and not the FP 250 and FP 500 products. Accordingly these data are not summarized in this section of this review.

7.1.3.9. Physical examination

Physical examinations were performed at Screening and at the Week 24 visit or the Discontinuation visit in each of these studies. Data were recorded on subject progress notes, but not on case report forms (CRFs). Physical examination abnormalities were recorded as AEs on the CRFs, but no summary of physical examinations was provided [NDA 20-833, SE1-004, BM, 9/17/01, page 3]. Any physical exam abnormalities are therefore included in the AE section each pivotal study, and are also included in the AE section of this safety summary.

7.1.3.10. Laboratory studies

Clinical laboratory tests were performed on samples collected at screening, Week 12, and Week 24 and/or the Discontinuation visit for each of the pivotal studies. Laboratory studies analyzed as safety endpoints included hematology studies and blood chemistry studies.

Small numbers of patients in the pivotal studies had shifts in % lymphocyte, % neutrophils, and WBC counts from baseline at Weeks 12 and 24 (<1% to 7%). Larger numbers of patients had shifts in lymphocyte, % neutrophils, and WBC counts at Discontinuation (2% to 22%).

There was a greater percentage of patients with shifts in % lymphocytes to low in patients treated with FP 500 (6%, 118/284) than for FP 250 (3%, 9/305), than placebo (1%, 5/420) at Week 12. The percentage of patients with shifts in % lymphocytes for FP 500, FP 250, and placebo were similar at Week 24. The percentage of patients with shifts in % lymphocytes to low at discontinuation for was higher for FP 500 (16%, 19/117), and SAL 50/FP 250 (22%, 9/41) than for placebo (9%, 16/177) [clinstat\iss\iss.pdf, page 102].

There was a greater percentage of patients treated with FP 500 (5%, 13/284) and FP 250 (5%, 15/305) with shifts in % neutrophils to high than placebo (2%, 9/420) at week 12. The percentage of patients with shifts in % neutrophils to high was similar at week 24 for FP 500 (4%, 9/241), FP 250 (4%, 11/268), and placebo (3%, 11/357). There was a greater percentage of patients treated with FP 500 (21%, 24/117) and SAL 50/FP 250 (20%, 8/41) with shifts in % neutrophils to high at discontinuation than for FP 250 (11%, 11/104), SAL 50/FP 500 (11%, 5/47), and placebo (11%, 619/177) [clinstat\iss\iss.pdf, page 102].

Shifts in WBC counts to high were similar for FP 500, FP 250, and placebo groups at Week 12, Week 24, and Discontinuation [clinstat\iss\iss.pdf, page 102].

Reviewer comment:
The shifts in % lymphocytes, % neutrophils, and WBC counts in FP-treated patients could be systemic corticosteroid effects of inhaled FP. The high percentage of patients with shifts in % lymphocytes, % neutrophils, and WBC counts at discontinuation are likely to be in patients discontinuing from COPD exacerbations who received treatment with systemic corticosteroids.

Increases from baseline in ALT were generally similar in each of the treatment groups at Week 12, Week 25, and Discontinuation. Exceptions were the SAL 50/FP 250 (12%, 5/42) and SAL 50/FP 500 (9%, 4/47) groups, which had a higher percentage of patients at Discontinuation with a shift in ALT to high than the placebo group (4%, 8/179) [clinstat\iss.iss.pdf, page 103].

Increases from baseline in AST were generally similar in each of the treatment groups at Week 12, Week 24, and Discontinuation. Exceptions were the SAL 50/FP 250 group (7%, 3/42) which had an higher percentage of patients at Discontinuation with a shift in AST to high than the placebo group (4%, 8/179) [clinstat\iss.iss.pdf, page 103].

There was a greater percentage of patients who had shifts in alkaline phosphatase to high for FP 250, FP 500, than placebo at Weeks 12, 24, and Discontinuation. The percentage of patients who had shifts from baseline to high in alkaline phosphatase at Week 12 for FP 500 was 3%, (9/287), compared with FP 250 (2%, 7/301) and placebo (1%, 5/414). The percentage of patients who had shifts from baseline to high in alkaline phosphatase at Week 24 for FP 500 was 2%, (4/244), compared with and FP 250 (2%, 4/265) and placebo (1%, 5/353). The percentage of patients who had shifts from baseline to high in alkaline phosphatase at Discontinuation for FP 500 was 2%, (2/116), compared with and FP 250 (3%, 43/103) and placebo (1%, 2/176) [clinstat\iss.iss.pdf, page 103].

Reviewer comment:
The higher percentage of patients with shifts of alkaline phosphatase to high for FP 250 and FP 500 is interesting. It is unclear if these shifts suggest a liver signal or a bone signal, as isoenzyme data was not provided. These data may be a chance occurrence, but may also suggest a systemic effect of inhaled FP.

In general, there was no meaningful difference in the percentage of patients who had shifts to high from baseline in glucose at Weeks 12, 24, and Discontinuation for each of the treatment groups. Exceptions were SAL 50/FP 500 (13%, 16/47) and SAL 50/FP 250 (12%, 5/43), which were higher than placebo (8%, 14/176) [clinstat\iss\iss.pdf, page 103]. It should be noted that the sponsor defined an exceptionally liberal definition for high glucose, >175 mg/dL in each of these studies. It is likely that this liberal definition of high glucose would result in a lower sensitivity of detecting a difference between treatment groups [clinstat\copd\flta3025.pdf, page 3598; clinstat\copd\sfca3006.pdf, page 6720; clinstat\copd\sfca3007.pdf, page 5787].

Reviewer comment:
Hyperglycemia is an effect of systemic corticosteroids. There were higher percentages of SAL 50/FP 500 and SAL 50/FP 250 patients with increases in glucose at Discontinuation than placebo patients. There were no other meaningful differences between treatment groups. This observation is much less reassuring because of the sponsor's liberal definition of elevated blood glucose, >175 mg/dL.

7.1.3.11. ECG

Twenty-four hour Holter monitoring was conducted at selected centers in SFCA3006. These data are pertinent to the SAL 50, SAL 50/FP 250, and SAL 50/FP 500 products. Holter monitoring results did not demonstrate significant differences among treatment groups [clinstat\iss\iss.pdf, page 127].

Twelve-lead ECGs were recorded at screening, Week 12, Week 24, and/or Discontinuation for each of the pivotal studies in this application. There were no differences between treatment groups in percentage of patients with clinically significant changes in ECGs from baseline. The types of clinically significant abnormalities were similar among treatment groups [clinstat\iss\iss.pdf, pages 128-131].

Mean QTc intervals, by both Bazette's and Fridericia's formulae, were similar among treatment groups at Weeks 12, 24, and Discontinuation [clinstat\iss\iss.pdf, page 136]. Approximately 95% of patients in each of the treatment groups had shifts in QTcB from baseline of <30 msec. The percentage of patients with shifts in QTcB from baseline of 30-50 msec, 50-70 msec, and ≥ 70 msec were similar among treatment groups [clinstat\iss\iss.pdf, page 137].

7.1.3.12. HPA axis effects in pivotal studies

HPA axis effects were studied by serum cortisol analyses in FLTA3025. HPA axis effects were studied at selected sites in SFCA3006 and SFCA3007 by morning plasma cortisol concentrations and short cosyntropin stimulation testing. These data are reviewed below.

7.1.3.12.a. Serum cortisol AUC_{12}, FLTA3025

In FLTA3025, blood samples for plasma FP and serum cortisol analyses were obtained at Week 4 at selected sites. Samples were to be collected immediately prior to dosing and at 0.5, 1, 2, 4, 8, and 12 hours post-dose [clinstat\copd\flta3025.pdf, page 5298]. Plasma was analyzed for FP concentration at each time point using solid phase extraction in combination with liquid chromatography tandem mass spectrometry. The sponsor states that this method has been validated to a limit of quantitation of 10 pg/mL for FP [clinstat\copd\flta3025.pdf, page 60].

There were 86 patients who participated in the clinical pharmacology component of this study, and 28 were treated with placebo, 31 with FP 250, and 27 with FP 500 [clinstat\copd\flta3025.pdf, page 166]. Key pharmacodynamic results are displayed in Table 7.8.

Table 7.8. Serum cortisol results, FLTA3025 [clinstat\copd\flta3025.pdf, pages 166, 4855].

Cortisol parameter	Placebo N = 28	FP 250 N = 31	FP 500 N = 27
Mean Cortisol AUC_{12}, pmol.hr/mL	2673.4	2404.2	2102.3
Δ vs. placebo	-	- 10.1%	- 21.4%
Mean C_{min}, pmol/mL	123.1	116.7	85.3

FP 250 and FP 500 treatment groups had lower mean cortisol AUC_{12} and mean C_{min} than the placebo group (10% and 21%, respectively, for serum cortisol AUC). There was a dose-response effect noted with the lowest cortisol AUC_{12} and C_{min} in FP 500 patients [clinstat\copd\flta3025.pdf, pages 166, 4855]. Higher mean cortisol AUC_{12} levels were noted for current smokers than for former smokers, consistent with the lower serum FP levels measured in current smoking. There was no relationship noted between cortisol levels and weight [clinstat\copd\flta3025.pdf, page 4857].

Reviewer comment:
Unfortunately, baseline cortisol levels were not planned for this study. Change from baseline in AM cortisol level or serum cortisol AUC would have been more informative than the cross-group comparisons available from these data derived from Week 4 samples alone. These data demonstrate measurable systemic effects of inhaled FP. These findings are not a surprise, given the large dose of FP used. It is important to note this is clear evidence of systemic activity of FP in this population, which is corroborated by the single dose crossover study conducted in normal volunteers (see FLTA1003, later in this section, and OCPB review). It should also be noted that these effects were noted early in the course of the study, at Week 4. It would have been interesting to examine similar data collected later in this study, for example, Week 24, where one might expect even a higher degree of suppression of cortisol AUC_{12} levels.

Another consideration is the sampling strategy, which was PK in design and timed around the anticipated C_{max} for inhaled FP. It is possible that greater differences between treatment groups in HPA axis effects could have been detected with more frequent sampling to ensure that the AM cortisol peak had been captured. For example FLTA1003, which used timed urinary cortisol and should have quantitatively included all excreted cortisol, showed a reduction to 40 – 60% of baseline following a single dose of 1000 mcg FP.

HPA axis effects were studied at selected sites in SFCA3006 and SFCA3007 with morning plasma cortisol concentrations and short cosyntropin stimulation testing. Results of cosyntropin stimulation testing are summarized in Table 7.9. The percentage of patients with pre-stimulation AM cortisol levels <4 mcg/dL at Day 1 and Endpoint were similar in each of the treatment groups. There were no differences between treatment groups in the percentage of patients with a change in post-stimulation cortisol <5.6 mcg/dL [clinstat\iss\iss.pdf, page 122].

FP 250 (15%), FP 500 (16%), and SAL 50/FP 500 (17%) had the largest percentage of patients with post-stimulation change in cortisol of <5.6 mcg/dL at endpoint, compared

with placebo (8%), SAL 50 (9%), and SAL 50/FP 250 (9%). However, SAL 50 (12%), FP 250 (10%), SAL 50/FP 250 (9%), and SAL 50/FP 500 (10%) also had fairly high percentages of patients with post-stimulation change in cortisol compared with placebo (5%) [clinstat\iss\iss.pdf, page 122].

There was an increase in the percentage of patients with post-stimulation cortisol levels <14.5 mcg/dL from Day 1 to Endpoint in all treatment groups. The largest increase in the percentage of patients with post-stimulation cortisol levels <14.5 mcg/dL from Day 1 to Endpoint was in the FP 250 group (6% to 12%). The percentage of patients with post-stimulation cortisol levels <14.5 mcg/dL in the other treatment groups were similar at Day 1 and Endpoint [clinstat\iss\iss.pdf, page 122].

Reviewer comment:
The data for cosyntropin stimulation testing show no evidence of adrenal suppression, however, cosyntropin stimulation testing is intended as a means to diagnose adrenal insufficiency and is a fairly insensitive measure of adrenal suppression and a fairly small number of patients (15-20%) were tested.

Table 7.9. Number and percentage of patients with abnormalities in cosyntropin stimulation testing, all patients with cortisol levels, pivotal studies in this application [clinstat\iss\iss.pdf, page 122].

	Day 1						**Endpoint**					
	Pbo N=576 n (%)	**SAL 50 N=341 n (%)**	**FP 250 N=399 n (%)**	**FP 500 N=391 n (%)**	**SAL 50/ FP 250 N=178 n (%)**	**SAL 50/ FP 500 N=169 n (%)**	**Pbo N=576 n (%)**	**SAL 50 N=341 n (%)**	**FP 250 N=399 n (%)**	**FP 500 N=391 n (%)**	**SAL 50/ FP 250 N=178 n (%)**	**SAL 50/ FP 500 N=169 n (%)**
Patients with cortisol levels	98 (100)	89 (100)	50 (100)	39 (100)	44 (100)	39 (100)	63 (100)	65 (100)	26 (100)	37 (100)	32 (100)	36 (100)
Pre-stim AM cortisol <4 mcg/dL	3 (3)	1 (1)	2 (4)	0 (0)	0 (0)	1 (3)	2 (3)	1 (2)	0 (0)	1 (3)	1 (3)	0 (0)
Post-stim change <5.6 mcg/dL	5 (5)	11 (12)	5 (10)	2 (5)	4 (9)	4 (10)	5 (8)	6 (9)	4 (15)	6 (16)	3 (9)	6 (17)
Post-stim cortisol <14.5 mcg/dL	3 (3)	4 (4)	3 (6)	1 (3)	1 (2)	1 (3)	4 (6)	3 (5)	3 (12)	2 (5)	1 (3)	2 (6)

7.1.4. Subgroup analyses of safety endpoints in pivotal studies

Subgroup analyses of safety endpoints by gender, age, and race follow. The safety endpoints analyzed include AEs, deaths and SAEs, withdrawals due to AEs, laboratory data, HPA axis effects, and ECGs.

7.1.4.1. Subgroup analyses of AEs

The frequency of AEs were higher in females (71% to 83%) than males (61% to 82%). URTI, headaches, musculoskeletal pain, throat irritation, viral respiratory infections, and URI were more common in females than in males, but this difference was present for all treatment groups, including placebo. There was no consistent association of gender with AEs for any of the treatment groups [clinstat\iss\iss.pdf, pages 70, 72].

The overall frequency of AEs was similar in patients <65 years of age (67% to 81%) and in those ≥65 years of age (64% to 80%). URTI, headaches, musculoskeletal pain, throat irritation, and viral respiratory infections were slightly more common in patients <65 years of age than in patients ≥65 years of age, but this difference was present for all treatment groups, including placebo. There was no consistent association of age with AEs for any of the treatment groups [clinstat\iss\iss.pdf, pages 70, 73].

The overall frequency of AEs differed by race. The overall frequency of AEs in Caucasian patients ranged from 69% (223/321) to 81% (298/367). The overall frequency of AEs in Black patients ranged from 47% (8/17) to 72% (13/18). The overall frequency of AEs in patients of Asian or Other race ranged from 33% (1/3) to 43% (3/7). The difference in frequencies between the races is likely to be a result of the small sample size of patients of Black and Asian/Other races. Review of the AEs for patients of Black and Asian/Other races does not reveal an obvious association with the type of treatment. The insufficient sample size of patients of color does not allow for a proper analysis of AEs by race, however.

Reviewer comments:
The under-representation of non-Caucasian patients in this study is a serious deficiency of these studies. The sponsor has not adequately studied the safety of FP in non-Caucasian patients with COPD. Additional study of the safety of FP in a more racially diverse study population is strongly encouraged .

7.1.4.2. Subgroup analyses of deaths and SAEs

All deaths were in placebo-treated patients. There was no association of gender for the four deaths in the pivotal studies. Two of the four patients that died were males and two were females. One of the four patients that died was <65 years of age (60 years). The other three were ≥65 years (66, 69, and 72 years). All patients that died in the pivotal studies were Caucasian [clinstat\iss\iss.pdf, page 83].

The overall frequency of SAEs was higher in males (4% to 9%) than females (3% to 6%). Pneumonia, syncope, and fractures were more common in males, and chest symptoms were more common in females. The frequency of SAEs by gender were similar among

active and placebo treatment groups [clinstat\iss\iss.pdf, pages 85, 87]. The overall frequency of SAEs was slightly lower in patients <65 years (3% to 7%) than in patients ≥65 years (4% to 8%). Pneumonia appeared to be more common in patients ≤65 years of age who were treated with FP 500 and SAL 50/FP 500. Fractures appeared to be more common in patients >65 years of age, but occurred at similar frequencies in the treatment groups [clinstat\iss\iss.pdf, page 88]. The small number of non-Caucasian patients did not allow for an analysis of SAEs by race [clinstat\iss\iss.pdf, pages 465-477].

7.1.4.3. Subgroup analyses of withdrawals due to AEs

The frequency of withdrawal due to AEs was fairly similar in males and females. Pneumonia, hoarseness/dysphonia, cardiovascular test findings, CVA, myocardial infarction, palpitations, and tachyarrhythmias were more common in males than in females, but frequencies were similar among the treatment groups [clinstat\iss\iss.pdf, page 96].

The frequency of withdrawal due to AEs was lower in patients <65 years of age than in patients ≥65 years of age. Withdrawals due to depressive disorders, URTI, and viral respiratory infection were more common in patients <65 years of age than in patients ≥65 years of age, but were at similar frequencies in the treatment groups. Withdrawals due to pneumonias were more common in patients ≥65 years of age who were treated with FP 500 and SAL 50/FP 500 [clinstat\iss\iss.pdf, page 97]. The small number of non-Caucasian patients did not allow for an analysis of withdrawals due to AEs by race [clinstat\iss\iss.pdf, pages 529-538].

7.1.4.4. Subgroup analyses of laboratory data

No consistent changes were noted in the percentage of patients with shifts from baseline in hematology results when analyzed by gender. AST shifts to high at Discontinuation were noted for more females (0% to 12%) than males (0% to 4%). Shifts from baseline to high glucose levels were noted in a slightly higher proportion of males (4% to 19%) than females (0% to 16%). These changes were noted for each of the treatment groups, including placebo [clinstat\iss\iss.pdf, pages 106-109].

More males than females had decreased hemoglobin (20 males, 3 females), decreased hematocrit (8 males, 0 females), and increased WBC (17 males, 0 females). These changes were noted in active as well as in placebo groups [clinstat\iss.\iss.pdf, pages 114-115]. Elevated glucose was noted in more males (42) than females (16), but these changes were noted in active as well as in placebo groups [clinstat\iss\iss.pdf, pages 114, 116].

No consistent changes in the percentage of patients with shifts from baseline in hematology or chemistry results were noted when analyzed by age [clinstat\iss\iss.pdf, pages 107, 110, 112]. No consistent changes in the percentage of patients with abnormal hematology or chemistry results were noted when examined by age [clinstat\iss\iss.pdf, pages 114, 117].

The sponsor did not provide an analysis of laboratory results by race. The small number of non-Caucasian patients would have prevented a meaningful analysis of these data.

7.1.4.5. Subgroup analyses of ECGs

Changes in baseline ECG were noted in more males than females. More clinically significant changes from baseline were noted in patients ≥65 years of age. These changes were noted in active as well as placebo treatment groups [clinstat\iss\iss.pdf, pages 132-134].

Median QTcB intervals were slightly increased (5-10 msec) in females compared with males for each of the treatment groups, active and placebo for each of the time points [clinstat\iss\iss.pdf, pages 141, 899-912]. This is an expected gender effect of QTc.

Median QTcB intervals were similar in patients <65 years of age and in patients ≥65 years of age for each of the treatment groups, active and placebo, for each of the time points [clinstat\iss\iss.pdf, pages 141, 941-954].

The sponsor did not provide an analysis of ECG results by race. The small number of non-Caucasian patients would have prevented a meaningful analysis of these data.

7.1.4.6. Subgroup analyses of HPA axis effects

The small number of patients who had cosyntropin stimulation testing precluded meaningful comparisons between treatment groups for subgroups [clinstat\iss\iss.pdf, pages 123, 846-862]. The sponsor provided no subgroup analysis of cortisol AUC_{12} data for FLTA3025.

7.1.5. Supportive safety data from other studies

The sponsor provided supportive safety data from other studies. These data include:

- AEs and HPA-axis data from clinical pharmacology study FLTA1003
- Blinded listings of deaths and SAEs from ongoing clinical studies SFCB3024, SCO30003
- Studies of Flovent MDI 500 mcg BID, FLIP63, FLIT78, FLIT97, FLIT98
- Bone mineral density data from two long-term studies in asthma, FLTA3001 and FLTA3017
- Blinded listings of deaths and SAEs from nine ongoing non-US studies used to support regional markets (SCO30001, SCO40002, SMS40026, SMS40308, FCO40002, FCO40003, FCO40004, SAM30001)

A review of these supportive safety data from other studies follows below.

7.1.5.1. AEs and HPA-axis data from clinical pharmacology study FLTA1003

FLTA1003 was a Phase 1 clinical pharmacology and pharmacodynamics study that was designed to assess the dose-proportionality and HPA-axis effects of FP when administered by the Diskus [hpbio\bio\flta1003.pdf, page 13]. The study was a single-center, open-label, randomized, single dose, 4-way crossover study. Twenty patients were

to be enrolled in the study. Patients were healthy male and female subjects, ages 18 to 50 years. Patients were randomized to one of the following single doses at each of the study's four treatment periods [hpbio\bio\flta1003.pdf, page 14]:

- 20 inhalations of 50 mcg strength of FP Diskus, total dose 1000 mcg
- 10 inhalations of 100 mcg strength of FP Diskus, total dose 1000 mcg
- 4 inhalations of 250 mcg strength of FP Diskus, total dose 1000 mcg
- 2 inhalations of 500 mcg strength of FP Diskus, total dose 1000 mcg

There was a minimum wash-out period of 5 days between each 24-hour treatment period. [hpbio\bio\flta1003.pdf, page 33].

The dose proportionality of the various dosage strengths will not be addressed in this section of the review. Dose proportionality is addressed briefly elsewhere in this review, and in detail in Dr. Suarez's clinical pharmacology and biopharmaceutics review.

The investigator was responsible for detecting and documenting AEs from screening until the end of the study [hpbio\bio\flta1003.pdf, page 25].

Twenty-four hour urine samples were collected before and after each dose of study medication. Subjects began urine collection the morning after they were admitted to the study site. The pre-dose collection ended with the first void of the following day. The post-dose urine collection began when the second void was collected on that same day and was continued for 24 hours. Cortisol levels were determined using a competitive immunoassay on an automated chemiluminescence system. The range of the assay was 6 nM to 2069 nM.

Twenty-two patients were exposed to study drug, and 20 subjects completed the study [hpbio\bio\flta1003.pdf, page 25]. Three of the 22 subjects experienced a total of eleven AEs. Headache was the most common AE and occurred in two patients. There were no other AEs that occurred in more than one patient [hpbio\bio\flta1003.pdf, pages 33, 69]. The frequency of AEs by treatment group is listed below in Table 7.10.

Table 7.10. AEs by treatment group, FLTA1003 [hpbio\bio\flta1003.pdf, page 33].

Treatment	AEs reported
50 mcg X 20 inhalations	1 dizziness, 1 chest pain
100 mcg X 10 inhalations	None
250 mcg X 4 inhalations	1 headache, 1 rhinorrhea
500 mcg X 2 inhalations	1 fever, 1 chest congestion, 1 weakness, 1 headache, 1 vertigo, 1 sore throat*

*AE not noted on CRF [crf\flta1003\54465]\p0041713.pdf page 18]

There were no deaths or SAEs. There was one patient that withdrew due to an AE. Subject 41713 received treatment with the 500 mcg dosage strength in the first of the four periods. This patient had a fever, vertigo, weakness, chest congestion, headache, sore throat. A rash was noted several days before the first dose [hpbio\bio\flta1003.pdf, page 33, crf\flta1003\54465]\p0041713.pdf page 18]. It is interesting to note that this subject's 24-hour urinary cortisol excretion decreased from 11.7 mcg pre-dose to 1.7 mcg post-dose [hpbio\bio\flta1003.pdf, page 138].

Reviewer comment:
AEs provide no evidence of new safety signal.

Significant decreases in post-treatment urinary cortisol levels were noted across all treatment groups. These data are displayed in Table 7.11. It is interesting to note that the majority of subjects had decreases of similar magnitude even after the first of the four treatment periods [hpbio\bio\flta1003.pdf, pages 138-143].

Table 7.11. Urinary cortisol excretion data, FLTA1003 [hpbio\bio\flta1003.pdf, page 67].

Treatment group	Mean urinary cortisol excretion, pre-dose, mcg	Mean urinary cortisol excretion, post-dose, mcg	Difference, Post-dose minus pre-dose
50 mcg X 20 inhalations	18.5	9.6	8.9
100 mcg X 10 inhalations	22.3	13.8	8.5
250 mcg X 4 inhalations	19.1	12.4	6.7
500 mcg X 2 inhalations	18.0	7.3	10.7

Reviewer comment:
These data show strong evidence of systemic HPA-axis effects in normal subjects when given 1000 mcg FP by Diskus. Decreases in cortisol excretion were noted in many subjects as soon as after the first dose of study treatment. Although COPD patients apparently have less systemic exposure from inhaled FP than normal subjects, the degree of suppression noted in this study after a short period of dosing is notable and gives concern about possible similar effects in the proposed population with long-term exposure. Cortisol data from FLTA3025 was obtained after 4 weeks of treatment, and cosyntropin stimulation data were obtained after 24 weeks of dosing in SFCA3006 and SFCA3007. Given that cortisol and cosyntropin data are less sensitive measures of systemic corticosteroid effects (see "Reviewer Comment" under "Serum Cortisol AUC_{12} FLTA3025", above) , additional long-term safety data of use of FP in the proposed population are needed.

7.1.5.2. Blinded listings of deaths and SAEs from two ongoing controlled clinical studies, SFCB3024 and SCO30003

Blinded listings of deaths and SAEs from two ongoing studies were provided to supplement the safety portion of this application. These studies were SFCB3024 and SCO30003. These safety data for each study are described below.

7.1.5.2.a. SFCB3024

SFCB3024 is a randomized, double blind, parallel group, placebo-controlled, non-US, multicenter trial to compared the efficacy and safety of SAL 50/FP 500 with SAL 50, and FP 500 administered with the Diskus in patients with COPD. Approximately 1200 patients with COPD are to be studied for a 52-week treatment period. There had been 1468 patients enrolled as of the cut-off date of 9/30/00 [clinstat\iss\iss.pdf, page 165].

There were 25 deaths in subjects in SFCB3024 as of the 9/30/00 safety cut-off date. No death was considered by the investigator to be related to study treatment. The majority of deaths were cardiovascular in nature, such as cardiac arrest, cardiac failure, myocardial infarction, among others. Three deaths were due to exacerbation of COPD [clinstat\iss\iss.pdf, page 167].

Most of the SAEs in SFCB3024 are related to exacerbation of COPD. Many are cardiovascular. There were 3 patients with fractures of the lower limb and two patients with fractures of the hip. One of the patients with hip fracture was coded as a drug interaction, overdose and trauma SAE (Patient #8328) and the other as a neurologic SAE (Patient #08457) One patient had a candidal infection of the esophagus [clinstat\iss\iss.pdf, pages 1235-1302].

Reviewer comment:
These blinded data do not provide useful information to support the safety of FP in patients with COPD. The final long-term safety data from these studies will be essential in determining the safety profile for FP in this population and to make an appropriate risk-benefit assessment, particularly given the all-cause and COPD-related mortality already observed.

7.1.5.2.b. SCO30003

SFCB30003 is a randomized, double blind, parallel group, placebo-controlled, multicenter trial to compared the long-term effects of SAL 50/FP 500 with SAL 50, and FP 500 administered with the Diskus in patients with COPD. Approximately 5040 patients with COPD are to be studied for a 36-month treatment period. There had been 8 patients enrolled as of the cut-off date of 9/30/00 [clinstat\iss\iss.pdf, page 165].

There were no deaths or SAEs reported in this study as of the safety cut-off date [clinstat\iss\iss.pdf, page 168].

Reviewer comment:
There are no data from this study at this time and no safety information for this application. This study is designed to investigate all-cause mortality, COPD-related mortality and morbidity, and change in lung function in COPD patients treated with FP. Results of this study will be critical to any regulatory decision regarding a COPD indication for FP.

7.1.5.3. Study summaries of four non-US studies of Flovent MDI in patients with COPD

Safety data from four completed non-US studies of Flovent MDI were provided in support of this application. These studies are FLIT78 (also known as the ISOLDE study), FLIT97, FLIT98, and FLIP63. The sponsor provided study reports for these studies. This document will review AEs, deaths, SAEs, and withdrawals due to AEs occurring in these studies. A brief description of the study design for each of these studies follows.

FLIT78 was a 3-year, non-US, multicenter, double blind, placebo-controlled, parallel group study of the efficacy and tolerability of long-term FP 500 mcg BID in COPD. This trial is also known as the ISOLDE study. The MDI formulation of FP was used with the Volumatic spacer device. The study included an optional 2-week acute corticosteroid trial prior to the start of the double-blind inhaled treatment period. Patients were 40 to 75

years of age. A total of 742 patients were included in the safety analysis, with 372 for FP and 370 for placebo [clinstat\iss\iss.pdf, page 149; clinstat\other\flit78.pdf, page 30].

FLIT97 was a 6-month, multicenter, international, randomized, double-blind, parallel group study of the efficacy and safety of inhaled FP 500 mcg BID with placebo in COPD. The MDI formulation of FP was used with the Volumatic spacer device, if desired. Patients were 50 to 75 years of age. A total of 281 patients were included in the safety analysis, with 142 for FP and 139 for placebo [clinstat\iss\iss.pdf, page 172; clinstat\other\flit97.pdf, pages 5, 20, 25, 29].

FLIT98 was a multicenter, randomized, double-blind, parallel group study of the efficacy and safety of inhaled FP 1000 mcg BID with placebo over a 4-week period to determine the number of days needed to recover from an acute exacerbation of COPD. The MDI formulation of FP was used. Patients were 50 to 75 years of age. A total of 249 patients were included in the safety analysis, with 126 for FP and 123 for placebo [clinstat\iss\iss.pdf, page 172; clinstat\other\flit98.pdf, page 5].

FLIT63 was a single center, randomized, double-blind, parallel group study of the effects of FP 750 mcg BID compared with placebo on the inflammatory processes in the lungs of patients with COPD. Patients received either FP 250 mcg 3 puffs BID via the MDI formulation and using a Volumatic spacer for an 8-week treatment period. Patients were 40 to 75 years of age. A total of 17 patients were included in the safety analysis, with 8 for FP and 9 for placebo [clinstat\iss\iss.pdf, pages 172, 193; clinstat\other\flit63.pdf, pages 15, 17].

7.1.5.3.a. AEs in FLIT78, FLIT97, FLIT98, and FLIP63

FLIT78

The frequency of patients AEs was similar in the FP group (95%, 355/372) and the placebo group (97%, 359/370). AEs occurring more frequently in FP than placebo are displayed in Table 7.12. The FP group experienced higher rates of lower, upper, and viral respiratory infections, throat irritation, candidiasis mouth/throat, hoarseness/dysphonia, and pneumonia.

Table 7.12. Most common AEs occurring more frequently in FP than placebo, FLIT78. Entries represent number (percent) of patients [clinstat\iss\iss.pdf, page 150].

Adverse event	Placebo N = 370 n	(%)	FP 500 mcg BID N = 372 n	(%)
Any AE	359	(97)	355	(95)
Lower respiratory infections	132	(36)	153	(41)
Upper respiratory tract infections	59	(16)	75	(20)
Viral respiratory tract infections	39	(11)	60	(16)
Throat irritation	27	(7)	43	(12)
Candidiasis mouth/throat	24	(6)	41	(11)
Hoarseness/dysphonia	16	(4)	35	(9)
Pneumonia	8	(2)	22	(6)

The sponsor argues that when the slightly overall higher exposure to drug was higher in the FP group is taken into account, that the event rates of all events and infections per

subject-year of exposure were similar between treatment groups. These data are displayed in Table 7.13.

Table 7.13. Infection AEs adjusted for exposure to medication, FLIT78. Entries represent number (percent) of patients [clinstat\iss\iss.pdf, page 150].

Adverse event	Event rate per subject-year of exposure	Event rate per subject-year of exposure
Any AE	1.68	1.51
Lower respiratory infections	0.48	0.46
Viral respiratory tract infections	0.06	0.10
Pneumonia	0.01	0.03

Reviewer comment:
Even if one accepts the sponsor's argument for adjusting the event rates for exposure to study medication, the event rate for pneumonia was three times higher for FP than for placebo, and the rate of viral respiratory tract infections was 1.7 times higher for FP than for placebo. These data suggest that respiratory infections, particularly viral respiratory tract infections and pneumonia may be a safety signal for FP in the COPD population.

Selected AEs of low frequency are found in Table 7.14. Most of these AEs represent effects noted with systemic corticosteroids. The frequencies of gastrointestinal hemorrhage, diabetes mellitus, hyperglycemia, ocular pressure disorders, decreased cortisol, abnormal adrenal hormone levels, Cushing's syndrome/symptoms, hypofunction of adrenal cortex, skin hemorrhage, acne and folliculitis, muscle atrophy, weakness, and tiredness were more common in FP than in placebo. The frequencies of glycosuria and ketonuria, cataracts, fractures, and osteoporosis were either higher in placebo than FP or occurred at similar frequencies.

Table 7.14. Notable AEs occurring at low frequency during inhaled treatment, FLIT78. Entries represent number (percent) of patients, grouped by body system [clinstat\other\flit78.pdf, pages 128, 523-539].

Adverse event	Placebo N = 370		FP 500 mcg BID N = 372	
	n	(%)	n	(%)
Any AE	359	(97)	355	(95)
Gastrointestinal hemorrhage	3	(<1)	10	(3)
Diabetes mellitus	3	(<1)	6	(2)
Hyperglycemia	5	(1)	6	(2)
Glycosuria and ketonuria	4	(1)	2	(<1)
Cataracts	7	(2)	5	(1)
Ocular pressure disorders	3	(<1)	6	(2)
Fractures	17	(5)	9	(2)
Osteoporosis	4	(1)	1	(<1)
Decreased cortisol	2	(<1)	12	(3)
Abnormal adrenal hormone levels	1	(<1)	3	(<1)
Cushing's syndrome/symptoms	0	(0)	1	(<1)
Hypofunction of adrenal cortex	0	(0)	1	(<1)
Skin hemorrhage	1	(<1)	9	(2)
Acne and folliculitis	0	(0)	4	(1)

Muscle cramps and spasms	10	(3)	19	(5)
Muscle atrophy, weakness, & tiredness	2	(<1)	7	(2)

Reviewer comment:
The occurrence of these AEs associated with systemic corticosteroids is concerning, and suggests that this dose of inhaled FP via the MDI formulation may result in clinically significant systemic exposure. The findings in this 3-year study underscore the importance of the recently started long-term study of FP 500 Diskus in a similar population of COPD patients, SCO30003.

FLIT97

The overall incidence of AEs was similar for FP (64%) and placebo (68%) groups. AEs occurring ≥3% and more frequently in FP than in placebo in FLIT97 are displayed in Table 7.15. URTI, throat irritation, viral respiratory tract infections, temperature regulation disturbances, headaches, hoarseness /dysphonia, urinary infections, nausea and vomiting, and candidiasis mouth/throat occurred more frequently in FP than in placebo [clinstat\iss\iss.pdf, page 172; clinstat\other\flit97.pdf, pages 176-177].

Table 7.15. AEs occurring ≥3% and more frequently in FP than placebo, FLIT97. Entries represent number (percent) of patients [clinstat\other\flit97.pdf, page 177].

Adverse event	Placebo N = 139 n	(%)	FP 500 mcg BID N = 142 n	(%)
Any AE	94	(68)	91	(64)
Upper respiratory tract infections	14	(10)	19	(13)
Throat irritation	5	(4)	8	(6)
Viral respiratory tract infections	4	(3)	8	(6)
Temperature regulation disturbances	2	(1)	8	(6)
Headaches	6	(4)	7	(5)
Hoarseness/dysphonia	0	(0)	5	(4)
Urinary infections	2	(1)	4	(3)
Nausea & vomiting	1	(<1)	4	(3)
Candidiasis mouth/throat	0	(0)	4	(3)

Notable AEs of low frequency are displayed in Table 7.16. There were small numbers of AEs associated with systemic corticosteroid effects, and these occurred at similar frequencies in both treatment groups.

Table 7.16. Notable AEs occurring at low frequency during inhaled treatment, FLIT97. Entries represent number (percent) of patients, grouped by body system [clinstat\other\flit97.pdf, pages 164-169].

Adverse event	Placebo N = 139 n	(%)	FP 500 mcg BID N = 142 n	(%)
Gastrointestinal hemorrhage	1	(<1)	0	(0)
Cataracts	7	(2)	5	(1)
Fractures	0	(0)	2	(1)
Decreased cortisol	3	(2)	2	(1)

Reviewer comment:
The AE data from this study are suggestive that that URTI and viral respiratory tract infections are associated with FP treatment. No signal suggestive of systemic corticosteroid effect was noted, however, this study was 6 months in duration and smaller in size than the 3-year FLIT78 study.

FLIT98

The incidence of AEs were similar in the FP (25%, 32/126) and placebo (28%, 35/123) groups. Chest symptoms and hoarseness were the only AEs that occurred ≥3% and more frequently in FP than in placebo [clinstat\other\flit98.pdf, page 157]. Two patients in the FP group (2%, 2/126) had decreased cortisols. No placebo patients had decreases in cortisol.

Table 7.17. AEs occurring ≥3% and more frequently in FP than placebo, FLIT98. Entries represent number (percent) of patients [clinstat\other\flit98.pdf, page 157].

Adverse event	Placebo N = 123		FP 500 mcg BID N = 126	
	n	(%)	n	(%)
Any AE	35	(28)	32	(25)
Chest symptoms	4	(3)	5	(4)
Hoarseness/dysphonia	0	(0)	4	(3)

Reviewer comment:
Decreased cortisol was noted in this small study of FP-MDI at 1000 mcg BID for one month.

FLIT63

The overall incidence of AEs during the treatment period was slightly higher in the placebo group (67%, 6/9) than in the FP group (50%, 4/8). The incidence of individual types of AEs was low with little difference between the treatment groups. Upper respiratory tract infection was the only AE that occurred in more than one patient, and the incidence was similar in the FP group (25%, 2/8) and the placebo group (22%, 2/9) [clinstat\other\flit63.pdf, pages 33, 68].

Reviewer comment:
There were few AEs in this study, and they reveal no evidence of a safety signal for FP.

7.1.5.3.b. Deaths in FLIT78, FLIT97, FLIT98, and FLIP63

FLIT78

There were 68 deaths that occurred during the inhaled treatment period in this study, with 36/370 (10%) in the placebo group and 32/372 (9%) in the FP group. The cause of deaths and their frequencies were fairly similar in FP and placebo groups [clinstat\other\flit78.pdf, page 121].

FLIT97

There were two deaths in this study, and both patients who died were treated with placebo [clinstat\other\flit97.pdf, page 61].

FLIT98

There was one death in this study. The patient was in the FP treatment group and had "dyspnea and precordalgia" [clinstat\other\flit98, page 56].

FLIT63
There were no deaths in this study [clinstat\other\flit63, page 33].

7.1.5.3.c. SAEs in FLIT78, FLIT97, FLIT98, and FLIP63

FLIT78
The frequency of SAEs were similar in the FP group (38%, 141/372) and the placebo group (40%, 148/370) [clinstat\other\flit78.pdf, page 562]. SAEs for COPD exacerbation were lower in the FP group (16%, 59/372) than in the placebo group (21%, 78/370). SAEs for pneumonia were more frequent in the FP group (5%, 18/372) than in the placebo group (2%, 8/370). Other SAEs occurred at similar frequencies for the two treatment groups [clinstat\other\flit78.pdf, page 125].

Reviewer comment:
The smaller frequency of SAEs for COPD exacerbation is suggestive of efficacy in the FP group. The higher frequency of SAEs for pneumonia in the FP group than in the placebo group is congruent with the AE reports for this study and supported by the AE profiles of several other studies included in this review.

FLIT97
The frequency of SAEs were similar in the FP group (9%, 13/142) and the placebo group (9%, 12/139). The types of SAEs noted were similar in the FP and placebo groups, except for chest pain/discomfort, which occurred in 4 patients in the FP group and in no patients in the placebo group [clinstat\other\flit97.pdf, pages 61-62].

Reviewer comment:
The small numbers of SAEs in this study do not suggest a safety signal for FP.

FLIT98
The frequency of SAEs were similar in the FP group (2%, 2/126) and the placebo group (2%, 2/123). One FP patient had a SAE for decreased cortisol. No narrative was provided for this patient. Another patient in the FP group suffered a fracture of the right humerus in a fall after completing treatment. Otherwise, the types of SAEs noted were similar in the FP and placebo groups [clinstat\other\flit98.pdf, pages 56, 161].

Reviewer comment:
The SAE for decreased cortisol is suggestive of a significant systemic corticosteroid effect in some patients treated with FP MDI, 1000 mcg BID.

FLIT63
There were two SAEs in this study. One placebo patient had an exacerbation of COPD leading to respiratory failure and one FP patient developed chest pain with a viral chest infection [clinstat\other\flit63.pdf, page 34].

Reviewer comment:
The small number of SAEs in this study provide little additional safety information.

7.1.5.3.d. Withdrawals due to AEs in FLIT78, FLIT97, FLIT98, and FLIP63

FLIT78
An analysis of withdrawals due to AEs was not presented in the study report for FLIT78 submitted with this application. The frequency of withdrawals due to AEs was lower in the FP group (29%, 109/376) than in the placebo group (35%, 131/375) [clinstat\other\flit78.pdf, page 320].

FLIT97
The frequency of withdrawals due to AEs was lower in the FP group (6%, 9/142) than in the placebo group (12%, 16/139) [clinstat\other\flit97.pdf, page 62]. The types of AEs resulting in withdrawal were similar in the two treatment groups [clinstat\other\flit97.pdf, pages 183-184].

FLIT98
The frequency of withdrawals due to AEs was lower in the FP group (2%, 3/126) than in the placebo group (5%, 6/123) [clinstat\other\flit98.pdf, page 56]. The types of AEs resulting in withdrawal were similar in the two treatment groups [clinstat\other\flit98.pdf, page 163].

FLIT63
There was one withdrawal due to AEs from this study, a placebo patient who developed an exacerbation of COPD with respiratory failure [clinstat\other\flit63.pdf, page 34].

7.1.5.4. Bone mineral density data from long-term asthma studies FLTA3001 and FLTA3017

The sponsor has conducted two controlled, long-term studies of FP in the treatment of asthma in which the effects on bone mineral density were studied. These studies were FLTA3001 and FLTA3017. The sponsor provided a brief summary of the bone mineral density results for these studies in support of this application.

In both trials, the sponsor measured bone mineral density in three areas. These areas were lumbar spine, proximal femur, and total body. The lumbar spine was the only area that underwent prospective quality assurance from the osteoporosis central laboratory. Results from the proximal femur and total body bone mineral density were collected for observational purposes only, as there was no prospective quality assurance for these measurements [clinstat\iss\iss.pdf, page 154].

FLTA3001 was a performed with FP administered with the MDI formulation. This study was submitted to IND 29,309 and NDA 20-548. Adult patients, male and premenopausal female, ages 18 to 40 years, with mild to moderate asthma were studied. There were 160 patients studied for a 104-week treatment period. Patients were randomized to either BID

treatment with placebo, FP 88 mcg, or FP 440 mcg. The sponsor states that lumbar spine bone mineral density measurements demonstrated no statistically different treatment effects at 24, 52, 76, and 104 weeks of double-blind treatment. At week 104, a mean percent increase in bone mineral density was observed in the placebo group (0.20%) and the FP 88 mcg BID group (0.68%). A mean decrease in bone mineral density was observed in the FP 440 mcg BID group (-0.28%). The sponsor reported no significant changes from baseline between treatment groups for the proximal femur and total body bone mineral density [clinstat\iss\iss.pdf, page 154].

Table 7.1.4.7. Bone mineral density results, FLTA3001 [clinstat\iss\iss.pdf, page 154].

Treatment group	Change from baseline at Week 104, %
Placebo	0.20
FP MDI 88 mcg BID	0.68
FP MDI 440 mcg BID	-0.28

FLTA3017 was a performed with FP administered with the Rotadisk formulation. This study was submitted to IND 40,142 and NDA 20-549. Adult patients, male and premenopausal female, ages 18 to 40 years, with mild persistent asthma were studied. There were 160 patients studied for a 104-week treatment period. Patients were randomized to either BID treatment with placebo or FP 500 mcg. The sponsor states that lumbar spine bone mineral density measurements demonstrated no statistically different treatment effects at 24, 52, 76, and 104 weeks of double-blind treatment. At week 104, a mean percent decreases in bone mineral density were observed in both the placebo group (-0.54%) and the FP 500 mcg BID group (-0.43%). The sponsor reported no significant changes from baseline between treatment groups for the proximal femur and total body bone mineral density [clinstat\iss\iss.pdf, page 154].

Table 7.1.4.2 Bone mineral density results, FLTA3017 [clinstat\iss\iss.pdf, page 154].

Treatment group	Change from baseline at Week 104, %
Placebo	-0.54
FP Rotadisk 500 mcg BID	-0.43

<u>Reviewer comment:</u>
The lumbar spine was only body site that underwent prospective quality assurance in both of these studies. It appears that from The Lung Health Study[1], the femoral neck is a more sensitive area to screen for decreased bone density. A decrease in bone mineral density in patients using 1200 mcg of triamcinolone per day was not noted until after three years of treatment. No changes in bone mineral density were noted at one or two years of treatment. Both FLTA3001 and FLTA3017 studied younger patients who had asthma. The Lung Health Study included COPD patients that represented an older population than was studied in FLTA3001 and FLTA3017. Patients studied in The Lung Health Study also included a high percentage of smokers, as well as postmenopausal women. The population studied in the Lung Health Study is more similar to the proposed population for this application, and represents a population that would be at higher risk for decreases in bone mineral density than the population studied in FLTA3001 and FLTA3017.

There is some suggestion of a signal for the FP MDI 440 mcg BID group in FLTA3001 for this site. The MDI formulation is more systemically bioavailable than the dry powder

formulation used in the Rotadisk and Diskus, however. One cannot draw useful conclusions in FLTA3001 and FLTA3017 from the lack of observed effect in the other body areas, as these areas did not have prospective quality assurance. At best, studies FLTA3001 and FLTA3017 show no evidence of effect on bone mineral density with these doses of FP after two years of treatment. However, lack of effect in these studies does not rule out effects in a more sensitive site or population, such as that proposed in this application. At worst, FLTA3001 suggests a decrease in bone mineral density at the end of 2 years of treatment. These studies provide little support for the safety of FP for the proposed indication and population.

The sponsor is planning to prospectively assess bone mineral density in COPD patients in SCO30003 [clinstat\iss\iss.pdf, page 149; clinstat\copd\sco30003.pdf, page 1]. Patients are to be treated with FP 500 mcg BID, SAL 50/FP 500 BID, SAL 50 BID, or placebo BID. The study will use the Diskus formulations of study treatment. Bone density will be evaluated over three years in a subpopulation of 600 patients. The study will also assess bone fractures and ocular events in the entire study population of 5000 patients [clinstat\iss\iss.pdf, page 149]. The long-term safety data that will be provided in this study will be critical in assessing the long-term risk/benefit analysis for this product in the proposed population.

7.1.5.5. Blinded listings of deaths and SAEs from ongoing non-US studies used to support regional markets

The sponsor provided blinded information on deaths and SAEs from nine ongoing local studies used to support regional markets. There were 3228 patients enrolled in these studies as of 9/30/00, which was the safety cut-off date. These studies were SCO30001, SCO40002, SMS40026, SMS40130, SMS40308, SAM30001, FCO40003, FCO30002, and FCO40004 [clinstat\iss\iss.pdf, page 177].

A total of 11 deaths were reported in the local studies as of the safety cut-off date of 9/30/00. Cardiovascular events were the cause of 8 of these 11 deaths. No deaths were considered by the investigator to be related to study drug treatment [clinstat\iss\iss.pdf, pages 177-178, 1303-1306].

A total of 123 SAEs occurred in 87 patients in the local studies as of the safety cut-off date. The majority of the SAEs were related to the lower respiratory tract. There were 72 SAEs that involved the lower respiratory tract. Most of these were exacerbation of COPD and pneumonia. Many were cardiovascular and involved cardiac failure, cardiac arrest, and cerebrovascular accident, among others [clinstat\iss\iss.pdf, pages 179, 1307-1326]. One patient (B0087880A) had exacerbation of diabetes mellitus and urosepsis [clinstat\iss\iss.pdf, page 1307].

Reviewer comment:
These data do not reveal any new safety signal for FP.

7.1.6. Spontaneous postmarketing reports

Spontaneous postmarketing reports are reviewed in Dr. Gilbert-McClain's medical officer review of the Advair product for the COPD indication, NDA 21-077, S003.

7.1.7. Safety update

The sponsor's safety update is reviewed in Dr. Gilbert-McClain's medical officer review of the Advair product for the COPD indication, NDA 21-077, S003.

7.1.8. References

1. The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. New Engl J Med 2000;343(26):1902-1909.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The pivotal studies were conducted using FP Diskus 500 mcg, 1 puff BID for the 24-week double-blind study periods (FLTA3025 and SFCA3006) and FP Diskus 250 mcg, 1 puff BID for the 24-week (FLTA3025 and SFCA3007).

The FP Diskus 500 mcg is not an approved product, and the sponsor is not seeking approval of this product for this indication in this application. The sponsor's proposed starting dosage for COPD is 1 inhalation (250 mcg) twice daily. The proposed labeling allows for increasing the dose to 2 inhalations (500 mcg) twice daily to provide additional control for patients who do not respond adequately to the starting dose [labeling\clean.pdf, page 23].

The sponsor has argued dose proportionality of the approved FP 250 mcg and proposed FP 500 mcg Diskus products in another study included in this submission, FLTA1003. However the FP 250 Diskus appears to be more than dose proportional to the FP 500 Diskus device in the multiple dose, 4-week study FLTA3025.

The primary efficacy endpoint data in the pivotal studies showed a statistically significant treatment effect for the FP 500 mcg BID when administered with the FP 500 Diskus. However, the effect was modest and was offset by the largely negative secondary efficacy endpoint data and by the lack of effect on health-related quality of life. Furthermore, most of the secondary efficacy variables and the health-related quality of life instrument did not support the efficacy of FP 500 mcg BID when administered with the FP 500 Diskus. The sponsor has not studied the efficacy or safety of FP 500 mcg BID when administered as 2 inhalations BID of the FP 250 Diskus. The pivotal studies do not appear to support the efficacy of the FP 250 BID when administered with the to-be-marketed FP 250 mcg Diskus product, as a statistically significant difference from placebo was not noted in replicate studies. The fact that the FP 250 mcg Diskus appears to be more than dose proportional to the FP 500 mcg Diskus raises additional concerns about the safety of the proposed labeled dose.

Examination of safety data for the pivotal studies reveals a dose response effect for FP 500 mcg BID and FP 250 mcg BID for upper respiratory tract infections (URTI), headaches, viral respiratory infections, candidiasis of the mouth or throat, nasal congestion/blockage, and muscle pain.

9. USE IN SPECIAL POPULATIONS

9.1. Efficacy in special populations

The under-representation of non-Caucasian patients in this study is a serious deficiency of these studies. The sponsor has not adequately studied the efficacy or safety of FP in non-Caucasian patients with COPD. Additional study of the safety of FP in a more racially diverse study population is indicated. Efficacy and safety data from future studies

should be examined to determine if the increases in COPD exacerbations in women and patients ≥65 years represent true safety signals.

9.1.1. Analysis of efficacy by gender

The sponsor provided subgroup analyses of efficacy by gender, race, and age. Males had greater absolute mean changes from baseline in FEV_1 at endpoint than women for all active treatment groups. Mean percent change from baseline in FEV_1 at endpoint was similar for men and women, however, indicating the larger absolute mean change in men was due to larger lung volumes. The mean change from baseline in CBSQ GAS was similar in men and women for treatment groups. Women had slightly greater TDI scores at endpoint than men. Women in FP 500 and FP 250 groups had slightly more COPD exacerbations than did men, but this observation was also present in the placebo group. Women in the FP 500 and FP 250 groups had more slightly more moderate or severe COPD exacerbations than men, when compared with data for the placebo group.

9.1.2. Analysis of efficacy by age

No consistent difference in mean change from baseline in FEV_1 was noted for all treatment groups when data for patients <65 years and ≥65 years were compared. Changes in the CBSQ GAS were similar among treatments for patients <65 years and ≥65 years. Changes in TDI scores were similar among treatments for patients <65 years and ≥65 years. Incidences of COPD exacerbations in the FP 500 and FP 250 groups relative to placebo were higher for patients ≥65 years than those <65 years. Incidences of COPD exacerbations in the FP 500 group relative to placebo were higher for patients ≥65 years than those <65 years.

9.1.3. Analysis of efficacy by race

As noted in each of the individual study reviews in this document, the vast majority of patients in this study were of Caucasian race. There were few patients of Black or Asian race. Non-Caucasian races represented 6% or less of each of the treatment groups. The small number of Non-Caucasian patients makes it difficult to draw firm conclusions. Mean percent change from baseline in FEV_1 at endpoint by race appeared to be greatest in patients of Other race, followed by patients of Black race, with the smallest in Caucasian patients. Changes in the CBSQ GAS appeared to be similar among racial subgroups. COPD exacerbations and moderate or severe COPD exacerbations appeared to be most frequent in patients of Black race, followed by Caucasian patients, and lowest in patients of Other race.

9.2. Safety in special populations

No patients were studied in the pediatric age group, and therefore there is no analysis of this subgroup. The sponsor has requested a waiver of pediatric studies in children 0-16 years of age. The sponsor's justification for this request for waiver is that COPD, as defined by the American Thoracic Society, does not occur in this age group [pediatricwaiverrequest.pdf, page 1].

There were no pregnancies reported in the conduct of the pivotal studies, and therefore there is no analysis of this subgroup.

Safety in other special populations is discussed below.

9.2.1. Analysis of safety by gender

The frequency of AEs was higher in females (71% to 83%) than males (61% to 82%). URTI, headaches, musculoskeletal pain, throat irritation, viral respiratory infections, and URI were more common in females than in males, but this difference was present for all treatment groups, including placebo. There was no consistent association of gender with AEs for any of the treatment groups. There was no association of gender for the four deaths in the pivotal studies. Two of the four patients that died were males and two were females.

The overall frequency of SAEs was higher in males (4% to 9%) than females (3% to 6%). Pneumonia, syncope, and fractures were more common in males, and chest symptoms were more common in females. The frequency of SAEs by gender was similar among active and placebo treatment groups. The frequency of withdrawal due to AEs was fairly similar in males and females. Pneumonia, hoarseness/dysphonia, cardiovascular test findings, CVA, myocardial infarction, palpitations, and tachyarrhythmias were more common in males than in females, but frequencies were similar among the treatment groups.

No consistent changes were noted in the percentage of patients with shifts from baseline in hematology results when analyzed by gender. AST shifts to high at Discontinuation were noted for more females (0% to 12%) than males (0% to 4%). Shifts from baseline to high glucose levels were noted in a slightly higher proportion of males (4% to 19%) than females (0% to 16%). These changes were noted for each of the treatment groups, including placebo.

More males than females had decreased hemoglobin (20 males, 3 females), decreased hematocrit (8 males, 0 females), and increased WBC (17 males, 0 females). These changes were noted in active as well as in placebo groups. Elevated glucose was noted in more males (42) than females (16), but these changes were noted in active as well as in placebo groups. Changes in baseline ECG were noted in more males than females.

Median QTcB intervals were slightly increased (5-10 msec) in females compared with males for each of the treatment groups, active and placebo for each of the time points. This is an expected gender effect of QTc.

9.2.2. Analysis of safety by age

The overall frequency of AEs was similar in patients <65 years of age (67% to 81%) and in those ≥65 years of age (64% to 80%). URTI, headaches, musculoskeletal pain, throat irritation, and viral respiratory infections were slightly more common in patients <65 years of age than in patients ≥65 years of age, but this difference was present for all treatment groups, including placebo. There was no consistent association of age with AEs

for any of the treatment groups. One of the four patients that died was <65 years of age (60 years). The other three were ≥65 years (66, 69, and 72 years).

The overall frequency of SAEs was slightly lower in patients <65 years (3% to 7%) than in patients ≥65 years (4% to 8%). Pneumonia appeared to be more common in patients ≤65 years of age who were treated with FP 500 and SAL 50/FP 500. Fractures appeared to be more common in patients >65 years of age, but occurred at similar frequencies in the treatment groups. The frequency of withdrawal due to AEs was lower in patients <65 years of age than in patients ≥65 years of age. Withdrawals due to depressive disorders, URTI, and viral respiratory infection were more common in patients <65 years of age than in patients ≥65 years of age, but were at similar frequencies in the treatment groups. Withdrawals due to pneumonias were more common in patients ≥65 years of age who were treated with FP 500 and SAL 50/FP 500.

No consistent changes in the percentage of patients with shifts from baseline in hematology or chemistry results were noted when analyzed by age. No consistent changes in the percentage of patients with abnormal hematology or chemistry results were noted when examined by age. More clinically significant changes from baseline were noted in patients ≥65 years of age. These changes were noted in active as well as placebo treatment groups. Median QTcB intervals were similar in patients <65 years of age and in patients ≥65 years of age for each of the treatment groups, active and placebo, for each of the time points.

9.2.3. Analysis of safety by race

The overall frequency of AEs differed by race. The overall frequency of AEs in Caucasian patients ranged from 69% (223/321) to 81% (298/367). The overall frequency of AEs in Black patients ranged from 47% (8/17) to 72% (13/18). The overall frequency of AEs in patients of Asian or Other race ranged from 33% (1/3) to 43% (3/7). The difference in frequencies between the races is likely to be a result of the small sample size of patients of Black and Asian/Other races. Review of the AEs for patients of Black and Asian/Other races does not reveal an obvious association with the type of treatment. The insufficient sample size of patients of color does not allow for a proper analysis of AEs by race, however. All patients that died in the pivotal studies were of Caucasian race. The small number of non-Caucasian patients did not allow for an analysis of SAEs, withdrawals due to AEs, laboratory results, or ECG results by race.

10. CONCLUSIONS AND RECOMMENDATIONS

This is an NDA supplement for a chronic obstructive pulmonary disease (COPD) indication for Flovent® Diskus®. The sponsor is GlaxoSmithKline. The proposed indication is the long-term maintenance treatment of COPD. The proposed starting dose for adults is one inhalation (250 mcg) twice daily. The proposed labeling allows for increasing the dose to 2 inhalations (500 mcg) twice daily to provide additional control for patients who do not respond adequately to the starting dose. The clinical program was also designed to pursue COPD indications for Serevent Diskus (salmeterol

xinafoate 50 mcg) and Advair Diskus (salmeterol xinafoate 50 mcg/fluticasone propionate 250 mcg and salmeterol xinafoate 50 mcg/fluticasone propionate 500 mcg). Submissions similar to the Flovent Diskus NDA supplement have been simultaneously submitted to the Serevent Diskus NDA (NDA 20-692) and to the Advair Diskus NDA (NDA 21-077).

These studies do not appear to sufficiently support the efficacy of FP 500 or FP 250 in the treatment of COPD. The main issues included the patient population studied, inconsistent findings in the three pivotal studies with the primary endpoint, the absence of strong support from the secondary endpoints, and the failure of the studies to fully support the clinical relevance of the primary endpoint, particularly with regard to the quality of life (QOL) instrument and COPD exacerbation.

With regard to the patient population, the sponsor has not adequately studied the efficacy of FP in non-Caucasian patients with COPD. Additional study of the efficacy of FP in a more racially diverse study population is indicated. There are serious questions about whether the patient population studied, of which 51% to 59% were highly reversible, is representative of the US COPD population as a whole, for which a broad indication is sought. Although statistical significance was shown for FP 500, the effect size was relatively modest, particularly for FLTA3025, where 24 weeks of treatment resulted in a net improvement in FEV_1 of only 50 mL. It should be noted that this result was also heavily driven by the "reversible" subgroup and by subjects who had stopped smoking. These studies do not appear to support the efficacy of FP 250 in the population studied, as a statistically significant difference from placebo was not noted in replicate studies. In general, most of the secondary efficacy variables did not support the efficacy of FP 500 or FP 250. Secondary efficacy variables that would be expected to be correlated to the primary endpoint, such as PEFR, showed modest treatment effects and therefore do not add substantially to the argument in favor of efficacy for this product.

The quality of life (QOL) instrument, the CRDQ, does not support the efficacy of FP 500 or FP 250. This is particularly concerning because all three of the pivotal studies had evaluation of QOL as one of their primary objectives. This was included because relatively short-term (6 months) changes in FEV_1 have uncertain clinical significance and do not have the same correlation with mortality that long-term (3 year) changes would have. The small effect size in FEV_1 combined with the observation that the patients experienced no detectable benefit vs. placebo in a well-validated QOL instrument argues strongly against a conclusion of efficacy for FP for the COPD indication.

The sponsor does not appear to have established the safety of FP in the proposed population. The sponsor has not adequately studied the safety of FP in non-Caucasian patients with COPD. Additional study of the safety of FP in a more racially diverse study population is indicated. The pivotal studies were likely to be of insufficient duration to detect differences between treatment groups for uncommon events such as fractures, cataracts, ocular pressure disorders, and disorders of glucose metabolism. The pivotal studies were not designed to specifically look for cataracts or systemic bone effects. Safety data from supportive studies raise concerns about a higher incidence of respiratory

infections, pneumonia, HPA axis effects, among others, in FP-treated patients, and do not adequately address bone effects in the proposed population.

The sponsor has recently started a 3-year study of FP 500 mcg BID in COPD patients (SCO30003). Bone density is to be evaluated over three years in a subpopulation of 600 patients. This study will also assess bone fractures and ocular events in the entire study population of 5000 patients. The long-term safety data that will be provided in this study will be critical in assessing the long-term risk/benefit analysis for this product in the proposed population.

The sponsor does not appear to have sufficiently established that the proposed dose of FP is effective or safe in the treatment of COPD.

11. APPENDIX: CLINICAL STUDIES

11.1. FLTA3025: A randomized, double-blind, parallel-group, comparative trial of inhaled fluticasone propionate 250 mcg BID, 500 mcg BID, and placebo BID via the Diskus in subjects with chronic obstructive pulmonary disease (COPD)

Study initiated: 8/8/98
Study completed: 3/8/00
Study report dated: 2/5/01
[clinstat\copd\flta3025.pdf, page 1]

11.1.1. Summary and reviewer's conclusion of study results

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter, 24-week trial designed to evaluate the efficacy and safety of fluticasone propionate (FP) Diskus 250 mcg and 500 mcg in patients with chronic obstructive pulmonary disease (COPD).

The patient population studied was characterized by a significant amount of reversibility with bronchodilator. The mean change in FEV_1 with bronchodilator for the study population was 22.9%. Of all study patients, 59% were considered to be reversible (≥12% and ≥200 mL increase in FEV_1 with bronchodilator). The mean change in FEV_1 with bronchodilator for the reversible group was 32.4%. The population that was considered to be non-reversible (41% of COPD patients recruited) had a mean increase of 9.2% in FEV_1 with bronchodilator. There are serious concerns as to whether this patient population is representative of the COPD population as a whole[1-4], as broadly stated in the labeling for the proposed indication. This is a critical deficiency of this study. Under-representation of non-Caucasian patients, who make up a substantial proportion of the COPD population[1-3] was another important deficiency of this study.

The primary efficacy endpoint was the mean change in FEV_1 from Baseline to study end point. A small mean change from baseline in FEV_1 (61 mL) was noted for the FP 500 group ($p = 0.010$ vs. placebo), compared to 38 mL ($p = 0.140$ vs. placebo) for the FP 250 group, and 11 mL for the placebo group. Values for the mean change in FEV_1 from Baseline for the FP 500 group at Weeks 6, 12, and 24 were also small and ranged from 56 mL to 67 mL more than the placebo group. Values for the mean change from baseline for the FP 250 group at Weeks 6, 12, and 24 ranged from 23 to 37 mL more than the placebo group. Subgroup analysis revealed that the small amount of efficacy observed was carried entirely by the population of patients who were former smokers.

Among secondary efficacy endpoints, the Global Assessment Score (GAS) of the Chronic Bronchitis Symptom Questionnaire (CBSQ) for FP 500, was numerically greater than placebo, but the difference between FP 500 and placebo was less than the minimally clinically important change. This instrument was also administered in such a fashion that the interviewer might have influenced patient responses. The sponsor reported

improvements in Transitional Dyspnea Indices (TDIs) for FP 500 and FP 250, but these were not significantly different from those noted for the placebo group. Furthermore, individual components of this instrument were likely to be highly correlated.

A lower frequency of COPD exacerbations was seen with FP 500 and FP 250, with dose ordering noted, but the standard definition of COPD exacerbation[5-7] was not used and the instrument that was selected likely favored the finding of efficacy for FP in a COPD population with a high degree of reversibility.

Small but clinically insignificant changes in other secondary endpoints were noted, including PEFR, supplemental Ventolin use, and nighttime awakenings requiring Ventolin use. It should also be noted that PEFR and use of bronchodilator would be expected to be more likely to show a treatment effect in a population of COPD patients with a high degree of reversibility. The overall score of the Chronic Respiratory Disease Questionnaire (CRDQ), a COPD-related quality of life instrument, did not show a clinically significant difference between treatment groups.

The sponsor performed a subgroup analysis of efficacy for non-reversible patients. On the primary endpoint, this subgroup analysis demonstrated only a small change in FEV_1 from baseline at study endpoint for FP 500 compared with FP 250 and placebo, indicating that efficacy for this study was "carried" by the reversible patients. Secondary endpoints in general corroborated the findings of the primary endpoint, in that each demonstrated either no change or small, clinically insignificant changes for FP 500 and FP 250 in the non-reversible population. In conclusion, subgroup analysis demonstrated little efficacy in the non-reversible population and indicates that efficacy was carried by those patients in the reversible population, who constituted the majority of COPD subjects recruited for this study (59%).

A steady state PK/PD assessment was performed at 4 weeks into this 24-week study. Mean FP AUC_{last} and FP C_{max} were 74% and 58% higher for FP 500 than FP 250, respectively, indicating a dose-related increase in systemic exposure that was not dose-proportional. Mean FP AUC_{last} for current smokers was lower than for former smokers. A linear relationship between weight and FP AUC_{last} was noted for FP 500, but not FP 250. The study was conducted using 500 mcg Flovent Diskus. The Flovent 250 mcg Diskus and the Flovent 500 mcg Diskus were not found to be dose-proportional. The lack of dose proportionality is discussed in depth in Dr. Suarez's biopharmaceutics review.

With regard to PD (HPA-axis assessment), FP treatment groups had lower mean cortisol AUC_{12} and mean C_{min} than the placebo group, with a dose response effect noted. Mean cortisol AUC_{12} was 21% lower than placebo for FP 500 and 10% lower than placebo for FP 250, indicating dose-related systemic absorption and systemic activity from Flovent Diskus that is both acute (see PK study FLTA1003) and chronic. The mean cortisol AUC_{12} was higher in current smokers than in former smokers. There was no relationship noted between cortisol levels and weight. It should be noted that samples were taken at Week 4, early in the study. These effects might be more pronounced if samples were drawn later in the study.

Duration of exposure was inadequate to fully assess safety, since the short efficacy endpoints in this study fail to address the safety consequences of long-term (> 6 months) use of high-dose, high-potency inhaled corticosteroids, particularly with regard to bone, dermatological, and ocular adverse events, as well as the potential for HPA axis recovery. A dose-response effect was noted for AEs. AEs occurred in 80% of FP 500-treated patients, 76% of FP 250-treated patients, and in 74% of placebo-treated patients. AEs occurring more frequently with FP 500 and FP 250 than with placebo included upper respiratory tract infection, headaches, candidiasis of the mouth or throat, throat irritation, musculoskeletal pain, viral respiratory infection, upper respiratory inflammation, nasal congestion/blockage, hoarseness/dysphonia, and sinusitis. A dose response effect for FP 500 and FP 250 was noted for candidiasis of the mouth or throat (placebo <1%, FP 250 6%, FP 500 13%), viral respiratory infections (placebo 51%, FP 250 6%, FP 500 9%), and upper respiratory inflammation (placebo 5%, FP 250 6%, FP 500 7%). There were no deaths in this study and the frequency of serious adverse events was similar in each treatment group (placebo 6%, FP 250 7%, FP 500 7%). Vital signs and ECGs showed no clinically significant differences between treatment groups.

In summary, small changes in FEV_1 were noted for the FP groups in this study, but whether the study population reflects the overall population of US COPD patients for which this drug is proposed is highly questionable[1-4]. There are also questions about the clinical relevance of isolated, short term changes in FEV_1 to overall benefit in COPD[8]. For this reason, the failure of secondary efficacy variables to support the efficacy of FP 250 or FP 500 are of serious concern. As noted above, efficacy was carried by the subgroup of "reversible" patients, particularly those who had ceased smoking. The latter observation confounds the interpretation of ICS as providing an "anti-inflammatory" benefit since cessation of smoking itself is associated with a reduction in ongoing airway inflammation[8]. Safety and PK/PD data raise concerns because of the evidence of dose-related systemic effects on the HPA axis. The study was of insufficient duration for known systemic corticosteroid effects such as osteoporosis, cataracts, hypertension, diabetes, or skin changes such as easy bruisability to become apparent. It should be noted that the study was not designed to specifically assess these AEs, and patients with prior pathological fracture, osteoporosis, significant hypertension or diabetes, cataracts, or glaucoma were specifically excluded. This study does not appear to support the efficacy of FP 250 or FP 500 in the treatment of COPD, and inadequately addresses the safety of these products in this population.

11.1.2. Study design

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter trial of 24 weeks duration. Approximately 600 patients were to be randomized at a minimum of 50 study centers. A total of 640 patients received treatment at 55 US study sites [clinstat\copd\flta3025.pdf, page 29]

11.1.3. Objectives

This study had four objectives [clinstat\copd\flta3025.pdf, page 5273]. They were:

1. To evaluate the efficacy of FP 250 mcg and 500 mcg BID compared to placebo when administered by the Diskus over a 24-week treatment period in the treatment of COPD patients
2. To evaluate the safety of FP 250 mcg and 500 mcg BID compared to placebo when administered via the Diskus over a 24-week treatment period in the treatment of COPD patients
3. To compare quality of life (QOL) in COPD patients receiving FP 250 mcg BID, FP 500 mcg BID, or placebo over a 24-week treatment period
4. To describe the steady-state FP pharmacokinetics and serum cortisol levels in COPD patients following 250 mcg and 500 mcg BID doses

11.1.4. Inclusion criteria

Inclusion criteria for this study are listed below. These reflect protocol amendments. [clinstat\copd\flta3025.pdf, pages 5275-5278, 5356, 5399]:

1. Age ≥40 years
2. Male or female gender
   - A female was eligible to enter and participate if she was of non-childbearing potential or was of child-bearing potential with a negative serum pregnancy test at screening and an acceptable method of contraception
3. Established history of COPD in accordance with the American Thoracic Society (ATS) definition[1]:
   - Abnormal tests of expiratory flow that do not change markedly over periods of several months
   - Airflow obstruction may be structural or functional
   - Bronchial hyperreactivity may be present as measured by improvement after inhalation of a beta-adrenergic agent or worsening after inhalation of methacholine or histamine
   - Emphysema and chronic bronchitis are incorporated into COPD, and any individual may have one or both of these conditions
4. A history of cough productive of sputum on most days for at least 3 months of the year, for at least 2 years, that is not attributed to another disease process. Patients must have a score of ≥8 on the Chronic Bronchitis Symptom Questionnaire (CBSQ) at Treatment Day 1
5. Current or prior history of at least 20 pack-years of cigarette smoking. If the patient is an ex-smoker, smoking must have been discontinued for at least 6 months prior to screening. Current smokers were counseled regarding the hazards of continuing to smoke and the benefits of discontinuation. Patient who decided to stop smoking at the Screening Visit were not eligible for participation in the study. Patients making a conscious decision to stop smoking at anytime during the study and who refrain from smoking for >4 weeks were to be discontinued from the study. Patients who start smoking during the study and smoke for at least 7 consecutive days were to be discontinued from the study.
6. Severity
   - Baseline FEV1<65% or predicted but >0.70 L, or FEV1 ≤0.70 L and >40% of the predicted normal value (Crapo), and
   - FEV_1/FVC ratio of ≤70% at screening

7. A score if ≥2 in the Modified Medical Research Council Dyspnea Scale at screening:

Modified Medical Research Council Dyspnea Scale

Grade	Description
0	Not troubled with breathlessness except with strenuous exercise
1	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
2	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	Stops to breathe after walking about 100 yards or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

8. Has not received systemic corticosteroid and/or high-dose inhaled corticosteroid therapy for at least 6 weeks prior to the Screening Visit. High dose inhaled corticosteroids are defined as:
   - Beclomethasone dipropionate ≥1008 mcg/day
   - Triamcinolone acetonide ≥1600 mcg/day
   - Flunisolide ≥2000 mcg/day
   - Fluticasone propionate MDI ≥880 mcg/day
   - Fluticasone propionate Diskus ≥1000 mcg/day
   - Budesonide ≥1600 mcg/day
9. Able to tolerate a 2-week run-in period during which the following medications were discontinued:
   - Inhaled corticosteroids
   - Ipratropium
   - Nedocromil sodium and cromolyn sodium
   - Anti-leukotriene agents
   - Intranasal steroids
   - Any beta-agonist other than Ventolin
   - Theophylline, unless at a stable dosage for one month
10. Able to complete a diary card and subject questionnaires
11. Able to effectively use the Diskus and MDI inhalers, spirometry equipment, and mini-Wright peak flow meter
12. Provide a signed, dated, and witnessed informed consent

Reviewer comment:
The sponsor's paraphrasing of the ATS definition of COPD places an emphasis on reversibility. While reversible obstruction does occur in the COPD population, it should not be considered central to the definition. The process underlying COPD is one of progressive loss of lung tissue, leading primarily to structural obstruction as opposed to functional[1-4]. The select nature of the subjects recruited for this study leads to serious concerns about the generalizability of its results to the COPD population as a whole. The ATS definition follows:

> *"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."[1]

The inclusion criteria allow for patients who were receiving fairly large doses of inhaled corticosteroids prior to enrollment. This may have the effect of enriching the study for patients who were responsive to inhaled corticosteroids, as one would expect patients with no response or a poor response to have their treatment discontinued.

11.1.5. Exclusion criteria

Exclusion criteria for this study are listed below. These reflect protocol amendments. [clinstat\copd\flta3025.pdf, pages 5278-5281, 5372, 5399]:

1. Current diagnosis of asthma in accordance with the ATS definition[1]:
   - Increased responsiveness of the tracheobronchial tree
   - Paroxysms of dyspnea, wheezing, and cough, which may vary from mild and almost undetectable to severe and unremitting
   - Primary physiological manifestation of hyperresponsiveness is variable airway obstruction
   - Variability may be manifest in improvements of obstruction following bronchodilators or corticosteroids or increased obstruction caused by drugs or other stimuli
2. Requirement for any of the following medications:
   - Beta-blockers
   - Digitalis
   - Ketoconazole, fluconazole
   - Monoamine oxidase inhibitors
   - Phenothiazines
   - Immunosuppressive agents including cyclosporine, methotrexate, and gold
   - Use of inhaled short-acting bronchodilator within 6 hours prior to screening
   - Use of any short acting form of oral beta-agonist, short-acting form of theophylline or other bronchodilator within 12 hours prior to screening
   - Use of any twice daily form of an inhaled or oral beta-agonist or controlled-release form of theophylline within 48 hours of screening
3. Requirement for pulmonary rehabilitation
4. A respiratory disorder other than COPD (e.g., lung cancer, bronchiectasis, sarcoidosis, tuberculosis, lung fibrosis); history of lobectomy within one year of the screening visit.
5. Requirement for a continuous positive pressure device
6. Any significant concurrent diseases that would place the subject at risk, interfere with clinical evaluations, or influence study participation, including but not limited to:
   - History of pathologic fractures
   - Clinically significant cardiac disease
   - Symptomatic or clinically significant pathological fractures
   - Systemic arterial hypertension if the subject is poorly compliant with medications, likely to require frequent changes in medication during the study period, or requires therapy with beta-blockers
   - Hepatic disease

- Renal disease requiring dialysis or at risk of requiring dialysis within 6 months of screening
- Neurologic disease
- Uncontrolled hyperthyroidism or hypothyroidism
- Diabetes mellitus that is either poorly controlled or complicated by significant renal or cardiovascular disease
- Severe hematologic disease
- Active peptic ulcer
- Disorders of humoral or cellular immunity
- Cushing's disease
- Addison's disease
- Presence of glaucoma requiring treatment with non-selective beta-blockers
- History of malignancy
- Inadequately controlled psychiatric illness
- Mental retardation
- Peripheral vascular disease

7. Requirement for supplemental oxygen with the following exceptions:
    - Lives at an altitude above 3000 feet and does not require more than 2 L of oxygen per minute for more than 12 hours per day
    - Does not require more than 2 L of oxygen per minute for exertion for more than 12 hours per day
8. A known or suspected hypersensitivity to inhaled corticosteroids, beta-agonists or lactose. Gastrointestinal lactose intolerance is not an exclusion criterion.
9. A known or suspected history of alcohol or drug abuse within the previous two years
10. 12-lead ECG at screening is abnormal and clinically significant
11. A moderate or severe exacerbation of COPD during the run-in period
12. Chest X-ray reveals clinically significant abnormalities not believed to be due to the presence of COPD
13. Received an investigational drug within 30 days prior to entry into the run-in period
14. A participating investigator, sub-investigator, study coordinator, or employee of a participating investigator, or an immediate family member of the aforementioned
15. An abnormal and clinically significant laboratory test a the screening visit which is still abnormal on repeat analysis
16. Previous participation in a fluticasone and/or salmeterol study via the Diskus for COPD

<u>Reviewer comment:</u>
The sponsor uses an ATS definition of asthma from 1987. This definition makes no reference to the role of inflammation in asthma. A more appropriate and up-to-date definition might be the National Asthma Education and Prevention Program (NAEPP) definition of asthma, which refers to the role of inflammation as well as reversible airway obstruction[9]. Taken strictly, this exclusion criterion would exclude all patients who have reversible airway obstruction, and that clearly did not occur during this study.

11.1.6. Protocol amendments

There were four protocol amendments, dated 7/1/98, 7/27/98, 7/22/98, and 12/14/98 [clinstat\copd\flta3025.pdf, page 5396] . The third protocol amendment was a substudy protocol for genotyping during the study. This substudy will not be reviewed.

Reviewer comment:
The most notable change to the protocol was included in Protocol Amendment 4. The FEV_1/FVC ratio required for entry into the study was changed from ≤65% to ≤70% [clinstat\copd\flta3025.pdf, page 5399]. The effect of this change would be to allow entry of patients with both those with milder obstruction (who would be perhaps more likely to have reversibility) and those with very severe obstruction with accompanying air trapping. This amendment was made after the study had been started. The inclusion criteria specifying the FEV_1 and the level of dyspnea will minimize any impact of this change. Protocol amendments otherwise included minor changes to wording and study design that were likely to have little impact on the evaluation of efficacy or safety.

11.1.7. Study procedures

Study procedures are displayed in Table 11.1.1. Patients provided an informed consent, and received a medical history and physical examination at the screening visit. Chest X-ray, pregnancy test, screening labs, and ECGs were performed. Spirometry with assessment of reversibility was also performed. Reversibility was assess by performing spirometry 30 minutes after patient self-administration of 4 puffs of Ventolin MDI without a spacer or holding chamber [clinstat\copd\flta3025.pdf, page 5288].

There was a two-week, single-blind, run-in period for patients meeting entrance criteria. Patients had all concurrent inhaled or oral bronchodilator treatment discontinued and were given Ventolin MDI or nebules to be used as needed for duration of the trial, including the run-in. Patients received placebo via the Diskus BID during the run-in, and baseline observations were made for peak expiratory flow rates (PEFR), Ventolin use, and night-time awakenings that required Ventolin use [clinstat\copd\flta3025.pdf, pages 5275]. The purpose of the single-blind run-in period was to establish baseline pulmonary function and diary card data for at least 10 of the 14 days. Patient compliance with medication and recording of diary data was also assessed [clinstat\copd\flta3025.pdf, page 5288]. Patient were to record daily morning PEFRs, nighttime awakenings requiring Ventolin use, use of rescue Ventolin, and any medical problems experienced [clinstat\copd\flta3025.pdf, pages 5289].

Criteria for patients to be eligible for randomization included the following [clinstat\copd\flta3025.pdf, pages 5289]:

- Satisfaction of inclusion and exclusion criteria
- At least 70% compliant with study medication during the run-in
- Completed diary data for at least 10 of the 14 days of the run-in
- Had not started or stopped smoking during the run-in
- Proficiency in use of the peak flow meter
- Able to safely withhold prohibited study medications

Patients who completed the run-in period and met all randomization criteria were assigned to one of three double-blind treatments via the Diskus for 24 weeks:

- FP 250 mcg BID
- FP 500 mcg BID
- Placebo BID

According to the study protocol, assignment to study drug was to be stratified according to the patients' response to reversibility testing with Ventolin at screening to a non-reversible group and a reversible group. Non-reversible patients were defined as having an absolute volume increase <200 mL or an absolute volume increase of ≥200 mL with baseline FEV_1 reversibility of <12%. Reversible patients were defined as having an absolute volume increase ≥200 mL with baseline FEV_1 reversibility of ≥12% [clinstat\copd\flta3025.pdf, pages 5283; IND 44,090 N134 PN, 8/4/98, page 25].

Reviewer comment:
The definition of reversibility is critical for this study. In addition, the proportion of patients with reversible obstruction is also critical, even if the proportion in each of the three treatment groups is similar. FP clearly is effective for treatment of asthma, and inclusion of a high proportion of patients with a significant degree of reversibility would be likely to result in an overstatement of efficacy for the entire group. Although assignment to study drug was stratified according to reversibility based on the above definition, no analysis was planned or provided for these subgroups. Instead, subgroup analysis was provided for subgroups based on a different definition of reversibility. This issue and its effects are discussed in Section 11.1.17.1 of this document, "Data sets analyzed".

Patients were evaluated weekly for the first four weeks of treatment, every two weeks until week 8, and then every four weeks for the remainder of the study. Patients who developed an exacerbation could be treated with antibiotic therapy as an outpatient for two exacerbations, but were discontinued from the study if a third exacerbation occurred. Subjects with exacerbations requiring treatment with systemic corticosteroids were to be discontinued from the study.

Patient evaluations at each of the clinic visits included spirometry. Symptoms were also evaluated with the Baseline/Transition Dyspnea Index (BDI/TDI), Chronic Bronchitis Symptom Questionnaire (CBSQ), and assessment of the severity of any COPD exacerbations since the last evaluations. Health outcomes were assessed with the Chronic Respiratory Disease Questionnaire (CRDQ), a health-related quality of life instrument [clinstat\copd\flta3025.pdf, pages 5291-5294]. The BDI/TDI, CBSQ, and CRDQ instruments and the instrument for assessment of COPD exacerbations are described below in Section 1.1.12, Assessment of signs and symptoms.

Patients completed diary cards during the treatment period. Patients measured PEFRs in triplicate prior to the morning dose of study medication. The highest of 3 PEFR values was recorded on diary card. Patients also were to record nighttime awakenings requiring

Ventolin use, the use of supplemental Ventolin, any medical problems, any need for other concomitant medication, and AEs [clinstat\copd\flta3025.pdf, pages 5293-5294].

Table 11.1.1. Study outline, FLTA3025 [clinstat\copd\flta3025.pdf, page 5322].

	Screen	Run-in	Double-blind treatment period											DC
Visit number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Treatment Day/Week		**Day –14 to 1**	**Day 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 6**	**Wk8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	
Informed consent	X													
Medical history	X													
Smoking cessation counseling	X												X	X
Chest X-ray	X													
Physical examination	X												X	X
Pregnancy test	X									X			X	X
Reversibility test	X													
Review inhalation technique	X		X	X	X	X	X	X	X	X	X	X		
Medical Research Council Questionnaire	X													
Clinical laboratory tests	X									X			X	X
12-lead ECG and rhythm strip	X									X			X	X
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X
Oropharyngeal exam	X		X	X	X	X	X	X	X	X	X	X	X	X
Review smoking status			X										X	X
AE detection	X		X	X	X	X	X	X	X	X	X	X	X	X
Spirometry testing	X		X	X	X	X	X	X	X	X	X	X	X	X
Exacerbation assessment			X	X	X	X	X	X	X	X	X	X	X	X
Dispense/review diary card	X		X	X	X	X	X	X	X	X	X	X	X	X
BDI/TDI dyspnea scale				X	X	X	X	X	X	X	X	X	X	X
Quality of life questionnaire			X		X		X		X				X	X
PK and serum cortisol samples							X							
Dispense PEFR devices and Ventolin MDI/nebules	X		X	X	X	X	X	X	X	X	X	X		
Dispense study medication			X				X		X	X	X	X		
Concurrent medication assessment	X		X	X	X	X	X	X	X	X	X	X	X	X
Discharge from study													X	X

11.1.8. Allowable concurrent medications

Allowable concurrent medications included [clinstat\copd\flta3025.pdf, page 5284]:

- Inhaled Ventolin MDI and/or nebules, provided by the sponsor for use as relief medication. Ventolin was to be withheld for at least 6 hours prior to each treatment visit.
- Antibiotics were permitted for treatment of two exacerbations. Patients were dropped from the study if a third COPD exacerbation occurred.
- Antidepressants other than MAO inhibitors
- Theophylline, if on a stable dose for at least one month prior to screening

11.1.9. Prohibited medications

The following medications were prohibited [clinstat\copd\flta3025.pdf, page 5285]:

- Any oral, intranasal, or inhaled corticosteroids other than the study medication
- Beta-agonists other than the Ventolin supplied by the sponsor
- Concurrent use of any other prescription or over-the-counter medication which may affect the course of COPD or interact with study medications. These medications were to be discontinued at least 2 weeks prior to randomization.

11.1.10. Drug product and placebo

The sponsor provided the following study treatments [clinstat\copd\flta3025.pdf, pages 43-44]:

- Placebo Diskus, for the single-blind run-in period and 24-week treatment period
- FP Diskus 250 mcg one puff BID for the 24-week double-blind study period
- FP Diskus 500 mcg one puff BID for the 24-week double-blind study period
- Ventolin MDI and nebules for each subject as rescue medication

Reviewer comment:
The FP Diskus 500 mcg is not an approved product. The sponsor has argued dose proportionality of the 250 mcg and 500 mcg products in another study included in this submission. The interpretation of these dose proportionality data is a review issue discussed elsewhere in this review, and discussed in depth in the clinical pharmacology review.

Study drug was packaged in identically appearing Diskus devices to blind treatments [clinstat\copd\flta3025.pdf, page 46]. The batch numbers of medication were used in this study are displayed in Table 11.1.2.

Table 11.1.2. Batch numbers of study medication, FLTA3025 [clinstat\copd\flta3025.pdf, page 44].

Product	Batch numbers
Placebo Diskus	WP1WF9 WP25L4
FP Diskus 250 mcg	U98/028A
FP Diskus 500 mcg	U98/024C
Ventolin MDI, 90 mcg/puff	8ZP0692 8ZP0909 8ZP1741 8ZP1924 8ZP1924

Product	Batch numbers
	9ZP0124
Ventolin nebules, 0.098%, 2.5 mg/3 mL	970963 980904 980905 980911 980901

The sponsor states that the formulations of Flovent used in this study were representative of the commercial product in terms of input materials, scale of manufacture, manufacturing equipment, and manufacturing process. The only differences between the batches of Flovent that were supplied for this study and the commercial product were the device coloration and the overwrap. All batches of Ventolin nebules and Ventolin MDI used in this study were the approved commercial product. The placebo used in this study was identical to the active product used in this study except for the absence of active drug [NDA 20-833, SE1-004, 9/17/01, page 3; NDA 20-833, SE1-004, 12/5/01, page 1].

11.1.11. Assessment of compliance

Patient compliance with the drug dosing schedule was determined from the dose counter on the Diskus devices. Patients who were less than 70% compliant with the use of study medication during the 2-week run-in were dropped from the study [clinstat\copd\flta3025.pdf, pages 46, 66].

11.1.12. Assessment of signs and symptoms

Patient COPD symptoms were evaluated with the Chronic Bronchitis Symptom Questionnaire (CBSQ), Baseline/Transition Dyspnea Index (BDI/TDI), and assessment of the severity of any COPD exacerbations since the last evaluations. These instruments are described below.

The CBSQ was composed of selected questions from the Petty Subject Evaluation Questionnaire[10] and the Revised Global Petty Questionnaire for Ease of Cough and Sputum Clearance[11]. The CBSQ evaluated cough frequency and severity, sputum release, and chest discomfort on a 0 to 4, 5-point scale. Individual scores were summed to provide a Global Assessment Score (GAS). As noted in the inclusion criteria, patients must have had a GAS of ≥4 at Treatment Day 1 to qualify for the study [clinstat\copd\flta3025.pdf, pages 48-49].

Additional data describing the CBSQ were included with the application. These data describe the administration of the CBSQ. The patient was allowed to read each question along with the interviewer and verbally select the response that best described the status of that particular symptom on a typical day during the past week. After reading the question, as written, with the subject, the interviewer used discussion questions and observations to assist the subject in providing as precise an answer as possible [clinstat\other\cbsqvalidationdocument.pdf, page 6]. A Minimally Clinically Important Change (MCIC) for the CBSQ was determined to be a change from baseline of 1.4 in the GAS [clinstat\other\cbsqvalidationdocument.pdf, page 11]. The calculation of the MCIC assessed the change in GAS for individual subjects by collecting them into one of four

categories to assess a Global Rating of Change (GRC) [clinstat\other\cbsqvalidationdocument.pdf, pages 8-9]:

1. GRC = 0, ±1: No change in symptoms of chronic bronchitis
2. GRC = ±2, ±3: A minimal change in symptoms of chronic bronchitis
3. GRC = ±4, ±5: A moderate change in symptoms of chronic bronchitis
4. GRC = ±6, ±7: A large change in symptoms of chronic bronchitis

However the validation package indicates that there was poor correlation between the GAS and the GRC used to calculate the MCIC. Pearson and Spearman's correlation coefficients between GAS and GRC were only from 0.25 to 0.34 [clinstat\other\cbsqvalidationdocument.pdf, page 9]. Furthermore, large standard deviations in the GRC and MCIC were noted. The standard deviations were large enough for each of the GRC categories to substantially overlap each other [clinstat\other\cbsqvalidationdocument.pdf, page 11].

Reviewer comment:
The CBSQ was administered in such a fashion that the interviewer might have influenced patient responses. The poor correlation between the GAS and GRC and the large standard deviation in the GRC indicate that the MCIC is not likely to be valid. This instrument will not be able to provide support for the efficacy of FP. Furthermore, this instrument was validated in a subset of patients from within this same study, FLTA3025 [clinstat\other\cbsqvalidationdocument.pdf, page 8].

The BDI/TDI was used to provide a clinical measurement of baseline and change in dyspnea. The degree of functional impairment at baseline due to dyspnea, the magnitude of task to provoke dyspnea, and the magnitude of effort that provoked dyspnea were rated on a 0 to 4, 5-point scale to derive the BDI. Changes from baseline in functional impairment, magnitude of task, and magnitude of effort were assessed at each subsequent visit with a -3 to +3, seven-point scale, the TDI [clinstat\copd\flta3025.pdf, pages 49-54].

The sponsor provided a reference for this instrument that showed a weak correlation of the BDI with FEV_1, FVC, and the 12-minute walk distance with correlation coefficients of 0.41, 0.56, and 0.60[12]. TDI correlated only weakly with change in the change in the 12-minute walk distance, with a correlation coefficient of 0.33. There was no correlation of TDI with change in FEV_1 or change in FVC. The sponsor considered a change from BDI to TDI of 1.0 to be clinically relevant [clinstat\copd\flta3025.pdf, page 67, Correspondence submitted to IND 50,703, Meeting request package, 2/6/98]. The sponsor did not include a validation package with this application or with the meeting request package of 2/6/98.

Reviewer comment:
Degree of functional impairment, magnitude of task, and magnitude of effort are likely to be highly correlated variables, in this reviewer's opinion, and therefore will tend to inflate any observed positive or negative treatment effect. This instrument will not be likely to provide support for the efficacy of FP.

The investigator assessed the severity of any COPD exacerbations at each clinic visit using a three-level scale, mild to severe. Mild exacerbations were defined as use of more than 12 puffs or 4 nebules of relief bronchodilator per day for more than 2 consecutive days, but without the need for additional medication. Moderate exacerbations were defined as requiring either antibiotics or corticosteroids. Severe exacerbations were defined as requiring inpatient admission for treatment [clinstat\copd\flta3025.pdf, pages 54-55].

Reviewer comment:
This is not the standard definition of COPD exacerbation. In fact, this definition describes situations that reflect a worsening of airway bronchoconstriction. This definition of exacerbation would be likely to favor the finding of efficacy of FP in patients who have a high degree of reversibility. The most widely accepted definition of COPD exacerbation follows[5]:

- *Type 1 = All of the following symptoms*
  - *Increased dyspnea, increased sputum volume, increased sputum purulence*
- *Type 2 = Two of the following symptoms*
  - *Increased dyspnea, increased sputum volume, increased sputum purulence*
- *Type 3 = One of the following symptoms*
  - *Increased dyspnea, increased sputum volume, increased sputum purulence and one of the following:*
    - *URI within 5 days, fever without non-respiratory cause, increased wheezing, increased coughing, increase in respiratory rate of heart rate ≥20%*

Patients were to complete diary records during the treatment period each morning. Patients recorded the highest of three PEFRs measurements performed each morning prior the dose of study medication, the number of inhalations of supplemental Ventolin use over the preceding 24 hours, and the number of nighttime awakenings requiring the use of Ventolin during the preceding night [clinstat\copd\flta3025.pdf, page 55].

11.1.13. Health-related quality of life instrument

Health outcomes were assessed with the Chronic Respiratory Disease Questionnaire (CRDQ), a health-related quality of life instrument[13] [clinstat\copd\flta3025.pdf, pages 55-56]. The sponsor states that the instrument is an interviewer-administered, disease-specific, validated, questionnaire designed to measure the impact of chronic respiratory disease and its treatments on the patient's COPD-related quality of life. The CRDQ is a 20-item questionnaire that evaluates health-related quality of life across four domains—dyspnea, fatigue, emotional function, and mastery over the disease. The responses for each of the 20 items were summed to provide an overall assessment of health-related quality of life. A physical score was calculated based on the sum of scores of the dyspnea and fatigue domains and an emotional score was calculated based on the sum of the scores of the emotional function and mastery domains. The CRDQ was completed at Day 1, and Weeks 2, 4, 8, 24, and Discontinuation.

11.1.14. Efficacy variables

Efficacy variables for this study are described below.

11.1.14.1. Primary efficacy variable

The primary efficacy variable for this study was the pre-dose FEV_1 collected at Day 1, and Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24. The primary analysis was the endpoint analysis comparing the mean morning pre-dose FEV_1 between treatment groups. The endpoint was defined in the protocol as the final evaluable measurement for the patient. For patients who discontinued from the study the endpoint was the last evaluable measurement taken prior to withdrawal [clinstat\copd\flta3025.pdf, page 5301]. Therefore, the FEV_1 at the Discontinuation Visit was not used for any efficacy analysis. The sponsor's rationale for not using the FEV_1 at the Discontinuation Visit was that patients might have stopped taking study drug prior to the visit and might have been taking another drug known to affect results [clinstat\copd\flta3025.pdf, page 66].

Reviewer comment:
The sponsor's concern about possible confounding of efficacy results as a result of FEV_1 values at the Discontinuation visit is acknowledged. However, the sponsor's plan to carry the last measurement from the preceding visit forward for discontinuing patients also affects the interpretation of efficacy results. Demonstration of efficacy of FP will be more difficult if the rate of withdrawals due to treatment failure is higher in the placebo group than in the FP groups. Demonstration of efficacy of FP will be easier if the rate of withdrawals is similar among all treatment groups or are higher in the FP groups.

Treatment groups were compared using ANCOVA F-tests with baseline, treatment group, and investigator as covariates. Mean morning pre-dose FEV_1 was also compared between treatment groups at each treatment visit as an additional analysis [clinstat\copd\flta3025.pdf, page 5301].

11.1.14.2. Secondary efficacy variables

Secondary efficacy variables included change from baseline in the global and individual domains of the CBSQ, the BDI/TDI score at each of the treatment visits, number and percent of exacerbations of COPD, time to first COPD exacerbation, number of withdrawals and time to withdrawals. Morning PEFR, daily use of Ventolin, percentage of nights with no awakenings requiring Ventolin, frequency of nighttime awakenings requiring Ventolin, and percent of days without using Ventolin were also summarized.

Summary statistics were provided for all secondary endpoints. Changes from baseline in the Global Assessment Score (GAS) of the CBSQ were compared between treatment groups using an ANCOVA F-test with baseline value as covariate. Overall and pairwise treatment comparisons of the BDI/TDI scores were performed by ANOVA F-test, Time to first COPD exacerbation, number of withdrawals, and time to withdrawals were analyzed using survival analysis. [clinstat\copd\flta3025.pdf, page 5303].

The CRDQ was also used to compare changes in the COPD-related quality of life for treatment groups, as measured by an overall score and for each of the four domains. An improvement of at least 10 in overall score was considered to be an overall improvement in COPD specific quality of life. At each visit, treatment group comparisons were made comparing the change from baseline using ANOVA, controlling for baseline and investigator. A difference between treatment groups in mean change from baseline was considered clinically meaningful if the difference was statistically significant and had a minimum of ≥0.5 point improvement per question per item [clinstat\copd\flta3025.pdf, page 5304].

11.1.15. Pharmacokinetics and pharmacodynamics

Blood samples for plasma FP and serum cortisol analyses were obtained at Week 4 at selected sites. Samples were to be collected immediately prior to dosing and at 0.5, 1, 2, 4, 8, and 12 hours post-dose [clinstat\copd\flta3025.pdf, page 5298]. Plasma was analyzed for PF concentration at each time point using solid phase extraction in combination with liquid chromatography tandem mass spectrometry. The sponsor states that this method has been validated to a limit of quantitation of 10 pg/mL for FP [clinstat\copd\flta3025.pdf, page 60].

11.1.16. Safety variables

Safety variables for this study included AEs, ECGs, hematology and clinical chemistry studies, oropharyngeal examinations, and vital signs [clinstat\copd\flta3025.pdf, page 5294]. Summary statistics were to be provided for each of the safety endpoints [clinstat\copd\flta3025.pdf, page 5305].

Reviewer comment:
Although the safety variables are appropriate to assess the local and systemic safety of FP, it would have been preferable to have formal ophthalmologic examinations and assessments of bone density.

11.1.17. Statistical considerations

Imputation of missing data was planned for the primary efficacy parameter and the humanistic outcomes. Last observation carried forward analysis was to be performed. [clinstat\copd\flta3025.pdf, page 5367].

11.1.17.1. Data sets analyzed

The primary population for the analysis of both efficacy and safety was the intent-to-treat population, defined as all randomized subjects who received at least one dose of study drug [clinstat\copd\flta3025.pdf, page 5300].

The sponsor planned a subgroup analysis for patients who have an increase in percent predicted FEV_1 of less than 10% after albuterol at the screening visit. This group was called the "non-reversible-percent of predicted patients" [clinstat\copd\flta3025.pdf, page 5300; IND 44,090 N134 PN, 8/4/98, page 42].

Reviewer comment:
This is apparently a typographic error, as this group is referred to as the "poorly-reversible population" in the study report [clinstat\copd\flta3025.pdf, page 62]. This analysis was to be provided to support the approval of the product outside the US [clinstat\copd\flta3025.pdf, page 90; IND 44,090 N134 PN, 8/4/98, page 41]. The sponsor indicates that this definition reflects current opinion of the European Respiratory Society [NDA 20-833, SE1-004, pages 1-2, 8/10/01].

As noted earlier in this document, assignment to study drug was to be stratified according to the patients' response to reversibility testing with bronchodilator at screening to non-reversible and reversible groups. The non-reversible group was defined earlier in the protocol as patients with an absolute volume increase of <200 mL or absolute volume increase ≥200 mL with baseline reversibility assessment of <12% , and is based on the ATS definition of reversibility [clinstat\copd\flta3025.pdf, page 5283; IND 44,090 N134 PN, 8/4/98, page 25; NDA 20-833, SE1-004, pages 1-2, 8/10/01]. The proportion of patients with reversibility will be critical to determine if the population studied accurately reflects the population of patients with COPD.

Assignment to study drug was stratified depending on whether patients were reversible (FEV_1 increase of ≥200 mL and ≥12% improvement in FEV_1 over baseline) or non-reversible (FEV_1 increase <200 mL or <12% improvement in FEV_1 over baseline), i.e., the ATS definition. As noted earlier, the sponsor did not initially provide a subgroup analysis for the non-reversible population with the original submission. The sponsor submitted in response to an information request by the Division.

The sponsor provided an extensive subgroup analysis of the "poorly-reversible population." As noted above, the "poorly-reversible population" was defined as those patients who had an increase in percent predicted FEV_1 of less than 10% after albuterol at the screening visit. Although this may be the accepted definition for the ERS, it is a curious way of expressing reversibility, as it uses a theoretical value as the baseline (percent predicted FEV_1), rather than an actually measured value, such as FEV_1 at baseline. The ERS definition and the subgroup analysis of the poorly reversible population are not relevant to approval of this drug for this indication in the US, however, and this subgroup analysis will receive only brief review.

The sponsor made no adjustment for multiple comparisons for any efficacy endpoint. The sponsor's reason was that there was only one primary efficacy endpoint [clinstat\copd\flta3025.pdf, page 63].

Reviewer comment:
This review will examine only the primary efficacy endpoint inferentially. This review will examine other efficacy endpoints numerically, as inferential analysis is appropriate for prospectively defined efficacy endpoints that have been corrected for multiple comparisons.

11.1.17.2. Statistical power

The sponsor calculated that a sample size of 145 patients per treatment arm would be necessary to provide >80% power to detect a clinically meaningful significant difference of 0.1 liter between treatment groups. The sponsor assumed a standard deviation for the change from baseline FEV_1 of 0.3 liters, and a level of significance of 0.05, using a two-sample t-test. The sponsor planned to enroll an additional 55 subjects per treatment arm for a separate analysis of patients with airway reversibility <10% in predicted FEV_1. Therefore, the sponsor planned to randomize 600 patients with a total of 200 patients per treatment arm [clinstat\copd\flta3025.pdf, page 5299].

11.1.18. Results

11.1.18.1. Populations enrolled/analyzed

There were 1030 patients screened for the study. There were 390 patients who were screening failures. A total of 640 patients were randomized. The most common reason for screening failure was FEV_1 /FVC <70% and baseline FEV_1 <65% predicted but >0.7 L (237/390, 61%). Other reasons for screening failure included inability to tolerate the 2-week run-in (29/390, 7%), abnormal and clinically significant 12-lead ECG (23/390, 6%), MMRC ≤2 (18/390, 5%), and significant concurrent disease (17/390, 4%) [clinstat\copd\flta3025.pdf, pages 74, 1002-1005].

Reviewer comment:
One might expect that failure to tolerate the 2-week run-in would be the most common reason for screening failure in this study. However, inability to meet the inclusion criterion for spirometry was the most common reason for screening failure. This is probably the reason for the change in Protocol Amendment 4 that changed FEV_1 /FVC ratio from ≤65% to ≤70%. The most likely effect of this change would be to allow entry of patients with milder obstruction. These patients might be more likely to have reversibility, and might be more likely to respond and inhaled corticosteroid such as FP.

Patient disposition is summarized in Table 11.1.3. There were a total of 640 patients randomized and 414 patients completed the study. There were 226 patients that discontinued the study prematurely. There were more discontinuations in the placebo group (79/206, 38%) than in the FP 250 group (76/216, 35%) or the FP 500 group (71/218, 22%). The most frequent reason for discontinuation for all groups was COPD exacerbation. Among patients discontinuing the study, there were 32 patients (41%, 32/79) who discontinued due to an occurrence reported as COPD exacerbation in the placebo group compared with 22 patients (29%, 22/76) in the FP 250 group and 20 patients (28%, 20/71) in the FP 500 group. Adverse events (AEs) leading to discontinuation were most common in the FP 500 group and were less common in the FP 250 and placebo groups. Lack of efficacy was a more frequent reason for discontinuation in the FP 250 (18%) and placebo (13%) groups than in the FP 500 group (6%) [clinstat\copd\flta3025.pdf, pages 75, 288].

Reviewer comment:
COPD exacerbations and lack of efficacy in the FP 250 and placebo groups give some weak support to the efficacy of FP 500. It should be noted that the most common reason for discontinuation in the FP 500 group was an AE.

Protocol violations included use of prohibited medications, cessation of smoking, use of the wrong Diskus during the run-in period, or diagnosis of another medical condition during the study [clinstat\copd\flta3025.pdf, pages 1441-1448].

Reviewer comment:
Protocol violations were fairly infrequent and evenly distributed between treatment groups and were not likely to affect the analysis of efficacy or safety.

Table 11.1.3. Patient disposition, FLTA3025, [clinstat\copd\flta3025.pdf, pages 75, 288]

	Placebo N	(%)	FP 250 N	(%)	FP 500 N	(%)	Total N	(%)
Patients randomized	206	(100)	216	(100)	218	(100)	640	(100)
Patients completed	127	(62)	140	(65)	147	(67)	414	(65)
Patients discontinued	79	(38)	76	(35)	71	(33)	226	(35)
Reason for discontinuation								
Adverse event	14	(18)	13	(17)	18	(25)	45	(20)
COPD exacerbation	32	(41)	22	(29)	20	(28)	74	(33)
Withdrawn consent	7	(9)	2	(3)	8	(11)	17	(8)
Lack of efficacy	10	(13)	18	(24)	4	(6)	32	(14)
Lost to follow-up	3	(4)	4	(5)	3	(4)	10	(4)
Protocol violation	10	(13)	14	(18)	14	(20)	38	(17)
Death	1*	(<1)	0	(0)	0	(0)	1	(<1)
Other	3	(4)	3	(4)	4	(6)	10	(4)

*Patient with ovarian adenocarcinoma discovered 17 days after final study visit, not included in total for discontinuations.

11.1.18.2. Protocol deviations

There were few patients who deviated from the protocol who were not discontinued from the study. These included patients who did not meet entry criteria at randomization (Table 11.1.4) or who had variations from the protocol during the study (Table 11.1.5). The most common protocol deviations due to variation from entry criteria were insufficient severity of disease or significant concurrent disease (Table 11.1.4). The most common protocol variation during the study was use of medication that interfered with objective assessments (Table 11.1.5) [clinstat\copd\flta3025.pdf, pages 74-75, 292-295, 1492-1496].

Table 11.1.4. Protocol deviations due to failure to meet entry criteria [clinstat\copd\flta3025.pdf, page 76].

	Placebo N = 206 n	(%)	FP 250 N = 216 n	(%)	FP 500 N = 218 n	(%)
Inclusion criteria	8	(4)	10	(5)	5	(2)
Severity of disease	4	(2)	8	(4)	4	(2)
Exclusion criteria	15	(7)	10	(5)	11	(5)
Significant concurrent disease	7	(3)	4	(2)	3	(1)
Concurrent medications	3	(1)	2	(<1)	4	(2)
Drug or alcohol abuse	4	(2)	1	(<1)	0	(0)

Table 11.1.5. Protocol deviations during conduct of the study [clinstat\copd\flta3025.pdf, page 295].

	Placebo N = 206 n (%)	FP 250 N = 216 n (%)	FP 500 N = 218 n (%)
All protocol deviations*	14 (7)	19 (9)	17 (8)
Used tobacco	1 (<1)	0 (0)	2 (<1)
Used a prohibited corticosteroid	5 (2)	5 (2)	4 (2)
Used other prohibited medication	7 (3)	11 (5)	7 (3)
Other	5 (2)	13 (6)	10 (5)

*Some patients had more than one protocol deviation, therefore totals within columns do not equal the total of all deviations.

11.1.18.3. Demographic and background characteristics

Demographics and background characteristics of patients are displayed in Table 11.1.6. The majority of patients in each of the treatment groups were 65 years of age or older. The mean age of patients was 64 years in the placebo group, 65 years in the FP 250 group, and 63 years in the FP 500 group. Patients ranged from 39 to 88 years of age. The proportion of patients aged 65 years or greater was similar in each of the treatment groups. The mean age and age range was similar in each of the treatment groups.

The majority of patients in this study were of male gender. Males represented from 66% to 72% of patients in each of the treatment groups. The distribution of male and female patients was similar in each of the treatment groups. The vast majority of patients in this study were of Caucasian race, approximately 95%. There were very few patients of Black or Asian race. Non-Caucasian races represented less than 5% of each of the treatment groups.

Patients in this study had fairly severe dyspnea. All patients experienced dyspnea with walking on level ground, and approximately one third of the patients in each of the treatment groups had dyspnea with walking on level ground for 100 yards or worse (MMRC Dyspnea Score ≥3). Patients had a history of COPD for approximately 7 years. Duration of COPD ranged from 1 year to 45 years. The majority of patients were former smokers, but a fairly large minority of patients were current smokers. Median history of smoking was approximately 50 pack-years in each of the treatment groups, much larger than the 20 pack-year history required for entry into the study.

Approximately 30% of each of the treatment groups used inhaled corticosteroids at the time of screening. Patients using inhaled corticosteroid at the time of screening were evenly distributed among the treatment groups.

The majority of patients in each treatment group had emphysema. The frequency of emphysema was similar among treatment groups and ranged from 74% to 81%.

Reviewer comments:
The under-representation of non-Caucasian patients in this study is a deficiency. The lack of Black, Asian, and Hispanic patients will make it impossible to assess efficacy or safety by race. The degree of dyspnea, duration of COPD, smoking status, and magnitude of smoking history were similar among treatment groups. The population studied is characterized by long smoking histories and significant dyspnea.

A fairly large minority of the patients was taking inhaled corticosteroids at the time of screening. As noted earlier in this review, one would expect these patients to more likely to be corticosteroid-responsive than those not taking inhaled corticosteroids, as one would expect patients with no response or a poor response to have their treatment discontinued. It would be preferable to perform the study on corticosteroid-naïve patients.

Table 11.1.6. Demographics, FLTA3025 [clinstat\copd\flta3025.pdf, pages 78, 296-300].

Characteristic	Placebo N = 206		FP 250 N = 216		FP 500 N = 218	
Age, years	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
<65	97	(47)	93	(43)	111	(51)
≥65	109	(53)	123	(57)	107	(49)
Mean age		64.8		65.2		63.3
SD		9.5		8.7		10.0
Range		42 – 87		40 – 88		39 – 85
Gender	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Female	66	(32)	60	(28)	74	(34)
Male	140	(68)	156	(72)	144	(66)
Race	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Caucasian	196	(95)	204	(94)	206	(94)
Black	6	(3)	9	(4)	9	(4)
Asian	0	(0)	1	(<1)	1	(<1)
Other	4	(2)	2	(<1)	2	(<1)
MMRC Dyspnea Score	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
2	138	(67)	141	(65)	140	(64)
3	62	(30)	70	(32)	68	(31)
4	6	(3)	5	(2)	10	(5)
Duration of COPD	**Years**		**Years**		**Years**	
Mean	7.35		8.39		7.74	
Range	1 – 45		1 – 43		1 – 39	
Smoking status	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Former smoker	118	(57)	119	(55)	115	(53)
Current smoker	88	(43)	97	(45)	103	(47)
Pack-years smoked						
Median	50		54.5		52.3	
Range	20 – 168		20 – 157		20 – 201	
Inhaled steroids at screening	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Yes	64	(31)	66	(31)	68	(31)
No	142	(69)	150	(69)	150	(69)
Emphysema	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Yes	160	(78)	175	(81)	161	(74)
No	46	(22)	41	(19)	57	(26)

Patients had fairly severe airway obstruction. Spirometry results at the time of screening are presented in Table 11.1.7. The mean FEV_1 for each treatment group of about 1250 mL, mean FEV_1 % predicted of about 40%, and mean FEV_1/FVC % of about 47%. The degree of airway obstruction was similar in each of the treatment groups [clinstat\copd\flta3025.pdf, page 305].

Reviewer comment:
The severity of airway obstruction observed is not unexpected given the fairly severe level of dyspnea reported by patients.

Table 11.1.7. Spirometry at screening, FLTA3025 [clinstat\copd\flta3025.pdf, page 305].

	Placebo n = 206	FP 250 n = 216	FP 500 n = 218
FEV_1, mL			
Mean	1254	1242	1266
SD	450	449	430
Median	1130	1155	1160
Range	470 – 2790	640 – 2730	610 – 2750
FEV_1, % predicted			
Mean	40.97	39.75	41.27
SD	11.79	11.76	12.23
Median	40.45	38.79	41.08
Range	16.8 – 64.4	17.8 – 66.5	18.0 – 68.5
FEV_1/FVC %			
Mean	47.19	46.62	47.78
SD	10.29	10.04	10.25
Median	47.44	45.92	47.83
Range	16.7 – 70.5	21.5 – 69.1	25.0 – 69.1

Patient response to treatment with bronchodilator at screening is summarized in Table 11.1.8. A patient was considered "non-reversible" if, after 4 puffs of Ventolin MDI, there was a change in FEV_1 of <12% from baseline or there was <200 mL absolute increase in the FEV_1. Reversible patients represented 59% of all patients in this study. The mean % change in FEV_1 for reversible patients was 32.4%. Non-reversible patients represented 41 % of all patients in this study. The mean % change in FEV_1 for non-reversible patients was 9.24%. The degree of reversibility in each of the treatment groups was similar. The mean % change in FEV_1 for all patients was 22.9%.

Reviewer comment:
The proportion of patients enrolled in the study with reversibility is much higher than is found in the population of COPD patients at large. There were 59% of patients in this study who had reversibility. One would expect that only up to 30% of patients to have in increase of ≥15% in FEV_1 after inhalation of a beta-agonist.[1, 3] *In addition, the degree of reversibility for the reversible population is high—32.43%. The mean degree of reversibility in the non-reversible population was also high—9.24%.*

The high proportion of patients with reversibility in this study is a critical consideration in determining whether the results of the study can be generalized to the COPD population as a whole. Reversible patients were over-represented relative to their prevalence in the COPD population as a whole[1, 2]*, and the degree of reversibility in these*

patients is much higher than would be expected for the general population of patients with COPD[1,2]. Enrichment for these highly reversible patients would be predicted to increase the effect size. While not a "fatal flaw" in this study, it does argue for restricted labeling, should the indication be granted, and against a broad "COPD" indication.

Although the sponsor stratified for reversible and non-reversible populations at randomization, initially the sponsor did not perform an analysis of efficacy for these subgroups. The subgroup analysis was provided by the sponsor in response to a request for information, and is reviewed in Section 11.1.18.7.

Table 11.1.8. Mean change in FEV_1 after bronchodilator treatment at screening*, FLTA3025 [clinstat\copd\flta3025.pdf, pages 306-307].

	Placebo	**FP 250**	**FP 500**	**All treatment groups**
Reversible patients				
n (%)	122 (60)	127 (59)	124 (57)	373 (59)
Mean % change in FEV_1	31.54	32.20	33.54	32.43**
Non-reversible (ATS) patients				
n (%)	83 (40)	87 (41)	92 (43)	262 (41)
Mean % change in FEV_1	10.08	8.10	9.56	9.24**
All patients				
n (%)	205 (100)	214 (100)	216 (100)	635 (100)
Mean % change in FEV_1	22.85	22.40	23.33	22.86**

*Calculation of response: $\frac{(\text{Post-BD } FEV_1 \text{ minus Pre-BD } FEV_1) \times 100}{\text{Pre-BD } FEV_1}$

Not reversible if result is <12% or <200 mL increase in FEV_1
Reversible if result is ≥12% and ≥200 mL increase in FEV_1

**Mean change derived from data for individual treatment group data

Compliance with study treatment is displayed in Table 11.1.9. More than 70% of patients in each treatment group took 90% or more of the prescribed doses of medication. The mean number of doses taken was approximately 93% in each treatment group [clinstat\copd\flta3025.pdf, pages 81, 361].

Reviewer comment:
Compliance seemed adequate to allow for assessment of efficacy and safety, given the trial design, although current compliance assessments are notoriously unreliable.

Table 11.1.9. Compliance with study treatment, FLTA3025 [clinstat\copd\flta3025.pdf, pages 81, 361].

	Placebo		FP 250		FP 500	
	n	(%)	n	(%)	n	(%)
All patients	206	(100)	216	(100)	218	(100)
<80% compliance	17	(8)	9	(4)	21	(10)
80-<90% compliance	37	(18)	35	(16)	39	(18)
≥90% compliance	151	(73)	170	(79)	156	(72)
Missing	1	(<1)	2	(<1)	2	(<1)

11.1.18.4. Primary efficacy endpoint

The primary efficacy endpoint was the mean change in FEV_1 from Baseline to study endpoint. These data are displayed in Table 11.1.10. Values for the mean change from baseline in FEV_1 were small and were 75 mL or less. The mean change from baseline to endpoint in FEV_1 compared to the placebo group for the FP 500 group was 50 mL. This comparison was statistically significant at p = 0.010. This change corresponds to an effect size of 4.0%[1]. Mean change from baseline in FEV_1 compared to placebo was 27 mL for the FP 250 group. This comparison was not statistically different from the placebo group. This change corresponds to an effect size of 2.2%[1]. Values for the mean change in FEV_1 from Baseline for the FP 500 group at Weeks 6, 12, and 24 were small and ranged from 56 mL to 67 mL more than the placebo group. Values for the mean change from baseline for the FP 250 group at Weeks 6, 12, and 24 ranged from 20 to 29 mL more than the placebo group. Values for the mean change from baseline for the placebo group at Weeks 6, 12, and 24 ranged from 3 to 11 mL.

Mean change from Baseline in FEV_1 for the FP 500 group at Weeks 1, 2, 3, 4, 8, 16, and 20 showed changes of 101 mL or less [clinstat\copd\flta3025.pdf, pages 91, 427-436]. Mean change from baseline for the FP 250 group at Weeks 1, 2, 3, 4, 8, 16, and 20 showed changes of 52 mL or less [clinstat\copd\flta3025.pdf, pages 91, 427-436]. Mean change from baseline for the placebo group at Weeks 1, 2, 3, 4, 8, 16, and 20 showed changes of 28 mL or less [clinstat\copd\flta3025.pdf, pages 91, 427-436].

Reviewer comment:
Although there was a statistical significant difference from placebo for the FP 500 group noted at endpoint and numerical superiority was noted at the interim points, the absolute change in FEV_1 is quite small and of questionable clinical importance. The small size of this change should be balanced against the high dose of inhaled corticosteroid required to achieve this effect size and the highly enriched patient population who showed reversibility with bronchodilator.

[1] Effect size = $\frac{\text{(mean change from Baseline in FEV1, active) minus (mean change from Baseline in FEV1, Pbo)}}{\text{Baseline FEV1, active}}$

Table 11.1.10. Mean change in FEV_1 from baseline, primary efficacy variable, FLTA3025 [clinstat\copd\flta3025.pdf, pages 91, 427-436].

	Placebo			FP 250			FP 500		
Study week	Mean FEV_1, mL	Mean change from baseline, mL	n	Mean FEV_1, mL	Mean change from baseline, mL	n	Mean FEV_1, mL	Mean change from baseline, mL	n
Baseline	1203	NA	204	1207	NA	215	1246	NA	218
Week 6	1248	11	164	1240	32	182	1325	67	191
Week 12	1254	3	153	1248	23	161	1315	64	167
Week 24	1275	8	125	1290	37	139	1319	75	146
Endpoint**	1221	11	199	1240	38	211	1301	61	210
p value vs. placebo	Overall 0.035			FP 250 vs. Pbo 0.140			FP 500 vs. Pbo 0.010		

*ANCOVA, Baseline as covariate
**Primary efficacy endpoint

11.1.18.5. Secondary efficacy endpoints

Secondary efficacy variables included change from baseline in the global and individual domains of the CBSQ, the BDI/TDI score at each of the treatment visits, number and percent of exacerbations of COPD, time to first COPD exacerbation, number of withdrawals and time to withdrawals. Morning PEFR, daily use of Ventolin, percentage of nights with no awakenings requiring Ventolin, frequency of nighttime awakenings requiring Ventolin, and percent of days without using Ventolin were also summarized.

Summary statistics were provided for all secondary endpoints. The sponsor provided an inferential statistical analysis of secondary efficacy endpoints. Individual secondary efficacy endpoints are reviewed below.

Reviewer comment:
Inferential analysis is appropriate only for the prospectively defined efficacy endpoint on which the study was powered, and not for these secondary efficacy endpoints. Therefore, this document will focus on the numerical differences between treatment groups for the secondary efficacy endpoints, and will not address the inferential statistical analysis.

11.1.18.5.a. Chronic Bronchitis Symptom Questionnaire

As noted earlier in this review, the CBSQ evaluated cough frequency and severity, sputum release, and chest discomfort on a 0 to 4, 5-point scale. Individual scores were summed to provide a Global Assessment Score (GAS). The maximum possible GAS was 16. Patients were required to have a minimum score of 4 at baseline to qualify for randomization. The sponsor determined that the Minimally Clinically Important Change (MCIC) in the CBSQ was 1.4 points in an analysis of patients completing at least 8 weeks of this study [clinstat\other\cbsqvalidationdocument.pdf, page 11]. Results of the Chronic Bronchitis Symptom Questionnaire are displayed in Table 11.1.11. The sponsor reported decreases in the COPD for FP 250 and FP 500, but the differences from placebo

for these treatment groups were less than the MCIC of 1.4 points [clinstat\copd\flta3025.pdf, pages 91, 427-436].

Reviewer comment:
The differences from placebo in the CBSQ for FP 250 and FP 500 were less than the MCIC of 1.4 points.

The population studied included a high percentage of patients with reversibility with bronchodilator and does not accurately represent the population of COPD patients. As noted earlier in this review, the CBSQ was administered in such a fashion that the interviewer might have influenced patient responses. The poor correlation between the GAS and GRC and the large standard deviation in the GRC lead to serious questions about the design of this instrument and suitability for the patient population. Of note, the CBSQ was "validated" using patients from the same study (FLTA 3025) in which it was used as an endpoint, which is clearly unacceptable. Furthermore, the differences from placebo for FP 250 and FP 500 were less than the MCIC of 1.4 points. These data will not be able to provide support for the efficacy of FP.

Table 11.1.11. Chronic Bronchitis Symptom Questionnaire, FLTA3025. See text for comments on validity of this instrument [clinstat\copd\flta3025.pdf, pages 93, 440-445].

	Pbo			FP 250			FP 500		
Study week	GAS*	Mean change from baseline	n	GAS*	Mean change from baseline	n	GAS*	Mean change from baseline	n
Baseline	7.1	NA	205	7.1	NA	215	7.4	NA	218
Week 1	6.5	0.5	199	6.3	0.8	209	6.5	0.9	211
Week 2	6.2	0.7	186	6.1	1.0	205	6.1	1.3	201
Week 3	5.8	1.1	177	5.9	1.2	201	6.0	1.4	197
Week 4	5.9	1.1	175	5.8	1.3	196	5.8	1.5	198
Week 6	5.7	1.3	166	5.9	1.1	183	5.9	1.5	193
Week 8	5.7	1.2	165	5.7	1.4	175	5.7	1.6	183
Week 12	5.4	1.4	153	5.6	1.4	161	3.0	1.3	168
Week 16	5.6	1.0	138	5.5	1.5	152	5.6	1.7	159
Week 20	5.3	1.3	127	5.7	1.3	143	5.7	1.5	149
Week 24	5.3	1.3	125	5.2	1.7	139	5.6	1.7	147
Endpoint	6.1	0.9	199	5.7	1.4	211	6.0	1.4	211

*GAS: Global Assessment Score. Minimally clinically important change = 1.4 points.

11.1.18.5.b. Baseline/Transition Dyspnea Indices

The degree of functional impairment at baseline due to dyspnea, the magnitude of task to provoke dyspnea, and the magnitude of effort that provoked dyspnea were rated on a 0 to 4, 5-point scale to derive the BDI. The maximum BDI score was 12. The TDI assessed

changes from baseline in functional impairment, magnitude of task, and magnitude of effort were assessed at each subsequent visit with a -3 to +3, seven-point scale [clinstat\copd\flta3025.pdf, pages 49-54]. The sponsor considered a clinically important TDI score to be ≥1.0 [clinstat\copd\flta3025.pdf, page 67, Correspondence submitted to IND 50,703, Meeting request package, 2/6/98]. Results of the BDI/TDI are presented in Table 11.1.12. The sponsor reported small clinically significant TDIs for FP 500 endpoint and at all visits except Visit 1. The sponsor reported small, clinically significant TDIs for FP 250 at Weeks 8, 12, 16, and 24, but not at endpoint. The sponsor reported a small clinically significant TDI for the placebo group was noted at Week 24. However, none of the TDIs for FP 250 or FP 500 were significantly different from TDIs noted for placebo [clinstat\copd\flta3025.pdf, pages 94, 478-481].

Reviewer comment:
The population studied included a high percentage of patients with reversibility with bronchodilator and does not accurately represent the population of COPD patients. Degree of functional impairment, magnitude of task, and magnitude of effort are likely to be highly correlated variables, in this reviewer's opinion, and therefore will tend to inflate any observed positive or negative treatment effect. This instrument has not been validated in a COPD population with a high degree of reversibility, and it is not a widely used scale or one that is held in high regard. These data do not provide support for the efficacy of FP.

Table 11.1.12. Baseline/Transition Dyspnea Index, FLTA3025. See text for comments on validity of this instrument [clinstat\copd\flta3025.pdf, pages 94, 478-481].

	Pbo		FP 250		FP 500	
Study week	Baseline score	n	Baseline score	n	Baseline score	n
Baseline	5.8	204	6.3	213	5.9	216
	Transition* Score		Transition Score		Transition Score	
Week 1	0.1	199	0.4	209	0.8	211
Week 2	0.2	186	0.7	204	1.0	201
Week 3	0.3	177	0.7	200	1.0	197
Week 4	0.4	175	0.8	196	1.0	198
Week 6	0.6	166	0.9	183	1.2	193
Week 8	0.6	165	1.0	175	1.5	183
Week 12	0.6	152	1.1	161	1.2	168
Week 16	0.7	138	1.1	152	1.5	159
Week 20	0.8	127	0.9	143	1.5	149
Week 24	1.2	125	1.4	139	1.8	147
Endpoint	0.5	199	0.9	211	1.2	211

*Minimally clinically significant TDI = 1.0 point.

11.1.18.5.c. COPD exacerbations

The incidence of COPD exacerbation was slightly lower for FP 250 and FP500 than with placebo. This relationship was dose-related. The incidence of moderate to severe COPD exacerbations was slightly lower with FP 250 and FP 500 than placebo. This relationship was also dose-related. Moderate to severe exacerbations of COPD were defined as those requiring oral antibiotics, inhaled or oral corticosteroids, or inpatient admission for treatment. These data are displayed in Table 11.1.13.

Reviewer comment:
The lower frequency of any COPD exacerbation, lower frequency of moderate or severe COPD exacerbations, and dose ordering provide some weak support for the efficacy of FP 250 and FP 500 for the population studied. However, it is important to note that the definition of COPD exacerbation was not the standard definition[1, 5,6.] The sponsor's definition of COPD exacerbation describes situations that reflect a worsening of airway bronchoconstriction, and would be likely to favor the finding of efficacy of FP in patients who have a high degree of reversibility. Accordingly, any weak support for the efficacy of FP for this endpoint is further weakened. In addition it should be noted that the magnitude of the decrease in COPD exacerbations is quite small.

Table 11.1.13. Incidence of COPD exacerbations, FLTA3025 [clinstat\copd\flta3025.pdf, pages 96, 503-504].

	Placebo N = 206 n	(%)	FP 250 N = 216 n	(%)	FP 500 N = 218 n	(5)
Patients with any COPD exacerbation	106	(51)	104	(48)	98	(45)
Patients with moderate or severe COPD exacerbations	88	(43)	87	(40)	83	(38)

Time to COPD exacerbation or withdrawal is summarized in Table 11.1.14. In general, there were fewer first COPD exacerbations, first moderate to severe COPD exacerbations, study withdrawals, and withdrawals due to COPD exacerbation in the FP 250 and FP 500 groups than the placebo group for each month of the study. In general, this tended to be a dose-related observation, with most events in the placebo group, followed next by the FP 250 group, with the least in the FP 500 group.

Table 11.1.14. Time to COPD exacerbation or withdrawal, FLTA3025

Time to First COPD Exacerbation [clinstat\copd\flta3025.pdf, pages 506-508]						
	Pbo		FP 250		FP 500	
	Patients at risk	Events	Patients at risk	Events	Patients at risk	Events
Month 1	149	45	174	36	173	33
Month 2	129	62	142	56	148	51
Month 3	107	82	118	75	130	67
Month 4	96	90	98	89	112	82
Month 5	84	99	86	98	97	94
Month 6	0	104	0	103	0	98

Time to First Moderate to Severe COPD Exacerbation [clinstat\copd\flta3025.pdf, pages 510-512]						
	Pbo		FP 250		FP 500	
	Patients at risk	Events	Patients at risk	Events	Patients at risk	Events
Month 1	161	33	191	19	188	17
Month 2	141	49	162	35	162	35
Month 3	122	66	140	52	141	53
Month 4	110	74	116	69	122	69
Month 5	98	81	102	79	109	78
Month 6	0	86	0	86	0	83
Time to Study Withdrawal [clinstat\copd\flta3025.pdf, pages 514-516508]						
	Pbo		FP 250		FP 500	
	Patients at risk	Events	Patients at risk	Events	Patients at risk	Events
Month 1	181	24	202	14	205	13
Month 2	170	35	182	35	192	26
Month 3	159	46	171	45	178	40
Month 4	147	58	158	57	169	49
Month 5	133	71	147	68	158	60
Month 6	0	76	0	72	0	70
Time to Study Withdrawal due to COPD Exacerbation [clinstat\copd\flta3025.pdf, pages 518-520]						
	Pbo		FP 250		FP 500	
	Patients at risk	Events	Patients at risk	Events	Patients at risk	Events
Month 1	181	12	202	6	205	1
Month 2	170	18	182	12	192	6
Month 3	159	25	171	18	178	14
Month 4	147	30	158	21	169	20
Month 5	133	36	147	26	158	22
Month 6	0	38	0	28	0	27

11.1.18.5.d. PEFR

Overall, there was a small mean increase from baseline in AM PEFR for the FP 250 (8.8 L/min) and FP 500 (9.4 L/min) groups. A similar small increase from baseline in AM PEFR was noted for FP 250 and FP 500 at the end of each month during the treatment period. The increases were less than 15 L/min for each of the FP treatment groups for each of the months [clinstat\copd\flta3025.pdf, page 97, 526-529].

Reviewer comment:
The differences in mean AM PEFRs between treatment groups were quite small, unlikely to be measurable in an individual patient, and are well within the range of variation for this measurement. The absolute change from baseline in FP 250 and FP 500 was <4% and these differences are not clinically significant.

Table 11.1.15. Mean change from baseline in AM PEFR [clinstat\copd\flta3025.pdf, page 97, 526-529]

	Placebo	FP 250	FP 500
Baseline			
N	205	213	218
Mean PEFR, L/min	249.6	254.7	254.2
Overall			
N	205	212	215
Mean PEFR, L/min	247.5	262.3	263.8
Mean change from baseline, L/min	-1.9	8.8	9.4

11.1.18.5.e. Supplemental Ventolin use

Supplemental Ventolin use is summarized in Table 11.1.16. Overall, the FP 250 and FP 500 groups had a small decrease in the number of puffs of Ventolin used per day. This decrease was much less than one puff per day. The decrease in Ventolin use for FP 250 and FP 500 for each study month was never more than 0.3 puffs per day. Overall, the FP 250 and FP 500 groups had a small increase in the number of days without Ventolin use, approximately 2%. The increase in days without Ventolin use for FP 250 and FP 500 for each study month was never more than 3.3% of days.

Reviewer comment:
The changes in Ventolin use are quite small and not clinically significant.

Table 11.1.16. Mean change from baseline in supplemental Ventolin use [clinstat\copd\flta3025.pdf, page 98, 526-529]

	Placebo	FP 250	FP 500
Number of puffs of Ventolin used per day			
Baseline			
N	205	213	218
Mean number of puffs	5.4	5.7	5.7
Overall			
N	204	212	215
Mean number of puffs	6.2	5.6	5.2
Mean change from baseline, puffs	0.7	-0.1	-0.2
Percent of days without Ventolin use			
Baseline			
N	205	213	218
Mean % days without Ventolin use	16.6	18.3	16.6
Overall			
N	204	212	215
Mean % days without Ventolin use	14.7	19.8	18.8
Mean change from baseline, % days	-1.7	2.0	2.1

Nighttime awakenings requiring Ventolin use are summarized in Table 11.1.17. Overall, the FP 250 and FP 500 groups had a small decrease from baseline in the number of awakenings per night. Overall the FP 250 and FP 500 groups had a small increase in the percent of nights with no awakenings requiring Ventolin use.

Reviewer comment:
The small changes from baseline in nighttime awakenings and percent of nights with no awakenings requiring Ventolin are not clinically significant.

Table 11.1.17. Mean change from baseline in nighttime awakenings requiring Ventolin use [clinstat\copd\flta3025.pdf, pages 99-100]

	Placebo	FP 250	FP 500
Number of awakenings per night requiring Ventolin			
Baseline			
N	202	212	217
Mean number of awakenings	0.22	0.25	0.29
Overall			
N	202	211	212
Mean number of awakenings	0.33	0.20	0.25
Mean change from baseline, awakenings	0.11	-0.05	-0.05
Percent of nights with no awakenings requiring Ventolin			
Baseline			
N	202	212	217
Mean % nights with no awakenings	84.0	82.2	81.7
Overall			
N	202	211	212
Mean % nights with no awakenings	79.6	86.1	85.5
Mean change from baseline, % nights with no awakenings	-4.3	4.2	3.4

11.1.18.5.f. Health-related quality of life instrument

COPD-related quality of life was evaluated using the Chronic Respiratory Disease Questionnaire (CRDQ)[13]. The CRDQ contains 20 questions in 4 domains: dyspnea, fatigue, emotional function, and mastery. An overall score, the sum of the scores for all 20 questions, was the primary health-related quality of life endpoint. A physical score was calculated based on the sum of scores in the dyspnea and fatigue domains and an emotional score was calculated based on the sum of scores of the emotional function and mastery domains [clinstat\copd\flta3025.pdf, page118]. A clinically significant improvement was considered to be 0.5 points per item. Therefore, an improvement in the Overall score of at least 10.0 points was considered to be a clinically significant improvement in COPD-specific quality of life. As there were different numbers of items per domain, the clinically significant changes for each domain and summary scores are as follows [clinstat\copd\flta3025.pdf, pages 68-69, 118]:

- Fatigue domain: 2.0 points
- Dyspnea domain: 2.5 points
- Physical summary: 4.5 points

- Emotional function domain: 3.5 points
- Mastery domain: 2.0 points
- Emotional summary: 5.5 points

Study endpoint was defined as the last available post-baseline score for the CDRQ. This was different from the other analyses, which did not include values for the Discontinuation visit [clinstat\copd\flta3025.pdf, page 118]. In addition, the sponsor excluded patients with an overall baseline score greater than 130 from the analysis of the overall score at any visit. These patients were excluded because baseline scores would be mathematically unable to attain a clinically meaningful change

[clinstat\copd\flta3025.pdf, page 119]. Similar exclusions were made for the patients with the following scores [clinstat\copd\flta3025.pdf, page 118]:

- Fatigue score >26
- Dyspnea score >32
- Physical summary >58

- Emotional function score >45
- Mastery score >26
- Emotional summary >71

The population analyzed, which excluded these patients, was referred to the "reduced intent-to-treat population" (reduced ITT population) [clinstat\copd\flta3025.pdf, page 119].

Reviewer comment:
It is true that it is be mathematically impossible for patients whose baseline scores are higher than those noted above to attain a clinically meaningful change. However, the necessity to exclude a substantial number of patients indicates that the instrument is inappropriate for the patient population. This tends to reinforce this reviewer's previously expressed concerns about how well the study population reflects the overall COPD population. Nevertheless, it is not appropriate to exclude these patients from the analysis. It would have been preferable to set these maximum scores as inclusion criteria for the study. As it turns out, there were no patients excluded for the Overall score and the Emotional function summary score and the ITT and "reduced ITT populations" were identical for these scores [clinstat\copd\flta3025.pdf, page 118-119]. There were 22 patients excluded from the calculation of the Emotional summary score, 23 patients from the Emotional domain score, 53 patients from the Mastery domain score, 6 patients from the Fatigue domain score, and 2 patients from the Dyspnea domain score, however. This review will examine CDRQ results for the ITT group and not the reduced ITT population.

Although there was a dose-related increase from baseline in the overall CDRQ score for FP, this increase was less than the specified minimally clinically significant change of 10.0 points. These data are displayed in Table 11.1.18. Data displayed is for the ITT population. Dose-related increases from baseline were also noted for FP 250 and FP 500 in the Physical summary score and the Emotional summary score. Like the change in the Overall score, the changes in these scores were less than the specified minimally clinically significant changes, with the exception of the Physical summary score for FP 500. There was less than a 4.5 point difference from the change from baseline for the placebo group for the Physical summary score for FP 500, however, and therefore no clinically significant difference from the placebo group [clinstat\copd\flta3025.pdf, pages 1256-1292].

Individual domains showed similar small, dose-related, but not clinically significant increases from baseline for FP 250 and FP 500, with the exception of the Dyspnea domain, which showed a dose-related clinically significant improvement from baseline

for FP 250 and FP 500. However, there was less than a 2.5 point difference from the change from baseline for the placebo group for the Dyspnea domain scores, and therefore no clinically significant difference from the placebo group [clinstat\copd\flta3025.pdf, pages 1256-1292].

Table 11.1.18. Chronic Respiratory Disease Questionnaire (CRDQ), COPD-related quality of life instrument, ITT population, FLTA3025 [clinstat\copd\flta3025.pdf, pages 1256-1292].

	Pbo			FP 250			FP 500		
	Score	Mean change from baseline	n	Overall score	Mean change from baseline	n	Overall score	Mean change from baseline	n
Overall score*									
Baseline	87.6	NA	203	88.8	NA	214	83.6	NA	213
Endpoint	89.6	1.0	199	94.2	5.1	211	92.8	9.1	210
Physical summary score**									
Baseline	33.3	NA	203	34.1	NA	214	32.6	NA	213
Endpoint	34.9	1.2	199	37.8	3.7	211	37.4	4.8	210
Emotional summary score***									
Baseline	54.3	NA	204	54.9	NA	215	51.0	NA	216
Endpoint	54.7	-0.1	201	56.5	1.4	212	55.4	4.4	213

*Clinically significant change in Overall Score = 10.0 points
**Clinically significant change in Physical Summary Score = 4.5 points
***Clinically significant change in Emotional Summary Score = 5.5 points

Reviewer comment:
The CRDQ is a widely used and well-validated instrument[13]. No clinically significant change from baseline was observed in the Overall score. In general, most of the individual domain and summary scores also did not show clinical significance, and none showed a clinically significant difference from the placebo group. As there was not a clinically significant change in the Overall score, other changes in individual domains or summary scores provide no meaningful information. These data provide no support for the efficacy of FP 250 or FP 500 for this population. More importantly, the small (50 mL) but "statistically significant" increase in FEV_1 noted for the primary endpoint is not supported as being clinically important because there is no discernable benefit to the patient that could be measured using this instrument.

11.1.18.6. Smoking status, post-hoc subgroup analysis

The sponsor provided a post-hoc analysis of efficacy by patient smoking status for exploratory purposes. Former smokers had the largest mean change from baseline in FEV_1 at endpoint. This finding was dose-related [clinstat\copd\flta3025.pdf, page 101]. These data are displayed in Table 11.1.19. Among the former smokers, those treated with FP 500 had the largest change in FEV_1 (100 mL), followed by those treated with FP 250

(72 mL), and with the smallest change in those treated with placebo (-5 mL). There were no meaningful differences in the mean change from baseline in FEV_1 between the treatment groups for patients who were smokers during the conduct of the study.

Table 11.1.19. Mean change from baseline in FEV_1 at endpoint, by smoking status [clinstat\copd\flta3025.pdf, page 101].

Smoking status	Placebo	FP 250	FP 500
	Mean change, mL (n)	Mean change, mL (n)	Mean change, mL (n)
Current smokers	31 (88)	-5 (97)	17 (103)
Former smokers	-5 (118)	72 (119)	100 (115)

The sponsor also examined other efficacy endpoints by patient smoking status. In general, where there were differences between the groups, efficacy was favored in the former smokers. This was true for the CBSQ and the BDI/TDI. Very small differences were noted in COPD exacerbations, AM PEFR, Ventolin use, and nighttime awakenings were noted favoring efficacy of FP 250 and FP 500 in the former smokers. The magnitudes of these very small changes were similar to those noted for the secondary efficacy endpoints. There were no meaningful differences between the treatment groups for secondary efficacy endpoints for patients who were smokers during the conduct of the study [clinstat\copd\flta3025.pdf, page 101]. The Overall CRDQ score at endpoint for former smokers in the FP 500 group showed a clinically meaningful increase from baseline of 11.5 points. However, this increase from baseline was not clinically meaningfully different from the increase from baseline in the placebo group [clinstat\copd\flta3025.pdf, page 124].

Reviewer comment:
Although these data are of a post-hoc exploratory nature, they strongly suggest that patients who stopped smoking prior to the conduct of the study carried the small amount of efficacy observed in the primary endpoint. It has been well established by the Lung Health Study[8] that smoking cessation has a far greater impact on lung function and long-term survival of the COPD patient than any pharmacological intervention. It is therefore not unreasonable to attribute some of the improvement in FEV_1 observed during the study to abstention from smoking.

11.1.18.7. "Non-reversible" population, subgroup analysis

Assignment to study drug was to be stratified according to the patients' response to reversibility testing with Ventolin at screening to a non-reversible group and a reversible group. Non-reversible patients were defined as having an absolute volume increase <200 mL or an absolute volume increase of ≥200 mL with baseline FEV_1 reversibility of <12%. Reversible patients were defined as having an absolute volume increase ≥200 mL with baseline FEV_1 reversibility of ≥12% [clinstat\copd\flta3025.pdf, pages 5283; IND 44,090 N134 PN, 8/4/98, page 25]. Despite having assignment stratified based on "non-reversibility," the sponsor did not initially include an analysis for this subgroup. The sponsor was asked to provide a subgroup analysis of the non-reversible group in an IR on 10/2/01. The sponsor submitted this information in a document dated 1/17/01 [NDA 20-833, SE1 004 BZ, 10/17/01]. The results of the subgroup analysis for the non-reversible population are briefly reviewed below.

Table 11.1.20 summarizes the mean change in FEV_1 from baseline for the "non-reversible" population. There was only a small change in FEV_1 from baseline at study endpoint for FP 500 (21 mL), FP 250 (-15 mL) and placebo (-17 mL). Changes of 28 mL and 13 mL were seen for FP 500 at Weeks 12 and 24. Small increases from baseline were noted for FP 250 at Weeks 12 and 24. Small decreases in FEV_1 from baseline were noted for placebo at Weeks 12 and 24 [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 18].

Table 11.1.20. Mean change in FEV_1 from baseline, primary efficacy variable, non-reversible population, FLTA3025 [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 18].

	Placebo			FP 250			FP 500		
Study week	Mean FEV_1, mL	Mean change from baseline, mL	n	Mean FEV_1, mL	Mean change from baseline, mL	n	Mean FEV_1, mL	Mean change from baseline, mL	n
Baseline	1151	NA	82	1153	NA	87	1175	NA	92
Week 12	1218	-11	58	1150	-14	67	1263	28	68
Week 24	1224	-25	49	1199	-2	51	1231	13	60
Endpoint	1147	-17	80	1144	-15	86	1204	21	88

Response of the reversible population in the mean change in FEV_1 from baseline is summarized in Table 11.1.21. The difference from placebo for mean change from baseline at endpoint for the reversible group for FP 500 was 64 mL and for FP 250 was 41 mL. This was greater than the difference from placebo for mean change from baseline at endpoint for the non-reversible group, which for FP 500 was 38 mL and for FP 250 was 2 mL [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 18].

Table 11.1.21. Mean change in FEV_1 from baseline, primary efficacy variable, reversible population, FLTA3025 [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 18].

	Placebo			FP 250			FP 500		
Study week	Mean FEV_1, mL	Mean change from baseline, mL	n	Mean FEV_1, mL	Mean change from baseline, mL	n	Mean FEV_1, mL	Mean change from baseline, mL	n
Baseline	1237	NA	122	1250	NA	126	1296	NA	124
Week 12	1276	12	95	1326	50	92	1352	93	97
Week 24	1308	29	76	1345	56	87	1388	119	85
Endpoint	1271	29	119	1306	70	123	1204	93	120

In general, secondary endpoints demonstrated either no change or small, clinically insignificant changes for FP 500 and FP 250 in the non-reversible population. Changes in the GAS of the CBSQ or the TDI showed no clinically meaningful changes for FP 250 or FP 500 in the non- reversible population [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 18]. The incidence and frequency of exacerbations due to COPD were slightly lower in the FP 500 group than the FP 250 and placebo groups,

which had similar incidences and frequencies of COPD exacerbations. The incidences and frequencies of moderate/severe COPD exacerbations were similar across treatment groups for this population [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 19].

The probability of COPD exacerbation was lower during the first half of the study in the FP groups compared with placebo, but by the end of the study the FP 250 group and the placebo groups were similar [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 23]. In general, small and clinically insignificant changes from baseline favoring FP 250 and FP 500 were noted in for the non-reversible population for the following secondary endpoints: AM PEFR, number of puffs of Ventolin used per day, and awakenings per night requiring Ventolin [clinstat\copd\flta3025.pdf, pages 20, 148, 156, 164]. There were no meaningful differences between treatment groups in the overall score of the health-related quality of life instrument, the CRDQ [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 169]

Reviewer comment:
Analysis of the non-reversible population demonstrates little efficacy in this population. Efficacy in this study was carried by those patients in the reversible population.

11.1.18.8. Pharmacokinetics and pharmacodynamics

Blood samples for plasma FP and serum cortisol analyses were obtained at Week 4 at selected sites. Samples were to be collected immediately prior to dosing and at 0.5, 1, 2, 4, 8, and 12 hours post-dose [clinstat\copd\flta3025.pdf, page 5298]. Plasma was analyzed for FP concentration at each time point using solid phase extraction in combination with liquid chromatography tandem mass spectrometry. The sponsor states that this method has been validated to a limit of quantitation of 10 pg/mL for FP [clinstat\copd\flta3025.pdf, page 60].

Reviewer comment:
Unfortunately, baseline cortisol levels were not planned for this study. Change in AM cortisol level or the AUC for cortisol from baseline would have been more informative than these data derived from Week 4 samples alone.

There were 86 patients who participated in the clinical pharmacology component of this study. Of these 86 patients, 28 were treated with placebo, 31 with FP 250, and 27 with FP 500 [clinstat\copd\flta3025.pdf, page 166]. The placebo group in the PK/PD component was slightly older than the total study population (47% <65 years in the PK/PD population compared with 36% in the total study population). There were fewer females in the placebo group of the PK/PD component (14% in the PK/PD component vs. 32% in the total study population). The PK/PD population had a slightly longer duration of COPD in all treatment groups (approximately 8 to 10 years for the PK populations vs. 7 to 8 years for the study population). Otherwise, the PK/PD population was similar to that of the total study population in demographics [clinstat\copd\flta3025.pdf, pages 4889-4897].

Key pharmacokinetic results are displayed in Table 11.1.22. FP AUC_{last} and FP C_{max} were higher for FP 500 than FP 250 and data suggest that 2 inhalations of FP 250 Diskus may be more than dose proportional than one inhalation of FP 500 Diskus. Mean FP AUC_{last} was somewhat lower in current smokers than in former smokers. In addition, a linear relationship was observed between weight and FP AUC_{last} for FP 500, with lower FP levels for heavier patients. This association was not noted with FP 250 [clinstat\copd\flta3025.pdf, pages 166, 4857, 4881].

Table 11.1.22. Key pharmacokinetic results, FLTA 3025 [clinstat\copd\flta3025.pdf, page 166].

PK parameter	FP 250 N = 31	FP 500 N = 27
Mean AUC_{last}, pg.hr/mL	310.6	539.0
Mean C_{max}, pg/ml	52.9	83.6

Key pharmacodynamic results are displayed in Table 11.1.23.

Table 11.1.23. Serum cortisol results, FLTA3025 [clinstat\copd\flta3025.pdf, pages 166, 4855].

Cortisol parameter	Placebo N = 28	FP 250 N = 31	FP 500 N = 27
Mean Cortisol AUC_{12}, pmol.hr/mL	2673.4	2404.2	2102.3
Δ vs. placebo	-	- 10.1%	- 21.4%
Mean C_{min}, pmol/mL	123.1	116.7	85.3

FP 250 and FP 500 treatment groups had lower mean cortisol AUC_{12} and mean C_{min} than the placebo group (10% and 21%, respectively, for serum cortisol AUC). There was a dose-response effect noted with the lowest cortisol AUC_{12} and C_{min} in FP 500 patients [clinstat\copd\flta3025.pdf, pages 166, 4855]. Higher mean cortisol AUC_{12} levels were noted for current smokers than for former smokers, consistent with the lower serum FP levels measured in current smoking. There was no relationship noted between cortisol levels and weight [clinstat\copd\flta3025.pdf, page 4857].

Reviewer comment:
These PK and PD data demonstrate measurable systemic effects of inhaled FP. These findings are not a surprise, given the large dose of FP used. It is important to note this is clear evidence of systemic activity of FP in this population, which is corroborated by the single dose crossover study conducted in normal volunteers (see FLTA1003, OCPB review). It should also be noted that these effects were noted early in the course of the study, at Week 4. It would have been interesting to examine similar data collected later in this study, for example, Week 24, where one might expect even a higher degree of suppression of cortisol AUC_{12} levels. These data will influence any risk benefit analysis of FP in this population, given the small treatment effect noted.

It is interesting that lower FP AUC_{last} and higher cortisol AUC_{12} levels were seen in smokers, as one might expect increased FP absorption in the presence of increased inflammation associated with smoking.

11.1.18.9. Safety outcomes

In addition to serum cortisol AUC, discussed above, safety variables for this study included AEs, ECGs, hematology and clinical chemistry studies, oropharyngeal examinations, and vital signs [clinstat\copd\flta3025.pdf, page 5294]. Each variable is discussed below.

11.1.18.9.a. Total drug exposure

Total drug exposure is summarized in Table 11.1.24. Approximately 50% of each group completed ≥24 weeks of study treatment. The mean duration of treatment was 128.8 days for placebo, 133.2 days for FP 250, and 136.1 days for FP 250.

Table 11.1.24. Total drug exposure, FLTA3025 [clinstat\copd\flta3025.pdf, pages 129, 801].

Duration of treatment	Placebo N = 206		FP 250 N = 216		FP 500 N = 218	
	n	(%)	n	(%)	n	(%)
Any treatment	206	(100)	216	(100)	218	(100)
≥4 weeks	180	(87)	200	(93)	202	(93)
≥8 weeks	166	(81)	181	(84)	187	(86)
≥12 weeks	156	(76)	168	(78)	175	(80)
≥16 weeks	146	(71)	156	(72)	161	(74)
≥20 weeks	130	(63)	144	(67)	152	(70)
≥24 weeks	104	(50)	105	(49)	122	(56)
Treatment days, mean	128.8		133.2		136.1	

Reviewer comment:
Drug exposure appears to be adequate to allow for assessment of safety, given limitations with the design and duration of this study, and recognizing that compliance reporting is commonly unreliable. Compliance assessment was based on data from the Diskus dose counter, which cannot accurately assess whether patients actually received the drug that was dispensed.

11.1.18.9.b. Adverse events

Adverse events (AEs) were common in this study. These data are summarized in Table 11.1.25. A small dose response effect was noted for all AEs with FP 500 and FP 250. AEs occurred in 80% of FP 500-treated patients, 76% of FP 250-treated patients, and in 74% of placebo-treated patients. AEs occurring more frequently with FP 500 and FP 250 than with placebo included upper respiratory tract infection, headaches, candidiasis of the mouth or throat, throat irritation, musculoskeletal pain, viral respiratory infection, upper respiratory inflammation, nasal congestion/blockage, hoarseness/dysphonia, and sinusitis, among others. A dose response effect was noted for candidiasis of the mouth or throat, viral respiratory infections, and upper respiratory inflammation with FP 500 and FP 250 [clinstat\copd\flta3025.pdf, pages 802-820].

Reviewer comment:
It remains unexplained why there were many more patients in FP 250 and FP 500 than in placebo who reported upper and lower respiratory tract AE's that could be construed as "COPD exacerbations" (URTI, viral RTI, upper respiratory inflammation, among others see below), yet these did not seem to be reflected in the secondary efficacy endpoint of "COPD exacerbations."

Many of the AEs noted are noted in the labels for Flovent MDI and Flovent Rotadisk. These include upper respiratory tract infection, headaches, candidiasis, viral respiratory infections, nasal congestion, dysphonia, sinusitis, diarrhea, and rhinitis. AEs reported in this study that are not noted in current labeling for other Flovent products include musculoskeletal pain, edema and swelling, nausea and vomiting, dyspepsia, airway irritation (throat irritation, cough, rhinorrhea), and neurologic AEs (sleep disorder, dizziness, anxiety, malaise and fatigue) [clinstat\copd\flta3025.pdf, pages 802-820].

Table 11.1.25. Adverse events more frequent than placebo and occurring ≥3%, FLTA3025 [clinstat\copd\flta3025.pdf, pages 802-820].

Adverse event	Placebo N = 206		FP 250 N = 216		FP 500 N = 218	
	n	(%)	n	(%)	n	(%)
All adverse events*	152	(74)	165	(76)	174	(80)
Upper respiratory tract infection	41	(20)	45	(21)	45	(21)
Headaches	19	(9)	30	(14)	30	(14)
Candidiasis mouth/throat	1	(<1)	12	(6)	29	(13)
Throat irritation	9	(4)	25	(12)	25	(11)
Musculoskeletal pain	19	(9)	27	(13)	22	(10)
Viral respiratory infections	11	(5)	12	(6)	19	(9)
Upper respiratory inflammation	11	(5)	14	(6)	15	(7)
Nasal congestion/blockage	8	(4)	16	(7)	13	(6)
Hoarseness/dysphonia	2	(1)	13	(6)	10	(5)
Sinusitis**	6	(3)	12	(6)	10	(5)
Cough	9	(4)	17	(8)	9	(4)
Fever	6	(3)	7	(3)	9	(4)
Diarrhea	7	(3)	8	(4)	8	(4)
Chest symptoms	8	(4)	4	(2)	8	(4)
Muscle pain	3	(1)	3	(1)	8	(4)
Nausea and vomiting	1	(<1)	8	(4)	7	(3)
Malaise and fatigue	2	(1)	7	(3)	7	(3)
COPD	5	(2)	5	(2)	6	(3)
Sleep disorders	2	(1)	8	(4)	5	(2)

Adverse event	Placebo N = 206		FP 250 N = 216		FP 500 N = 218	
	n	(%)	n	(%)	n	(%)
Rhinorrhea/post nasal drip	5	(2)	7	(3)	5	(2)
Rhinitis	4	(2)	7	(3)	4	(2)
Edema and swelling	4	(2)	7	(3)	4	(2)
Dyspeptic symptoms	4	(2)	6	(3)	4	(2)
Dizziness	2	(1)	6	(3)	2	(1)
Anxiety	3	(1)	6	(3)	1	(<1)

*AEs with dose response effect are highlighted
**Composed of AEs for sinusitis and sinusitis/sinus infection

The highest incidence of AEs was in the first month of treatment (42% placebo, 43% FP 250, 46% FP 500). Throat irritation and dysphonia/hoarseness were most prevalent early in the study [clinstat\copd\flta3025.pdf, page 131]. The most common-drug related AEs included candidiasis of the mouth or throat, throat irritation, hoarseness/dysphonia, and headaches [clinstat\copd\flta3025.pdf, page 132].

A listing of AEs of low frequency that have been associated with use of corticosteroids, such as infection, GI bleeding, diabetes and glucose intolerance, is found in Table 11.1.26.
Small numbers of these AEs were observed without a strong association with FP 250 or FP 500 [clinstat\copd\flta3025.pdf, pages 802-820].

Reviewer comment:
Other than the few patients reported as having "skin hemorrhage," there were no patients who were reported as having bruising or purpura. One would expect a fairly significant number of patients to have had this AE, given the large doses of FP used and given the older ages of the patients studied. Unfortunately this study was not designed to specifically look for cataract or systemic bone effects, both known to be associated with systemic effects of corticosteroids. Ophthalmologic examination and studies to assess osteoporosis would have been helpful to address these concerns, although the 6-month duration of this study would have been inadequate to fully assess the bone, ocular, endocrine (diabetes, adrenal suppression), and cardiovascular (hypertension) consequences of chronic high-dose ICS.

Table 11.1.26. Selected adverse events of low frequency, FLTA3025 [clinstat\copd\flta3025.pdf, pages 802-820].

Adverse event	Placebo N = 206		FP 250 N = 216		FP 500 N = 218	
	n	(%)	n	(%)	n	(%)
All adverse events*	152	(74)	165	(76)	174	(80)
Fungal gastrointestinal infections	0	(0)	0	(0)	1	(<1)
Gastrointestinal hemorrhage	0	(0)	1	(<1)	0	(0)
Gastrointestinal ulcers	1	(<1)	0	(0)	0	(0)
Pneumonia	3	(1)	3	(1)	4	(2)
Muscle atrophy, weakness	0	(0)	2	(<1)	0	(0)
Candidiasis, unspecified site	1	(<1)	2	(<1)	2	(1)
Fractures	5	(2)	2	(<1)	3	(1)
Skin hemorrhage	0	(0)	1	(<1)	2	(1)
Hypertension	2	(<1)	3	(1)	4	(2)
Increased blood pressure	1	(<1)	0	(0)	1	(<1)

Adverse event	Placebo N = 206		FP 250 N = 216		FP 500 N = 218	
	n	(%)	n	(%)	n	(%)
Hyperglycemia	1	(<1)	2	(<1)	1	(<1)
Diabetes mellitus	0	(0)	0	(0)	1	(<1)
Impaired glucose tolerance	0	(0)	0	(0)	1	(<1)
Cataracts	0	(0)	0	(0)	1	(<1)
Ocular pressure disorders	1	(<1)	0	(0)	0	(0)

Subgroup analysis of AEs by gender, age, and race will be reviewed in the Integrated Review of Safety section of this document.

11.1.18.9.c. Deaths and serious adverse events

There were no deaths reported during the study. One placebo-treated patient, #38176, died after completing the study. She was a 72-year old woman who presented to the emergency room 17 days after her final study visits with abdominal pain and was found to have ovarian adenocarcinoma. She died eight days later [clinstat\copd\flta3025.pdf, page 134].

Serious adverse events (SAEs) occurred in treatment groups at similar frequencies (placebo 6%, FP 250 7%, FP 500 7%). The most common SAEs were COPD exacerbation and pneumonia, which occurred at similar frequencies in placebo-treated, FP 250-treated, and FP 500-treated patients [clinstat\copd\flta3025.pdf, pages 825-827].

SAEs due to fractures occurred only in FP-treated patients. There were no SAEs due to fractures in placebo-treated patients. There were two patients with fractures in the FP 250 group. Patient #36401, was a 70-year old white male, who fractured the left ulna, and sustained a compression fracture of the thoracic spine and a lumbar vertebral fracture after falling from a ladder. Patient #36172, was a 63-year old white male who developed a spinal fracture after falling from a ladder. There was one FP 500-treated patient who had a SAE due to a fracture. He was patient #37809, a 50-year old male who developed a fracture to the neck after an automobile accident [clinstat\copd\flta3025.pdf, pages 202, 204, 225, 3557, 3558, 3569].

Other SAEs occurred less commonly and had comparable frequencies in the treatment groups.

Reviewer comment:
It is interesting that SAEs due to fractures occurred only in FP-treated patients. It is possible that this may represent a hint of a safety signal, however, there was associated trauma in each of these events, and there was only a small number of SAEs due to fractures reported. Also, any patient with pre-existing osteoporosis or pathological fractures was specifically excluded from this study, and a rapid progression from asymptomatic to pathological fracture seems very unlikely. AEs and SAEs should be followed closely for similar occurrences during future trials of longer duration.

11.1.18.9.d. Withdrawals due to adverse events

Patients withdrew due to AEs at slightly higher rates in the FP 500-treated group (10%, 22/218) than in the FP 250-treated group (6%, 6/216), or the placebo-treated group (6%, 13/206). The most common AE that led to withdrawal from the study was exacerbation of COPD (FP 500 2%, FP 250, 2%, placebo 2%). Although there were small numbers of patients with withdrawals due to AEs, only FP-treated patients and no placebo-treated patients had withdrawals for pneumonia or pneumonitis, upper respiratory tract infection, throat irritation, hoarseness/dysphonia, and fractures [clinstat\copd\flta3025.pdf, pages 828-830]. Other than COPD exacerbation, there were no more than 3 patients in any treatment group for any individual AE leading to withdrawal.

Reviewer comment:
Throat irritation and hoarseness/dysphonia are recognized to be associated with the use of inhaled corticosteroids. Pneumonia/pneumonitis and fracture may be represent a safety signal, as these the occurrence of these withdrawals exclusively in FP-treated patients, and these have been associated with the use of systemic corticosteroids.

11.1.18.9.e. Vital signs

There were no clinically significant changes from baseline in median values of vital signs for any of the treatment groups [clinstat\copd\flta3025.pdf, pages 147, 903-905]. Patient #38574 was a 71-year old black male who was treated with FP-250 who had an episode of dizziness associated with hypotension, bradycardia, tingling of the fingers, and shortness of breath. This episode resolved without treatment [clinstat\copd\flta3025.pdf, page 3252].

11.1.18.9.f. Physical examination

Physical examinations were performed at Screening and at the Week 24 visit or the Discontinuation visit. Data were recorded on subject progress notes, but not on case report forms (CRFs). Physical examination abnormalities were recorded as AEs on the CRFs, but no summary of physical examinations was provided [NDA 20-833, SE1-004, BM, 9/17/01, page 3]. Evidence of skin bruising would have been useful to record.

11.1.18.9.g. Oropharyngeal examination

Oropharyngeal examinations were performed at screening, at each treatment visit, and at the Discontinuation visit [clinstat\copd\flta3025.pdf, page 59]. Data was recorded on subject progress notes, but not on case report forms (CRFs). Oropharyngeal examination abnormalities were recorded as AEs on the CRFs, but no summary of oropharyngeal examinations was provided [NDA 20-833, SE1-004, BM, 9/17/01, page 2].

11.1.18.9.h. Laboratory studies

Small numbers of patients had shifts in % lymphocyte, % neutrophils, and WBC counts from baseline at Weeks 12 and 24 and Discontinuation.

There was a greater percentage of patients with shifts in % lymphocytes to low in patients treated with FP 500 (7%, 11/165) and FP 250 (4%, 6/161), than placebo (0%, 0/151) at

week 12. This observation was also present at week 24 for FP 500 (3%, 4/143), FP 250 (5%, 7/135), and placebo (4%, 5/124), and at discontinuation for FP 500 (16%, 9/56), FP 250 (12%, 8/66), and placebo (9%, 6/70) [clinstat\copd\flta3025.pdf, pages 831-840].

There was a greater percentage of patients treated with FP 500 (5%, 9/165) and FP 250 (6%, 10/161) with shifts in % neutrophils to high than placebo (1%, 2/151) at week 12. The percentage of patients with shifts in % neutrophils to high was similar at week 24 for FP 500 (3%, 4/143), FP 250 (4%, 5/135), and placebo (2%, 3/124). There was a greater percentage of FP 500 (23%, 13/56) and FP 250 (17%, 11/66) with shifts in % neutrophils to high at discontinuation than for placebo (9%, 6/70) [clinstat\copd\flta3025.pdf, pages 831-840].

There was a greater percentage of patients with shifts in WBC count to high in patients treated with FP 500 (5%, 8/165) and FP 250 (5%, 8/161), than for placebo (<1%, 1/151) at week 12. Shifts in WBC count to high were present at week 24 for patients treated with FP 500 (3%, 5/143), FP 250 (8%, 11/135), and placebo. Shifts in WBC counts to high were also noted at discontinuation for patients treated with FP 500 (23%, 13/56), FP 250 (17%, 11/66), and placebo (9%, 6/70) [clinstat\copd\flta3025.pdf, pages 831-840].

Reviewer comment:
The shifts in % lymphocytes, % neutrophils, and WBC counts in FP-treated patients at week 12 could be systemic corticosteroid effects of inhaled FP. The differences between FP and placebo groups are absent or smaller at week 24. It is unclear why the differences between FP and placebo groups are less pronounced at week 24 if they are related to systemic effects of FP. It is possible that the less prominent difference between treatment groups could be due to tolerance of this effect, or due to dropouts. It is possible that the difference the treatment groups is not related to FP, however. The high percentage of patients with shifts in % lymphocytes, % neutrophils, and WBC counts at discontinuation are likely to be in patients discontinuing from COPD exacerbations who received treatment with systemic corticosteroids. It should be noted that there was a slightly higher rate of viral respiratory infection and sinusitis in FP-treated patients. These AEs could be also be manifestations of immunologic effects (i.e., lymphopenia and impaired neutrophil function) of inhaled FP.

An increase from baseline in ALT was noted in a higher percentage of patients treated with FP 500 (5%, 8/157) than with FP 250 (0%, 0/160) or placebo (<1%, 1/150) at week 12. An increase from baseline in ALT was noted in a higher percentage of patients treated with FP 500 (6%, 9/146) than with FP 250 (<1%, 1/137) or placebo (<1%, 1/124) at week 24. Increases from baseline in ALT at discontinuation were noted in similar percentages of patients for FP 500 (2%, 1/56), FP 250 (3%, 2/66), and placebo (4%. 3/71) [clinstat\copd\flta3025.pdf, pages 842-850].

Increases from baseline were noted for AST and alkaline phosphatase in a small percentage of patients treated with FP 500, FP 250, and placebo. The percentage with increases was slightly greater for FP 500 and FP 250 than for placebo at week 12 and week 24, but not at discontinuation [clinstat\copd\flta3025.pdf, pages 842-850].

Reviewer comment:
The higher percentage of patients in the FP groups with increases in ALT, AST, and alkaline phosphatase may be related to the hepatic metabolism of FP. FP is a Cyp3A4 substrate, and the liver would clear any systemically absorbed drug. Differences between treatment groups were less prominent at Week 24. Increases in LFTs are not noted in current labeling for other FP products, although drug interaction with 3A4 inhibitors has recently been added. It should be noted that there was only one AE reported for increased liver function tests, patient #36375, a 49-year old white female treated with FP-500. This patient had mildly elevated ALT and AST values at baseline [clinstat\copd\flta3025.pdf, page 140].

There was a greater percentage of patients who had increases from baseline in glucose at week 12 for FP 500 (8%, 14/167) and FP 250 (9%, 15/160) than with placebo (5%, 8/149). There was no meaningful difference in the percentage of patients who had increases from baseline in glucose at week 24 between FP 500 (5%, 8/146), FP 250 (2%, 3/137), and placebo (6%, 7/123). There was no meaningful difference in the percentage of patients who had increases from baseline in glucose at discontinuation for FP 500 (9%, 5/56), FP 250 (5%, 3/66), and placebo (7%, 5/69) [clinstat\copd\flta3025.pdf, pages 842-850]. It should be noted that the sponsor defined an exceptionally liberal definition for high glucose, >175 mg/ml. It is likely that this liberal definition of high glucose would result in a lower sensitivity of detecting a difference between treatment groups [clinstat\copd\flta3025.pdf, page 3598].

Reviewer comment:
Hyperglycemia is an effect of systemic corticosteroids. Although there are higher percentages of FP 500 and FP 250 patients with increases in glucose at Week 12 than placebo patients, there is no meaningful difference between treatment groups at week 24 and at discontinuation. The significance of this finding is unclear, although it is interesting to speculate that it may be due to lack of compliance with a therapy that has no perceived benefit to the patient (see CDRQ). This may represent a tolerance to a drug-related systemic effect. There were no meaningful differences between treatment groups in the frequency of the small number of AEs due to diabetes mellitus, hyperglycemia, or impaired glucose tolerance This observation is much less reassuring because of the sponsor's exceptionally liberal definition of elevated blood glucose.

There were few patients with hematology or chemistry results outside of values specified as normal by the sponsor. The few patients with results outside of the range specified as normal by the sponsor were evenly distributed between treatment groups [clinstat\copd\flta3025.pdf, pages 851-872]. Patients with notable abnormal laboratory values are noted below.

Patient #36933, a 70-year old white male who was treated with FP 250, discontinued due to hyperglycemia [crf\flta3025\6234\p0036933.pdf]. Patient # 37434, a 60-year old white male treated with FP 500, developed uncontrolled diabetes mellitus that resolved after 77 days. He did not withdraw from the study [clinstat\copd\flta3025.pdf, pages 140, 3376].

Patient #36375, was a 49-year old white female treated with FP-500 who had mildly elevated values for ALT (238 U/L) and AST (134 U/L) at baseline that remained elevated throughout the study [clinstat\copd\flta3025.pdf, page 140].

11.1.18.9.i. ECGs

There were a few clinically significant changes in ECGs from baseline for each of the treatment groups in the study. Patients with clinically significant changes in ECGs are summarized in Table 11.1.27. There was no significant difference between treatment groups in the number or character of the changes in ECGs.

Table 11.1.27. Patients with clinically significant changes in ECGs from baseline, FLTA3025 [clinstat\copd\flta3025.pdf, pages 141-146].

Patient number	Treatment	Time of abnormality	ECG abnormality
36879	Placebo	Discontinuation	Recent anteroseptal MI, anterolateral ischemia
36971	Placebo	Weeks 12, 24	Atrial flutter
38176	Placebo	Week 12	Sinus tachycardia, ischemic ST depression
38232	Placebo	Discontinuation	Atrial flutter
36978	FP 250	Week 12 Week 24	Prolonged QT interval Ischemic changes, RBBB
37034	FP 250	Week 12 Week 12 repeat Week 24	Non-specific STT changes Infero-apical ischemia, STT changes New inferior MI
37371	FP 250	Discontinuation	Atrial flutter
37837	FP 250	Week 12	Old MI, increase in ST depression
38079	FP 500	Week 24	Possible new MI, repeat ECG was normal
38573	FP 500	Week 24	New onset atrial fibrillation/flutter
38736	FP 500	Week 24	Atrial fibrillation
38746	FP 500	Week 24	Evolving anterolateral ischemic changes

Median QTc intervals by both Bazette and Fridericia formulae were similar for each of the treatment groups. The incidence of QT, QTcB, and QTcF intervals ≥440 msec was similar for each of the treatment groups. There were eight patients with changes in QTc greater than 470 msec. One was treated with placebo, three were treated with FP 250, and four were treated with FP 500. These patients are summarized in Table 11.1.28.

Table 11.1.28. Patients with QTcB intervals >470 msec post-screening, FLTA3025 [clinstat\copd\flta3025.pdf, page 146]

Patient number	Treatment	Screening QTcB, msec	Week 12 QTcB, msec	Week 24 or DC QTcB, msec
36284	Placebo	436	458	482
37494	FP 250	413	428	484
38030	FP 250	452	472	472
38482	FP 250	426	416	498
35934	FP 500	475	473	491
37984	FP 500	468	--	479
38276	FP 500	438	472	450
38748	FP 500	414	420	500

Reviewer comment:
Although there was a slightly higher incidence of patients with QTcB >470 post-screening in the FP 250 and FP 500 groups than the placebo group, these findings were present in only small number of patients and could be a chance occurrence.

11.1.19. References

1. Position Statement, American Thoracic Society: Standards for the Diagnosis and Car of Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 1995;152:S77-S120.

2. Anthonisen NR, Wright EC, et al. Bronchodilator Response in Chronic Obstructive Pulmonary Disease. Am Rev Respir Dis 1986;133: 814-819.

3. Barnes PJ. Chronic Obstructive Pulmonary Disease. New Engl J Med 2000;343:269-280.

4. Eliasson, O and Degraff AC. The Use of Criteria for Reversibility and Obstruction to Define patient Groups for Bronchodilator Trials. Am Rev Respir Dis 1985;132:858-864.

5. Anthonisen NR et al. Antibiotic Therapy in Exacerbations of Chronic Obstructive Pulmonary Disease. Ann Int Med 1987;106:196-204.

6. Snow V, et al. The Evidence Base for Management of Acute Exacerbations of COPD: ACCP-ASIM Clinical Practice Guideline, Part 1. Chest 2001;119;1185-1189.

7. McCrory DC, et al . Management of Acute Exacerbations of COPD: A Summary and Appraisal of Published Evidence. Chest 2001;119:1190-1209.

8. The Lung Health Study Research Group. Effect of Inhaled Triamcinolone on the Decline in Pulmonary Function in Chronic Obstructive Pulmonary Disease. New Engl J Med 2000;343:1902-1909.

9. National Asthma Education and Prevention Program. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Publication Number 97-4051. Bethesda, MD, 1997.

10. 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.

11. 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;109:348-352.

12. Mahler DA, Weinberg DH, et. al. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 1984;97:751-758.

13. Guyatt GH, Berman LB, Townsend M, et. al. A measure of quality of life for clinical trials in chronic lung diseases. Thorax 1987;42:773-778.

11.2. SFCA3006: A randomized, double-blind, parallel-group trial of 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

Study initiated: 9/24/98
Study completed: 5/5/00
Study report dated: 3/22/01
[clinstat\copd\sfca3006.pdf, page 1]

11.2.1. Summary and reviewer's conclusion of study results

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter, 24-week trial designed to evaluate the efficacy and safety of salmeterol xinafoate (SAL) 50 mcg BID, fluticasone propionate FP 500 mcg BID, the combination of SAL 50 mcg /FP 500 mcg BID, and placebo in patients with chronic obstructive pulmonary disease (COPD).

As in Study FLTA3025, the proportion of patients with reversibility enrolled in this study is much higher than is found in the population of COPD patients at large[1-4]. Of all study patients, there were 54% of patients who were considered to be "reversible" (≥12% and ≥200 mL increase in FEV_1 with bronchodilator). In addition, the degree of reversibility for the reversible population was high—29.8%. The mean degree of reversibility in the 46% of the patients who comprised the "non-reversible" population, 8.8%, was similar to the mean reversibility described in studies of COPD patients as a whole[1-4]. Therefore, there are serious concerns as to whether the patient population studied in this clinical trial is representative of the COPD population as a whole[1-4], as broadly stated in the labeling for the proposed indication. This is a critical deficiency of this study. Non-Caucasian patients, who make up a substantial proportion of the COPD population[1,3], were also under-represented in this study.

The primary efficacy endpoint was the mean change in FEV_1 from Baseline to study endpoint. The primary efficacy endpoint supports the efficacy of FP 500 compared to placebo in this population. The mean change from baseline in FEV_1 for the FP 500 group at endpoint was 109 mL, 113 mL more than the placebo group at endpoint. This comparison was statistically significant at $p < 0.001$. This change corresponds to an effect size of 9.6%.

Small decreases in the Chronic Bronchitis Symptom Questionnaire (CBSQ) were noted for all active treatment groups at Weeks 3 to 24 and at endpoint. In general, decreases were numerically superior to the placebo group, which also showed an improvement in score. Decreases in the CBSQ were not clinically significantly different from the placebo group for any of the active treatment groups at any time, however. The differences between the Transition Dyspnea Indices (TDIs) for FP 500 and placebo were not greater than the minimal clinically significant TDI of 1.0 point at Endpoint. Week-by-week analysis failed to show significance at any of the 10 interim measurements from Weeks 1

to 24, except for Week 24. Neither the CBSQ nor the TDI provide support for the efficacy of FP in COPD.

The incidence of COPD exacerbations was similar for all treatment groups. First COPD exacerbations, first moderate to severe COPD exacerbations, study withdrawals, and withdrawals due to COPD exacerbation were similar in the FP 500 and placebo groups. First COPD exacerbations, first moderate to severe COPD exacerbations, study withdrawals, and withdrawals due to COPD exacerbation were similar in the SAL 50 and SAL 50/FP 500 groups, which were less frequent than in the placebo group. A non-standard definition of COPD exacerbation was used that would have favored the finding of efficacy of FP in a COPD population with a high degree of reversibility. As a general statement, incidence or severity of COPD exacerbations did not provide support for the efficacy of FP in COPD.

A small mean increase from baseline in AM PEFR was noted in the FP 500 (12.9 L/min) and SAL 50 (16.8 L/min) groups at the end of the study. A larger mean increase was observed in the SAL 50/FP 500 group (31.9 L/min). Overall, the FP 500, SAL 50, and SAL 50/FP 500 groups had small decreases in the number of puffs of Ventolin used per day, in the number of awakenings per night, and had small increases in the percent of nights with no awakenings requiring Ventolin use. Increases in the overall Chronic Respiratory Disease Questionnaire (CDRQ) score for FP 500 and SAL 50/FP 500 were less than the specified clinically significant difference from the change in baseline in the placebo group, and provide no support for efficacy. This is an important negative finding, since one of the stated objectives of this study was to compare the health-related quality of life (QOL) in COPD patients receiving active treatment compared to placebo over this 24-week study.

The sponsor performed a subgroup analysis of efficacy by smoking status. In general, larger effects for primary and secondary efficacy endpoints were noted in patients who stopped smoking prior to the conduct of the study.

The sponsor performed a subgroup analysis of efficacy for non-reversible patients. This subgroup analysis demonstrated numerically greater changes in FEV_1 from baseline at study endpoint for all active treatments compared with placebo. Similar results were also noted for most secondary endpoints. The difference from placebo for mean change from baseline at endpoint for the reversible group for FP 500 was 124 mL. This was 23% greater than the difference from placebo for mean change from baseline at endpoint for the non-reversible group, which for FP 500 was 101 mL.

There was a suggestion of a systemic corticosteroid effect in some patients in the FP 500 and SAL 50/FP 500 groups for post-cosyntropin stimulation change <5.6 mcg/dL. The larger decrease in mean post-cosyntropin stimulation cortisol levels from Day 1 to Endpoint for FP 500 and SAL 50/FP 500 is suggestive of a systemic effect, as was the smaller increase in mean cortisol levels in the FP 500 and SAL 50/FP 500 groups at Endpoint.

Duration of exposure was inadequate to fully assess safety, since the short efficacy endpoints in this study fail to address the safety consequences of long-term (> 6 months) use of high-dose, high-potency inhaled corticosteroids, particularly with regard to bone, dermatological, and ocular adverse events, as well as the potential for HPA axis recovery. AEs occurred in 80% of FP 500-treated patients, 78% of SAL 50/FP 500-treated patients, and in 69% of placebo-treated patients. AEs occurring more frequently with FP 500 and SAL 50/FP 500 than with placebo included headaches, upper respiratory tract infection, throat irritation, upper respiratory inflammation, viral respiratory infection, candidiasis of the mouth or throat, nasal congestion/blockage, and muscle cramps and spasms. There were three deaths in this study, all in the placebo group. The percentage of patients was SAEs during the treatment phase were similar among the treatment groups, with the highest in the FP 500 group (7%, 12/173), followed by placebo (6%, 11/185), and SAL 50/FP 500 (5%, 9/169). Vital signs and ECGs showed no clinically significant differences between treatment groups.

In summary, based on the primary endpoint, efficacy was demonstrated for the FP 500 group in this study. An open issue is whether the study population adequately reflects the overall population of US COPD patients, although both the reversible and the non-reversible subgroups showed some change from baseline on this endpoint. Subgroup analysis demonstrated a numerically greater effect size for the reversible compared to the non-reversible population, although the difference was not as marked as in FLTA3025. Efficacy measurements that supported FP 500 included FEV_1, PEFR, and measures of bronchodilator use. COPD exacerbations did not support the efficacy of FP 500. The health-related quality of life instrument (CRDQ), the Transitional Dyspnea Index (TDI), and the Chronic Bronchitis Symptoms Questionnaire (CBSQ) provided no support for the efficacy of FP 500. Data for the safety endpoints chosen for this study are generally inadequate to make a determination of the long-term safety of FP in the population studied because the study was of insufficient duration for known systemic corticosteroid effects such as osteoporosis, cataracts, hypertension, diabetes, or skin changes such as easy bruisability or skin thinning to become apparent. It should be noted that the study was not designed to specifically assess these AEs, and patients with prior pathological fracture, osteoporosis, significant hypertension or diabetes, cataracts, or glaucoma were specifically excluded. Although not specifically addressed in this document (see review by Dr. L. Gilbert-McClain), the safety issue of long-term systemic corticosteroid effects will be similar for SAL 50/FP 500 (Advair®) in this population.

11.2.2. Study design

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter trial of 24-weeks duration. Approximately 600 patients were to be randomized at approximately 55 study centers. A total of 691 patients were enrolled at 64 study sites [clinstat\copdsfca3006.pdf, pages 45, 11,818].

11.2.3. Objectives

This study had three objectives [clinstat\copd\sfca3006.pdf, pages 44, 11822]. They were:

1. To compare the efficacy of SAL 50 mcg BID, FP 500 mcg BID, the combination of SAL 50 mcg /FP 500 mcg BID, and placebo when administered by the Diskus over a 24-week treatment period in the treatment of COPD patients
2. To compare the safety of SAL 50 mcg BID, FP 500 mcg BID, the combination of SAL 50 mcg /FP 500 mcg BID, and placebo when administered by the Diskus over a 24-week treatment period in the treatment of COPD patients
3. To compare quality of life (QOL) in COPD patients receiving SAL 50 mcg BID, FP 500 mcg BID, the combination of SAL 50 mcg/FP 500 mcg BID, and placebo when administered by the Diskus over a 24-week treatment period

11.2.4. Inclusion criteria

Inclusion criteria for this study are listed below. These reflect protocol amendments. [clinstat\copd\sfca3006.pdf, pages 11824-11826]:

1. Age ≥40 years
2. Male or female gender
   - A female was eligible to enter and participate if she was of non-childbearing potential or was of child-bearing potential with a negative serum pregnancy test at screening and an acceptable method of contraception
3. Established history of COPD in accordance with the American Thoracic Society (ATS) definition[1]:
   - Abnormal tests of expiratory flow that do not change markedly over periods of several months
   - Airflow obstruction may be structural or functional
   - Bronchial hyperreactivity may be present as measured by improvement after inhalation of a beta-adrenergic agent or worsening after inhalation of methacholine or histamine
   - Emphysema and chronic bronchitis are incorporated into COPD, and any individual may have one or both of these conditions
4. A history of cough productive of sputum on most days for at least 3 months of the year, for at least 2 years, that is not attributed to another disease process. Patients must have a score of ≥4 on the Chronic Bronchitis Symptom Questionnaire (CBSQ) at Treatment Day 1
5. Current or prior history of at least 20 pack-years of cigarette smoking. If the patient is an ex-smoker, smoking must have been discontinued for at least 6 months prior to screening. Current smokers were counseled regarding the hazards of continuing to smoke and the benefits of discontinuation. Patient who decided to stop smoking at the Screening Visit were not eligible for participation in the study. Patients making a conscious decision to stop smoking at anytime during the study and who refrain from smoking for >4 weeks were to be discontinued from the study. Patients who start smoking during the study and smoke for at least 7 consecutive days were to be discontinued from the study.
6. Severity
   - Baseline FEV_1 <65% or predicted but >0.70 L, or FEV_1 <0.70 L and >40% but still <65% of the predicted normal value (Crapo), and
   - FEV_1/FVC ratio of ≤70% at screening
7. A score if ≥2 in the Modified Medical Research Council Dyspnea Scale at screening:

Modified Medical Research Council Dyspnea Scale[clinstat\copd\sfca3006.pdf, page 11876]

Grade	Description
0	Not troubled with breathlessness except with strenuous exercise
1	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
2	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	Stops to breathe after walking about 100 yards or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

8. Has not received systemic corticosteroid and/or high-dose inhaled corticosteroid therapy for at least 6 weeks prior to the Screening Visit. High dose inhaled corticosteroids are defined as:
   - Beclomethasone dipropionate ≥1008 mcg/day
   - Triamcinolone acetonide ≥1600 mcg/day
   - Flunisolide ≥2000 mcg/day
   - Fluticasone propionate MDI ≥880 mcg/day
   - Fluticasone propionate Diskus ≥1000 mcg/day
   - Budesonide ≥1600 mcg/day
9. Able to tolerate a 2-week run-in period during which the following medications were discontinued:
   - Inhaled corticosteroids
   - Ipratropium
   - Nedocromil sodium and cromolyn sodium
   - Anti-leukotriene agents
   - Intranasal steroids
   - Any beta-agonist other than Ventolin
   - Theophylline, unless at a stable dosage for one month
10. Able to complete a diary card and subject questionnaires
11. Able to effectively use the Diskus and MDI inhalers, spirometry equipment, and mini-Wright peak flow meter
12. Provide a signed, dated, and witnessed informed consent

Reviewer comment:
The sponsor's paraphrase of the ATS definition of COPD places an emphasis on reversibility. While reversible obstruction does occur in the COPD population, it should not be considered central to the definition. The process underlying COPD is one of progressive loss of lung tissue, leading primarily to structural obstruction as opposed to functional[1]. The ATS definition follows:

> *"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."[1]*

The inclusion criteria allow for patients who were receiving fairly large doses of inhaled corticosteroids prior to enrollment. This may have the effect of enriching the study for patients who were responsive to inhaled corticosteroids, as one would expect patients with no response or a poor response to have their treatment discontinued.

11.2.5. Exclusion criteria

Exclusion criteria for this study are listed below. These reflect protocol amendments. [clinstat\copd\sfca3006.pdf, pages 11826-11830]:

1. Current diagnosis of asthma in accordance with the ATS definition:
   - Increased responsiveness of the tracheobronchial tree
   - Paroxysms of dyspnea, wheezing, and cough, which may vary from mild and almost undetectable to severe and unremitting
   - Primary physiological manifestation of hyperresponsiveness is variable airway obstruction
   - Variability may be manifest in improvements of obstruction following bronchodilators or corticosteroids or increased obstruction caused by drugs or other stimuli
2. Requirement for any of the following medications:
   - Beta-blockers
   - Digitalis
   - Ketoconazole, fluconazole
   - Monoamine oxidase inhibitors
   - Tricyclic antidepressants
   - Phenothiazines
   - Immunosuppressive agents including cyclosporine, methotrexate, and gold
   - Use of inhaled short-acting bronchodilator within 6 hours prior to screening
   - Use of any short acting form of oral beta-agonist, short-acting form of theophylline or other bronchodilator within 12 hours prior to screening
   - Use of any twice daily form of an inhaled or oral beta-agonist or controlled-release form of theophylline within 48 hours of screening
3. Requirement for pulmonary rehabilitation that is initiated during the study. Participation in a maintenance pulmonary rehabilitation program was allowed.
4. A respiratory disorder other than COPD (e.g., lung cancer, bronchiectasis, sarcoidosis, tuberculosis, lung fibrosis); history of lobectomy within one year of the screening visit. Patients with alpha-1-antitrypsin deficiency were excluded.
5. Requirement for a continuous positive pressure device for COPD or sleep apnea.
6. Any significant concurrent diseases that would place the subject at risk, interfere with clinical evaluations, or influence study participation, including but not limited to:
   - History of symptomatic or clinically significant pathologic fractures
   - Clinically significant cardiac disease
   - Systemic arterial hypertension if the subject is poorly compliant with medications, likely to require frequent changes in medication during the study period, or requires therapy with beta-blockers
   - Hepatic disease

- Renal disease requiring dialysis or at risk of requiring dialysis within 6 months of screening
- Neurologic disease
- Uncontrolled hyperthyroidism or hypothyroidism
- Diabetes mellitus that is either poorly controlled or complicated by significant renal or cardiovascular disease
- Severe hematologic disease
- Active peptic ulcer
- Disorders of humoral or cellular immunity
- Cushing's disease
- Addison's disease
- Presence of glaucoma requiring treatment with non-selective beta-blockers
- History of malignancy except for localized basal cell or squamous cell carcinoma of the skin that has been resected and patients curatively treated and disease free for at least 2 years may be considered for entry after discussion with the Glaxo Wellcome medical advisor
- Inadequately controlled psychiatric illness
- Mental retardation
- Peripheral vascular disease
- Use of a pacemaker

7. Requirement for supplemental oxygen with the following exceptions:
   - Lives at an altitude above 3000 feet and does not require more than 2 L of oxygen per minute for more than 12 hours per day
   - Does not require more than 2 L of oxygen per minute for more than 2 hours per day for exertion
8. A known or suspected hypersensitivity to inhaled corticosteroids, beta-agonists or lactose. Gastrointestinal lactose intolerance is not an exclusion criterion.
9. A known or suspected history of alcohol or drug abuse within the previous two years
10. 12-lead ECG at screening is abnormal and clinically significant
11. A patient has clinically significant abnormalities found on 24-hour Holter monitoring (at selected sites)
12. A moderate or severe exacerbation of COPD during the run-in period
13. Chest X-ray reveals clinically significant abnormalities not believed to be due to the presence of COPD
14. Received an investigational drug within 30 days prior to entry into the run-in period
15. A participating investigator, sub-investigator, study coordinator, or employee of a participating investigator, or an immediate family member of the aforementioned
16. An abnormal and clinically significant laboratory test a the screening visit which is still abnormal on repeat analysis
17. Previous participation in a fluticasone and/or salmeterol study via the Diskus for COPD

Reviewer comment:
The sponsor uses an ATS definition of asthma from 1987. This definition makes no reference to the role of inflammation in asthma. A more appropriate definition might be the National Asthma Education and Prevention Program (NAEPP) definition of asthma,

which refers to inflammation as well as reversible airway obstruction[5]. Taken strictly, this exclusion criterion would exclude all patients who have reversible airway obstruction, and such patients were not excluded in this study.

11.2.6. Protocol amendments

There were four protocol amendments, dated 9/4/98, 12/17/98, 2/11/00, and 6/23/00 [clinstat\copd\sfca.pdf, page 11932]. A substudy protocol for genotyping during the study was also added on 9/9/98 [clinstat\copd\sfca.pdf, page 11937]. This substudy will not be reviewed.

Originally, the protocol called for approximately 600 patients to be randomized at approximately 55 study centers. The protocol was amended on 2/11/00 to allow for approximately 700 patients to be randomized at approximately 65 study centers [clinstat\copd\sfca3006.pdf, pages 11930]. Urinalyses were not performed and were removed in Protocol Amendment 1 [clinstat\copd\sfca3006.pdf, page11919]. The protocol was amended to provide subgroup analyses of patients who had an increase in percent of predicted FEV_1 less than 10% after albuterol at the screening visit, of former smokers, and of current smokers [clinstat\copd\sfca3006.pdf, pages 12009-12010]. The FEV_1/FVC ratio required for entry into the study was changed from ≤65% to ≤70% in Protocol Amendment 2 [clinstat\copd\sfca3006.pdf, page 11923].

Reviewer comment:
The effect of the change in the FEV_1/FVC ratio would be to allow entry of patients with both those with milder obstruction (who would be perhaps more likely to have reversibility) and those with very severe obstruction with accompanying air trapping. This amendment was made after the study had been started. The inclusion criteria specifying the FEV_1 and the level of dyspnea will minimize any impact of this change. Other protocol amendments otherwise included minor changes to wording and study design that had little impact on the evaluation of efficacy or safety.

11.2.7. Study procedures

Study procedures are displayed in Table 11.2.1. Patients provided an informed consent, and received a medical history and physical examination at the screening visit. Chest X-ray, pregnancy test, screening labs, and ECGs were performed. Twenty-four hour Holter monitoring was performed at selected sites. Spirometry with assessment of reversibility was also performed. Reversibility was assess by performing spirometry 30 minutes after patient self-administration of 4 puffs of Ventolin MDI without a spacer or holding chamber [clinstat\copd\sfca3006.pdf, page 11837].

There was a two-week, single-blind, run-in period for patients meeting entrance criteria. Patients had all prohibited concurrent medication discontinued and were given Ventolin MDI or nebules to be used as needed for duration of the trial, including the run-in. Patients received placebo via the Diskus BID during the run-in, and baseline observations were made for morning peak expiratory flow rates (PEFR), Ventolin use, and night-time awakenings that required Ventolin use [clinstat\copd\sfca3006.pdf, pages 11836-11837]. The purpose of the single-blind run-in period was to establish baseline pulmonary

function and diary card data for at least 10 of the 14 days. Patient compliance with medication and recording of diary data was also assessed [clinstat\copd\flta3025.pdf, page 11837]. Patient were to record daily morning PEFRs, nighttime awakenings requiring Ventolin use, use of rescue Ventolin, and any medical problems experienced [clinstat\copd\sfca3006.pdf, page 11837].

Criteria for patients to be eligible for randomization included the following [clinstat\copd\sfca3006.pdf, pages 11837-11838]:

- Satisfaction of inclusion and exclusion criteria
- At least 70% compliant with study medication during the run-in
- Completed diary data for at least 10 of the 14 days of the run-in
- Had not started or stopped smoking during the run-in
- Proficiency in use of the peak flow meter
- Able to safely withhold prohibited study medications
- Had not experienced a moderate or severe COPD exacerbation

Patients who completed the run-in period and met all randomization criteria were assigned to one of four double-blind treatments via the Diskus for 24 weeks [clinstat\copd\sfca3006.pdf, page 11830]:

- FP 500 mcg BID via Diskus (1 inhalation BID)
- Salmeterol (SAL) 50 mcg BID via Diskus (1 inhalation BID)
- Salmeterol (SAL) 50 mcg/FP 500 mcg via Diskus (1 inhalation BID)
- Placebo via Diskus BID

Assignment to study drug was to be stratified according to the patients' response to reversibility testing with Ventolin at screening to a non-reversible group and a reversible group. Non-reversible patients were defined as having an absolute volume increase <200 mL or an absolute volume increase of ≥200 mL with baseline FEV_1 reversibility of <12%. Reversible patients were defined as having an absolute volume increase ≥200 mL with baseline FEV_1 reversibility of ≥12% [clinstat\copd\sfca3006.pdf, page 11832].

Reviewer comment:
The definition of reversibility is critical for this study. In addition, the proportion of patients with reversible obstruction is also critical, even if the proportion in each of the four treatment groups is similar. FP and SAL are effective for treatment of asthma, and inclusion of a high proportion of patients with a significant degree of reversibility would be likely to result in an overstatement of efficacy for the entire group. Although assignment to study drug was stratified according to reversibility based on the above definition, no analysis was planned or provided for these subgroups. Instead, the sponsor provided a subgroup analysis that was based on a different definition. This issue and its effects are discussed in Section 11.2.16.1 of this document, "Data sets analyzed".

Patients were evaluated weekly for the first four weeks of treatment, every two weeks until week 8, and then every four weeks for the remainder of the study. Patients who developed an exacerbation could be treated with antibiotic therapy as an outpatient for two exacerbations, but were discontinued from the study if a third exacerbation occurred.

Subjects with exacerbations requiring treatment with systemic corticosteroids were to be discontinued from the study [clinstat\copd\scfa3006.pdf, page 11823].

Patient evaluations at each of the clinic visits included spirometry. Symptoms were also evaluated with the Baseline/Transition Dyspnea Index (BDI/TDI), Chronic Bronchitis Symptom Questionnaire (CBSQ), and assessment of the severity of any COPD exacerbations since the last evaluations. Health outcomes were assessed with the Chronic Respiratory Disease Questionnaire (CRDQ), a health-related quality of life instrument [clinstat\copd\sfca3006.pdf, page 11874]. The BDI/TDI, CBSQ, and CRDQ instruments and the instrument for assessment of COPD exacerbations are described below in Section 1.2.12, Assessment of signs and symptoms. Cosyntropin stimulation testing, 12-hour serial FEV_1, and 24-hour Holter monitoring were performed at selected sites .

Patients completed diary cards during the treatment period. Patients measured PEFRs in triplicate prior to the morning dose of study medication. The highest of 3 PEFR values was recorded on diary card. Patients also were to record nighttime awakenings requiring Ventolin use, the use of supplemental Ventolin, any medical problems, any need for other concomitant medication, and AEs [clinstat\copd\sfca3006.pdf, pages 11842-11843].

Table 11.2.1. Study outline, SFCA3006 [clinstat\copd\sfca3006.pdf, page 11873].

	Screen	Run-in	Double-blind treatment period											DC
Visit number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Treatment Day/Week		**Day –14 to 1**	**Day 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 6**	**Wk8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	
Informed consent	X													
Medical history	X													
Smoking cessation counseling	X												X	X
Chest X-ray	X													
Physical examination	X												X	X
Pregnancy test	X									X			X	X
Reversibility test	X													
Review inhalation technique	X		X	X	X	X	X	X	X	X	X	X		
Medical Research Council Questionnaire	X													
Clinical laboratory tests	X									X			X	X
24-hr Holter monitoring*	X						X							
12-lead ECG and rhythm strip	X									X			X	X
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X
Cosyntropin stimulation testing*			X										X	X
Oropharyngeal exam	X		X	X	X	X	X	X	X	X	X	X	X	X
Review smoking status			X										X	X
AE detection	X		X	X	X	X	X	X	X	X	X	X	X	X
Spirometry testing	X		X	X	X	X	X	X	X	X	X	X	X	X
12-hr serial FEV_1*			X							X				
Exacerbation assessment			X	X	X	X	X	X	X	X	X	X	X	X
Dispense/review diary card	X		X	X	X	X	X	X	X	X	X	X	X	X
Chronic bronchitis symptom questionnaire			X	X	X	X	X	X	X	X	X	X	X	X
BDI/TDI dyspnea scale				X	X	X	X	X	X	X	X	X	X	X
Quality of life questionnaire			X		X		X		X				X	X
Dispense PEFR devices and Ventolin MDI/nebules	X		X	X	X	X	X	X	X	X	X	X		
Dispense study medication			X				X		X	X	X	X		
Concurrent medication assessment	X		X	X	X	X	X	X	X	X	X	X	X	X
Discharge from study													X	X

*Selected sites

11.2.8. Allowable concurrent medications

Allowable concurrent medications included [clinstat\copd\sfca3006.pdf, page 11833]:

- Inhaled Ventolin MDI and/or nebules, provided by the sponsor for use as relief medication. Ventolin was to be withheld for at least 6 hours prior to each treatment visit.
- Antibiotics were permitted for treatment of two exacerbations. Patients were dropped from the study if a third COPD exacerbation occurred.
- Antidepressants other than MAO inhibitors and tricyclic antidepressants
- Theophylline, if on a stable dose for at least one month prior to screening

11.2.9. Prohibited medications

The following medications were prohibited [clinstat\copd\scfa3006.pdf, page 11833-11834]:

- Corticosteroids other than the study medication
- Beta-agonists other than the Ventolin supplied by the sponsor
- Concurrent use of any other prescription or over-the-counter medication which may affect the course of COPD or interact with study medications. These medications were to be discontinued at least 2 weeks prior to randomization.

11.2.10. Drug product and placebo

The sponsor provided the following study treatments [clinstat\copd\sfca3006.pdf, pages 55-56]:

- Placebo Diskus, for the single-blind run-in period and 24-week treatment period
- FP Diskus 500 mcg, 1 puff BID for the 24-week double-blind study period
- SAL Diskus 50 mcg, 1 puff BID for the 24-week double-blind study period
- SAL 50 mcg/FP Diskus 500 mcg, 1 puff BID for the 24-week double-blind study period
- Market-image Ventolin MDI and nebules for each subject as rescue medication
- Cortrosyn 0.25 mg injection for cosyntropin stimulation testing at selected sites

Reviewer comment:
The FP Diskus 500 mcg is not an approved product. The sponsor has argued dose proportionality of the approved 250 mcg and proposed 500 mcg products in another study included in this submission. The interpretation of these dose proportionality data is a review issue discussed elsewhere in this review, and discussed in depth in the clinical pharmacology review.

The batch numbers of medication were used in this study are displayed in Table 11.2.2.

Table 11.2.2. Batch numbers of study medication, SFCA3006 [clinstat\copd\scfa3006.pdf, page 56].

Product	Batch numbers
Placebo Diskus	WP25L4 WP31R9 WP2GHW
FP Diskus 500 mcg	U98/024C
SAL Diskus 50 mcg	WP2D8B WP2NLT

Product	Batch numbers
	WP2T35
SAL Diskus 50 mcg/FP Diskus 500 mcg	U97/061C WP2NPB B003371
Ventolin MDI, 90 mcg/puff	8ZP0909 9ZP0259
Ventolin nebules, 0.098%, 2.5 mg/3 mL	980905 990903 980901
Cortrosyn 0.25 mg injection	2240697731 2300199731 2310299731

The sponsor states that the formulations of Flovent used in this study were representative of the commercial product in terms of input materials, scale of manufacture, manufacturing equipment, and manufacturing process. The only difference between the batches of Flovent that were supplied for this study and the commercial product was the device coloration. All batches of Ventolin nebules and Ventolin MDI used in this study were the approved commercial product. The placebo used in this study was identical to the active product used in this study except for the absence of active drug [NDA 20-833, SE1-004, 9/17/01, page 3].

11.2.11. Assessment of compliance

Patient compliance with the drug dosing schedule was determined from the dose counter on the Diskus devices. Patients who were less than 70% compliant with the use of study medication during the 2-week run-in were not eligible to be randomized into the study [clinstat\copd\scfa3006.pdf, pages 58, 81].

11.2.12. Assessment of signs and symptoms

Patient COPD symptoms were evaluated with the Chronic Bronchitis Symptom Questionnaire (CBSQ), Baseline/Transition Dyspnea Index (BDI/TDI), and assessment of the severity of any COPD exacerbations since the last evaluations. These instruments are described below.

The CBSQ was composed of selected questions from the Petty Subject Evaluation Questionnaire[6] and the Revised Global Petty Questionnaire for Ease of Cough and Sputum Clearance[7] The CBSQ evaluated cough frequency and severity, sputum release, and chest discomfort on a 0 to 4, 5-point scale. Individual scores were summed to provide a Global Assessment Score (GAS). As noted in the inclusion criteria, patients must have had a GAS of ≥4 at Treatment Day 1 to qualify for the study [clinstat\copd\sfca3006.pdf, page 49].

Additional data describing the CBSQ were included with the application. These data describe the administration of the CBSQ. The patient was allowed to read each question along with the interviewer and verbally select the response that best described the status of that particular symptom on a typical day during the past week. After reading the question, as written, with the subject, the interviewer used discussion questions and observations to assist the subject in providing as precise an answer as possible [clinstat\other\cbsqvalidationdocument.pdf, page 6]. A Minimally Clinically Important

Change (MCIC) for the CBSQ was determined to be a change from baseline of 1.4 in the GAS [clinstat\other\cbsqvalidationdocument.pdf, page 11]. The calculation of the MCIC assessed the change in GAS for individual subjects by collecting them into one of four categories to assess a Global Rating of Change (GRC) [clinstat\other\cbsqvalidationdocument.pdf, pages 8-9]:

1. GRC = 0, ±1: No change in symptoms of chronic bronchitis
2. GRC = ±2, ±3: A minimal change in symptoms of chronic bronchitis
3. GRC = ±4, ±5: A moderate change in symptoms of chronic bronchitis
4. GRC = ±6, ±7: A large change in symptoms of chronic bronchitis

However the validation package indicates that there was poor correlation between the GAS and the GRC used to calculate the MCIC. Pearson and Spearman's correlation coefficients between GAS and GRC were only from 0.25 to 0.34 [clinstat\other\cbsqvalidationdocument.pdf, page 9]. Furthermore, large standard deviations in the GRC and MCIC were noted. The standard deviations were large enough for each of the GRC categories to substantially overlap each other [clinstat\other\cbsqvalidationdocument.pdf, page 11].

Reviewer comment:
The CBSQ was administered in such a fashion that the interviewer might have influenced patient responses. The poor correlation between the GAS and GRC and the large standard deviation in the GRC indicate that the MCIC is not likely to be valid. This instrument will not be able to provide support for the efficacy of FP.

The BDI/TDI was used to provide a clinical measurement of baseline and change in dyspnea. The degree of functional impairment at baseline due to dyspnea, the magnitude of task to provoke dyspnea, and the magnitude of effort that provoked dyspnea were rated on a 0 to 4, 5-point scale to derive the BDI. Changes from baseline in functional impairment, magnitude of task, and magnitude of effort were assessed at each subsequent visit with a -3 to +3, seven-point scale, the TDI [clinstat\copd\sfca3006.pdf, pages 62-67].

The sponsor provided a reference for this instrument that showed a weak correlation of the BDI with FEV_1, FVC, and the 12-minute walk distance with correlation coefficients of 0.41, 0.56, and 0.60[8]. TDI correlated only weakly with change in the change in the 12-minute walk distance, with a correlation coefficient of 0.33. There was no correlation of TDI with change in FEV_1 or change in FVC. Although not noted in this study, the sponsor had noted in FLTA3025 that they considered a change from BDI to TDI of 1.0 to be clinically relevant [clinstat\copd\flta3025.pdf, page 67, Correspondence submitted to IND 50,703, Meeting request package, 2/6/98]. The sponsor did not include a validation package with this application or with the meeting request package of 2/6/98.

Reviewer comment:
Degree of functional impairment, magnitude of task, and magnitude of effort are likely to be highly correlated variables, in this reviewer's opinion, and therefore will inflate any

observed positive or negative treatment effect. This instrument will not be likely to provide support for the efficacy of FP because of this deficiency and because of the lack of validation.

The investigator assessed the severity of any COPD exacerbations at each clinic visit using a three-level scale, mild to severe. Mild exacerbations were defined as use of more than 12 puffs or 4 nebules of relief bronchodilator per day for more than 2 consecutive days, but without the need for additional medication. Moderate exacerbations were defined as requiring either antibiotics or corticosteroids. Severe exacerbations were defined as requiring inpatient admission for treatment [clinstat\copd\sfca3006.pdf, page 68].

Reviewer comment:
This is not the standard definition of COPD exacerbation. In fact, this definition describes situations that reflect a worsening of airway bronchoconstriction. This definition of exacerbation would be likely to favor the finding of efficacy of FP in patients who have a high degree of reversibility. The most widely accepted definition of COPD exacerbation follows[9]:

- *Type 1 = All of the following symptoms*
  - *Increased dyspnea, increased sputum volume, increased sputum purulence*
- *Type 2 = Two of the following symptoms*
  - *Increased dyspnea, increased sputum volume, increased sputum purulence*
- *Type 3 = One of the following symptoms*
  - *Increased dyspnea, increased sputum volume, increased sputum purulence and one of the following:*
    - *URI within 5 days, fever without non-respiratory cause, increased wheezing, increased coughing, increase in respiratory rate of heart rate ≥20%*

Patients were to complete diary records during the treatment period each morning. Patients recorded the highest of three PEFRs measurements performed each morning prior the dose of study medication, the number of inhalations of supplemental Ventolin use over the preceding 24 hours, and the number of nighttime awakenings requiring the use of Ventolin during the preceding night [clinstat\copd\sfca3006.pdf, pages 68-69].

11.2.13. Health-related quality of life instrument

Health outcomes were assessed with the Chronic Respiratory Disease Questionnaire (CRDQ), a health-related quality of life instrument[10] [clinstat\copd\sfca3006.pdf, page 69]. It is worth noting that comparative quality of life (QOL) was one of the three primary objectives that the sponsor identified as important outcomes of the study. The sponsor states that the instrument is an interviewer-administered, disease-specific, validated questionnaire designed to measure the impact of chronic respiratory disease and its treatments on the patient's COPD-related quality of life. The CRDQ is a 20-item questionnaire that evaluates health-related quality of life across four domains—dyspnea, fatigue, emotional function, and mastery over the disease. The responses for each of the 20 items were summed to provide an overall assessment of health-related quality of life.

A physical score was calculated based on the sum of scores of the dyspnea and fatigue domains and an emotional score was calculated based on the sum of the scores of the emotional function and mastery domains. The CRDQ was completed at Day 1, and Weeks 2, 4, 8, 24, and Discontinuation.

11.2.14. Efficacy variables

Efficacy variables for this study are described below.

11.2.14.1. Primary efficacy variable

The primary efficacy variables for this study was the pre-dose FEV_1 and the 2-hour post dose FEV_1 collected at Day 1, and Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 [clinstat\copd\sfca3006.pdf, page 11853].

For primary efficacy measures, treatments were compared as follows [clinstat\copd\sfca3006.pdf, page 11853].

- SAL 50/FP 500 to SAL 50: Pre-dose FEV_1, to evaluate the contribution of FP 500 to the combination product
- SAL 50/FP 500 to FP 500: Two-hour post dose FEV_1, to evaluate the contribution of SAL 50 to the combination product
- SAL 50 to placebo: Two-hour post-dose FEV_1, to evaluate the efficacy of the individual component
- FP 500 to placebo: Pre-dose FEV_1, to evaluate the efficacy of the individual component

Reviewer comment:
Only the pre-dose FEV_1 is relevant to the assessment of efficacy for FP 500 relevant to placebo, therefore this comparison will be the focus of the review. Other active treatment arms will only be discussed only if relevant to the efficacy and/or safety assessment of FP 500.

The baseline FEV_1 was the pre-dose FEV_1 at treatment Day 1. The primary analyses compared endpoint and baseline measurements for the primary efficacy variables. The endpoint was defined in the protocol as the final evaluable measurement for the patient. For patients who discontinued from the study the endpoint was the last evaluable measurement taken prior to withdrawal [clinstat\copd\sfca3006.pdf, page 11853]. Therefore, the FEV_1 at the Discontinuation Visit was not used for any efficacy analysis.

Reviewer comment:
As this review is concerned with the efficacy of FP in the treatment of COPD, only pre-dose FEV_1 measurements will be examined. Two-hour post-dose FEV_1 measurements were performed by the sponsor to help assess the efficacy of SAL 50 and the contribution of SAL to the efficacy of the combination SAL 50/FP 500 product.

In FLTA3025, the sponsor stated that their rationale for not using the FEV1 at the Discontinuation Visit was that patients might have stopped taking study drug prior to the visit and might have been taking another drug that could affect results

[clinstat\copd\flta3025.pdf, page 66]. Although it is not stated in this study, it is likely the sponsor had the same rationale in this study. The sponsor's plan to carry the last measurement from the preceding visit forward for discontinuing patients also affects the interpretation of efficacy results, however.

Treatment groups were compared using ANCOVA F-tests with baseline as the covariate. All inferential analyses were performed on the mean change from Baseline. Ninety-five percent confidence intervals were provided for treatment differences in the mean changes from Baseline [clinstat\copd\sfca3006.pdf, pages 11853, 81-82].

11.2.14.2. Secondary efficacy variables

Secondary efficacy variables included change from baseline in the global and individual domains of the CBSQ, the BDI/TDI score at each of the treatment visits, number and percent of exacerbations of COPD, time to first COPD exacerbation, number of withdrawals and time to withdrawals. Morning PEFR, daily use of Ventolin, percentage of nights with no awakenings requiring Ventolin, frequency of nighttime awakenings requiring Ventolin, and percent of days without using Ventolin were also summarized. The sponsor performed 12-hour serial spirometry at Day 1 and Week 12 in a subset of patients at selected sites to demonstrate that SAL 50- and SAL 50/FP 500-induced increases were sustained for 12 hours [clinstat\copd\sfca3006.pdf, pages 113, 11854].

Summary statistics were provided for all secondary endpoints. Changes from baseline in the Global Assessment Score (GAS) of the CBSQ were compared between treatment groups using an ANCOVA F-test with treatment group, investigator, and baseline value as covariates. Overall and pairwise treatment comparisons of the BDI/TDI scores were performed by ANOVA F-test. Time to first COPD exacerbation, number of withdrawals, and time to withdrawals were analyzed using survival analysis [clinstat\copd\sfca3006.pdf, pages 11854-11855].

The CRDQ was also used to compare changes in the COPD-related quality of life for treatment groups as measured by an overall score and for each of the four domains. An improvement of at least 10 in overall score was considered to be an overall improvement in COPD specific quality of life. At each visit, treatment group comparisons were made comparing the change from baseline using ANCOVA, controlling for baseline and investigator. A difference between treatment groups in mean change from baseline was considered clinically meaningful the difference was statistically significant and had a minimum of ≥0.5 point improvement per question per item [clinstat\copd\scfa3006.pdf, pages 11855-11866].

11.2.15. Safety variables

Safety variables for this study included AEs, ECGs, hematology and clinical chemistry studies, oropharyngeal examinations, and vital signs [clinstat\copd\sfca3006.pdf, pages 11844-11849]. Summary statistics were to be provided for each of the safety endpoints [clinstat\copd\sfca3006.pdf, pages 11857-11858].

Reviewer comment:
Although the safety variables that were chosen are appropriate to assess the local and systemic safety of FP, it would have been preferable to also have formal ophthalmologic examinations and assessments of bone density, although given the duration of the study, it is unclear whether such tests would be sufficiently sensitive to detect a change.

Cosyntropin (Cortrosyn®) stimulation testing was performed at selected study sites on Day 1 and Week 24 or Discontinuation [clinstat\copd\sfca3006.pdf, pages 11857-11858]. The sponsor performed the short cosyntropin stimulation test according to the cosyntropin package insert. Blood samples were to be drawn 30-60 minutes after administration of cosyntropin [clinstat\copd\sfca3006.pdf, page 11849]. Threshold values of 14.5 mcg/dL and 5.6 mcg/dL were used in the analysis because a HPLC assay was used. The sponsor states that a less specific radioimmunoassay was used for the higher reference values given in the cosyntropin package insert [clinstat\copd\sfca3006.pdf, page 90].

Twenty-four hour Holter monitoring was to be conducted at approximately 14 study centers on approximately 160 patients. Baseline monitoring was performed during the run-in period. Post-treatment monitoring was to be performed at Week 4. Monitoring was to start approximately 1 our prior to administration of the morning dose of study medication and continued for 24 hours [clinstat\copd\sfca3006.pdf, page 11845-11847].

11.2.16. Statistical considerations

Imputation of missing data was planned for the primary efficacy parameter and the humanistic outcomes. Last observation carried forward analysis was to be performed. [clinstat\copd\sfca3006.pdf, page 11852].

11.2.16.1. Data sets analyzed

The primary population for the analysis of both efficacy and safety was the intent-to-treat population, defined as all randomized subjects who received at least one dose of study drug [clinstat\copd\sfca3006.pdf, pages 11851-11852].

Originally, the sponsor did not plan any subgroup analyses [clinstat\copd\sfca3006.pdf, page 11852]. In Protocol Amendment 3 (2/11/00), the sponsor added a subgroup analysis for patients who have an increase in percent predicted FEV_1 of less than 10% after albuterol at the screening visit. This group was called the "poorly-reversible-percent of predicted patients" [clinstat\copd\sfca3006.pdf, page 11931]. Subgroup analyses of former smokers and current smokers were added in Protocol Amendment 4 (6/23/00) [clinstat\copd\sfca3006.pdf, page 11935].

Reviewer comment:
This analysis was to be provided to support the approval of the product outside the US. [clinstat\copd\sfca3006.pdf, page 107]. The sponsor indicates that this definition reflects current opinion of the European Respiratory Society [NDA 20-833, SE1-004, pages 1-2, 8/10/01].

As in FLTA3025 and as noted earlier in this document, assignment to study drug was to be stratified according to the patients' response to reversibility testing with bronchodilator at screening to non-reversible and reversible patients. The non-reversible group was defined earlier in the protocol as patients with an absolute volume increase of <200 mL or absolute volume increase ≥200 mL with baseline reversibility assessment of <12% , and is based on the ATS definition of reversibility [clinstat\copd\sfca3006.pdf, page 11832; NDA 20-833, SE1-004, pages 1-2, 8/10/01]. As noted earlier, subgroup analysis initially was not provided for these either the non-reversible or reversible groups. The proportion of patients with reversibility will be critical to determine if the population studied accurately reflects the population of patients with COPD.

The sponsor provided an extensive subgroup analysis of the "poorly-reversible population." As noted above, the poorly-reversible population" was defined as those patients who had an increase in percent predicted FEV_1 of less than 10% after albuterol at the screening visit. Although this may be the accepted definition for the ERS, it is a curious way of expressing reversibility, as it uses a theoretical value as the baseline (percent predicted FEV_1), rather than an actually measured value, such as FEV_1 at baseline. The ERS definition and the subgroup analysis of the poorly reversible population are not relevant to approval of this drug for this indication in the US, however, and this subgroup analysis will receive only brief review.

11.2.16.2. Statistical power

The sponsor calculated that a sample size of 145 patients per treatment arm would be necessary to provide >85% power to detect a clinically meaningful significant difference of 0.1 liter between treatment groups. The sponsor assumed a standard deviation for the change from baseline FEV_1 of 0.28 liters, and a level of significance of 0.05, using a two-sample t-test [clinstat\copd\sfca3006.pdf, page 11851].

The sponsor amended the protocol in Protocol Amendment 3 to allow for randomization of 700 patients with a total of 175 patients per treatment arm [clinstat\copd\sfca3006.pdf, page 11930]. The sponsor increased the planned sample size to account for any data which required exclusion from the primary efficacy analysis, such as an investigator not meeting study standards or subjects that have a baseline FEV_1 assessment without a subsequent FEV_1 assessment [clinstat\copd\sfca3006.pdf, page 11930].

11.2.17. Results

The sponsor excluded data from patients enrolled at the site of Investigator #[ ] from population and efficacy analyses as a result of a quality assurance assessment. The sponsor indicates that there was reason to doubt the integrity of the data from patients enrolled at this site. Data for these patients were included in the analyses of safety [clinstat\copd\sfca3006.pdf, page 92]. Investigator #[ ] was Dr. [ ], who was at study Site #[ ] [clinstat\other\listofinvestigators.pdf, page 8]. Dr. [ ] enrolled [ ] patients in the study [clinstat\copd\sfca3006.pdf, page 2235].

The sponsor received a letter from Investigator #[ ]stating that the data generated from this study might be unreliable. The sponsor performed an impact analysis to

determine if the removal of the data submitted by this investigator would change interpretation of the data. The impact analysis showed that there would be no change in the interpretation of the data, and included data from this investigator in the study report [clinstat\copd\sfca3006.pdf, page 92]. Investigator #[ ] was Dr. [ ], who was at Site #[ ] [clinstat\other\listofinvestigators.pdf, page 9]. Dr. [ ] enrolled [ ] patients in the study [clinstat\copd\sfca3006.pdf, page 2263-2264].

Reviewer comment:
This reviewer compared results for the primary efficacy endpoint from the impact analysis with the data including Investigator #[ ] in the analysis. There was essentially no difference in the change from baseline in FEV_1 at endpoint and at other times for treatment groups during the treatment period. There was no impact on the inferential statistical analysis for the primary efficacy parameter. This document will review the data excluding Investigator #[ ], but including Investigator #[ ], as presented in the sponsor's primary analysis.

Review of this study will focus on the efficacy of FP. Therefore discussion will focus primarily on the comparison of FP 500 and placebo, with less detailed review of comparisons of SAL 50 with SAL 50/FP 500 and SAL 50/FP 500 with placebo.

11.2.17.1. Populations enrolled/analyzed

There were 1335 patients screened for the study. There were 661 patients who were screening failures. A total of 674 patients were randomized. The most common reason for screening failure was FEV_1/FVC <70% and baseline FEV_1 <65% predicted but >0.7 L (454/661, 69%). Other reasons for screening failure included significant concurrent disease (36/661, 5%), inability to tolerate the 2-week run-in (32/661, 5%), moderate or severe COPD exacerbation during run-in (26/661, 4%), abnormal and clinically significant 12-lead ECG (24/661, 4%), and clinically significant chest X-ray abnormality, not due to COPD (21/661, 3%) [clinstat\copd\sfca3006.pdf, pages 92, 1717-1720].

Reviewer comment:
One might expect that failure to tolerate the 2-week run-in would be the most common reason for screening failure in this study. However, inability to meet the inclusion criterion for spirometry was the most common reason for screening failure. This is probably the reason for the change in Protocol Amendment 2 that changed FEV_1/FVC ratio from ≤65% to ≤70%. The most likely effect of this change would be to allow entry of patients with milder obstruction. These patients might be more likely to have reversibility, and might be more likely to respond to an inhaled corticosteroid such as FP.

Patient disposition is summarized in Table 11.2.3. There were 674 patients randomized and 440 patients completed the study. There were 234 patients that discontinued the study prematurely. The frequency of discontinuations were fairly similar among treatment groups, with the lowest frequency in SAL 50 (45/160, 28%). The most frequent reason for discontinuation for all groups was COPD exacerbation. Among patients discontinuing the study, there were 25% (17/68) who discontinued due to COPD exacerbation in the FP 500 group, compared with 23%, (16/69) in the placebo group, 27% (14/52) in the SAL

50/FP 500 group, and 20% (9/45) in the SAL 50 group. The frequency of adverse events (AEs) leading to discontinuation was highest in the FP 500 group (31%, 21/68), followed by the placebo group (25%, 17/69), the SAL 50 grou0 (24%, 11/45), and the SAL 50/FP 500 group (21%, 11/52). Lack of efficacy was a less frequent reason for discontinuation in the FP 500 group (4%, 3/68) than for SAL 50/FP 500 (6%, 3/52) SAL 50 (16%, 7/45) and placebo (16%, 11/69) groups.

Table 11.2.3. Patient disposition, SFCA3006, [clinstat\copd\sfca3006.pdf, pages 93, 378]

	Placebo		SAL 50		FP 500		SAL 50/FP 500		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Patients randomized	181	(100)	160	(100)	168	(100)	165	(100)	674	(100)
Patients completed	112	(62)	115	(72)	100	(60)	113	(68)	440	(65)
Patients discontinued	69	(38)	45	(28)	68	(40)	52	(32)	234	(35)
Reason for discontinuation										
Adverse event	17	(25)	11	(24)	21	(31)	11	(21)	60	(26)
COPD exacerbation	16	(23)	9	(20)	17	(25)	14	(27)	74	(32)
Withdrawn consent	11	(16)	4	(9)	5	(7)	10	(19)	30	(13)
Lack of efficacy	11	(16)	7	(16)	3	(4)	3	(6)	24	(10)
Lost to follow-up	2	(3)	1	(2)	3	(4)	1	(2)	7	(3)
Protocol violation	8	(12)	10	(22)	14	(21)	8	(15)	40	(17)
Other	4	(6)	3	(7)	5	(7)	5	(10)	17	(7)
Death*	3*	(2)	0	(0)	0	(0)	0	(0)	3	(1)

*Deaths are also included in the adverse event category

11.2.17.2. Protocol deviations

The most common violations of inclusion and exclusion criteria included significant concurrent disease and use of prohibited medications. Significant concurrent disease ranged from 2% to 7%. Use of concurrent medications that interfere with objective assessments ranged from 2% to 5% in the treatment groups [clinstat\copd\sfca3006.pdf, pages 94, 383-385].

Reviewer comment:
Violations of inclusion criteria were fairly infrequent and evenly distributed between treatment groups and were not likely to affect the analysis of efficacy or safety.

There were few patients who varied from the protocol who were not discontinued from the study, as presented in Table 11.2.4. The most common protocol variations were use of a prohibited corticosteroid and use of a prohibited non-corticosteroid medication [clinstat\copd\scfa3006.pdf, pages 94, 386]. Other protocol variations included significant concurrent disease, vital signs and spirometry performed late or not performed [clinstat\copd\scfa3006.pdf, pages 2278-2285].

Table 11.2.4. Protocol variations during conduct of the study, not leading to discontinuation [clinstat\copd\sfca3006.pdf, page 386].

	Placebo N = 181 n (%)	SAL 50 N = 160	FP 500 N = 168 n (%)	SAL 50/FP 500 N = 165 n (%)
All protocol variations	12 (7)	17 (11)	13 (8)	14 (8)
Used a prohibited corticosteroid	3 (2)	4 (3)	3 (2)	3 (2)
Used other prohibited medication	6 (3)	7 (4)	7 (4)	8 (5)
Used pulmonary rehabilitation	0 (0)	0 (0)	0 (0)	1 (<1)
Used oxygen	0 (0)	1 (<1)	0 (0)	0 (0)
Other	5 (3)	9 (6)	8 (5)	4 (2)

As noted above, all [ ] patients from Investigator #[ ] were excluded from study population and efficacy analyses. Of these [ ] patients, [ ] were in the placebo group, [ ]were in the SAL 50 group, [ ] were in the FP 500 group, and [ ] in the SAL 50/FP 500 group. There were 23 patients in the ITT group who only had only baseline data for PFT, CBSQ, and TDI. These patients were not included in the analyses for their respective endpoints. There were 11 patients who had no baseline data for PFT, CBSQ, TDI, diary, or CRDQ. These patients were excluded from the analyses of the endpoints were their data was missing [clinstat\copd\scfa3006.pdf, page 95].

11.2.17.3. Demographic and background characteristics

Demographics and background characteristics of patients are displayed in Table 11.2.5. The majority of patients in each of the treatment groups were 65 years of age or older. The mean age of patients was 64 years in the placebo group, 63.5 years in the SAL 50 group, 64.4 years in the FP 500 group, and 61.9 years in the SAL 50/FP 500 group. Patients ranged from 40 to 90 years of age. The proportion of patients aged 65 years or less was somewhat greater in the SAL 50/FP 500 group. The mean age was also somewhat lower in the SAL 50/FP 500 group. The age range was similar in each of the treatment groups.

The majority of patients in this study were of male gender. Males represented from 61% to 75% of patients in each of the treatment groups. There were proportionately more males in the placebo group. The distribution of male and female patients was similar in the other treatment groups. The vast majority of patients in this study were of Caucasian race. There were few patients of Black or Asian race. Non-Caucasian races represented 6% or less of each of the treatment groups.

Patients in this study had fairly severe dyspnea. All patients experienced dyspnea with walking on level ground, and approximately one third of the patients in each of the treatment groups had dyspnea with walking on level ground for 100 yards or worse (MMRC Dyspnea Score ≥3). The patients in the placebo group had slightly milder dyspnea, with 71% having a MMRC Dyspnea Score of 2, compared with 56% to 67% with MMRC Dyspnea Scores of 2 in the other treatment groups. Mean duration of COPD was approximately 7 years for each of the treatment groups. Duration of COPD ranged from 1 year to 45 years.

There was a larger proportion of current smokers in the placebo group (54%, 97/181) than the other treatment groups (56% for each group). The placebo group had a larger

median history of smoking (60.0 pack years) than the other treatment groups (52.5 to 55.0 pack years). The median history of smoking was much larger than the 20 pack-year history required for entry into the study.

A smaller proportion of the placebo group (18%, 33/181) was using inhaled corticosteroids at screening than the other treatment groups (25%-31%). The majority of patients in each treatment group had emphysema. The frequency of emphysema was similar among treatment groups and ranged from 74% to 78%.

Reviewer comments:
The under-representation of non-Caucasian patients in this study is a serious deficiency. The lack of Black, Asian, and Hispanic patients will make it impossible to assess to efficacy or safety by race.

Overall, the population studied is characterized by long smoking histories, significant dyspnea, and about an 8 year history of COPD. It is unclear how the diagnosis of "emphysema" was made for the approximately 75% of the patients who reported it, since the diagnosis would require HRCT, DLCO, or an invasive procedure. The placebo group has slightly higher percentage of patients with milder dyspnea. The placebo group had a lower percentage of patients who were using inhaled steroids at screening, a higher proportion of patients who were current smokers, and had a slightly longer history of smoking. The effects of these characteristics of the placebo group might be to favor the demonstration of efficacy in the active treatment groups. These effects may need to be considered if study results are not robust.

Overall, a fairly large minority of the patients was taking inhaled corticosteroids at the time of screening. As noted earlier in this review, one would expect these patients to more likely to be corticosteroid-responsive than those not taking inhaled corticosteroids, as one would expect patients with no response or a poor response to have their treatment discontinued.

Table 11.2.5. Demographics, SFCA3006 [clinstat\copd\sfca3006.pdf, pages 96, 387-391].

Characteristic	Placebo N = 181		SAL 50 N = 160		FP 500 N = 168		SAL 50/FP 500 N = 165	
Age, years	**n**	**(%)**			**n**	**(%)**	**n**	**(%)**
<65	91	(50)	81	(51)	76	(45)	98	(59)
≥65	90	(50)	79	(49)	92	(55)	67	(41)
Mean age	64.0		63.5		64.4		61.9	
SD	8.3		9.4		9.3		9.3	
Range	44 – 90		40 – 84		42 – 82		40 – 86	
Gender	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Female	45	(25)	57	(36)	65	(39)	62	(38)
Male	136	(75)	103	(64)	103	(61)	103	(62)
Race	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Caucasian	166	(92)	152	(95)	156	(93)	156	(95)
Black	11	(6)	6	(4)	8	(5)	7	(4)
Asian	3	(2)	1	(<1)	2	(1)	2	(1)
Other	1	(<1)	1	(<1)	2	(1)	0	(0)

Characteristic	Placebo N = 181		SAL 50 N = 160		FP 500 N = 168		SAL 50/FP 500 N = 165	
MMRC Dyspnea Score	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
2	129	(71)	90	(56)	112	(67)	108	(65)
3	47	(26)	62	(39)	51	(30)	55	(33)
4	5	(3)	8	(5)	5	(3)	2	(1)
Duration of COPD	**Years**		**Years**		**Years**		**Years**	
Mean	8.00		7.84		8.18		8.10	
Range	1 – 36		1 – 46		1 – 35		1 – 41	
Smoking status	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Former smoker	84	(46)	86	(54)	91	(54)	89	(54)
Current smoker	97	(54)	74	(46)	77	(46)	76	(46)
Pack-years smoked								
Median	60.0		52.5		54.0		55.0	
Range	20 – 165		20 – 193		20 – 200		15 – 150	
Inhaled steroids at screening	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Yes	33	(18)	49	(31)	42	(25)	46	(28)
No	148	(82)	111	(69)	126	(75)	119	(72)
Emphysema	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Yes	142	(78)	125	(78)	125	(74)	123	(75)
No	39	(22)	35	(22)	43	(26)	42	(25)

Patients had fairly severe airway obstruction. Spirometry results at the time of screening are presented in Table 11.2.6. The mean FEV_1 for each treatment group of approximately 1250 mL, mean FEV_1 % predicted of about 41%, and mean FEV_1/FVC % of about 48%. The degree of airway obstruction was similar in each of the treatment groups [clinstat\copd\sfca3006.pdf, page 396].

Table 11.2.6. Spirometry at screening, SFCA3006 [clinstat\copd\sfca3006.pdf, page 396].

	Placebo n = 181	SAL 50 n = 160	FP 500 n = 168	SAL 50/FP 500 N = 165
FEV_1, mL				
Mean	1317	1237	1233	1268
SD	471	425	408	472
Median	1220	1165	1145	1130
Range	680 – 2720	660 – 2630	700 – 2590	530 – 2520
FEV_1, % predicted				
Mean	41.48	40.25	41.40	40.85
SD	12.44	11.54	11.91	11.91
Median	40.76	40.17	40.77	41.56
Range	18.1 – 90.0	18.4 – 71.6	19.4 – 64.9	20.5 – 65.1
FEV_1/FVC %				
Mean	49.02	48.58	47.64	49.41
SD	10.55	9.47	10.89	9.81
Median	49.48	48.95	47.01	47.92
Range	21.7 – 68.7	23.5 – 74.4	23.6 – 67.9	28.8 – 78.6

Patient response to treatment with bronchodilator at screening is summarized in Table 11.2.7. A patient was considered "non-reversible" if, after 4 puffs of Ventolin MDI, there was a change in FEV_1 of <12% from baseline or there was <200 mL absolute increase in the FEV_1. Therefore, a patient could be considered irreversible if they had a change in FEV_1 < 200 cc associated with FEV_1 > 12% or FEV_1 > 200 cc associated with FEV_1 <12%. Reversible patients represented 59% of all patients in this study. The mean %

change in FEV_1 for reversible patients was 32.4%. Non-reversible patients represented 41 % of all patients in this study. The mean % change in FEV_1 for non-reversible patients was 9.24%. The degree of reversibility in each of the treatment groups was similar. The mean % change in FEV_1 for all patients was 22.9%.

Reviewer comment:
As with Study FLTA3025, the proportion of patients with reversibility enrolled in this study is much higher than is found in the population of COPD patients at large. There were 54% of patients in this study who had reversibility. In addition, the degree of reversibility for the reversible population was high—29.83%. As noted earlier in this review, one would expect that only up to 30% of patients to have in increase of ≥15% in FEV_1 after inhalation of a beta-agonist.[1-4] The mean degree of reversibility in the non-reversible population was also high—8.78%.

The high proportion of patients with reversibility in this study is a critical consideration in determining whether the results of the study can be generalized to the COPD population as a whole. Reversible patients were over-represented relative to their prevalence in the COPD population as a whole, and the degree of reversibility in these patients is much higher than would be expected for the general population of patients with COPD. As with FLTA3025, this may have a major impact on the interpretation of the efficacy results of this study.

Table 11.2.7. Mean change in FEV_1 after bronchodilator treatment at screening*, SFCA3006 [clinstat\copd\sfca3006.pdf, pages 97, 397-398].

	Placebo	SAL 50	FP 500	SAL50/FP 500	All treatment groups
Reversible patients					
n (%)	101 (56)	82 (51)	90 (54)	88 (53)	361 (54)
Mean % change in FEV_1	28.05	31.55	28.56	31.56	29.83**
Non-reversible (ATS) patients					
n (%)	80 (44)	78 (49)	78 (46)	77 (47)	313 (46)
Mean % change in FEV_1	8.33	10.28	8.46	8.04	8.78**
All patients					
n (%)	181 (100)	160 (100)	168 (100)	165 (100)	674 (100)
Mean % change in FEV_1	19.33	21.18	19.23	20.58	20.05**

*Calculation of response: $\frac{(\text{Post-BD } FEV_1 \text{ minus Pre-BD } FEV_1) \times 100}{\text{Pre-BD } FEV_1}$

Not reversible if result is <12% or <200 mL increase in FEV_1
Reversible if result is ≥12% and ≥200 mL increase in FEV_1

**Mean change derived from data for individual treatment group data

Compliance with study treatment was reported as high in this study. These data are displayed in Table 11.2.8. More than 70% of patients in each treatment group took 90% or more of the prescribed doses of medication. The mean number of doses taken was approximately 93% in each treatment group [clinstat\copd\sfca3006.pdf, pages 99, 447].

Table 11.2.8. Compliance with study treatment, SFCA3006 [clinstat\copd\sfca3006.pdf, pages 99, 447].

	Placebo		SAL 50		FP 500		SAL 50/FP 500	
	n	(%)	n	(%)	n	(%)	n	(%)
All patients	181	(100)	160	(100)	168	(100)	165	(100)
<80% compliance	19	(10)	14	(9)	14	(8)	14	(8)
80-<90% compliance	33	(18)	21	(13)	25	(15)	22	(13)
≥90% compliance	126	(70)	123	(77)	127	(76)	126	(76)
Missing	3	(2)	2	(1)	2	(1)	3	(2)

11.2.17.4. Primary efficacy endpoint

The primary efficacy endpoint was the mean change in FEV_1 from Baseline to study endpoint. As noted earlier in this review, this review is concerned with the efficacy of FP in the treatment of COPD. Therefore only pre-dose FEV_1 measurements will be examined. The two-hour post-dose FEV_1 measurements were performed by the sponsor to help assess the efficacy of SAL 50 and the contribution of SAL to the efficacy of the combination SAL 50/FP 500 product, and these will not be examined in this review. Data for the primary efficacy variable are displayed in Table 11.2.9. and inferential analysis of the primary efficacy variable is displayed in Table 11.2.10.

The mean change from baseline in FEV_1 for the FP 500 group at endpoint was 109 mL, which was 113 mL more than the placebo group at endpoint. This comparison was statistically significant at $p < 0.001$. This change corresponds to an effect size of 9.6%[1]. Mean change from baseline in FEV_1 for the SAL 50/FP 500 group at endpoint was 156 mL, which was 49 mL more than the SAL 50 group. This comparison was statistically different from the SAL 50 group at $p = 0.012$. Values for the mean change in FEV_1 from Baseline for the FP 500 group at Weeks 6, 12, and 24 ranged from 96 mL to 131 mL. Values for the mean change in FEV_1 for the placebo group at Weeks 6, 12, and 24 ranged from –18 mL to 15 mL. Values for the mean change from baseline in FEV_1 for the SAL 50/FP 500 group at Weeks 6, 12, and 24 ranged from 180 to 192 mL. Values for the mean change from baseline in FEV_1 for the SAL 50 group at weeks 6, 12, and 24 ranged from 110 mL to 114 mL [clinstat\copd\sfca3006.pdf, pages 108, 512-521].

Mean change from baseline in FEV_1 for the FP 500 group at Weeks 1, 2, 3, 4, 8, 16, and 20 increased from 76 mL at Week 1 to 122 mL at Week 20 [clinstat\copd\sfca3006.pdf, pages 108, 512-517].

The mean percent change from baseline in FEV_1 for FP 500 rose quickly at the Week 1 visit, with a slow rise to endpoint levels over the remaining course of treatment.

Reviewer comments:
Only the primary endpoint of change from baseline to endpoint in pre-dose FEV_1 , FP500 met the pre-defined criteria for efficacy. FP was numerically better than placebo at endpoint and for the interim time points in the course of therapy. All three active treatments showed clinically significant differences from placebo at Week 1. The rapid increase from baseline in FEV_1 for FP 500 is somewhat of a surprise, as one would have

[1] Effect size = $\frac{\text{(mean change from Baseline in } FEV_1\text{, FP 500) minus (mean change from Baseline in } FEV_1\text{, Pbo)}}{\text{Baseline } FEV_1\text{, FP 500}}$

expected a slower rise for an inhaled corticosteroid. This rapid increase is likely to be a manifestation of the high dose of FP used in this study. The slower rise from Week 1 to endpoint levels for FP 500 is more representative of the expected response to inhaled corticosteroids.

Table 11.2.9. Mean change in pre-dose FEV_1 from baseline, primary efficacy variable, SFCA3006 [clinstat\copd\sfca3006.pdf, pages 108, 512-521].

	Pbo			SAL 50			FP 500			SAL 50/FP 500		
Study week	**Mean FEV_1, mL**	**Mean change from baseline, mL**	**n**	**Mean FEV_1, mL**	**Mean change from baseline, mL**	**n**	**Mean FEV_1, mL**	**Mean change from baseline, mL**	**n**	**Mean FEV_1, mL**	**Mean change from baseline, mL**	**n**
Baseline	1282	NA	181	1192	NA	159	1174	NA	166	1254	NA	163
Week 6	1338	15	141	1329	114	138	1295	96	141	1440	192	142
Week 12	1334	-12	127	1340	110	131	1289	81	121	1440	186	132
Week 24	1344	-18	112	1383	116	114	1362	131	99	1432	180	113
Endpoint*	1292	-4	171	1303	107	158	1298	109	161	1410	156	157

*Primary efficacy endpoint

Table 11.2.10. Inferential analysis of baseline and change from baseline in pre-dose FEV_1, primary efficacy variable, SFCA3006, [clinstat\copd\sfca3006.pdf, pages 518-521].

Study week	**Overall** **p value***	**Pbo** **vs. FP 500** **p value***	**Pbo** **vs. SAL 50/FP 500** **p value***	**SAL 50** **vs. SAL 50/FP 500** **p value***
Endpoint**	<0.001	<0.001	<0.001	0.012

*ANCOVA, Baseline as covariate
**Primary efficacy endpoint

11.2.17.5. Secondary efficacy endpoints

Secondary efficacy variables included change from baseline in the global and individual domains of the CBSQ, the BDI/TDI score at each of the treatment visits, number and percent of exacerbations of COPD, time to first COPD exacerbation, number of withdrawals and time to withdrawals. Morning PEFR, daily use of Ventolin, percentage of nights with no awakenings requiring Ventolin, frequency of nighttime awakenings requiring Ventolin, and percent of days without using Ventolin were also summarized. The CRDQ was also used to compare changes in the COPD-related quality of life for treatment groups as measured by an overall score and for each of the four domains.

Summary statistics were provided for all secondary endpoints. Changes from baseline in the Global Assessment Score (GAS) of the CBSQ were compared between treatment groups using an ANCOVA F-test with treatment group, investigator, and baseline value as covariates. Overall and pairwise treatment comparisons of the BDI/TDI scores were performed by ANOVA F-test. Time to first COPD exacerbation, number of withdrawals, and time to withdrawals were analyzed using survival analysis [clinstat\copd\sfca3006.pdf, pages 11854-11855]. For the CRDQ, treatment group comparisons were made comparing the change from baseline at each visit using ANCOVA, controlling for baseline and investigator [clinstat\copd\sfca3006.pdf, pages 11855-11866].

Reviewer comment:
Inferential analysis is appropriate only for the prospectively defined efficacy endpoint on which the study was powered, and not for these secondary efficacy endpoints. Therefore, this document will focus on the numerical differences between treatment groups for the secondary efficacy endpoints, and will not address the inferential statistical analysis.

11.2.17.5.a. Chronic Bronchitis Symptom Questionnaire

The CBSQ evaluated cough frequency and severity, sputum release, and chest discomfort on a 0 to 4, 5-point scale. Individual scores were summed to provide a Global Assessment Score (GAS). The maximum possible GAS was 16 [clinstat\copd\sfca3006.pdf, page 116]. Patients were required to have a minimum score of 4 at baseline to qualify for randomization. The sponsor determined that the Minimally Clinically Important Change (MCIC) in the CBSQ was 1.4 points in an analysis of patients completing at least 8 weeks of this study [clinstat\other\cbsqvalidationdocument.pdf, page 11]. Results of the Chronic Bronchitis Symptom Questionnaire are displayed in Table 11.2.11. The sponsor reported clinically important decreases in the CBSQ for FP 500 at Week 3 through Week 24 and at endpoint. The sponsor reported clinically important decreases in the CBSQ for SAL 50 and SAL 50/FP 500 at endpoint and Week 2 through Week 24. The sponsor reported clinically important decreases in the CBSQ for the placebo group at Weeks 8, 16, 24, and

Table 11.2.11. Chronic Bronchitis Symptom Questionnaire, SFCA3006. See text for comments. [clinstat\copd\sfca3006.pdf, pages 117, 574-579]

	Pbo			SAL 50			FP 500			SAL 50/FP 500		
Study week	**GAS***	**Mean change from baseline**	**n**	**GAS***	**Mean change from baseline**	**n**	**GAS***	**Mean change from baseline**	**n**	**GAS***	**Mean change from baseline**	**n**
Baseline	7.3	NA	180	7.4	NA	159	7.0	NA	167	6.9	NA	164
Week 1	6.7	0.5	169	6.2	1.2	157	5.9	1.1	161	5.6	1.3	157
Week 2	6.3	0.8	156	5.9	1.4	152	5.7	1.3	157	5.4	1.5	153
Week 3	6.1	1.0	154	5.6	1.8	143	5.6	1.5	150	5.0	1.8	149
Week 4	5.8	1.3	148	5.4	1.9	141	5.6	1.6	148	5.3	1.6	147
Week 6	5.9	1.2	141	5.7	1.6	139	5.3	1.8	141	4.9	1.9	142
Week 8	5.3	1.8	142	5.7	1.7	134	5.2	1.9	138	4.8	2.1	139
Week 12	5.7	1.3	127	5.6	1.8	131	5.0	2.0	120	4.8	2.1	132
Week 16	5.6	1.4	119	5.4	1.9	124	5.2	1.8	108	5.3	1.5	126
Week 20	5.9	1.1	113	5.3	2.1	120	5.2	1.9	103	4.6	2.2	116
Week 24	5.4	1.6	112	4.9	2.4	115	5.2	1.9	100	4.8	2.1	112
Endpoint	5.7	1.5	172	5.5	1.9	158	5.5	1.6	161	5.1	1.8	157

*GAS: Global Assessment Score. Minimally clinically important change = 1.4 points.

at endpoint. Decreases in the CBSQ for active treatment groups were numerically superior to placebo at all visits and at endpoint, except for Week 8. Improvements in the CBSQ were not clinically significantly different from improvements noted in the placebo group for any of the active treatment groups at any time, however [clinstat\copd\sfca3006.pdf, pages 117, 574-579].

Reviewer comment:
Small decreases in the CBSQ were noted for FP 500, SAL 50, and SAL 50/FP 500 at Weeks 3 to 24 and at endpoint. In general, changes were numerically superior to placebo. However, the differences from placebo for all active treatment groups were less than the MCIC of 1.4 points.

11.2.17.5.b. Baseline/Transition Dyspnea Indices

The degree of functional impairment at baseline due to dyspnea, the magnitude of task to provoke dyspnea, and the magnitude of effort that provoked dyspnea were rated on a 0 to 4, 5-point scale to derive the BDI. The maximum BDI score was 12. The TDI assessed changes from baseline in functional impairment, magnitude of task, and magnitude of effort were assessed at each subsequent visit with a -3 to +3, seven-point scale [clinstat\copd\sfca3006.pdf, page 61-67]. The sponsor considered a clinically important TDI score to be ≥1.0 [clinstat\copd\sfca3006.pdf, page 118, Correspondence submitted to IND 50,703, Meeting request package, 2/6/98].

Results of the BDI/TDI are presented in Table 11.2.12. All treatment groups, including placebo, had clinically significant changes from baseline, however, the differences between the FP 500 TDIs and placebo were greater than the minimal clinically significant TDI of 1.0 point at Week 24 only [clinstat\copd\sfca3006.pdf, pages 119, 588-591].

Reviewer comment:
The population studied included a high percentage of patients with reversibility with bronchodilator and does not accurately represent the population of COPD patients. Degree of functional impairment, magnitude of task, and magnitude of effort are likely to be highly correlated variables, in this reviewer's opinion, and therefore will tend to inflate any observed positive or negative treatment effect. This instrument has not been validated in a COPD population with a high degree of reversibility, and it is not a widely used scale or one that is held in high regard. These data do not provide support for the efficacy of FP.

Table 11.2.12. Baseline/Transition Dyspnea Index (BDI/TDI), SFCA3006. See text for comments. [clinstat\copd\sfca3006.pdf, pages 119, 588-591]

	Pbo		SAL 50		FP 500		SAL 50/FP 500	
Study week	BDI	n	BDI	n	BDI	n	BDI	n
Baseline	5.8	179	5.9	154	6.0	164	6.2	160
	TDI*	n	TDI	n	TDI	n	TDI	n
Week 1	0.1	169	1.0	157	0.8	161	1.6	157
Week 2	0.3	156	0.9	152	0.9	157	1.4	153
Week 3	0.9	154	1.2	143	1.2	150	1.4	149
Week 4	0.9	148	1.1	141	1.3	148	1.6	147
Week 6	0.9	141	1.1	139	1.0	141	2.0	142
Week 8	1.2	142	1.4	134	1.5	138	2.4	139
Week 12	0.6	127	1.3	131	1.4	120	2.0	132
Week 16	0.5	119	1.4	124	1.3	108	1.9	126
Week 20	0.4	113	1.7	120	1.6	103	2.4	117
Week 24	0.6	112	1.6	116	1.9	100	2.7	113
Endpoint	0.4	172	0.9	158	1.3	161	2.1	157

*Minimally clinically significant TDI = 1.0 point.

11.2.17.5.c. COPD exacerbations

The incidence of COPD exacerbation was similar for all treatment groups. The incidence of moderate to severe COPD exacerbations was similar for all treatment groups. Moderate to severe exacerbations of COPD were defined as those requiring oral antibiotics, inhaled or oral corticosteroids, or inpatient admission for treatment. These data are displayed in Table 11.2.13.

Reviewer comment:
It is important to note that the definition of COPD exacerbation was not the standard definition. The sponsor's definition of COPD exacerbation describes situations that reflect a worsening of airway bronchoconstriction, and would be likely to favor the finding of efficacy of FP in patients who have a high degree of reversibility. Even so, and despite the improvements in FEV_1 noted, patients treated with active drug had similar incidences of COPD exacerbations to patients treated with placebo.

Table 11.2.13. Incidence of COPD exacerbations, SFCA3006 [clinstat\copd\sfca3006.pdf, pages 122, 613-614].

	Placebo N = 181		SAL 50 N = 160		FP 500 N = 168		SAL 50/FP 500 N = 165	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with any COPD exacerbation	79	(44)	63	(39)	77	(46)	68	(41)
Patients with moderate or severe COPD exacerbations	63	(35)	60	(38)	67	(40)	61	(37)

Time to COPD exacerbation or withdrawal is summarized in Table 11.2.14. In general, first COPD exacerbations, first moderate to severe COPD exacerbations, study withdrawals, and withdrawals due to COPD exacerbation were similar in the FP 500 and placebo groups.

Reviewer comment:
These data provide no support for the efficacy of FP in the population studied.

Table 11.2.14. Time to COPD exacerbation or withdrawal, SFCA3006

Time to First COPD Exacerbation [clinstat\copd\sfca3006.pdf, pages 616-619]								
	Pbo		**SAL 50**		**FP 500**		**SAL 50/ FP 500**	
	Patients at risk	**Events**	**Patients at risk**	**Events**	**Patients at risk**	**Events**	**Patients at risk**	**Events**
Month 1	135	32	132	21	131	29	134	20
Month 2	109	50	113	34	101	50	114	36
Month 3	91	63	96	49	86	59	104	44
Month 4	81	69	91	53	76	64	89	55
Month 5	72	76	87	56	61	74	78	61
Month 6	0	78	0	62	0	77	0	67
Time to First Moderate to Severe COPD Exacerbation [clinstat\copd\sfca3006.pdf, pages 621-624]								
	Pbo		**SAL 50**		**FP 500**		**SAL 50/ FP 500**	
	Patients at risk	**Events**	**Patients at risk**	**Events**	**Patients at risk**	**Events**	**Patients at risk**	**Events**
Month 1	147	16	136	15	140	19	139	15
Month 2	123	32	117	28	113	37	118	32
Month 3	104	45	98	45	98	46	109	39
Month 4	91	53	92	50	85	52	94	50
Month 5	81	60	88	53	68	64	83	55
Month 6	0	62	0	59	0	67	0	60
Time to Study Withdrawal [clinstat\copdsfca3006.pdf, pages 626-629]								
	Pbo		**SAL 50**		**FP 500**		**SAL 50/ FP 500**	
	Patients at risk	**Events**	**Patients at risk**	**Events**	**Patients at risk**	**Events**	**Patients at risk**	**Events**
Month 1	156	25	149	11	157	11	151	14
Month 2	143	38	138	22	141	27	142	23
Month 3	136	45	132	28	131	37	138	27
Month 4	124	57	129	31	117	51	133	32
Month 5	116	65	124	36	105	63	121	44
Month 6	0	68	0	41	0	65	0	50

Time to Study Withdrawal due to COPD Exacerbation [clinstat\copd\sfca3006.pdf, pages 631-634]								
	Pbo		SAL 50		FP 500		SAL 50/ FP 500	
	Patients at risk	Events	Patients at risk	Events	Patients at risk	Events	Patients at risk	Events
Month 1	156	7	149	2	157	2	151	3
Month 2	143	11	138	4	141	9	142	8
Month 3	136	12	132	7	131	13	138	9
Month 4	124	17	129	8	117	20	133	10
Month 5	116	20	124	10	105	24	121	15
Month 6	0	21	0	12	0	26	0	18

11.2.17.5.d. PEFR

PEFR data are presented in Table 11.2.15. Overall, there was a small mean increase from baseline in AM PEFR was for the FP 500 (12.9 L/min) and SAL 50 (16.8 L/min) groups at the end of the study. A larger mean increase was observed in the SAL 50/FP 500 group (31.9 L/min). Similar increases from baseline in AM PEFR was noted for FP 500, SAL 50, and SAL 50/FP 500 at the end of each month during the treatment period. The increases ranged from 7.2 L/min at Month 1 to 22.0 L/min at Month 6 [clinstat\copd\sfca3006.pdf, pages 125, 641-644].

Reviewer comment:
Small increases in AM PEFR for the FP 500 group and the SAL 50/FP 500 group compared with placebo and SAL 50 give support for efficacy of FP 500 in this population and are concordant with the findings of the primary endpoint of change from baseline in pre-dose FEV_1.

Table 11.2.15. Mean change from baseline in AM PEFR [clinstat\copd\sfca3006.pdf, pages 125, 641-644].

	Placebo	SAL 50	FP 500	SAL 50/FP 500
Baseline				
N	181	158	167	162
Mean PEFR, L/min	269.5	252.1	243.7	254.0
Overall				
N	179	157	166	162
Mean PEFR, L/min	267.1	268.7	256.6	284.7
Mean change from baseline, L/min	-2.7	16.8	12.9	31.9

11.2.17.5.e. Supplemental Ventolin use

Supplemental Ventolin use is summarized in Table 11.2.16. Overall, the FP 500 and SAL 50, and SAL 50/FP 500 groups had small decreases in the number of puffs of Ventolin used per day. The decrease for FP 500 was much less than that for SAL 50 or for SAL 50/FP 500. The decrease in Ventolin use for FP 500 ranged from 0.2 to 0.6 puffs per day for each study month. Overall, the FP 500, SAL 50, and SAL 50/FP 500 groups had increases in the number of days without Ventolin use. The decrease for FP 500 was less than that for SAL 50 or for SAL 50/FP 500. The decrease in Ventolin use for FP 500 ranged from 4.1% to 7.9% for each study month.

Table 11.2.16. Mean change from baseline in supplemental Ventolin use [clinstat\copd\sfca3006.pdf, pages 126, 646-653]

	Placebo	SAL 50	FP 500	SAL 50/FP 500
Number of puffs of Ventolin used per day				
Baseline				
N	181	158	166	161
Mean number of puffs	4.9	4.6	4.5	4.2
Overall				
N	179	157	164	161
Mean number of puffs	5.4	3.6	4.1	3.0
Mean change from baseline, puffs	0.5	-0.9	-0.4	-1.2
Percent of days without Ventolin use				
Baseline				
N	181	158	166	161
Mean % days without Ventolin use	19.0	21.4	22.1	28.0
Overall				
N	179	159	165	165
Mean % days without Ventolin use	19.5	31.0	28.5	43.7
Mean change from baseline, % days	0.3	9.3	6.2	16.3

Nighttime awakenings requiring Ventolin use are summarized in Table 11.2.17. Overall, the FP 500, SAL 50, and SAL 50/FP 500 groups had very small decreases from baseline in the number of awakenings per night. Overall the FP 500, SAL 50, and SAL 50/FP 500 groups had small increases in the percent of nights with no awakenings requiring Ventolin use. Of the active treatment groups, the FP 500 group had the smallest increase in percent of nights with no awakenings.

Reviewer comment:
The small changes from baseline in nighttime awakenings and percent of nights with no awakenings requiring Ventolin provide some weak support of the efficacy of FP 500 in this population.

Table 11.2.17. Mean change from baseline in nighttime awakenings requiring Ventolin use [clinstat\copd\sfca3006.pdf, pages 128-129]

	Placebo	SAL 50	FP 500	SAL 50/FP 500
Number of awakenings per night requiring Ventolin				
Baseline				
N	177	156	163	157
Mean number of awakenings	0.27	0.26	0.24	0.22
Overall				
N	175	153	162	157
Mean number of awakenings	0.36	0.17	0.16	0.19
Mean change from baseline, awakenings	0.10	-0.09	-0.08	-0.04
Percent of nights with no awakenings requiring Ventolin				
Baseline				
N	177	156	163	157
Mean % nights with no awakenings	82.9	82.2	86.4	84.4
Overall				
N	177	157	165	163
Mean % nights with no awakenings	78.9	89.0	89.5	89.8
Mean change from baseline, % nights with no awakenings	-4.3	6.8	3.0	5.7

11.2.17.5.f. 12-hour serial spirometry

The sponsor performed 12-hour serial spirometry at Day 1 and Week 12 in a subset of patients at selected sites to demonstrate that SAL 50- and SAL 50/FP 500-induced increases were sustained for 12 hours [clinstat\copd\sfca3006.pdf, pages 113, 11854]. This secondary efficacy endpoint was chosen to support the SAL 50 and SAL 50/FP 500 applications, and is not pertinent to the FP 500 application. This secondary endpoint will not be reviewed in this document.

11.2.17.5.g. Health-related quality of life instrument

QOL assessment was one of the pre-specified objectives of this study. COPD-related quality of life was evaluated using the Chronic Respiratory Disease Questionnaire (CRDQ).[10] The CRDQ contains 20 questions in 4 domains: dyspnea, fatigue, emotional function, and mastery. An overall score, the sum of the scores for all 20 questions, was the primary health-related quality of life endpoint. A physical score was calculated based on the sum of scores in the dyspnea and fatigue domains and an emotional score was calculated based on the sum of scores of the emotional function and mastery domains [clinstat\copd\sfca3006.pdf, page 87]. A clinically significant improvement was considered to be 0.5 points per item. Therefore, an improvement in the Overall score of at least 10.0 points was considered to be a clinically significant improvement in COPD-specific quality of life. As there were different numbers of items per domain, the clinically significant changes for each domain and summary scores are as follows [clinstat\copd\sfca3006.pdf, pages 86-88]:

- Fatigue domain: 2.0 points
- Dyspnea domain: 2.5 points
- Physical summary: 4.5 points

- Emotional function domain: 3.5 points
- Mastery domain: 2.0 points
- Emotional summary: 5.5 points

Study endpoint was defined as the last available post-baseline score for the CDRQ. This was different from the other analyses, which did not include values for the Discontinuation visit [clinstat\copd\sfca3006.pdf, page 160]. In addition, the sponsor excluded patients with an overall baseline score greater than 130 from the analysis of the overall score at any visit. These patients were excluded because baseline scores would be mathematically unable to attain a clinically meaningful change [clinstat\copd\sfca3006.pdf, page 161]. Similar exclusions were made for the patients with the following scores [clinstat\copd\sfca3006.pdf, page 87]:

- Fatigue score >26
- Dyspnea score >32
- Physical summary >58

- Emotional function score >45
- Mastery score >26

- Emotional summary >71

The population analyzed, which excluded these patients, was referred to the "reduced intent-to-treat population" (reduced ITT population) [clinstat\copd\sfca3006.pdf, page 87].

Reviewer comment:
It is true that it is be mathematically impossible for patients whose baseline scores are higher than those noted above to attain a clinically meaningful change. However, it is not appropriate to exclude these patients from the analysis. It would have been preferable to set these maximum scores as inclusion criteria for the study. As it turns out, there were no patients excluded for the Overall score and the Dyspnea domain score and the ITT and "reduced ITT populations" were identical for these scores [clinstat\copd\sfca3006.pdf, pages 161, 1134, 2009, 2105].

There were a total of 27 patients among all treatment groups excluded from the calculation of the Emotional summary score and 1 patient excluded from the Physical summary score. There were 25 patients excluded from the Emotional function domain score, 62 patients from the Mastery domain score, and 4 patients from the Fatigue domain score [clinstat\copd\sfca3006.pdf, pages 1134, 1140, 1146, 1152, 1158, 1164, 2015, 2021, 2027, 2033, 2039, 2045]. This review will examine CDRQ results for the ITT group and not the reduced ITT population.

There was a small, clinically significant increase from baseline in the overall CDRQ score for SAL 50/FP 500 only (10.0 points). However, the change in the overall CDRQ score for SAL 50/FP 500 was less than a 10.0 point difference from the change in the placebo group, and therefore was not a clinically significant difference from the placebo group. The increase in the overall CDRQ score for FP 500 (4.8 points) was similar to placebo (5.0 points), less than the specified clinically significant change of 10.0 points. These data are displayed in Table 11.2.18. The data displayed reflects the ITT population. Only SAL 50/FP 500 had a small, clinically significant increase from baseline in the Physical summary score (6.1 points). However, this increase was not clinically significantly different than the placebo group, as there was less than a 4.5 point difference between them. The increase in the Physical summary score for FP 500 (3.4 points) was slightly greater than to placebo (2.7 points), but less than the specified clinically significant change of 4.5 points. No treatment group had a clinically significant increase from baseline in the Emotional summary score [clinstat\copd\sfca3006.pdf, pages 2009, 2027, 2045].

In general, individual domains showed small, but not clinically significant increases from baseline for SAL 50 and FP 500. Exceptions included the Dyspnea domain, which showed small clinically significant increases from baseline for SAL 50 and SAL 50/FP 500. These increases were less than a 2.5 point difference from the change for the placebo group, and therefore not clinically significantly different than the placebo group. The Emotional function and Mastery domains showed larger increases for placebo than for FP 500 [clinstat\copd\sfca3006.pdf, pages 2009-2045].

Examination of the "reduced ITT population" revealed similar findings as the ITT population, with the exception of the Fatigue domain which showed a small clinically significant increase from baseline for SAL 50/FP 500. This change was not significantly different from the change from baseline in the placebo group, however [clinstat\copd\sfca3006.pdf, pages 1128-1164].

Table 11.2.18. Chronic Respiratory Disease Questionnaire (CRDQ), COPD-related quality of life instrument, ITT population, SFCA3006 [clinstat\copd\sfca3006.pdf, pages 2009, 2027, 2045].

	Pbo			SAL 50			FP 500			SAL 50/FP 500		
	Score	Mean change from baseline	n	Score	Mean change from baseline	n	Score	Mean change from baseline	n	Score	Mean change from baseline	n
Overall score*												
Baseline	86.2	NA	177	87.6	NA	157	88.5	NA	166	87.1	NA	163
Endpoint	91.3	5.0	175	95.8	8.0	155	93.5	4.8	163	97.1	10.0	161
Physical summary score**												
Baseline	32.5	NA	177	33.4	NA	157	33.9	NA	166	33.5	NA	163
Endpoint	35.2	2.7	175	38.1	4.6	155	37.4	3.4	163	39.6	6.1	161
Emotional summary score***												
Baseline	53.8	NA	178	54.4	NA	159	54.7	NA	167	53.7	NA	164
Endpoint	56.2	2.3	176	57.9	3.4	157	56.0	1.2	164	57.6	3.9	162

*Clinically significant change in Overall Score = 10.0 points
**Clinically significant change in Physical Summary Score = 4.5 points
***Clinically significant change in Emotional Summary Score = 5.5 points

Reviewer comment:
A clinically significant increase from baseline was observed in the Overall score for SAL 50/FP 500 only. This increase was not clinically significantly different from the increase from baseline for the placebo group, however. In general, most of the individual domain and summary scores also did not show clinically significant increases, and none were clinically significantly different from the placebo group. As there was no clinically significant difference from the placebo group in the Overall score, any changes in individual domains or summary scores provide little meaningful information. These data provide no additional support for the efficacy of FP in this population.

11.2.17.6. Smoking status, subgroup analysis

The sponsor provided an analysis of efficacy by patient smoking status. Former smokers had the largest mean change from baseline in pre-dose FEV_1 at endpoint [clinstat\copd\sfca3006.pdf, page 130]. These data are displayed in Table 11.2.19. Among the former smokers, those treated with SAL 50/FP 500 had the largest change in FEV_1 (179 mL), followed by those treated with FP 500 (139 mL), SAL 50 (132 mL), and

with the smallest change in those treated with placebo (16 mL). Patients who were smokers during the conduct of the study had smaller mean changes from baseline in pre-dose FEV_1, with the largest change in patients treated with SAL 50/FP 500 (130 mL), and followed by SAL 50 (78 mL) and FP 500 (73 mL). The smallest change was in placebo patients (-21 mL).

Table 11.2.19. Mean change from baseline in pre-dose FEV_1 at endpoint, by smoking status [clinstat\copd\sfca3006.pdf, page 130].

Smoking status	Placebo		SAL 50		FP 500		SAL 50/FP 500	
	Mean Change, mL	(n)	Mean change, mL	(n)	Mean change, mL	(n)	Mean change, mL	(n)
Current smokers	-21	(97)	78	(74)	73	(77)	130	(76)
Former smokers	16	(84)	132	(86)	139	(91)	179	(89)

The sponsor also examined other efficacy endpoints by patient smoking status. As with FLTA3025, in general, where there were differences between the groups, efficacy was favored in the former smokers. There was little difference between the FP 500 group and the placebo group for the change in baseline in the CBSQ GAS for both current and former smokers. The TDI for FP 500 was similar for current and former smokers, however, there was a larger increase in current smokers treated with placebo. Current smokers treated with FP 500 had a lower percentage of COPD exacerbations than former smokers treated with FP 500. Current smokers treated with placebo had a higher percentage of COPD exacerbations than former smokers treated with placebo. Changes in PEFRs for patients treated with FP 500 were slightly higher in former smokers than in current smokers, similar to the FEV_1 data. There was no clinically significant change in the Overall CRDQ score at endpoint in the FP 500 group for former smokers or current smokers, and the degree of change in these groups was no different than their respective placebo groups [clinstat\copd\sfca3006.pdf, page 165].

Reviewer comment:
These data suggest that in general, efficacy favored patients who stopped smoking prior to the conduct of the study.

11.2.17.7. "Non-reversible" population, subgroup analysis

Assignment to study drug was to be stratified according to the patients' response to reversibility testing with Ventolin at screening to a non-reversible group and a reversible group. Non-reversible patients were defined as having an absolute volume increase <200 mL or an absolute volume increase of ≥200 mL with baseline FEV_1 reversibility of <12%. Reversible patients were defined as having an absolute volume increase ≥200 mL with baseline FEV_1 reversibility of ≥12% [clinstat\copd\sfca3006.pdf, page 11832; IND 44,090 N134 PN, 8/4/98, page 25]. Despite having assignment stratified based on "non-reversibility," the sponsor did not initially include an analysis for this subgroup. The sponsor was asked to provide a subgroup analysis of the non-reversible group in an IR on 10/2/01. The sponsor submitted this information in a document dated 1/17/01 [NDA 20-833, SE1 004 BZ, 10/17/01]. The results of the subgroup analysis for the non-reversible population are briefly reviewed below.

Table 11.2.20 summarizes the mean change in FEV_1 from baseline for the "non-reversible" population. Increases from baseline in pre-dose FEV_1 at endpoint were noted in all active treatment groups. The largest increase was in the SAL 50/FP 500 group (116 mL), followed by FP 500 (93 mL), and SAL 50 (80 mL). The placebo group had a decrease from baseline at endpoint (-8 mL) [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 9, 196-201].

A similar pattern was noted for mean change from baseline in pre-dose FEV_1 at Weeks 12 and 24. The largest increases were for the SAL 50/FP 500 group, followed by FP 500 and SAL 50 with similar degrees of change. Decreases from baseline were noted at these visits for the placebo group [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 9, 196-201].

Table 11.2.20. Mean change in pre-dose FEV_1 from baseline, primary efficacy variable, non-reversible population, SFCA3006 [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 9, 196-201].

	Placebo			SAL 50			FP 500			SAL 50/FP 500		
Study week	Mean FEV_1, mL	Mean change, mL	n	Mean FEV_1, mL	Mean change, mL	n	Mean FEV_1, mL	Mean change, mL	n	Mean FEV_1, mL	Mean change, mL	n
Baseline	1230	NA	80	1132	NA	78	1114	NA	78	1129	NA	77
Week 12	1250	-16	52	1238	78	60	1191	66	54	1293	135	61
Week 24	1254	-23	46	1306	76	48	1271	108	44	1283	110	48
Endpoint	1238	-8	74	1220	80	77	1219	93	75	1256	116	73

Response of the reversible population in the mean change in FEV_1 from baseline is summarized in Table 11.2.21. The difference from placebo for mean change from baseline at endpoint for the reversible group for FP 500 was 124 mL. This was 23% greater than the difference from placebo for mean change from baseline at endpoint for the non-reversible group, which for FP 500 was 101 mL [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 9].

Table 11.2.21. Mean change in pre-dose FEV_1 from baseline, primary efficacy variable, reversible population, SFCA3006 [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 9, 202-207].

	Placebo			SAL 50			FP 500			SAL 50/FP 500		
Study week	Mean FEV_1, mL	Mean change, mL	n	Mean FEV_1, mL	Mean change, mL	n	Mean FEV_1, mL	Mean change, mL	n	Mean FEV_1, mL	Mean change, mL	n
Baseline	1322	NA	101	1250	NA	81	1228	NA	88	1366	NA	86
Week 12	1393	-9	75	1426	136	71	1367	93	67	1566	231	71
Week 24	1406	-14	66	1439	145	66	1436	150	55	1542	232	65
Endpoint	1134	-1	97	1382	132	81	1367	123	86	1545	191	84

In general, secondary endpoints demonstrated small changes from baseline for SAL 50, FP 500, and SAL 50/FP 500 in the non-reversible population.

Changes at endpoint from baseline in the GAS of the CBSQ were noted for all treatment groups, but there were no clinically significant differences from the placebo group [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 10, 298]. Changes at endpoint from baseline in the TDI showed a clinically significant difference from placebo for the SAL 50/FP 500 group, but not the SAL 50 or FP 500 groups [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 298]. The incidence and frequency of exacerbations due to COPD were similar across the active and placebo treatment groups. The incidences and frequencies of moderate/severe COPD exacerbations were similar across the active and placebo treatment groups for this population [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 11, 306, 308].

Reviewer comment:
As noted earlier in this review, neither the CBSQ nor the TDI are likely to provide useful information because of insufficient validation.

There was a slightly lower probability of first COPD exacerbation during the first third of the study for the SAL 50/FP 500 group compared with the other treatment groups. However, the probabilities for first COPD exacerbation were similar for all treatment groups by the end of the study [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 176]. The probabilities for first moderate to severe COPD exacerbation were similar for all treatment groups throughout the entire duration of the study [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 178].

In general, small changes from baseline favoring SAL 50, FP 500, and SAL 50/ FP 500 were noted in for the non-reversible population for the following secondary endpoints: AM PEFR, and number of puffs of Ventolin used per day. In general, effects for these endpoints were greatest for SAL 50/FP 500, followed by SAL 50, with FP 500 having the smallest effect for these endpoints [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 12, 329, 337]. Awakenings per night requiring Ventolin showed little difference between treatment groups [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 345].

The overall score of the CRDQ, the health-related quality of life instrument, showed a clinically significant increase from baseline at endpoint for the SAL 50/FP 500 group. However this increase was not clinically significantly different from the placebo group [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 350].

Reviewer comment:
This analysis of primary efficacy variable and selected secondary variables in the non-reversible population provide some support for efficacy of FP, in contrast to similar data in study FLTA 3025. The reason for the discordance between this study and FLTA 3025 is unclear.

11.2.17.8. Safety outcomes

Safety variables for this study included AEs, ECGs, hematology and clinical chemistry studies, oropharyngeal examinations, and vital signs [clinstat\copd\sfca3006.pdf, pages 11844-11849].

Cosyntropin (Cortrosyn) stimulation testing was performed at selected study sites on Day 1 and Week 24 or Discontinuation [clinstat\copd\sfca3006.pdf, pages 11857-11858]. Twenty-four hour Holter monitoring was to be conducted at approximately 14 study centers on approximately 160 patients [clinstat\copd\sfca3006.pdf, page 11845-11847].

11.2.17.8.a. Total drug exposure

Total drug exposure is summarized in Table 11.2.22. Approximately 60% of each group completed ≥24 weeks of study treatment. The mean duration of treatment was 123.6 days for placebo, 141.1 days for SAL 50, 126.5 days for FP 500, and 137.8 days for SAL 50/FP 500.

Table 11.2.22. Total drug exposure, SFCA3006 [clinstat\copd\sfca3006.pdf, pages 172, 1380].

Duration of treatment	Placebo N = 185		SAL 50 N = 164		FP 500 N = 173		SAL 50/FP 500 N = 169	
	n	(%)	n	(%)	n	(%)	n	(%)
Any treatment	185	(100)	164	(100)	173	(100)	169	(100)
≥4 weeks	158	(85)	150	(92)	153	(88)	153	(90)
≥8 weeks	146	(79)	139	(80)	141	(82)	143	(85)
≥12 weeks	139	(75)	134	(82)	129	(75)	137	(81)
≥16 weeks	124	(67)	131	(80)	115	(66)	132	(78)
≥20 weeks	119	(64)	125	(76)	105	(61)	123	(73)
≥24 weeks	101	(55)	109	(66)	97	(56)	100	(59)
Treatment days, mean	123.6		141.1		126.5		137.8	

Reviewer comment:
Drug exposure appears to be adequate to allow for assessment of short-term safety, and noting the limitations that the design and duration of this study impose, and recognizing that compliance reporting is commonly unreliable. Compliance assessment was based on data from the Diskus dose counter, which cannot accurately assess whether patients actually received the drug that was dispensed.

11.2.17.8.b. Cosyntropin stimulation testing

Cosyntropin (Cortrosyn) stimulation testing was performed at selected study sites on Day 1 and Week 24 or Discontinuation [clinstat\copd\sfca3006.pdf, pages 11857-11858]. Cosyntropin stimulation was to be performed according to the package insert for Cortosyn® [clinstat\copd\sfca3006.pdf, pages 118549]. The sponsor used an HPLC assay for analysis of cortisol levels. The study report states that the threshold values for interpretation of the cosyntropin stimulation testing were adjusted downward from those in the package insert for Cortrosyn® because the values in the package insert were based on a less specific radioimmunoassay [clinstat\copd\sfca3006.pdf, page 90]. The sponsor states that this adjustment is consistent with previously published data[11, 12]. Abnormalities for this test was defined as:

- AM plasma cortisol <4 mcg/dL

- Peak post-stimulation cortisol <14.5 mcg/dL
- Change from baseline of <5.6 mcg/dL
- Peak post-stimulation cortisol <14.5 mcg/dL and change from baseline of <5.6 mcg/dL

There is no mention in the protocol of the type of assay that was to be used for cortisol, or of the definitions for abnormalities in cortisol levels.

Reviewer comment:
The definitions for abnormalities in cortisol levels with the cosyntropin stimulation test are consistent with the sponsor's references. It would have been preferable to specify in the protocol both the assay to be used and the definitions of an abnormal test, however.

The number and percentage of patients with abnormalities in cosyntropin stimulation testing is displayed in Table 11.2.23. The numbers of patients with cortisols were incorrect in the initial submission, but were corrected in a subsequent response NDA 20-833 SE1 004, BZ, 10/26/01\response.pdf]. The correct numbers are displayed in Table 1.2.23 and are reviewed in this section.

There were no differences between treatment groups in the percentage of patients who had pre-stimulation AM cortisol levels <4 mcg/dL at Day 1 and Endpoint. There was an increase in the percentage of patients with a change in post-stimulation cortisol <5.6 mcg/dL from Day 1 to Endpoint for SAL 50 (11% to 14%), for FP 500 (5% to 16%), and SAL 50/FP 500 (10% to 17%). There was no increase in the percentage of patients with a change in post-stimulation cortisol <5.6 mcg/dL for the placebo group (7% to 5%). There was an increase in the percentage of patients with post-stimulation cortisol levels <14.5 mcg/dL from Day 1 to Endpoint for the FP 500 group (3% to 8%) the SAL 50/FP 500 group (3% to 6%), and the placebo group (2% to 8%). There was no increase in the percentage of patients with post-stimulation cortisol levels <14.5 mcg/dL from Day 1 to Endpoint for the SAL 50 group (5% to 3%).

Table 11.2.23. Number and percentage of patients with abnormalities in cosyntropin stimulation testing, all patients with cortisol levels, SFCA3006 [clinstat\copd\sfca3006.pdf, pages 1464, 1467; NDA 20-833 SE1 004, BZ, 10/26/01\response.pdf, page 6].

	Day 1				Endpoint			
	Pbo N=185 n (%)	SAL 50 N=164 n (%)	FP 500 N=173 n (%)	SAL 50/ FP 500 N=169 n (%)	Pbo N=185 n (%)	SAL 50 N=164 n (%)	FP 500 N=173 n (%)	SAL 50/ FP 500 N=169 n (%)
Patients with cortisol levels	44 (100)	38 (100)	39 (100)	39 (100)	37 (100)	36 (100)	38 (100)	36 (100)
Pre-stim AM cortisol <4 mcg/dL	0 (0)	1 (3)	0 (0)	1 (3)	0 (0)	0 (0)	1 (3)	0 (0)
Post-stim change <5.6 mcg/dL	3 (7)	4 (11)	2 (5)	4 (10)	2 (5)	5 (14)	6 (16)	6 (17)
Post-stim cortisol <14.5 mcg/dL	1 (2)	2 (5)	1 (3)	1 (3)	3 (8)	1 (3)	3 (8)	2 (6)

Mean cortisol levels for cosyntropin stimulation testing are displayed in Table 11.2.24. Mean pre-stimulation cortisol levels were slightly lower at Endpoint than at Day 1 for the SAL 50 group, FP 500 group, and the SAL 50/FP 500 groups, but not the placebo group. Mean post-stimulation cortisol levels were slightly lower for all treatment groups at Endpoint than at Day 1. Mean post-stimulation cortisol levels decreased the most for the FP 500 (24.01 mg/dL to 21.42 mg/dL) and SAL 50/FP 500 (24.71 mg/dL to 21.92 mg/dL) groups. A smaller decrease was noted in the placebo (24.19 mg/dL to 23.61 mg/dL) and SAL 50 (24.12 mg/dL to 23.20 gm/dL) groups. A smaller rise in mean cortisol levels were noted with cortisol stimulation at Endpoint for the FP 500 and SAL 50/FP 500 groups than for the SAL 50 and placebo groups.

Table 11.2.24. Mean cortisol levels, pre-and post-cosyntropin stimulation, SFCA3006 [clinstat\copd\sfca3006.pdf, pages 1462-1463].

	Day 1				**Endpoint**			
	Pbo N=185	**SAL 50 N=164**	**FP 500 N=173**	**SAL 50/ FP 500 N=169**	**Pbo N=185**	**SAL 50 N=164**	**FP 500 N=173**	**SAL 50/ FP 500 N=169**
Pre-stimulation cortisol, mcg/dL (SD)	12.75 (5.30)	12.37 (4.93)	13.09 (4.89)	13.66 (6.65)	12.89 (5.13)	11.77 (4.29)	12.04 (5.08)	12.14 (5.34)
Post-stimulation cortisol, mcg/dL (SD)	24.19 (5.28)	24.12 (5.35)	24.01 (5.20)	24.71 (6.51)	23.61 (6.79)	23.20 (4.95)	21.42 (5.22)	21.92 (5.94)
Difference in means, pre-stimulation to post-stimulation*	11.44	11.75	10.92	11.05	10.72	11.43	9.38	9.78

*Calculated from sponsor's data.

Reviewer comment:
Although there were small numbers of patients who had cosyntropin stimulation testing, and fairly large standard deviations were noted, there is a suggestion of a systemic corticosteroid effect in some patients in the FP 500 and SAL 50/FP 500 groups for post-stimulation change <5.6 mcg/dL (Table 1.2.24). The larger decrease in mean post-stimulation cortisol levels from Day to Endpoint for FP 500 and SAL 50/FP 500 is suggestive of a small systemic effect, as is the smaller increase in mean cortisol levels in the FP 500 and SAL 50/FP 500 groups at Endpoint. It should be noted that cosyntropin stimulation testing is fairly insensitive, and the suggestion of a systemic effect in a small number of patients is notable.

11.2.17.8.c. 24-Hour Holter Monitoring

Twenty-four hour Holter monitoring was conducted at 18 study centers on 158 patients. Baseline monitoring was performed during the run-in period at screening. Post-treatment monitoring was performed at Week 4. Monitoring was to be started approximately 1 hour prior to administration of the morning dose of study medication and continued for 24 hours [clinstat\copd\sfca3006.pdf, pages 194-196, 11857-11858].

The median numbers of ventricular and supraventricular events increased from the screening visit for placebo, SAL 50, and FP 500 and decreased in the SAL50/ FP 500. There was a fairly high range of variability in the median number of ventricular and supraventricular events at the screening visit [clinstat\copd\sfca3006.pdf, page 195].

Cardiac rates as determined by Holter monitoring were similar among treatment groups at screening, and at Week 4. There was no significant change from screening in cardiac rates as determined by Holter monitoring at Week 4 [clinstat\copd\sfca3006.pdf, pages 195, 1504-1507].

There were five patients who had significant changes from screening in the interpretation of Holter evaluations at Week 4. There was one FP 500 patient who experienced atrial fibrillation/flutter, one SAL 50/FP 500 who experienced heart block, and one patient each for placebo, FP 500, and SAL 50 who experienced ventricular tachycardia.

Reviewer comment:
Holter monitoring results do not demonstrate significant differences among treatment groups. The increase in median numbers of ventricular and supraventricular events for placebo, SAL 50, and FP 500 are likely to be due to the high range of variability noted, and not related to a treatment effect.

11.2.17.8.d. Adverse events

Adverse events (AEs) were common in this study. These data are summarized in Table 11.2.25. AEs were more common in FP 500 (80%, 138/173) and SAL 50/FP 500 (78%, 131/169) patients than for placebo (69%, 127/185). AEs occurring at a frequency ≥3% and more frequently with FP 500 or SAL 50/FP 500 than with placebo included headaches, upper respiratory tract infection, viral respiratory infection, candidiasis of the mouth or throat, chest symptoms, sinusitis/sinus infection, hypertension, hoarseness/dysphonia, dyspeptic symptoms, muscle pain, and ear signs and symptoms. AEs coded as "chest symptoms" were reported as chest pain, chest tightness, and chest discomfort [clinstat\copd\sfca3006.pdf, pages 5920-6667]. Throat irritation, upper respiratory inflammation, and muscle cramps and spasms were reported at a frequency ≥3% and more frequently with SAL 50/FP 500 than FP 250 and placebo.

Many of the AEs noted are noted in the labels for Flovent MDI and Flovent Rotadisk. These include upper respiratory tract infection, headaches, candidiasis, viral respiratory infections, nasal congestion, dysphonia, and sinusitis. AEs reported in this study that are not noted in current labeling for other Flovent products include muscle cramps, spasms, and pain, chest symptoms (chest pain, chest tightness), hypertension, dyspeptic symptoms, and ear signs and symptoms. Muscle cramps, spasms, and pain may represent a new safety signal. It is difficult to assess whether other AEs noted in this study that were not noted in current Flovent labeling represent new safety signals because of their low frequencies.

Reviewer comment:
There were many more patients with COPD exacerbations reported for the secondary efficacy endpoint than were reported as AEs.

Table 11.2.25. Adverse events occurring more frequently in FP 500 or SAL 50/FP 500 than in placebo and ≥3%, SCFA3006 [clinstat\copd\sfca3006.pdf, page 174].

Adverse event	Placebo N = 185		FP 500 N = 173		SAL 50/FP 500 N = 169	
	n	(%)	n	(%)	n	(%)
All adverse events	127	(69)	138	(80)	131	(78)
Headaches	25	(14)	35	(20)	30	(18)
URTI	18	(10)	25	(14)	28	(17)
Throat irritation	14	(8)	11	(6)	19	(11)
Upper respiratory inflammation	12	(6)	11	(6)	15	(9)
Viral respiratory infections	6	(3)	17	(10)	14	(8)
Candidiasis mouth/throat	1	(<1)	17	(10)	12	(7)
Nasal congestion/blockage	7	(4)	13	(8)	7	(4)
Muscle cramps and spasms	4	(2)	3	(2)	13	(8)
Chest symptoms	6	(3)	7	(4)	6	(4)
Sinusitis/sinus infection	4	(2)	6	(3)	7	(4)
Hypertension	4	(2)	5	(3)	5	(3)
Hoarseness/dysphonia	4	(2)	9	(5)	5	(3)
Dyspeptic symptoms	1	(<1)	5	(3)	4	(2)
COPD	2	(1)	5	(3)	2	(1)
Muscle pain	1	(<1)	5	(3)	7	(4)
Ear signs and symptoms	2	(1)	3	(2)	4	(2)

AEs beginning after a patient discontinued study medication were infrequent and occurred at similar frequencies in active treatment groups and placebo [clinstat\copd\sfca3006.pdf, page 175]. The highest incidence of AEs was in the first month of treatment (45% placebo, 45% FP 500, 47% SAL 50/FP 500). Throat irritation and dysphonia/hoarseness tended to be more prevalent early in the study [clinstat\copd\sfca3006.pdf, pages 177, 2083-2125]. The most common-drug related AEs included candidiasis of the mouth or throat, throat irritation, hoarseness/dysphonia, and headaches [clinstat\copd\sfca30006.pdf, page 176].

A listing of AEs of low frequency is found in Table 11.2.26. This listing includes AEs that have been associated with use of corticosteroids, such as candidiasis, hoarseness/dysphonia, infection, and AEs of low frequency that suggest an association with FP. There were slightly higher frequencies of infections of various types in FP-treated patients than in placebo-treated patients. Candidiasis and hoarseness/dysphonia are known to be associated with the use of inhaled corticosteroids. Dental and gum disorders of various types occurred slightly more frequently in FP-treated patients, and may be suggestive of a new safety signal. Few cases of osteoporosis, cataracts and ocular pressure disorders were noted, however these AEs were not specifically examined by bone densitometry or formal ophthalmologic examination. The frequency of fractures was 2% (3/169) for SAL 50/FP 500, <1% (1/173) for FP 500, and <1% (1/185) for placebo. Small numbers of other AEs were observed without a strong association with FP 500 or SAL 50/FP 500 [clinstat\copd\sfca3006.pdf, pages 1381-1404].

Table 11.2.26. Selected adverse events of low frequency, SFCA3006 [clinstat\copd\sfca3006.pdf, pages 1381-1404].

Adverse event	Placebo N = 185		FP 500 N = 173		SAL5 50/FP 500 N = 169	
	n	(%)	n	(%)	n	(%)
All adverse events*	127	(69)	138	(80)	131	(78)
Candidiasis mouth/throat	1	(<1)	17	(10)	12	(7)
Hoarseness/dysphonia	4	(2)	9	(5)	5	(3)
Hypertension	4	(2)	5	(3)	5	(3)
Urinary infections	3	(2)	4	(2)	1	(<1)
Bronchitis	1	(<1)	3	(2)	3	(2)
Pneumonia	1	(<1)	3	(2)	2	(1)
Anxiety	2	(1)	2	(1)	5	(3)
Dental discomfort & pain	0	(0)	2	(1)	4	(2)
Contusions and hematomas	1	(<1)	2	(1)	1	(<1)
Depressive disorders	3	(2)	2	(1)	1	(<1)
Cataracts	1	(<1)	2	(1)	0	(0)
Fractures	1	(<1)	1	(<1)	3	(2)
Muscle atrophy weakness & tiredness	0	(0)	1	(<1)	1	(<1)
Hyperglycemia	0	(0)	1	(<1)	1	(<1)
Weight gain	0	(0)	1	(<1)	0	(0)
Bacterial respiratory infections	0	(0)	1	(<1)	0	(0)
Fungal skin infections	0	(0)	1	(<1)	0	(0)
Agitation	1	(<1)	1	(<1)	0	(0)
Mood disorders	0	(0)	1	(<1)	0	(0)
Ocular pressure disorders	1	(<1)	0	(0)	2	(1)
Diabetes mellitus	1	(<1)	0	(0)	2	(1)
Disorders of hard tissues of teeth	0	(0)	0	(0)	1	(<1)
Dental & gum inflammation	0	(0)	0	(0)	1	(<1)
Gastrointestinal hemorrhage	1	(<1)	0	(0)	1	(<1)
Fungal urinary infections	0	(0)	0	(0)	1	(<1)
Fungal reproductive infections	1	(<1)	0	(0)	1	(<1)
Increased blood pressure	0	(0)	0	(0)	1	(<1)
Fungal infections	0	(0)	0	(0)	1	(<1)
Peptic ulcers	1	(<1)	0	(0)	0	(0)
Osteoporosis	1	(<1)	0	(0)	0	(0)

Subgroup analysis of AEs by gender, age, and race will be reviewed in the Integrated Review of Safety section of this document.

Reviewer comment:

The relatively high frequency of oropharyngeal thrush in the groups receiving FP is worth noting and may be indicative of a more globally immunosuppressed condition. There were a few patients reported as having "contusions and hematomas," and one patient was reported to have "skin hemorrhage." Otherwise, there were no other patients who were reported as having bruising or purpura. One would expect a fairly significant number of patients to have had this AE, given the large doses of FP used and given the older ages of the patients studied. Unfortunately this study was not designed to specifically look for cataract or systemic bone effects, both known to be associated with systemic effects of corticosteroids. Ophthalmologic examination and studies to assess osteoporosis would have been helpful to address these concerns.

11.2.17.8.e. Deaths and serious adverse events

There were three patients who died during the conduct of the study. Each of these patients was in the placebo group. There were no patients who died who were treated with active drug. The three deaths in this study are described below.

One patient, #10798, a 66-year old woman, developed severe abdominal pain and was discovered to have adenocarcinoma of the small bowel. She died approximately one month after onset of the pain. The second patient, #11283, was a 60-year old male who was diagnosed as having multiple colonic tumors, and after a subtotal colectomy, developed an aspiration pneumonia and died. The third patient, #11379, was a 69-year old male who was discovered to have recurrent thyroid cancer. This patient had a surgical resection and tracheostomy, but did not receive radiation or chemotherapy and died [clinstat\copd\sfca3006.pdf, pages 178-179, 6667].

There were 39 patients (39/691) who experienced a serious adverse event (SAE) during the treatment phase of the study. The percentage of patients was SAEs during the treatment phase were similar among the treatment groups, with the highest in the FP 500 group (7%, 12/173), followed by placebo (6%, 11/185), and SAL 50/FP 500 (5%, 9/169). SAEs occurring in more than one patient are displayed in Table 11.2.27. SAEs due to chronic obstructive airways disease were most frequent in FP 500 (3%, 6/173) compared with placebo (1%, 2/185) and SAL 50/FP 500 (1%, 2/169). SAEs for pneumonias occurred only in FP 500 (1%, 2/173) and SAL 50/FP 500 (1%, 2/169). Chest symptoms (literal term "chest pain") occurred in equal frequencies for placebo (1%, 2/185) and in SAL 50/FP 500 (1%, 2/169).

Table 11.2.27. SAEs occurring in more than one patient during the treatment period, SFCA3006 [clinstat\copd\sfca3006.pdf, pages 252-253, 1411-1413].

Serious adverse event	Placebo N = 185		FP 500 N = 173		SAL 50/FP 500 N = 169	
	n	(%)	n	(%)	n	(%)
Any serious adverse event	11	(6)	12	(7)	9	(5)
Chronic obstructive airways disease*	2	(1)	6	(3)	2	(1)
Pneumonia	0	(0)	2	(1)	2	(1)
Chest symptoms**	2	(1)	0	(0)	2	(1)

*Includes one FP 500 patient (#10931) with respiratory failure due to COPD exacerbation that was coded as "respiratory failure."
**All events coded as chest symptoms were due to chest pain.

There was one patient in the FP 500 group that had a SAE for fracture. This patient, #11029, was a 69-year old male who was involved in a motor vehicle accident and sustained a concussion and fracture of C1 and C2 vertebrae, but sustained no spinal cord damage [clinstat\copd\sfca3006.pdf, page 289]. There were no other SAEs for fracture.

Reviewer comment:
The higher frequency of SAEs for COPD and pneumonia in the FP 500 and SAL 50/FP 500 groups than in the placebo group is interesting. As noted earlier in this review, AEs for bronchitis and pneumonia were more also more common in FP 500 and SAL 50/FP 500 than in placebo. Although there was a fairly small number of patients with these SAEs, it is possible that this may suggest a higher risk of infection or exacerbation of COPD for FP 500 and SAL 50/FP 500.

11.2.17.8.f. Withdrawals due to adverse events

Withdrawals due to adverse events (AEs) are displayed in Table 11.2.28. Withdrawals due to AEs were most common in the FP 500 group (12%, 20/173), followed by the placebo group (8%, 15/185) and the SAL 50/FP 500 groups (7%, 11/169). Withdrawals due to COPD were most common in the FP 500 group 3%, 6/173), followed by the placebo group (1%, 2/185) and the SAL 50/FP 500 group (1%, 2/169). Withdrawals due to pneumonia were more common in FP 500 (1%, 2/173) and SAL 50/FP 500 (1%, 2/169), than in the placebo group (<1%, 1/185). Candidiasis of the mouth and throat and hoarseness/dysphonia, both known to be associated with the use of inhaled corticosteroids, were most common in the FP 500 group.

Table 11.2.28. Withdrawals due to adverse events occurring in more than one patient, SFCA3006 [clinstat\copd\sfca3006.pdf, page 181].

Adverse event	Placebo N = 185		FP 500 N = 173		SAL 50/FP 500 N = 169	
	n	(%)	n	(%)	n	(%)
Any adverse event	15	(8)	20	(12)	11	(7)
Chronic obstructive airways disease*	2	(1)	6	(3)	2	(1)
Pneumonia	1	(<1)	2	(1)	2	(1)
Candidiasis mouth/throat	0	(0)	2	(1)	0	(0)
Hoarseness/dysphonia	1	(<1)	2	(1)	0	(0)
Chest symptoms**	1	(<1)	0	(0)	2	(1)
Malaise and fatigue	2	(1)	0	(0)	0	(0)
Headaches	2	(1)	0	(0)	0	(0)

*Includes one FP 500 patient (#10931) with respiratory failure due to COPD exacerbation that was coded as "respiratory failure."
**All events coded as chest symptoms were due to chest pain.

Reviewer comment:
As with AEs and SAEs, withdrawals due to pneumonia were more common for FP 500 and SAL 50/FP 500 than for placebo. Withdrawals due to COPD were most common in the FP 500 group, with similar frequencies in placebo and SAL 50/FP 500.

11.2.17.8.g. Vital signs

There were no clinically significant changes from baseline in median values of vital signs for any of the treatment groups [clinstat\copd\sfca3006.pdf, pages 1521-1520].

11.2.17.8.h. Physical examination

Physical examinations were performed at Screening and at the end of the study [clinstat\copd\sfca3006.pdf, page 74]. Data was recorded on subject progress notes, but not on case report forms (CRFs). Physical examination abnormalities were recorded as

AEs on the CRFs, but no summary of physical examinations was provided [NDA 20-833, SE1-004, BM, 9/17/01, page 3].

11.2.17.8.i. Oropharyngeal examination

Oropharyngeal examinations were performed at the screening visit, at each treatment visit and at the end of the study [clinstat\copd\sfca3006.pdf, page 74]. Data was recorded on subject progress notes, but not on case report forms (CRFs). Oropharyngeal examination abnormalities were recorded as AEs on the CRFs, but no summary of oropharyngeal examinations was provided [NDA 20-833, SE1-004, BM, 9/17/01, page 2].

11.2.17.8.j. Laboratory studies

Small numbers of patients had shifts in % lymphocyte, % neutrophils, and WBC counts from baseline at Weeks 12 and 24 and Discontinuation.

There was a decrease in % lymphocytes in patients treated with FP 500 (6%, 7/119) and SAL 50/FP 500 (4%, 5/130), but not placebo (<1%, 1/131) at week 12. The frequency of low % lymphocytes were similar among treatment groups at Week 24 and at endpoint [clinstat\copd\sfca3006.pdf, pages 182, 1420-1430].

Shifts in % neutrophils and WBC were similar among treatment groups at Week 12, Week 24, and Discontinuation [clinstat\copd\sfca3006.pdf, pages 182, 1420-1430].

There was a greater percentage of patients who had increases from baseline in glucose at Discontinuation for FP 500 (9%, 5/58) and SAL 50/FP 500 (13%, 6/47) than with placebo (5%, 3/58). There was no meaningful difference in the percentage of patients who had increases from baseline in glucose at Week 12 between FP 500 (3%, 4/122), SAL 50/FP 500 (5%, 7/131), and placebo (8%, 11/131). There was no meaningful difference in the percentage of patients who had increases from baseline in glucose at Week 24 for FP 500 (6%, 6/98), SAL 50/FP 500 (6%, 6/98), and placebo (7%, 8/111) [clinstat\copd\sfca3006.pdf, pages 182, 1420-1430]. It should be noted that the sponsor defined an exceptionally liberal definition for high glucose, >175 mg/ml. It is likely that this liberal definition of high glucose would decrease the sensitivity of detecting a difference between treatment groups for this laboratory test [clinstat\copd\sfca3006.pdf, page 6720].

There were no meaningful differences among treatment groups in the percentage of patients with changes in other laboratory studies [clinstat\copd\sfca3006.pdf, pages 182, 1420-1430].

Reviewer comment:
Lympholysis is associated with systemic effects of corticosteroids. The higher percentage of patients with decrease in % lymphocytes in FP 500 and SAL 50/FP 500 at Week 12 could be a manifestation of a systemic corticosteroid effect. This effect was not noted at Week 24 and at Discontinuation, perhaps due to dropouts. This may be a manifestation of systemic corticosteroid activity. The higher percentage of patients with increases from baseline in glucose at discontinuation could also be a manifestation of a systemic

corticosteroid effect. This effect was not noted at Week 12 or Week 24. It is possible that this signal would have been stronger if the sponsor had not chosen such a liberal definition of elevated blood glucose.

There were few patients with hematology or chemistry results outside of values specified as normal by the sponsor. The few patients with results outside of the range specified as normal by the sponsor were evenly distributed between treatment groups [clinstat\copd\sfca3006.pdf, pages 1440-1461].

11.2.17.8.k. ECGs

There were a few clinically significant changes in ECGs from baseline for each of the treatment groups in the study. Patients with clinically significant changes in ECGs are summarized in Table 11.2.29. There was no significant difference between treatment groups in the number or character of the changes in ECGs.

Table 11.2.29. Patients with clinically significant changes in ECGs from baseline, SFCA3006 [clinstat\copd\sfca3006.pdf, pages 188, 191, 1474-1485].

Patient number	Treatment	Time of abnormality	ECG abnormality
11343	Placebo	Discontinuation	Subendocardial ischemia
11384	Placebo	Week 12	P mitrale
9250	FP 500	Discontinuation	Sinus tachycardia, repolarization abnormalities
9846	SAL 50/FP 500	Discontinuation	Nodal tachycardia
10588	SAL 50/FP 500	Week 12	Atrial flutter

Median QTc intervals by both Bazette and Fridericia formulae were similar for each of the treatment groups [clinstat\copd\sfca3006.pdf, pages 190-191, 1486-1493]. Two patients with QTcB greater than 470 msec were treated with FP 500, and six were treated with SAL 50/FP 500. These patients are summarized in Table 11.2.30.

Table 11.2.30. Patients with QTcB intervals >470 msec post-screening, SCFA3006 [clinstat\copd\sfca3006.pdf, pages 9181-9185]

Patient number	Treatment	Screening QTcB, msec	Week 12 QTcB, msec	Week 24 or DC QTcB, msec
11539	FP 500	456.8	480.8	454.4
9711	FP 500	488.0	NA	480.7
10185	SAL 50/FP 500	493.3	485.6	482.4
10237	SAL 50/FP 500	463.8	517.7	488.6
10730	SAL 50/FP 500	440.0	458.0	471.4
11128	SAL 50/FP 500	481.7	481.7	511.8
15878	SAL 50/FP 500	459.6	484.4	458.0
9691	SAL 50/FP 500	406.6	499.9	420.1

Reviewer comment:
There was a higher incidence of patients with QTcB >470 post-screening in the FP 500 and SAL50/FP 500 groups than in the placebo group. These findings were present in only small number of patients, however, and could be a chance occurrence.

11.2.18. References

1. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152:S77-S121.

2. Anthonisen NR, Wright EC, et al. Bronchodilator response in chronic obstructive pulmonary disease. Am Rev Respir Dis 1986;133: 814-819.

3. Barnes PJ. Chronic Obstructive Pulmonary Disease. New Engl J Med 2000;343:269-280.

4. Eliasson O and Degraff AC. The Use of Criteria for Reversibility and Obstruction to Define patient Groups for Bronchodilator Trials. Am Rev Respir Dis 1985;132:858-864.

5. National Asthma Education and Prevention Program. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Publication Number 97-4051. Bethesda, MD, 1997.

6. 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.

7. 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;109:348-352.

8. Mahler DA, Weinberg DH, et. al. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 1984;97:751-758.

9. Anthionisen NR, Manfreda J, Warren CPW, et. al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Int Med 1987;106:196-204.

10. Guyatt GH, Berman LB, Townsend M, et. al. A measure of quality of life for clinical trials in chronic lung diseases. Thorax 1987;42:773-778.

11. Pulmicort package insert. Astra Inc., USA. Westborough, MA October 1998.

12. Scott MB, Skoner DP. Short term and long term safety of budesonide inhalation suspension in infants and young children with persistent asthma. J Allergy Clin Immunol 1999;104: S200-209.

11.3. SFCA3007: A randomized, double-blind, parallel-group trial of 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

Study initiated: 11/10/98
Study completed: 8/2800
Study report dated: 3/21/01
[clinstat\copd\sfca3007.pdf, page 1]

11.3.1. Summary and reviewer's conclusion of study results

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter trial designed to evaluate the efficacy and safety of salmeterol xinafoate (SAL) 50 mcg BID, fluticasone propionate FP 250 mcg BID, the combination of SAL 50 mcg /FP 250 mcg BID, and placebo in patients with chronic obstructive pulmonary disease (COPD).

As with studies FLTA3025 and SFCA3006, the proportion of patients with reversibility enrolled in this study is much higher than is found in the population of COPD patients at large[1-4]. Of all study patients, there were 55% of patients in this study who were considered to be reversible (≥12% and ≥200 mL increase in FEV_1 with bronchodilator). In addition, the degree of reversibility for the reversible population was high—29.8%. The mean degree of reversibility in the 45% of the patients who comprised the "non-reversible" population, 8.6%, was similar to the mean reversibility described in studies of the COPD population as a whole[1-4], as broadly stated in the labeling for the proposed indication. This is a critical deficiency of this study. Non-Caucasian patients, who make up a substantial proportion of the COPD population[1, 3], were also under-represented in this study.

The primary efficacy endpoint was the mean change in FEV_1 from baseline to study endpoint. The primary efficacy endpoint supports the efficacy of FP 250 compared to placebo in this population. The mean change from baseline in FEV_1 for the FP 250 group at endpoint was 109 mL, 108 mL more than the placebo group at endpoint. This comparison was statistically significant at $p < 0.001$. This change corresponds to an effect size of 8.7%.

Small decreases in the Chronic Bronchitis Symptom Questionnaire (CBSQ) were noted for all active treatment groups at Weeks 1 to 24 and at endpoint. In general, decreases were numerically superior to the placebo group, which also showed an improvement in score. Decreases in the CBSQ were not clinically significantly different from the placebo group for any of the active treatment groups at any time, however. The differences between the Transitional Dyspnea Indices (TDIs) for FP 250 and placebo were not greater than the minimally clinically significant TDI of 1.0 point at Endpoint, or at any of the 10 interim measurements from Weeks 1 to 24. Neither the CBSQ nor the TDI provide support for the efficacy of FP in COPD.

The incidence of COPD exacerbation and moderate to severe COPD exacerbation was slightly higher for FP 250 than for the other treatment groups. The proportion of patients who withdrew from the study, and withdrawals due to COPD exacerbation were similar across treatment groups. A non-standard definition of COPD exacerbation was used that would have favored the finding of efficacy of FP in a COPD population with a high degree of reversibility. As a general statement, incidence or severity of COPD exacerbations did not provide support for the efficacy of FP in COPD.

A small mean increase from baseline in AM PEFR was noted in FP 250 (11.3 L/min) and SAL 50 (14.7 L/min) groups at the end of the study. A larger mean increase was observed in the SAL 50/FP 500 group (30.6 L/min). Overall, the SAL 50 and SAL 50/FP 250 groups had small decreases in the number of puffs of Ventolin used per day. The FP 250 and placebo groups had little change in the number of puffs of Ventolin used per day. All active treatment groups had small increases in the percent of days without Ventolin use compared with placebo. Overall, the FP 250, SAL 50, and SAL 50/FP 250 groups had very small decreases from baseline in the number of awakenings per night and small increases in the percent of nights with no awakenings requiring Ventolin use. Of the active treatment groups, the FP 250 group had the smallest decrease number of awakenings per night requiring Ventolin and the smallest increase in percent of nights with no awakenings.

Increases in the Overall score of the Chronic Respiratory Disease Questionnaire (CRDQ), a health-related quality of life instrument, were less than the specified clinically significant difference from the change in baseline in the placebo, and provide no support for efficacy. This is an important negative finding, since one of the stated objectives of this study was to compare the health-related quality of life in COPD patients receiving active treatment compared to placebo over this 24-week study.

The sponsor provided an analysis of efficacy by smoking status. In general, efficacy was favored for the FP 250 and SAL 50/FP 250 groups in patients who stopped smoking prior to the conduct of the study, compared with patients who continued to smoke during the study.

The sponsor performed a subgroup analysis of efficacy for non-reversible patients. This subgroup analysis demonstrated numerically greater changes in FEV_1 from baseline at study endpoint for all active treatments compared with placebo. The difference from placebo for mean change from baseline at endpoint for the reversible group for FP 250 was 153 mL. This was 98 mL greater than the difference from placebo for mean change from baseline at endpoint for the non-reversible group, which for FP 250 was 55 mL. Secondary endpoints provide no support for the efficacy of FP 250 in non-reversible population.

Data for cosyntropin stimulation testing show no evidence of HPA-axis suppression for FP 250 or SAL 50/FP 250. Duration of exposure was inadequate to fully assess safety, since the short efficacy endpoints in this study fail to address the safety consequences of long-term (>6 months) use of high-dose, high-potency inhaled corticosteroids,

particularly with regard to bone, dermatological, and ocular adverse events, was well as the potential for HPA axis recovery. AEs occurred in 70% of FP 250-treated patients, 70% of SAL 50/FP 250-treated patients, and in 64% of placebo-treated patients. AEs occurring more frequently with FP 500 and SAL 50/FP 500 than with placebo included headaches, musculoskeletal pain, sinusitis, throat irritation, candidiasis of the mouth/throat, viral respiratory infection, upper respiratory tract inflammation, ear signs and symptoms, chest symptoms, sinusitis/sinus infection, muscle injuries, hoarseness/dysphonia, fever, muscle cramps and spasms, pain, epistaxis, edema and swelling, dizziness, nasal congestion/blockage, and constipation. There were no deaths in this study. The percentage of patients was SAEs during the treatment phase was similar among the treatment groups, with the highest in the placebo group (6%, 11/185), followed by FP 250 (5%, 10/183), and SAL 50/FP 500 (4%, 8/178). Withdrawals due to AEs occurred at similar frequencies among treatment groups. Vital signs and ECGs showed no clinically significant differences between treatment groups.

In summary, based on the primary endpoint, efficacy was demonstrated for the FP 250 group in this study. An open issue is whether the study population adequately reflects the overall population of US COPD patients, although both the reversible and the non-reversible subgroups showed some change from baseline for this endpoint. Subgroup analysis demonstrated a numerically greater effect in the reversible compared to the non-reversible population. Efficacy measurements that supported FP 250 included FEV_1, and PEFR. Other measures of bronchodilator use and COPD exacerbations did not support the efficacy of FP 250. The health-related quality of life instrument (CRQD), the Transitional Dyspnea Index (TDI), and the Chronic Bronchitis Symptom Questionnaire (CBSQ) provided no support for the efficacy of FP 250. Data for the safety endpoints chosen for this study are generally inadequate to make a determination of the long-term safety of FP in the population studied because the study was of insufficient duration for known systemic corticosteroid effects such as osteoporosis, cataracts, hypertension, diabetes, or skin changes such as easy bruisability or skin thinning to become apparent. It should be noted that the study was not designed to specifically assess these AEs, and patients with prior pathological fracture, osteoporosis, significant hypertension, or diabetes, cataracts, or glaucoma were specifically excluded. Although not specifically addressed in this document (see review by Dr. L. Gilbert-McClain), the safety issue of long-term systemic corticosteroid effects will be similar for SAL 50/FP 500 (Advair®) in this population.

11.3.2. Study design

This was a randomized, double-blind, placebo-controlled, parallel group, multicenter trial. Approximately 600 patients were to be randomized at approximately 55 study centers. A total of 723 patients were enrolled at 76 study sites [clinstat\copdsfca3007.pdf, pages 80, 7105].

11.3.3. Objectives

This study had three objectives [clinstat\copd\sfca3007.pdf, pages 37, 7104]. They were:

1. To compare the efficacy of SAL 50 mcg BID, FP 250 mcg BID, the combination of SAL 50 mcg /FP 250 mcg BID, and placebo when administered by the Diskus over a 24-week treatment period in the treatment of COPD patients
2. To compare the safety of SAL 50 mcg BID, FP 250 mcg BID, the combination of SAL 50 mcg /FP 250 mcg BID, and placebo when administered by the Diskus over a 24-week treatment period in the treatment of COPD patients
3. To compare quality of life (QOL) in COPD patients receiving FSAL 50 mcg BID, FP 500 mcg BID, the combination of SAL 50 mcg/FP 250 mcg BID, and placebo when administered by the Diskus over a 24-week treatment period

11.3.4. Inclusion criteria

Inclusion criteria for this study are listed below. These reflect protocol amendments. [clinstat\copd\sfca3007.pdf, pages 7105-7108]:

1. Age ≥40 years
2. Male or female gender
   - A female was eligible to enter and participate if she was of non-childbearing potential or was of child-bearing potential with a negative serum pregnancy test at screening and an acceptable method of contraception
3. Established history of COPD in accordance with the American Thoracic Society (ATS) definition[1]:
   - Abnormal tests of expiratory flow that do not change markedly over periods of several months
   - Airflow obstruction may be structural or functional
   - Bronchial hyperreactivity may be present as measured by improvement after inhalation of a beta-adrenergic agent or worsening after inhalation of methacholine or histamine
   - Emphysema and chronic bronchitis are incorporated into COPD, and any individual may have one or both of these conditions
4. A history of cough productive of sputum on most days for at least 3 months of the year, for at least 2 years, that is not attributed to another disease process. Patients must have a score of ≥4 on the Chronic Bronchitis Symptom Questionnaire (CBSQ) at Treatment Day 1
5. Current or prior history of at least 20 pack-years of cigarette smoking. If the patient is an ex-smoker, smoking must have been discontinued for at least 6 months prior to screening. Current smokers were counseled regarding the hazards of continuing to smoke and the benefits of discontinuation. Patient who decided to stop smoking at the Screening Visit were not eligible for participation in the study. Patients making a conscious decision to stop smoking at anytime during the study and who refrain from smoking for >4 weeks were to be discontinued from the study. Patients who start smoking during the study and smoke for at least 7 consecutive days were to be discontinued from the study.
6. Severity
   - Baseline FEV_1 <65% or predicted but >0.70 L, or FEV_1 <0.70 L and >40% but still <65% of the predicted normal value (Crapo), and
   - FEV_1/FVC ratio of ≤70% at screening
7. A score if ≥2 in the Modified Medical Research Council Dyspnea Scale at screening:

Modified Medical Research Council Dyspnea Scale[clinstat\copd\sfca3007.pdf, page 7154]

Grade	Description
0	Not troubled with breathlessness except with strenuous exercise
1	Troubled by shortness of breath when hurrying on the level or walking up a slight hill
2	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	Stops to breathe after walking about 100 yards or after a few minutes on the level
4	Too breathless to leave the house or breathless when dressing or undressing

8. Has not received systemic corticosteroid and/or high-dose inhaled corticosteroid therapy for at least 6 weeks prior to the Screening Visit. High dose inhaled corticosteroids are defined as:
   - Beclomethasone dipropionate ≥1008 mcg/day
   - Triamcinolone acetonide ≥1600 mcg/day
   - Flunisolide ≥2000 mcg/day
   - Fluticasone propionate MDI ≥880 mcg/day
   - Fluticasone propionate Diskus ≥1000 mcg/day
   - Budesonide ≥1600 mcg/day
9. Able to tolerate a 2-week run-in period during which the following medications were discontinued:
   - Inhaled corticosteroids
   - Ipratropium
   - Nedocromil sodium and cromolyn sodium
   - Anti-leukotriene agents
   - Intranasal steroids
   - Any beta-agonist other than Ventolin
   - Theophylline, unless at a stable dosage for 14 days
10. Able to complete a diary card and subject questionnaires
11. Able to effectively use the Diskus and MDI inhalers, spirometry equipment, and mini-Wright peak flow meter
12. Provide a signed, dated, and witnessed informed consent

Reviewer comment:

The sponsor's paraphrase of the ATS definition of COPD places an emphasis on reversibility. While reversible obstruction does occur in the COPD population, it should not be considered central to the definition. The process underlying COPD is one of progressive loss of lung tissue, leading primarily to structural obstruction as opposed to functional [1]. The ATS definition follows:

> *"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."[1]*

The inclusion criteria allow for patients who were receiving fairly large doses of inhaled corticosteroids prior to enrollment. This may have the effect of enriching the study for patients who were responsive to inhaled corticosteroids, as one would expect patients with no response or a poor response to have their treatment discontinued.

11.3.5. Exclusion criteria

Exclusion criteria for this study are listed below. These reflect protocol amendments. [clinstat\copd\sfca3007.pdf, pages 7108-7111]:

1. Current diagnosis of asthma in accordance with the ATS definition:
   - Increased responsiveness of the tracheobronchial tree
   - Paroxysms of dyspnea, wheezing, and cough, which may vary from mild and almost undetectable to severe and unremitting
   - Primary physiological manifestation of hyperresponsiveness is variable airway obstruction
   - Variability may be manifest in improvements of obstruction following bronchodilators or corticosteroids or increased obstruction caused by drugs or other stimuli
2. Requirement for any of the following medications:
   - Beta-blockers
   - Digitalis
   - Ketoconazole, fluconazole
   - Monoamine oxidase inhibitors
   - Tricyclic antidepressants
   - Phenothiazines
   - Immunosuppressive agents including cyclosporine, methotrexate, and gold
   - Use of inhaled short-acting bronchodilator within 6 hours prior to screening
   - Use of any short acting form of oral beta-agonist, short-acting form of theophylline or other bronchodilator within 12 hours prior to screening
   - Use of any twice daily form of an inhaled or oral beta-agonist or controlled-release form of theophylline within 48 hours of screening
3. Requirement for pulmonary rehabilitation that is initiated during the study. Participation in a maintenance pulmonary rehabilitation program was allowed.
4. A respiratory disorder other than COPD (e.g., lung cancer, bronchiectasis, sarcoidosis, tuberculosis, lung fibrosis), history of lobectomy within one year of the screening visit. Patients with alpha-1-antitrypsin deficiency were excluded.
5. Requirement for a continuous positive pressure device for COPD or sleep apnea.
6. Any significant concurrent diseases that would place the subject at risk, interfere with clinical evaluations, or influence study participation, including but not limited to:
   - History of symptomatic or clinically significant pathologic fractures
   - Clinically significant cardiac disease
   - Systemic arterial hypertension if the subject is poorly compliant with medications, likely to require frequent changes in medication during the study period, or requires therapy with beta-blockers
   - Hepatic disease

- Renal disease requiring dialysis or at risk of requiring dialysis within 6 months of screening
- Neurologic disease
- Uncontrolled hyperthyroidism or hypothyroidism
- Diabetes mellitus that is either poorly controlled or complicated by significant renal or cardiovascular disease
- Severe hematologic disease
- Active peptic ulcer
- Disorders of humoral or cellular immunity
- Cushing's disease
- Addison's disease
- Presence of glaucoma requiring treatment with non-selective beta-blockers
- History of malignancy except for localized basal cell or squamous cell carcinoma of the skin that has been resected and patients curatively treated and disease free for at least 2 years may be considered for entry after discussion with the Glaxo Wellcome medical advisor
- Inadequately controlled psychiatric illness
- Mental retardation
- Peripheral vascular disease
- Use of a pacemaker

7. Requirement for supplemental oxygen with the following exceptions:
   - Lives at an altitude above 3000 feet and does not require more than 2 L of oxygen per minute for more than 12 hours per day
   - Does not require more than 2 L of oxygen per minute for more than 2 hours per day for exertion
8. A known or suspected hypersensitivity to inhaled corticosteroids, beta-agonists or lactose. Gastrointestinal lactose intolerance is not an exclusion criterion.
9. A known or suspected history of alcohol or drug abuse within the previous two years
10. 12-lead ECG at screening is abnormal and clinically significant
11. A moderate or severe exacerbation of COPD during the run-in period
12. Chest X-ray reveals clinically significant abnormalities not believed to be due to the presence of COPD
13. Received an investigational drug within 30 days prior to entry into the run-in period
14. A participating investigator, sub-investigator, study coordinator, or employee of a participating investigator, or an immediate family member of the aforementioned
15. An abnormal and clinically significant laboratory test a the screening visit which is still abnormal on repeat analysis
16. Previous participation in a fluticasone and/or salmeterol study via the Diskus for COPD

Reviewer comment:
The sponsor uses an ATS definition of asthma from 1987. This definition makes no reference to the role of inflammation in asthma. A more appropriate definition might be the National Asthma Education and Prevention Program (NAEPP) definition of asthma, which refers to inflammation as well as reversible airway obstruction[5]. Taken strictly, this exclusion criterion would exclude all patients who have reversible airway obstruction.

11.3.6. Protocol amendments

There were three protocol amendments, dated 12/17/98, 2/14/00, and 6/23/00 [clinstat\copd\sfca3007.pdf, page 7208]. A substudy protocol for genotyping during the study was also added on 11/4/98 [clinstat\copd\sfca3007.pdf, page 7214]. This substudy will not be reviewed.

The FEV_1/FVC ratio required for entry into the study was changed from ≤65% to ≤70% in Protocol Amendment 1 [clinstat\copd\sfca3007.pdf, page 7198]. Originally, the protocol called for approximately 600 patients to be randomized at approximately 55 study centers. The protocol was amended on 2/15/00 in Protocol Amendment 2 to allow for approximately 720 patients to be randomized at approximately 75 study centers and to provide a subgroup analysis of patients who had an increase in percent of predicted FEV_1 less than 10% after albuterol at the screening visit [clinstat\copd\sfca3007.pdf, pages 7206]. The protocol was amended to provide subgroup analyses of former smokers, and of current smokers in Protocol Amendment 3 [clinstat\copd\sfca3007.pdf, pages 7212].

Reviewer comment:
The effect of the change in the FEV_1/FVC ratio would be to allow entry of patients with both those with milder obstruction (who would be perhaps more likely to have reversibility) and those with very severe obstruction with accompanying air trapping. This amendment was made after the study had been started. The inclusion criteria specifying the FEV_1 and the level of dyspnea will minimize any impact of this change. Other protocol amendments otherwise included minor changes to wording and study design that had little impact on the evaluation of efficacy or safety.

11.3.7. Study procedures

Study procedures are displayed in Table 1.3.1. Patients provided an informed consent, and received a medical history and physical examination at the screening visit. Chest X-ray, pregnancy test, screening labs, and ECGs were performed. Spirometry with assessment of reversibility was also performed. Reversibility was assess by performing spirometry 30 minutes after patient self-administration of 4 puffs of Ventolin MDI without a spacer or holding chamber [clinstat\copd\sfca3007.pdf, page 7118].

There was a two-week, single blind, run-in period for patients meeting entrance criteria. Patients discontinued all prohibited concurrent medications and were given Ventolin MDI or nebules to be used as needed for the duration of the trial, including the run-in. Patients received placebo via the Diskus BID during the run-in [clinstat\copd\sfca3007.pdf, pages 7118-7119]. The purpose of the single blind run-in

period was to establish baseline pulmonary function and diary card data for at least 10 of the 14 days. Patient compliance with medication and recording of diary data was also assessed [clinstat\copd\sfca3007.pdf, page 7118]. Patient were to record daily morning PEFRs, nighttime awakenings requiring Ventolin use, use of rescue Ventolin, and any medical problems experienced [clinstat\copd\sfca3007.pdf, page 7119].

Criteria for patients to be eligible for randomization included the following [clinstat\copd\sfca3007.pdf, page 7119]:

- At least 70% compliant with study medication during the run-in
- Completed diary data for at least 10 of the 14 days of the run-in
- Had not started or stopped smoking during the run-in
- Proficiency in use of the peak flow meter
- Able to safely withhold prohibited study medications
- Had not experienced a moderate or severe COPD exacerbation
- Scores ≥4 on the Chronic Bronchitis Symptom Questionnaire (CBSQ)

Patients who completed the run-in period and met all randomization criteria were assigned to one of four double-blind treatments via the Diskus for 24 weeks [clinstat\copd\sfca3007.pdf, pages 7111-7112]:

- FP 250 mcg BID via Diskus (1 inhalation BID)
- Salmeterol (SAL) 50 mcg BID via Diskus (1 inhalation BID)
- Salmeterol (SAL) 50 mcg/FP 250 mcg via Diskus (1 inhalation BID)
- Placebo via Diskus BID

Assignment to study drug was to be stratified according to the patients' response to reversibility testing with Ventolin at screening to a non-reversible group and a reversible group. Non-reversible patients were defined as having an absolute volume increase <200 mL or an absolute volume increase of ≥200 mL with baseline FEV_1 reversibility of <12%. Reversible patients were defined as having an absolute volume increase ≥200 mL with baseline FEV_1 reversibility of ≥12% [clinstat\copd\sfca3007.pdf, page 7113].

Reviewer comment:
The definition of reversibility is critical for this study. In addition, the proportion of patients with reversible obstruction is also critical, even if the proportion in each of the four treatment groups is similar. FP and SAL are effective for treatment of asthma, and inclusion of a high proportion of patients with a significant degree of reversibility would be likely to result in an overstatement of efficacy for the entire group. Although assignment to study drug was stratified according to reversibility based on the above definition, no analysis was planned or provided for these subgroups. Instead, subgroup analysis was provided for subgroups based on a different definition. This issue and its effects are discussed in Section 11.3.16.1 of this document, "Data sets analyzed".

Patients were evaluated weekly for the first four weeks of treatment, every two weeks until week 8, and then every four weeks for the remainder of the study. Patients who developed an exacerbation could be treated with antibiotic therapy as an outpatient for two exacerbations, but were discontinued from the study if a third exacerbation occurred.

Subjects with exacerbations requiring treatment with systemic corticosteroids were to be discontinued from the study [clinstat\copd\scfa3007.pdf, page 7015].

Patient evaluations at each of the clinic visits included spirometry. Symptoms were also evaluated with the Baseline/Transition Dyspnea Index (BDI/TDI), Chronic Bronchitis Symptom Questionnaire (CBSQ), and assessment of the severity of any COPD exacerbations since the last evaluations. Health outcomes were assessed with the Chronic Respiratory Disease Questionnaire (CRDQ), a health-related quality of life instrument [clinstat\copd\sfca3007.pdf, page 7119]. The BDI/TDI, CBSQ, and CRDQ instruments and the instrument for assessment of COPD exacerbations are described below in Section 11.3.12, Assessment of signs and symptoms. Cosyntropin stimulation testing was performed at selected sites.

Patients completed diary cards during the treatment period. Patients measured PEFRs in triplicate prior to the morning dose of study medication. The highest of 3 PEFR values was recorded on diary card. Patients also were to record nighttime awakenings requiring Ventolin use, the use of supplemental Ventolin, any medical problems, any need for other concomitant medication, and AEs [clinstat\copd\sfca3006.pdf, page 7123].

Table 11.3.1. Study outline, SFCA3007 [clinstat\copd\sfca3007.pdf, page 7202].

	Screen	Run-in	Double-blind treatment period											DC
Visit number			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
Treatment Day/Week		**Day –14 to 1**	**Day 1**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 6**	**Wk8**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	
Informed consent	X													
Medical history	X													
Smoking cessation counseling	X												X	X
Chest X-ray	X													
Physical examination	X												X	X
Pregnancy test	X									X			X	X
Reversibility test	X													
Review inhalation technique	X		X	X	X	X	X	X	X	X	X	X		
Medical Research Council Questionnaire	X													
Clinical laboratory tests	X									X			X	X
12-lead ECG and rhythm strip	X									X			X	X
Vital signs	X		X	X	X	X	X	X	X	X	X	X	X	X
Cosyntropin stimulation testing*			X										X	X
Oropharyngeal exam	X		X	X	X	X	X	X	X	X	X	X	X	X
Review smoking status			X	X	X	X	X	X	X	X	X	X	X	X
AE detection				X	X	X	X	X	X	X	X	X	X	X
Spirometry testing	X		X	X	X	X	X	X	X	X	X	X	X	X
Exacerbation assessment			X	X	X	X	X	X	X	X	X	X	X	X
Dispense/review diary card	X		X	X	X	X	X	X	X	X	X	X	X	X
Chronic bronchitis symptom questionnaire	X		X	X	X	X	X	X	X	X	X	X	X	X
BDI/TDI dyspnea scale				X	X	X	X	X	X	X	X	X	X	X
Quality of life questionnaire			X		X		X		X				X	X
Dispense PEFR devices and Ventolin MDI/nebules	X		X	X	X	X	X	X	X	X	X	X		
Dispense study medication			X				X		X	X	X	X		
Concurrent medication assessment	X		X	X	X	X	X	X	X	X	X	X	X	X
Discharge from study													X	X

*Selected sites

11.3.8. Allowable concurrent medications

Allowable concurrent medications included [clinstat\copd\sfca3007.pdf, page 7114]:

- Inhaled Ventolin MDI and/or nebules, provided by the sponsor for use as relief medication. Ventolin was to be withheld for at least 6 hours prior to each treatment visit.
- Antibiotics were permitted for treatment of two exacerbations. Patients were dropped from the study if a third COPD exacerbation occurred.
- Antidepressants other than MAO inhibitors and tricyclic antidepressants
- Theophylline, if on a stable dose for at least one month prior to screening

11.3.9. Prohibited medications

The following medications were prohibited [clinstat\copd\scfa3007.pdf, page 7115]:

- Corticosteroids other than the study medication
- Beta-agonists other than the Ventolin supplied by the sponsor
- Concurrent use of any other prescription or over-the-counter medication which may affect the course of COPD or interact with study medications. These medications were to be discontinued at least 2 weeks prior to randomization.

11.3.10. Drug product and placebo

The sponsor provided the following study treatments [clinstat\copd\sfca3007.pdf, pages 46-47]:

- Placebo Diskus, for the single-blind run-in period and 24-week treatment period
- FP Diskus 250 mcg, 1 puff BID for the 24-week double-blind study period
- SAL Diskus 50 mcg, 1 puff BID for the 24-week double-blind study period
- SAL 50 mcg/FP Diskus 250 mcg, 1 puff BID for the 24-week double-blind study period
- Market-image Ventolin MDI and nebules for each subject as rescue medication
- Cortrosyn 0.25 mg injection for cosyntropin stimulation testing at selected sites

The batch numbers of medication were used in this study are displayed in Table 11.3.2.

Table 11.3.2. Batch numbers of study medication, SFCA3007 [clinstat\copd\scfa3007.pdf, page 47].

Product	Batch numbers
Placebo Diskus	WP25L4 WP31R9 WP2GHW
FP Diskus 250 mcg	U98/028A B006597
SAL Diskus 50 mcg	WP2D8B WP2NLT WP2T35 B003516
SAL Diskus 50 mcg/FP Diskus 250 mcg	U97/060C WP2PY5 E99B157 E99B158
Ventolin MDI, 90 mcg/puff	7ZP0053 7ZP0727 8ZP0909 9ZP1288 0ZP0164

Product	Batch numbers
Ventolin nebules, 0.098%, 2.5 mg/3 mL	980905 990903
Cortrosyn 0.25 mg injection	2240697731 2300199731 2310299731

The sponsor states that the formulations of Flovent used in this study were representative of the commercial product in terms of input materials, scale of manufacture, manufacturing equipment, and manufacturing process. The only differences between the batches of Flovent that were supplied for this study and the commercial product was the device coloration. All batches of Ventolin nebules and Ventolin MDI used in this study were the approved commercial product. The placebo used in this study was identical to the active product used in this study except for the absence of active drug [NDA 20-833, SE1-004, 9/17/01, page 3].

11.3.11. Assessment of compliance

Patient compliance with the drug dosing schedule was determined from the dose counter on the Diskus devices. Patients who were less than 70% compliant with the use of study medication during the 2-week run-in were not eligible to be randomized into the study [clinstat\copd\scfa3007.pdf, pages 71, 7121].

11.3.12. Assessment of signs and symptoms

Patient COPD symptoms were evaluated with the Chronic Bronchitis Symptom Questionnaire (CBSQ), Baseline/Transition Dyspnea Index (BDI/TDI), and assessment of the severity of any COPD exacerbations since the last evaluations. These instruments are described below.

The CBSQ was composed of selected questions from the Petty Subject Evaluation Questionnaire[6]and the Revised Global Petty Questionnaire for Ease of Cough and Sputum Clearance[7]. The CBSQ evaluated cough frequency and severity, sputum release, and chest discomfort on a 0 to 4, 5-point scale. Individual scores were summed to provide a Global Assessment Score (GAS). As noted in the inclusion criteria, patients must have had a GAS of ≥4 at Treatment Day 1 to qualify for the study [clinstat\copd\sfca3007.pdf, pages 7122, 7133].

Additional data describing the CBSQ were included with the application. These data describe the administration of the CBSQ. The patient was allowed to read each question along with the interviewer and verbally select the response that best described the status of that particular symptom on a typical day during the past week. After reading the question, as written, with the subject, the interviewer used discussion questions and observations to assist the subject in providing as precise an answer as possible [clinstat\other\cbsqvalidationdocument.pdf, page 6]. A Minimally Clinically Important Change (MCIC) for the CBSQ was determined to be a change from baseline of 1.4 in the GAS [clinstat\other\cbsqvalidationdocument.pdf, page 11]. The calculation of the MCIC assessed the change in GAS for individual subjects by collecting them into one of four categories to assess a Global Rating of Change (GRC) [clinstat\other\cbsqvalidationdocument.pdf, pages 8-9]:

1. GRC = 0, ±1: No change in symptoms of chronic bronchitis
2. GRC = ±2, ±3: A minimal change in symptoms of chronic bronchitis
3. GRC = ±4, ±5: A moderate change in symptoms of chronic bronchitis
4. GRC = ±6, ±7: A large change in symptoms of chronic bronchitis

However the validation package indicates that there was poor correlation between the GAS and the GRC used to calculate the MCIC. Pearson and Spearman's correlation coefficients between GAS and GRC were only from 0.25 to 0.34 [clinstat\other\cbsqvalidationdocument.pdf, page 9]. Furthermore, large standard deviations in the GRC and MCIC were noted. The standard deviations were large enough for each of the GRC categories to substantially overlap each other [clinstat\other\cbsqvalidationdocument.pdf, page 11].

Reviewer comment:
The CBSQ was administered in such a fashion that the interviewer might have influenced patient responses. The poor correlation between the GAS and GRC and the large standard deviation in the GRC indicate that the MCIC is not likely to be valid. This instrument will not be able to provide support for the efficacy of FP.

The BDI/TDI was used to provide a clinical measurement of baseline and change in dyspnea. The degree of functional impairment at baseline due to dyspnea, the magnitude of task to provoke dyspnea, and the magnitude of effort that provoked dyspnea were rated on a 0 to 4, 5-point scale to derive the BDI. Changes from baseline in functional impairment, magnitude of task, and magnitude of effort were assessed at each subsequent visit with a -3 to +3, seven-point scale, the TDI [clinstat\copd\sfca3007.pdf, pages 104-105, 7122, 7191-7193].

The sponsor provided a reference for this instrument which showed a weak correlation of the BDI with FEV_1, FVC, and the 12-minute walk distance with correlation coefficients of 0.41, 0.56, and 0.60[8]. TDI correlated only weakly with change in the change in the 12-minute walk distance, with a correlation coefficient of 0.33. There was no correlation of TDI with change in FEV_1 or change in FVC. Although not noted in this study, the sponsor had noted in FLTA3025 that they considered a change from BDI to TDI of 1.0 to be clinically relevant [clinstat\copd\flta3025.pdf, page 67, Correspondence submitted to IND 50,703, Meeting request package, 2/6/98]. The sponsor did not include a validation package with this application or with the meeting request package of 2/6/98.

Reviewer comment:
Degree of functional impairment, magnitude of task, and magnitude of effort are likely to be highly correlated variables, in this reviewer's opinion, and therefore will inflate any observed positive or negative treatment effect. This instrument will not be likely to provide support for the efficacy of FP because of this deficiency and because of the lack of validation.

The investigator assessed the severity of any COPD exacerbations at each clinic visit using a three-level scale, mild to severe. Mild exacerbations were defined as use of more than 12 puffs or 4 nebules of relief bronchodilator per day for more than 2 consecutive days, but without the need for additional medication. Moderate exacerbations were defined as requiring either antibiotics or corticosteroids. Severe exacerbations were defined as requiring inpatient admission for treatment [clinstat\copd\sfca3007.pdf, page 7122].

Reviewer comment:
This is not the standard definition of COPD exacerbation. In fact, this definition describes situations that reflect a worsening of airway bronchoconstriction. This definition of exacerbation would be likely to favor the finding of efficacy of FP in patients who have a high degree of reversibility. The most widely accepted definition of COPD exacerbation follows[9]:

- *Type 1 = All of the following symptoms*
  - *Increased dyspnea, increased sputum volume, increased sputum purulence*
- *Type 2 = Two of the following symptoms*
  - *Increased dyspnea, increased sputum volume, increased sputum purulence*
- *Type 3 = One of the following symptoms*
  - *Increased dyspnea, increased sputum volume, increased sputum purulence and one of the following:*
    - *URI within 5 days, fever without non-respiratory cause, increased wheezing, increased coughing, increase in respiratory rate of heart rate ≥20%*

Patients were to complete diary records during the treatment period each morning. Patients recorded the highest of three PEFRs measurements performed each morning prior the dose of study medication, the number of inhalations of supplemental Ventolin use over the preceding 24 hours, and the number of nighttime awakenings requiring the use of Ventolin during the preceding night [clinstat\copd\sfca3007.pdf, page 7123].

11.3.13. Health-related quality of life instrument

Health outcomes were assessed with the Chronic Respiratory Disease Questionnaire (CRDQ), a health-related quality of life instrument[10] [clinstat\copd\sfca3007.pdf, page 7124]. It is worth noting that comparative quality of life (QOL) was one of the three primary objectives that the sponsor identified as important outcomes of the study. The sponsor states that the instrument is an interviewer-administered, disease-specific, validated questionnaire designed to measure the impact of chronic respiratory disease and its treatments on the patient's COPD-related quality of life. The CRDQ is a 20-item questionnaire that evaluates health-related quality of life across four domains—dyspnea, fatigue, emotional function, and mastery over the disease. The responses for each of the 20 items were summed to provide an overall assessment of health-related quality of life. A physical score was calculated based on the sum of scores of the dyspnea and fatigue domains and an emotional score was calculated based on the sum of the scores of the emotional function and mastery domains. The CRDQ was completed at Day 1, and Weeks 2, 4, 8, 24, and Discontinuation.

11.3.14. Efficacy variables

Efficacy variables for this study are described below.

11.3.14.1. Primary efficacy variable

The primary efficacy variables for this study was the pre-dose FEV_1 and the 2-hour post dose FEV_1 collected at Day 1, and Weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 [clinstat\copd\sfca3007.pdf, page 7132].

For primary efficacy measures, treatments were compared as follows [clinstat\copd\sfca3007.pdf, page 7132].

- SAL 50/FP 250 to SAL 50: Pre-dose FEV_1, to evaluate the contribution of FP 500 to the combination product
- SAL 50/FP 250 to FP 250: Two-hour post dose FEV_1, to evaluate the contribution of SAL 50 to the combination product
- SAL 50 to placebo: Two-hour post-dose FEV_1, to evaluate the efficacy of the individual component
- FP 250 to placebo: Pre-dose FEV_1, to evaluate the efficacy of the individual component

Reviewer comment:
Only the pre-dose FEV_1 is relevant to the assessment of efficacy for FP 250 versus placebo, therefore this comparison will be the focus of this review. Other active treatment arms will only be discussed only if relevant to the efficacy and/or safety of FP 250.

The baseline FEV_1 was the pre-dose FEV_1 at treatment Day 1. The primary analyses compared endpoint and baseline measurements for the primary efficacy variables. The endpoint was defined in the protocol as the final evaluable measurement for the patient. For patients who discontinued from the study the endpoint was the last evaluable measurement taken prior to withdrawal [clinstat\copd\sfca3007.pdf, page 7132]. Therefore, the FEV_1 at the Discontinuation Visit was not used for any efficacy analysis.

Reviewer comment:
As this review is concerned with the efficacy of FP in the treatment of COPD, only pre-dose FEV_1 measurements will be examined. Two-hour post-dose FEV_1 measurements were performed by the sponsor to help assess the efficacy of SAL 50 and the contribution of SAL to the efficacy of the combination SAL 50/FP 250 product.

In FLTA3025, the sponsor stated that their rationale for not using the FEV_1 at the Discontinuation Visit was that patients might have stopped taking study drug prior to the visit and might have been taking another drug that could affect results [clinstat\copd\flta3025.pdf, page 66]. Although it is not stated in this study, it is likely the sponsor had the same rationale in this study. The sponsor's plan to carry the last measurement from the preceding visit forward for discontinuing patients also affects the interpretation of efficacy results, however.

Treatment groups were compared using ANCOVA F-tests with baseline as the covariate. All inferential analyses were performed on the mean change from Baseline. Ninety-five percent confidence intervals were provided for treatment differences in the mean changes from Baseline [clinstat\copd\sfca3007.pdf, pages 71, 7132].

11.3.14.2. Secondary efficacy variables

Secondary efficacy variables included change from baseline in the global and individual domains of the CBSQ, the BDI/TDI score at each of the treatment visits, number and severity of exacerbations of COPD, time to first COPD exacerbation, number of withdrawals and time to withdrawals. Morning PEFR, daily use of Ventolin, percentage of nights with no awakenings requiring Ventolin, frequency of nighttime awakenings requiring Ventolin, and percent of days without using Ventolin were also summarized [clinstat\copd\sfca3007.pdf, pages 7122-7123].

Summary statistics were provided for all secondary endpoints. Changes from baseline in the Global Assessment Score (GAS) of the CBSQ were compared between treatment groups using an ANCOVA F-test with treatment group, investigator, and baseline value as covariates. Overall and pairwise treatment comparisons of the BDI/TDI scores were performed by ANOVA F-test. Time to first COPD exacerbation, number of withdrawals, and time to withdrawals were analyzed using survival analysis [clinstat\copd\sfca3007.pdf, pages 7132-7133].

The CRDQ was used to compare changes in the COPD-related quality of life for treatment groups as measured by an overall score and for each of the four domains. An improvement of at least 10 in overall score was considered to be an overall improvement in COPD-specific quality of life. At each visit, treatment group comparisons were made comparing the change from baseline using ANCOVA, controlling for baseline and investigator. A difference between treatment groups in mean change from baseline was considered clinically meaningful if the difference was statistically significant and had a minimum of ≥0.5 point improvement per question per item [clinstat\copd\scfa3007.pdf, pages 7134-7135].

11.3.15. Safety variables

Safety variables for this study included AEs, ECGs, hematology and clinical chemistry studies, oropharyngeal examinations, and vital signs [clinstat\copd\sfca30007.pdf, pages 60-64, 7124-7128]. Summary statistics were to be provided for each of the safety endpoints [clinstat\copd\sfca3007.pdf, pages 7135-7136].

Reviewer comment:
Although the safety variables that were chosen are appropriate to assess the local and systemic safety of FP, it would have been preferable to also have formal ophthalmologic examinations and assessments of bone density, although given the duration of the study, it is unclear whether such tests would be sufficiently sensitive to detect a change.

Cosyntropin (Cortrosyn®) stimulation testing was performed at selected study sites on Day 1 and Week 24 or Discontinuation [clinstat\copd\sfca3007.pdf, page 7128]. The

sponsor performed the short cosyntropin stimulation test according to the cosyntropin package insert. Blood samples were to be drawn 30-60 minutes after administration of cosyntropin [clinstat\copd\sfca3007.pdf, page 7128]. Threshold values of 14.5 mcg/dL and 5.6 mcg/dL were used in the analysis because a HPLC assay was used. The sponsor states that a less specific radioimmunoassay was used for the higher reference values given in the cosyntropin package insert [clinstat\copd\sfca3007.pdf, pages 78-79].

11.3.16. Statistical considerations

Imputation of missing data was planned for the primary efficacy parameter and the humanistic outcomes. Last observation carried forward analysis was to be performed. [clinstat\copd\sfca3007.pdf, page 7131].

11.3.16.1. Data sets analyzed

The primary population for the analysis of both efficacy and safety was the intent-to-treat population, defined as all randomized subjects who received at least one dose of study drug [clinstat\copd\sfca3007.pdf, pages 7130-7131].

Originally, the sponsor did not plan any subgroup analyses [clinstat\copd\sfca3007.pdf, page 7131]. In Protocol Amendment 2 (2/17/00), the sponsor added a subgroup analysis for patients who have an increase in percent predicted FEV_1 of less than 10% after albuterol at the screening visit. This group was called the "poorly-reversible-percent of predicted patients" [clinstat\copd\sfca3007.pdf, page 7207]. Subgroup analyses of former smokers and current smokers were added in Protocol Amendment 3 (6/23/00) [clinstat\copd\sfca3007.pdf, page 7212].

Reviewer comment:
This analysis was to be provided to support the approval of the product outside the US. [clinstat\copd\sfca3007.pdf, pages 80, 96]. *The sponsor indicates that this definition reflects current opinion of the European Respiratory Society [NDA 20-833, SE1-004, pages 1-2, 8/10/01].*

As in FLTA3025, SFCA3006, and as noted earlier in this document, assignment to study drug was to be stratified according to the patients' response to reversibility testing with bronchodilator at screening to non-reversible and reversible patients. The non-reversible group was defined earlier in the protocol as patients with an absolute volume increase of <200 mL or absolute volume increase ≥200 mL with baseline reversibility assessment of <12% , and is based on the ATS definition of reversibility [clinstat\copd\sfca3007.pdf, pages 48 7113-7114; NDA 20-833, SE1-004, pages 1-2, 8/10/01]. As noted earlier, subgroup analysis initially was not provided for these either the non-reversible or reversible groups. The proportion of patients with reversibility will be critical to determine if the population studied accurately reflects the population of patients with COPD.

The sponsor provided an extensive subgroup analysis of the "poorly-reversible population." As noted above, the poorly-reversible population" was defined as those patients who had an increase in percent predicted FEV_1 of less than 10% after albuterol

at the screening visit. Although this may be the accepted definition for the ERS, it is a curious way of expressing reversibility, as it uses a theoretical value as the baseline (percent predicted FEV_1), rather than an actually measured value, such as FEV_1 at baseline. The ERS definition and the subgroup analysis of the poorly reversible population are not relevant to approval of this drug for this indication in the US, however, and this subgroup analysis will receive only brief review.

11.3.16.2. Statistical power

The sponsor calculated that a sample size of 145 patients per treatment arm would be necessary to provide >85% power to detect a clinically meaningful significant difference of 0.1 liter between treatment groups. The sponsor assumed a standard deviation for the change from baseline FEV_1 of 0.28 liters, and a level of significance of 0.05, using a two-sample t-test [clinstat\copd\sfca3007.pdf, page 7130].

The sponsor amended the protocol in Protocol Amendment 2 to allow for randomization of 720 patients instead of 600 and an increase in the number of participating centers from 55 to 75 [clinstat\copd\sfca3007.pdf, page 7206]. The sponsor increased the planned sample size to account for any data which required exclusion from the primary efficacy analysis, such as an investigator not meeting study standards or subjects that have a baseline FEV_1 assessment without a subsequent FEV_1 assessment. The increase in sample size was also to satisfy the requirement for additional COPD patients to who meet the European definition of "poorly-reversible" to allow for subgroup analyses of patient data [clinstat\copd\sfca3007.pdf, page 7206].

11.3.17. Results

Efficacy and safety results of this study are reviewed below.

<u>Reviewer comment:</u>
Review of this study will focus on the efficacy of FP. Therefore discussion will focus primarily on the comparison of FP 250 and placebo. Less emphasis will be placed on the comparison of SAL 50 with SAL 50/FP 250, and SAL 50/FP 250 with placebo.

11.3.17.1. Populations enrolled/analyzed

There were 1489 patients screened for the study. There were 723 patients who were screening failures. A total of 723 patients were randomized. The most common reason for screening failure was FEV_1/FVC <70% and baseline FEV_1 <65% predicted but >0.7 L (516/766, 67%). Other reasons for screening failure included significant concurrent disease (49/766, 5%), withdrew consent (45/766, 4%), moderate or severe COPD exacerbation during run-in (36/766, 45%), and inability to tolerate the 2-week run-in (32/766, 4%) [clinstat\copd\sfca3007.pdf, pages 80, 1111-1114].

Reviewer comment:
One might expect that failure to tolerate the 2-week run-in would be the most common reason for screening failure in this study. However, inability to meet the inclusion criterion for spirometry was the most common reason for screening failure. This is probably the reason for the change in Protocol Amendment 1 that changed FEV_1/FVC ratio from ≤65% to ≤70%. The most likely effect of this change would be to allow entry of patients with milder obstruction. These patients might be more likely to have reversibility, and might be more likely to respond to an inhaled corticosteroid such as FP.

Patient disposition is summarized in Table 11.3.3. There were a total of 723 patients randomized and 505 patients completed the study. There were 218 patients that discontinued the study prematurely. The frequency of discontinuations were fairly similar, with the lowest frequency in FP 250 (50/183, 27%). The most frequent reason for discontinuation for all groups was COPD exacerbation. Among patients discontinuing the study, there were 30% (17/32) who discontinued due to COPD exacerbation in the SAL 50 group, compared with 28% (15/53) in the SAL 50/FP 250 group, 26% (13/50) in the FP 250 group, and 24% (14/59) in the placebo group. The frequency of adverse events (AEs) leading to discontinuation was highest in the FP 250 group (18%, 9/50), followed by the SAL 50/FP 250 group (17%, 9/53), the placebo group (12%, 7/59), and the SAL 50 group (11%, 6/56). Lack of efficacy was a less frequent reason for discontinuation in the SAL 50/FP 250 group (6%, 3/53) than for the FP 250 (12%, 6/50), SAL 50 (14%, 8/56) and placebo (14%, 24/59) groups [clinstat\copd\sfca3007.pdf, pages 81, 335].

Reviewer comment:
It should also be noted that the FP 250 and SAL 50/FP 250 groups withdrew more frequently because of AEs.

Table 11.3.3. Patient disposition, SFCA3007, [clinstat\copd\sfca3007.pdf, pages 81, 335]

	Placebo		SAL 50		FP 250		SAL 50/FP 250		Total	
	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Patients randomized	185	(100)	177	(100)	183	(100)	178	(100)	723	(100)
Patients completed	126	(68)	121	(68)	133	(73)	125	(70)	505	(70)
Patients discontinued	59	(32)	56	(32)	50	(27)	53	(30)	218	(30)
Reason for discontinuation										
Adverse event	7	(12)	6	(11)	9	(18)	9	(17)	31	(14)
COPD exacerbation	14	(24)	17	(30)	13	(26)	15	(28)	59	(27)
Withdrawn consent	11	(19)	9	(16)	5	(10)	10	(19)	35	(16)
Lack of efficacy	14	(24)	8	(14)	6	(12)	3	(6)	31	(14)
Lost to follow-up	0	(0)	3	(5)	4	(8)	6	(11)	13	(6)
Protocol violation	9	(15)	8	(14)	9	(18)	7	(13)	33	(15)
Other	4	(7)	5	(9)	4	(8)	3	(6)	16	(7)
Death	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)

11.3.17.2. Protocol deviations

The most common violations of inclusion and exclusion criteria included severity of disease and significant concurrent disease, respectively. Significant concurrent disease ranged from 2% to 4%. Use of concurrent medications that interfere with objective assessments ranged from 2% to 5% in the treatment groups [clinstat\copd\sfca3007.pdf, pages 82, 340-341].

Reviewer comment:
Violations of inclusion criteria were fairly infrequent and evenly distributed between treatment groups and were not likely to affect the analysis of efficacy or safety.

There were few patients who varied from the protocol who were not discontinued from the study, as presented in Table 11.3.4. The most common protocol variations were use of a prohibited corticosteroid, use of a prohibited non-corticosteroid medication, use of oxygen outside bounds of protocol, and use of tobacco outside bounds of protocol [clinstat\copd\scfa3007.pdf, pages 82, 344, 1902-1909]. Other protocol variations included inability to use Diskus, inability to complete diary card, and inability to tolerate the run-in period [clinstat\copd\scfa3007.pdf, pages 1902-1909].

Table 11.3.4. Protocol variations during conduct of the study, not leading to discontinuation, SFCA3007 [clinstat\copd\sfca3007.pdf, pages 344, 1902-1909].

	Placebo N = 185 n	(%)	SAL 50 N = 177		FP 250 N = 183 n	(%)	SAL 50/FP 250 N = 178 n	(%)
All protocol variations	19	(10)	15	(8)	11	(6)	16	(9)
Used a prohibited corticosteroid	5	(3)	5	(3)	6	(3)	6	(3)
Used other prohibited medication	7	(4)	5	(3)	3	(2)	6	(3)
Used oxygen	1	(<1)	0	(0)	0	(0)	1	(<1)
Used tobacco	0	(0)	1	(<1)	0	(0)	2	(1)
Other	7	(4)	4	(2)	2	(1)	4	(2)

11.3.17.3. Demographic and background characteristics

Demographics and background characteristics of patients are displayed in Table 11.3.5. The majority of patients in each of the treatment groups were 65 years of age or older. The mean age of patients was 64.8 years in the placebo group, 64.2 years in the SAL 50 group, 63.3 years in the FP 250 group, and 663.4 years in the SAL 50/FP 250 group. Patients ranged from 40 to 87 years of age. The proportion of patients aged 65 years or less was similar in each of the treatment groups. The age range was similar in each of the treatment groups.

The majority of patients in this study were of male gender. Males represented from 58% to 68% of patients in each of the treatment groups. There were proportionately more males in the placebo group, and proportionately fewer in the SAL 50 group. The vast majority of patients in this study were of Caucasian race. There were few patients of Black, Asian, or Other race. Non-Caucasian races represented 9% or less of each of the treatment groups.

Patients in this study had fairly severe dyspnea. All patients experienced dyspnea with walking on level ground, and approximately one third of the patients in each of the treatment groups had dyspnea with walking on level ground for 100 yards or worse (MMRC Dyspnea Score ≥3). The patients in the placebo group had slightly milder dyspnea, with 68% having a MMRC Dyspnea Score of 2, compared with 61% to 64% with MMRC Dyspnea Scores of 2 in the other treatment groups. Mean duration of COPD was approximately 7 to 8 years for each of the treatment groups. Duration of COPD ranged from 1 year to 53 years.

There was a slightly larger proportion of current smokers in the SAL 50 group (51%, 90/177) than the other treatment groups (43% to 48% for other groups). The FP 250 group had a slightly larger median history of smoking (60.0 pack years) than the other treatment groups (523.0 to 57.0 pack years). The median history of smoking was much larger than the 20 pack-year history required for entry into the study.

SAL 50 (20%, 35/177) and SAL 50/FP 250 (41/178, 23%) groups had a smaller proportion of patients who were using inhaled steroids at screening than the placebo (55/185, 30%) and FP 250 groups (28%, 51/183). The majority of patients in each treatment group had emphysema. The frequency of emphysema was similar among treatment groups and ranged from 63% to 71%.

Reviewer comments:
The under-representation of non-Caucasian patients in this study is a deficiency, as in FLTA3025 and SFCA3006. The lack of Black, Asian, and Hispanic patients will make it impossible to assess efficacy or safety by race.

Overall, the population studied is characterized by long smoking histories, significant dyspnea, and a 7 to 8 year history of COPD. It is unclear how the diagnosis of "emphysema" was made for the approximately 65% of the patients who reported it, since the diagnosis would require HRCT, DLCO, or an invasive procedure. Overall, a fairly large minority of the patients was taking inhaled corticosteroids at the time of screening. As noted earlier in this review, one would expect these patients to more likely to be corticosteroid-responsive than those not taking inhaled corticosteroids, as one would expect patients with no response or a poor response to have their treatment discontinued.

Table 11.3.5. Demographics, SFCA3007 [clinstat\copd\sfca3007.pdf, pages 84, 345-349].

Characteristic	Placebo N = 185		SAL 50 N = 177		FP 250 N = 183		SAL 50/FP 250 N = 178	
Age, years	**n**	**(%)**			**n**	**(%)**	**n**	**(%)**
<65	85	(46)	89	(50)	95	(52)	93	(52)
≥65	100	(54)	88	(50)	88	(48)	85	(48)
Mean age	64.8		64.2		63.3		63.4	
SD	8.7		9.8		9.4		10.6	
Range	40-81		42-87		40-84		40 – 87	
Gender	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Female	59	(32)	75	(42)	62	(34)	70	(39)
Male	126	(68)	102	(58)	121	(66)	108	(61)
Race	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Caucasian	173	(94)	165	(93)	167	(91)	170	(96)
Black	6	(3)	7	(4)	9	(5)	5	(3)
Asian	1	(<1)	0	(0)	1	(<1)	0	(0)
Other	5	(3)	5	(3)	6	(3)	3	(2)
MMRC Dyspnea Score	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
2	118	(64)	120	(68)	116	(63)	109	(61)
3	58	(31)	49	(28)	63	(34)	63	(35)
4	9	(5)	8	(5)	2	(1)	6	(3)
Missing	0	(0)	0	(0)	2	(1)	0	(0)

Characteristic	Placebo N = 185	SAL 50 N = 177	FP 250 N = 183	SAL 50/FP 250 N = 178
Duration of COPD	**Years**	**Years**	**Years**	**Years**
Mean	8.02	6.96	8.22	7.53
Range	1 – 36	1 – 30	1 – 53	1 – 43
Smoking status	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Former smoker	98 (53)	87 (49)	95 (52)	101 (57)
Current smoker	87 (47)	90 (51)	88 (48)	77 (43)
Pack-years smoked				
Median	56.0	57.0	60.0	53.0
Range	20 – 165	20 – 224	20 – 162	20 – 220
Inhaled steroids at screening	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Yes	55 (30)	35 (20)	51 (28)	41 (23)
No	130 (70)	142 (80)	132 (72)	137 (77)
Emphysema	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Yes	126 (68)	116 (66)	115 (63)	126 (71)
No	59 (32)	61 (34)	68 (37)	52 (29)

Patients had fairly severe airway obstruction. Spirometry results at the time of screening are presented in Table 11.3.6. The mean FEV_1 for each treatment group of approximately 1275 mL, mean FEV_1 % predicted of about 41%, and mean FEV_1/FVC % of about 42%. The degree of airway obstruction was slightly less in the FP 250 group (FEV_1 = 1313 mL, FEV_1/FVC% 51.27%) than the other treatment groups [clinstat\copd\sfca3007.pdf, page 354].

Table 11.3.6. Spirometry at screening, SFCA3007 [clinstat\copd\sfca3007.pdf, page 354].

	Placebo n = 185	SAL 50 n = 177	FP 250 n = 183	SAL 50/FP 250 N = 178
FEV_1, mL				
Mean	1289	1245	1313	1252
SD	425	432	439	404
Median	1190	1120	1240	1175
Range	620 – 2580	700 – 2600	640 – 2690	660 – 2830
FEV_1, % predicted				
Mean	42.05	41.94	41.96	41.37
SD	12.24	12.04	11.33	11.28
Median	40.74	40.63	41.60	41.21
Range	17.9 – 67.6	18.3 – 70.4	18.9 – 66.2	17.1 – 64.1
FEV_1/FVC %				
Mean	49.63	50.83	51.27	49.48
SD	11.45	9.82	10.11	10.01
Median	50.44	50.99	51.34	49.07
Range	18.0 – 72.8	25.4 – 69.6	27.2 – 72.1	27.2 – 71.9

Patient response to treatment with bronchodilator at screening is summarized in Table 11.3.7. A patient was considered "non-reversible" if, after 4 puffs of Ventolin MDI, there was a change in FEV_1 of <12% from baseline or there was <200 mL absolute increase in the FEV_1. Reversible patients represented 55% of all patients in this study. The mean % change in FEV_1 for reversible patients was 29.84%. Non-reversible patients represented 45 % of all patients in this study. The mean % change in FEV_1 for non-reversible patients was 8.57%. The degree of reversibility in each of the treatment groups was similar. The mean % change in FEV_1 for all patients was 20.30% [clinstat\copd\sfca3007.pdf, pages 85, 354-356].

Reviewer comment:
As with Studies FLTA3025 and SFCA3006, the proportion of patients with reversibility enrolled in this study is much higher than is found in the population of COPD patients at large. There were 55% of patients in this study who had reversibility. In addition, the degree of reversibility for the reversible population was high—29.84%. As noted earlier in this review, one would expect that only up to 30% of patients to have in increase of ≥15% in FEV_1 after inhalation of a beta-agonist.[1-4] The mean degree of reversibility in the non-reversible population was also high—8.57%.

The high proportion of patients with reversibility in this study is a critical consideration in determining whether the results of this population can be generalized to the COPD population as a whole. Reversible patients were over-represented relative to their prevalence in the COPD population as a whole, and the degree of reversibility in these patients is much higher than would be expected for the general population of patients with COPD. As with FLTA3025 and SFCA3006, this may have a major impact on the interpretation of the efficacy results of this study.

Table 11.3.7. Mean change in FEV_1 after bronchodilator treatment at screening, SFCA3007 [clinstat\copd\sfca3007.pdf, pages 85, 354-356].

	Placebo N = 185	SAL 50 N = 177	FP 250 N = 183	SAL50/FP 250 N = 178	All treatment groups N = 723
Reversible patients					
n (%)	102 (55)	97 (55)	100 (55)	99 (56)	398 (55)
Mean % change in FEV_1	29.72	30.87	28.93	29.88	29.84**
Non-reversible (ATS) patients					
n (%)	83 (45)	79 (45)	83 (45)	79 (44)	324 (45)
Mean % change in FEV_1	8.58	9.56	8.19	7.93	8.57**
All patients					
n (%)	185 (100)	176 (100)	183 (100)	178 (100)	722 (100)
Mean % change in FEV_1	20.24	21.31	19.53	20.14	20.30**

*Calculation of response: $\frac{(\text{Post-BD } FEV_1 \text{ minus Pre-BD } FEV_1) \times 100}{\text{Pre-BD } FEV_1}$

Not reversible if result is <12% or <200 mL increase in FEV_1
Reversible if result is ≥12% and ≥200 mL increase in FEV_1

**Mean change derived from data for individual treatment group data

Compliance with study treatment was high in this study. These data are displayed in Table 11.3.8. Approximately 75% to 80% of patients in each treatment group took 90% or more of the prescribed doses of medication. The mean number of doses taken was approximately 94% in each treatment group [clinstat\copd\sfca3007.pdf, pages 87, 411].

Table 11.3.8. Compliance with study treatment, SFCA3007 [clinstat\copd\sfca3007.pdf, pages 87, 411].

	Placebo		SAL 50		FP 250		SAL 50/FP 250	
	n	(%)	n	(%)	n	(%)	n	(%)
All patients	184	(100)	175	(100)	180	(100)	174	(100)
<80% compliance	10	(5)	14	(8)	16	(9)	14	(8)
80-<90% compliance	28	(15)	16	(9)	25	(14)	30	(14)
≥90% compliance	146	(79)	145	(82)	139	(77)	130	(74)
Missing	0	(0)	1	(<1)	1	(<1)	1	(<1)

11.3.17.4. Primary efficacy endpoint

The primary efficacy endpoint was the mean change in FEV_1 from Baseline to study endpoint. As noted earlier in this review, this review is concerned with the efficacy of FP in the treatment of COPD. Therefore only pre-dose FEV_1 measurements will be examined. The two-hour post-dose FEV_1 measurements were performed by the sponsor to help assess the efficacy of SAL 50 and the contribution of SAL to the efficacy of the combination SAL 50/FP 250 product, and these will not be examined in this review. Data for the primary efficacy variable are displayed in Table 11.3.9. Inferential analysis of the primary efficacy variable is displayed in Table 11.3.10.

The mean change from baseline in FEV_1 for the FP 250 group at endpoint was 109 mL, which was 108 mL more than the placebo group at endpoint. This comparison was statistically significant at $p < 0.001$. This change corresponds to an effect size of 8.7%[1]. Mean change from baseline in FEV_1 for the SAL 50/FP 250 group at endpoint was 165 mL, which was 74 mL more than the SAL 50 group. SAL 50/FP 250 was statistically different from the SAL 50 group at $p = 0.012$. Values for the mean change in FEV_1 from baseline for the FP 250 group at Weeks 6, 12, and 24 were 77 mL, 83 mL, and 118 mL, respectively. Values for the mean change in FEV_1 for the placebo group at Weeks 6, 12, and 24 were 47 mL, 11 mL, and 3 mL, respectively. Values for the mean change from baseline in FEV_1 for the SAL 50/FP 250 group at Weeks 6, 12, and 24 were 179 mL, 166 mL, and 165 mL, respectively. Values for the mean change from baseline in FEV_1 for the SAL 50 group at weeks 6, 12, and 24 were 129 mL, 107 mL, and to 102 mL, respectively [clinstat\copd\sfca3006.pdf, pages 97, 479-484].

The mean change from baseline in FEV_1 for the FP 250 group at Weeks 1, 2, 3, 4, 8, 16, and 20 increased from 83 mL at Week 1 to 113 mL at Week 20 [clinstat\copd\sfca3007.pdf, pages 479-484].

The mean percent change from baseline in FEV_1 for FP 250 rose quickly at the Week 1 visit, with a slow rise to endpoint levels over the remaining course of treatment [Sponsor Figure 7.2, clinstat\copd\sfca3007.pdf, page 122].

Reviewer comments:
FP 250 met the pre-defined criteria for efficacy for the primary endpoint, change from baseline to endpoint in pre-dose FEV_1. FP 250 contributed to the efficacy of the SAL 50/FP 250 combination, as evidenced in the comparison of SAL 50 with SAL 50/FP 250.

[1] Effect size = $\frac{\text{(mean change from Baseline in } FEV_1\text{, FP 250) minus (mean change from Baseline in } FEV_1\text{, Pbo)}}{\text{Baseline } FEV_1\text{, FP 250}}$

All three active treatments were numerically superior to placebo at Week 1. As seen with FP 500 in SFCA 3006, the rapid increase from baseline in FEV_1 for FP 250 is somewhat of a surprise, as one would have expected a slower improvement in FEV_1 for an inhaled corticosteroid. The slower rise from Week 1 to endpoint levels for FP 250 is more representative of the expected response to inhaled corticosteroids.

Table 11.3.9. Mean change in pre-dose FEV_1 from baseline, primary efficacy variable, SFCA3007 [clinstat\copd\sfca3007.pdf, pages 97, 479-484].

	Pbo			SAL 50			FP 250			SAL 50/FP 250		
Study week	**Mean FEV_1, mL**	**Mean change from baseline, mL**	**n**	**Mean FEV_1, mL**	**Mean change from baseline, mL**	**n**	**Mean FEV_1, mL**	**Mean change from baseline, mL**	**n**	**Mean FEV_1, mL**	**Mean change from baseline, mL**	**n**
Baseline	1232	NA	185	1205	NA	177	1236	NA	183	1207	NA	178
Week 6	1318	47	148	1352	129	145	1322	77	157	1386	179	158
Week 12	1284	11	139	1334	107	135	1326	83	147	1375	166	144
Week 24	1287	3	125	1359	102	119	1386	118	133	1412	165	124
Endpoint*	1240	1	172	1303	91	168	1351	109	175	1375	165	171

*Primary efficacy endpoint

Table 11.3.10. Inferential analysis of baseline and change from baseline in pre-dose FEV_1, primary efficacy variable, SFCA3007, [clinstat\copd\sfca3007.pdf, pages 485-486].

Study week	**Overall** **p value***	**Pbo** **vs. FP 250** **p value***	**Pbo** **vs. SAL 50/FP 250** **p value***	**SAL 50** **vs. SAL 50/FP 250** **p value***
Endpoint**	<0.001	<0.001	<0.001	0.012

*ANCOVA, Baseline as covariate
**Primary efficacy endpoint

11.3.17.5. Secondary efficacy endpoints

Secondary efficacy variables included change from baseline in the global and individual domains of the CBSQ, the BDI/TDI score at each of the treatment visits, number and percent of exacerbations of COPD, time to first COPD exacerbation, number of withdrawals and time to withdrawals. Morning PEFR, daily use of Ventolin, percentage of nights with no awakenings requiring Ventolin, frequency of nighttime awakenings requiring Ventolin, and percent of days without using Ventolin were also summarized [clinstat\copd\sfca3007.pdf, pages 7122-7123]. The CRDQ was also used to compare changes in the COPD-related quality of life for treatment groups as measured by an overall score and for each of the four domains.

Summary statistics were provided for all secondary endpoints. Changes from baseline in the Global Assessment Score (GAS) of the CBSQ were compared between treatment groups using an ANCOVA F-test with treatment group, investigator, and baseline value as covariates. Overall and pairwise treatment comparisons of the BDI/TDI scores were performed by ANOVA F-test. Time to first COPD exacerbation, number of withdrawals, and time to withdrawals were analyzed using survival analysis [clinstat\copd\sfca3007.pdf, pages 7132-7133]. For the CRDQ, treatment group comparisons were made comparing the change from baseline at each visit using ANCOVA, controlling for baseline and investigator [clinstat\copd\sfca3007.pdf, pages 7134-7135].

Reviewer comment:
Inferential analysis is appropriate only for the prospectively defined efficacy endpoint on which the study was powered, and not for these secondary efficacy endpoints. Therefore, this document will focus on the numerical differences between treatment groups for the secondary efficacy endpoints, and will not address the inferential statistical analysis.

11.3.17.5.a. Chronic Bronchitis Symptom Questionnaire

The CBSQ evaluated cough frequency and severity, sputum release, and chest discomfort on a 0 to 4, 5-point scale. Individual scores were summed to provide a Global Assessment Score (GAS). The maximum possible GAS was 16 [clinstat\copd\sfca3007.pdf, pages 7122, 7123]. Patients were required to have a minimum score of 4 at baseline to qualify for randomization. The sponsor determined that the Minimally Clinically Important Change (MCIC) in the CBSQ was 1.4 points in an analysis of patients completing at least 8 weeks of this study [clinstat\other\cbsqvalidationdocument.pdf, page 11]. Results of the Chronic Bronchitis Symptom Questionnaire are displayed in Table 11.3.11. The sponsor reported clinically important decreases in the CBSQ for FP 250 at Week 2 through Week 24 and at endpoint. The sponsor reported clinically important decreases in the CBSQ for SAL 50 at endpoint and Week 6 through Week 24. The sponsor reported clinically important decreases in the CBSQ for SAL 50/FP 250 at endpoint and Week 2 through Week 24. The sponsor reported clinically important decreases in the CBSQ for the placebo group at Weeks 4, 8, 12, 20, 24, and at endpoint. Decreases in the CBSQ for active treatment

Table 11.3.11. Chronic Bronchitis Symptom Questionnaire, SFCA3007. See text for comments. [clinstat\copd\sfca3007.pdf, pages 102, 508-513]

	Pbo			SAL 50			FP 250			SAL 50/FP 250		
Study week	**GAS***	**Mean change from baseline**	**n**	**GAS***	**Mean change from baseline**	**n**	**GAS***	**Mean change from baseline**	**n**	**GAS***	**Mean change from baseline**	**n**
Baseline	7.5	NA	185	7.0	NA	177	7.4	NA	183	7.3	NA	178
Week 1	7.0	0.5	170	6.3	0.8	166	6.7	0.7	174	6.2	1.0	170
Week 2	6.6	0.8	167	6.0	1.1	161	5.9	1.4	166	5.4	1.9	165
Week 3	6.5	0.9	158	5.9	1.2	157	5.6	1.8	161	5.1	2.1	159
Week 4	6.0	1.4	155	5.9	1.2	154	5.7	1.7	160	5.1	2.1	161
Week 6	6.1	1.3	149	5.5	1.7	145	5.6	1.8	158	5.1	2.1	159
Week 8	6.0	1.4	147	5.5	1.6	144	5.5	1.8	151	5.2	2.1	152
Week 12	6.0	1.4	139	5.4	1.6	136	5.2	2.2	147	5.0	2.3	144
Week 16	6.0	1.3	132	5.3	1.8	135	5.2	2.2	138	5.1	2.3	136
Week 20	5.9	1.5	127	5.1	2.0	123	5.1	2.3	133	4.9	2.4	129
Week 24	5.6	1.8	126	5.2	1.9	121	4.9	2.5	133	4.8	2.5	125
Endpoint	6.1	1.4	172	5.6	1.5	169	5.2	2.2	175	5.2	2.1	172

*GAS: Global Assessment Score. Minimally clinically important change = 1.4 points.

groups were numerically superior to placebo at all visits and at endpoint, except for Week 4 [clinstat\copd\sfca3007.pdf, pages 508-513].

Reviewer comment:
Small decreases in the CBSQ were noted for FP 250, SAL 50, and SAL 50/FP 250 at Weeks 1 to 24 and at endpoint. In general, decreases were numerically superior to placebo. However, the differences from placebo for all active treatment groups were less than the MCIC of 1.4 points. These data will not be able to provide support for the efficacy of FP.

11.3.17.5.b. Baseline/Transition Dyspnea Indices

The degree of functional impairment at baseline due to dyspnea, the magnitude of task to provoke dyspnea, and the magnitude of effort that provoked dyspnea were rated on a 0 to 4, 5-point scale to derive the BDI. The maximum BDI score was 12. The TDI assessed changes from baseline in functional impairment, magnitude of task, and magnitude of effort were assessed at each subsequent visit with a -3 to +3, seven-point scale [clinstat\copd\sfca3007.pdf, pages 104-105, 7122, 7191-7193]. The sponsor considered a clinically important TDI score to be ≥1.0 [clinstat\copd\sfca3007.pdf, page 104, Correspondence submitted to IND 50,703, Meeting request package, 2/6/98].

Results of the BDI/TDI are presented in Table 11.3.12. All treatment groups, including placebo, had improvements from baseline in TDI. The differences between the treatment group TDIs and placebo were less than the minimal clinically significant TDI of 1.0 point, except for SAL 50/FP 250 at Weeks 2 and 3 [clinstat\copd\sfca3007.pdf, pages 105, 546-549].

Reviewer comment:
The population studied included a high percentage of patients with reversibility with bronchodilator and does not accurately represent the population of COPD patients. Degree of functional impairment, magnitude of task, and magnitude of effort are likely to be highly correlated variables, in this reviewer's opinion, and therefore will tend to inflate any observed positive or negative treatment effect. This instrument has not been validated in a COPD population with a high degree of reversibility, and it is not a widely used scale or one that is held in high regard. In general, none of the treatment groups had a clinically significant difference from placebo. These data do not provide support for the efficacy of FP.

Table 11.3.12. Baseline/Transition Dyspnea Index (BDI/TDI), SFCA3007. See text for comments. [clinstat\copd\sfca3007.pdf, pages 105, 546-549]

	Pbo		SAL 50		FP 250		SAL 50/FP 250	
Study week	BDI	n	BDI	n	BDI	n	BDI	n
Baseline	5.7	183	6.1	176	6.2	179	6.1	174
	TDI*	n	TDI	n	TDI	n	TDI	n
Week 1	0.3	170	1.0	165	0.4	172	1.1	170
Week 2	0.6	167	1.3	161	1.0	166	1.7	165
Week 3	0.6	157	1.2	155	1.0	161	1.6	159
Week 4	1.0	155	1.2	154	1.3	159	1.6	159
Week 6	1.2	149	1.4	145	1.6	157	1.7	159
Week 8	1.4	147	1.5	144	1.2	151	1.6	152
Week 12	1.5	139	1.5	136	1.6	147	1.8	144
Week 16	1.6	131	1.7	135	1.9	137	1.9	136
Week 20	1.6	127	2.0	123	1.9	133	2.0	129
Week 24	1.7	126	1.8	121	2.0	132	2.4	125
Endpoint	1.0	172	1.6	169	1.7	175	1.7	172

*Minimally clinically significant TDI = 1.0 point.

11.3.17.5.c. COPD exacerbations

The incidence of COPD exacerbation and moderate to severe COPD exacerbation was slightly higher for FP 250 than for the other treatment groups. Moderate to severe exacerbations of COPD were defined as those requiring oral antibiotics, inhaled or oral corticosteroids, or inpatient admission for treatment. These data are displayed in Table 11.3.13.

Reviewer comment:
It is important to note that the definition of COPD exacerbation was not the standard definition. The sponsor's definition of COPD exacerbation describes situations that reflect a worsening of airway bronchoconstriction, and would be likely to favor the finding of efficacy of FP in patients who have a high degree of reversibility. Even so, and despite the improvements in FEV_1 noted, patients treated with FP 250 had higher incidences of COPD exacerbations than patients treated with placebo.

Table 11.3.13. Incidence of COPD exacerbations, SFCA3007 [clinstat\copd\sfca3007.pdf, pages 107, 571-572].

	Placebo N = 185		SAL 50 N = 177		FP 250 N = 183		SAL 50/FP 250 N = 178	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with any COPD exacerbation	73	(39)	65	(37)	79	(43)	71	(40)
Patients with moderate or severe COPD exacerbations	63	(34)	55	(31)	69	(38)	61	(34)

Time to COPD exacerbation or withdrawal is summarized in Table 11.3.14. The proportion of patients with first COPD exacerbation at each month during the study was similar for the FP 250 and placebo groups. The proportion of patients with a moderate to severe COPD exacerbation at each month during the study was slightly higher for the FP 250 group than the placebo group. The proportion of patients who withdrew from the study and withdrawals due to COPD exacerbation was similar across treatment groups.

Reviewer comment:
These data provide no support for the efficacy of FP in the population studied.

Table 11.3.14. Time to COPD exacerbation or withdrawal, SFCA3007

Time to First COPD Exacerbation [clinstat\copd\sfca3007.pdf, pages 574-577]								
	Pbo		**SAL 50**		**FP 250**		**SAL 50/ FP 250**	
	Patients at risk	**Events**	**Patients at risk**	**Events**	**Patients at risk**	**Events**	**Patients at risk**	**Events**
Month 1	142	30	144	23	135	36	145	26
Month 2	117	48	121	39	117	51	130	39
Month 3	104	58	107	48	102	64	119	46
Month 4	91	67	101	51	94	70	109	53
Month 5	88	68	88	61	87	75	95	63
Month 6	0	71	0	65	0	79	0	71
Time to First Moderate to Severe COPD Exacerbation [clinstat\copd\sfca3007.pdf, pages 579-582]								
	Pbo		**SAL 50**		**FP 250**		**SAL 50/ FP 250**	
	Patients at risk	**Events**	**Patients at risk**	**Events**	**Patients at risk**	**Events**	**Patients at risk**	**Events**
Month 1	148	22	152	12	148	23	153	17
Month 2	126	36	129	27	131	37	140	26
Month 3	112	47	115	36	111	53	124	36
Month 4	99	56	108	40	103	59	114	43
Month 5	95	58	93	51	95	65	99	53
Month 6	0	61	0	55	0	69	0	61
Time to Study Withdrawal [clinstat\copdsfca3007.pdf, pages 584-587]								
	Pbo		**SAL 50**		**FP 250**		**SAL 50/ FP 250**	
	Patients at risk	**Events**	**Patients at risk**	**Events**	**Patients at risk**	**Events**	**Patients at risk**	**Events**
Month 1	162	23	162	15	169	14	167	11
Month 2	150	35	152	25	162	21	159	19
Month 3	145	40	140	37	150	33	149	29
Month 4	134	51	136	41	145	38	144	34
Month 5	130	55	128	49	138	45	135	43
Month 6	0	59	0	56	0	49	0	50

Time to Study Withdrawal due to COPD Exacerbation [clinstat\copd\sfca3007.pdf, pages 589-592]								
	Pbo		SAL 50		FP 250		SAL 50/ FP 250	
	Patients at risk	Events	Patients at risk	Events	Patients at risk	Events	Patients at risk	Events
Month 1	162	5	162	2	169	2	167	3
Month 2	150	8	152	4	162	6	159	7
Month 3	145	9	140	9	150	9	149	10
Month 4	134	13	136	11	145	11	144	11
Month 5	130	15	128	15	138	14	135	14
Month 6	0	16	0	20	0	16	0	17

11.3.17.5.d. PEFR

PEFR data are presented in Table 11.3.15. Overall, there was a small mean increase from baseline in AM PEFR was for the FP 250 (11.3 L/min) and SAL 50 (14.7 L/min) groups at the end of the study. A larger mean increase was observed in the SAL 50/FP 250 group (30.6 L/min). Similar increases from baseline in AM PEFR was noted for FP 250, SAL 50, and SAL 50/FP 250 for each month during the treatment period [clinstat\copd\sfca3007.pdf, pages 109, 599-602].

Reviewer comment:
Small increases in AM PEFR for the FP 250 group and the SAL 50/FP 250 group compared with placebo and SAL 50 give support for efficacy of FP 250 in this population and are concordant with the findings of the primary endpoint of change from baseline in pre-dose FEV_1.

Table 11.3.15. Mean change from baseline in AM PEFR [clinstat\copd\sfca3007.pdf, pages 109, 599-602].

	Placebo	SAL 50	FP 250	SAL 50/FP 250
Baseline				
N	184	176	182	175
Mean PEFR, L/min	220.3	210.3	220.0	206.1
Overall				
N	183	174	177	173
Mean PEFR, L/min	220.2	225.3	230.7	236.3
Mean change from baseline, L/min	0.8	14.7	11.3	30.6

11.3.17.5.e. Supplemental Ventolin use

Supplemental Ventolin use is summarized in Table 11.3.16. Overall the SAL 50 and SAL 50/FP 250 groups had small decreases in the number of puffs of Ventolin used per day compared with placebo. FP 250 had little change in the number of puffs of Ventolin used per day and the change was similar to that seen with placebo. The decrease in Ventolin use for FP 250 ranged from 0 to 0.5 puffs per day for each study month. Overall, the FP 250, SAL 50, and SAL 50/FP 250 groups had increases in the number of days without Ventolin use compared with placebo. The decrease for SAL 50/FP 250 was greater than that for SAL 50 or for FP 250. The decrease in Ventolin use for FP 250 ranged from 2.5% to 8.7% for each study month.

Reviewer comment:
The changes in Ventolin use provide little support for the efficacy of FP 250 in this population.

Table 11.3.16. Mean change from baseline in supplemental Ventolin use, SFCA3007 [clinstat\copd\sfca3007.pdf, pages 111, 604-607, 609-613].

	Placebo	SAL 50	FP 250	SAL 50/FP 250
Number of puffs of Ventolin used per day				
Baseline				
N	184	176	181	174
Mean number of puffs	4.8	4.6	4.6	5.1
Overall				
N	182	174	177	172
Mean number of puffs	5.0	3.9	4.4	4.1
Mean change from baseline, puffs	0.1	-0.7	-0.2	-1.0
Percent of days without Ventolin use				
Baseline				
N	184	176	181	174
Mean % days without Ventolin use	24.8	25.2	24.7	24.4
Overall				
N	182	174	177	172
Mean % days without Ventolin use	28.7	31.6	29.5	34.2
Mean change from baseline, % days	4.0	5.8	5.0	10.0

Nighttime awakenings requiring Ventolin use are summarized in Table 11.3.17. Overall, the FP 250, SAL 50, and SAL 50/FP 250 groups had very small decreases from baseline in the number of awakenings per night. Of the active treatment groups, the FP 250 group had the smallest decrease number of awakenings per night requiring Ventolin. Overall, the FP 250, SAL 50, and SAL 50/FP 250 groups had small increases in the percent of nights with no awakenings requiring Ventolin use. Of the active treatment groups, the FP 250 group had the smallest increase in percent of nights with no awakenings.

Reviewer comment:
The small changes from baseline in nighttime awakenings and percent of nights with no awakenings requiring Ventolin provide little support of the efficacy of FP 250 in this population.

Nighttime awakenings and percent of nights with no awakenings requiring Ventolin would also be likely to be highly correlated with the sponsor's definition of COPD exacerbation. As noted earlier the sponsor's definition of exacerbation would be expected to favor the demonstration of efficacy of FP in a study population with a high degree of reversibility.

Table 11.3.17. Mean change from baseline in nighttime awakenings requiring Ventolin use, SFCA30007 [clinstat\copd\sfca3007.pdf, pages 113, 614-617, 619-622]

	Placebo	SAL 50	FP 250	SAL 50/FP 250
Number of awakenings per night requiring Ventolin				
Baseline				
N	184	175	181	174
Mean number of awakenings	0.23	0.20	0.24	0.24
Overall				
N	181	174	177	172
Mean number of awakenings	0.25	0.174	0.20	0.12
Mean change from baseline, awakenings	0.02	-0.06	-0.03	-0.12

	Placebo	SAL 50	FP 250	SAL 50/FP 250
Percent of nights with no awakenings requiring Ventolin				
Baseline				
N	184	175	181	174
Mean % nights with no awakenings	83.2	84.7	84.9	82.7
Overall				
N	181	174	177	172
Mean % nights with no awakenings	83.3	89.9	89.9	90.8
Mean change from baseline, % nights with no awakenings	0.3	5.1	4.8	8.3

11.3.17.5.f. Health-related quality of life instrument

Quality of life assessment was one of the pre-specified objectives of this study. COPD-related quality of life was evaluated using the Chronic Respiratory Disease Questionnaire (CRDQ)[10]. The CRDQ contains 20 questions in 4 domains: dyspnea, fatigue, emotional function, and mastery. An overall score, the sum of the scores for all 20 questions, was the primary health-related quality of life endpoint. A physical score was calculated based on the sum of scores in the dyspnea and fatigue domains and an emotional score was calculated based on the sum of scores of the emotional function and mastery domains [clinstat\copd\sfca3007.pdf, page 7124]. A clinically significant improvement was considered to be 0.5 points per item. Therefore, an improvement in the Overall score of at least 10.0 points was considered to be a clinically significant improvement in COPD-specific quality of life. As there were different numbers of items per domain, the clinically significant changes for each domain and summary scores are as follows [clinstat\copd\sfca3007.pdf, pages 74-77, 7134-7135]:

- Fatigue domain: 2.0 points
- Dyspnea domain: 2.5 points
- Physical summary: 4.5 points

- Emotional function domain: 3.5 points
- Mastery domain: 2.0 points
- Emotional summary: 5.5 points

Study endpoint was defined as the last available post-baseline score for the CDRQ. This was different from the other analyses, which did not include values for the Discontinuation visit [clinstat\copd\sfca3007.pdf, page 142]. In addition, the sponsor excluded patients with an overall baseline score greater than 130 from the analysis of the overall score at any visit. These patients were excluded because baseline scores would be mathematically unable to attain a clinically meaningful change [clinstat\copd\sfca3006.pdf, page 142]. Similar exclusions were made for the patients with the following scores [clinstat\copd\sfca3007.pdf, page 76]:

- Fatigue score >26
- Dyspnea score >32
- Physical summary >58

- Emotional function score >45

- Mastery score >26
- Emotional summary >71

The population analyzed, which excluded these patients, was referred to the "reduced intent-to-treat population" (reduced ITT population) [clinstat\copd\sfca3006.pdf, page 76].

Reviewer comment:
It is true that it is be mathematically impossible for patients whose baseline scores are higher than those noted above to attain a clinically meaningful change. However, it is not appropriate to exclude these patients from the analysis. It would have been preferable to set these maximum scores as inclusion criteria for the study. As it turns out, there were no patients excluded for the Overall score and the Physical summary score and the ITT and "reduced ITT populations" were identical for these scores [clinstat\copd\sfca3007.pdf, pages 143, 769, 775, 1519, 1525].

There were a total of 26 patients among all treatment groups excluded from the calculation of the Emotional summary score. There were 23 patients excluded from the Emotional function domain score, 63 patients from the Mastery domain score, 3 patients from the Dyspnea domain, and 1 patient from the Fatigue domain score [clinstat\copd\sfca3007.pdf, pages 781, 787, 793, 799, 805, 1531, 1537, 1543, 1549, 1555]. This review will examine CDRQ results for the ITT group and not the reduced ITT population.

There were clinically significant improvements from baseline in the overall CDRQ score for FP 250 (10.4 points) and SAL 50/FP 250 (10.0 points). However, there was less than a 10.0 point difference in these values from the change from baseline for the placebo group, and therefore not a clinically significant difference from the placebo group. The change in the overall CDRQ score for SAL 50 (6.4 points) was similar to placebo (5.0 points). These data are displayed in Table 11.3.18. The data displayed reflects the ITT population.

FP 250 and SAL 50/FP 500 had clinically significant improvements from baseline in the Physical summary score. The change in the Physical summary score for FP 250 (5.6 points) and SAL 50/FP 250 (6.1 points) were slightly greater than placebo (3.8 points). However, there was less than a 4.5 point difference in these values from the change from baseline for the placebo group, and therefore there was not a clinically significant difference from the placebo group. No treatment group had a clinically significant change in the Emotional summary score [clinstat\copd\sfca3007.pdf, pages 1519, 1525, 1531].

In general, FP 250 and SAL 50/FP 250 had scores for change from baseline in individual domains that were numerically superior to scores for change from baseline for placebo. However, no individual domain score for FP 250 or SAL 50/PF 250 differed from placebo by the specified clinically significant amount [clinstat\copd\sfca3007.pdf, pages 1519, 1525, 1531, 1537, 1543, 1549, 1555].

Examination of the "reduced ITT population" revealed similar findings as the ITT population [clinstat\copd\sfca3007.pdf, pages 769, 775, 781, 787, 793, 799, 805].

Table 11.3.18. Chronic Respiratory Disease Questionnaire (CRDQ), COPD-related quality of life instrument, ITT population, SFCA3007 [clinstat\copd\sfca3007.pdf, pages 1519, 1525, 1531].

	Pbo			SAL 50			FP 250			SAL 50/FP 250		
	Score	Mean change from baseline	n	Score	Mean change from baseline	n	Score	Mean change from baseline	n	Score	Mean change from baseline	n
Overall score*												
Baseline	84.8	NA	180	86.3	NA	173	85.5	NA	177	84.1	NA	175
Endpoint	89.6	5.0	177	93.0	6.4	170	96.4	10.4	170	93.9	10.0	169
Physical summary score**												
Baseline	32.3	NA	180	33.1	NA	173	33.3	NA	177	32.0	NA	175
Endpoint	35.9	3.8	177	37.0	3.9	170	39.0	5.6	170	38.1	6.1	169
Emotional summary score***												
Baseline	52.6	NA	180	53.2	NA	173	52.2	NA	178	52.1	NA	175
Endpoint	53.6	1.2	177	56.0	2.6	170	57.3	4.7	171	55.8	3.9	169

*Clinically significant change in Overall Score = 10.0 points
**Clinically significant change in Physical Summary Score = 4.5 points
***Clinically significant change in Emotional Summary Score = 5.5 points

Reviewer comment:
Although there were clinically significant improvements from baseline in the Overall score and the Physical summary scores for FP 250 and SAL 50/FP 250, these improvements were less than the specified clinically significant difference from the change from baseline in the placebo group. Since the Overall score did not show any clinically significant differences from placebo, individual domains or summary scores provide no meaningful information. These data provide no additional support for the efficacy of FP in this population.

11.3.17.6. Smoking status, subgroup analysis

The sponsor provided an analysis of efficacy by patient smoking status. Former smokers had the largest mean change from baseline in pre-dose FEV_1at endpoint in all active treatment groups [clinstat\copd\sfca3007.pdf, page 115]. These data are displayed in Table 11.3.19. Among the former smokers, those treated with SAL 50/FP 250 had the largest change in FEV_1 (193 mL), followed by those treated with FP 250 (136 mL), and SAL 50 (86 mL). The smallest change for former smokers was noted in those treated with placebo (-3 mL). Patients who were smokers during the conduct of the study had smaller mean changes from baseline in pre-dose FEV_1, with the largest change in patients treated with SAL 50/FP 250 (127 mL), and followed by SAL 50 (96 mL) and FP 250 (80 mL). The smallest change was in placebo patients (4 mL).

Table 11.3.19. Mean change from baseline in pre-dose FEV_1 at endpoint, by smoking status, SFCA3007 [clinstat\copd\sfca3007.pdf, page 115].

Smoking status	Placebo		SAL 50		FP 250		SAL 50/FP 250	
	Mean Change, mL	(n)	Mean change, mL	(n)	Mean change, mL	(n)	Mean change, mL	(n)
Current smokers	4	(87)	96	(90)	80	(88)	127	(77)
Former smokers	-3	(98)	86	(87)	136	(95)	193	(101)

The sponsor also examined other efficacy endpoints by patient smoking status. In general, where there were differences between the groups, efficacy was favored in the former smokers for FP 250, as well as in other active treatment groups. Current smokers had a lower percentage of COPD exacerbations than former smokers in all treatment groups. Changes in PEFRs for patients treated with FP 250 were slightly higher in former smokers than in current smokers, similar to the FEV1 data.

Results of the Overall CRDQ score at endpoint for former smokers or current smokers in all treatment groups were similar to that seen for all patients in the intent-to-treat group. Larger changes from baseline were seen in the FP 250 and SAL 50/FP 500 groups than in SAL 50 and placebo groups. The degree of change from baseline for FP 350 and SAL 50/FP 250 was fairly similar in former smokers and in current smokers. However, there was less than a 10.0 point difference in these values from the change from baseline for the placebo group, indicating that there was not a clinically significant difference from the placebo group [clinstat\copd\sfca3007.pdf, page 1583, 1586].

Reviewer comment:
These data suggest that in general, efficacy favored patients who stopped smoking prior to the conduct of the study, as noted in FLTA3025 and SFCA3006. The observation that there were more COPD exacerbations in former smokers than in current smokers is interesting, but may be due to a higher number of withdrawals in the current smoker group.

11.3.17.7. "Non-reversible" population, subgroup analysis

Assignment to study drug was to be stratified according to the patients' response to reversibility testing with Ventolin at screening to a non-reversible group and a reversible group. Non-reversible patients were defined as having an absolute volume increase <200 mL or an absolute volume increase of ≥200 mL with baseline FEV_1 reversibility of <12%. Reversible patients were defined as having an absolute volume increase ≥200 mL with baseline FEV_1 reversibility of ≥12% [clinstat\copd\sfca3007.pdf, page 7113; IND 44,090 N134 PN, 8/4/98, page 25]. Despite having assignment stratified based on "non-reversibility," the sponsor did not initially include an analysis for this subgroup. The sponsor was asked to provide a subgroup analysis of the non-reversible group in an IR on 10/2/01. The sponsor submitted this information in a document dated 1/17/01 [NDA 20-833, SE1 004 BZ, 10/17/01]. The results of the subgroup analysis for the non-reversible population are briefly reviewed below.

Table 11.3.20 summarizes the mean change in FEV_1 from baseline for the "non-reversible" population. Increases from baseline in pre-dose FEV_1 at endpoint were noted in all active treatment groups. The largest increase was in the SAL 50/FP 500 group (126 mL), followed by FP 250 (74 mL), and SAL 50 (26 mL). The placebo group had a an increase from baseline at endpoint of 19mL [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 13, 377-382].

A similar pattern was noted for mean change from baseline in pre-dose FEV_1 at Weeks 12 and 24. The largest increases were for the SAL 50/FP 500 group, followed by FP 250 and SAL 50. Increases from baseline were noted at these visits for the placebo group and ranged from 23 mL to 41 mL [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 14, 377-382].

Table 11.3.20. Mean change in pre-dose FEV_1 from baseline, primary efficacy variable, non-reversible population, SFCA3007 [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 14, 377-382].

	Pbo			SAL 50			FP 250			SAL 50/FP 250		
Study week	Mean FEV_1, mL	Mean change, mL	n	Mean FEV_1, mL	Mean change, mL	n	Mean FEV_1, mL	Mean change, mL	n	Mean FEV_1, mL	Mean change, mL	n
Baseline	1116	NA	83	1151	NA	79	1098	NA	83	1111	NA	79
Week 12	1224	41	65	1235	83	59	1181	75	65	1270	147	64
Week 24	1213	23	55	1222	27	52	1210	83	59	1295	144	54
Endpoint	1141	19	79	1176	26	74	1170	74	79	1245	126	75

Response of the reversible population in the mean change in FEV_1 from baseline is summarized in Table 11.3.21. The difference from placebo for mean change from baseline at endpoint for the reversible group for FP 250 was 153 mL. This was 98 mL greater than the difference from placebo for mean change from baseline at endpoint for the non-reversible group, which for FP 500 was 55 mL [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 14].

Table 11.3.21. Mean change in pre-dose FEV_1 from baseline, primary efficacy variable, reversible population, SFCA3007 [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 14, 383-388].

	Pbo			SAL 50			FP 250			SAL 50/FP 250		
Study week	Mean FEV_1, mL	Mean change, mL	n	Mean FEV_1, mL	Mean change, mL	n	Mean FEV_1, mL	Mean change, mL	n	Mean FEV_1, mL	Mean change, mL	n
Baseline	1327	NA	102	1237	NA	97	1350	NA	100	1284	NA	99
Week 12	1337	-16	74	1396	127	75	1440	88	82	1459	181	80
Week 24	1346	-13	70	1445	157	66	1547	146	74	1502	180	70
Endpoint	1325	-15	93	1389	141	93	1500	138	96	1476	196	96

Reviewer comment:
Primary efficacy endpoint data provide some support for the efficacy of FP 250 and SAL 50/FP 250 in the non-reversible population.
In general, secondary endpoints demonstrated small improvements from baseline in the non-reversible population for SAL 50/FP 250, but not FP 250.

Changes at endpoint from baseline in the GAS of the CBSQ were noted for all treatment groups, but there were no clinically significant differences from the placebo group. Changes at endpoint from baseline in the GAS were greatest in the SAL 50/FP 250 group and the FP 250 group [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 15, 419]. Changes at endpoint from baseline in the TDI showed no clinically significant differences from placebo. Changes from baseline in the TDI were greatest for SAL 50/FP 250 and FP 250 [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 479]. The incidences and frequencies of COPD exacerbations were similar across the active and placebo treatment groups for this population. The incidence and frequency of moderate to severe exacerbations due to COPD were slightly higher in the SAL 50 and FP 250 groups than the SAL 50/FP 250 and placebo groups. [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, pages 16, 487, 489].

Reviewer comment:
Secondary efficacy endpoint data do not provide support for the efficacy of FP 250 in the non-reversible population.

There was a slightly lower probability of first COPD exacerbation during the first half of the study for the SAL 50/FP 250 group compared with the other treatment groups. There was a slightly higher probability of first COPD exacerbation during the first half of the study for the FP 250 group compared with the other treatment groups. However, the probabilities for first COPD exacerbation were similar for all treatment groups by the end of the study [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 357]. There was a slightly lower probability of first moderate to severe COPD exacerbation during the first half of the study for the SAL 50/FP 250 group compared with the other treatment groups. There was a slightly higher probability of first moderate to severe COPD exacerbation during the first half of the study for the FP 250 group compared with the other treatment groups. However, the probabilities for first COPD exacerbation were similar for all treatment groups by the end of the study [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 359].

In general, small changes from baseline favoring SAL 50/ FP 250, FP 250, SAL 50 were noted in for the non-reversible population for AM PEFR. The effect was greatest for the SAL 50/FP 250 group, followed by the SAL 50 and FP 250 groups [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 510].

There was a decrease in the number of puffs of Ventolin used per day for the SAL 50/FP 250 group. There was no meaningful decrease in the number of puffs of Ventolin used per day for the FP 250, SAL 50, or placebo groups [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 16]. Awakenings per night requiring Ventolin showed little

meaningful difference between treatment groups for the non-reversible group [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 526].

The overall score of the CRDQ, the health-related quality of life instrument, showed a clinically significant change from baseline for the SAL 50/FP 500 group. However this change was not clinically significantly different from the change from baseline for the placebo group [NDA 20-833 SE1 004, BZ, 10/17/01\response.pdf, page 531].

Reviewer comment:
AM PEFR was the only secondary endpoint that provided support for FP 250, and this is endpoint is likely to be fairly well correlated with the primary efficacy endpoint, which also supported FP 250. This analysis of primary efficacy variable and selected secondary variables in the non-reversible population provide little support for efficacy of FP 250.

11.3.17.8. Safety outcomes

Safety variables for this study included AEs, ECGs, hematology and clinical chemistry studies, oropharyngeal examinations, and vital signs [clinstat\copd\sfca30007.pdf, pages 60-64, 7124-7128].

Cosyntropin (Cortrosyn®) stimulation testing was performed at selected study sites on Day 1 and Week 24 or Discontinuation [clinstat\copd\sfca3007.pdf, page 7128].

11.3.17.8.a. Total drug exposure

Total drug exposure is summarized in Table 11.3.22. Approximately 62% of each group completed ≥24 weeks of study treatment. The mean duration of treatment was 131.6 days for placebo, 136.1 days for SAL 50, 138.5 days for FP 250, and 141.3 days for SAL 50/FP 250.

Table 11.3.22. Total drug exposure, SFCA3007 [clinstat\copd\sfca3007.pdf, pages 153, 895].

Duration of treatment	Placebo N = 185		SAL 50 N = 177		FP 250 N = 183		SAL 50/FP 250 N = 178	
	n	(%)	n	(%)	n	(%)	n	(%)
Any treatment	185	(100)	177	(100)	183	(100)	178	(100)
≥4 weeks	160	(86)	157	(89)	164	(90)	163	(92)
≥8 weeks	150	(81)	151	(85)	156	(85)	158	(89)
≥12 weeks	141	(76)	138	(78)	148	(81)	148	(83)
≥16 weeks	133	(72)	134	(76)	145	(79)	141	(79)
≥20 weeks	130	(70)	127	(72)	136	(74)	131	(74)
≥24 weeks	110	(59)	108	(61)	116	(63)	112	(63)
Treatment days, mean	131.6		136.1		138.5		141.3	

Reviewer comment:
Drug exposure appears to be adequate to allow for assessment of short-term safety, and noting the limitations that the design and duration of this study impose, and recognizing the compliance reporting is commonly unreliable. Compliance assessment was based on data from the Diskus dose counter, which cannot assess whether patients actually received the drug that was dispensed.

11.3.17.8.b. Cosyntropin stimulation testing

Cosyntropin (Cortrosyn®) stimulation testing was performed at selected study sites on Day 1 and Week 24 or Discontinuation [clinstat\copd\sfca3007.pdf, page 7128]. The sponsor performed the short cosyntropin stimulation test according to the cosyntropin package insert. Blood samples were to be drawn 30-60 minutes after administration of cosyntropin [clinstat\copd\sfca3007.pdf, page 7128]. Threshold values of 14.5 mcg/dL and 5.6 mcg/dL were used in the analysis because a HPLC assay was used. The sponsor states that a less specific radioimmunoassay was used for the higher reference values given in the cosyntropin package insert [clinstat\copd\sfca3007.pdf, pages 78-79].

The sponsor states that this adjustment is consistent with previously published data[11, 12]. Abnormalities for this test was defined as:

- AM plasma cortisol <4 mcg/dL
- Peak post-stimulation cortisol <14.5 mcg/dL
- Change from baseline of <5.6 mcg/dL
- Peak post-stimulation cortisol <14.5 mcg/dL and change from baseline of <5.6 mcg/dL

There is no mention in the protocol of the type of assay that was to be used for cortisol, or of the definitions for abnormalities in cortisol levels.

Reviewer comment:
The definitions for abnormalities in cortisol levels with the cosyntropin stimulation test are consistent with the sponsor's references. It would have been preferable to specify in the protocol both the assay to be used and the definitions of an abnormal test, however.

The number and percentage of patients with abnormalities in cosyntropin stimulation testing is displayed in Table 11.3.23. The numbers of patients with cortisols were incorrect in the initial submission, but were corrected in a subsequent response NDA 20-833 SE1 004, BZ, 10/26/01\response.pdf]. The correct numbers are displayed in Table 1.3.23 and are reviewed in this section. There were no differences between treatment groups in the percentage of patients who had pre-stimulation AM cortisol levels <4 mcg/dL at Day 1 and Endpoint. There were no differences between treatment groups in the percentage of patients with a change in post-stimulation cortisol <5.6 mcg/dL

FP 250 had the largest percentage of patients with post-stimulation change in cortisol at endpoint of <5.6 mcg/dL (15%). However, the percentage of patient with post-stimulation change in cortisol at endpoint of <5.6 mcg/dL in the SAL 50/FP 250 group (9%) was similar to that in the placebo group (11%).

There was an increase in the percentage of patients with post-stimulation cortisol levels <14.5 mcg/dL from Day 1 to Endpoint in all treatment groups. The largest increase in the percentage of patients with post-stimulation cortisol levels <14.5 mcg/dL from Day 1 to Endpoint was in the FP 250 group (6% to 12%). However, the percentage of patients with post-stimulation cortisol levels <14.5 mcg/dL in the SAL 50/FP 250 group had a small decrease (4% to 3%). The results of patients with post-stimulation cortisol levels <14.5 mcg/dL in the SAL 50 group (4% to 7%) and placebo group (4% to 7%) were similar [clinstat\copd\sfca3007.pdf, pages 166, 969, 972].

Table 11.3.23. Number and percentage of patients with abnormalities in cosyntropin stimulation testing, all patients with cortisol levels, SFCA3007 [clinstat\copd\sfca3007.pdf, pages 166, 969, 972; NDA 20-833 SE1 004, BZ, 10/26/01\response.pdf, page 30].

	Day 1				Endpoint			
	Pbo N=185 n (%)	SAL 50 N=177 n (%)	FP 250 N=183 n (%)	SAL 50/ FP 250 N=178 n (%)	Pbo N=185 n (%)	SAL 50 N=177 n (%)	FP 250 N=183 n (%)	SAL 50/ FP 250 N=178 n (%)
Patients with cortisol levels	54 (100)	53 (100)	50 (100)	45 (100)	27 (100)	29 (100)	26 (100)	32 (100)
Pre-stim AM cortisol <4 mcg/dL	3 (6)	0 (0)	2 (4)	0 (0)	2 (7)	1 (3)	0 (0)	1 (3)
Post-stim change <5.6 mcg/dL	2 (4)	7 (13)	5 (10)	4 (9)	3 (11)	1 (3)	4 (15)	3 (9)
Post-stim cortisol <14.5 mcg/dL	2 (4)	2 (4)	3 (6)	2 (4)	2 (7)	2 (7)	3 (12)	1 (3)

Mean cortisol levels for cosyntropin stimulation testing are displayed in Table 11.3.24. Mean pre-stimulation cortisol levels were slightly lower at Endpoint than at Day 1 for each of the treatment groups, including the placebo group. Mean post-stimulation cortisol levels were slightly lower for all treatment groups at Endpoint than at Day 1 for all treatment groups except SAL 50/FP 250.

Table 11.3.24. Mean cortisol levels, pre-and post-cosyntropin stimulation, SFCA3007 [clinstat\copd\sfca3007.pdf, pages 965-966].

	Day 1				Endpoint			
	Pbo N=185	SAL 50 N=177	FP 250 N=183	SAL 50/ FP 250 N=178	Pbo N=185	SAL 50 N=177	FP 250 N=183	SAL 50/ FP 250 N=178
Pre-stimulation cortisol, mcg/dL	12.43	12.98	11.56	13.40	11.13	12.24	10.55	12.38
(SD)	(5.57)	(5.12)	(4.07)	(6.76)	(5.59	(7.05)	(3.63)	(5.72)
Post-stimulation cortisol, mcg/dL	25.94	24.61	23.96	23.89	23.23	23.57	22.14	23.19
(SD)	(6.57)	(5.18)	(5.69)	(6.12)	(6.83)	(7.60)	(6.79)	(4.38)

	Day 1				Endpoint			
Difference in means, pre-stimulation to post-stimulation*	13.51	11.63	12.40	10.49	12.10	11.33	11.59	10.81

*Calculated from sponsor's data.

Reviewer comment:
The data for cosyntropin stimulation testing show no evidence of adrenal suppression. It should be noted, however, that cosyntropin stimulation testing is intended as a means to diagnose adrenal insufficiency and is fairly insensitive as a measure of adrenal suppression.

11.3.17.8.c. Adverse events

Adverse events (AEs) were common in this study. These data are summarized in Table 11.3.25. AEs were more common in FP 250 (70%, 129/177) and SAL 50/FP 250 (70%, 124/178) patients than for placebo (64%, 118/185). AEs occurring at a frequency ≥3% and more frequently with FP 250 or SAL 50/FP 250 than with placebo included headaches, musculoskeletal pain, sinusitis, throat irritation, candidiasis of the mouth/throat, viral respiratory infection, upper respiratory tract inflammation, ear signs and symptoms, chest symptoms, sinusitis/sinus infection, muscle injuries, hoarseness/dysphonia, fever, muscle cramps and spasms, pain, epistaxis, edema and swelling, dizziness, nasal congestion/blockage, and constipation [clinstat\copd\sfca3007.pdf, pages 155, 896-910].

Many of the AEs noted are noted in the labels for Flovent MDI and Flovent Rotadisk. These include upper respiratory tract infection, headaches, musculoskeletal pain, sinusitis, candidiasis, viral respiratory infections, muscle injuries, hoarseness/dysphonia, fever, epistaxis, dizziness, and nasal congestion. AEs reported in this study that are not noted in current labeling for other Flovent products include ear signs and symptoms and muscle cramps and spasms. These may represent new safety signals. It is difficult to assess whether other AEs noted in this study that were not noted in current Flovent labeling represent new safety signals because of their low frequencies.

Reviewer comment:
There were more patients with COPD exacerbations reported for the secondary efficacy endpoint than were reported as AEs.

Table 11.3.25. Adverse events occurring more frequently in FP 250 or SAL 50/FP 250 than in placebo and ≥3%, SCFA3007. Entries represent number (percent) of patients [clinstat\copd\sfca3007.pdf, pages 155, 896-910].

Adverse event	Placebo N = 185		FP 250 N = 177		SAL 50/FP 250 N = 178	
	n	(%)	n	(%)	n	(%)
All adverse events	118	(64)	129	(70)	124	(70)
Headaches	22	(12)	21	(11)	28	(16)

Adverse event	Placebo N = 185		FP 250 N = 177		SAL 50/FP 250 N = 178	
	n	(%)	n	(%)	n	(%)
Musculoskeletal pain	16	(9)	14	(8)	16	(9)
Sinusitis	5	(3)	14	(8)	6	(3)
Throat irritation	13	(7)	10	(5)	15	(8)
Candidiasis mouth/throat	2	(1)	11	(6)	17	(10)
Viral respiratory infections	6	(3)	8	(4)	10	(6)
Upper respiratory inflammation	6	(3)	7	(4)	4	(2)
Ear signs and symptoms	2	(1)	6	(3)	4	(2)
Muscle injuries	2	(1)	6	(3)	2	(1)
Hoarseness/dysphonia	0	(0)	5	(3)	9	(5)
Fever	5	(3)	5	(3)	8	(4)
Muscle cramps and spasms	2	(1)	5	(3)	6	(3)
Pain	3	(2)	5	(3)	2	(1)
Epistaxis	2	(1)	5	(3)	1	(<1)
Edema and swelling	2	(1)	3	(2)	5	(3)
Dizziness	3	(2)	1	(<1)	7	(4)
Nasal congestion/blockage	4	(2)	1	(<1)	5	(3)
Constipation	4	(2)	1	(<1)	5	(3)

AEs beginning after a patient discontinued study medication were infrequent and occurred at similar frequencies in active treatment groups and placebo [clinstat\copd\sfca3007.pdf, page 156]. The highest incidence of AEs was in the first month of treatment (35% placebo, 44% FP 250, 41% SAL 50/FP 250). The most common-drug related AEs included candidiasis of the mouth or throat, headaches, throat irritation, and hoarseness/dysphonia [clinstat\copd\sfca3007.pdf, page 157].

A listing of AEs of low frequency is found in Table 11.3.26. This listing includes AEs that have been associated with use of corticosteroids, such as candidiasis, and hoarseness/dysphonia, infection. Candidiasis of the mouth/throat, viral respiratory infections, hoarseness/dysphonia, candidiasis of unspecified site, pharyngitis/throat infection, and laryngitis, were more frequent in FP 250 and SAL 50/FP 500-treated patients than in placebo. The frequency of fractures was similar among treatment groups. Although there were no AEs reported as diabetes mellitus, hyperglycemia was noted only in the FP 250 and SAL 50/FP 250 groups. One patient treated with SAL 50/FP 250, Patient #17781, was reported as having polyuria and diuresis, but was not one of the patients who was reported as having hyperglycemia, [clinstat\copd\sfca3007.pdf, page 5749].

There were no cases of osteoporosis noted in the FP 250 and SAL 50/FP 250 groups, and there were no cases of cataract, glaucoma, or increased intraocular pressure in any of the treatment groups. It should be noted however that neither formal ophthalmologic examination nor bone densitometry were used to specifically look for these AEs. Small numbers of other AEs were observed without a strong association with FP 250 or SAL 50/FP 250 [clinstat\copd\sfca3007.pdf, pages 896-910].

Table 11.3.26. Selected adverse events of low frequency, SFCA3007. Entries represent number (percent) of patients [clinstat\copd\sfca3007.pdf, pages 896-910].

Adverse event	Placebo N = 185		FP 250 N = 183		SAL5 50/FP 250 N = 178	
	n	(%)	n	(%)	n	(%)
All adverse events*	118	(64)	129	(70)	124	(70)
Candidiasis mouth/throat	2	(1)	11	(6)	17	(10)
Viral respiratory infections	6	(3)	8	(4)	10	(6)
Hoarseness/dysphonia	0	(0)	5	(3)	9	(5)
Candidiasis unspecified site	0	(0)	4	(2)	3	(2)
Dental discomfort & pain	2	(1)	4	(2)	1	(<1)
Pharyngitis/throat infection	1	(<1)	3	(2)	4	(2)
Contusions and hematomas	2	(1)	3	(2)	2	(1)
Gastrointestinal infections	2	(1)	3	(2)	2	(1)
Anxiety	3	(2)	3	(2)	0	(1)
COPD	1	(<1)	3	(2)	1	(0)
Viral infections	2	(1)	2	(1)	4	(2)
Hypertension	5	(3)	2	(1)	4	(2)
Fractures	3	(2)	2	(1)	3	(2)
Abnormal liver function tests	1	(<1)	2	(1)	2	(1)
Hyperglycemia	0	(0)	2	(1)	1	(<1)
Viral skin infections	3	(2)	2	(1)	1	(<1)
Depressive disorders	3	(2)	2	(1)	1	(<1)
Pneumonia	0	(0)	2	(1)	0	(0)
Gum signs and symptoms	1	(<1)	2	(1)	1	(<1)
Laryngitis	0	(0)	1	(<1)	4	(2)
Urinary infections	4	(2)	1	(<1)	3	(2)
Eye infections	1	(<1)	1	(<1)	2	(1)
Situational disorders	1	(<1)	1	(<1)	1	(<1)
Hypokalemia	0	(0)	1	(<1)	0	(0)
Hypoglycemia	1	(<1)	1	(<1)	0	(0)
Psychogenic disorders	0	(0)	1	(<1)	0	(0)
Fungal reproductive infections	0	(0)	1	(<1)	0	(0)
Fungal infection mouth and throat	0	(0)	1	(<1)	0	(0)
Viral gastrointestinal infections	1	(<1)	1	(<1)	0	(0)
Tooth decay	1	(<1)	1	(<1)	0	(0)
Dental operations	0	(0)	1	(<1)	0	(0)
Gastroenteritis	0	(0)	1	(<1)	0	(0)
Increased blood pressure	1	(<1)	1	(<1)	0	(0)
Nocturia	0	(0)	1	(<1)	0	(0)
Purpura	0	(0)	1	(<1)	0	(0)
Ear, nose, and throat infections	0	(<1)	0	(0)	3	(2)
Fungal skin infections	2	(1)	0	(0)	2	(1)
Bacterial infections	1	(<1)	0	(0)	2	(1)
Lower respiratory hemorrhage	2	(1)	0	(0)	2	(1)
Musculoskeletal infections	0	(0)	0	(0)	1	(<1)
Agitation	1	(<1)	0	(0)	1	(<1)
Disorders of hard tissues of teeth	2	(1)	0	(0)	1	(<1)
Polyuria and diuresis	0	(0)	0	(0)	1	(<1)
Increased white cells	0	(0)	0	(0)	1	(<1)
Skin infections	1	(<1)	0	(0)	1	(<1)
Viral eye infections	0	(0)	0	(0)	1	(<1)
Electrolyte disturbances	0	(0)	0	(0)	1	(<1)
Osteoporosis	1	(<1)	0	(0)	0	(0)
Infections	1	(<1)	0	(0)	0	(0)
Bacterial skin infections	1	(<1)	0	(0)	0	(0)

Subgroup analysis of AEs by gender, age, and race will be reviewed in the Integrated Review of Safety section of this document.

Reviewer comment:
The high frequency of oropharyngeal thrush in the groups receiving FP is worth noting and may be indicative of a more globally immunosuppressed condition. There were a few patients reported as having "contusions and hematomas," and one patient was reported to have "purpura." Otherwise, there were no other patients who were reported as having bruising. One would expect a fairly significant number of patients to have had this AE, given the large doses of FP used and given the older ages of the patients studied. Unfortunately this study was not designed to specifically look for cataract or systemic bone effects, both known to be associated with systemic effects of corticosteroids. Ophthalmologic examination and studies to assess osteoporosis would have been helpful to address these concerns. It is notable that hyperglycemia was noted only in the FP 250 and SAL 50/FP 250 groups, and not in the placebo group. Hyperglycemia is likely to represent a safety signal for the FP 250 and SAL 50/FP 250 groups.

11.3.17.8.d. Deaths and serious adverse events

There were no deaths that occurred during the study [clinstat\copd\sfca3007.pdf, page 158].

There were 34 patients (34/723) who experienced a serious adverse event (SAE) during the treatment phase of the study. The percentage of patients was SAEs during the treatment phase were similar among the treatment groups, with the highest in the placebo group (6%, 11/185), followed by FP 250 (5%, 10/183), and SAL 50/FP 250 (4%, 8/178). SAEs occurring in more than one patient are displayed in Table 11.3.27. SAL 50-treated patients are not represented in this table. SAEs due to chronic obstructive airways disease were most frequent in FP 250 (3%, 2/183) compared with placebo (<1%, 1/185) and SAL 50/FP 250 (0%, 0/178). Chest symptoms (literal term "chest pain") occurred in equal at fairly similar frequencies among treatment groups. Cholelithiasis occurred most frequently in FP 250 (1%, 2/183), followed by placebo (<1%, 1/185), and SAL 50/FP 250 (0%, 0/178). Cholecystitis occurred at similar frequencies in FP 250 (<1%, 1/183) and SAL 50/250 (<1%, 1/178). One FP 250 patient, #13964, was reported as having both cholelithiasis and cholecystitis [clinstat\copd\sfca3007.pdf, page 5764].

Table 11.3.27. SAEs occurring in more than one patient during the treatment period, SFCA3007 [clinstat\copd\sfca3007.pdf, pages 159, 1411-1413].

Serious adverse event	Placebo N = 185		FP 250 N = 183		SAL 50/FP 250 N = 178	
	n	(%)	n	(%)	n	(%)
Any serious adverse event	11	(6)	10	(5)	8	(4)
Chronic obstructive airways disease	1	(<1)	3	(2)	0	(0)
Cholelithiasis	1	(<1)	2	(1)	0	(0)
Chest symptoms*	2	(1)	0	(0)	1	(<1)
Cholecystitis	0	(0)	1	(<1)	1	(<1)
Fractures	1	(<1)	0	(0)	1	(<1)

*All events coded as chest symptoms were due to chest pain.

There was one patient each in the SAL 50/FP 250 group and placebo group that had a SAE for fracture. The SAL 50/FP 250 patient, #16741, was a 58 year-old female who fractured her femur due to a fall. This patient withdrew from the study

[clinstat\copd\sfca3007.pdf, pages 160, 5769]. The placebo patient, #13531, a 57 year-old man who sustained fractured ribs and a chest contusion in an auto accident. This patient continued in the study [clinstat\copd\sfca3007.pdf, pages 160, 5753].

Reviewer comment:
The higher frequency of SAEs for COPD in the FP 250 group is interesting, as there was a higher frequency of SAEs for COPD and pneumonia in the FP 500 and SAL 50/FP 500 groups in SFCA3006. It is also interesting that the only hip fracture occurred in a FP 250-treated patient. Although this SAE could be drug-related, a woman of this age would also be at a higher risk for fracture from pre-existing osteoporosis.

11.3.17.8.e. Withdrawals due to adverse events

Withdrawals due to adverse events (AEs) are displayed in Table 11.3.28. Withdrawals due to AEs occurred at similar frequencies for FP 250 (5%, 10/183), SAL 50/FP 250 (5%, 9/178), and placebo (4%, 8/185). Withdrawals due to COPD were most common in the FP 250 group (2%, 2/183), followed by the placebo group (<1%, 1/185) and the SAL 50/FP 500 group (0%, 0/178). There were two withdrawals due to fractures, and both patients were in the SAL 50/FP 250 group. Patient #16636 was a 79 year-old woman who fractured three ribs in an auto accident [clinstat\copd\sfca3007.pdf, pages 160, 5785; crf\sfca3007\66\p0016636.pdf, page 1]. Patient #16741 was a 58 year-old woman who fell on her flexed left knee and fractured the supracondylar and intercondylar areas of her femur in a fall [clinstat\copd\sfca3007.pdf, pages 160, 5785; crf\sfca3007\68\p0016741.pdf, page 1, NDA 20-833, SE1 004 C, 12/3/01, page 5].

Table 11.3.28. Withdrawals due to adverse events occurring in more than one patient, SFCA3007 [clinstat\copd\sfca3007.pdf, page 161].

Adverse event	Placebo N = 185		FP 250 N = 183		SAL 50/FP 250 N = 178	
	n	(%)	n	(%)	n	(%)
Any adverse event	8	(4)	10	(5)	9	(5)
Chronic obstructive airways disease	1	(<1)	3	(2)	0	(0)
Fractures	0	(0)	0	(0)	2	(1)
Depressive disorders	2	(1)	0	(0)	0	(0)
Pneumonia	0	(0)	1	(<1)	0	(0)
Malignant breast neoplasia	1	(<1)	0	(0)	1	(<1)
Viral respiratory infections	0	(0)	1	(<1)	1	(<1)

Reviewer comment:
Withdrawals due to COPD were most common in the FP 250 group, a pattern seen with SAEs in this study and with FP 500 in SFCA3006.

11.3.17.8.f. Vital signs

There were no clinically significant changes from baseline in median values of vital signs for any of the treatment groups [clinstat\copd\sfca3007.pdf, pages 999-1004].

11.3.17.8.g. Physical examination

Physical examinations were performed at Screening and at the end of the study [clinstat\copd\sfca3007.pdf, page 64]. Data was recorded on subject progress notes, but

not on case report forms (CRFs). Physical examination abnormalities were recorded as AEs on the CRFs, but no summary of physical examinations was provided [NDA 20-833, SE1-004, BM, 9/17/01, page 3].

11.3.17.8.h. Oropharyngeal examination

Oropharyngeal examinations were performed at each treatment visit, every treatment visit, and at the end of the study [clinstat\copd\sfca3007.pdf, page 64]. Data was recorded on subject progress notes, but not on case report forms (CRFs). Oropharyngeal examination abnormalities were recorded as AEs on the CRFs, but no summary of oropharyngeal examinations was provided [NDA 20-833, SE1-004, BM, 9/17/01, page 2].

11.3.17.8.i. Laboratory studies

Shifts in hematology studies from baseline at Weeks 12 and 24 were similar among treatment groups [clinstat\copd\sfca3007.pdf, pages 162, 923-933].

There was a higher proportion of patients in the SAL 50/FP 250 (22%) and SAL 50 (15%) groups that had a shift in lymphocyte count to low at the Discontinuation visit as compared with the placebo (10%) and FP 250 (3%) groups [clinstat\copd\sfca3007.pdf, pages 162, 923-933].

There was a higher proportion of patients in the SAL 50/FP 250 (20%) and SAL 50 (17%) groups that had a shift in neutrophil count to high at the Discontinuation visit as compared with the placebo (12%) and FP 250 (0%) groups [clinstat\copd\sfca3007.pdf, pages 162, 923-933].

There was a higher proportion of patients in the FP 250 (18%), SAL 50 (17%), and FP 250 (18%) groups that had a shift in WBC count to high at the Discontinuation visit as compared with the placebo (10%) group [clinstat\copd\sfca3007.pdf, pages 162, 923-933].

There was no meaningful difference between treatment groups in the percentage of patients who had increases from baseline in glucose at Week 12, Week 24, and Discontinuation [clinstat\copd\sfca3007.pdf, pages 163, 934-942]. However, it should be noted that the sponsor defined an exceptionally liberal definition for high glucose, >175 mg/ml. It is likely that this liberal definition of high glucose would decrease the sensitivity of detecting a difference between treatment groups for this laboratory test [clinstat\copd\sfca3007.pdf, page 5787].

There was a higher proportion of patients in the SAL 50/FP 250 group (12%) that had a shift in ALT to high at the Discontinuation visit as compared with the placebo (6%), SAL 50 (4%), and FP 250 (5%) groups [clinstat\copd\sfca3007.pdf, pages 162, 923-933].

There was a higher proportion of patients in the FP 250 (3%) and SAL 50/FP 250 (4%) groups that had a shift in alkaline phosphatase to high at Week 12, compared with the placebo (2%), SAL 50 (<1%), and FP 250 (5%) groups. This was not noted at the 24

Week visit, but was noted at the Discontinuation visit, with the largest shifts of alkaline phosphatase in the SAL 50/FP 250 (7%) and FP 250 (3%) groups, compared with placebo (0%) and SAL 50 (2%) [clinstat\copd\sfca3007.pdf, pages 162, 923-933].

There were no meaningful differences among treatment groups in the percentage of patients with changes in other laboratory studies [clinstat\copd\sfca3007.pdf, pages 162, 923-933].

Reviewer comment:
The higher percentage of patients with decrease in % lymphocytes, and increases in WBC and % neutrophils in FP 500 and SAL 50/FP 500 at the Discontinuation visit could be a manifestation of a systemic corticosteroid effect. This effect was not noted at Weeks 12 or 24, and could be a manifestation COPD, the most common reason for discontinuation in all treatment groups.

The lack of a noted effect in shifts of glucose is much less reassuring because of the high value chosen as a definition for elevated glucose. Changes alkaline phosphatase could represent liver or bone effects of FP, but also may be a chance occurrence.

There were few patients with hematology or chemistry results outside of values specified as normal by the sponsor. The few patients with results outside of the range specified as normal by the sponsor were evenly distributed between treatment groups [clinstat\copd\sfca3007.pdf, pages 953-964].

Reviewer comment:
As with shifts in glucose, the lack of difference between treatment groups in the percentage of patients with elevated glucose is much less reassuring because of the high value chosen as the definition.

11.3.17.8.j. ECGs

There were more patients with clinically significant changes in ECGs from baseline in the placebo group at Week 12 (<1%, 1/135), Week 24 (2%, 2/121), and Discontinuation (4%, 2/49), than FP 250 and SAL 50/FP 250 groups (0%, 0 patients at each of the visits) [clinstat\copd\sfca3007.pdf, page 167].

There were five clinically significant changes in ECGs from baseline in four patients in the placebo group. There were no clinically significant changes in ECGs from baseline for FP 250 or SAL 50/FP 250 groups [clinstat\copd\sfca3007.pdf, pages 167, 979-984].

Median QTc intervals by both Bazette and Fridericia formulae were similar for each of the treatment groups, as was the percentage of patients with change from baseline in QTc intervals [clinstat\copd\sfca3007.pdf, pages 169-170, 985-992]. Two patients in the placebo group, one patient in the FP 500 group, and two patients in the SAL 50/FP 250 group had QTcB >470 msec at Weeks 12, 24, and Discontinuation [clinstat\copd\sfca3007.pdf, page 171].

Reviewer comment:
Review of ECG results reveals no evidence of a safety signal for FP in the population studied.

11.3.18. References

1. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152:S77-S121.

2. Anthonisen NR, Wright EC, et al. Bronchodilator response in chronic obstructive pulmonary disease. Am Rev Respir Dis 1986;133: 814-819.

3. Barnes PJ. Chronic obstructive pulmonary disease. New Engl J Med 2000;343: 269-280.

4. Eliasson O and Degraff AC. The use of criteria for reversibility and obstruction to define patient groups for bronchodilator trials. Am Rev Respir Dis 1985;132: 858-864.

5. National Asthma Education and Prevention Program. Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma. National Institutes of Health Publication Number 97-4051. Bethesda, MD, 1997.

6. 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.

7. 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;109:348-352.

8. Mahler DA, Weinberg DH, et. al. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. Chest 1984;97:751-758.

9. Anthionisen NR, Manfreda J, Warren CPW, et. al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Int Med 1987;106:196-204

10. Guyatt GH, Berman LB, Townsend M, et. al. A measure of quality of life for clinical trials in chronic lung diseases. Thorax 1987;42:773-778

11. Pulmicort package insert. Astra Inc., USA. Westborough, MA October 1998.

12. Scott MB, Skoner DP. Short term and long term safety of budesonide inhalation suspension in infants and young children with persistent asthma. J Allergy Clin Immunol 1999;104: S200-209.

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